APPROACHES TOWARDS THE SYNTHESIS OF GALBULIMIMA ALKALOIDS.

A THESIS

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by

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CONTENTS

SUMMARY

Two approaches towards the synthesis of GB 13, a pentacyclic alkaloid isolated from Galbulimima species, have been developed.

In the first approach, 1-acetoxy-1,2,3,4-tetrahydro-6-methoxy-10-oxo-1,3-ethano-naphthalene was prepared by a novel reductive cyclisation of methyl-1,2,3,4-tetrahydro-7-methoxy-4-oxo-naphthalene-2-acetate. The annelation of this intermediate with 1-acetylcyclohexene was unsuccessful.

The second approach was based on a proposed solvolysis of isoGB 13, a rearrangement product of GB 13. Hydrocyanation of 7, 8, 9, 10, 10a, 10b, 11, 12-octahydro-2-methoxy-6(6aH)-chrysenone with hydrogen cyanide-diethylaluminium chloride gave 4b-cyano-4b, 5, 7, 8, 9, 10, 10a, 10b, 11, 12-decahydro-2-methoxy-6(6aH)-chrysenone. This keto-nitrile, which possessed the trans-anti-trans backbone and axial substituent at C-4b necessary for the synthesis of isoGB 13, has been elaborated to the important model intermediate, 4b-diazoacetyl-6,6'-ethylenedioxy-4b, 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11, 12-dodecahydro-2-methoxychrysene.

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ACKNOWLEDGEMENTS

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I am also indebted to my wife and to those members of the Organic Chemistry Department who helped in compiling this thesis.

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STATEMENT

This thesis contains no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

JOHN A. HALLEDAY

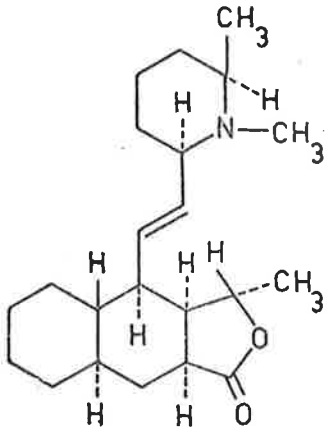
INTRODUCTION.

The chemistry of twentyeight of the alkaloids isolated from the Galbulimima species has been extensively investigated[1-9] since they were first isolated in 1955 by Hughes, Ritchie, Taylor, and coworkers.[10,11] Structural similarities allow the majority of these alkaloids to be grouped into three classes.

Class (1) contains four tricyclic lactones[1-3] which are simple analogues of himbacine (1), the major alkaloid of the genus.

Class (2) consists of fifteen hexacyclic esters[4-6] of high oxygen content which are typified by the alkaloids himandridine (2a), the major member of the group, and himandrine (2b).

The final group of alkaloids, class (3), namely himbadine (3a),[8] GB 13 (3b),[8] and himgaline (4)[9] has fewer substituents than the other classes. One interesting feature of the members of this class which initially hindered structural studies was their skeletal rearrangements; GB 13 for example, undergoes a postulated vinylogous ketol rearrangement to isoGB 13 (Scheme 1) for which the structure (5) has been proposed.[8] Another important feature is the similarity of their basic ring structure with that of the alkaloids of class (2) and this was emphasised when the structure of GB 13 was confirmed[8] by partial synthesis from the ester alkaloid himandrine (2b). Because of this similarity the total synthesis of any alkaloid in class (3) would also serve as a useful model and/or intermediate for the



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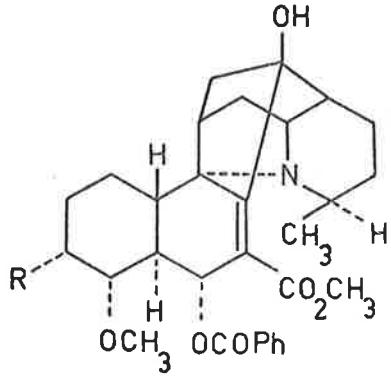
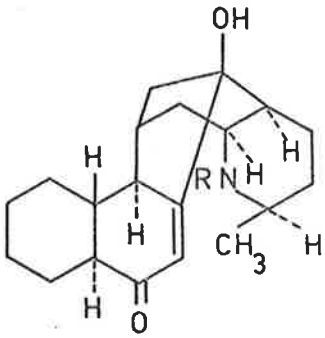


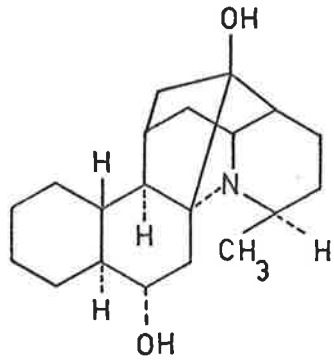
(2a) R = OH

(2b) R = H



(3a) R = CH_3

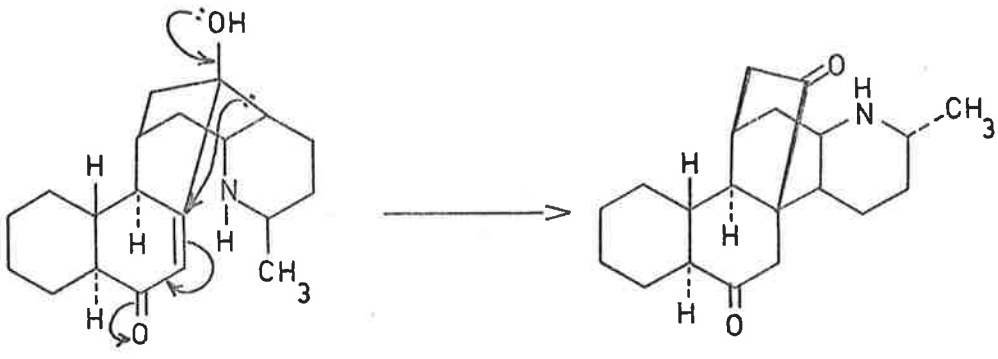
(3b) R = H



(4)

synthesis of alkaloids in classes (2) or (3).

With this consideration in mind, attention was focussed on methods suitable for the synthesis of GB 13 by a scheme that could be modified later to incorporate the functionality necessary for the synthesis of the ester alkaloids in class (2). This thesis will



(3b) (5)

Scheme 1.

describe these initial approaches.

Alkaloid GB 13 was chosen as a suitable representative of class (3) because of its relative simplicity and its unusual rearrangement to isoGB 13. A synthetic scheme is outlined later in which iscGB 13 is a proposed intermediate in the synthesis of GB 13. Several features of the GB 13 structure are readily distinguished as critical units in the design of a synthetic plan. They are:

(1) the lability of the vinylogous ketol system to mildly acidic and basic conditions,[8]

(2) the establishment of the eight asymmetric centres in the natural configuration, and

(3) the incorporation of a bicyclo[3.2.1]octane system

with a bridgehead[≠] hydroxyl group within the centre of a pentacyclic carbon skeleton. This ring system is unprecedented.

The difficulties associated with the first problem can be minimised by introducing the vinyl ketol system at the latest stage possible in the synthetic scheme.

The second problem, the introduction of eight asymmetric centres, is probably not as formidable as it at first seems because of the relationships between the various centres. The 8-9 and 19-20 bonds[*] are necessarily cis-oriented at C_8 and C_{20} and this defines the asymmetry at these positions. The anti-trans backbone of the A-, B-, and C-rings as shown in structure (3b) represents the most stable configuration with least H-H interactions and is the most likely to be formed under thermodynamically controlled conditions. If the stereochemical relationship between C_8 and C_{10} can be controlled, it

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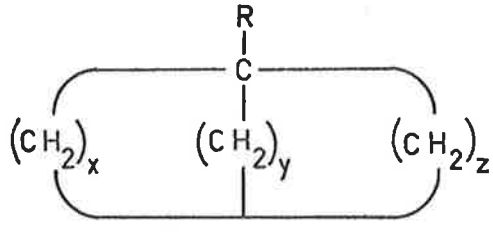
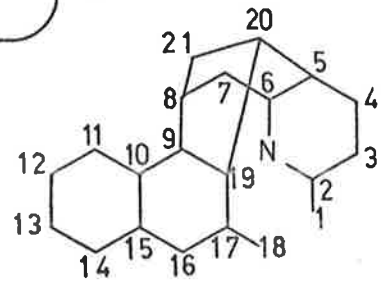
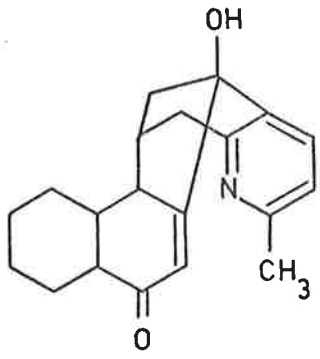
≠ A "bridgehead" group in this thesis will refer to any group R where x, y, z ≠ 0



* The numbering system used in this thesis for GB 13 derivatives is that of Mander and coworkers.[8]



should be possible to introduce the correct asymmetry at carbons 8, 9, 10, 15, and 20. Fortunately a simple and attractive solution to obviate the stereochemical difficulties of the E-ring is also available, provided that the picoline intermediate (6) is considered; the molecular model of (6) suggests that adsorption and hence hydrogenation of the concave molecule on an active catalyst must occur on the α-face to give the desired stereochemistry at carbons 2, 5, and 6.



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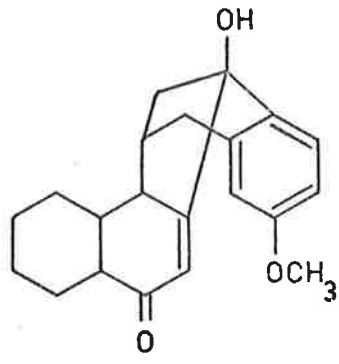


(7)

Although a useful precursor to GB 13 stereochemically, the picoline derivative would be a difficult synthetic objective. The α-hydrogens of 2-alkyl pyridines are very reactive giving rise to prototropic reactions[12] - this reactivity would impede the condensation reactions necessary to build a molecule of this size. However this picoline derivative represents a synthon that may be derived

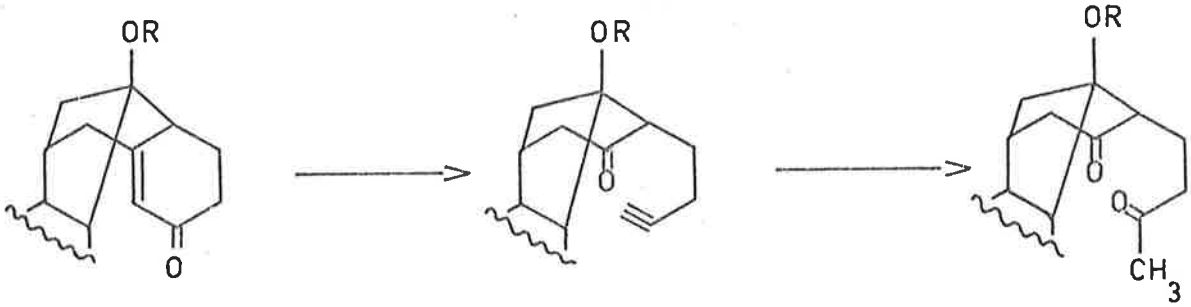
from a less reactive methoxylated aromatic ring such as that present in compound (7). A procedure by which this transformation may be accomplished is suggested by previous work by Tanabe[13] and Eschenmoser.[14] Fragmentation of the α,β-epoxyketone (8) with p-tosylhydrazine under mild conditions gave the cyclohexanone (9) in 35% yield (Scheme 2).[13]

(8) (9)

Scheme 2.

Thus a Birch reduction of the E-ring of the anisole intermediate (7), followed by acid hydrolysis, should yield the α,β-unsaturated ketone (10).[15] Epoxidation and fragmentation under Eschenmoser's conditions[14] should give the acetylenic ketone (11) and after hydration,[13] the diketone (12). δ-Diketones, on condensation with hydroxylamine, yield pyridine derivatives.[16]

As the anisole derivative (7) would present fewer synthetic difficulties than the picoline (6), a consideration of the synthetic

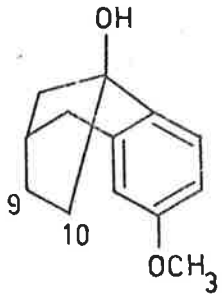


(10) (11) (12)

routes to this intermediate is in order.

The construction of the bicyclo[3.2.1]octanol portion of the skeleton offers an interesting challenge. A logical approach to this problem would be the preparation of the bicyclo[3.2.1]octanol with the aromatic ring attached e.g. (13); this compound would then only require a functional group at either the C-9 or C-10 position to develop the A- and B-rings. Either of the ketols (14) or (15) would be suitable for this purpose, but (14) appears to be the more attractive intermediate because condensation with 1-acetylcyclohexene[17,18] could be expected to give the desired anisole intermediate (7) in a single step.

There are no reported benzobicyclo[3.2.1]octan-10-ones with or without a 1-hydroxyl group and at first glance there seems no obvious or simple way to prepare them. However Gutsche and coworkers[19] have obtained a related acyloin system (17) by a novel reductive



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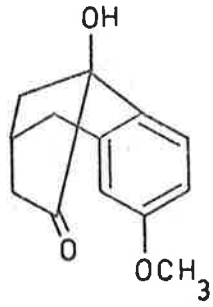

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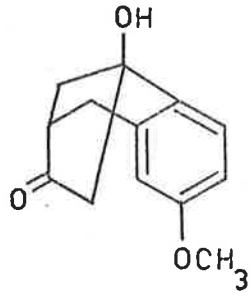


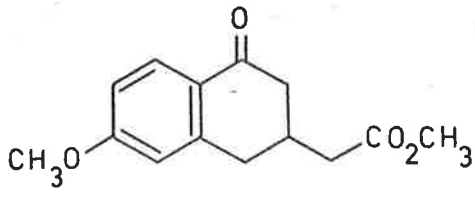
(15)

cyclisation of the keto-ester (16) (Scheme 3). Although this

(16) (17)

Scheme 3.

reaction gave a low yield of product, it appeared suitable for the preparation of the ketol (14) from the keto-ester (18) which should be readily available in large quantities by following a sequence similar to that used by Wilkinson[20] for the preparation of the keto-acid (19).



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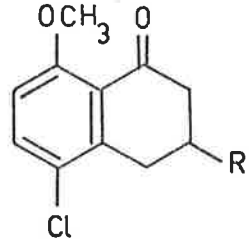
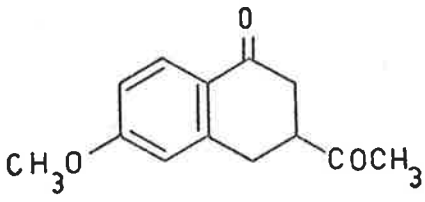


(19) R = CH_2CO_2H

(19a) R = CO_2H

As there is no precedent for the formation of a bridged system by a reductive cyclisation procedure, the alternative approach via the ketol (15) cannot be ignored. A survey of the literature revealed one report of a preparation of a benzobicyclo[3.2.1]octan-9-one.[21] Unfortunately this sequence gives the ketone in very low yield and cannot be modified for the introduction of a tertiary hydroxyl group. However intramolecular condensation of the diketone (20), which should be readily obtainable from the acid (21), could be expected to yield the ketol (15).[22,23] The elaboration of the remainder of the skeleton by established methods[24] would require the transposition of a functional group to the C-16 position.

A possible approach which introduces the carbonyl group directly into this position could be based on the reductive cyclisa-



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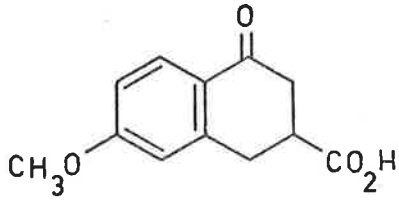
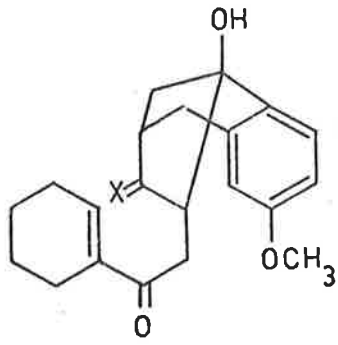


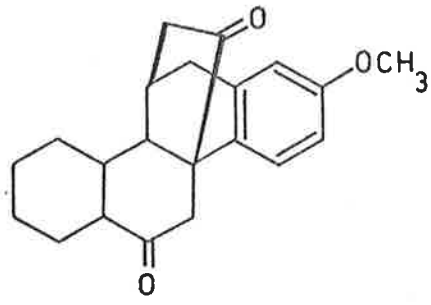
(21)

tion[25] of a species of the general structure (22).



X = O, OTs, etc.

(22)



(23)

Part A of this thesis will describe the various approaches to the synthesis of GB 13 that were developed. Although this route proved to be unsatisfactory, the synthesis of the most challenging portion of the molecule, the bicyclo[3.2.1]octanol, has been accomplished.

Perhaps the most interesting and informative approach to

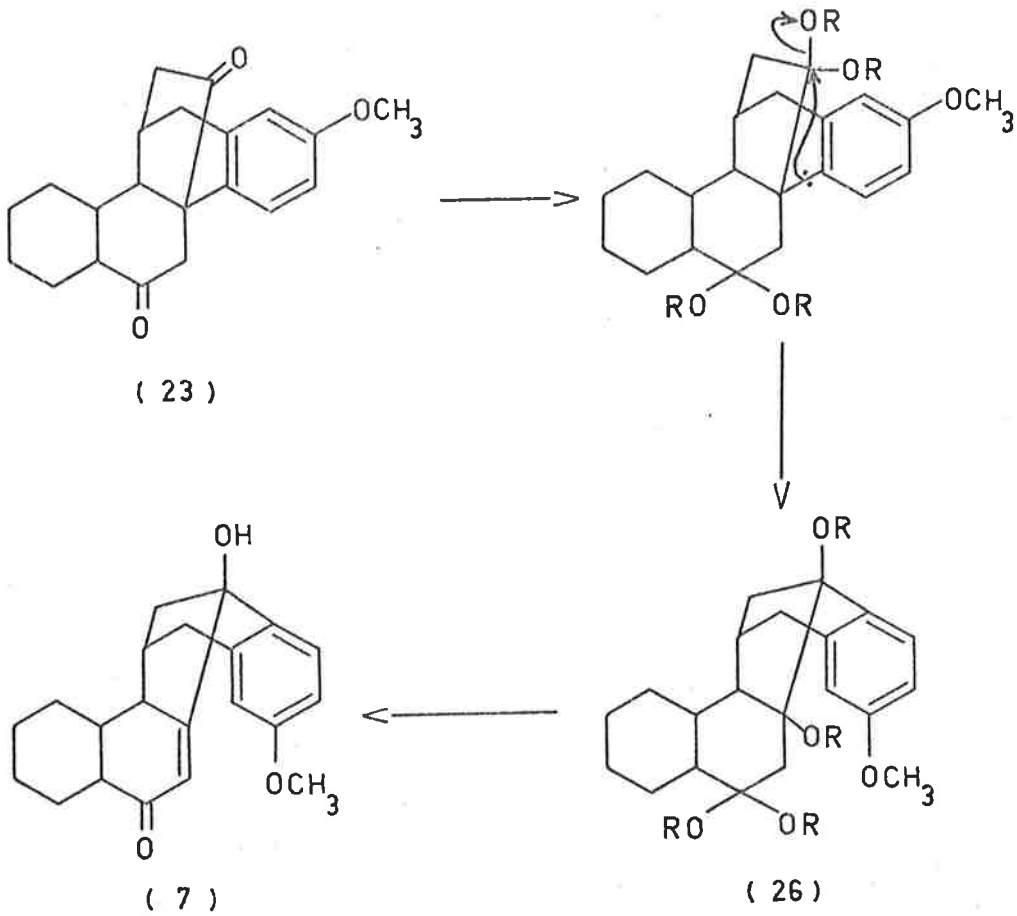
GB 13 would be via iscGB 13, i.e. reverse the vinylogous ketol rearrangement. Not only would this introduce a new approach to the total synthesis, but it would also confirm the proposed structure[8] for iscGB 13. As before, in order to simplify the problems involved in the formation of the heterocyclic E-ring, it would be preferable to carry out investigations on the anisole derivative (23).

Camphor (24), on treatment with trichloroacetic anhydride, rearranges[26] to 1-trichloroacetoxycamphene (26) as shown in Scheme 4.

(24) (25)

Scheme 4.

Reaction of the diketone (23) under similar conditions should result in the formation of (26) (Scheme 5) and careful basic hydrolysis of this would then give the anisole model of GB 13 (7). A possible alternative could be solvolysis of the tosylate (27) to the enone (28). Oxidative coupling[27] of the saturated axial alcohol (29) with



(23)

(7)

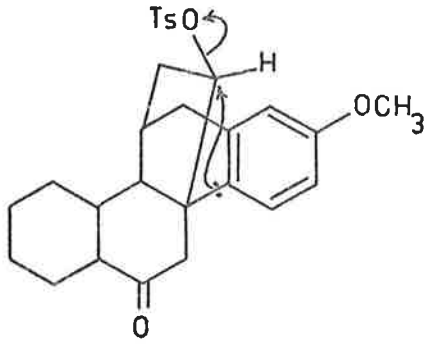
(26)

R=COCCl$_3$

Scheme 5.

C20 is geometrically favourable and should provide a useful method of oxygen functionalisation at the C-20 position.

The basic carbon skeleton of the model compound for isoGB 13 (23) is a dodecahydrochrysen-6-one diaxially substituted in the C-4b



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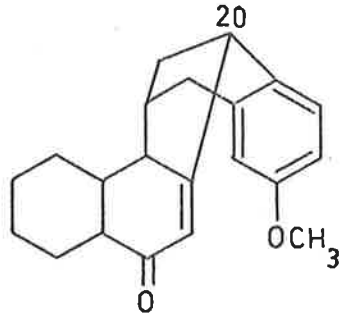

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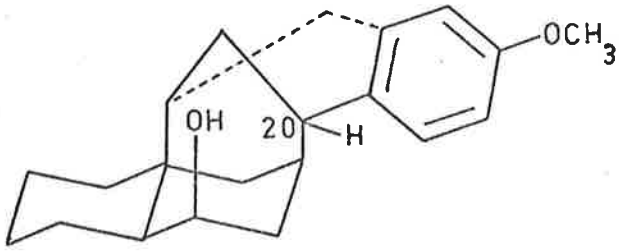

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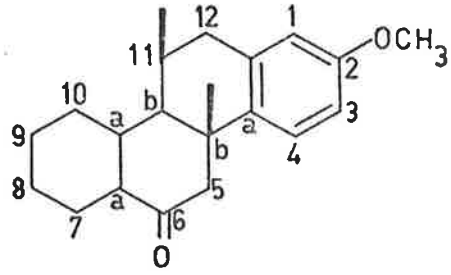

(30)

and C-11 positions e.g. (30),≠ to enable the formation of the cyclopentanone bridge. Robinson and coworkers have described[17] an excellent method of preparing a suitable precursor, the enone (32), in good yield

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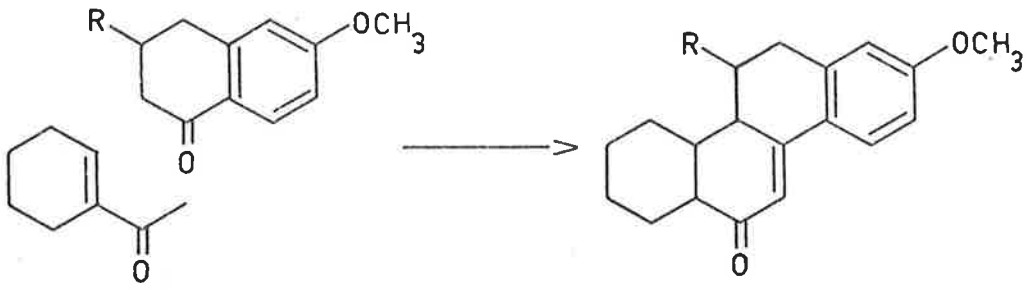
≠ The chrysenone numbering system shown in structure (30) is used in this thesis for derivatives of isoGB 13.

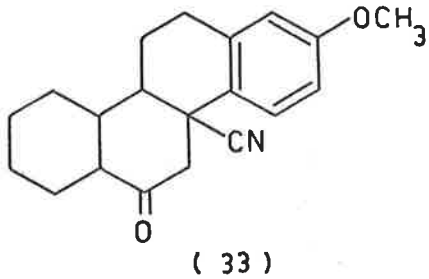
by the condensation of 6-methoxytetralone (31) with 1-acetylcyclohexene (Scheme 6).



(31) R = H (32) R = H

Scheme 6.

This enone has the advantage that hydrocyanation with hydrogen cyanide in the presence of diethylaluminium chloride should give the keto-nitrile (33) with the nitrile group in the desired axial configuration.[48,49,50]

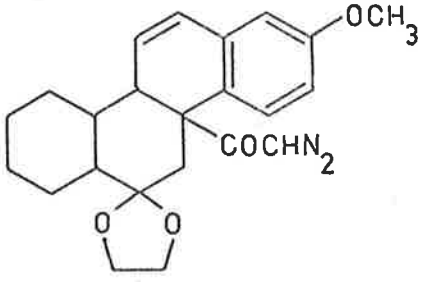


(33)

From this point two broad alternatives are possible for the establishment of the necessary bridge.

The first is the incorporation of a suitable substituent, e.g. acetic ester, in the C-11 position. Such a side chain should undergo a Dieckmann type condensation with the nitrile group to give, after acid hydrolysis, the desired cyclopentanone bridge. The introduction of this C-11 substituent might be accomplished either by choosing a suitably substituted tetralone, e.g. Scheme 6 where R = CH_2CO_2Et, and carrying out the annelation and subsequent hydrocyanation on this or by elaboration of the ketonitrile (33). Another possibility for the introduction of the acetic ester substituent should be an intermolecular insertion of the carbene derived from diazoacetic ester[42] into a double bond in the Δ11-position. Ring cleavage of the cyclopropane should then give the desired C-11 ester substituent.

The second and more interesting alternative for the establishment of the bridge would utilise the recent developments and uses of diazoketone insertion reactions.[29,30] Intramolecular insertion of the diazoketone function of compound (34) into the Δ11 double bond should give the bridged cyclopropane (35). Ring cleavage with hydrogen bromide and hydrogenolysis should then yield the desired diketone (23). A synthesis of the olefinic diazoketone (34) from the ketonitrile (33) should be possible by conventional methods.



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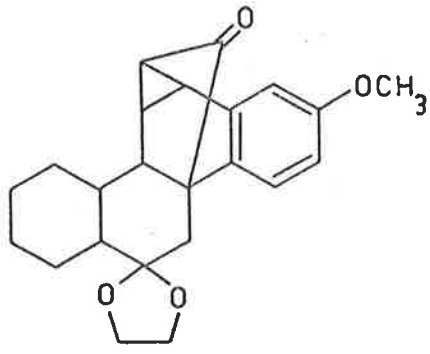


(35)

Part B of this thesis will describe the application of these synthetic routes towards the preparation of iso-GB 13. While the synthesis itself was not completed, these investigations propound a possible route to the preparation of the olefinic diazoketone (34).

DISCUSSION.

PART A. Approaches towards the synthesis of GB 13.

1) Preparation of Ketol (14) and its Reaction with 1-Acetyl-cyclohexene.

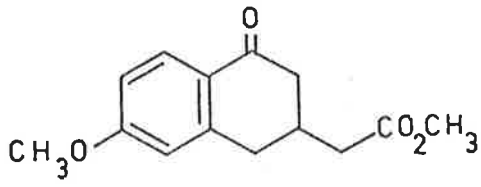
Although the synthesis of fused ring acyloins of the type (17) by the reductive cyclisation of keto-esters, e.g. Scheme 3, is well established,[19] no efforts to utilise this reaction for the formation of bridgehead acyloins like that required in the synthesis of the GB 13 model compound have been reported.

(17)

Scheme 3.

The tetralone (18), which is the keto-ester necessary for the formation of the acyloin (14), was prepared from m-methoxybenzyl bromide by either of two methods.

The first method, which utilised the homologation of the keto-acid (21) (Scheme 7), proved useful because this tetralone also served as an intermediate in the attempted synthesis of the isomeric ketol



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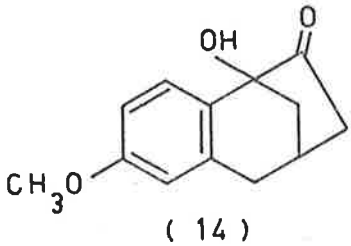

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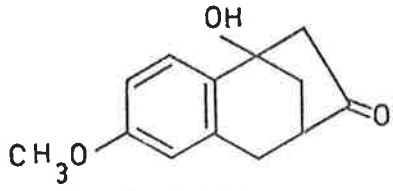
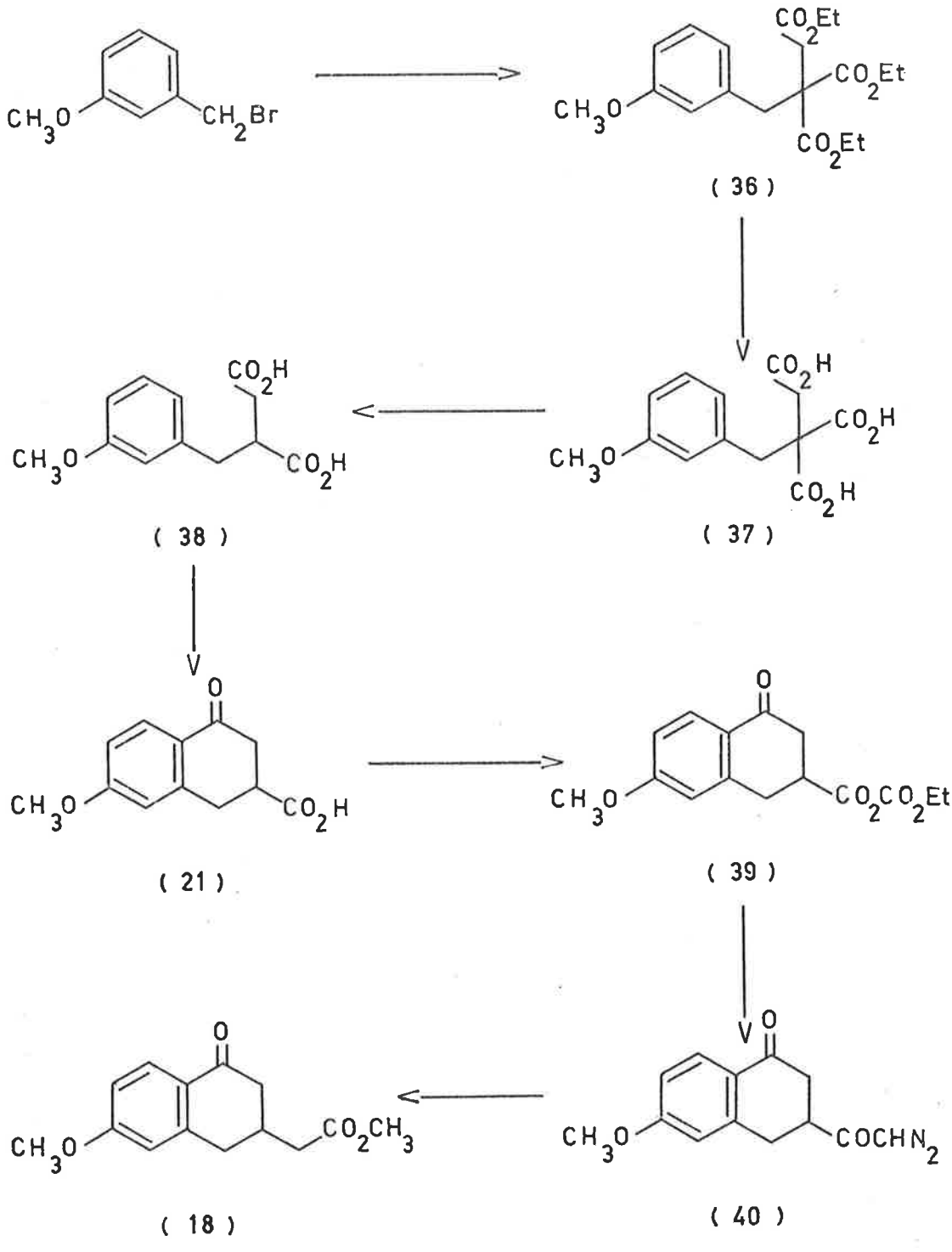


(15)

(15) (see below). The preparation was modelled on a sequence used by Muxfeldt[31] for the synthesis of 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthoic acid (19a).

Base-catalysed condensation of m-methoxybenzyl bromide with triethylethane-1,1,2-tricarboxylate in the presence of sodium ethoxide gave the triester (36). Saponification of this with potassium hydroxide yielded the triacid (37) which was decarboxylated to the known[45] m-methoxybenzylsuccinic acid (38) either by heating to 190° or by refluxing with 50% sulphuric acid for one hour. The latter method also afforded a small yield of the keto-acid (21) directly. This acid was obtained in 82% yield, however, by treating m-methoxybenzylsuccinic acid with polyphosphoric acid. In order to prepare the homologous acid it was first necessary to synthesise the diazoketone (40) and effect a Wolff rearrangement. The keto-acid, when


CH3O
CH2Br
CO2Et
CO2Et
CO2Et
(36)
CO2H
CO2H
CO2H
(37)
(38)
(21)
O
CO2CO2Et
(39)
COCHN2
(40)
CO2CH3
(18)

Scheme 7

treated with ethyl chloroformate in the presence of triethylamine≠ gave a quantitative yield of the mixed anhydride (39). The diazoketone (40) was then obtained by allowing this anhydride[52] to react with diazomethane. Subsequent rearrangement of (40) in methanol in the presence of silver oxide gave the desired keto-ester (18).

The same product was obtained more conveniently and in better yield from the sequence outlined in Scheme 8.[20]

Condensation of m-methoxybenzyl bromide with diethylmalonate in the presence of sodium ethoxide gave m-methoxybenzyldiethylmalonate (41). Reduction of the diester with lithium aluminium hydride in ether afforded a good yield of the diol (42) after the granular precipitate of aluminium oxide, obtained in work-up, had been exhaustively extracted with hot ethanol. The methanesulphonate ester (43), formed from the diol and methanesulphonyl chloride in the presence of pyridine, was treated with potassium cyanide and the product hydrolysed with base to β-m-methoxybenzylglutaric acid (44). Treatment of this diacid with concentrated sulphuric acid followed by esterification gave the desired keto-ester (18).

Initial investigations into the reductive cyclisation of the keto-ester were carried out using the conditions devised by Gutsche and coworkers.[19] It was found, however, that this reaction proceeded in

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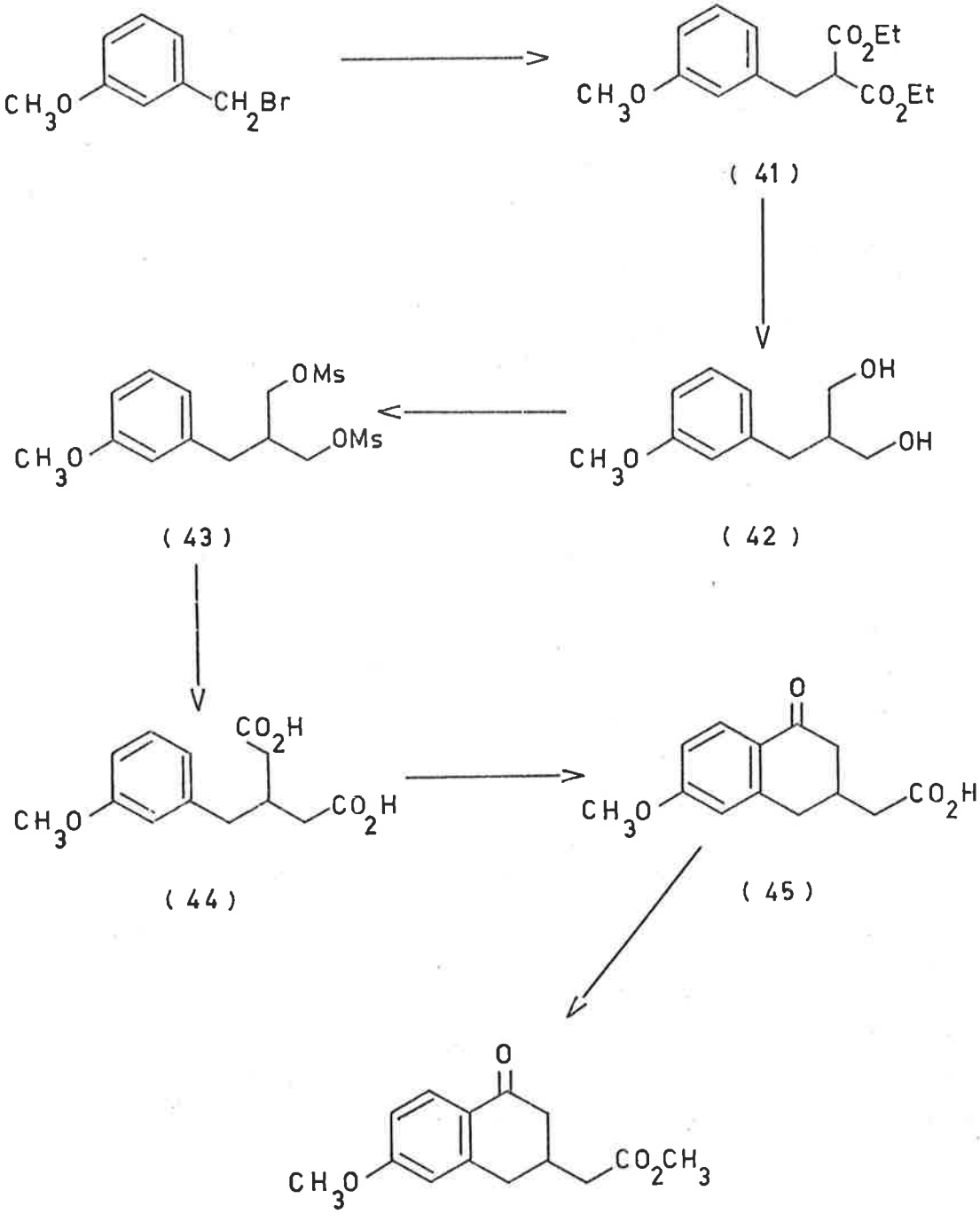
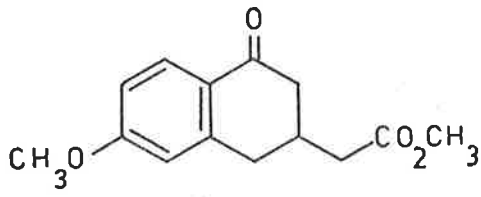
≠ γ-Keto acids are known to form chloro-lactones on treatment with thionyl chloride;[51] mixed anhydrides avoid this complication because they are formed under essentially neutral conditions.

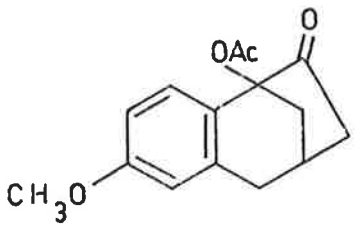

CH3O
CH2Br
CO2Et
CO2Et
(41)
OH
OH
(42)
OMs
OMs
(43)
CO2H
CO2H
(44)
O
CO2H
(45)
O
CO2CH3
(18)

Scheme 8

slightly higher yield by using dimethoxyethane as solvent in place of tetrahydrofuran. Another useful modification was the quenching of the reaction mixture with acetyl chloride, instead of acetic acid, to give the more stable crystalline keto-acetate (46). Thus, treatment of the keto-ester (18) with sodium and naphthalene in dimethoxyethane (Scheme 9), followed by work-up with acetyl chloride, gave an oily mixture which could not be completely separated into its components by column chromatography. Fortunately a solid crystallised from some of the

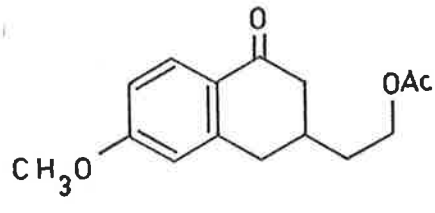


(18)



(46)

+



(47)

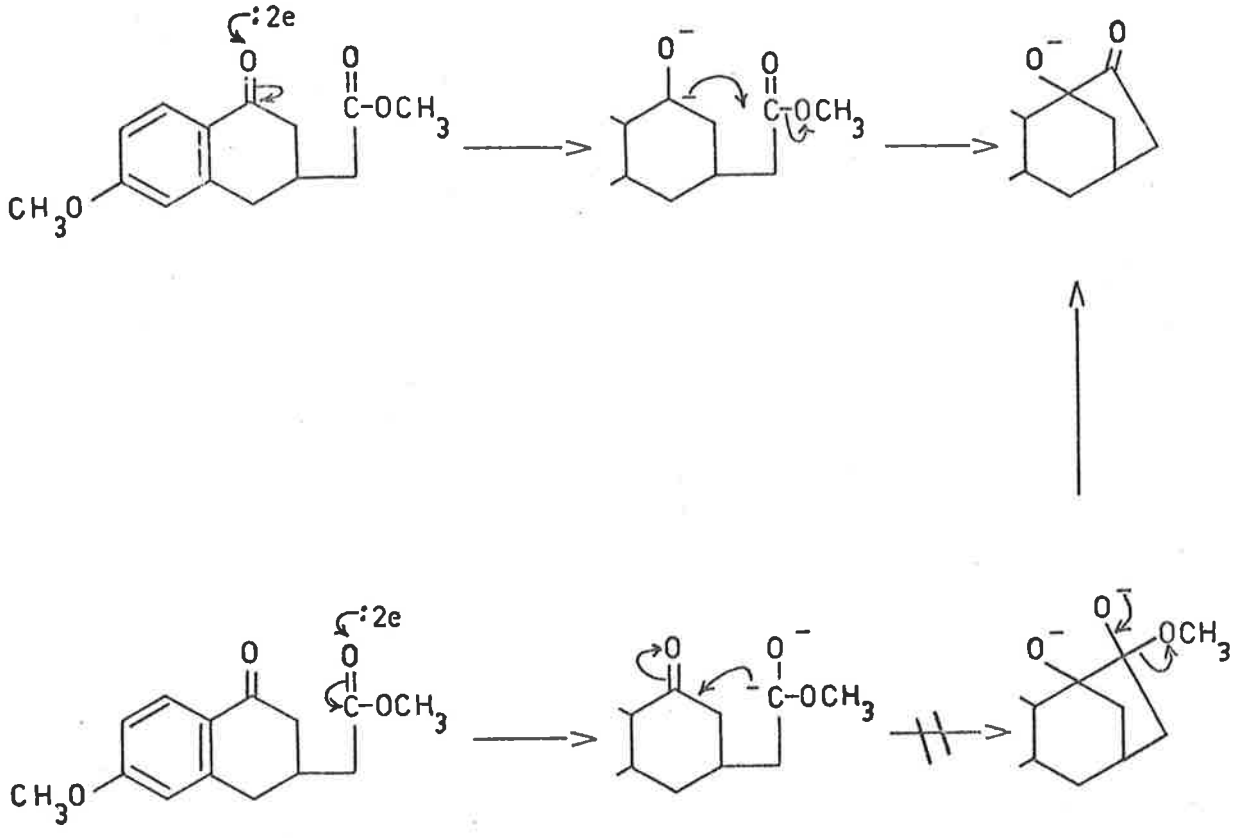
Scheme 9.

fractions. The infrared spectrum of this material showed the absence of the aromatic ketone band at 1670 cm^{-1} and the presence of bands at 1750 and 1735 cm^{-1} corresponding to the carbonyl frequencies of an acetate and a cyclopentanone. Mass spectrometry, n.m.r., and analysis confirmed the structure as that of the keto-acetate (46). The yield was only 6%. Other impure fractions, exhibiting carbonyl frequencies at 1750 and 1670 cm^{-1} in the infrared spectrum, were believed to contain the compound (47).

In explaining the mechanism for this reaction, Gutsche assumed[19] that the reductive cyclisation of keto-esters was initiated by the addition of an electron to the ketone group. He postulated that it was easier to add a second electron to the ketone radical anion than to the ester, which had a higher redox potential, and that the coupling step proceeded via a nucleophilic displacement by the ketone dianion on the carbonyl group of the ester. However the formation of products of the type (47) in the reductive cyclisation of the keto-ester (18) suggested that the mechanism for this reaction took a different course. The presence of both acyloin (46) and uncyclised keto-acetate (47) indicated that the addition of electrons was occurring at both the ketone and ester groups. In this series, then, the presence of an aromatic ring with an electron-donating methoxyl substituent has increased the value of the redox potential of the ketone and equated it with that of the ester group. Although the addition of two electrons≠ to either

≠ An equally feasible mechanism involving one electron addition may also be postulated.

function should give the acyloin product, it would be difficult for the ester dianion to cyclise with the ketone function (Scheme 10) because of the decreased electrophilicity of the aryl ketone. Instead, protonation of the ester dianion and further reduction would yield the observed uncyclised products.

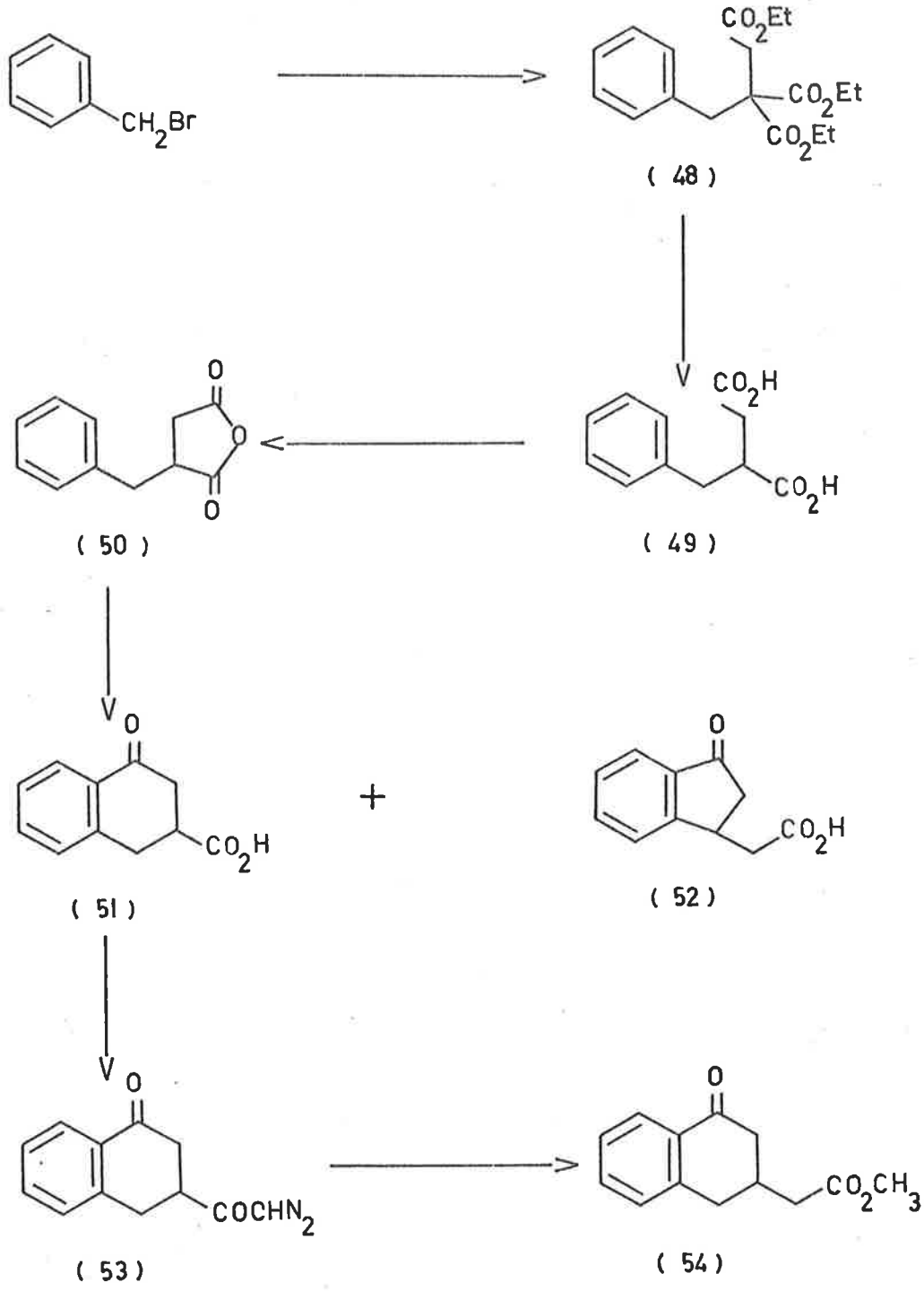


Scheme 10.

These observations posed an interesting question; whether removal of the methoxyl group would increase the amount of acyloin obtained? To answer this, it was first necessary to prepare the benzene keto-ester (54).

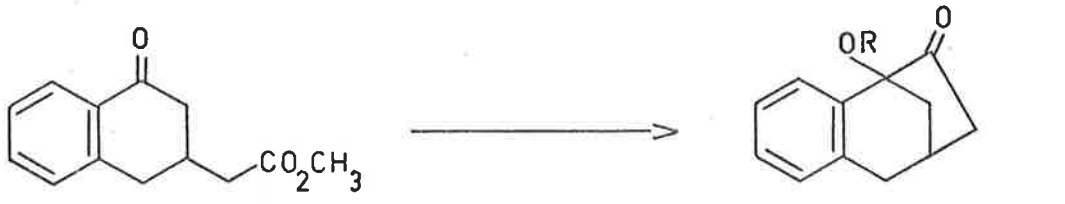
This ester was prepared by methods similar to those used for the methoxyl derivative (18) but with a few minor modifications. Haworth and coworkers[32] have synthesised the keto-acid (51) in 30% overall yield from diethylacetylsuccinate and benzyl chloride, but the method outlined in Scheme 11 gave (51) in 49% yield. Benzyl bromide, on condensation with triethylethane-1,1,2-tricarboxylate in the presence of sodium ethoxide, yielded the triester (48). Basic hydrolysis of this, followed by acidification, gave benzylsuccinic acid (49). However in contrast to the methoxyl series, treatment of (49) with polyphosphoric acid afforded only a low yield of the keto-acid (51). It was preferable to follow Haworth's conditions for the cyclisation and convert the diacid to the anhydride (50) and then carry out a Friedel Craft intramolecular acylation with aluminium chloride. A second, isomeric acid, identified as the indanone (52), was also isolated from this reaction in low yield. Treatment of the keto-acid (51) with oxalyl chloride, followed by diazomethane, gave the diazoketone (53) which underwent a Wolff rearrangement with silver oxide and methanol to the keto-ester (54).

The same ester was also prepared by the sequence outlined in Scheme 8 using benzyl bromide in place of m-methoxybenzyl bromide.


CH2Br
CO2Et
CO2Et
CO2Et
(48)
CO2H
CO2H
(49)
O
O
O
(50)
O
CO2H
(51)
+
O
CO2H
(52)
O
COCHN2
(53)
O
CO2CH3
(54)

Scheme 11

Reductive cyclisation of this ester, employing the same conditions as for the methoxyl species, gave a much improved yield (19%) of the acyloin (55) (Scheme 12). Therefore, it would appear that the redox potential of the aromatic ketone function is fundamental in determining the success of this reaction.



(54)

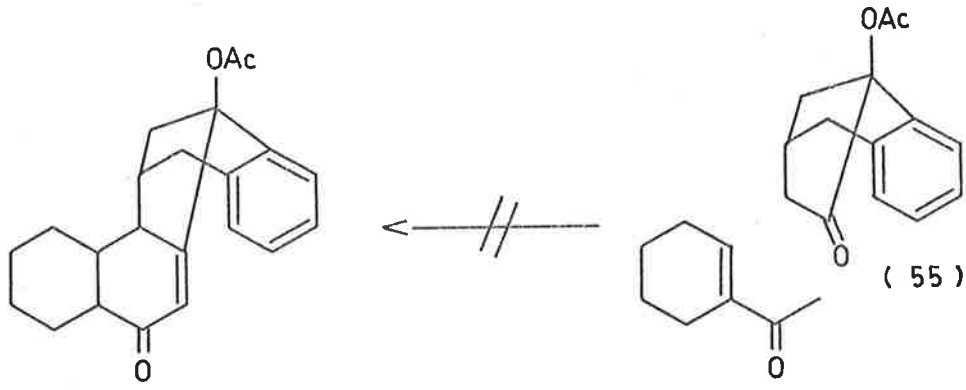
(55) R = $COCH_3$

(55a) R = H

Scheme 12.

Although this cyclisation proceeded in low yield, it represented a convenient preparation of the required bicyclo[3.2.1]octanol, because of the ready availability of the starting material and the simplicity of the reduction.

Since the keto-acetate (55) was available in larger quantities than the anisyl derivative, its condensation with 1-acetylcyclohexene in the presence of sodium amide[18] to elaborate the model enone (56) was investigated first. Unfortunately this reaction was unsuccessful, as it was found that prolonged reflux of (55) with sodium amide in ether,

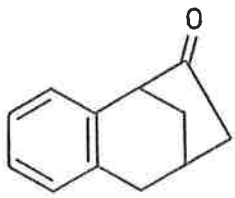


(56)

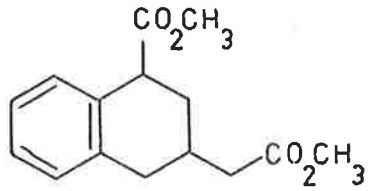
(55)

followed by addition of 1-acetylcyclohexene resulted in the recovery of the 1-acetylcyclohexene and an impure product, possibly the acyloin (55a). This failure to effect the condensation is probably due to reaction of the base with the acetate group to form the alkoxide which would inhibit the formation of the enolate anion. With this in mind, the preparation of the tricyclic ketone (57) with no bridgehead hydroxyl function was initiated. If the condensation of this with 1-acetylcyclohexene proved successful, the hydroxyl group might be introduced at a later stage.

One possible way to synthesise this ketone was by a Dieckmann condensation of the diester (58) which was prepared by the sequence shown in Scheme 13. A Wittig reaction on the keto-ester (54) with triphenylmethylphosphonium iodide in the presence of potassium t-butoxide



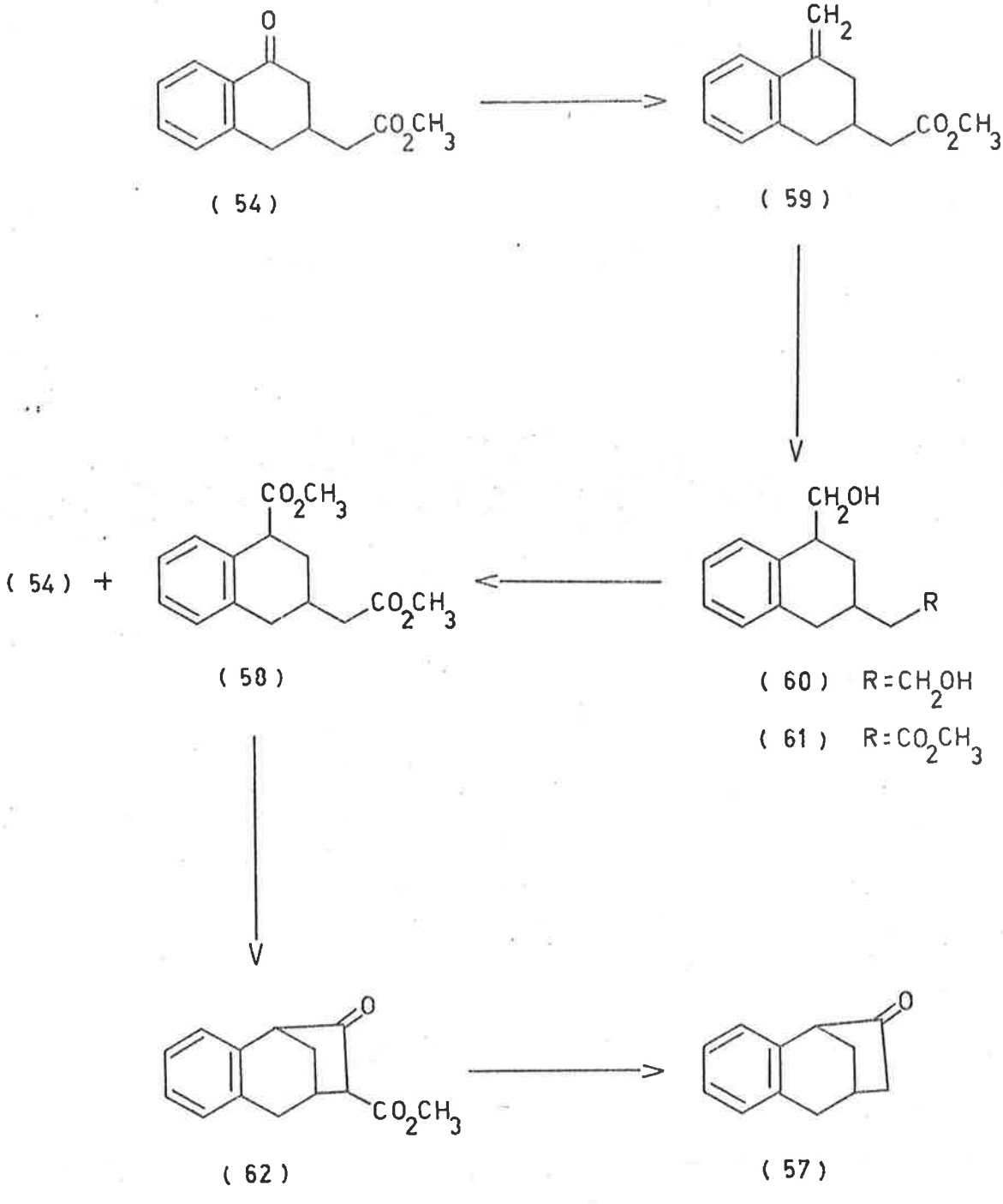
(57)



(58)

gave the methylene ester (59).

Hydroboration of this olefin at room temperature, followed by oxidative work-up with hydrogen peroxide-sodium hydroxide gave a mixture of the diol (60) and some hydroxy-ester (61). When the hydroboration was carried out at 0°, the hydroxyester was the major product. The mixture was not separated but oxidised with Jones reagent and then esterified with methanol and a trace of acid. A mixture of esters was obtained and this was chromatographed on silica gel. Partial separation was achieved and the required diester (58) was obtained in 21% yield together with a much higher yield ($\sim$ 50%) of the keto-ester (54). This byproduct presumably arose from oxidation of the enol form of the aldehyde, i.e. (63) - the intermediate in the oxidation of the primary alcohol to the acid. Treatment of the crude diester (58) with sodium hydride gave the cyclised keto-ester (62) which was hydrolysed



(54)

(59)

(54) +

(58)

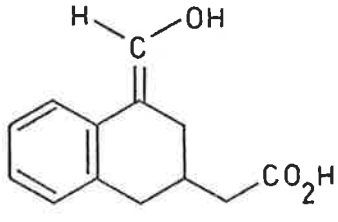
(60) R=CH_2OH

(61) R=CO_2CH_3

(62)

(57)

Scheme 13



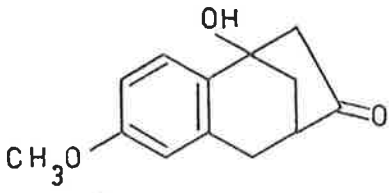
(63)

and decarboxylated to the tricyclic ketone (57). This was characterised as its semicarbazone derivative. The infrared spectrum of (57) had the required carbonyl frequency at 1735 cm^{-1} for a cyclopentanone and the n.m.r. spectrum was consistent with the proposed structure.

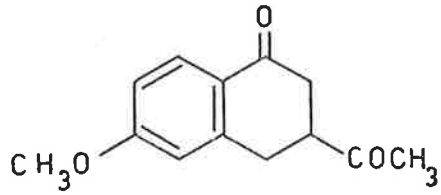
All attempts to condense the enolate anion of this ketone with 1-acetylcyclohexene failed, and only starting materials were recovered. Therefore, although 1-acetylcyclohexene is a useful compound for the annelation of some ketones,[17,18] it would seem from this work and that of others that such condensations are impractical when the ketone is hindered[17] or strained.[33]

With this effort frustrated, attention was concentrated on the alternative route to the model compound of GB 13 (7) via the ketol (15).

2) Attempted Preparation of Ketol (15).

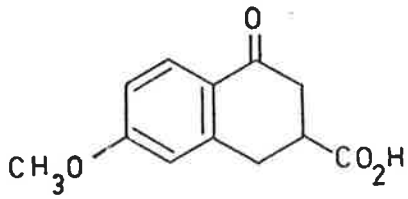


(15)

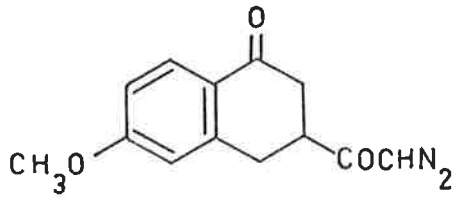


(20)

An obvious way to synthesise the diketone (20), which was required for the preparation of the ketol (15) by an intramolecular aldol cyclisation,[22,23] was from the already available keto-acid (21).



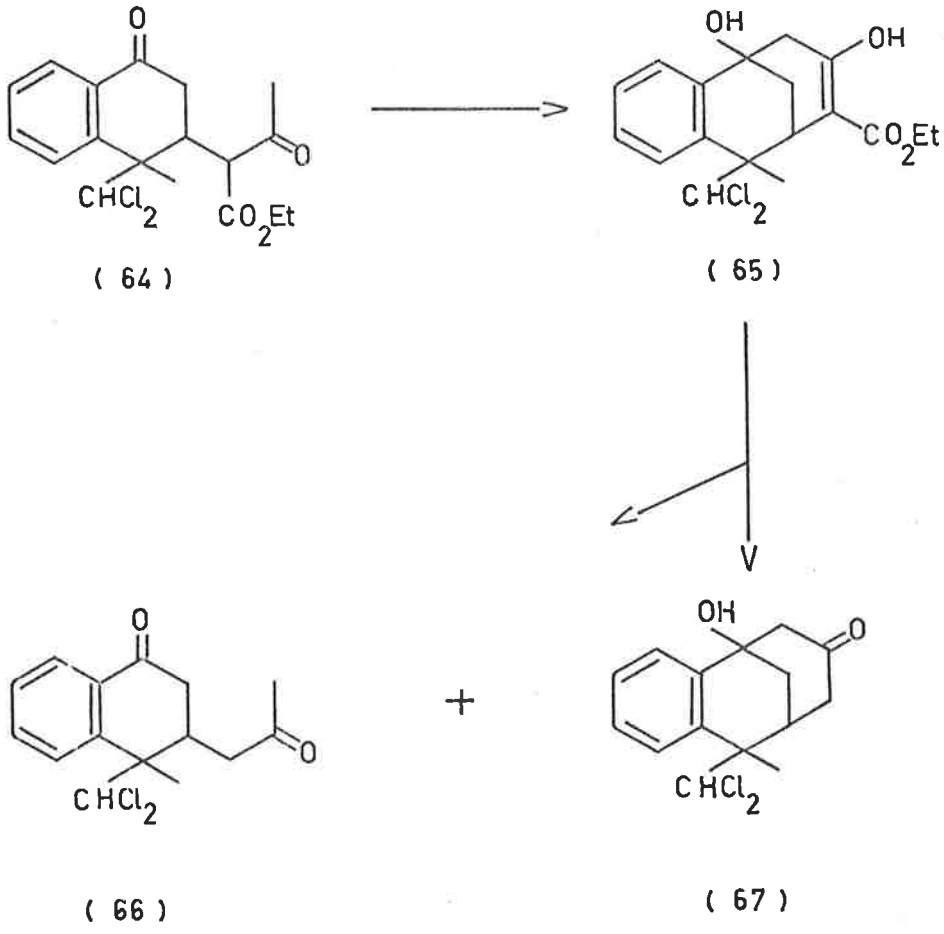
(21)



(40)

All attempts to protect the aromatic ketone group in (21) as the ethylenedioxyacetal both in the methoxyl and the benzene series

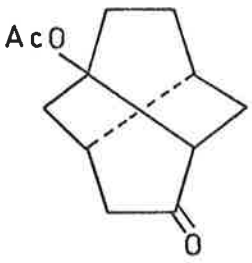
failed, because of the low reactivity of these ketones to nucleophilic attack.[34] Therefore, to convert the acid to a methyl ketone group, it was necessary to employ a method which would allow the survival of the aromatic ketone group, and to this end, the diazoketone (40), prepared previously, was treated with hydriodic acid[35] to afford an excellent yield of the diketone (20).



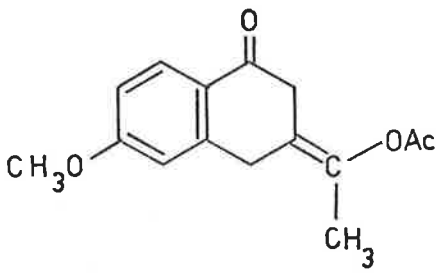
(64) (65) (66) (67)

Scheme 14.

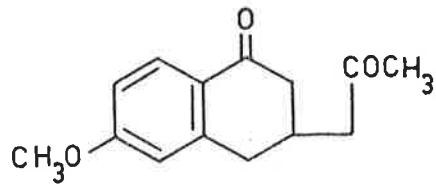
Wenkert and Stevens[23] have carried out an intramolecular aldol cyclisation on the tetralone (64) and obtained the aldol (65) in 35% yield (Scheme 14). Acid hydrolysis of (65) yielded an equilibrium mixture of diketone (66) and ketol (67) in the ratio 3:1. The attempted aldol cyclisation in the present case using potassium hydroxide,[22] potassium t-butoxide or borontrifluoride etherate-acetic acid-acetic anhydride[36] failed both for the diketone (20) and its desmethoxy analogue (72). The last set of conditions which was successful in the synthesis of the highly strained twistanone (68),[36] gave only the enol-acetate (69) and starting material. Intramolecular condensation of



(68)

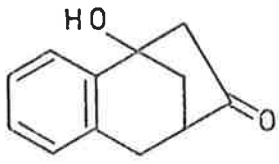


(69)

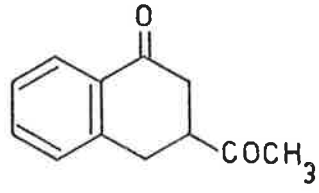


(70)

the homologous methyl ketone (70) also failed. The success or failure of this aldol cyclisation would appear to depend on a number of factors. Wenkert's work illustrated that the aromatic ketone function, at least in the benzene series, was sufficiently reactive to undergo this type of reaction. From this it seemed that other factors were involved in the failure of the ketol (71) to form.



(71)



(72)

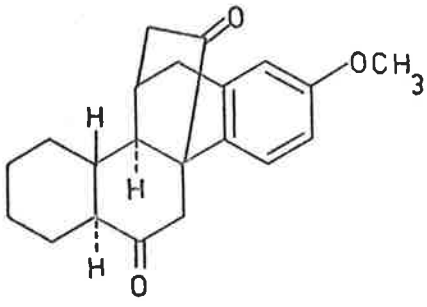
The isolation of an equilibrium mixture of diketone (66) and aldol (67), which favoured the open form, suggested that these aldol condensations were thermodynamically controlled; in the present case, the diketone (72) would be the more stable, and therefore, the expected product. Another possible explanation was that the reaction did not proceed at all because of a combination of two effects, steric compression and the low reactivity of the aryl ketone. Whatever the correct explanation, the likelihood of an aldol condensation proceeding in the anisole diketone (20) seemed very remote.

This phase of the work was terminated when the isoGB 13 approach, which is described in the next section, showed particular promise.

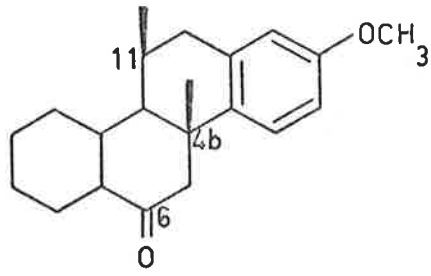
DISCUSSION.

PART B. Approaches towards the synthesis of iso-GB 13.

The basic carbon skeleton of the model compound for isoGB 13 (23) was a dodecahydrochrysene diaxially substituted in the C-4b and C-11 positions and with a ketone group in the C-6 position, e.g. (30).

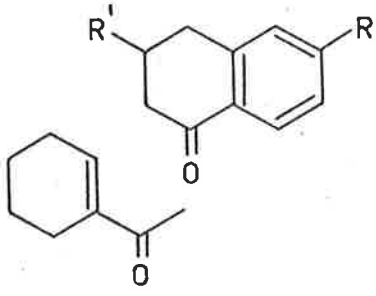


(23)



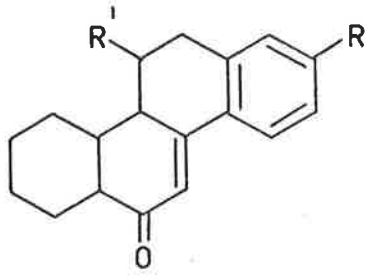
(30)

The key reaction to the synthesis of this skeleton was the annelation of an α-tetralone, e.g. (73), with 1-acetylcyclohexene in the presence of sodium amide[17,18] to give the enone (74) (Scheme 15). It was



(73) R = R' = H

(31) R = OCH_3, R' = H



(74) R = R' = H

(32) R = OCH_3, R = H

Scheme 15.

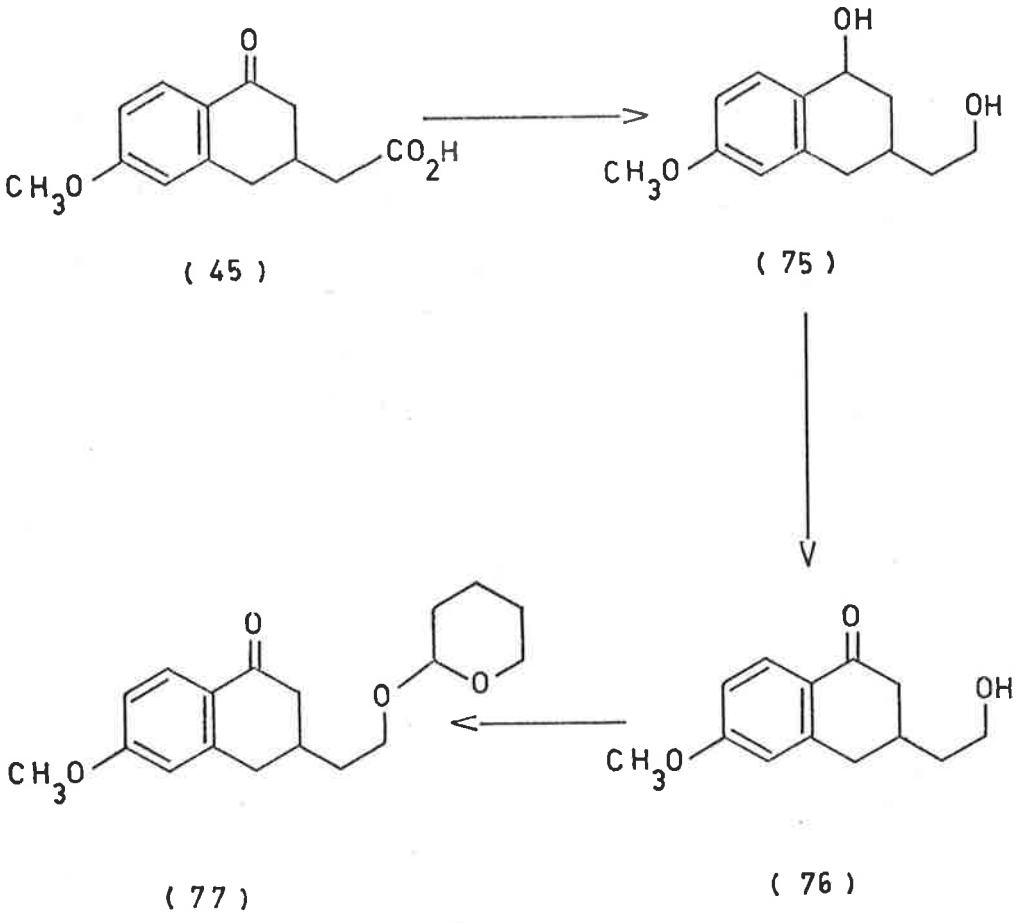
reasonable to assume that this reaction, because of the conditions used, would be thermodynamically controlled and therefore lead to the most stable product. The molecular model of structure (74) showed that the anti-trans backbone not only represented the most stable configuration with the most favourable non-bonded interactions, but also allowed maximum overlap of the π-orbitals of the conjugated enone. Fortunately this anti-trans backbone was the one required for the model compound of isoGB 13 (23).

The work described in this section is concerned with the methods that were developed for the construction of the rings B and C substitution patterns, initially on the model compound (74), but later on the anisyl derivative (32).

One possibility for the construction of the C-11 sidechain involved attachment of a suitable group R' to the tetralone and condensation of this with 1-acetylcyclohexene to give the substituted enone (Scheme 15). A primary alcohol, protected as the tetrahydropyranyl ether, was chosen as a suitable group R' because of its stability to base and also the ease with which it could be oxidised to a more useful carboxylic acid function.

Reduction of the keto-acid (45) from the previous section with lithium aluminium hydride gave the diol (75) (Scheme 16). Selective oxidation of the benzylic alcohol group[37] with activated manganese dioxide in acetone produced the ketol (76) and subsequent treatment

of this with dihydropyran and a trace of acid yielded the tetrahydropyranyl ether (77).



(45) (75) (77) (76)

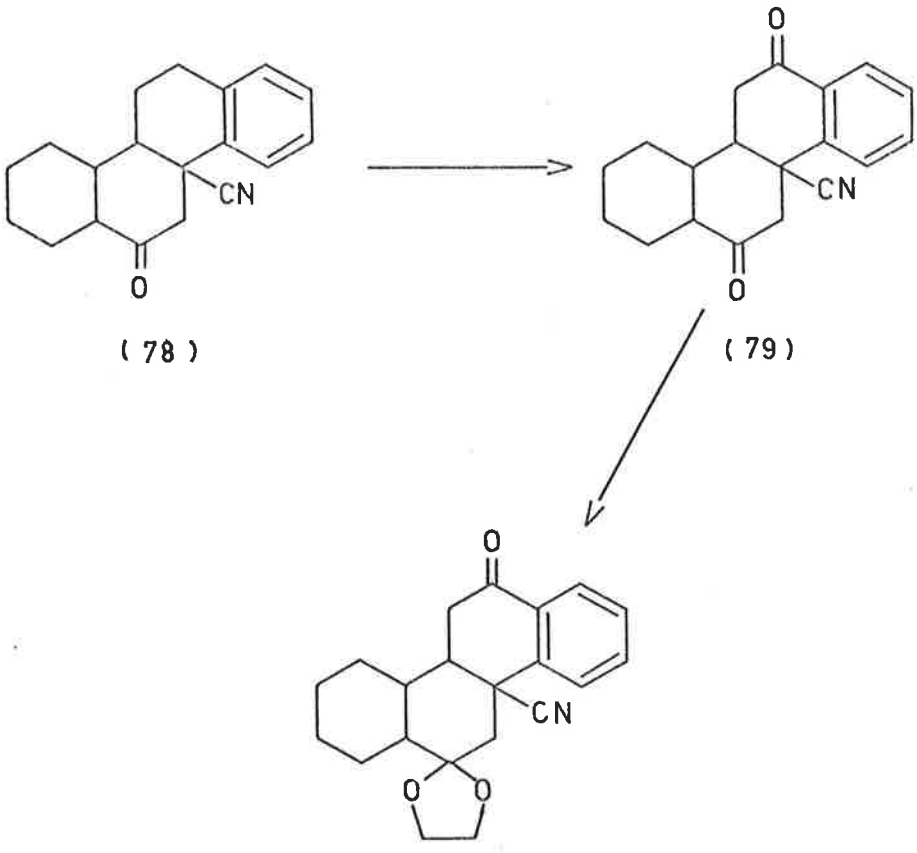
Scheme 16.

All attempts to condense the enolate anion of this tetralone with 1-acetylcyclohexene failed and only starting materials were

recovered. In accordance with the observations in Part A of the Discussion, this failure would be due to the tetrahydropyranyl ether side-chain hindering the approach of the 1-acetylcyclohexene to the enolate anion.

The stereoselectivity of the hydrocyanation of α,β-unsaturated ketones with an alkyl aluminium compound and hydrogen cyanide or a dialkyl aluminium cyanide has been demonstrated by Nagata and co-workers;[48,49,50] their results suggested that this reaction would be suitable for the introduction of the C-4b substituent in the model enone (74) which was synthesised from the readily available α-tetralone (73).[18] Difficulties were expected, however, in the hydrocyanation of this enone with triethylaluminium and hydrogen cyanide because of the presence of the aromatic ring. Not only would this additional conjugation decrease the electrophilicity of the 4b carbon atom, but it would also increase the base-induced reverse reaction of the keto-nitrile (78) to the enone (74) because of the stability of this system. Fortunately Nagata found[22] that the less basic diethylaluminium chloride overcame these difficulties and he obtained nitrile compounds from similar aromatic enone systems in good yields. When this modification was tried on the enone (74), the keto-nitrile (78) was obtained in 69% yield. An inspection of a molecular model of the keto-nitrile with the desired trans-anti-trans backbone showed that this configuration placed one of the C-5 methylene hydrogen atoms in the plane of the aromatic ring. In accordance with this requirement, the n.m.r.

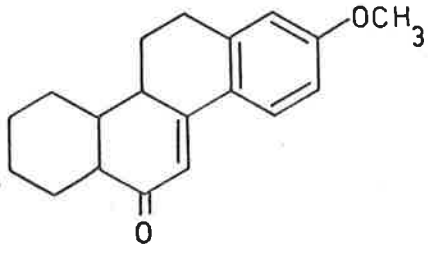
spectrum of the keto-nitrile obtained from the hydrocyanation showed an AB quartet at δ 2.55 and 3.38, J = 14 Hz for the C-5 methylene. At this stage then, the C-4b axial substituent for the formation of the cyclopentanone bridge had been realised and the next objective was the introduction of the C-11 functional group.



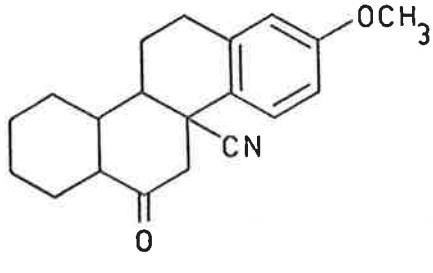
(78) (79) (80)

Scheme 17.

Benzylic oxidation of the keto-nitrile (78) to the diketo-nitrile (79) with chromium trioxide in 95% acetic acid, followed by selective protection of the aliphatic ketone as the ethylene dioxy-acetal, gave compound (80) (Scheme 17). Attempts to formylate (80) by modification of the method of Turner and coworkers[38] with ethyl formate and sodium ethoxide failed, as did similar attempts with sodium hydride under forcing conditions. Moreover, only starting materials were recovered when the enolate anion of the ketone group, formed by treatment of (80) with sodium amide, was allowed to react with ethyl-bromo-acetate. The failure of this ketone to react under these conditions may be compared with the inability of the tetrahydropyranyl ether (77) to condense with 1-acetylcyclohexene. In the present case, the axial nitrile group would further hinder the C-11 position, which may be compared with the hindered C-11 position of steroid molecules. Having failed in these attempts to introduce a C-11 functional group in the model series, it was considered desirable at this stage to attempt the hydrocyanation of the less reactive anisyl enone (32).



(32)



(33)

Treatment of this enone with hydrogen cyanide-diethylaluminium chloride under the same conditions as those used for the benzene enone (74) (chart 1, reaction 1), gave the keto-nitrile (33) in only 54% yield.

Chart 1.

Reaction	mole ratio			Time (Hours)	% Yield
	enone	HCN	Et_2AlCl		
1	1	5	7	48	54
2	1	2.6	2.7	120	89

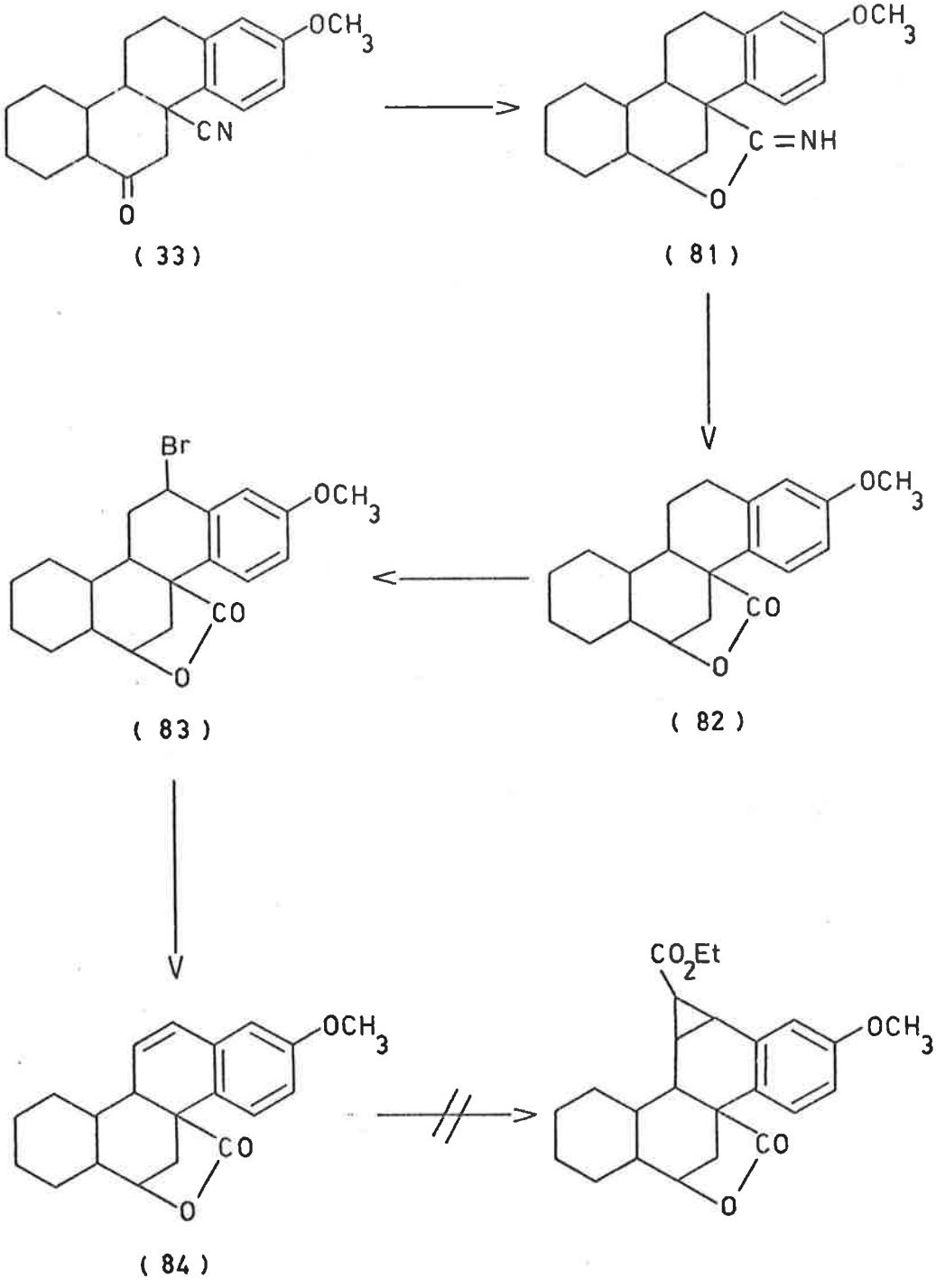
The recovery of a considerable amount of starting material (~ 35%) in a reaction where a large excess of reagents was used, suggested that the reaction may have been interrupted before completion. When the enone was allowed to react with considerably less reagent (reaction 2) for a much longer time, an excellent yield of the keto-nitrile was obtained.

With the keto-nitrile available in large quantities by this modified hydrocyanation reaction, other methods were sought for the introduction of the C-11 substituent.

Since a functional group could not be introduced into the hindered position by conventional condensation reactions, it was thought that a suitable substituent might be realised by the insertion of a

reactive carbene species into a double bond in the Δ11-position. Recently House achieved angular alkylation in an indane system by the insertion of ethyl diazo-acetate into a double bond in the presence of copper sulphate;[42] subsequent cleavage of the cyclopropyl ester gave the desired angular acetic acid residue. This sequence seemed ideally suited for the introduction of an acetic ester functional group at C-11. The olefinic lactone (84) was chosen as a suitable substrate for this insertion because the lactone group would not only conveniently protect the C-4b and C-6 functional groups, but also serve as a useful group to undergo a Dieckmann condensation with a C-11 acetic ester substituent. This should give the desired cyclopentanone bridge.

A successful approach to the olefinic lactone (84) was initiated by the reduction of the keto-nitrile (33) with sodium borohydride. The lower energy transition state for this reduction should involve approach of the hydride ion from the side opposite the nitrile group to yield the β-alcohol. This would then add to the nitrile group to give the imino-lactone (81). In fact, reduction of the keto-nitrile (33) with sodium borohydride yielded the imino-lactone (81) exclusively (Scheme 18). Acidic hydrolysis of (81) produced the lactone (82). Benzylic bromination of this to the bromo-lactone (83) with N-bromosuccinimide, and subsequent dehydrobromination of (83) with calcium carbonate in refluxing dimethylformamide, gave the olefinic

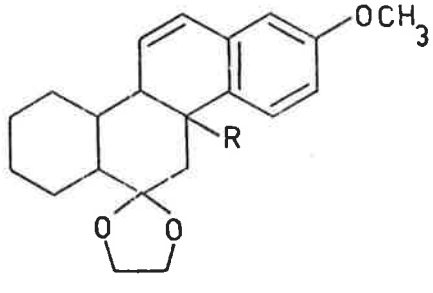

OCH3
CN
O
(33)
OCH3
C=NH
O
(81)
OCH3
CO
O
(82)
Br
OCH3
CO
O
(83)
OCH3
CO
O
(84)
CO2Et
OCH3
CO
O

Scheme 18

lactone (84) in 95% overall yield from the lactone.

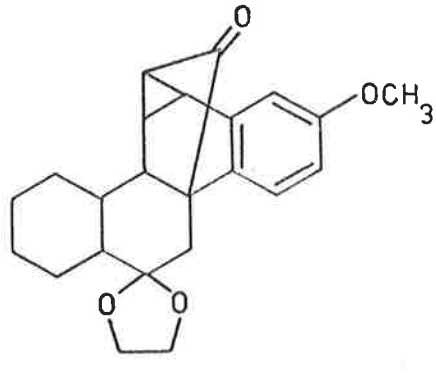
When the olefinic lactone (84) was treated with ethyl diazoacetate in the presence of copper powder, only unreacted starting material and a mixture of ethyl fumarate and maleate were isolated, suggesting that the Δ11-olefin was too hindered for an intermolecular insertion reaction.

Nevertheless, prospects of an intramolecular insertion[29] occurring in the compound (34) appeared excellent, because the carbene species would be positioned directly above the double bond. This insertion should give the bridged cyclopropane (35). Ring cleavage with hydrogen bromide followed by hydrogenolysis should then yield the model compound for isoCB 13. The most likely precursor of the diazoketone



(34) R=COCHN$_2$

(85) R=CO$_2$H



(35)

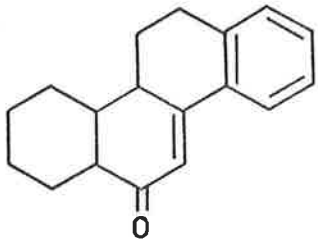
(34) was the olefinic acetal acid (85) and this became the next synthetic objective.

Initial investigations into the hydrolysis of the nitrile group of the benzene keto-nitrile (78) demonstrated that this reaction was unsuitable for the preparation of the carboxylic acid function. Some elimination of hydrogen cyanide occurred, presumably via the enolate anion (86), to give the enone (74). The other product was the very stable lactamol (87) (Scheme 19). Since the C-6 ketone group influenced the formation of both these undesirable products, it was protected as the ethylene dioxyacetal. However, the nitrile group in the compound (88) of the anisyl series could not be hydrolysed even under the extreme conditions of potassium hydroxide in ethylene glycol at 190°. In contrast to this, the ease of hydrolysis of the keto-nitrile (78) may be rationalised in terms of the addition of hydroxyl ion to the C-6 ketone and intramolecular attack of the nitrile group as shown in Scheme 20.

Another possible preparation of the carboxylic acid function at the C-4b position should be by oxidation of an aldehyde group. Nagata[39] has successfully reduced a hindered nitrile group to the aldimine with lithium aluminium hydride. Since complete reduction to the amine would have involved the conversion of an sp_2 hybridised aldimine to a more bulky sp_3 species, the reaction stopped at the aldimine. Hydrolysis of the aldimine followed by oxidation should then yield the desired acid function.

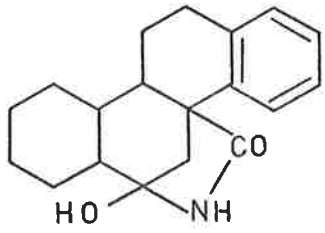
Reduction of the acetal nitrile (88) with lithium aluminium

(78)



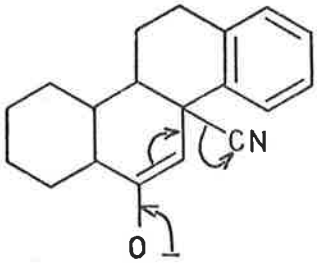
(74)

+

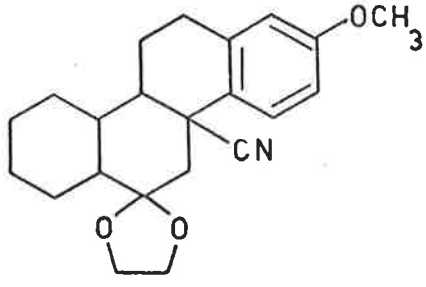


(87)

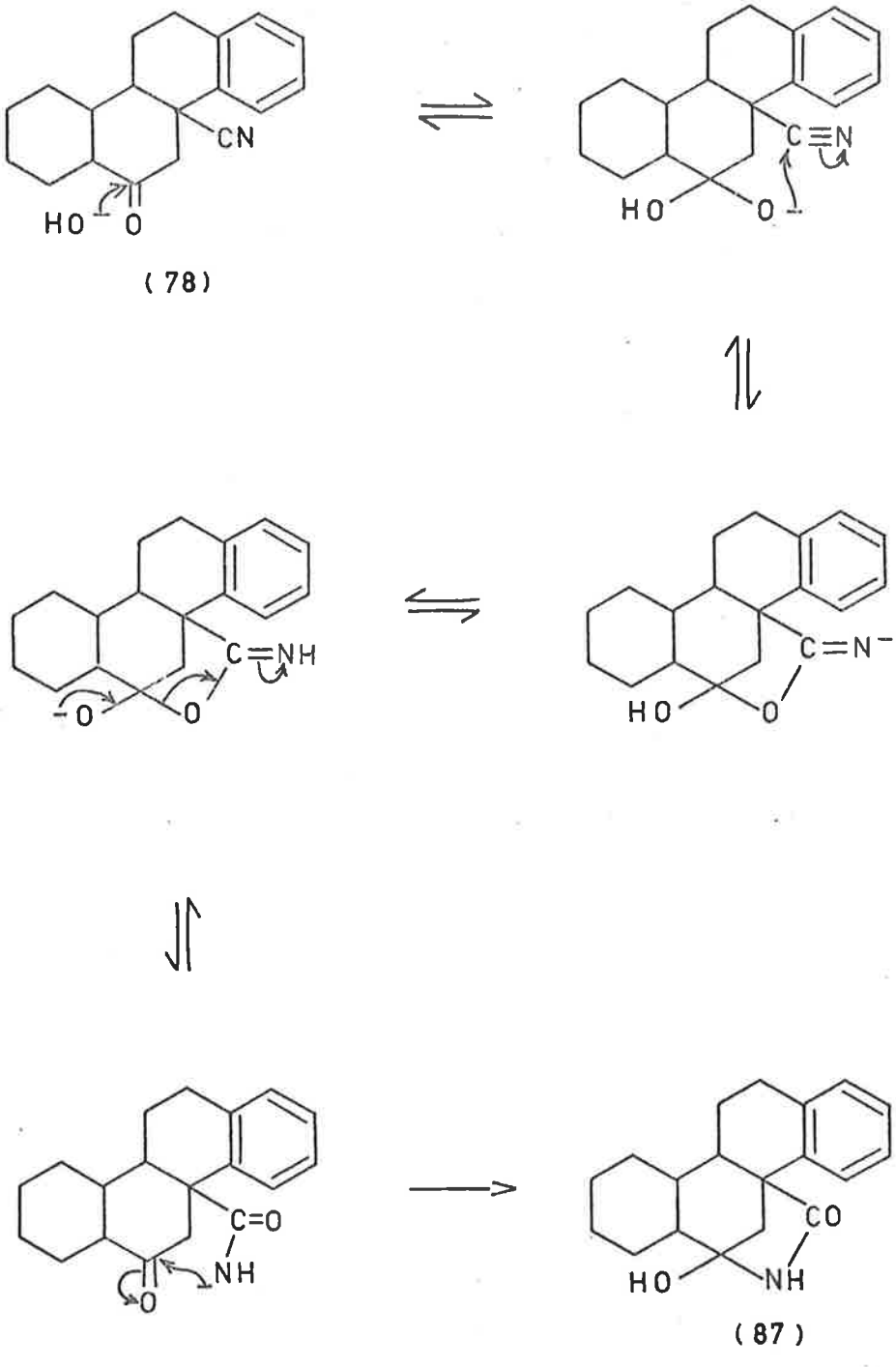
Scheme 19



(86)



(88)



(78)

(87)

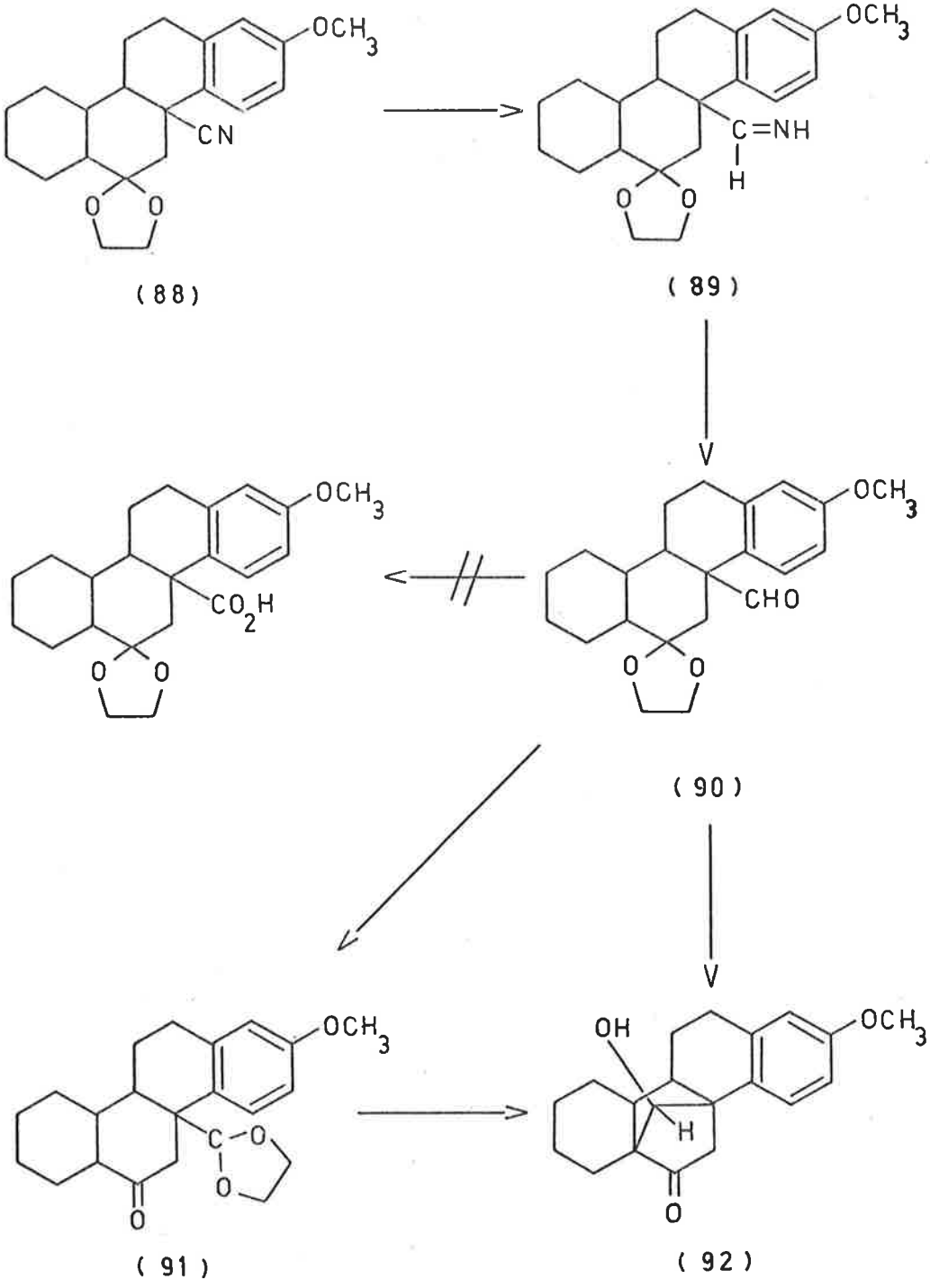
Scheme 20

hydride produced the aldimine (89) and subsequent hydrolysis of this with sodium acetate-buffered acetic acid gave the acetal aldehyde (90) (Scheme 21). Attempts to oxidise this aldehyde group under basic conditions using either silver oxide[40] or potassium permanganate[41] failed. It became obvious that more forcing conditions were required, but first it was considered preferable to remove the acetal group.

An attempt to carry this out by exchange with acetone using p-toluenesulphonic acid as catalyst gave a surprising product, believed to be the keto-acetal (91), i.e. acetal exchange between the ketone and the aldehyde group had occurred. The infrared spectrum of the product showed the absence of the aldehyde C — H band at 2680 cm^{-1} and the aldehyde carbonyl band at 1720 cm^{-1} but indicated the presence of a carbonyl band at 1700 cm^{-1}. The product was too insoluble for an n.m.r. spectrum to be determined, but the mass spectrum showed an $M-C_3H_5O_2$ peak, i.e. loss of the whole acetal side chain. In comparison, the mass spectrum of the acetal aldehyde (90) showed the presence of an intense (M-1) peak followed by loss of carbon monoxide.

No sound explanation can be offered to account for the transfer of the acetal to the more hindered aldehyde group as the reaction could not be repeated. Later reactions of the acetal aldehyde with acetone showed no acetal exchange either with the aldehyde group or with the acetone.

Treatment of the acetal aldehyde (90) with 3% hydrochloric

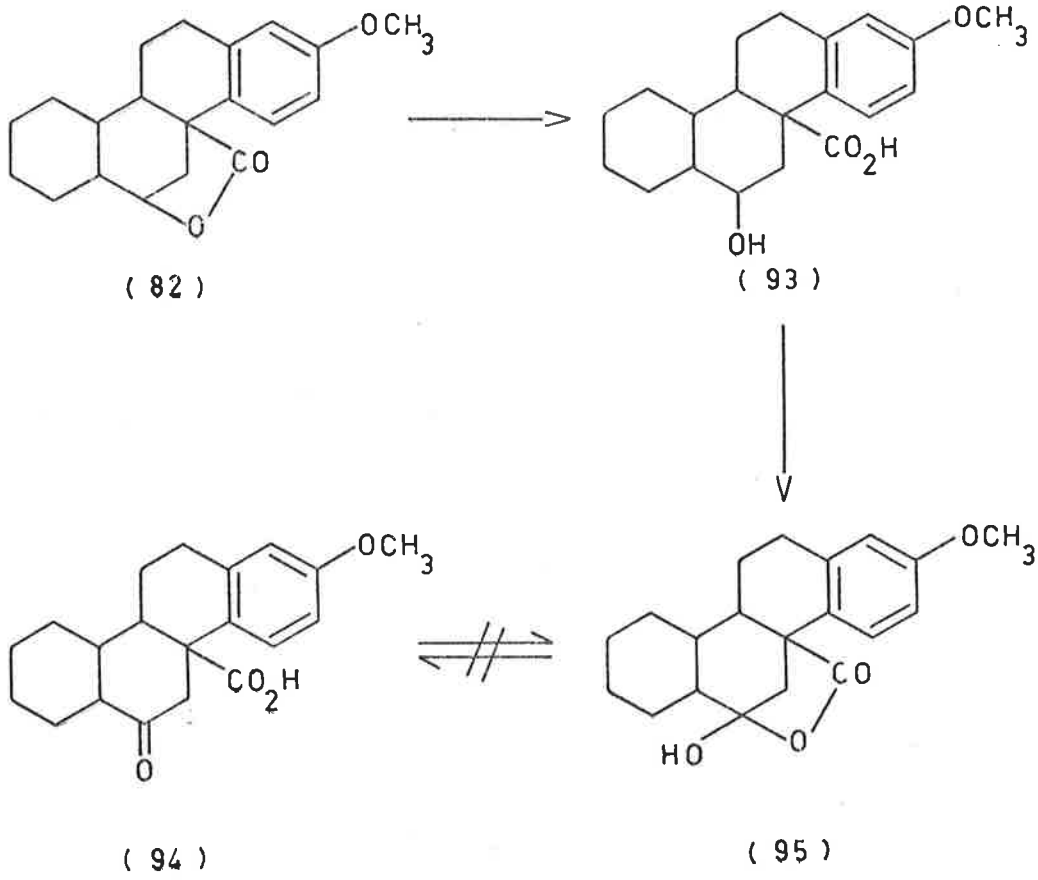

OCH3
CN
O
O
(88)
OCH3
C=NH
H
O
O
(89)
V
OCH3
CHO
O
O
(90)
OCH3
CO2H
O
O
OCH3
C
O
O
O
(91)
V
OH
OCH3
H
O
(92)

Scheme 21

acid in tetrahydrofuran did not yield the expected keto-aldehyde but instead gave the aldol product (92) (Scheme 21), which was characterised as its acetate. The compound proposed as the keto-acetal (91) also gave the same aldol product under these conditions.

A successful approach to the olefinic acetal acid (85) was achieved by elaborating the readily available olefinic lactone (84). Using the saturated lactone (82) as a model, it was found that treatment of this with sodium hydroxide, followed by careful acidification at 0°, gave the hydroxy acid (93) (Scheme 22). An inspection of its infrared spectrum showed the required bands at 3200 and 1660 cm^{-1} for the hydroxyl and acid functions respectively. Oxidation of (93) with Jones reagent at 0°, and subsequent careful work-up, did not give the desired keto-acid (94) but the lactol (95). No equilibrium between the lactol and keto-acid was observed. A modification of this sequence which avoided this lactol formation was then carried out on the olefinic lactone (84).

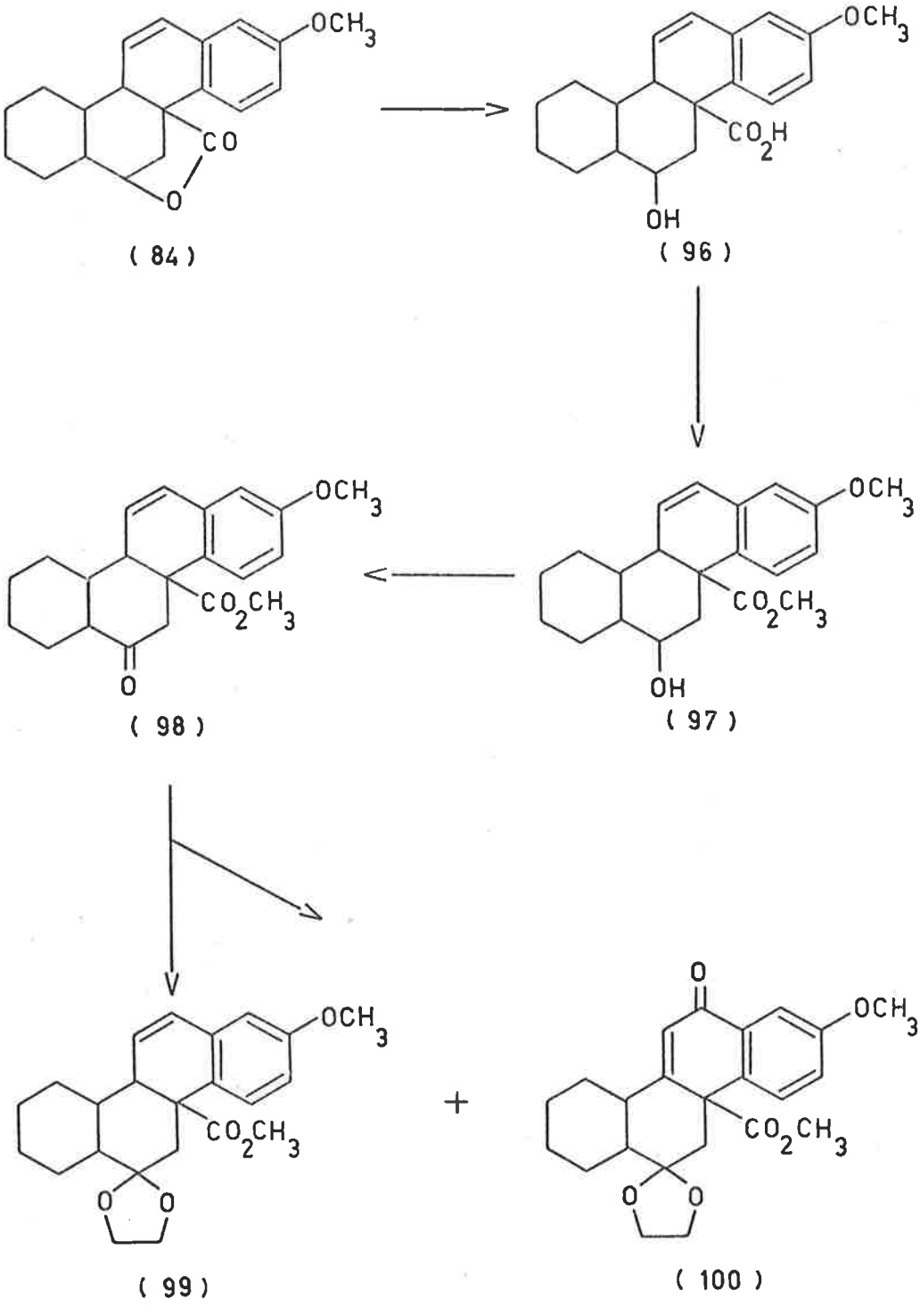
Cleavage of the lactone ring of (84) with base followed by careful acidification, gave the hydroxy-acid (96) which was immediately esterified with diazomethane to the hydroxy-ester (97) (Scheme 23). Oxidation of this with Jones reagent gave a mixture of products. Some keto-ester (98) crystallised from the mixture; the remainder was treated with ethylene glycol and p-toluenesulphonic acid. Careful chromatography of the resulting mixture on alumina gave the acetal



(82) (93) (94) (95)

Scheme 22.

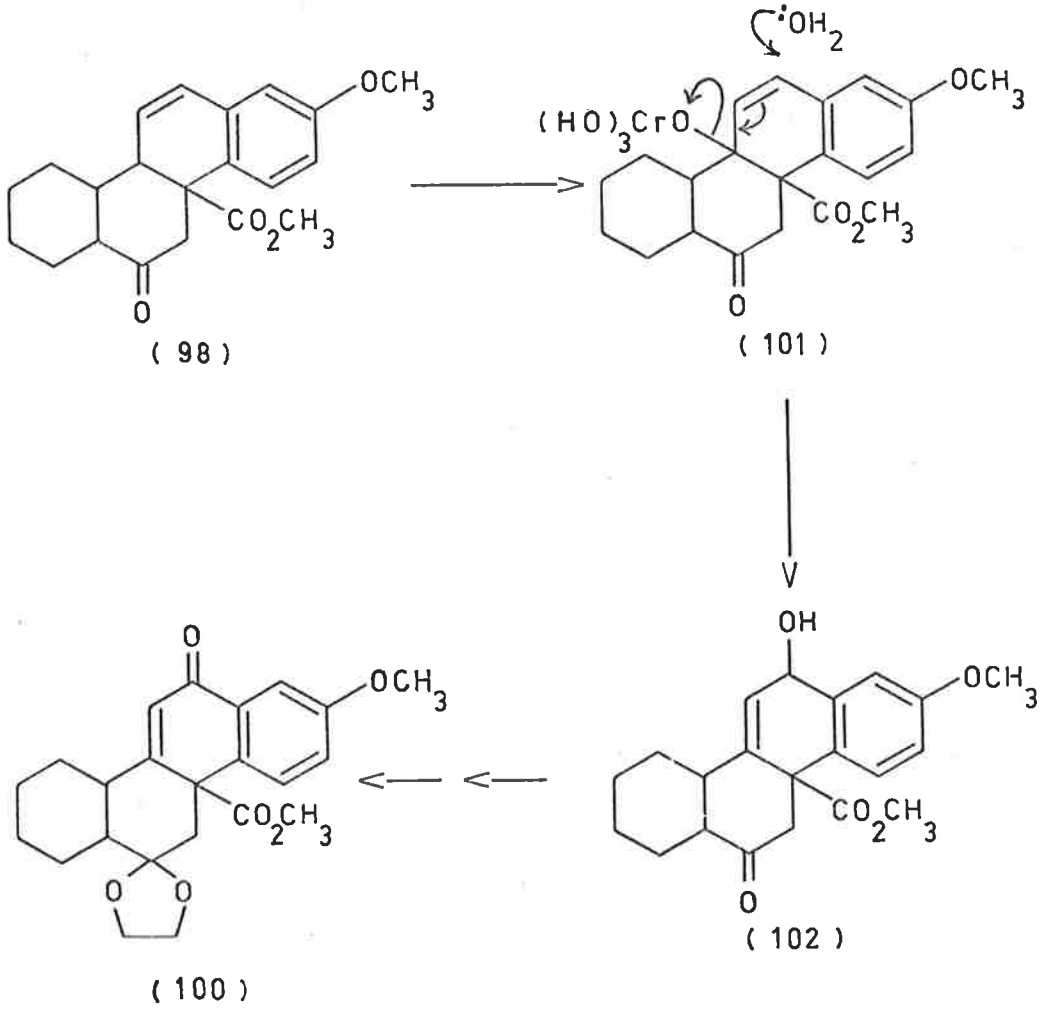
ester (99) and two other products. The major byproduct had infrared absorption bands at 1725, 1655, and 1630 cm^{-1}, which suggested the presence of the ester and a conjugated ketone group. The n.m.r. spectrum showed the presence of an ethylene dioxyacetal group at δ4 and



(84) (96) (97) (98) (99) (100)

Scheme 23

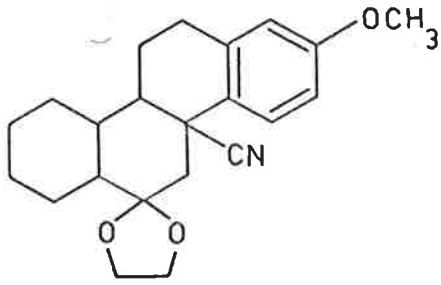
a doublet at δ6.5, J = 1.5 Hz (allylic coupling) integrating for one hydrogen. This spectral data is consistent with the proposed structure (100), and the mass spectrum and analysis confirmed it. The structure of the minor byproduct was not investigated. One plausible reaction sequence for the surprising formation of (100) from the keto-ester (98) is outlined in Scheme 24. Allylic oxidation[53] of the C-10b



Scheme 24.

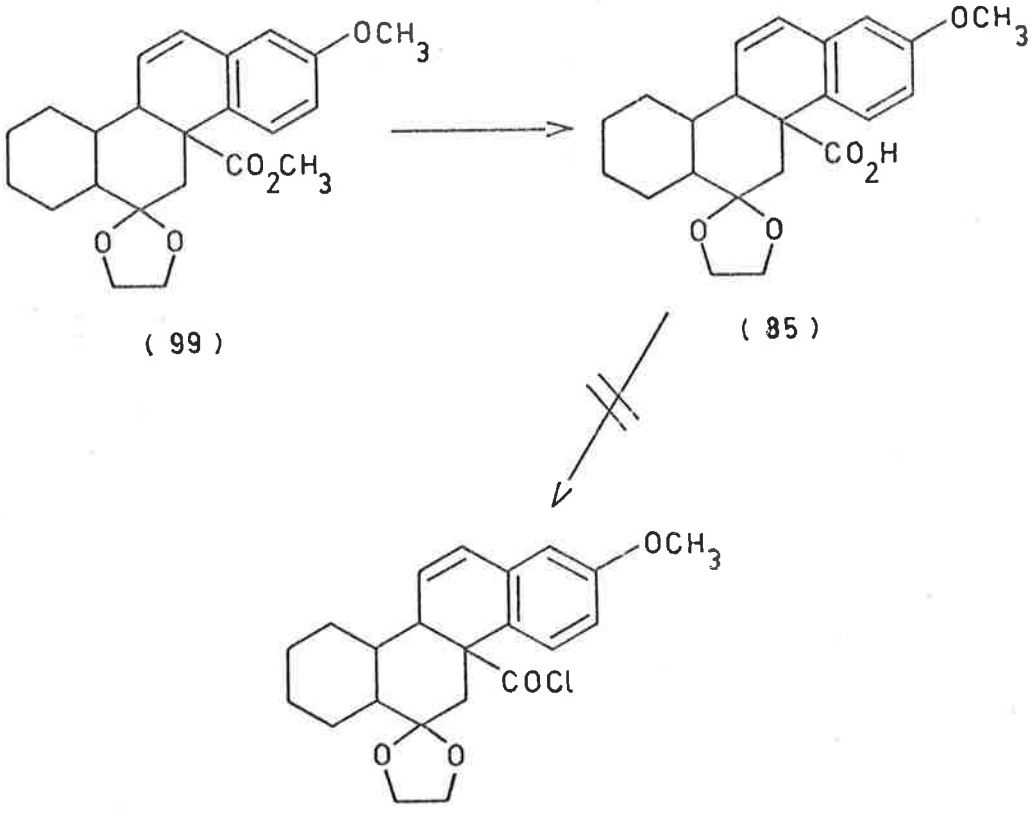
position of (98) would yield the chromate species (101). Nucleophilic attack on the Δ11-olefinic bond by water might then give the benzylic alcohol (102) which would undergo further oxidation to the enone (100).

When the olefinic lactone (84) was treated with Jones reagent under similar conditions, no reaction occurred. This suggests that the mechanism proposed in Scheme 24 is oversimplified and that the ester group must be implicated in the formation of (100) either by coordination with the chromic acid or by direct involvement in the reaction itself.



(88)

The failure of the nitrile group of the acetal-nitrile (88) to hydrolyse even under forcing conditions did not augur well for the hydrolysis of the ester (99) and difficulties were expected. However, treatment of the ester with potassium hydroxide in ethylene glycol at 180° and careful acidification gave the desired olefinic acetal acid (85) in 85% yield (Scheme 25).



(99) (85) (103)

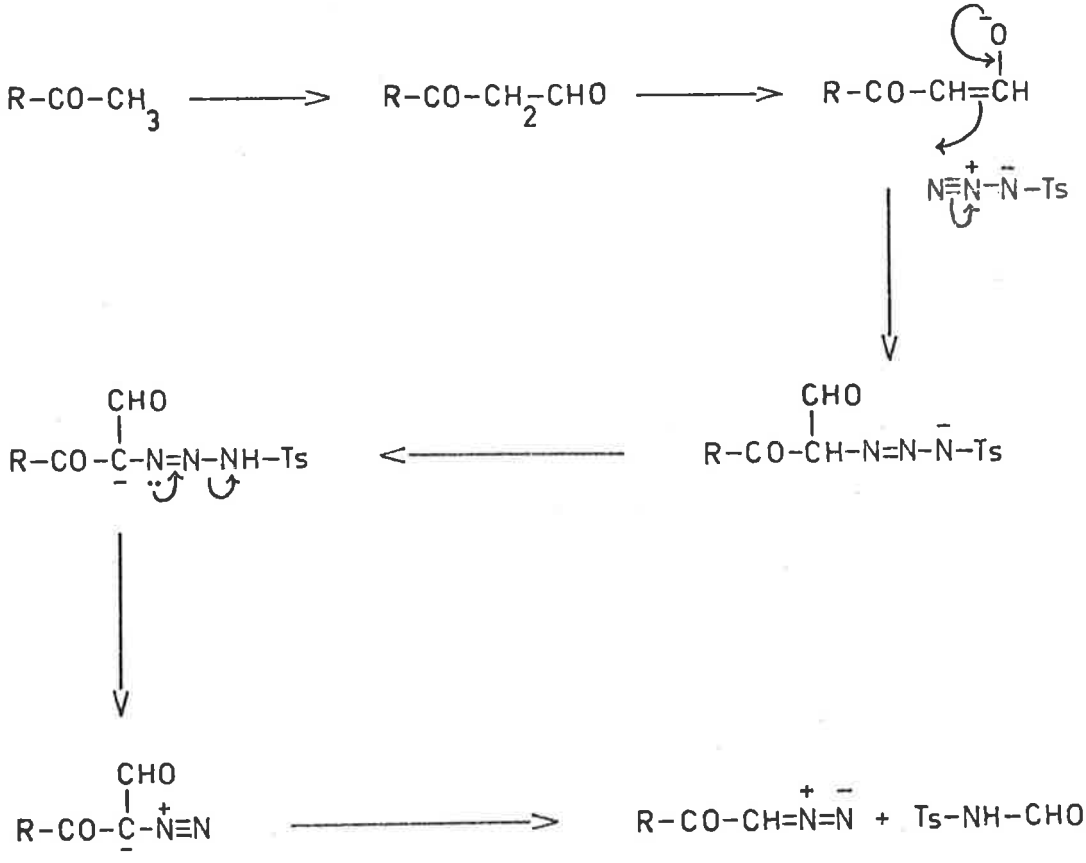
Scheme 25.

Although the hindered nature of the carbonyl function attached to C-4b did not affect this hydrolysis, from here on it presented repeated difficulties.

Treatment of the sodium salt of the acid (85) with oxalyl chloride at 0° for one hour showed no appreciable formation of acid chloride (103). When the reaction time was increased to three hours at room temperature, some acid chloride was observed (band at 1780 cm^{-1} in the infrared spectrum) together with unreacted acid and a considerable amount of product believed to be the result of opening of the acetal and further reaction with oxalyl chloride. When this mixture was allowed to react with diazomethane for periods of up to 96 hours, only trace amounts of diazoketone were isolated≠. Treatment of the acid with oxalyl chloride in the presence of pyridine under more forcing conditions gave similar undesirable products which would not undergo any reaction with diazomethane. With this effort frustrated, a search for other methods of diazoketone formation was initiated.

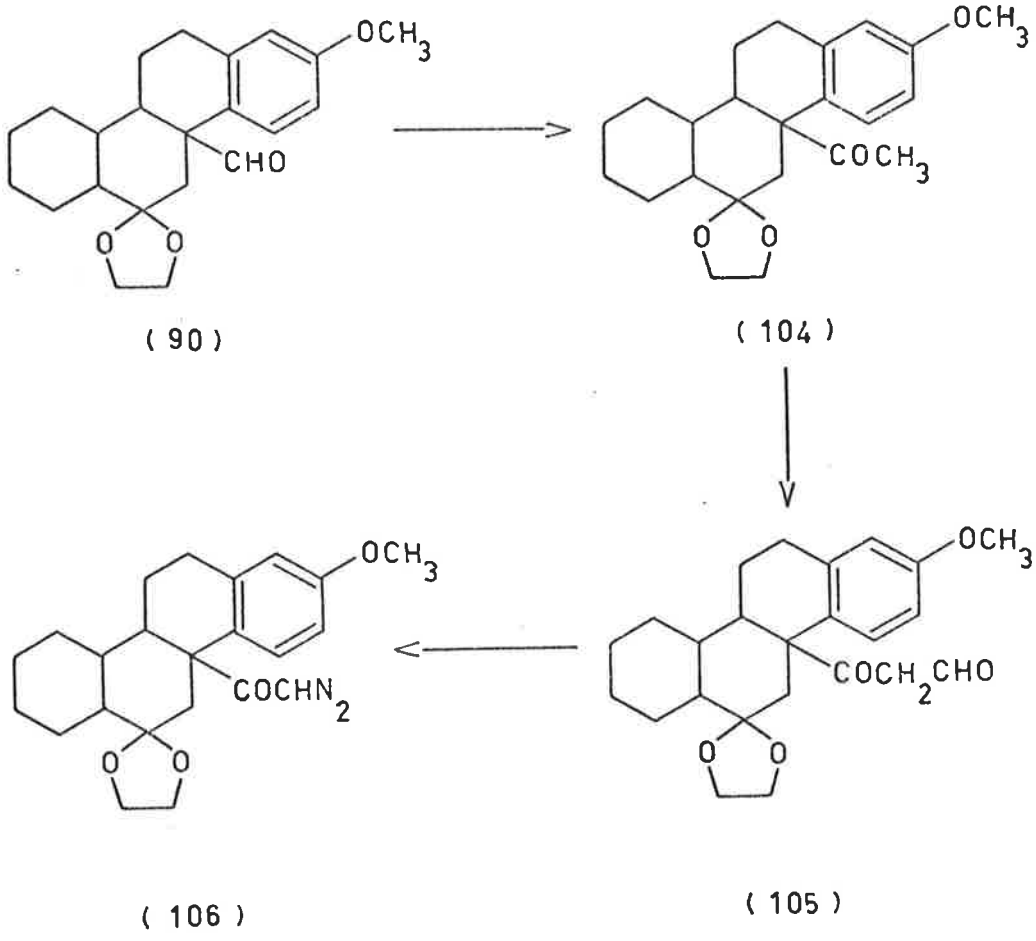
The most promising approach seemed to be that of Wolf and Hendrickson[44] who prepared diazoketones by treatment of activated methyl ketones with tosyl azide (Scheme 26).

≠ This result is in direct contrast to the attempted formation of the diazoketone from the hindered carboxyl group in 0-methyl-podocarpic acid. In this case, the acid chloride forms readily but will not undergo reaction with diazomethane.[43]



Scheme 26.

The feasibility of utilising this method was tested on the more readily available acetal aldehyde (90). To this end, treatment of (90) with methyl magnesium iodide gave the alcohol which was immediately oxidised to the methyl ketone (104) with Jones reagent (Scheme 27). Formylation of the methyl ketone with ethyl formate in the presence of sodium

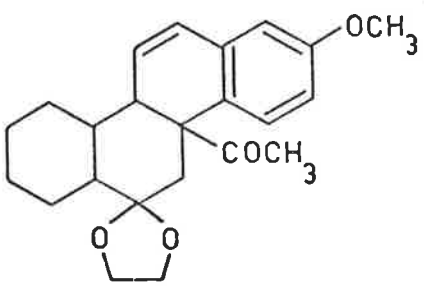


Scheme 27.

hydride gave the α-keto-aldehyde (105). The presence of the enol group was confirmed by a positive ferric chloride test and an inspection of the infrared spectrum. The crude α-keto-aldehyde was treated directly, without further purification, with tosyl azide and sodium

hydride and the crystalline diazoketone (106) was obtained.

The preceding work demonstrates an efficient method for the introduction of a diazo-acetyl function into the hindered C-4b position of a model compound for isoGB 13. This method should be readily adaptable to the olefinic methylketone (107) to allow for the synthesis of the diazoketone (34), a useful precursor in the synthesis of the isoGB 13 model compound (23).



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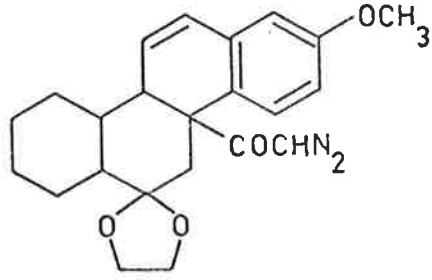

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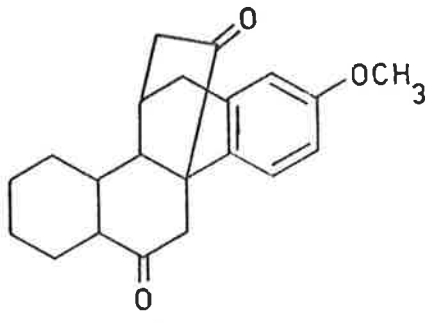

(23)

EXPERIMENTAL.

GENERAL.

Melting points were determined on a Kofler heating stage and were uncorrected. Analyses were carried out by the Australian Microanalytical Service, Melbourne.

Infrared spectra were determined with Perkin-Elmer 337 and Unicam SP200 instruments and the infrared absorption maxima refer to Nujol mulls, unless otherwise specified. Ultraviolet spectra were recorded in ethanol on a Perkin-Elmer 137 instrument. All mass spectra were determined with an Hitachi Perkin-Elmer RMU 6D double focussing mass spectrometer. The nuclear magnetic resonance spectra were recorded on Varian DA-60-IL and T60 spectrometers operating at 60 mc/s using approximately 10% solutions in deuterochloroform unless stated otherwise. Each signal is described in terms of multiplicity, intensity, chemical shift in p.p.m. from tetramethylsilane, assignment and coupling constants in Hz in that order with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; (b), broad. Signals due to OH disappeared with D_2O.

Whatman S.G 31 silica gel was used for column chromatography and light petroleum refers to the fraction of b.p. 60-80°.

Compounds were identified by m.p., mixed m.p., and a comparison of their infrared spectra. The expression "work-up in the normal manner" implies that the organic layer was washed with water, dried over anhydrous magnesium sulphate, and concentrated under reduced

pressure.

The preparations and reactions described in the experimental are listed in their order of appearance in the discussion.

PART A.

1. Preparation of Ketol (14) and its Reaction with 1-Acetyl-cyclohexene.

Triethyl-3,m-methoxyphenylpropane-1,2,2-tricarboxylate (36).

A solution of sodium ethoxide (prepared from 8.8 g of sodium) in ethanol (200 ml) was slowly added dropwise to a vigorously stirred, ice-cooled solution of m-methoxybenzyl bromide (51.7 g, 0.26 mole) and triethylethane-1,1,2-tricarboxylate (63 g, 0.26 mole). Stirring was continued for one hour at room temperature before water (700 ml) was added and the organic layer separated. The aqueous solution was extracted with ether (3 x 200 ml) and work-up in the normal manner afforded a yellow oil. Distillation under reduced pressure gave the triester (36) (86.1 g, 93%) as a clear oil, b.p. 172° at 0.8 mm (Found: C, 62.3; H, 7.2. $C_{19}H_{26}O_7$ requires C, 62.1; H, 7.2%). λ_{max} 223, 278 nm, ε 8100, 1800; ν_{max} (film) 1730 cm^{-1} (ester); n.m.r. spectrum (CCl_4): m, 4H, 6.42-7.10, aromatic H; m, 6H, 3.87-4.35, 3 x $-OCH_2CH_3$; s, 3H, 3.68, $-OCH_3$; s, 2H, 3.23, C3-H_2; s, 2H, 2.70, C1-H_2; t, 9H, 1.23, 3 x $-OCH_2CH_3$, 7.

m-Methoxybenzylsuccinic Acid (38).

The triester (36) (86.0 g, 0.24 mole), potassium hydroxide (66.0 g, 1.18 mole) and absolute ethanol (600 ml) were refluxed with stirring for 16 hours. The reaction mixture was then cooled, diluted

with water (11) and the ethanol distilled off at atmospheric pressure. Acidification with concentrated hydrochloric acid and cooling deposited a white solid. Recrystallisation from aqueous ethanol gave 56.4 g (86%) of the triacid (37) as colourless needles, m.p. 168-170°; λ_{max} 208, 221, 275, 281 nm, ε 10000, 8000, 3400, 3000; ν_{max} 1700 cm^{-1} (acid); n.m.r. spectrum (d6 DMSO): s(b), 3H, ~11.5, 3 x COOH; m, 4H, 6.50-7.37, aromatic H; s, 3H, 3.73, $-OCH_3$; s, 2H, 3.23, C3-H_2, s, 2H, 2.8, C1-H_2.

The triacid (37) (5.0 g) was heated at 190° until the evolution of carbon dioxide ceased. The oily residue was crystallised from acetone-light petroleum to give a quantitative yield of m-methoxybenzylsuccinic acid m.p. 130-131°,(lit.[45] m.p. 131-132°) (Found: C, 60.8; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%). λ_{max} 208, 221, 275, 281 nm, ε 7900, 7000, 1900, 1800; ν_{max} 1700 cm^{-1} (acid); n.m.r. spectrum (d6 DMSO): s(b), 2H, ~11.5, 2 x -COOH; m, 4H, 6.53-7.40, aromatic H; s, 3H, 3.77, $-OCH_3$; m, 5H, 2.20-3.30, aliphatic H.

1,2,3,4-Tetrahydro-7-methoxy-4-oxo-2-naphthoic Acid (21).

The triacid (37) (5.0 g) was heated at 190° until the evolution of carbon dioxide ceased. After cooling, the syrupy diacid (38) was mixed with polyphosphoric acid (20 g) and heated to 90° for one hour with occasional stirring. The dark-brown mixture was then cooled to 60° and digested in water (100 ml). Further cooling in an ice-

bath deposited 3.4 g of dark yellow solid which was recrystallised from aqueous ethanol (charcoal). The keto-acid (21) (3.2 g, 82%) was obtained as colourless needles, m.p. 204-206°. An analytical sample, m.p. 206-208°, was recrystallised twice from ether (Found: C, 65.8; H, 5.6. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%). λ_{max} 211, 226, 277 nm, ε 12000, 12000, 14000; ν_{max} 1710 (acid) 1635 cm^{-1} (ketone); n.m.r. spectrum (d6 DMSO): s(b), 1H, 8.7 -COOH; d, 1H, 7.92, C5-H, 10; d, 1H, 6.83, C6-H, 10; s, 1H, 6.78, C8-H; s, 3H, 3.82, $-OCH_3$; m, 5H, 2.4-3.4, aliphatic H.

3-Diazoacetyl-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (40).

A solution of the keto-acid (21) (5.0 g, 0.023 mole) in ether (100 ml) and triethylamine (2.3 g, 0.023 mole) was cooled to 0° with stirring and a solution of ethyl chloroformate (2.6 g, 0.024 mole) in ether (10 ml) added dropwise over 15 minutes. The mixture was stirred at 0° for 10 minutes more, then at room temperature for one hour. The triethylamine hydrochloride was filtered off, and the filtrate concentrated under reduced pressure at room temperature. The residue slowly crystallised on standing to yield 6.5 g of the mixed anhydride (39) m.p. 57-60°; ν_{max} 1800, 1755 (-CO-O-COEt), 1670 cm^{-1} (ketone); n.m.r. spectrum (CCl_4): d, 1H, 7.85, C5-H, 8.5; d of d, 1H, 6.75, C6-H, $J_{5,6}$ 8.5, $J_{6,8}$ 2.5; s, 1H, 6.63, C8-H; q, 2H, 4.25 $-OCH_2CH_3$, 7; s, 3H, 3.80, $-OCH_3$; m, 5H, 2.57-3.33, aliphatic H; t,

3H, 1.35, $-OCH_2-\underline{CH_3}$, 7. The mixed anhydride was used in the next step without further purification.

A cooled solution of the mixed anhydride (6.4 g) in ether (100 ml) and chloroform (10 ml) was added to a solution of diazomethane (prepared from 8 g of N-nitrosomethylurea) in ether (100 ml) at 0° and the reaction mixture allowed to reach room temperature overnight (16 hours). The pale yellow precipitate was filtered off and recrystallised from acetone-light petroleum to yield 4.2 g (77% from acid) of the diazoketone (40) as a white crystalline compound, m.p. 123-125°. An analytical sample melted at 124.5-125.5°, (Found: C, 63.8; H, 4.8; N, 11.5. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 5.0; N, 11.5%). ν_{max} 2100 (diazo), 1670 (aromatic ketone), 1620 cm^{-1} (diazoketone); n.m.r. spectrum : d, 1H, 7.93, C5-H, 8; d of d, 1H, 6.67, 6.87, C6-H, $J_{5,6}$ 8, $J_{6,8}$ 2.5; s, 1H, 6.70, C8-H; s, 1H, 5.37, $-COCHN_2$; s, 3H, 3.80, $-OCH_3$; m, 5H, 2.57-3.22, aliphatic H.

Methyl-1,2,3,4-tetrahydro-7-methoxy-4-oxo-naphthalene-2-acetate (18).

Silver oxide was prepared by treating a solution of silver nitrate (1.0 g) in water (10 ml) with an excess of 10% sodium hydroxide solution. The brown silver oxide was filtered off, washed well with water, and dried at 35° for 4 hours at 0.05 mm.

A solution of the diazoketone (40) (1.0 g) in absolute methanol (15 ml) was gently refluxed for 2 hours with the dry silver

oxide prepared above. The silver oxide was then filtered off, the filtrate concentrated under reduced pressure, and the residue chromatographed on silica gel (25 g). The keto-ester (18) (620 mg, 61%), m.p. 62-63°, was eluted with benzene and recrystallisation from ether-light petroleum gave an analytical sample m.p. 63-64.5° (Found: C, 67.9; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). λ_{max} 226, 278 nm, ε 5500, 12100; ν_{max} 1730 (ester), 1680 cm^{-1} (ketone); n.m.r. spectrum: d, 1H, 7.93, C5-H, 8.5; d of d, 1H, 6.93, C6-H, $J_{5,6}$ 8.5, $J_{6,8}$ 2.5; s, 1H, 6.67, C8-H; s, 3H, 3.82, $-O\underline{CH_3}$; s, 3H, 3.67, $-COO\underline{CH_3}$; m, 5H, 2.33-3.23, aliphatic H.

m-Methoxybenzyldiethylmalonate (41).

Freshly-distilled diethylmalonate (98 g, 0.61 mole) was added to a stirred solution of sodium ethoxide (prepared from 10.2 g of sodium) in absolute ethanol (300 ml) and the solution stirred for 30 minutes at room temperature before cooling to 5°. m-Methoxybenzyl bromide (82.5 g, 0.42 mole) was slowly added dropwise and the mixture stirred at room temperature overnight (16 hours). Water (500 ml) was then added and the reaction mixture acidified and extracted with ether (3 x 200 ml). Work-up in the normal manner gave a yellow oil which, when distilled under reduced pressure, gave the diester (41) (79 g, 69%) as a clear oil b.p. 145-148° at 0.7 mm (Found: C, 64.0; H, 7.5. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%). ν_{max} (film) 1730 cm^{-1} (ester);

n.m.r. spectrum: m, 1H, 6.83-7.27, 1 x aromatic H; m, 3H, 6.47-6.80, 3 x aromatic H; q, 4H, 4.08, 2 x $-O\underline{CH_2}CH_3$, 7; s, 3H, 3.70, $-O\underline{CH_3}$; m, 3H, 2.93-3.62, aliphatic H; t, 6H, 1.33, 2 x $-OCH_2\underline{CH_3}$, 7.

2,m-Methoxybenzylpropan-1,3-diol (42).

A solution of the diester (41) (78 g, 0.28 mole) in dry ether (200 ml) was added, under an atmosphere of dry nitrogen, to a stirred suspension of lithium aluminium hydride (16.2 g, 0.43 mole) in dry ether (500 ml) at such a rate as to maintain gentle refluxing. The mixture was then refluxed for a further 4 hours before the excess of lithium aluminium hydride was destroyed by the dropwise addition of water (16 ml), 15% sodium hydroxide solution (16 ml) and water (48 ml). The granular precipitate of aluminium hydroxide was filtered off and the filtrate concentrated under reduced pressure to yield 1.1 g of diol (42). Exhaustive extraction of the aluminium hydroxide with hot ethanol gave a further 45.0 g (total 86%) of the diol m.p. 76-78°. Recrystallisation from benzene raised the m.p. to 80-82°; ν_{max} 3200 cm^{-1} (hydroxyl).

2,m-Methoxybenzylpropan-1,3-diol-bismethanesulphonate (43).

A solution of the diol (42) (45 g, 0.23 mole) in dry benzene (250 ml) and pyridine (54 g, 0.68 mole) was cooled to 0°. Methanesulphonyl chloride (79 g, 0.54 mole) was added, with stirring, over a one hour period; the temperature of the reaction mixture being

maintained between 5-15°. After the mixture had been stored at 6° for 24 hours, the precipitate was filtered off and washed with benzene (5 x 50 ml). The combined washings and filtrate were washed with 1N sodium bicarbonate solution (125 ml) and work-up in the normal manner gave 70 g of crude diester (43). The product was recrystallised from ethanol to yield 61 g (76%) of white needles, m.p. 92-93°. Further recrystallisation from ethanol gave an analytical sample m.p. 93° (Found: C, 44.5; H, 5.9. $C_{13}H_{20}O_7S_2$ requires C, 44.3; H, 5.7%); n.m.r. spectrum : m, 1H, 7.00-7.42, 1 x aromatic H; m, 3H, 6.57-6.90, 3 x aromatic H; s, 2H, 4.22, C1-H, C3-H; d, 2H, 4.14, C1-H, C3-H, 1.5; s, 3H, 3.75, $-O\underline{CH_3}$; s, 6H, 2.98, 2 x $-OSO_2\underline{CH_3}$; m, 3H, 2.17-2.83, aliphatic H.

β,m-Methoxybenzylglutaric Acid (44).

A solution of potassium cyanide (27.0 g, 0.41 mole) in water (160 ml) was added to a solution of the diester (43) (60.5 g, 0.17 mole) in ethanol (300 ml) and the mixture refluxed for 5 hours. A solution of 10N sodium hydroxide (170 ml) was added and the mixture refluxed, with stirring, for a further 16 hours. After most of the ethanol had been distilled off, the solution was acidified with concentrated hydrochloric acid, charcoal added, and the mixture evaporated to two-thirds of its volume. The charcoal was filtered off and a pale yellow oil, which slowly crystallised on standing, precipitated from

the filtrate as it cooled. The diacid (44) (36.3 g, 84%) was recrystallised from acetone-ether, m.p. 95-97°; λ_{max} 2130 (acid OH), 1700 cm^{-1} (acid); n.m.r. spectrum (d6 DMSO): s, 2H, 12.0, 2 x -COOH; m, 1H, 7.07-7.57, 1 x aromatic H; m, 3H, 6.70-6.97, 3 x aromatic H; s, 3H, 3.80, $-OCH_3$; m, 7H, 2.0-2.8, aliphatic H.

1,2,3,4-Tetrahydro-7-methoxy-4-oxo-naphthalene-2-acetic Acid (45).

β-Methoxybenzylglutaric acid (14 g) was treated with concentrated sulphuric acid (70 ml) and the mixture allowed to stand at room temperature for 16 hours. The reaction mixture was then poured onto ice and the pale yellow solid collected. Recrystallisation from aqueous ethanol gave the keto-acid (45) as pale yellow needles m.p. 146-150°. An analytical sample, m.p. 150-152° was recrystallised from ether (Found: C, 66.3; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.6; H, 6.0%). ν_{max} 1720 (acid), 1640 cm^{-1} (hydrogen bonded aromatic ketone); n.m.r. spectrum (d6 DMSO) s, 1H, 8.4, -COOH; d, 1H, 7.63, C5-H, 9; d of d, 1H, 6.85, C6-H, $J_{5,6}$ 9, $J_{6,8}$ 2.5; s, 1H, 6.77, C8-H; s, 3H, 3.83, $-OCH_3$; m, 7H, 2.2-3.2, aliphatic H.

Methyl-1,2,3,4-tetrahydro-7-methoxy-4-oxo-naphthalene-2-acetate (18).

A solution of the keto-acid (45) (6.0 g) in methanol (70 ml) was cautiously treated with concentrated sulphuric acid (3.5 ml) and the reaction mixture refluxed for 2 hours. Water (300 ml) was added

and the aqueous solution extracted with chloroform (2 x 100 ml). Work-up in the normal manner gave 6.5 g of pale yellow oil which slowly crystallised on cooling. Recrystallisation from ether-light petroleum gave the keto-ester (18) (5.8 g, 92%) m.p. 62-63° which was identical in all respects to that obtained from the Wolff rearrangement of the diazoketone (40).

1-Acetoxy-1,2,3,4-tetrahydro-6-methoxy-10-oxo-1,3-ethano-naphthalene (46).

Sodium (1.82 g, 0.08 g atom) was added to a stirred solution of naphthalene (10.2 g, 0.08 mole) in dry dimethoxyethane (800 ml) in an atmosphere of nitrogen. The solution, which turned a dark green colour after approximately 15 minutes, was stirred at room temperature for 4 hours and then a solution of the keto-ester (18) (4.9 g, 0.02 mole) in dry dimethoxyethane (150 ml) added dropwise over 7 hours. The reaction mixture was stirred an additional 13 hours and then quenched with acetyl chloride (9.5 g, 0.12 mole). After it had been stirred for a further hour, water (500 ml) was added and the aqueous solution extracted with ether (3 x 100 ml). The ethereal extracts were washed with saturated sodium bicarbonate solution (2 x 100 ml), water (100 ml), and dried over anhydrous magnesium sulphate. Evaporation of the ether under reduced pressure gave a yellow semi-solid residue which was chromatographed on silica gel (300 g). Elution with 2% ether-

light petroleum (1.5 l) removed the naphthalene and a clear oil was eluted with 20% ether-light petroleum. The keto-acetate (46) crystallised from these fractions and the crude product was collected and recrystallised from acetone-light petroleum to give 310 mg (6%) of white plates m.p. 155.5-157°, (Found: C, 69.0; H, 6.2. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%). λ_{max} 216, 241, 293 nm, ε 11200, 7000, 2200; ν_{max} 1750 (acetate) 1735 cm^{-1} (cyclopentanone); n.m.r. spectrum: d, 1H, 7.40, C8-H, 8.5; d of d, 1H, 6.85, C7-H, $J_{7,8}$ 8.5, $J_{5,7}$ 2.5; s, 1H, 6.68, C5-H; s, 3H, 3.77, $-OCH_3$; s, 3H, 2.23, $-OCOCH_3$; mass spectrum : parent ion m/e 260.

The infrared spectrum of another product, possibly (47), which was eluted with the keto-acetate, showed bands at 1750 (acetate) and 1670 cm^{-1} (aromatic ketone). This compound could not be separated from other impurities.

Triethyl-3-phenylpropane-1,2,2-tricarboxylate (48).

A solution of sodium ethoxide (prepared from 13.6 g sodium) in absolute ethanol (200 ml) was slowly added dropwise to a vigorously stirred, ice-cooled solution of benzyl bromide (100 g, 0.58 mole) and triethylethane-1,1,2-tricarboxylate (148 g, 0.60 mole). Stirring was continued for a further 45 minutes at room temperature, before water (400 ml) was added and the mixture extracted with ether (3 x 200 ml). Work-up in the normal manner gave a yellow oil which was distilled under reduced pressure to yield the triester (48) (167 g, 85%) as a

clear oil, b.p. 200-205° at 10 mm (Found: C, 64.3; H, 7.1. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.2%). λ_{max} 213 nm, ε 6600; ν_{max} (film) 1720 (ester); n.m.r. spectrum (CCl_4), m, 5H, 6.92-7.33, aromatic H; m, 6H, 3.87-4.37, 3 x $-O\underline{CH_2}CH_3$; s, 2H, 3.28, C3-H_2; s, 2H, 2.70, C1-H_2; t, 9H, 1.23, 3 x $-OCH_2\underline{CH_3}$, 7.

Benzylsuccinic Acid (49).

A solution of the triester (48) (167 g, 0.5 mole) in ethanol (1 l) and potassium hydroxide (139 g, 2.5 mole) were heated under reflux for 16 hours with stirring. Water (700 ml) was added to the cooled mixture and the ethanol distilled off. The mixture was acidified with a large excess of concentrated hydrochloric acid, and refluxed for 3 hours. On cooling, the acidic solution deposited a white precipitate which was filtered off, washed well with cold water, and dried. Benzylsuccinic acid (101 g, 98%) had a melting point of 161-162° after recrystallisation from acetone-light petroleum, (lit.[32] m.p. 157-160°).

Benzylsuccinic Anhydride (50).

A mixture of benzylsuccinic acid (71 g, 0.34 mole) and redistilled acetyl chloride (82 g, 1.02 mole) was gently refluxed for 90 minutes. After the solution had been cooled in an ice-bath, the white solid was filtered off and washed with ether (2 x 80 ml) to give 60 g (93%) of the anhydride (50), m.p. 96-98° (lit.[32] m.p. 95-97°).

1,2,3,4-Tetrahydro-4-oxo-2-naphthoic Acid (51).

The method was adapted from that used by Haworth and co-workers.[32] Benzylsuccinic anhydride (50) (60 g, 0.31 mole) was slowly added to a solution of aluminium chloride (86 g, 0.65 mole) in nitrobenzene (300 ml). After 24 hours, the dark mixture was poured into concentrated hydrochloric acid (300 ml) in ice (1 kg), and the nitrobenzene steam distilled off. After the acidic solution had been cooled, the crude product was filtered off and recrystallised from water (charcoal). The keto-acid (51) (37.1 g, 61%) was obtained as colourless plates, m.p. 145-147° (lit.[32] m.p. 145-147°); λ_{max} 213, 251, 296 nm, ε 11800, 10900, 1600; ν_{max} 1690 (ketone, acid superimposed); n.m.r. spectrum (d6 acetone), d of d, 1H, 7.97, C5-H, $J_{5,6}$ 6, $J_{5,7}$ 2; m, 3H, 7.17-7.70, C6-H, C7-H, C8-H; s(b), 1H, 6.00, -COOH.

Concentration of the filtrate deposited 4.2 g of the isomeric indanone acetic acid (52) which, after recrystallisation from water, melted at 142-143.5° (Found: C, 69.2; H, 5.4. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%). λ_{max} 212, 247, 294 nm, ε 11400, 11000, 2100; ν_{max} 1735 (cyclopentanone) 1680 cm^{-1} (acid); n.m.r. spectrum: s, 1H, 9.93, -COOH; m, 4H, 7.16-7.88, 4 x aromatic H; m, 5H, 2.33-3.83, aliphatic H.

1,2,3,4-Tetrahydro-4-oxo-2-naphthoyl Chloride.

A solution of the keto-acid (51) (20.0 g, 0.11 mole) in pyridine (10.5 g, 0.12 mole) and benzene (100 ml) was slowly added, with stirring, to an ice-cooled solution of oxalyl chloride (27.0 g, 0.21 mole) in benzene (50 ml). The mixture was stirred at room temperature for 2 hours and then refluxed for a further hour. The pyridine hydrochloride was then filtered off, washed with benzene (100 ml) and the filtrate and washings concentrated under reduced pressure to remove the benzene and excess oxalyl chloride. Further portions of benzene (2 x 100 ml) were added and distilled to ensure the complete removal of all oxalyl chloride. The pale yellow solid was recrystallised from benzene to yield 20.2 g (91%) of the acid chloride, m.p. 72-75°; ν_{max} 1770 (acid chloride), 1675 cm^{-1} (ketone). The acid chloride was used in the next reaction without further purification.

3-Diazoacetyl-3,4-dihydro-1(2H)naphthalenone (53).

A solution of the acid chloride (20 g) in ether (200 ml) was slowly added to an ice-cooled solution of diazomethane (prepared from 60 g of N-nitrosomethyl urea) in ether (600 ml). The mixture was kept at room temperature overnight (16 hours) and then the excess of diazomethane removed by warming on a steam-bath. The pale yellow precipitate of diazoketone (13.5 g) was filtered off and the filtrate chromatographed on alumina (100 g). Elution with 50% benzene-light petroleum gave a further 3.0 g of (53) (total 16.5 g, 81%) as pale yellow needles

m.p. 87-89°; ν_{max} 2090 (diazo), 1675 (aromatic ketone) 1615 cm^{-1} (diazoketone); n.m.r. spectrum: d, 1H, 8.0, C5-H, 7; m, 3H, 7.1-7.7, C6-H, C7-H, C8-H; s, 1H, 5.43, $-COCHN_2$; m, 5H, 2.6-3.3, aliphatic H.

Methyl-1,2,3,4-tetrahydro-4-oxo-naphthalene-2-acetate (54).

Silver oxide was prepared by treating a solution of silver nitrate (5.0 g) in water (50 ml) with an excess of 10% sodium hydroxide solution. The brown silver oxide was filtered off, washed well with water, and dried at 40° for 4 hours at 0.1 mm.

A solution of the diazoketone (53) (4.5 g) in absolute methanol (100 ml) was gently refluxed for 2 hours with the dry silver oxide prepared above. The mixture was filtered, concentrated under reduced pressure, and the dark oil chromatographed on silica gel. The keto-ester (54) (3.5 g, 76%), m.p. 52-54°, was eluted with 20% ether-light petroleum. An analytical sample, m.p. 54°, was recrystallised from ether-light petroleum (Found: C, 71.3; H, 6.5. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%). λ_{max} 213, 249, 297 nm, ε 10500, 11200, 1500; ν_{max} 1720 (ester) 1680 cm^{-1} (aromatic ketone); n.m.r. spectrum: d of d, 1H, 7.92, C5-H, $J_{5,6}$ 7, $J_{5,7}$ 2; m, 3H, 6.83-7.58, C6-H, C7-H, C8-H; s, 3H, 3.63, $-COOCH_3$.

Benzyldiethylmalonate.

Redistilled diethylmalonate (140 g, 0.87 mole) was added dropwise to a refluxing solution of sodium ethoxide (prepared from

20 g of sodium) in absolute ethanol (600 ml). A solution of benzyl bromide (100 g, 0.58 mole) in absolute ethanol (200 ml) was then added at such a rate as to keep the reaction under control. The mixture was refluxed for a further 4 hours before water (600 ml) was added. Work-up as for compound (41) gave 82.5 g (57%) of the diester as a clear oil, b.p. 118° at 0.5 mm (Found: C, 67.1; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%). ν_{max} (film) 1730 cm^{-1} (ester); n.m.r. spectrum (CCl_4): s, 5H, 7.13, aromatic H; q, 4H, 4.06, 2 x $-OCH_2CH_3$; m, 3H, 2.97-3.63, aliphatic H; t, 6H, 1.17, 2 x $-OCH_2CH_3$, 7.

2-Benzylpropan-1,3-diol.

A solution of benzyldiethylmalonate (82.0 g, 0.33 mole) in dry ether (300 ml) was added dropwise, with stirring, to a suspension of lithium aluminium hydride (18.6 g, 0.48 mole) in dry ether (700 ml) under an atmosphere of nitrogen. The mixture was stirred and refluxed for 5 hours before wet ether was added to destroy the excess of hydride. The solution was filtered, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give 54.4 g (97%) of the diol as a pale yellow oil which was used without further purification in the next reaction; ν_{max} (film) 3300 cm^{-1} (hydroxyl); n.m.r. spectrum: s, 5H, 7.17, aromatic H; m, 3H, 3.33-4.07, C1-H_2, C3-H_2; s(b), 2H, 3.00, 2 x $-OH$; d, 2H, 2.57, 2 x benzylic H, 7; m, 1H, 1.67-2.33, C2-H.

2-Benzylpropan-1,3-diol-bismethanesulphonate.

A solution of 2-benzylpropan-1,3-diol (52.5 g, 0.32 mole) in dry benzene (250 ml) and pyridine (75.0 g, 0.95 mole) was cooled to 5°. Methanesulphonyl chloride (90.0 g, 0.78 mole) was added, with stirring, over a one hour period; the temperature of the reaction mixture being maintained between 5 and 15°. The mixture was stored at 6° for 16 hours and then work-up and purification as for compound (43) gave 78 g (78%) of the diester as white needles, m.p. 87-88°. Recrystallisation from ethanol gave an analytical sample m.p. 89°, (Found: C, 44.9; H, 5.9. $C_{12}H_{18}O_6S_2$ requires C, 44.7; H, 5.6%); n.m.r. spectrum: s, 5H, 7.22, aromatic H; s, 2H, 4.22, C1-H, C3-H; d, 2H, 4.13, C1-H, C3-H, 1.5; s, 6H, 2.97, 2 x $-OSO_2\underline{CH}_3$; m, 3H, 2.25-2.87, aliphatic H.

β-Benzylglutaric Acid.

A solution of potassium cyanide (35.0 g, 0.54 mole) in water (200 ml) was added to a solution of the diester from the previous experiment (78.0 g, 0.24 mole) in ethanol (350 ml) and the mixture refluxed for 5 hours. A solution of 10N sodium hydroxide (200 ml) was added and the mixture refluxed, with stirring, for a further 16 hours. Work-up, as described for compound (44), gave a pale yellow oil which slowly crystallised on standing. Recrystallisation from benzene afforded 36.1 g (67%) of the diacid, m.p. 100-101° (lit.[46] m.p. 101°; ν_{max} 2630 (acid OH), 1705 cm^{-1} (acid).

1,2,3,4-Tetrahydro-4-oxo-naphthalene-2-acetic Acid.

The method was adapted from that used by Stevenson and Thorpe.[46]

β-Benzylglutaric acid (23 g) was treated with concentrated sulphuric acid (115 ml) and the mixture kept at room temperature for 16 hours. The reaction mixture was then poured onto ice and the pale yellow solid collected. Recrystallisation from aqueous ethanol gave the keto-acid as a white crystalline solid (19.0 g, 90%), m.p. 110-111° (lit.[46] m.p. 110-111°); ν_{max} 1705 (acid), 1675 cm^{-1} (aromatic ketone).

Methyl-1,2,3,4-tetrahydro-4-oxo-naphthalene-2-acetate (54).

A solution of the keto-acid from the previous experiment (18.0 g) in methanol (200 ml) was cautiously treated with concentrated sulphuric acid (10 ml) and the mixture refluxed for 2 hours. Water (500 ml) was then added and work-up in the normal manner gave 20 g of a pale red oil which was chromatographed on alumina (400 g). Elution with 50% ether-light petroleum gave 18.8 g (98%) of the keto-ester (54), m.p. 52-54°, which was identical in all respects to that prepared from the Wolff rearrangement of the diazoketone (53).

1-Acetoxy-1,2,3,4-tetrahydro-10-oxo-1,3-ethano-naphthalene (55).

Sodium (220 mg, 9.6 mg atom) was added to a stirred solution of naphthalene (1.21 g, 9.5 mmole) in dry dimethoxyethane (90 ml) in

an atmosphere of nitrogen. The mixture was stirred at room temperature for 3 hours and then a solution of the keto-ester (54) (540 mg, 2.5 mmole) in dimethoxyethane (50 ml) was added dropwise over 5 hours. The reaction mixture was stirred for an additional 16 hours and then quenched with acetyl chloride (1.0 g, 13 mmole). After one hour, water (200 ml) was added and the aqueous solution extracted with ether (3 x 50 ml). The ethereal extracts were washed with saturated sodium bicarbonate solution (2 x 50 ml), water (100 ml), and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a yellow oil which was chromatographed on alumina (40 g). Elution with light petroleum (500 ml) removed the naphthalene and further elution with ethyl acetate (300 ml) gave the monomeric products. The keto-acetate (55) (108 mg, 19%), a white crystalline solid m.p. 115-116°, was separated from this mixture by preparative scale vapour phase chromatography on a 5 foot, 20% B.D.S. column at an oven temperature of 200°. (Found: C, 72.9; H, 6.3. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%). ν_{max} 1750 (acetate), 1735 cm^{-1} (cyclopentanone); n.m.r. spectrum: m, 4H, 6.83-7.53, aromatic H; s, 3H, 2.17, $-OCO\underline{CH_3}$; mass spectrum : parent ion m/e 230.

Attempted Annelation of Keto-acetate (55) with 1-Acetylcyclohexene.

When sodium amide (50 mg, 1.3 mmole) was added to a solution of

the keto-acetate (55) (100 mg, 0.43 mmole) in ether (5 ml) in an atmosphere of nitrogen, an exothermic reaction ensued and the mixture immediately turned a dark brown colour. The reaction mixture was stirred for 5 hours at room temperature and then a solution of 1-acetylcyclohexene (55 mg, 0.44 mmole) in ether (2 ml) added. After it had been refluxed for 4 hours, the mixture was acidified with dilute hydrochloric acid and extracted with chloroform (2 x 30 ml). Work-up in the normal manner gave 132 mg of a darkly coloured oil. An infrared spectrum of this oil showed the presence of the enone system of 1-acetylcyclohexene at 1655 and 1620 cm^{-1} and other bands at 3400 (hydroxyl) and 1735 cm^{-1} (possibly cyclopentanone). The acetate band at 1750 cm^{-1} was absent. Chromatography of this oil on alumina (6 g) gave only the one product - unreacted 1-acetylcyclohexene (41 mg).

Methyl-1,2,3,4-tetrahydro-4-methylenenaphthalene-2-acetate (59).

A suspension of triphenylmethylphosphonium iodide (78.0 g, 0.19 mole) and potassium t-butoxide in dry benzene (250 ml) was stirred at 5° for 30 minutes in an atmosphere of nitrogen. A solution of the keto-ester (54) (14.0 g, 0.064 mole) in benzene (50 ml) was added and the mixture stirred at 5° for 3 hours and then at room temperature for 13 hours. Hexane (100 ml) and 75% methanol-water (200 ml) were added, the mixture shaken, and the layers separated. The aqueous layer was extracted again with hexane (100 ml) and work-up of the combined hexane extracts in the normal manner gave 31.2 g of yellow

oil. This was filtered through a silica gel column (600 g) under reduced pressure with 20% ether-light petroleum as elutant. The olefinic ester (59) (11.3 g, 81%) was isolated as a pale yellow oil. An analytical sample distilled at 78-80° at 0.1 mm (Found: C, 78.0; H, 7.8. $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%). ν_{max} (film) 1725 (ester), 1625 cm^{-1} (olefin); n.m.r. spectrum (CCl_4) m, 1H, 7.33-7.67, C5-H; m, 3H, 6.83-7.23, C6-H, C7-H, C8-H; s, 1H, 5.42, methylene H; s, 1H, 4.90, methylene H; s, 3H, 3.60, $-COO\underline{CH}_3$.

Methyl-1,2,3,4-tetrahydro-4-methoxycarbonylnaphthalene-2-acetate (58).

A solution of boron trifluoride etherate (35.0 g, 0.25 mole) in dry tetrahydrofuran (40 ml) was slowly added over one hour to a stirred suspension of sodium borohydride (7.0 g, 0.185 mole) in dry tetrahydrofuran (100 ml) at 0° in an atmosphere of nitrogen. The mixture was stirred for a further 2 hours at 0° before a solution of the olefinic ester (59) (10.0 g, 0.046 mole) in dry tetrahydrofuran (100 ml) was added. The reaction mixture was then warmed to 25° and kept at this temperature for 3 hours. The excess of diborane was destroyed by the dropwise addition of water and the organoborane oxidised at 30° by the addition of 3N sodium hydroxide solution (20 ml) followed by 30% hydrogen peroxide solution (20 ml). After one hour, the reaction mixture was saturated with sodium chloride and the organic layer separated, washed with saturated sodium chloride solution (100 ml), and dried over

anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure yielded 11.0 g of crude diol (61) which was dissolved in acetone (150 ml) and cooled to 0°. Jones reagent was added dropwise until the orange colour persisted (~ 35 ml). After the addition of water (200 ml) the mixture was extracted with chloroform (2 x 100 ml), and work-up in the normal manner gave 12.2 g of an oily mixture of acids. A solution of the crude mixture in methanol (120 ml) was cautiously treated with concentrated sulphuric acid (8 ml) and the mixture refluxed for 3 hours. Water (300 ml) was added and the mixture extracted with ether (3 x 100 ml). Work-up in the normal manner yielded 10.1 g of an oil which was chromatographed on silica gel (300 g). Elution with 20% ether-light petroleum gave 2.5 g (21%) of the diester (58) as a clear oil, ν_{max} (film) 1720 cm^{-1} (ester); n.m.r. spectrum (CCl_4): s, 4H, 7.00, aromatic H; s, 3H, 3.63, $-COO\underline{CH_3}$; s, 3H, 3.60, $-COO\underline{CH_3}$.

Further elution with 20% ether-light petroleum afforded 5.7 g of the keto-ester (54) m.p. 53-54°.

1,2,3,4-Tetrahydro-10-oxo-1,3-ethanonaphthalene (57).

A solution of the diester (58) (1.77 g, 4.5 mmole) in dry tetrahydrofuran (40 ml), and sodium hydride (0.66 g, 27.5 mmole) were stirred in an atmosphere of nitrogen at room temperature for 16 hours and then at reflux for 4 hours. After the addition of water (100 ml), the solution was acidified with dilute hydrochloric acid and extracted

with ether (3 x 50 ml). Work-up in the normal manner gave 1.6 g of β-keto-ester (62), ν_{max} (film) 1735 (cyclopentanone), 1720 cm^{-1} (ester).

The β-keto-ester was refluxed with 25% hydrochloric acid (50 ml) for 16 hours then cooled, basified, and extracted with ether (2 x 100 ml). Work-up in the normal manner gave 1.3 g of a dark oil which was chromatographed on alumina (40 g). Elution with 5% ether-light petroleum yielded 1.1 g (95%) of the tricyclic ketone (57) as a clear oil, ν_{max} (film) 1735 cm^{-1} (cyclopentanone); n.m.r. spectrum (CCl_4): s, 4H, 7.01, aromatic H; m, 8H, 1.60-3.50, aliphatic H; mass spectrum: parent ion m/e 172.

The semicarbazone of the tricyclic ketone formed white needles from ethanol, m.p. 211-212°, (Found: C, 68.1; H, 6.7. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6%).

Attempted Annelation of Tricyclic Ketone (57) with 1-Acetylcyclohexene.

A solution of the tricyclic ketone (57) (100 mg, 0.58 mmole) in dry ether (5 ml) was treated with sodium amide (34 mg, 0.87 mmole) and the mixture refluxed in an atmosphere of nitrogen for 5 hours. After the addition of a solution of 1-acetylcyclohexene (80 mg, 0.65 mmole) in dry ether (2 ml), the mixture was refluxed for a further 16 hours. Water (30 ml) was added and the aqueous solution acidified and extracted with ether (2 x 50 ml). Work-up in the normal manner gave

196 mg of pale yellow oil which was chromatographed on a silica gel thick plate using 5% ether-light petroleum as elutant. Impure tricyclic ketone (57) (87 mg), ν_{max} (film) 1735 cm^{-1}, was recovered.

2. Attempted Preparation of Ketol (15).

3-Acetyl-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (20).

Hydriodic acid (55% in water) was added dropwise to a solution of the diazoketone (40) (0.5 g) in chloroform (10 ml) until the evolution of nitrogen ceased. The mixture was allowed to stand for 30 minutes and then water (50 ml) added. The chloroform layer was separated, washed with 10% sodium thiosulphate solution until no more colour was removed, and work-up in the normal manner gave a pale yellow oil which was chromatographed on alumina (20 g). Elution with benzene yielded 420 mg (96%) of the methyl ketone (20) as a white solid, m.p. 106-107°. Recrystallisation from benzene-light petroleum gave an analytical sample as white needles, m.p. 107.5-108° (Found: C, 71.7; H, 6.6. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%). λ_{max} 215, 226, 278 nm, ε 9900, 11100, 15000; ν_{max} 1690 (methyl ketone), 1660 cm^{-1} (aromatic ketone); n.m.r. spectrum: d, 1H, 7.92, C5-H, 8.5; d of d, 1H, 6.77, C6-H, $J_{5,6}$ 8.5, $J_{6,8}$ 2.5; s, 1H, 6.68, C8-H; s, 3H, 3.81, $-O\underline{CH_3}$; m, 5H, 2.50-3.27, aliphatic H; s, 3H, 2.20, $-CO\underline{CH_3}$.

Attempted Aldol Cyclisation of the Methyl Ketone (20).

1) A solution of the methyl ketone (100 mg) in ethanol (10 ml) was refluxed with 1N potassium hydroxide solution (14 ml) for 4 hours. Work-up in the normal manner gave a crystalline residue which was identified as the unchanged methyl ketone (20), m.p. 106-107°.

2) A solution of the methyl ketone (100 mg) in dry tetrahydrofuran (5 ml) was added to a solution of potassium t-butoxide (prepared from 39 mg of potassium) in dry t-butanol (5 ml) in an atmosphere of nitrogen. The mixture was warmed to 60° for 4 hours, then cooled, and diluted with water (60 ml). Work-up in the normal manner gave unchanged methyl ketone (87 mg).

3) A solution of the methyl ketone (100 mg) in acetic acid (2.5 ml) and acetic anhydride (2.5 ml) was treated with boron trifluoride etherate (0.75 ml) and allowed to stand at room temperature for 24 hours. Water (20 ml) was then added and the aqueous solution extracted with chloroform (2 x 30 ml). Work-up in the normal manner gave a pale yellow oil (60 mg) believed to be a mixture of the enol acetate (69), ν_{max} (film) 1760 (acetate), 1660 (aromatic ketone), 1630 cm^{-1} (olefin); n.m.r. spectrum: δ1.43 ($>C=C(-\underline{CH_3})-OCOCH_3$); and methyl ketone (20) ν_{max} (film) 1690 (methyl ketone) 1660 cm^{-1} (aromatic ketone); n.m.r. spectrum δ2.20 ($-COCH_3$).

3-Acetyl-3,4-dihydro-1(2H)-naphthalenone (72).

Hydriodic acid (55% in water) was slowly added dropwise to a solution of the diazoketone (53) (1.0 g) in chloroform (20 ml) until the evolution of nitrogen ceased. The mixture was allowed to stand for 30 minutes and then work-up, as described for compound (20), gave a pale yellow oil. Distillation of this under reduced pressure gave

540 mg (61%) of the diketone (72) as a clear oil which slowly crystallised on standing, m.p. 54-56°. An analytical sample, m.p. 56-57°, was recrystallised from ether-light petroleum (Found: C, 76.4; H, 6.5. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%). λ_{max} 213, 252, 297 nm, ε 11500, 10500, 1500; ν_{max} 1700 (methyl ketone), 1675 cm^{-1} (aromatic ketone); n.m.r. spectrum (CCl_4): d of d, 1H, 7.83, C5-H, $J_{5,6}$ 8, $J_{5,7}$ 2; m, 3H, 7.00-7.50, C6-H, C7-H, C8-H; s, 3H, 2.13, $-COCH_3$.

3,4-Dihydro-6-methoxy-3-(2'-oxo-propyl)-1(2H)-naphthalenone (70).

A stirred suspension of the keto-acid (45) (2.0 g, 8.5 mmole), in benzene (50 ml) was cooled to 4° and oxalyl chloride (2.2 g, 17.2 mmole) slowly added. Stirring was continued for 3 hours at room temperature before the benzene and excess of oxalyl chloride were distilled off under reduced pressure. Further portions of benzene (2 x 50 ml) were added and distilled to ensure the complete removal of oxalyl chloride. The resulting yellow oil was dissolved in ether (50 ml) and slowly poured into a solution of diazomethane (prepared from 5 g of N-nitrosomethylurea) in ether (50 ml). The mixture was kept at room temperature overnight (16 hours) before the ether was removed under reduced pressure and the diazoketone dissolved in chloroform (20 ml). Hydriodic acid (55% in water) was added dropwise to this solution until the evolution of nitrogen ceased. Work-up, as described for compound (20) gave a pale yellow oil which crystallised from ether

as white needles (1.6 g, 81%), m.p. 100-101°. An analytical sample, m.p. 100.5-101°, was recrystallised from benzene-light petroleum (Found: C, 72.7; H, 7.0. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%). ν_{max} 1700 (methyl ketone), 1675 cm^{-1} (aromatic ketone); n.m.r. spectrum: d, 1H, 7.95, C5-H, 9; d of d, 1H, 6.78, C6-H, $J_{5,6}$ 9, $J_{6,8}$ 3; s, 1H, 6.67, C8-H; s, 3H, 3.83, $-OCH_3$; m, 7H, 2.4-3.3, aliphatic H; s, 3H, 2.17, $-COCH_3$.

Attempted Aldol Cyclisation of the Homologous Methyl Ketone (70).

A solution of the methyl ketone (100 mg) in dry ethanol (5 ml) was added to a solution of sodium ethoxide (prepared from 25 mg of sodium) in dry ethanol (5 ml.) under an atmosphere of nitrogen. After 48 hours, water (50 ml) was added and the aqueous solution extracted with chloroform (2 x 30 ml). Work-up in the normal manner gave unchanged methyl ketone (96 mg), m.p. 99-100°.

PART B.

Approaches towards the synthesis of iscGB 13.

3-(Ethan-2'-ol)-1,2,3,4-tetrahydro-1-hydroxy-6-methoxy-naphthalene (75).

The keto-acid (45) (3.0 g, 0.016 mole) was added in small portions to a stirred suspension of lithium aluminium hydride (0.73 g, 0.018 mole) in dry tetrahydrofuran (50 ml) at room temperature in an atmosphere of nitrogen. The mixture was then refluxed, with stirring, for 3 hours before water (0.7 ml), 15% sodium hydroxide solution (0.7 ml) and finally water (2.2 ml) were added dropwise to destroy the excess of lithium aluminium hydride. The granular precipitate was filtered off, washed with tetrahydrofuran, and the combined washings and filtrate dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave 3.1 g (quantitative) of clear oil which slowly crystallised on standing. An analytical sample, recrystallised twice from ethanol-ether, melted at 97-98° (Found: C, 70.3; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%). ν_{max} 3300 cm^{-1} (hydroxyl). The diol was too insoluble for an n.m.r. spectrum to be determined.

3-(Ethan-2'-ol)-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (76).

Activated manganese dioxide[47] (20.0 g) was added to a solution of the diol (75) (2.0 g, 0.009 mole) in pure acetone (120 ml) and the mixture stirred at room temperature for 24 hours in an atmosphere

of nitrogen. The manganese dioxide was filtered off, washed with acetone (3 x 50 ml), and the combined washings and filtrate concentrated under reduced pressure. Crystallisation of the resulting oil from ether gave 1.88 g (94%) of the ketol as white needles, m.p. 100-101° (Found: C, 70.5; H, 7.2. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). ν_{max} 3400 (hydroxyl), 1660 cm^{-1} (aromatic ketone); n.m.r. spectrum: d, 1H, 7.95, C5-H, 8.5; d of d, 1H, 6.75, C6-H, $J_{5,6}$ 8.5, $J_{6,8}$ 2.5; s, 1H, 6.68, C8-H; s, 3H, 3.81, $-O\underline{CH}_3$; t, 2H, 3.73, $-\underline{CH}_2OH$. 6.5.

Tetrahydropyranyl Ether (77).

A solution of the ketol (76) (1.7 g) in dihydropyran (10 ml), and p-toluenesulphonic acid (20 mg) were allowed to stand at room temperature for one hour and then ether (50 ml) was added. The ethereal solution was washed with 10% sodium hydroxide solution (2 x 25 ml) before work-up in the normal manner gave 2.1 g of crude ether which was chromatographed on alumina (70 g). Elution with benzene yielded 1.36 g (58%) of (77) as a clear oil. An analytical sample was distilled at 150° at 0.02 mm (Found: C, 70.6; H, 8.1. $C_{18}H_{24}O_4$ requires C, 71.0; H, 8.0%). ν_{max} (film) 1670 cm^{-1} (aromatic ketone); n.m.r. spectrum: d, 1H, 8.08, C5-H, 8.5; d of d, 1H, 6.90, C6-H, $J_{5,6}$ 8.5, $J_{6,8}$ 2.5; s, 1H, 6.80, C8-H; s, 1H, 4.63, $-O\underline{CH}-O$; s, 3H, 3.90, $-O\underline{CH}_3$; m, 4H, 3.3-4.1, 2 x $-O\underline{CH}_2-$.

Attempted Annelation of the Tetrahydropyranyl Ether (77) with 1-Acetylcyclohexene.

A mixture of the ether (77) (1.0 g, 3.3 mmole), finely powdered sodamide (0.2 g, 3.4 mmole), and dry ether (50 ml) was refluxed in an atmosphere of nitrogen for 6 hours. 1-Acetylcyclohexene (0.45 g, 3.6 mmole) was added and the mixture kept at room temperature for 16 hours and then refluxed for one hour. The mixture was then diluted with water (50 ml), carefully acidified to pH 7, and extracted with chloroform (2 x 30 ml). Work-up in the normal manner gave a pale yellow oil which was chromatographed on alumina (40 g). Elution with benzene yielded only 1-acetylcyclohexene (0.37 g) and unchanged ether (0.65 g).

7,8,9,10,10a,10b,11,12-Octahydro-6(6aH)-Chrysenone (74).

This compound was prepared using the method of Peak and Robinson.[18] Annelation of α-tetralone with 1-acetylcyclohexene, in the presence of sodium amide, gave two isomeric enones A and B.

Isomer A, the major product and the one used in this synthesis, had a m.p. 199-199.5° (lit.[18] m.p. 200-200.5°) (Found: C, 85.9; H, 8.0. $C_{18}H_{20}O$ requires C, 85.7; H, 8.0%). ν_{max} 1660, 1580 cm^{-1} (enone); n.m.r. spectrum m, 1H, 7.53-7.97, C4-H; m, 3H, 6.90-7.47, C1-H, C2-H, C3-H; d, 1H, 6.60, C5-H, 2; ABq, 2H, 2.83, 2.98, $C12-H_2$, 3.

Isomer B, the minor product had a m.p. 152-153° (lit.[18] m.p. 152-153°) (Found: C, 85.9; H, 8.1. $C_{18}H_{20}O$ requires C, 85.7; H, 8.0%).

ν_{max} 1660, 1580 cm^{-1} (enone); n.m.r. spectrum: m, 1H, 7.57-8.03, C4-H; m, 3H, 7.00-7.47, C1-H, C2-H, C3-H; d, 1H, 6.57, C5-H, 2; ABq, 2H, 2.91, 3.08, C12-H_2, 3.

4b-Cyano-4b,5,7,8,9,10,10a,10b,11,12-decahydro-6(6aH)-chrysenone (78).

A solution of hydrogen cyanide (7.3 g, 0.26 mole) in dry tetrahydrofuran (50 ml) was slowly added to a stirred solution of diethylaluminium chloride (37.5 g, 0.31 mole) in dry tetrahydrofuran (100 ml) at 0° in an atmosphere of nitrogen. This solution of hydrogen cyanide-diethylaluminium chloride in tetrahydrofuran was then poured slowly into a stirred suspension of the enone (74) (12.5 g, 0.05 mole) in tetrahydrofuran (150 ml) in a nitrogen atmosphere. After 30 minutes, the enone had all dissolved but the mixture was stirred for a further 65 hours at room temperature. The dark solution was then slowly poured onto a mixture of 50% potassium hydroxide solution (200 ml) and ice (500 g), the precipitate collected, and the filtrate extracted with chloroform (2 x 500 ml). The precipitate was successively washed with water (200 ml), methanol (100 ml), and ether (2 x 100 ml). Work-up of the chloroform extract in the normal manner and crystallisation of the yellow oil from acetone gave more keto-nitrile; total yield 9.6g(69%), m.p. 166-168°. Recrystallisation from ethanol-ether gave white plates m.p. 169.5-170° (Found: C, 81.5; H, 7.4; N, 4.9. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%). ν_{max}

2240 (nitrile), 1710 cm^{-1} (ketone); n.m.r. spectrum: s, 4H, 7.22, aromatic H; ABq, 2H, 2.55, 3.38, C5-H_2, 14; m, 2H, 2.77-3.12, C12-H_2.

4b-Cyano-4b,5,7,8,9,10,10a,11-octahydrochrysen-6,12(6aH,10bH)-dione (79).

The keto-nitrile (78) (3.0 g, 0.011 mole) was added to a solution of chromium trioxide (4.3 g, 0.043 mole) in 95% acetic acid (100 ml) and the mixture stirred for 72 hours at room temperature. Water (500 ml) was added, and the pale yellow precipitate filtered off, dried, and recrystallised from ethanol-chloroform to yield 2.0 g (63%) of diketo-nitrile (79) as white crystals, m.p. 242-245° (Found: C, 77.6; H, 6.6; N, 4.8. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.6; N, 4.8%). ν_{max} 2240 (nitrile), 1720 (aliphatic ketone), 1680 cm^{-1} (aromatic ketone); n.m.r. spectrum: m, 1H, 8.0-8.3, C1-H; m, 3H, 7.3-7.75, C2-H, C3-H, C4-H; ABq, 2H, 2.68, 3.52, C5-H_2, 14.

4b-Cyano-6,6'-ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,11-decahydro-12(10bH)-chrysenone (80).

A mixture of diketo-nitrile (79) (1.4 g, 4.8 mmole), ethylene glycol (0.355 g, 5.7 mmole), and p-toluenesulphonic acid (50 mg) in benzene (60 ml) was heated under reflux in a Dean Stark water separator for 16 hours. Chloroform (10 ml) was added to the cooled solution and the organic layer washed with saturated sodium bicarbonate solution (2 x 30 ml). Work-up in the normal manner and recrystallisation of the

residue from ethanol-chloroform gave white crystals of the acetal (80), m.p. 177-179° (Found: C, 74.0; H, 6.9; N, 3.80. $C_{21}H_{23}NO_3$ requires C, 74.7; H, 6.9; N, 4.1%). ν_{max} 2240 (nitrile), 1680 cm^{-1} (aromatic ketone); n.m.r. spectrum: m, 1H, 7.9-8.17, C1-H; m, 3H, 7.0-7.7, C2-H, C3-H, C4-H; s(b), 4H, 4.08, $-OCH_2CH_2O-$, ABq, 2H, 3.40, 3.72, $C5-H_2$, 14; m, 2H, 2.6-3.0, $C11-H_2$.

Attempted Formylation of Keto-acetal-nitrile (80).

The conditions outlined in Chart 2 for the formylation of (80) were unsuccessful.

Chart 2.

Reaction	Base	Molar Ratio			Solvent	Conditions
		acetal	base	ethyl formate		
1	NaOEt	1	5	5	EtOH	16 hours at 20°
2	NaH	1	5	5	T.H.F.	18 hours at 20°; 1 hour at reflux
3	NaOEt	1	3	3	benzene	16 hours at 20°

Attempted Alkylation of Keto-acetal-nitrile (80) with Ethyl Bromoacetate.

A mixture of keto-acetal-nitrile (80) (100 mg, 0.3 mmole), finely powdered sodamide (44 mg, 0.9 mmole), and dry ether (5 ml) was refluxed in an atmosphere of nitrogen for 5 hours. Ethyl bromo-acetate (150 mg, 0.9 mmole) was added and the mixture refluxed for a

further 4 hours. Work-up of the reaction mixture gave only unchanged keto-acetal-nitrile (93 mg). More forcing conditions using tetrahydrofuran as solvent and longer reaction times also failed.

Hydrolysis of Keto-nitrile (78).

Potassium hydroxide (200 mg) was added to a solution of the keto-nitrile (78) (100 mg) in ethanol (5 ml) and the mixture refluxed for 20 hours. Acidification of the reaction mixture with 10% hydrochloric acid deposited 43 mg of white solid, m.p. 198-200°, identified as the enone (74). Concentration of the filtrate gave 51 mg of the lactamol as white needles, m.p. 231-233°, (Found: C, 75.3; H, 7.5; N, 4.5. $C_{19}H_{23}NO_2$ requires C, 76.7; H, 7.8; N, 4.7%). ν_{max} 3300 (hydroxyl), 3200 (amide N-H), 1680 cm^{-1} (lactam); the lactamol was too insoluble for an n.m.r. spectrum to be determined; mass spectrum: parent ion m/e 297.

7,8,9,10,10a,10b,11,12-Octahydro-2-methoxy-6(6aH)-chrysenone (32).

This compound was prepared by the annelation of 6-methoxytetralone with 1-acetylcyclohexene in the presence of sodium amide according to the method of Rapson and Robinson;[17] m.p. 226-228° (lit.[17] m.p. 228-229°); ν_{max} 1645, 1615 cm^{-1} (enone); n.m.r. spectrum: d, 1H, 7.67, C4-H, 8; d, 1H, 6.73, C3-H, 8; s, 1H, 6.67, C1-H; d, 1H, 6.47, C5-H, 2; s, 3H, 3.80, $-OCH_3$.

4b-Cyano-4b,5,7,8,9,10,10a,10b,11,12-decahydro-2-methoxy-6(6aH)-chrysenone (33).

A solution of hydrogen cyanide (22.8 g, 0.84 mole) in dry tetrahydrofuran (40 ml) was slowly added to a stirred solution of diethylaluminium chloride (106.8 g, 0.88 mole) in dry tetrahydrofuran (80 ml) at 0° in an atmosphere of nitrogen. This solution was then slowly poured into a stirred suspension of the enone (32) (91.0 g, 0.32 mole) in dry tetrahydrofuran (1.4 l) in a nitrogen atmosphere. Stirring was continued for 5 days at room temperature and then the darkly coloured solution was poured cautiously, with vigorous stirring, into ice-water (1.2 kg) containing sodium hydroxide (120 g). The yellow precipitate was collected and successively washed with water (500 ml), 3N hydrochloric acid (500 ml), water (6 x 500 ml), methanol (200 ml), and ether (3 x 200 ml). The crystalline keto-nitrile (87.5 g, 89%), m.p. 189-191°, did not require further purification. An analytical sample was recrystallised from acetone as shiny white platelets, m.p. 192-193° (Found: C, 77.4; H, 7.5; N, 4.4. $C_{20}H_{23}NO_2$ requires C, 77.6; H, 7.5; N, 4.5%). λ_{max} 214, 233, 279, 286 nm, ε 9100, 8500, 1900, 1900; ν_{max} 2220 (nitrile), 1700 cm^{-1} (ketone); n.m.r. spectrum: d, 1H, 7.27, C4-H, 8; d, 1H, 6.73, C3-H, 8; s, 1H, 6.7, C1-H; s, 3H, 3.82, $-OCH_3$; ABq, 2H, 3.42, 2.58, C5-H_2, 14.

4b,5,6,6a,7,8,9,10,10a,10b,11,12-Dodecahydro-6-hydroxy-4b-iminocarboxy-2-methoxychrysene-4b,6-lactone (81).

Sodium borohydride (6.7 g, 0.18 mole) was slowly added to a stirred suspension of the keto-nitrile (33) (20 g, 0.065 mole) in absolute ethanol (1.2 l). After the mixture had been stirred at room temperature overnight (16 hours), water (3 l) was added and the solution extracted with chloroform (3 x 200 ml). Work-up in the normal manner gave a pale yellow oily residue which crystallised from ether to yield 18.1 g (90%) of the iminolactone (81). An analytical sample, m.p. 167.5-168°, was recrystallised from acetone-light petroleum (Found: C, 77.4; H, 8.4; N, 4.8. $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%). λ_{max} 211, 228, 279, 286 nm, ε 13900, 9800, 1500, 1500; ν_{max} 3230 (imino NH), 1665 cm^{-1} (imine); n.m.r. spectrum: d, 1H, 7.1, C4-H, 8; d, 1H, 6.72, C3-H, 8; s, 1H, 6.63, C1-H; s, 1H, 6.43, >C=NH; d, 1H, 4.37, C6-H, 6; s, 3H, 3.75, $-OCH_3$.

4b-Carboxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-6-hydroxy-2-methoxychrysene-4b,6-lactone (82).

A solution of the iminolactone (81) (18.1 g) in tetrahydrofuran (1.2 l) and 10% hydrochloric acid (600 ml) was heated under reflux for 48 hours. Water (2 l) was added and then most of the tetrahydrofuran distilled off at atmospheric pressure. After it had been stored at 0° overnight, the mixture was filtered and the white precipitate washed well with water. Recrystallisation from acetone

gave 14.1 g (78%) of the lactone (82) as white needles, m.p. 188-190°. An analytical sample melted at 189.5-190° (Found: C, 76.8; H, 7.7. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%). λ_{max} 209, 231, 280, 287 nm, ε 13200, 7800, 1500, 1500; ν_{max} 1765 cm^{-1} (lactone); n.m.r. spectrum: d, 1H, 7.07, C4-H, 8; d of d, 1H, 6.73, C3-H, $J_{3,4}$ 8, $J_{1,3}$ 3; d, 1H, 4.48, C6-H, 6; s, 3H, 3.75, $-O\underline{CH_3}$; d of d, 1H, 3.03, C5-H, J_{gem} 12, $J_{5,6}$ 6; d, 1H, 1.93, C5-H, 12.

12-Bromo-4b-carboxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-6-hydroxy-2-methoxychrysene-4b,6-lactone (83).

A mixture of the lactone (82) (14.8 g, 0.047 mole), N-bromosuccinimide (9.4 g, 0.053 mole), and dibenzoyl peroxide (50 mg) in dry carbon tetrachloride (300 ml) was heated under reflux for one hour and then cooled. The succinimide was filtered off, washed with more carbon tetrachloride (20ml), and the combined filtrates concentrated under reduced pressure. Crystallisation of the pale yellow oil from ether yielded the bromolactone (18.0 g, quantitative) as a white solid m.p. 168-172°. Recrystallisation from acetone gave an analytical sample as white plates, m.p. 169-172° (Found: C, 61.1; H, 5.8; Br, 20.5. $C_{20}H_{23}O_3Br$ requires C, 61.4; H, 5.9; Br, 20.4%). λ_{max} 215, 280, 288 nm, ε 13800, 1400, 1400; ν_{max} 1760 cm^{-1} (lactone); n.m.r. spectrum: m, 3H, 6.67-7.22, aromatic H; t, 1H, 5.57, C12-H, 2; d, 1H, 4.53, C6-H, 6; s, 3H, 3.77, $-O\underline{CH_3}$; d of d, 1H, 3.05, C5-H, $J_{5,6}$ 6, J_{gem} 11; d, 1H, 2.08, C5-H, 11.

4b-Carboxy-4b,5,6,6a,7,8,9,10,10a,10b-decahydro-6-hydroxy-2-methoxychrysene-4b,6-lactone (84).

A mixture of the bromolactone (83) (18.0 g, 0.046 mole) and dry powdered calcium carbonate (45 g, 0.45 mole) in dry dimethylformamide (500 ml) was heated under reflux for 4 hours. The calcium carbonate was then filtered off, washed well with dimethylformamide (2 x 100 ml), and the combined washings and filtrate poured into cold water (4 l). The pale pink precipitate was filtered off, washed well with water, and recrystallised from acetone. The olefinic lactone (84) (13.6 g, 95%) was obtained as colourless prisms, m.p. 169-172°. An analytical sample melted at 174-175° (Found: C, 77.6; H, 7.1. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%). λ_{max} 228, 270, 303 nm, ε 27000, 4700, 1800; ν_{max} 1760 (lactone) 1630 cm^{-1} (olefin); n.m.r. spectrum: d, 1H, 7.08. C4-H, 9; m, 2H, 6.53-6.80, C1-H, C3-H; d of d, 1H, 6.50, C11-H, $J_{11,12}$ 10, $J_{10b,11}$ 3; d of d, 1H, 5.75, C12-H, $J_{11,12}$ 10, $J_{10b,12}$ 1.5; d, 1H, 4.45, C6-H, 6; s, 3H, 3.78, $-OCH_3$; d of d, 1H, 3.17, C5-H, J_{gem} 12, $J_{5,6}$ 6; d, 1H, 1.87, C5-H, 12.

Attempted Insertion of Ethyl Diazo-acetate into the Olefinic Lactone (84).

A solution of the olefinic lactone (84) (200 mg, 0.64 mmole) in dry tetrahydrofuran (2 ml) was diluted with dry cyclohexane (5 ml). Copper powder (1.0 g) was added and the mixture heated to reflux. A solution of ethyl diazo-acetate (333 mg, 1.46 mmole) in cyclohexane

(10 ml) was slowly added to this mixture over a period of 5 hours and then it was refluxed for a further 18 hours. The mixture was then cooled, filtered, and concentrated under reduced pressure to yield a clear oil which was chromatographed on silica gel (15 g). Elution with 5-10% ether-light petroleum gave a mixture of ethyl fumarate and ethyl maleate and further elution with 20% ether-light petroleum yielded 188 mg of white solid, m.p. 168-172° which was identified as unchanged olefinic lactone (84) by infrared and n.m.r. spectroscopy.

4b-Cyano-6,6'-ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-2-methoxychrysene (88).

A mixture of keto-nitrile (33) (2.0 g, 6.5 mmole), ethylene glycol (1.6 g, 25.8 mmole), and p-toluenesulphonic acid (50 mg) in benzene (60 ml) was heated under reflux for 16 hours in a Dean Stark water separator. After it had been cooled, the benzene solution was washed with saturated sodium bicarbonate solution (100 ml), and work-up in the normal manner gave a clear oil, which crystallised from ether to yield 2.2 g (96%) of the acetalnitrile (88) as a white solid, m.p. 176-178°. Recrystallisation from ether gave shiny plates, m.p. 178-179° (Found: C, 74.5; H, 7.7; N, 4.1. $C_{22}H_{27}NO_3$ requires C, 74.7; H, 7.7; N, 4.0%). λ_{max} 210, 231, 278, 285 nm, ε 13700, 9400, 1400, 1400; ν_{max} 2220 cm^{-1} (nitrile); n.m.r. spectrum: d, 1H, 7.17, C4-H, 8; d, 1H, 6.70, C3-H, 8; s, 1H, 6.60, C1-H, s(b), 4H, 4.07, $-OCH_2CH_2O-$; s, 3H, 3.73, $-OCH_3$; ABq, 2H, 1.57, 2.80, C5-H_2, 14.

6,6'-Ethylenedioxy-4b-formyl-4b,5,6,8a,7,8,9,10,10a,10b,11,12-dodecahydro-2-methoxychrysene (90).

A solution of the acetal-nitrile (88) (5.27 g, 0.015 mole) in dry tetrahydrofuran (100 ml) was added dropwise over a period of 15 minutes to a stirred suspension of lithium aluminium hydride (1.12 g, 0.03 mole) in dry tetrahydrofuran (100 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 2 hours and then water (1.2 ml), 10% sodium hydroxide solution (1.4 ml), and water (3.6 ml) were added dropwise to destroy the excess of lithium aluminium hydride. The granular precipitate was filtered off, washed with tetrahydrofuran (2 x 50 ml) and the combined washings and filtrate dried over anhydrous magnesium sulphate. Distillation of the solvent under reduced pressure gave 5.4 g (quantitative) of the acetal-imine (89) as a clear oil, ν_{max} (film), 3300 (imine NH), 1650 cm^{-1} (imine).

A solution of the crude imine (5.2 g, 0.015 mole) in tetrahydrofuran (200 ml) was refluxed for 5 minutes with a solution of acetic acid (30 g, 0.5 mole) and sodium acetate (10 g, 0.12 mole) in water (80 ml). The cooled reaction mixture was diluted with water (500 ml), extracted with chloroform (3 x 150 ml) and work-up in the normal manner gave a clear oil, which crystallised on the addition of acetone-hexane as white needles of the acetalaldehyde (90), m.p. 169.5-170.5° (Found: C, 74.0; H, 8.0. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%). λ_{max} 213, 242, 279, 286 nm, ε 14600, 7000, 2000, 1900;

ν_{max} 2680 (aldehyde C-H) 1720 cm^{-1} (aldehyde); n.m.r. spectrum: d, 1H, 9.43, -CHO, 2; d, 1H, 7.23, C4-H, 8; d, 1H, 6.73, C3-H, 8; s, 1H, 6.67, C1-H; s, 4H, 3.77, $-OCH_2CH_2O-$; s, 3H, 3.73, $-OCH_3$.

Attempted Oxidation of the Acetalaldehyde (90).

A solution of sodium hydroxide (90 mg) in water (1 ml) and ethanol (10 ml) was added over a period of 10 minutes to a stirred solution of the acetalaldehyde (90) (100 mg, 0.28 mmole) and silver nitrate (100 mg, 0.59 mmole) in ethanol (20 ml) at room temperature under an atmosphere of nitrogen. After 64 hours, the silver oxide was filtered off and washed well with ethanol. The filtrate and washings were combined, concentrated under reduced pressure, and water (50 ml) added. The aqueous solution was cooled to 0° and carefully acidified with dilute hydrochloric acid. The white precipitate (93 mg) was collected but was found to be identical in all respects to the acetal-aldehyde (90).

Hydrolysis of the Acetalaldehyde (90).

1) A solution of the acetalaldehyde (100 mg) and p-toluene-sulphonic acid (5 mg) in acetone (30 ml) was heated under reflux for 4 hours. Water (50 ml) was added and the aqueous solution extracted with chloroform (2 x 30 ml). Work-up in the normal manner gave a residue which crystallised from ether to give 95 mg of the keto-acetal (91). White needles, m.p. 205-207°, were obtained when the sample was recrystallised from chloroform-acetone. (Satisfactory

analytical figures could not be obtained because of a small amount of ketol (92) present). ν_{max} 1700 cm^{-1} (ketone); mass spectrum: parent ion m/e 356; $(M-C_3H_5O_2)$ ion 283.

2) A solution of the acetalaldehyde (3.1 g) in tetrahydrofuran (100 ml) was heated under reflux with 10% hydrochloric acid (50 ml) for 2 hours. After the cooled solution had been diluted with water (500 ml), it was extracted with chloroform (3 x 50 ml) and the chloroform extracts washed with saturated sodium bicarbonate solution (50 ml). Work-up in the normal manner yielded 3.1 g of the ketol (92) as a crude oil which crystallised, after prolonged scratching, as a white solid, m.p. 86-90°; ν_{max} 3350 (hydroxyl), 1720 cm^{-1} (ketone). The ketol was characterised as its acetate, m.p. 157.5-159° (Found: C, 74.7; H, 7.3. $C_{22}H_{26}O_4$ requires C, 74.6; H, 7.4%). λ_{max} 209, 228, 280, 286 nm, ε 11900, 8500, 1600, 1600; ν_{max} 1735 (acetate), 1720 cm^{-1} (ketone); n.m.r. spectrum: d, 1H, 7.23, C4-H, 8; d, 1H, 6.72, C3-H, 8; s, 1H, 6.63, C1-H; s, 1H, 5.22, $>\underline{CH}-OCOCH_3$; s, 3H, 3.77, $-O\underline{CH}_3$; s, 3H, 1.88, $-OCO\underline{CH}_3$.

Hydrolysis of Keto-acetal (91).

Treatment of the keto-acetal (91) with dilute hydrochloric acid in tetrahydrofuran as in the previous experiment, part 2), gave the same ketol (92) as the acetalaldehyde (90).

4b-Carboxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-6,6'-dihydroxy-2-methoxychrysene-4b,6-lactone (95).

The lactone (82) (2.2 g, 0.007 mole) was dissolved in ethanol (50 ml.) containing 10% aqueous sodium hydroxide solution (4.3 ml, 0.014 mole) by warming on a steam-bath. Heating was continued for a further hour to evaporate most of the ethanol, and after the addition of water (50 ml), the aqueous solution was extracted with chloroform (50 ml) to remove any neutral material. The alkaline solution was cooled to 5°, chloroform (50 ml) added, and the stirred mixture carefully acidified to pH2 by the dropwise addition of 5% hydrochloric acid. After separation from the chloroform layer, the aqueous solution was extracted with more chloroform (2 x 50 ml) and work-up of the combined chloroform extracts in the normal manner gave 2.1 g of the hydroxy acid (93) as a white solid; ν_{max} 3200 (hydroxyl), 1660 cm^{-1} (acid). The hydroxy acid was dissolved in acetone (50 ml) and Jones reagent added dropwise until an orange colour persisted. After dilution with water (200 ml), the white precipitate was filtered off, washed well with water, and recrystallised from acetone to yield 1.8 g (78%) of the lactol (95) as white plates, m.p. 202-204°. An analytical sample melted at 203-205° (Found: C, 73.1; H, 7.3. $C_{20}H_{24}O_4$ requires C, 73.1; H, 7.4%). λ_{max} 209, 226, 280, 287 nm, ε 13500, 7900, 1900, 1900; ν_{max} 3330 (hydroxyl), 1740 cm^{-1} (lactone). The lactol was too insoluble for an n.m.r. spectrum to be determined.

4b,5,7,8,9,10,10a,10b-Octahydro-2-methoxy-4b-methoxycarbonyl-6(6aH)-chrysenone (98).

A solution of the olefinic lactone (84) (13.6 g, 0.049 mole) in ethanol (100 ml) was treated with 10% aqueous potassium hydroxide solution (37 ml, 0.066 mole) and the mixture heated on a steam-bath for one hour to evaporate most of the ethanol. Work-up, as described for compound (93), gave 14.3 g of the hydroxy acid (96); ν_{max} 3500 (hydroxyl), 1680 cm^{-1} (acid).

A solution of the hydroxy acid in chloroform (200 ml) was slowly added to an excess of diazomethane (prepared from 18.0 g of N-nitrosomethylurea) in ether (200 ml) to give 14.8 g of the hydroxy ester (97) as a clear oil; ν_{max} (film) 3430 (hydroxyl), 1720 (ester), 1625 cm^{-1} (olefin).

A solution of the hydroxy ester in acetone (150 ml) was treated with Jones reagent until the orange colour persisted (12.4 ml). The mixture was then diluted with water (400 ml), and extracted with chloroform (2 x 100 ml). Work-up in the normal manner gave a yellow oil, some of which crystallised on the addition of ether. The keto-ester (98) (2.5 g), m.p. 135-140°, was collected and the filtrate concentrated to 10.0 g of an oily crystalline mixture. An analytical sample of the keto-ester, m.p. 149-152°, was recrystallised from benzene-light petroleum (Found: C, 74.1; H, 7.0. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%). λ_{max} 227, 267, 304 nm, ε 20000, 5200, 2200; ν_{max} 1720

(ester), 1705 (ketone), 1630 cm^{-1} (olefin); n.m.r. spectrum: d, 1H, 7.23, C4-H, 8; d of d, 1H, 6.78, C3-H, $J_{3,4}$ 8, $J_{1,3}$ 2; s, 1H, 6.67, C1-H; d of d, 1H, 6.55, C11-H, $J_{11,12}$ 10, $J_{10b,11}$ 3; d of d, 1H, 6.42, C12-H, $J_{11,12}$ 10, $J_{10b,12}$ 2; s, 3H, 3.80, $-OCH_3$; s, 3H, 3.47, $-COOCH_3$; ABq, 2H, 2.68-3.22, C5-H_2, 14.

6,6'-Ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,10b-decahydro-2-methoxy-4b-methoxycarbonylchrysene (99).

1) Crystalline keto-ester (98) (2.4 g, 6.2 mmoles) from the previous experiment, p-toluenesulphonic acid (100 mg), ethylene glycol (1.83 g, 30 mmoles), and benzene (100 ml) were heated together under reflux in a Dean Stark water separator for 16 hours. The addition of sodium bicarbonate solution and work-up in the normal manner afforded the acetal-ester (99) which crystallised from ether as colourless cubes (2.6 g, 93%), m.p. 187-189°. Recrystallisation from benzene gave an analytical sample, m.p. 189.5-190° (Found: C, 71.7; H, 7.3. $C_{23}H_{28}O_5$ requires C, 71.8; H, 7.3%). λ_{max} 236, 272 nm, ε 20800, 3500; ν_{max} 1720 (ester), 1630 cm^{-1} (olefin); n.m.r. spectrum: d, 1H, 7.23, C4-H, 8; m, 2H, 6.37-6.87, C1-H, C3-H; s, 2H, 6.30, C11-H, C12-H; s(b), 4H, 3.88, $-OCH_2CH_2O-$; s, 3H, 3.77, $-OCH_3$; s, 3H, 3.48, $-COOCH_3$; ABq, 2H, 1.72, 3.02, C5-H_2, 14.

2) Crude oily keto-ester (10.0 g) from the previous experiment, ethylene glycol (7.3 g), p-toluenesulphonic acid (200 mg), and benzene

(300 ml) were heated under reflux in a Dean Stark water separator for 16 hours. The addition of saturated sodium bicarbonate solution and work-up in the normal manner gave a pale orange oil. Acetal-ester (99) (1.2 g) crystallised on the addition of ether and the remaining 9.8 g of oil was chromatographed on alumina (250 g). Elution with benzene afforded a further 5.1 g of acetal-ester. Further elution with 5% ethyl acetate-benzene gave two products; the minor product (0.12 g) was not characterised but the major product (1.2 g) was identified as the enone (100), m.p. 220-223° (Found: C, 69.2; H, 6.4. $C_{23}H_{26}O_6$ requires C, 69.3; H, 6.6%). ν_{max} 1725 (ester) 1655, 1630 cm^{-1} (enone); n.m.r. spectrum: d, 1H, 7.75, C4-H, 8.5; d, 1H, 7.63, C1-H, 3; m, 1H, 6.93-7.53, C3-H; d, 1H, 6.5, C11-H, 1.5; s(b), 4H, 4.05, $-O\underline{CH_2CH_2}O-$; s, 3H, 3.87, $-O\underline{CH_3}$; s, 3H, 3.63, $-COO\underline{CH_3}$; ABq, 2H, 1.57, 3.27, C5-H_2, 14; mass spectrum: parent ion m/e 398.

4b-Carboxy-6,6'-ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,10b-decahydro-2-methoxychrysene (85).

The acetal ester (99) (4.0 g, 0.01 mole) and potassium hydroxide (4.7 g, 0.084 mole) in ethylene glycol (100 ml) were heated at 180° for 4 hours. After the addition of water (600 ml) to the cooled mixture, it was extracted with chloroform (2 x 50 ml) to remove any neutral material. The alkaline solution was then cooled to 5°, chloroform (200 ml) added, and the mixture carefully acidified to pH4, with stirring, by the dropwise addition of 5% hydrochloric acid.

After separation from the chloroform layer, the aqueous solution was extracted with more chloroform (2 x 100 ml) and work-up of the combined chloroform extracts in the normal manner gave a residue which crystallised from ether as the acetal-acid (85) (3.3 g, 86%), m.p. 220-222°, (a small amount of lactol, formed by hydrolysis of the acetal group, could not be separated from the acetal-acid and the C analysis was always too low); ν_{max} 2620 (acid OH) 1690 cm^{-1} (acid); n.m.r. spectrum (d6 DMSO) s(b), 1H, ~10, -COOH; d, 1H, 7.55, C4-H, 8; m, 3H, 6.5-6.9, C1-H, C3-H, C12-H; s(b), 1H, 5.8, C11-H; m, 4H, 3.8-4.2, $-OCH_2CH_2O-$; s, 3H, 3.73, $-OCH_3$; ABq, 2H, 1.4, 3.17, $C5-H_2$, 14; mass spectrum: parent ion m/e 370.

Attempted Preparation of Olefinic Diazoketone (34).

The acetal acid (85) (410 mg, 1.1 mmole) was dissolved in a minimum of ethanol and the solution diluted with water (5 ml). Anhydrous sodium carbonate (60 mg, 0.56 mmole) was added and the mixture warmed until the evolution of carbon dioxide ceased. The solvent was removed under reduced pressure and the sodium salt dried at 40° at 0.05 mm for 16 hours. The dry salt was covered with benzene (10 ml) containing pyridine (0.1 ml), the mixture cooled until the benzene just started to freeze, and then oxalyl chloride (210 mg, 1.6 mmole) added. The reaction mixture was stirred for one hour at 0° and then for 3 hours at room temperature, before it was filtered and the solvent removed under reduced pressure. Further benzene was added to

codistill the excess of oxalyl chloride. An inspection of the infrared spectrum of the pale yellow oil (456 mg) revealed the presence of unreacted acid (1690 cm^{-1}), possibly the acid chloride (1780 cm^{-1}) and impurities (1640, 1670 cm^{-1}). The mixture was re-dissolved in benzene (20 ml) and poured into an excess of diazomethane (prepared from 1 g of N-nitrosomethylurea) in ether (30 ml). After 16 hours an aliquot was removed from the reaction mixture and the infrared spectrum of this showed the presence of some diazoketone (bands at 2100 and 1630 cm^{-1}) and other bands at 1700, 1740, and 1760 cm^{-1}. No further reaction had occurred at 96 hours and the mixture was chromatographed on alumina (20 g) and the impure diazoketone (20 mg) eluted with benzene. An inspection of the infrared spectrum showed bands at 2100 (diazo), 1720 (ester), and 1630 cm^{-1} (ketone); the n.m.r. spectrum showed the diazoketone hydrogen at $\delta 5.4$ and the acetal group as a multiplet at 3.8-4.3.

4b-Acetyl-6,6'-ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-2-methoxychrysene (104).

A solution of the acetalaldehyde (90) (2.2 g, 6.2 mmole) in dry tetrahydrofuran (10 ml) was slowly added to a solution of methylmagnesium iodide (prepared from 6.0 g of methyliodide and 0.82 g of magnesium) in ether (30 ml) under an atmosphere of nitrogen. The mixture was stirred overnight at room temperature and then hydrolysed by the addition of saturated ammonium chloride solution (3 ml).

Anhydrous sodium sulphate was also added and, after 30 minutes, the solid was filtered off, washed well with ether-tetrahydrofuran (3:1, 2 x 50 ml) and the filtrate concentrated. The pale yellow oil (2.1 g) was dissolved in acetone (30 ml) and treated with a slight excess of Jones reagent at 0°. The mixture was then diluted with water (150 ml), extracted with chloroform (2 x 50 ml), and work-up in the normal manner gave 1.8 g of a clear oil. Chromatography on alumina (40 g) and elution with 5% ethylacetate-benzene afforded the methyl ketone (1.2 g, 52%) as white plates, m.p. 162-165°. Recrystallisation from benzene-light petroleum gave an analytical sample, m.p. 163-165° (Found: C, 74.6; H, 8.5. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%). ν_{max} 1690 cm^{-1} (methyl ketone); n.m.r. spectrum: d, 1H, 7.27, C4-H, 8; d of d, 1H, 6.73, C3-H, $J_{3,4}$ 8, $J_{1,3}$ 2; s, 1H, 6.67, C1-H; s, 4H, 3.97, $-OCH_2CH_2O-$; s, 3H, 3.77, $-OCH_3$; s, 3H, 1.87, $-COCH_3$.

4b-Diazoacetyl-6,6'-ethylenedioxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-2-methoxychrysene (106).

A mixture of the methyl ketone (104) (280 mg, 0.76 mmole) in dry tetrahydrofuran (20 ml), ethyl formate (560 mg, 7.6 mmole), and sodium hydride (182 mg, 7.6 mmole) was stirred for 16 hours at room temperature in an atmosphere of nitrogen. The resulting red solution was then heated under reflux for 2 hours, cooled, and carefully acidified with oxalic acid solution. The yellow solution was extracted with chloroform (2 x 30 ml) and work-up in the normal manner yielded

the α-keto-aldehyde (105) (287 mg) as a pale yellow oil which gave a positive enol test with ferric chloride solution; ν_{max} (film) 1720 (aldehyde), 1690 (ketone), 1630 cm^{-1} (enol).

A solution of the crude keto-aldehyde (280 mg, 0.7 mmole) in dry tetrahydrofuran (10 ml) was stirred with sodium hydride (73 mg, 3.0 mmole) for 2 hours at room temperature in an atmosphere of nitrogen. Tosyl azide (600 mg, 3.0 mmole) was added and the mixture stirred overnight (16 hours). After dilution with water (50 ml), the solution was extracted with chloroform (2 x 30 ml) and work-up in the normal manner gave a pale yellow oil which was chromatographed on alumina (30 g). Elution with benzene afforded a clear oil (105 mg) which crystallised on the addition of ether. The diazoketone (106) melted at 150-155° with decomposition (Found: C, 70.0; H, 7.4; N, 6.8. $C_{23}H_{28}N_2O_4$ requires C, 69.7; H, 7.1; N, 7.1%). ν_{max} 2100 (diazo) 1620 cm^{-1} (ketone); n.m.r. spectrum: d, 1H, 7.2, C4-H, 8; d of d, 1H, 6.73, C3-H, $J_{3,4}$ 8, $J_{1,3}$ 2; s, 1H, 6.67, C1-H; s, 1H, 5.0, $-COCHN_2$; s(b), 4H, 4.0, $-OCH_2CH_2O-$; s, 3H, 3.8, $-OCH_3$; ABq, 2H, 1.75, 2.75, C5-H_2, 14; mass spectrum: parent ion m/e 396; $(M-N_2)$ m/e 368.

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