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CYCLOHEXADIENONES AS INTERMEDIATES IN GIBBERELLIN SYNTHESIS

A THESIS

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by

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CONTENTS

SUMMARY

This thesis investigates the preparation of tricyclic compounds containing a cyclohexa-2,4- or a 2,5-dienone moiety, that should be suitable for elaboration to the gibberellins.

In Chapter 1, the syntheses of the cyclohexa-2,4-dienone ketones 6 and 49 are described. They are the first reported examples of dienone ketones formed by intramolecular ortho-alkylation of protonated diazoketones. Exploratory experiments on dienone ketone 6, which confirm its potential for conversion to tetracyclic diterpenes, are also described.

In Chapters 2,3 and 4 the acid catalysed cyclization of a number of more highly substituted diazoketones is examined. The synthetic potential of the dienone ketones formed in these reactions, especially dienone ketone 123, is discussed.

Chapter 5 describes an attempt to prepare a dienone ketone which possesses a gibberellin-like A-ring.

In Chapter 6, from the results presented in Chapters 1-4, the possible mechanism, the scope and the limitations of the diazoketone cyclization reaction are summarized.

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.

D.W.JOHNSON

ACKNOWLEDGEMENTS

It is with sincere appreciation that I would like to thank Dr. L.N.Mander for his guidance and inspiration during the supervision of this work.

I am particularly grateful to Professor A.J.Birch for his assistance in allowing me to complete the last six months of my degree in the Research School of Chemistry at the Australian National University, Canberra.

I would like to thank also my colleagues for their help; and my parents for their continued interest and encouragement.

This work was carried out during the tenure of a Commonwealth Postgraduate Research Award, for which I am grateful.

INTRODUCTION

Gibberellins are an important class of plant growth regulators[1] which, during the past twenty years, have found considerable practical use in agriculture,[2,3] as modifiers of normal plant development, to improve the quality or quantity of fruit and to alter harvest times. The first members of the class were isolated in 1938 by Yabuta and Sumiki[4] from the fungus Gibberella fujikuroi and to date forty-five have been identified[5] in various plants and fungi.[6] Gibberellic acid (gibberellin A_3) 1[7,8] is commerically available as are gibberellins A_4 and A_7 and a mixture of these two, "Pro-Gibb 47". The functions of these plant hormones are so varied in character, and so interrelated with those of other growth regulators, it is impossible to suggest that their behaviour derives from a single reaction within the plant cell.

Many of the responses initiated by the exogenous application of gibberellic acid may be explained by an increased production of α-amylase which causes rapid release of sugars in the plant.[9-13] The change from dormancy to active growth in plants is associated with a mobilization of starch reserves and their transformation into sugars. It runs parallel to an increase of endogenous gibberellins and indeed dormancy may be artificially broken by providing gibberellins of exogenous origin.

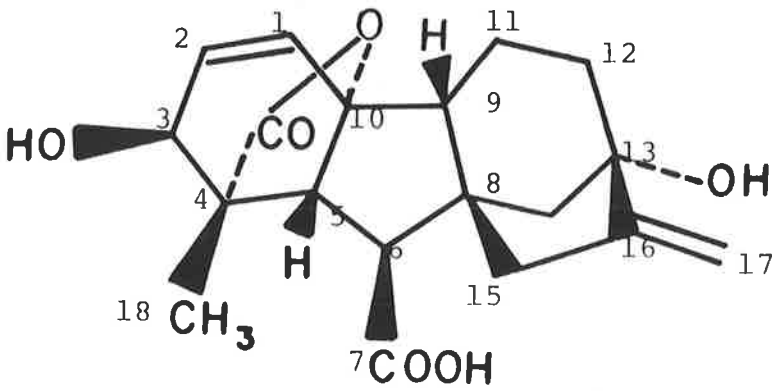
There is considerable evidence that gibberellins mediate the action of auxins in plants for the visible response of a plant to gibberellins is often the same as its response to auxins. It has been shown,[14] for example, that

gibberellic acid antagonises the production of indolacetic acid oxidases which, in turn, prevent the destruction of the auxin, indolylacetic acid. The well known effect of gibberellic acid increasing the internodal distances of bean stalks can also be accomplished with auxins.

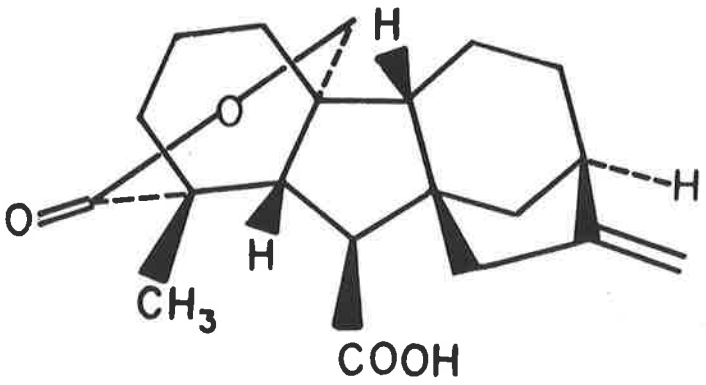
Yet another function of the gibberellins is their ability to alter the osmotic concentration of cells in the growing regions of plants through an increase in hydrolytic and proteolytic enzymes[15]. Tissues with a high gibberellin gradient attract water and nutrients selectively, and it is those fruits which contain greater quantities of gibberellins that can compete successfully for the water and solutes entering the tree or plant. Fruits which contain an insufficient number of seeds, in which the gibberellins are concentrated, will be poorly developed.

Gibberellic acid increases the height of plants and the size of leaves, especially in vegetables, when applied to seedlings. The set of fruit and its yield can be improved by spraying at full bloom (e.g. pears[16]). Gibberellic acid can also be applied to offset damage to blossom caused by frost or for the development of seedless fruits such as grapes[17] (e.g. an application of 16-48 g/acre). At later stages of fruit development it prevents the fall of fruit such as apples and it delays senescence of the skin of citrus fruits and bananas thereby extending their marketable period.[18]

Despite the considerable knowledge of their function in plants, and their many applications, the precise mode of action of gibberellins in the plant cell, in relation to


HO
CO
O
H
OH
H
CH_3
^{7}COOH
1
2
3
4
5
6
7
8
9
10
11
12
13
15
16
17
18

1


O
H
O
H
H
CH_3
COOH

2

structure, is not known. Thus, it would be useful to have a synthetic source of the gibberellins and their analogues for the investigation of their structure - activity relationships.

A number of the simpler gibberellins have been synthesised but by protracted and inefficient routes. The preparation of gibberellin A_{15}[19] 2 required thirty-nine steps, from an elaborate substrate, with an overall yield of 0.006%. The syntheses of gibberellins A_2, A_4, A_9, and A_{10}[20] relied on four relay compounds which were linked to these gibberellins by procedures which were as low as 5% efficient. Additionally, the synthetic relay compounds were not resolved.

Before attempting to design a synthesis of a molecule as complex as gibberellic acid 1 it was considered relevant to analyse critically previous approaches. The number of partial syntheses and specific ring constructions make it convenient to divide this analysis into three sections. Each section is meant to summarize the basic approaches and to outline the desirable features of the construction of a particular ring.

1. Elaboration of the A-ring

The lability of the trans-fused γ-lactone and the allylic alcohol of the A-ring of gibberellic acid 1 preclude their introduction until late in any sequence. This has led to two distinct approaches to the construction of the A-ring. In the first approach the A-ring originates as an aromatic[20-25] or alicyclic[19] precursor ring, with functional groups at the future C3 and C4 positions, which are elaborated at the very end of the synthesis. Where these conversions have been

demonstrated, however, they are characterised by the notable ommission of the Δ^1 olefinic bond.

The second approach which has been pioneered by Dolby[26,27] (see Scheme 1.) and by Corey[28,29] (see Scheme 2.) involves the addition of the A-ring to a completed B-ring or a BCD-ring system. All of the necessary functional groups may be incorporated by this method.

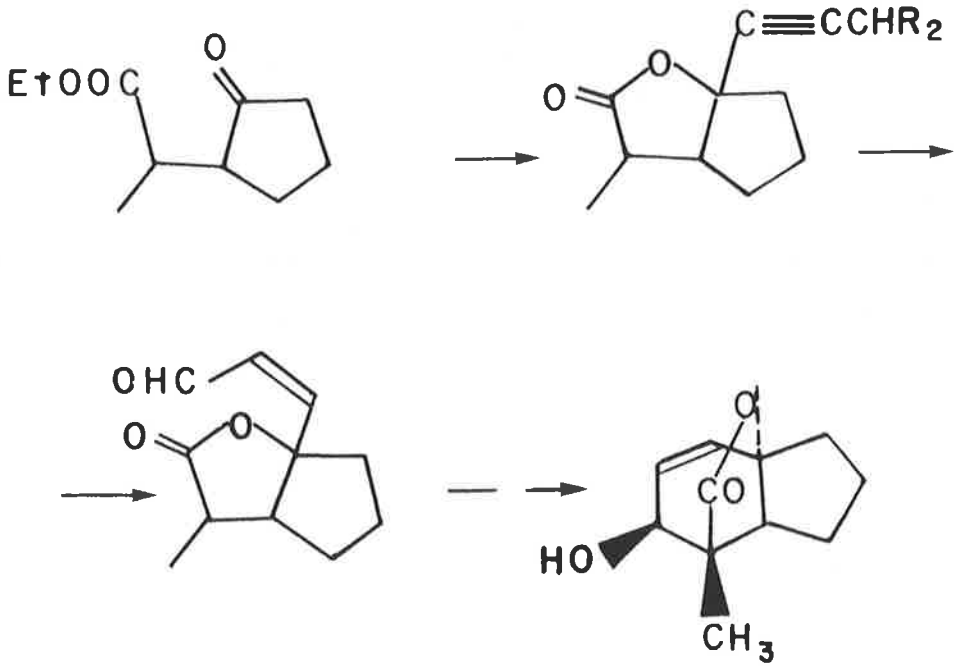
2. Elaboration of the BC-ring system

A common approach to the construction of the BC-ring system has been to generate the basic indane skeleton, as for example in the tricyclic compounds X and Z, and to elaborate the carboxylic acid group at the future C7 position, to give compounds of generalized structure Y[22,23,30]. The carboxylic acid group has also been introduced simultaneously with the B-ring construction[20].

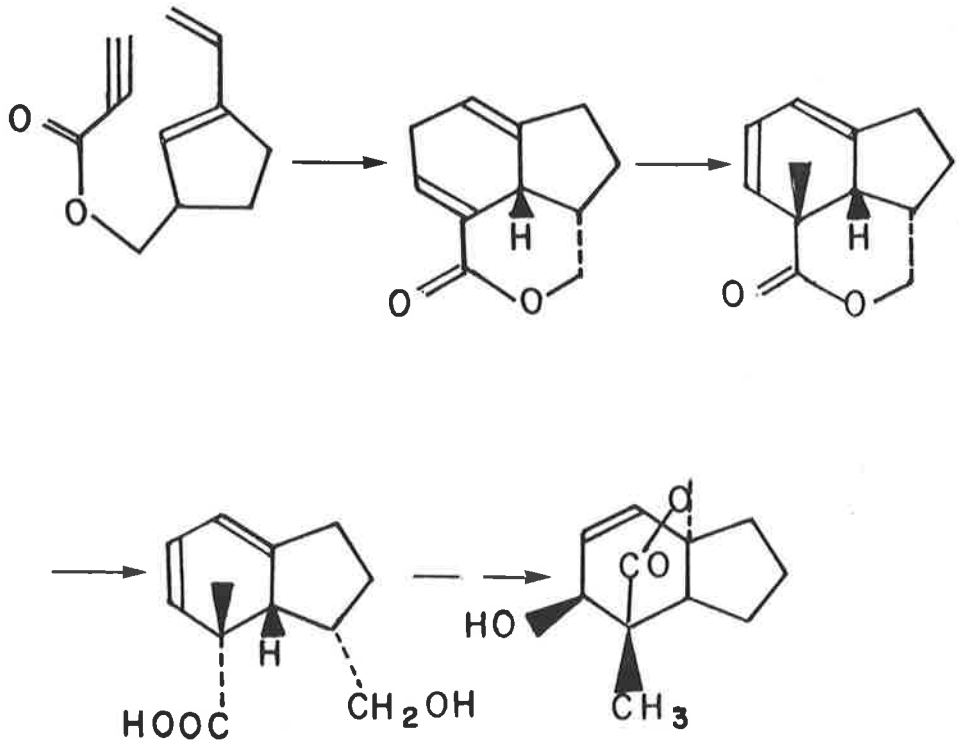
An important variation has been the use of a perhydronaphthalene BC-ring precursor in which the correct stereochemistry of the ring junctions should be easily obtained. For instance Nagata[19] has demonstrated that the central ring of a perhydrophenanthrene system adopts the trans-anti relationship of C5, C9 and C10 in gibberellic acid 1. The six membered B-ring precursor has then been contracted[31-35], often with the concomitant formation of the future C7 carboxylic acid group.

3. Elaboration of the D-ring

The addition of the D-ring can be accomplished by



Scheme 1.



Scheme 2.

many processes, chiefly of the condensation[36-42], alkylation [35,43-47,25], acylation[43,48,49], and carbenoid addition[50,51] type, but the majority are not compatible with the incorporation of the bridgehead hydroxyl group at C13 of gibberellic acid 1. Those designed to include this feature are :

(i) Aldol cyclization of a ketoaldehyde followed by degradation of a bridgehead acetyl group (Scheme 3.)[42]

(ii) Reductive cyclization of γ-ethynyl ketones[52]

(iii) Reductive cyclization of ketoesters[53-55]

(iv) Aldol cyclization of β-keto sulphoxides[56]

(v) Solvolysis of tosylmethyl cyclobutanes (Scheme 4.)[57]

(vi) Rearrangement of bicyclo [2.2.2] octanediones[58-61]

(vii) Intramolecular cyclization of δ-haloketones[62]

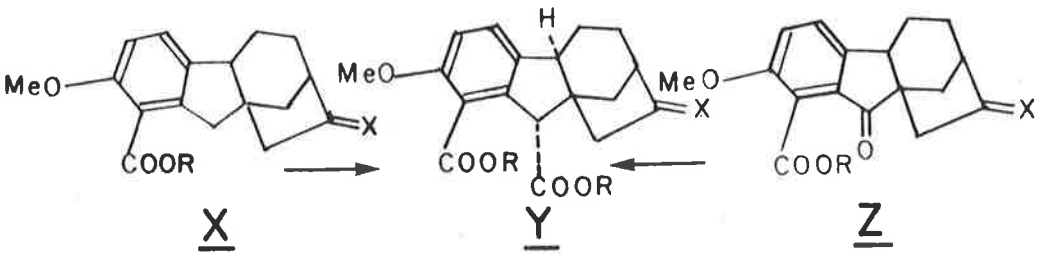
(viii) Intramolecular cyclization of trifluoroacetoxy diazoketones (Scheme 5.)[14,32,33]

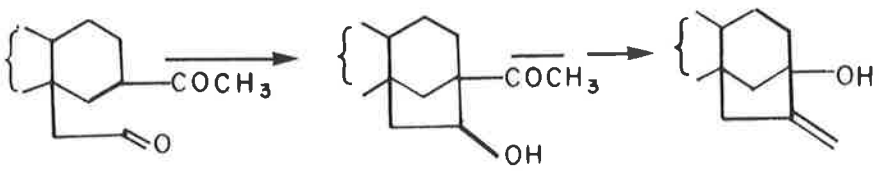
(ix) Pinacolic cyclization of a ketoaldehyde[63]

Ketol interconversions, shown in an abridged form in Scheme 6., have been observed in the formation of bicyclo [3.2.1] octanes with bridgehead hydroxyl groups in condensation reactions[61,66]. In principle a means therefore exists to invert the stereochemistry of the bridgehead hydroxyl group of a gibberellin analogue if this should be necessary.

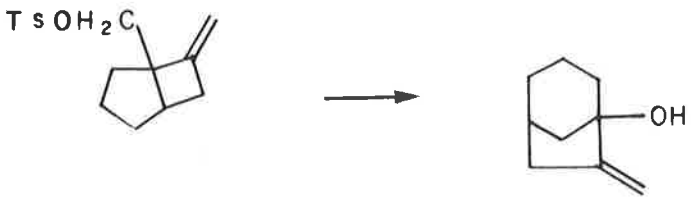
Three areas of importance, to be considered in an approach to the synthesis of gibberellins, emerge from this analysis. They are :

(i) The stereochemical control of the eight asymmetric centres.

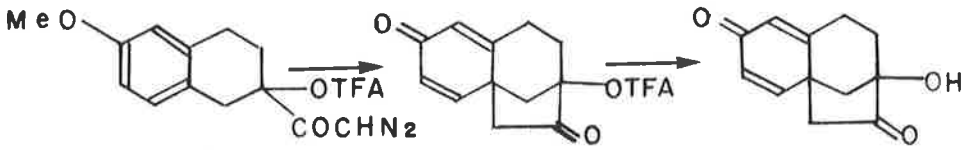




Scheme 3.



Scheme 4.



Scheme 5.

(ii) The construction and survival of the A-ring with its labile, allylic lactone group.

(iii) The inclusion of the bridgehead hydroxyl group with the correct stereochemistry.

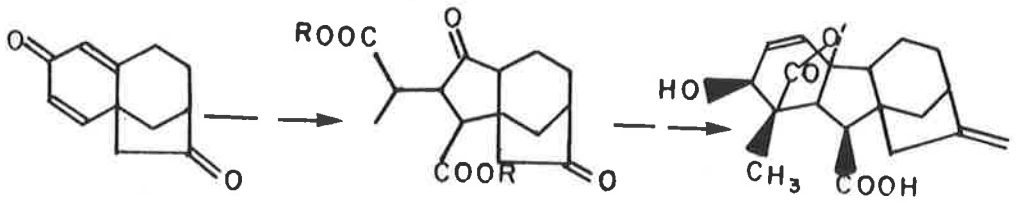
All approaches, by the traditional sequence of ring construction (i.e. AB+C+D), have failed in at least one of these areas. An alternative approach to the synthesis of gibberellins, which has the objective of bypassing the limitations of the AB+C+D method yet retaining its advantages, is described in this thesis.

The new approach originated from the observation that dienone ketone 3, prepared by the acid catalysed cyclization of diazoketone 5[65], contains a gibberellin-like CD-ring system, is formed by a procedure which is compatable with the introduction of a bridgehead hydroxyl group and contains a cyclohexa-2,5-dienone group which should be suitable for further elaboration. It was envisaged that the addition of appropriate functional groups to the cyclohexa-2, 5-dienone moiety followed by a ring contraction would lead to the ketoester 4 (Scheme 7.). This would be an ideal substrate for the application of the sequence developed by Dolby, outlined in Scheme 1., for the addition of the A-ring and the lactone group.

The outcome of this approach is presented in Chapter 1, along with its extension to include the dienone ketone 6 when dienone ketone 3 was found unsuitable.

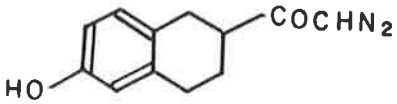
The presence of further substituents on the cyclohexadienone rings may be of use in directing the addition of

Scheme 6.



3 4

Scheme 7.



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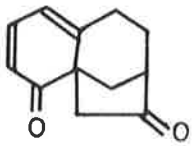

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the A-ring and in the ring contraction step, where a 1,2 or 1,3 relationship between an oxygen atom and a further heteroatom is often required. The synthesis of such polyfunctionalized intermediates is described in Chapters 2, 3 and 4.

Chapter 5 describes an attempt to synthesise derivatives of dienone ketone 6 which contain a gibberellin A-ring. In Chapter 6, a discussion of the probable mechanism, the scope and the limitations of the diazoketone cyclization reaction, pertinent to those examples described in Chapters 1-4, is presented.

RESULTS AND DISCUSSION

CHAPTER 1

CYCLIZATIONS OF DIAZOKETONES WITH A SINGLE OXYGEN SUBSTITUENT

(a) Attempted elaboration of dienone ketone 3

(b) Phenolic acid 14

(c) Synthesis of dienone ketone 6

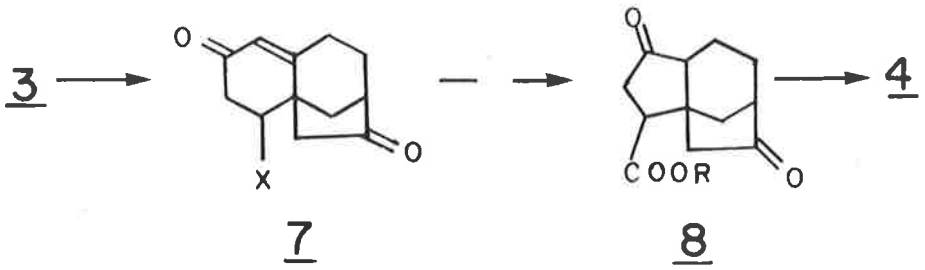
(d) Synthesis of dienone ketone 49

(e) Elaboration of dienone ketone 6

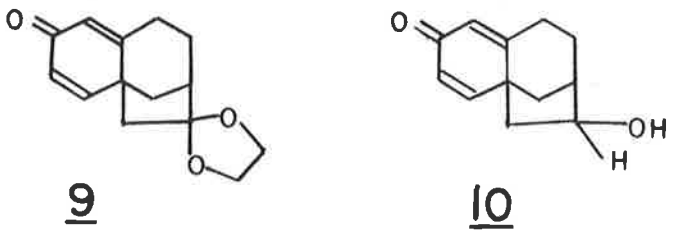
(a) Attempted elaboration of dienone ketone 3

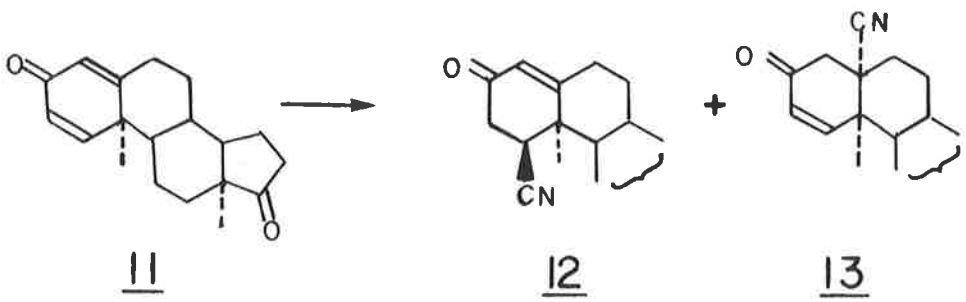
The plan was briefly discussed in the introduction and is outlined in Scheme 7. A possible solution for the conversion of dienone ketone 3 to the proposed intermediate, ketoester 4 was a 1,4-addition of a carbon nucleophile X (see Scheme 8.) followed by conversion of the X group to an ester group and ring contraction to afford the ketoester 8. Ketoester 4 would then be available from alkylation with a propionate equivalent.

A 1,4-addition reagent which has been used successfully with enones to introduce a nitrile group is Nagata's diethylaluminium cyanide[66]. Unfortunately when this was employed on acetal 9 or alcohol 10, derived from dienone ketone 3, with various equivalents of reagent, a mixture of at least five (by tlc) products formed. The result was not unexpected, for Nagata[67] obtained a mixture of products (including nitriles 12 and 13)from the addition of diethyl aluminium cyanide to dienone ketone 11 (Scheme 9.) which reflects the similarity in reactivity of the two enone olefinic bonds. An alternative procedure[68] with potassium cyanide and ammonium chloride in dimethylformamide merely hydrolysed the acetal group of dienone 9. Another carbon nucleophile, the anion of nitromethane[69] failed to react. The addition of nitrogen and sulphur containing nucleophiles such as dimethylamine perchlorate, pyrrolidine perchlorate and p-toluenethiol/potassium t-butoxide each in dimethylsulphoxide was also attempted. No addition products could be detected.



Scheme 8.





Scheme 9.

The lack of reactivity displayed by dienone ketone 3 to 1,4-addition may be attributed to (a) the spread, over two double bonds, of the electron withdrawal of the carbonyl group and (b) the severe steric crowding at the positions where the addition was desired. For the isomeric compound, dienone ketone 6, the 1,4-addition of, for instance, a propionate equivalent would be to the most exposed part of the molecule and it should be possible to form the adduct, ketoester 58. This could be modified, in a similar manner to that envisaged for enone ketone 7, to ketoester 4 (see Scheme 10.). Clearly dienone ketone 6 was an attractive intermediate for gibberellin synthesis but was it possible to make this compound with its very labile cyclohexa-2,4-dienone* moiety? In particular would it survive the acidic conditions which would be required for its formation? The answers to these questions are found in later parts of this Chapter.

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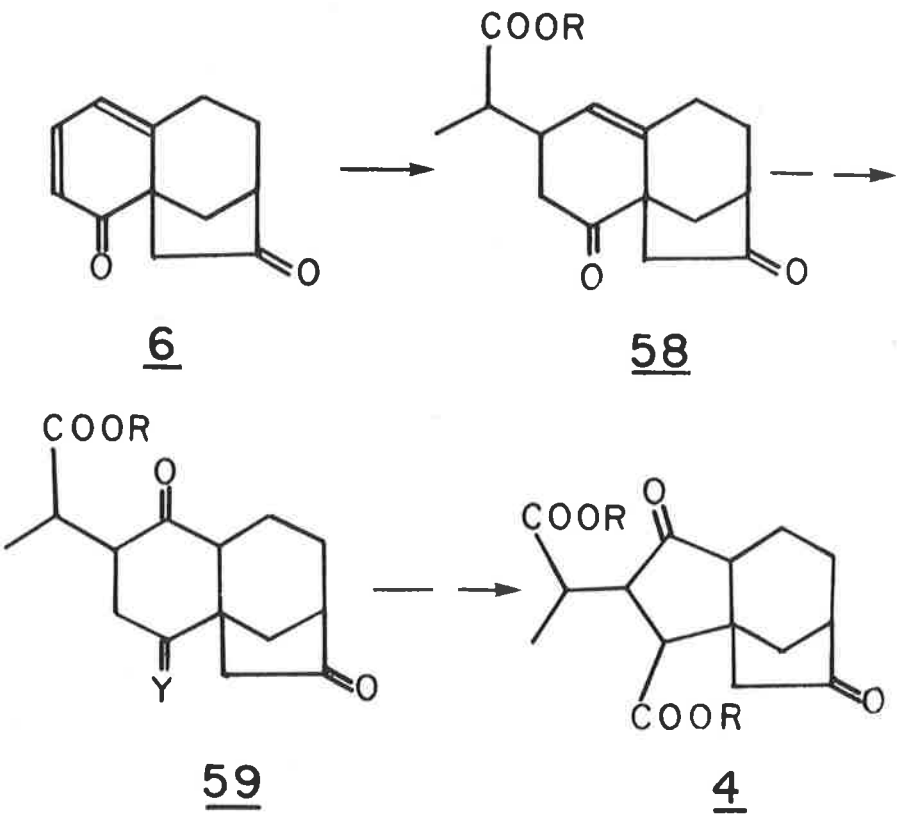
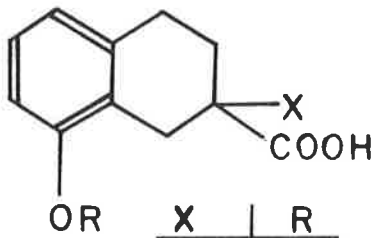
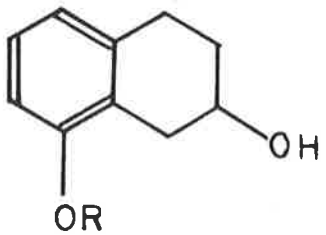
* A comprehensive review of the reactions of cyclohexa-2,4-dienones may be found in reference 70.



Scheme 10.



	X	R
14	H	H
15	H	Me
16	OH	H
17	OH	Me



20 R = H

21 R = Me

(b) Preparation of phenolic acid 14

By analogy with the preparation of dienone ketone 3, the obvious precursor of dienone ketone 6 is the phenolic acid 14 or the methoxy acid 15. In designing a synthesis of these compounds, it was desirable to devise a route which would include the facility for preparing the α-hydroxy acids 16 and 17 as precursors to the C13-hydroxylated gibberellins. For this reason, use of the traditional route via the Stobbe condensation product of a suitable aldehyde and diethyl succinate which has been used with dubious success to prepare the methoxy acid 15[71], was precluded. Accordingly, the tetralones 18 and 19 were chosen as substrates since conversion of the carbonyl group to a carboxyl group is a common synthetic procedure and the hydroxy acid should be available from the cyanohydrin.

Birch-Dryden reduction of 1,7-naphthalenediol with three g-atom equivalents of lithium afforded tetralone 18 in 44% yield. The tetralone was exceedingly labile and required purification by chromatography under an atmosphere of nitrogen. Tetralol 20, a byproduct of over-reduction in this reaction was obtained in quantitative yield when a large excess of lithium was employed. Fortunately it was possible to convert tetralol 20 to tetralone 19, in high yield and it was not necessary to use the labile, phenolic tetralone 18 in later schemes. The conversion of tetralol 20 to tetralone 19 involved a Collins oxidation[71] of the partially methylated tetralol 21. Tetralone 19 was also prepared by reduction of 1,7-dimethoxynaphthalene with sodium and (excess) ethanol

followed by acidic hydrolysis (75% yield).*†

The tetralones 18 and 19 were converted to their cyanohydrins 22 and 23 respectively and thence to the hydroxy acids 16 and 17 (Scheme 11.) simply and efficiently by established methods[24].

The reductive elimination of a group such as halo[75], amino[76], acyloxy[77] or hydroxy[78] adjacent to a carbonyl group is well documented. Ideally, an α-acyloxy acid should undergo a reaction of this type to eliminate an acetate group but a Birch-Dryden reduction of the α-acetoxy acid 24 and its ester 25 derived from methoxy acid 17 failed to give methoxy acid 15. Instead, simple cleavage of the acetyl group resulted.

A dehydration - reduction procedure was then chosen to remove the unwanted hydroxyl group. Neither the methoxy acid 17 nor its methyl ester could be cleanly dehydrated but, in contrast, cyanohydrin 22 readily formed the unsaturated

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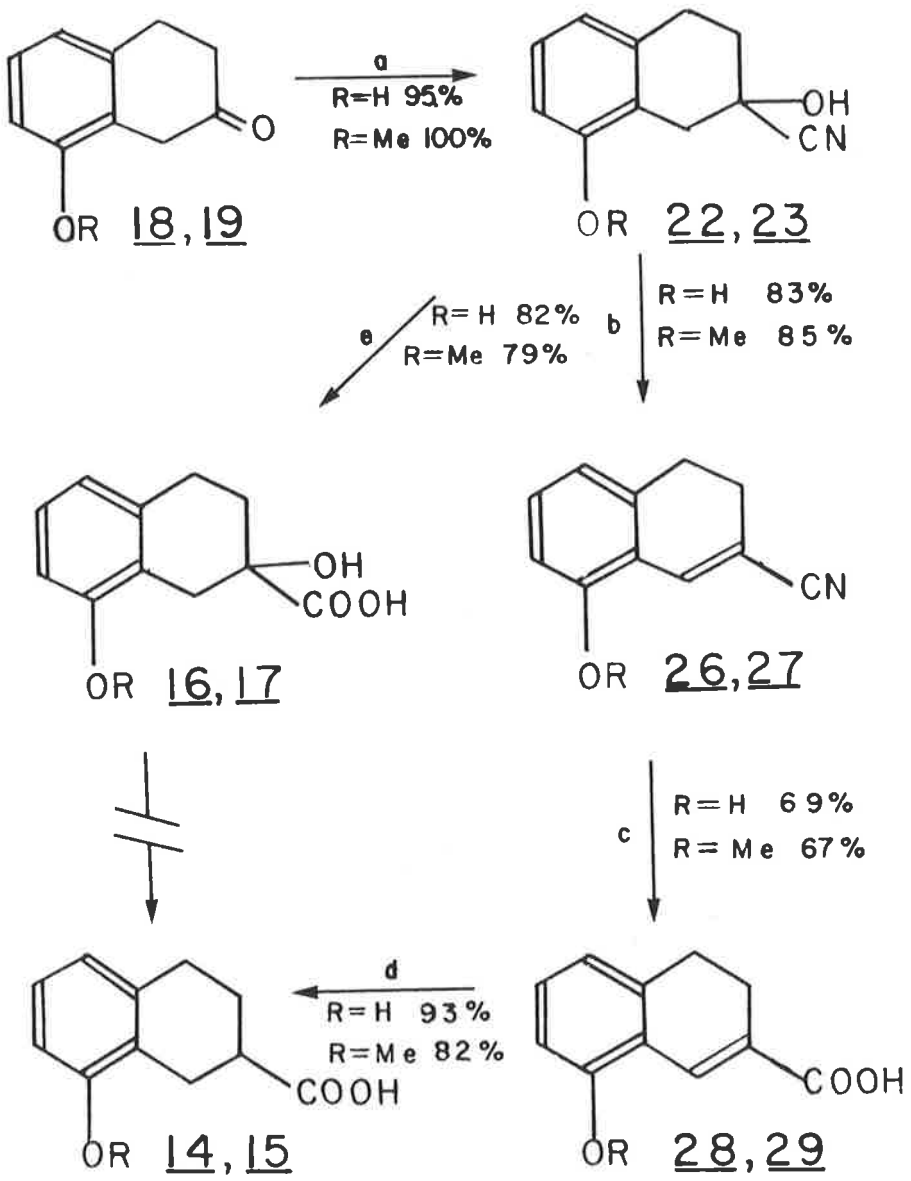
* A Birch-Dryden reduction with 2-4g-atom equivalents of lithium gave after hydrolysis a 23% yield of tetralone 19. The remainder of the reduced material was 5-methoxytetralin, a reductive demethoxylation product[72,73].

† Reduction with sodium in the absence of an alcohol and quenching with ammonium chloride is reported[74] to give a near quantitative yield of the intermediate enol ether but a poorer yield of tetralone 19 than that obtained by the classical procedure, was observed when repeated.



Scheme 11. Reagents: (a)NaCN, HCl; (b)$SOCl_2$, py; (c)NaOH, H_2O; (d)Na, NH_3, t-BuOH; (e) HCl.

nitrile 26 on treatment with thionyl chloride in pyridine[79]. Nitrile 26 was unreactive to the acidic conditions employed for the hydrolysis of cyanohydrin 22 but hydrolysis to acid 28 was achieved in a basic solution. The peri-hydroxyl group of acid 28 inhibited the removal of the double bond by catalytic hydrogenation and recourse was made to reduction by sodium in liquid ammonia to afford acid 14. The procedure required no modification to convert the methoxy cyanohydrin 23 to the methoxy acid 15, which was demethylated to acid 14 by fusion with pyridine hydrochloride at 200-220°.

This was not an ideal route for a large scale preparation of acid 14 and a suitable alternative was sought. The displacement of a mesylate derived from tetralol 21 with a carbon nucleophile was an attractive solution. Mesylate 30 in the presence of sodium cyanide and under aprotic dipolar conditions, however, rather than forming the nitrile, gave instead a mixture of olefins 31 and 32. While this was a disappointing result, olefin 31 should be readily oxidized to diacid 33, an important intermediate in Loewenthal's synthetic approach to gibberellin A_4[22].

The ratio of olefins 31 to 32 in the mixture was not improved by other base-solvent systems (NaCN-MeCN; NaCl-DMSO; NaOMe-MeOH) and additionally, in the case of the strongest base, sodium methoxide, a displacement product, the diether 34, was isolated. Secondary tosylates are reported[80] to eliminate in a more predictable manner than the corresponding mesylates and this was confirmed when tosylate 35, on treatment with potassium t-butoxide in dimethylformamide gave

a near quantitative yield of olefin 31. The diacid 33* was then obtained by oxidation of olefin 31 with a solution of potassium permanganate (solubilized by tetra-n-butyl ammonium bromide) in benzene[81].

The next plan devised to prepare acid 14 was to add a one carbon atom unit to the double bond of olefin 31. There are numerous examples[83-85] of the addition of carbon residues to isolated double bonds and the majority may be classified as either electrophilic acylation or alkylation. These reactions, however, cannot be employed on the styrene double bond of olefin 31 for the same conditions also cause electrophilic substitution on aromatic rings[86].

A less obvious approach lay in the hydrolysis of the β-lactam[87], formed in the condensation of the double bond with an isocyanate, to its amino acid (Scheme 12., pathway a). Removal of the amino group then completes the transformation from a double bond to a one carbon extended carboxylic acid. The isocyanate addition to olefin 31 can proceed in two ways because of the asymmetry of the double bond, but by analogy with the product from the addition of chlorosulphonyl isocyanate (CSI) to cis-β-methylstyrene[88] the addition to olefin 31 should be in the manner required.

Olefin 38 (Scheme 13.) was chosen as a substrate to test this hypothesis. Since chlorosulphonyl β-lactams are thermally labile, the product from the addition of CSI (37)

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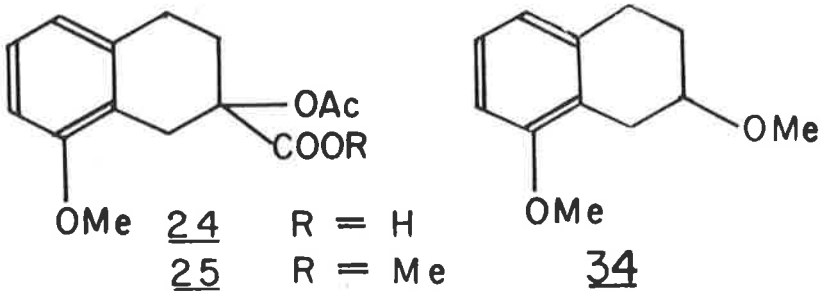
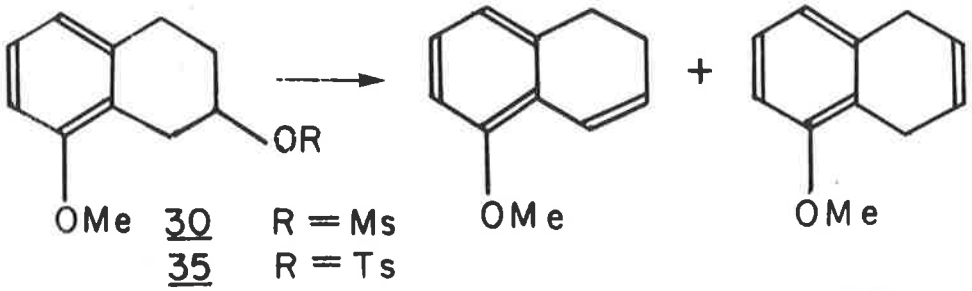
* The new route to the diacid, which is comparable in length to the original, does not require its expensive starting material, the chromanone 36[82].



24 R = H
25 R = Me

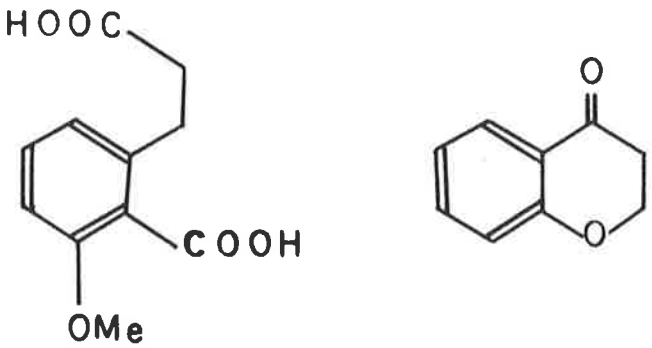
34



30 R = Ms
35 R = Ts

31

32



33

36

to olefin 38 was not isolated, but was treated directly with concentrated hydrochloric acid. A white solid precipitated from the mixture and this was identified as the unsaturated amide 39 (35% yield). Only unreacted starting material was recovered from the residue. When a larger excess of CSI (37) was used there was little change in the product composition.

The appearance of amide 39 can be explained by an alternative breakdown pathway of the β-lactam (Scheme 12., pathway b). Presumably the Hoffmann - type elimination was assisted by the para-methoxyl substituent on the aromatic ring. This is not an unexpected result for Moriconi[89] observed the same type of product during the addition of CSI (37) to 1,2-dihydronaphthalene. While amide 39 was not the anticipated product the objective of the plan was realized in its conversion to acid 40* simply by reduction of the double bond and acidic hydrolysis of the amide group.

Direct application of the route to the conversion of olefin 31 to acid 15 proved possible. An unexpected result was the high yield (92%) of the unsaturated amide 41. The excellent yields of this and previous steps combine to make this the most efficient way of making acids 14 and 15. Because of the wide variations in yields of amides 39 and 41, however, further experimentation is still necessary to establish whether this is a general synthetic route to tetrahydronaphthoic acids.

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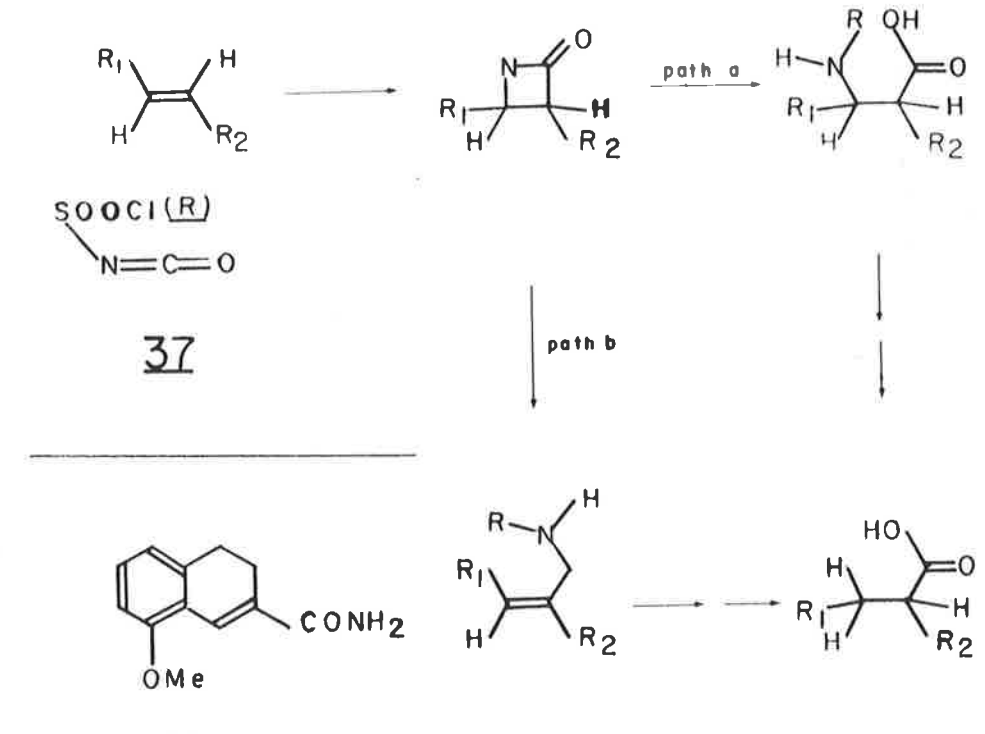
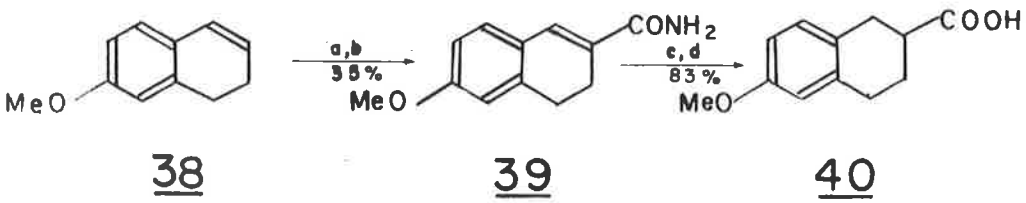
* The structure of acid 40 and hence the validity of the route was confirmed by its comparison with an authentic sample[90].



Scheme 12.



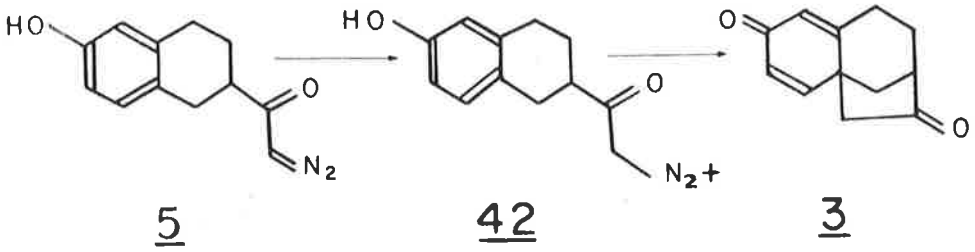
Scheme 13. Reagents: (a) $ClSO_2NCO$; (b) HCl; (c) Na, NH_3, t-BuOH; (d) H_2SO_4.

(c) Synthesis of dienone ketone 6

In this Department it has been shown[46] that the phenolic diazoketone 5, when treated with boron trifluoride etherate, fluoroboric acid or trifluoroacetic acid, cyclizes to the cyclohexa-2,5-dienone ketone 3. This product is believed to be the result of electrophilic attack para to the oxygen substituent on the aromatic ring of the intermediate diazonium ion 42 with the resultant displacement of nitrogen (Scheme 14.). It was of interest to see if this type of cyclization could be extended to a diazoketone (e.g. the phenolic diazoketone 45) with an ortho-substituent on the aromatic ring. This should lead to a compound containing a cyclohexa-2,4-dienone chromophore which, although potentially very labile, has considerable synthetic potential[70]. Accordingly, diazoketone 45 was prepared by the sequence outlined in Scheme 15.

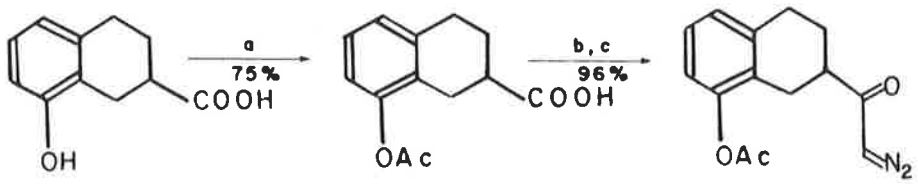
The hydroxyl group of acid 14 was protected as the acetate 43 and the diazoketone 44 was prepared in the standard way[91]. The acetyl group of diazoketone 44 was removed by a suspension of sodium carbonate in aqueous methanol to afford diazoketone 45 in good overall yield.

Despite previous success in the cyclization of other phenolic diazoketones with a catalytic amount of boron trifluoride etherate in nitromethane the best yield of dienone ketone 6 obtained from diazoketone 45 under these conditions was 35%. Treatment with a trace of trifluoroacetic acid in chloroform gave a similar result, but when trifluoroacetic acid was chosen as both the catalyst and the solvent, there was a drastic improvement in the yield (to 96%) of dienone

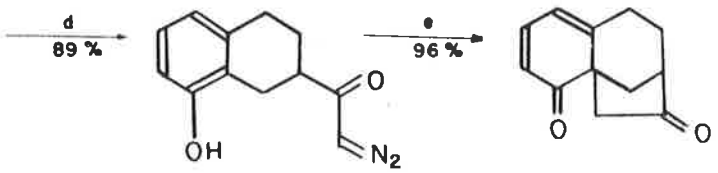


5 42 3

Scheme 14.



14 43 44



45 6

Scheme 15. Reagents: (a) Ac_2O, NaOAc; (b) $(COCl)_2$; (c) CH_2N_2; (d) Na_2CO_3, MeOH, H_2O; (e) TFA.

ketone 6.

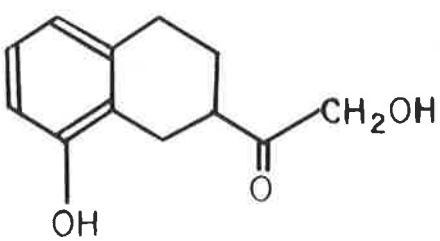
The reaction was particularly sensitive to the concentration of the diazoketone, and competing formation of the trifluoroacetoxymethylketone (usually isolated as the hydroxymethylketone 46) became significant when this concentration exceeded 1 g per 100 ml of trifluoroacetic acid. In view of the expense of trifluoroacetic acid this is a severe limitation to the viability of dienone ketone 6 as an intermediate. One solution to this problem was to recover the trifluoroacetic acid by reduced pressure distillation after the cyclization, since dienone ketone 6 is quite stable. Indeed, in a control experiment, it was essentially unchanged by treatment with trifluoroacetic acid for 6 h at 50°. Some further experiments on this dienone ketone are included in part (e) of this Chapter.

Dienone ketone 6 was also prepared from the acid catalysed cyclization of diazoketone 47, prepared in turn from acid 15. Under optimized conditions (-30°, trifluoroacetic acid) a 68% yield of the dienone ketone was afforded. This was a much shorter route than the one outlined in Scheme 15. since demethylation of acid 15 and protection - deprotection steps were not required.

(d) Synthesis of dienone ketone 49

In principle dienone ketone 49, isomeric to dienone ketone 6 is available by ortho-alkylation of phenolic diazoketone 48 and its preparation by this method would further attest to the generality of the reaction. The precursor acid 52 to diazoketone 48 was prepared by the route outlined in Scheme 16., starting from the commercially available tetralone 50. The conversion of acid 52 to diazoketone 48 was by an identical route to the preparation of diazoketone 45 from acid 14 (Scheme 15.).

As expected, a good yield (74%) of the dienone ketone 49 was obtained on treatment of diazoketone 48 with trifluoroacetic acid. In contrast to dienone ketone 6, dienone ketone 49 was unstable to normal atmospheric conditions and rapidly formed a red polymer. Nevertheless, its spectra were characteristic of its structure, and this result certainly demonstrated the desired generality of the diazoketone cyclization reaction and forms the basis for attempting the cyclization of a number of other diazoketones in subsequent Chapters of this thesis.



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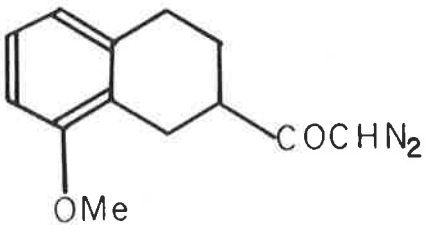

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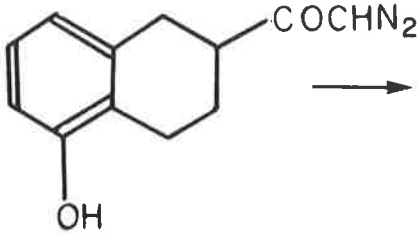

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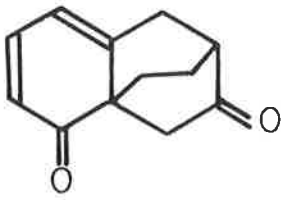

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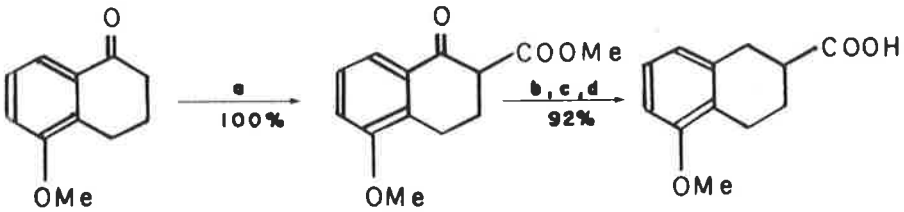

50 51 52

Scheme 16. Reagents: (a) $(MeO)_2CO$, NaH; (b) H_2, Pd/C, H^+; (c) NaOH, MeOH, H_2O; (d) py.HCl.

(e) Elaboration of dienone ketone 6

Dienone ketone 6 has proved quite amenable to elaboration and the results of some preliminary experiments are recorded and discussed below (Scheme 17.).

Catalytic reduction of this dienone ketone gave the diketone 54 as a mixture of diastereoisomers*. The more exposed double bond was selectively removed by reduction with sodium borohydride in ethanol and reoxidation of the product afforded the enedione 55†. Surprisingly, hydrogenation in the presence of the soluble metal catalyst, tris (triphenylphosphine) chlororhodium, failed to exhibit this selectivity. Attempts[92,93] to prepare the ethylene acetal 53 from dienone ketone 6 were unsuccessful and either starting material or phenolic material, which appeared to have formed from nucleophilic attack alpha to the saturated carbonyl function, was returned.

In section (a) of this Chapter the potential for gibberellin synthesis of the product, ketoester 58, from the 1,4-addition of a propionate equivalent to dienone ketone 6, was discussed (see Scheme 10.). The preparation of this adduct was therefore attempted. The addition of malonic ester to dienone ketone 6 in the presence of various basic

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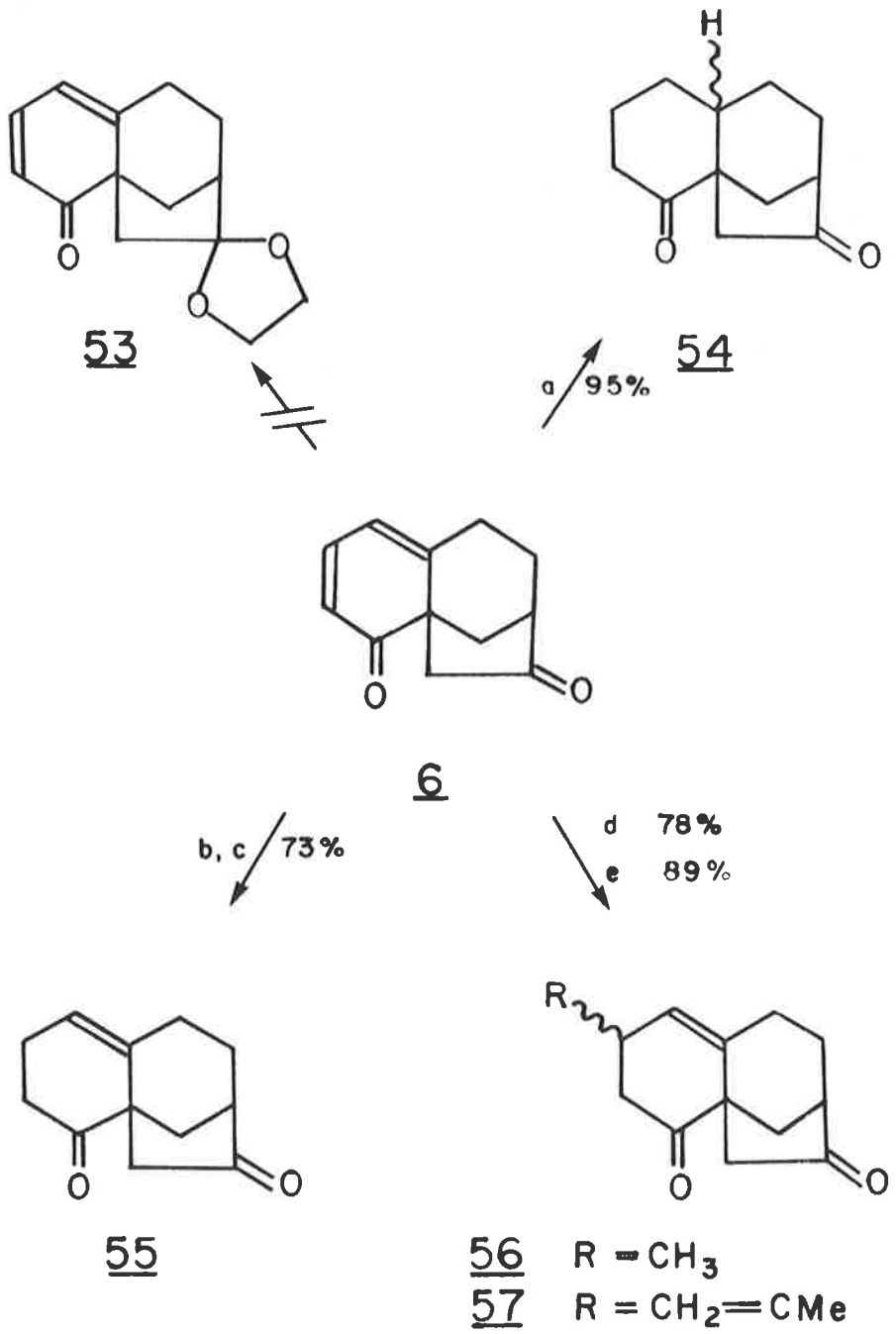
* This was confirmed by formylation of diketone 55 to give a product with two distinct formyl proton resonances (ratio 7:3) in its nmr spectrum.

† The use of isopropanol in this reaction appeared to favour reduction of the saturated carbonyl function.

catalysts failed, even under forcing conditions, and starting material was returned on each occasion. Since the prop-2-enyl anion may be regarded as an equivalent (by way of hydroboration and oxidation) to propionate, the addition of isopropenylmagnesium bromide[94] was tried. Although the addition was copper iodide mediated, 1,2-addition occured. The desired 1,4-addition to dienone ketone 6 was finally achieved by the addition of mixed cuprates[95]. Dimethyl copper lithium afforded a high yield of enone ketone 56 and diisopropenyl copper lithium gave enone ketone 57.

The conversion of enones 55 and 57 into ketoesters with the generalized structure 59 (Scheme 10.) has yet to be attempted because of a shortage of the starting material, 1,7-naphthalenediol. It would appear, however, to be straightforward in view of the distinct environment of each functional group.



Scheme 17. Reagents: (a) Pd/C, H_2; (b) $NaBH_4$, EtOH; (c) CrO_3, H_2SO_4, H_2O, Me_2CO; (d) Me_2CuLi; (e) $[CH_2=CMe]_2CuLi$.

CHAPTER 2

CYCLIZATION OF DIAZOKETONES WITH TWO (PARA) OXYGEN SUBSTITUENTS

(a) Diazoketone 64

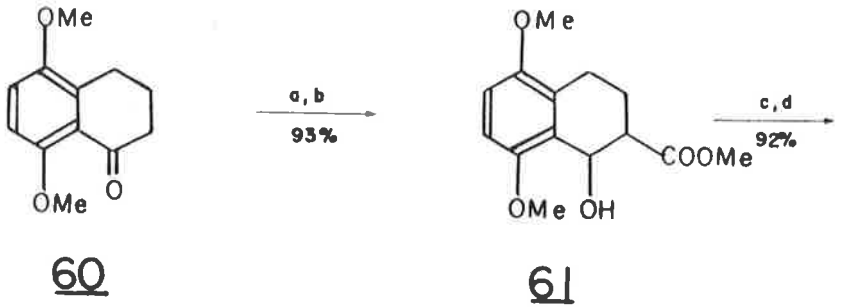
(b) Diazoketone 70

(a) Cyclization of diazoketone 64

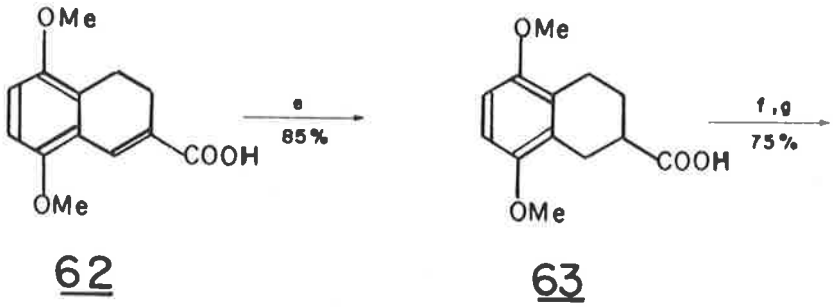
In Chapter 1 it was intimated that dienone ketone 6 should be capable of elaboration to the ketoester 59 (see Scheme 10.) and ultimately to a gibberellin. One of the steps in this proposed scheme was the conversion of olefin 58 to ketone 59. While this could be accomplished by hydroboration and subsequent oxidation, a potentially shorter and hence a more attractive solution was to generate the ketone from an oxygen substituent which had been incorporated in that position. It was also expected that, with this feature, there would be fewer problems in the manipulation of the two ketone groups of the proposed analogue of dienone ketone 6. Accordingly, the synthesis of the methoxy dienone ketone 65, by cyclization of the appropriately substituted diazoketone 64 was undertaken.

The preparation of diazoketone 64 from tetralone 60[96] is outlined in Scheme 18. Hydrogenolysis of the ketone group of the β-ketoester derived from tetralone 60 was prevented by the presence of the peri-methoxyl group. It was possible, however, to reduce this β-ketoester with sodium borohydride in dry isopropyl alcohol to the hydroxyester 61. The use of methanol instead of isopropyl alcohol in this reaction gave the 1,3-diol. The conversion of hydroxyester 61 to the unsaturated acid 62 by dehydration and base hydrolysis was straightforward, as was the subsequent metal-ammonia reduction of acid 62 to acid 63 and conversion of the latter to diazoketone 64.

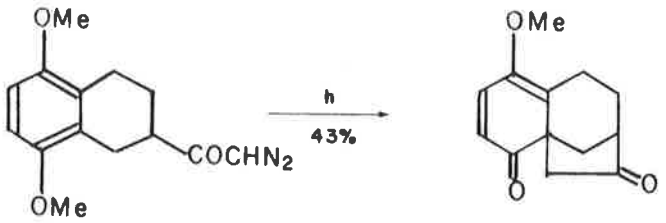
Treatment of diazoketone 64 with trifluoroacetic



60 61



62 63



64 65

Scheme 18. Reagents: (a) $(MeO)_2CO$; (b) $NaBH_4$, iso-PrOH; (c) AcOH, p-TsOH; (d) KOH, MeOH, H_2O; (e) Na, NH_3, t-BuOH; (f) $(COCl)_2$; (g) CH_2N_2; (h) TFA.

acid at 0^{o} afforded a yellow oil from which only one cyclized product (in 42% yield) was isolated. This compound gave rise to olefinic proton resonances at δ 6.0 (s), 5.4 (d, J=7.5Hz) and 5.0 p.p.m. (d, J=7.5Hz) in its nmr spectrum and no infra red absorptions in the region ν 1660 - 1750 cm^{-1}. From a consideration of the more likely reaction pathways in this reaction (see Scheme 19.*) it was assigned the structure of trienone 66.

When the temperature, at which the cyclization of diazoketone 64 was conducted, was lowered to -15^{o} there was a reduced yield of the trienone 66 (14%) and the appearance of a new cyclized product (43%). The spectral data for this compound indicated that it contained a cyclohexa-2,4-dienone chromophore (ir : ν_{max} 1670, 1630 and 1565 cm^{-1})[70] which was consistent with either of two structures : dienone ketone 65 or dienone ketone 67.† In the nmr spectrum, an additional small coupling (1Hz) of the high field olefinic proton was

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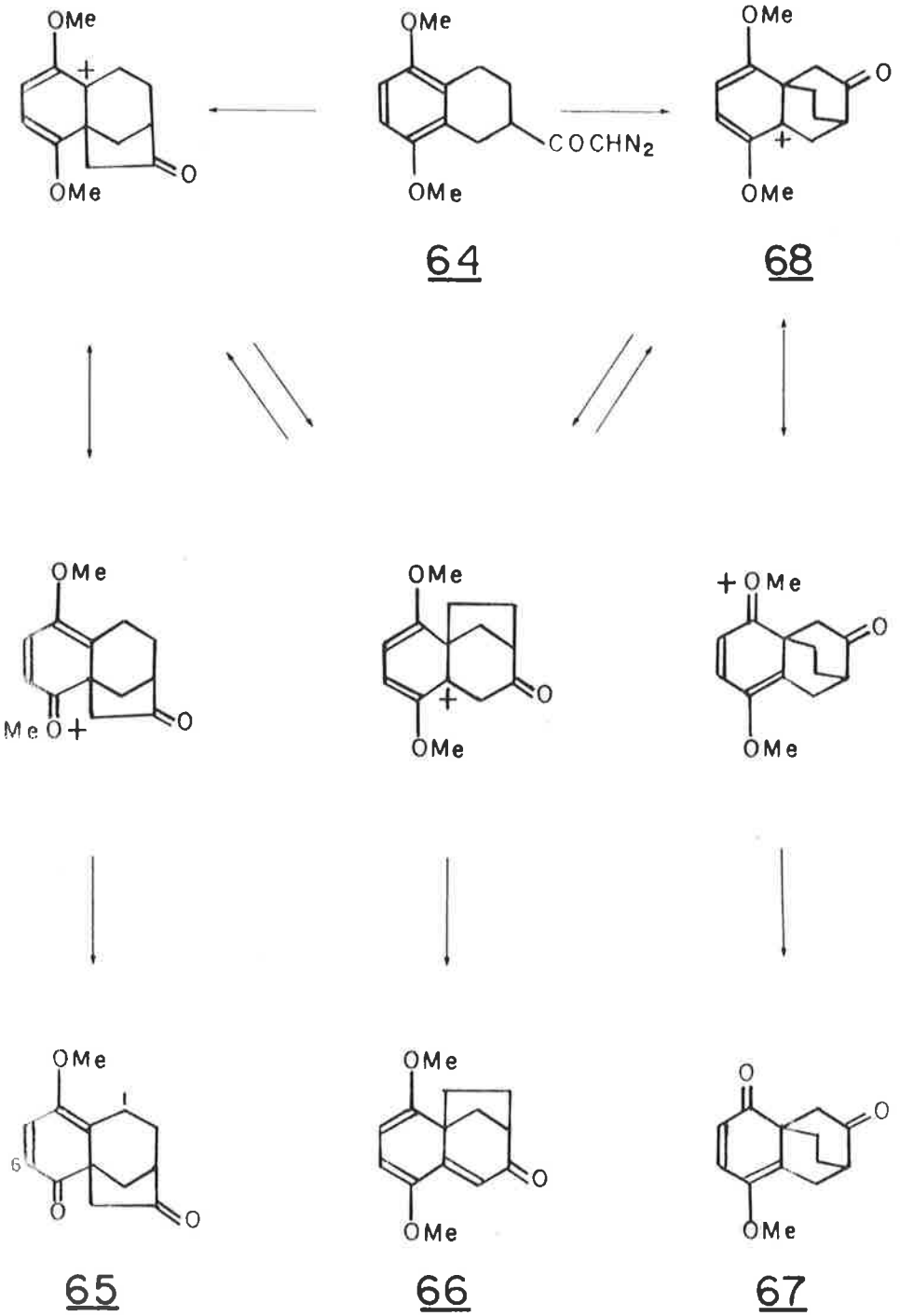
* It must be emphasised that Scheme 19. contains neither all possible intermediates nor all possible contributing structures of the intermediates that are shown.

† The assignment of structure on the basis of ν_{max} for the saturated carbonyl group was not possible because an overlap in the stretching frequencies of cyclohexanones and cyclopentanones in related dienone ketones has been observed.

observed. This was consistent only with the structure of dienone ketone 65 since a long range coupling of the proton of C6 to the pseudo equatorial proton at C1 was expected by analogy with closely related compounds[57]. From an examination of models such a coupling is not possible in dienone ketone 67.

It is important to note that the non-appearance of dienone ketone 67 does not preclude the intermediacy of its precursor carbonium ion 68 (one of a number of contributing structures) since this may undergo a 1,2-alkyl shift (Scheme 19.) more rapidly than dealkylation to give dienone ketone 67.

The disappointing yield of dienone ketone 65 in the cyclization step, the necessity for its purification by chromatography and the lengthy route of its preparation clearly dictate that dienone ketone 65 is not a viable intermediate for the evaluation of the scheme outlined at the beginning of this Chapter.



Scheme 19.

(b) Cyclization of diazoketone 70

Two conclusions were made from the results of the treatment of diazoketone 64 with trifluoroacetic acid that account for the poor yield of dienone ketone 65 :

(i) The rate of solvolysis of the diazomethyl ketone group was comparable to the rate of formation of cyclized products.

(ii) The extra methoxyl group, which did not assist in the cyclization, helped to stabilize carbonium ions in the pathway to the rearrangement product, trienone 66.

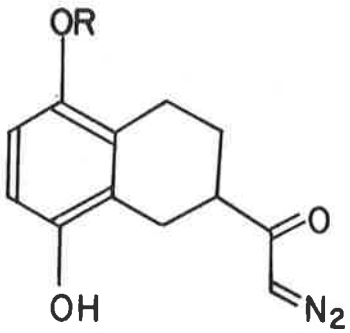
It was felt that a solution to this problem lay in the cyclization of a phenolic diazoketone, e.g. diazoketones 69 and 70. Not only does the phenolic group activate the aryl ring more effectively, but deprotonation of the cyclic intermediate to give the dienone ketone, in contrast to the necessary dealkylation for an ether derivative, should be much faster than the rearrangement.

There appeared to be no way of selectively demethylating the appropriate methoxyl group of the dimethoxy acid 63 and, to prepare diazoketone 69, it appeared necessary that a carboxylic acid with two different ether functions, one of which could be removed selectively, would have to be synthesised. A benzyl ether group, which is commonly used for such a purpose would probably not survive some of the reaction conditions. It was decided, therefore, to employ the strategy of Ireland in his synthesis of the triterpene alnusenone[98] for the selective demethylation of the pentacyclic diether 73 (see Scheme 20.). He found that a mixture of lithium diphenylphosphide and phenyl lithium would selectively

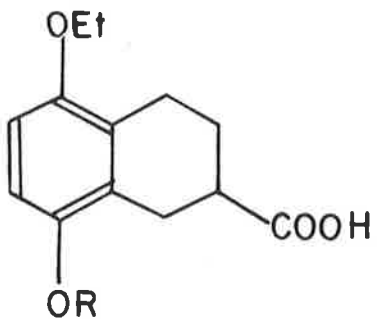
remove a methyl group in the presence of an ethyl group.

A rather novel route, outlined in Scheme 21., was required to prepare ethoxy methoxy acid 72. Peracid oxidation of the commercially available tetralone 75 for three days in boiling dichloromethane afforded a good yield of lactone 76. Acidic hydrolysis of this lactone generated a phenolic acid which possessed the required para disposition of two different oxygenated substituents on the aromatic ring. The traditional method of ethylation (NaOH, Et_2SO_4, H_20) not only ethylated the phenolic group but the carboxylic acid residue as well. The product could be de-esterified but this introduced an unnecessary step into the sequence. A recent method[99] for the methylation of a phenolic group in the presence of a carboxylic acid group was adapted and found very satisfactory. Acid 77 was then cyclized with polyphosphoric acid to tetralone 78. The application of the process, developed for the preparation of dimethoxy acid 63 (Scheme 18.), to the tetralone 78 resulted in a high yield conversion to acid 72.

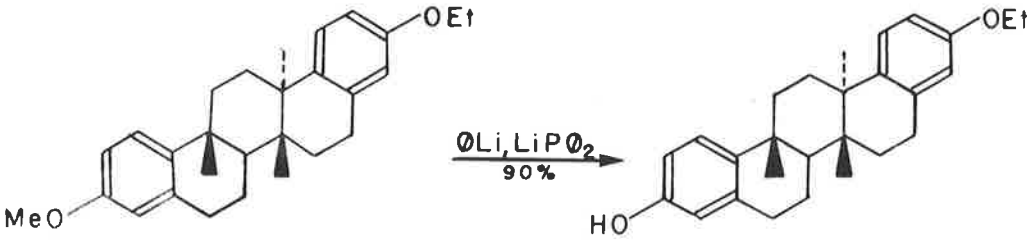
In a trial experiment, diazoketone 79, prepared from acid 72, was treated with trifluoroacetic acid under the normal conditions. In marked contrast to the cyclization of the corresponding dimethoxy diazoketone 64 no rearrangement product was detected and the yield of dienone ketone 80 was 63%. It is difficult to explain why the subtle change from a methyl group to an ethyl group had this effect but the result clearly reinforced the expectation for a high yield of dienone ketone 80 in the cyclization of the phenolic



69 R = Me
70 R = Et

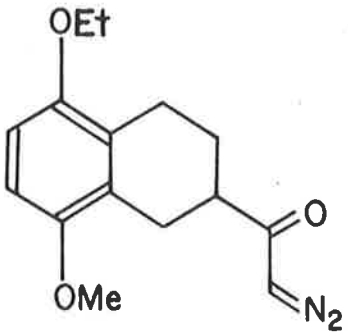


71 R = H
72 R = Me



73 74

Scheme 20.



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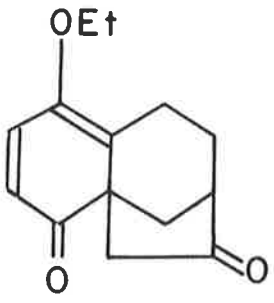

80

diazoketone 70.

Selective demethylation of acid 72, with lithium diphenylphosphide and phenyl lithium gave, as expected, the phenolic acid 71 in 71% yield. Acid 71 was then converted to diazoketone 70 by the standard procedure of acetylation, diazoacetylation and deacetylation. Although this diazoketone was particularly labile, being decomposed by traces of acetic acid in the ethyl acetate employed in its isolation, it underwent "quantitative" conversion to dienone ketone 80 when treated with trifluoroacetic acid.

Dienone ketone 80 decomposed slowly to a red polymer and satisfactory elemental analysis results could not be obtained for it. All spectral data, however, including an accurate molecular weight determination, were consistent with its proposed structure and, in addition, they were identical with the spectra of the product from the cyclization of diazoketone 79.

It was possible to hydrolyse the enol ether group of dienone ketone 80 under mild, acidic conditions (trifluoroacetic acid, 25°) to give the enedione ketone 81 (Scheme 22.). This rapidly formed the red "polymer" which had been observed previously. Accordingly, the very reactive olefinic bond of enedione ketone 81 was removed, by reduction with zinc in acetic acid, to give the stable trione 82*.

Implementation of the route outlined in Scheme 10.

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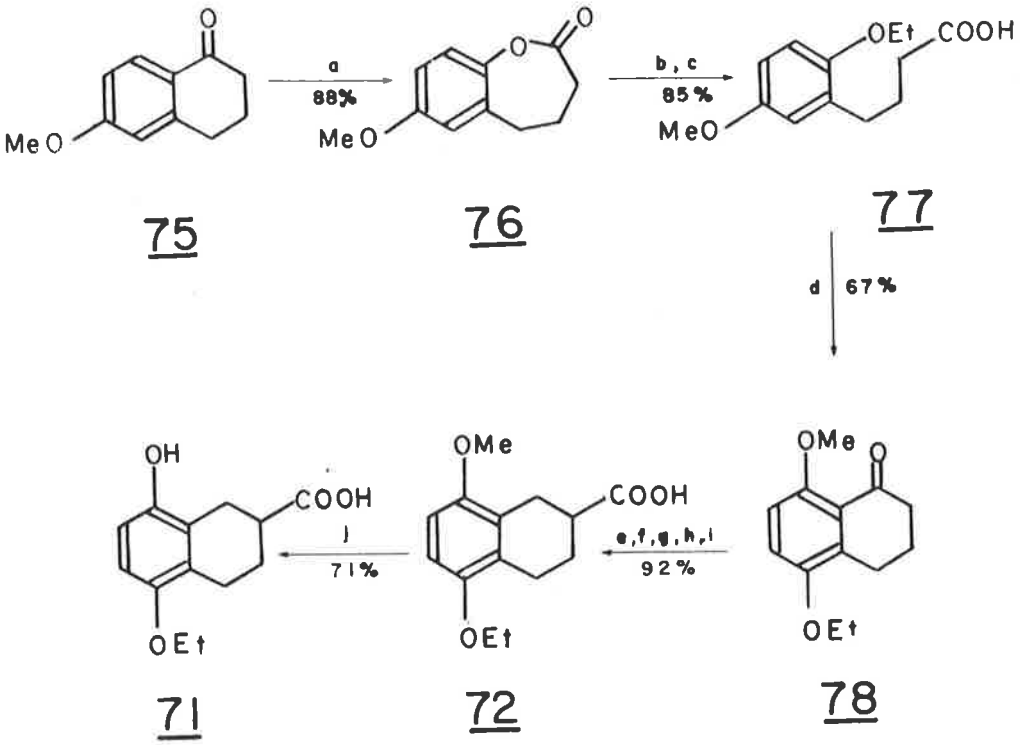
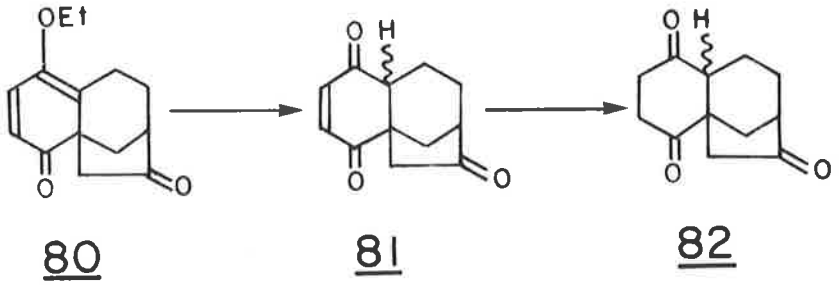
* The stereochemistry at C8a was not determined.



Scheme 21. Reagents: (a) m-CPBA; (b) HCl; (c) NaH, EtI; (d) PPA; (e) NaH, $(EtO)_2CO$; (f) $NaBH_4$, iso-PrOH; (g) p-TsOH, AcOH; (h) KOH, MeOH, H_2O; (i) Na, NH_3, t-BuOH; (j) PhLi, $LiPPh_2$.



Scheme 22.

was once again not possible because of the logistics of the fourteen steps employed in the synthesis of dienone ketone 80. Clearly a more direct route to acid 71 is required.

CHAPTER 3

CYCLIZATION OF DIAZOKETONES WITH TWO (ORTHO) OXYGEN SUBSTITUENTS

The proposed scheme for the elaboration of dienone ketone 3 to the gibberellins, discussed in the Introduction (see Scheme 7.) and expanded in Chapter 1, contains the conversion of enone ketone 7 (see Scheme 8.) to ester 8. One of the steps involved in this transformation is a ring contraction. A survey of the methods of ring contraction indicates that a 1,2-relationship between an oxygen atom and a further hetero atom is a common requisite. For example :

(i) Lewis acid treatment of αβ-epoxyketones[100]

(ii) Photolysis of αβ-epoxyketones[101-103]

(iii) The photochemical Wolff rearrangement[104,105]

(iv) Silver salt catalysed bromohydrin rearrangements[106]

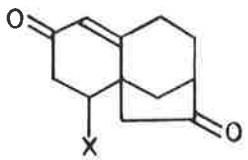
(v) Oxidation of 1,2-cyclohexanediols[107]

(vi) The benzilic acid rearrangement[108,109]

The diketones of generalized structure 83 and 84 (Y=hal, OH ect.) should accordingly be ideal substrates for the ring contraction. It is unlikely, however, that these compounds would be directly available from dienone ketone 3 considering its lack of reactivity displayed in Chapter 1. A logical alternative is to include the group Y in precursors, to diketones 83 and 84, such as the dienone ketones 85 and 86.

It was apparent that dienone ketone 85 would be the easier of the two to prepare since its obvious precursor, acid 87, is a readily accessible compound[110].

There was one difficulty envisaged in the conversion of acid 87 through diazoketone 88 to dienone ketone 85. Diazoketone 88 has a methoxyl group para to each of the two ring junctions and there is the possibility of a second



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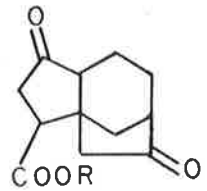

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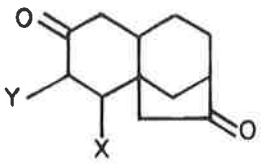

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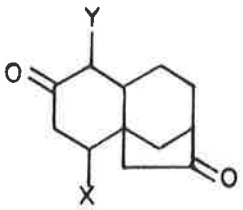

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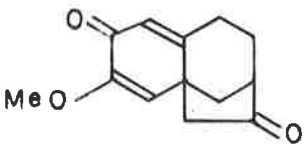

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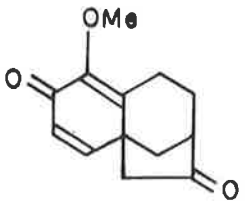

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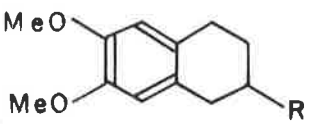
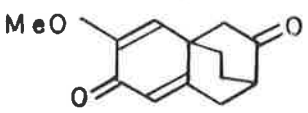


87 R = COOH
88 R = $COCHN_2$



89

primary cyclization product, dienone ketone 89.

When diazoketone 88* was added to trifluoroacetic acid at -30° two cyclized products were isolated. The major product (71%) of these two was readily identified as the dienone ketone 85 by analogy with the spectral data of dienone ketone 3. The minor product (23%) of the mixture, which in fact became the major product when the reaction was performed at 0°, was obtained as a yellow gel which could not be freed from traces of dienone ketone 85. The ultraviolet spectrum obtained from this gel showed a strong absorption at 386 nm which was diagnostic of a chromophore with extended conjugation.

If this yellow gel was allowed to remain in contact with trifluoroacetic acid at room temperature, a further product, a pale yellow solid, formed. The ultraviolet-vis. spectrum afforded by this compound showed a strong absorption at 324 nm and, after the addition of sodium hydroxide solution, further bands at 275 and 450 nm. This change could be rationalized in terms of a base induced enolization of a carbonyl group, and appeared to be consistent with dienedione structure 91 as the product. By inference, the structure of the yellow gel was almost certainly that of trienone 90.

The good yield of dienone ketone 85 was offset by its tedious separation from the rearrangement product, trienone 90. It was decided, however, to proceed to the next step, the hydrolysis of the enol ether group of dienone

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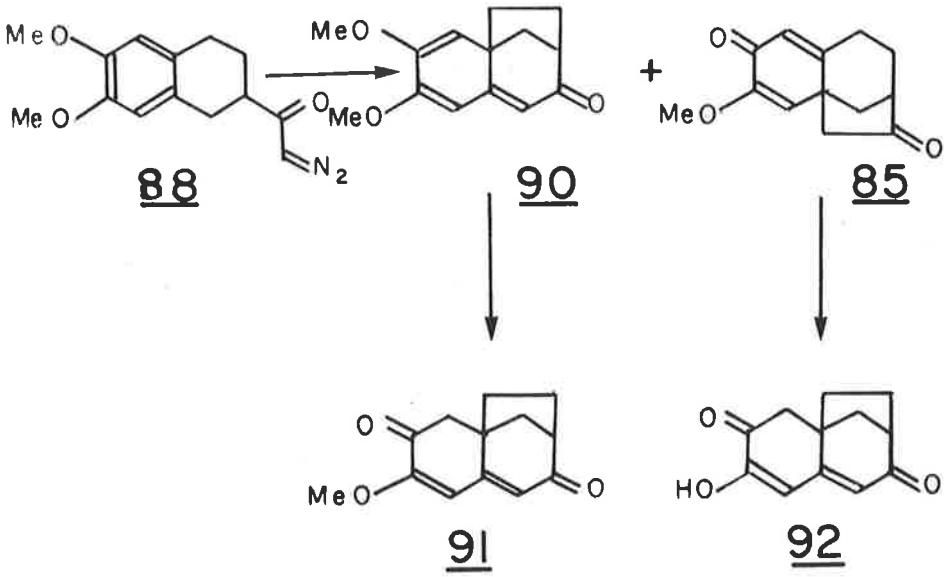
* This compound was prepared by Mr. T.J. Masters in a preliminary study.

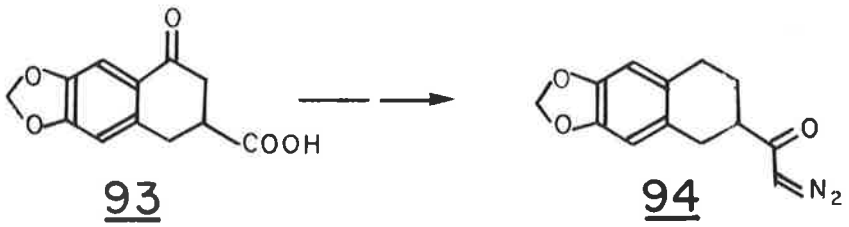
ketone 85, since this should afford hydroxy dienone ketone 95 which was a possible substrate for a benzilic acid rearrangement. Treatment of dienone ketone 85 with 50% aqueous hydrochloric acid at room temperature afforded, as expected, a product which gave rise to no methoxyl protons in its nmr spectrum. Unfortunately it also showed no cyclopentanone absorption in its infra red spectrum and in addition, a long wavelength ultraviolet absorption at 415 nm. The similarity of its spectra to those of dienedione 91 led to the assignment of its structure as that of hydroxy dienedione 92.

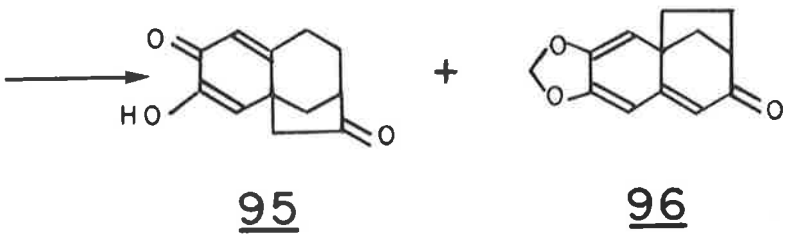
While seeking a means of avoiding the rearrangement prone hydrolysis step, the cyclization of diazoketone 94 was examined. It was reasoned that the methylenedioxy group should be lost under the conditions of the cyclization and the hydroxy dienone ketone 95 would be afforded directly. The diazoketone was prepared from the known ketoacid 93 by a procedure of hydrogenolysis and diazoacetylation. When it was treated with trifluoroacetic acid at -30° (see Scheme 24.) two cyclized products were again isolated. By analogy with the products from the previous cyclization they were deduced to be hydroxy dienone ketone 95 (42%) and trienone 96 (22%).

The decrease in the total amount of cyclized material was due to the reduced activation by the methylene dioxy group compared to the methoxyl group. The lone pair electron orbitals of the oxygen atoms of the rigid methylene dioxy group cannot adopt maximum overlap with the aryl ring. The higher ratio of rearrangement product to primary



Scheme 23.





Scheme 24.

cyclization product was observed presumably because demethylenation is a slower process than demethylation.

Clearly hydroxy dienone ketone 95 is not a viable intermediate for any extended scheme and a more efficient way of making dienone ketones with suitable substituents to aid in the ring contraction is required. The results of further investigations in this vein are presented in the next Chapter.

CHAPTER 4

CYCLIZATION OF DIAZOKETONES WITH THREE OXYGEN SUBSTITUENTS

(a) Diazoketones 107 and 117

(b) Cyclization of diazoketones 107 and 117

(c) Dienone ketone 123

It has been shown that the acid catalysed cyclizations of tetrahydronaphthyl diazoketones, are in many cases, a promising means for the preparation of synthetically useful cyclohexadienones. It was considered desirable to extend this study to the cyclization of trialkoxy tetrahydronaphthyl diazoketones for the following reasons.

(i) It was not possible to utilize dienone ketones 85 and 94, derived from the dialkoxy diazoketones 88 and 93 respectively, along the lines discussed in Chapter 3. If the dienone ketones, which are potentially available from the trialkoxy diazoketones, could be prepared in sufficient quantity they would appear to be suitable alternatives.*

(ii) The complex interaction of the directing effects of the alkoxy groups on the cyclization would provide interesting results with respect to the product composition and perhaps give further insight into the relative rates of formation of the different intermediates possible in these cyclizations.

(iii) The dialkoxy dienone ketones which could be derived from the trialkoxy diazoketones contain cyclohexadienone rings analogous to those found in morphinandiones e.g. the alkaloids 97[111], 98[112], 99[113], and 100[114]. Any transformations achieved on these tricyclic dienone ketones could hopefully be applied to the considerably less accessible precursors to the alkaloids.

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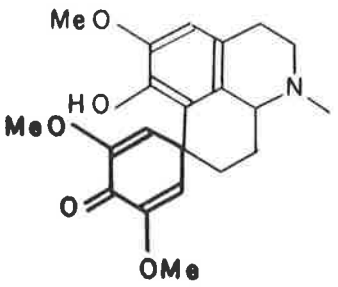
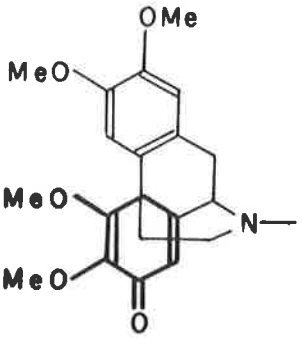
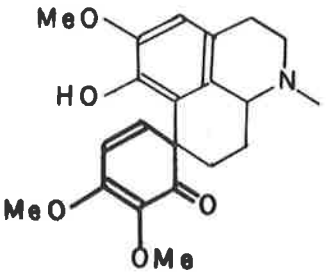
* Research by Kubota on the synthesis of A-norsteroids[123,124] indicates that oxidation of the trione derived from a dialkoxy dienone ketone should afford the required ring contraction.


MeO
HO
MeO
O
OMe
N

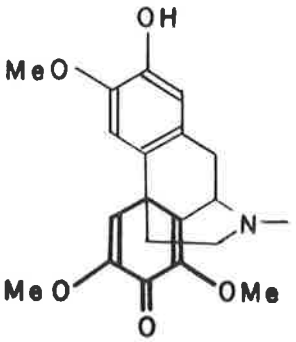
97


OMe
MeO
MeO
MeO
N
O

98


MeO
HO
MeO
O
OMe
N

99


OH
MeO
MeO
OMe
O
N

100

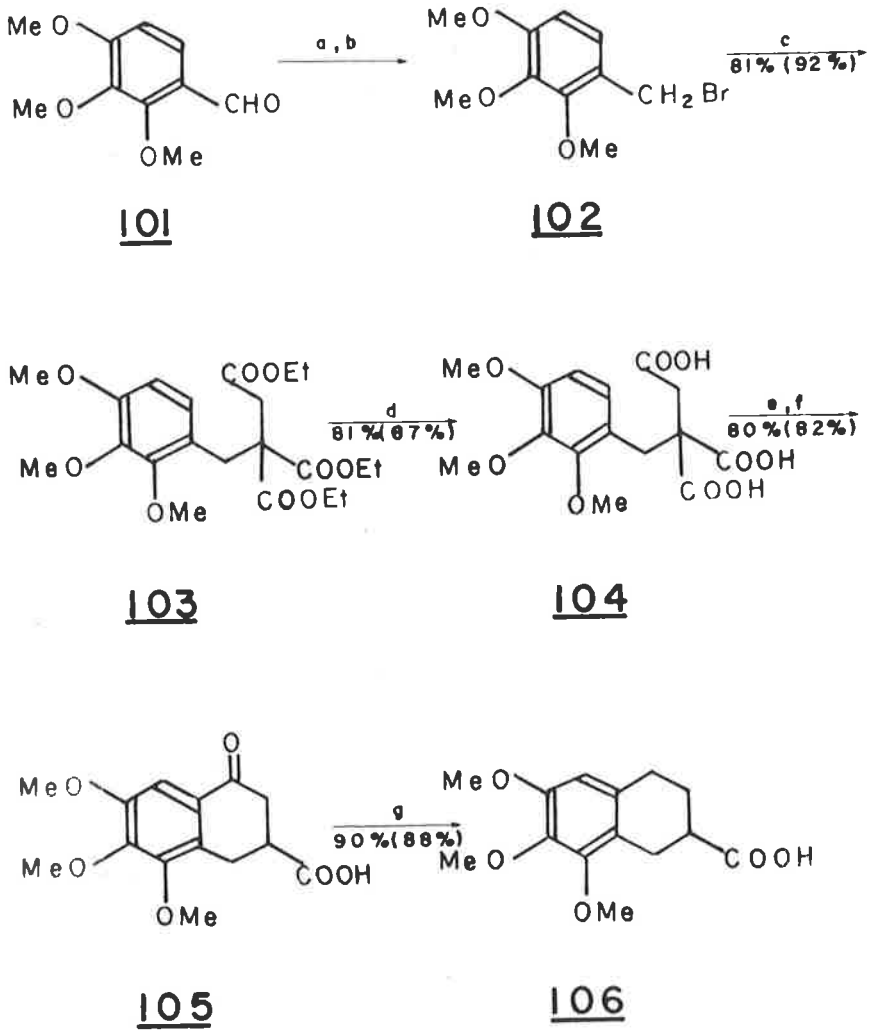
The syntheses of two trialkoxy diazoketones 107 and 117 were undertaken and the results are presented in section (a) of this Chapter. Their cyclizations are described in section (b).

(a) Diazoketones 107 and 117

The precursor acid 106 to diazoketone 107 was prepared by the route outlined in Scheme 25. The aldehyde 101 was available by methylation of pyrogallol followed by a Vilsmeier formylation[115]. The approach, based on the elaboration of the condensation product of aldehyde 101 and dimethyl succinate, which has been used to prepare other tetrahydronaphthoic acids[71,110], was tried, without success, and an alternative method was employed[116].

Aldehyde 101 was converted to the bromide 102 which alkylated triethyl-1,1,2-ethanetricarboxylate under mild conditions. The crude triester 103 was de-esterified to the deliquescent triacid 104 which was in turn decarboxylated at 180^{o} and cyclized with polyphosphoric acid (without isolation of the intermediate diacid) to keto acid 105. A Clemmenson reduction of ketoacid 105 gave acid 106 in good overall yield. Diazoketone 107 was then prepared from this acid in the usual way.

The isomeric diazoketone 117 was synthesised in an identical manner from the commercially available 3,4,5-trimethoxybenzaldehyde. The yields of the individual steps are included in brackets in Scheme 25.



Scheme 25. Reagents: (a) $LiAlH_4$; (b) PBr_3; (c) $CH_2(CO_2Et)$-$CH(CO_2Et)_2$, NaOEt; (d) KOH, EtOH; (e) Δ; 180°; (f) PPA; (g) Zn(Hg), HCl.

Figures in brackets are the yields for the isomeric compounds. See text.

(b) Cyclization of diazoketones 107 and 117.

In the cyclization of diazoketone 107 (see Scheme 26.) there should be two methoxyl groups assisting five membered ring formation and one methoxyl group assisting six membered ring formation. Since six membered ring formation is a slower process only cyclized products arising from a five membered ring intermediate such as the oxonium ion 108 would be expected. This proposed intermediate 108 can then lead to either the cyclohexa-2,4-dienone ketone 109 or the cyclohexa-2,5-dienone ketone 110. Which of these two dienone ketones predominates will no doubt depend on a combination of electronic and steric effects.

Treatment of diazoketone 107 with trifluoroacetic acid at -30° gave one cyclized product (isolated in 55% yield). Its ultraviolet spectrum exhibited absorption maxima at 245 and 291 nm which were close to those calculated for dienone ketone 110 (ca 245 and 298 nm*). It was not, however, possible to reject conclusively dienone ketone 109 as the product, from the other spectral data. The unambiguous preparation of a compound containing the dimethoxy cyclohexa-2,4-dienone chromophore was therefore undertaken to enable an assignment of structure to be made.

A compound of this type should be available from an ortho-phenolic diazoketone, such as diazoketone 114, by

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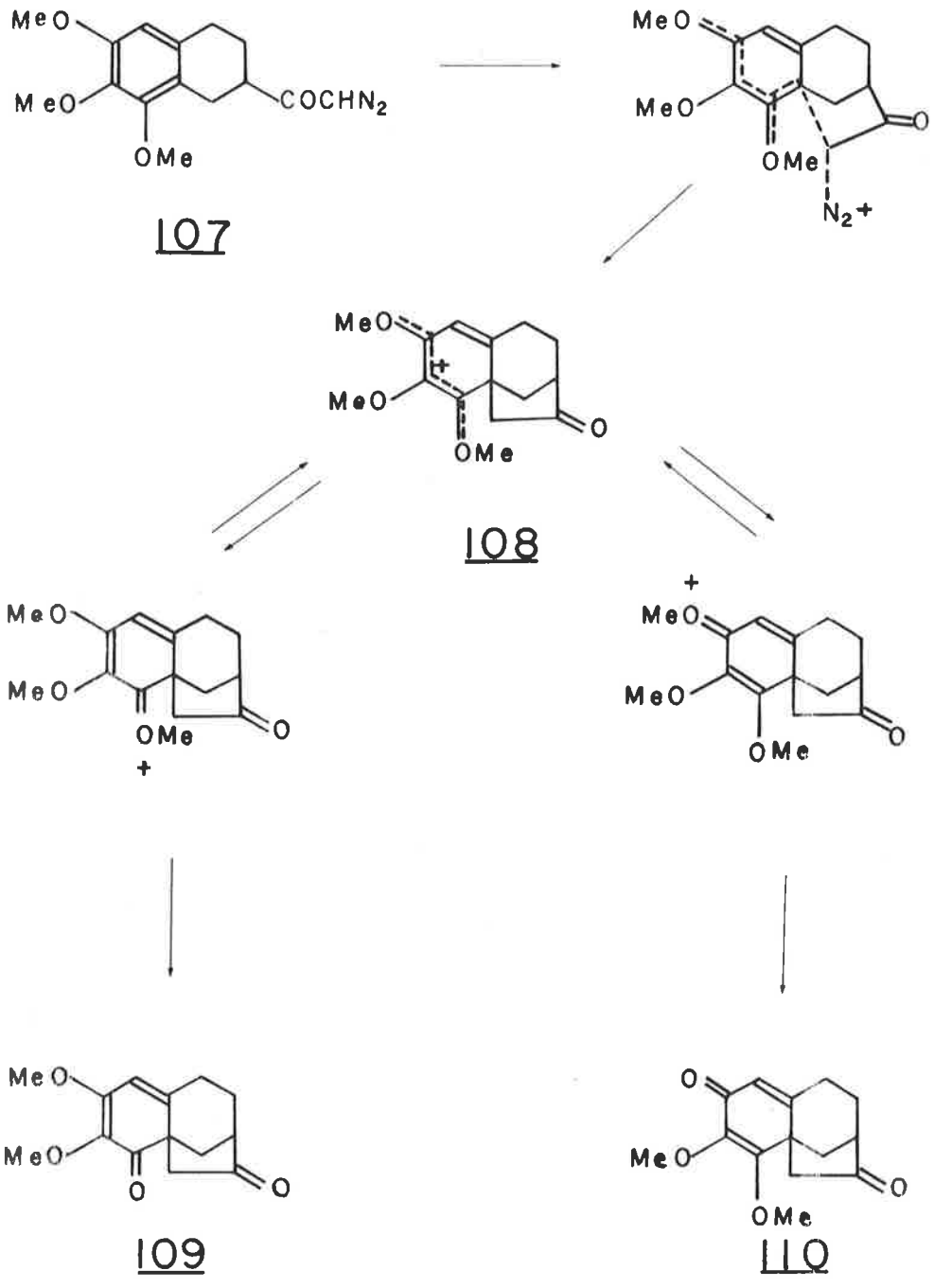
* The ultraviolet absorption maxima were calculated from the tables of reference 117.


MeO
MeO
OMe
COCHN2
107
MeO
MeO
OMe
N2+
MeO
MeO
OMe
108
MeO
MeO
OMe
+
MeO
MeO
OMe
+
MeO
MeO
O
O
109
O
MeO
OMe
O
110

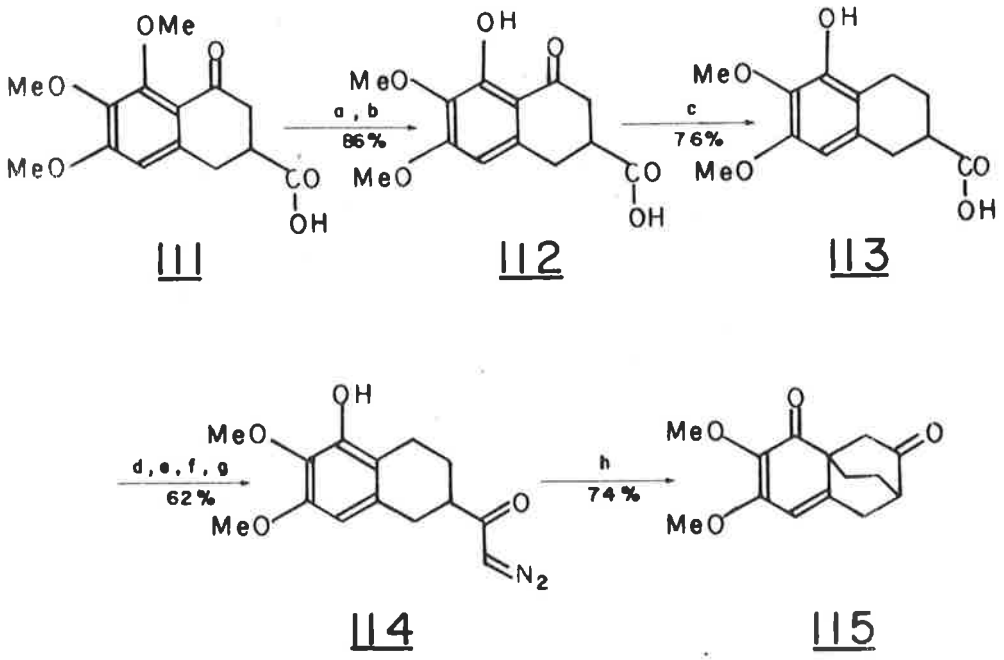
Scheme 26.

analogy with cyclizations discussed in previous Chapters. The preparation of diazoketone 114 is outlined in Scheme 27. The keto acid 111 (for preparation see section (a) of this Chapter) was cleanly demethylated to the keto acid 112 with boron trichloride in dichloromethane : a reaction which exploited the peri-relationship of the ketone group to the methoxyl group[118]. The ketone group of keto acid 112 was removed in a Clemmenson reduction to give acid 113. This acid was converted to diazoketone 114 by the standard procedure of acetylation, diazoacetylation and deacetylation. Treatment of this diazoketone with trifluoroacetic acid at -30^{o} gave, as expected, dienone ketone 115 (in 74% yield). It was uncontaminated by any other detectable, cyclized product.

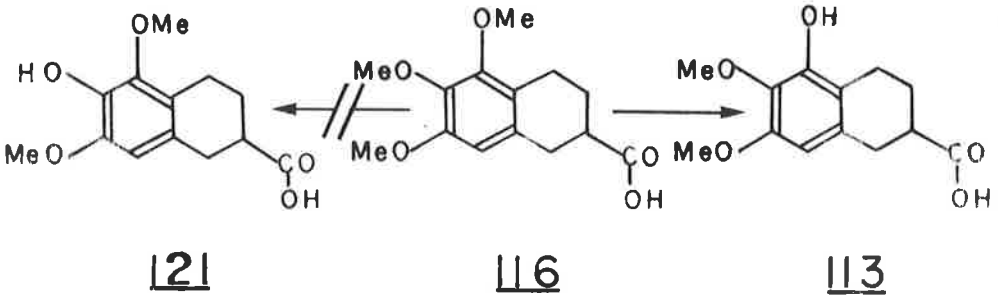
A comparison of the spectra of dienone ketone 115 with those of the compound suspected to be dienone ketone 110 revealed distinct differences. In particular, the ultra-violet absorption spectrum of dienone ketone 115 had a maximum at 344 nm (ca 348 nm). Thus the product from the cyclization of diazoketone 107 can be assigned the structure of dienone ketone 110 with complete confidence.

The cyclization of diazoketone 117 to a bicyclo [2.2.2] octane system (e.g. dienone ketone 119) should be assisted by two methoxyl groups while cyclization to the more favoured bicyclo [3.2.1] octane system (e.g. dienone ketone 118) should be assisted by one methoxyl group. Thus it was impossible to predict the product composition of this reaction.

Diazoketone 117 was prepared from acid 116 and was



Scheme 27. Reagents: (a)BCl_3; (b)H_2O; (c)Zn(Hg), HCl; (d)Ac_2O, NaOAc; (e)$(COCl)_2$; (f)CH_2N_2; (g) py; (h)TFA.



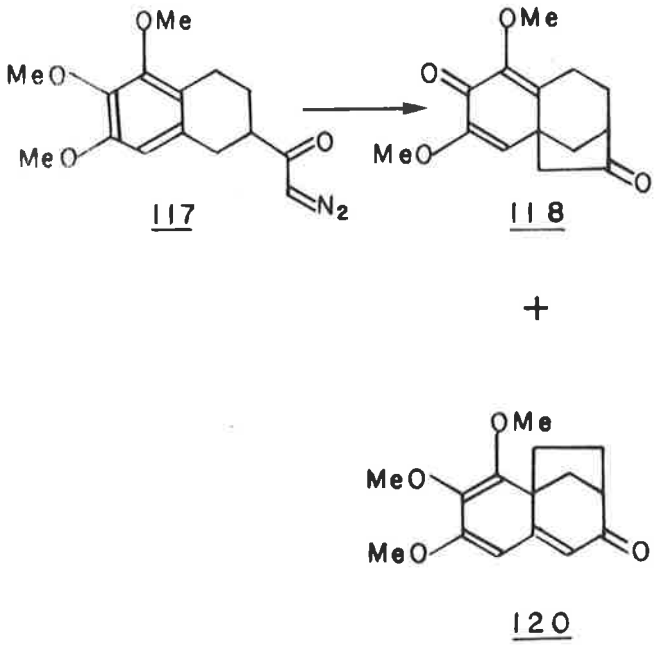
Scheme 28.

treated with trifluoroacetic acid at -20°. A mixture of three cyclized products was obtained and they were assigned the structures of dienone ketone 118, dienone ketone 119 and trienone 120 (see Scheme 29.). If the temperature of the cyclization was lowered to -30°, none of the rearrangement product, trienone 120, could be detected. Since the yield of dienone ketone 118 also increased, there is strong evidence to suggest that both trienone 120 and dienone ketone 118 originated from the same intermediate.

Obviously dienone ketone 118, when made by this route, was not an attractive substrate for further elaboration and a method was sought for preparing it in higher yield. One possible solution was to demethylate the central methoxyl group of acid 116 to afford the phenolic acid 121 (see Scheme 28.). This phenolic acid could then be converted to its corresponding diazoketone which should give rise to a high yield of dienone ketone 118 on treatment with trifluoroacetic acid.

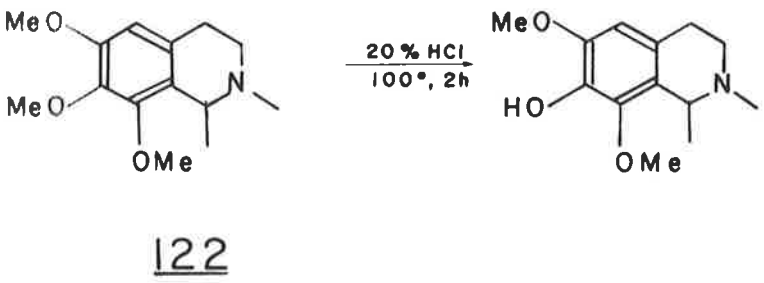
The central methoxyl group of the isoquinoline derivative 122 (Scheme 30.) has been shown[119,120] to be the most basic and it was hoped that the same would be true for acid 116. Treatment of this acid under the same conditions, however, gave instead a product which was identical with the previously prepared phenolic acid 113.

It is difficult to explain the two different positions of demethylation in acid 116 and isoquinoline 122 on steric grounds so it seems likely that in the latter compound, electron withdrawal by the protonated nitrogen atom



T	-20°	-30°
118	20%	24%
119	20%	17%
120	13%	-

Scheme 29.



122

Scheme 30.

makes the peri-methoxyl group less basic than the central one.

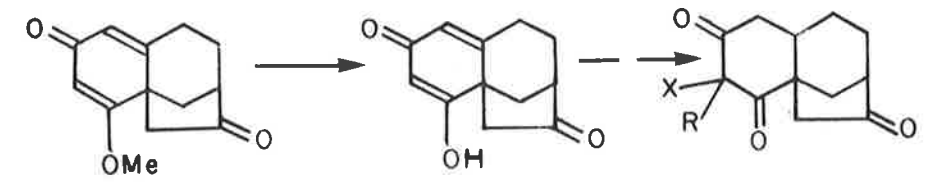
While it has been demonstrated that dienone ketones 110 and 118 can be synthesised, they, like dienone ketones 85 and 94, were not obtainable in sufficient quantity to warrant attempts at further elaboration.

(c) Dienone ketone 123

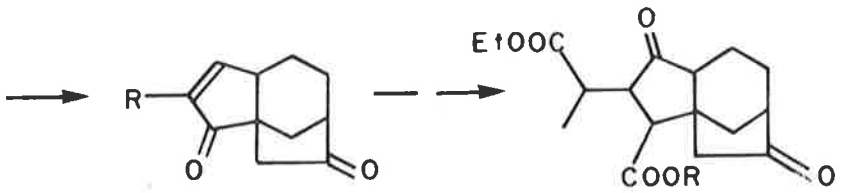
The cyclization of diazoketone 130 to dienone ketone 123 (see Scheme 33.) should be assisted by two methoxyl groups and a high yield of the dienone ketone would be expected. The 1,3-relationship of the two oxygen substituents of this dienone may be exploited in a modified Favorskii rearrangement[121] on a triketone of generalized structure 125 to give the ring contracted enone ketone 126 (Scheme 31.). It should be possible to elaborate this enone ketone to the ketoester 4 and provide another route to the gibberellins.

The synthesis of diazoketone 130, outlined in Scheme 33., was prompted by a method for the reductive elimination of the central methoxyl group of tetralone 127 (Scheme 32.)[122]. As expected, the readily available ketoacid 105 was converted to ketoacid 128 when treated with sodium in liquid ammonia. An nmr spectrum of the reaction mixture indicated that it contained approximately 50% of ketoacid 128. Since one of the byproducts of the reaction was acid 129, the reaction mixture was subjected to a Clemmenson reduction before purification. The overall yield of acid 124 from ketoacid 105 was 47%.

Diazoketone 130, prepared from acid 129 in the usual way, underwent virtually quantitative conversion to dienone ketone 123 when treated with trifluoroacetic acid. The dienone ketone was stable to a boiling solution of 10% aqueous sodium hydroxide in methanol and to a boiling solution of 10% aqueous hydrochloric acid in tetrahydrofuran. It was, however, cleanly demethylated to the dienone ketone 124 when treated with

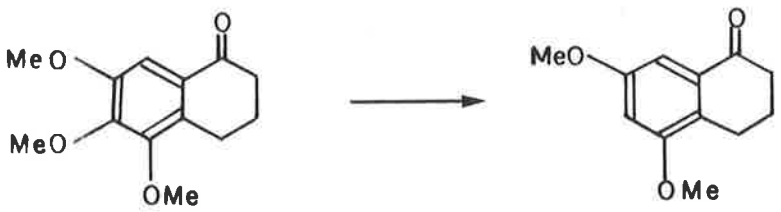


123 124 125



126 4

Scheme 31.

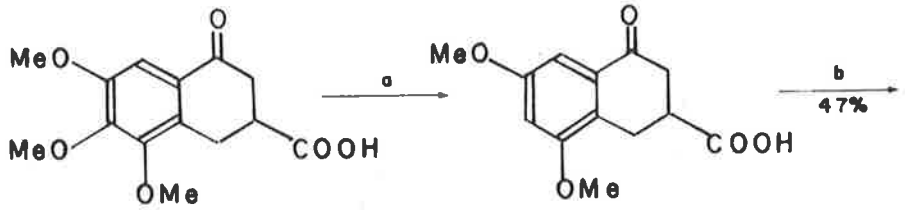


127

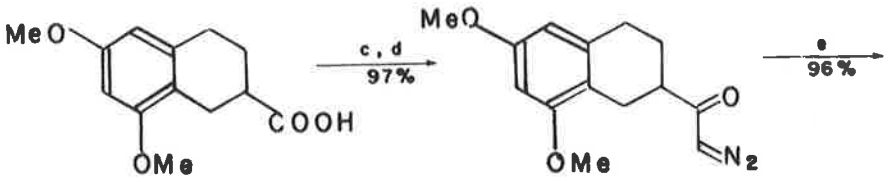
Scheme 32.

concentrated hydrochloric acid at room temperature.

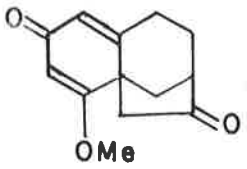
While no further reactions have been attempted, dienone ketone 124 appears to have excellent potential for elaboration in the manner outlined in Scheme 31.



105 128



129 130



123

Scheme 33. Reagents: (a)Na, NH_3; (b)Zn(Hg), HCl; (c) $(COCl)_2$; (d)CH_2N_2; (e)TFA.

CHAPTER 5

ELABORATION OF INTERMEDIATES WITH A GIBBERELLIN A-RING

Dienone ketone 6 which can be prepared from 1,7-dimethoxynaphthalene appears to be an ideal source of the BCD portion of the gibberellins. While the addition of the A-ring to it seems quite feasible by the method outlined in Scheme 1., another possibility is to include the elements of the A-ring on a precursor to this dienone ketone e.g. aldehyde 137. It should be possible to convert aldehyde 137 to acid 138 (X=H) (see Scheme 35.) by the same route which was used to prepare acid 15. This acid (138) has good potential for further elaboration to the gibberellins e.g. gibberellin A_{10} 139 (X=H).

The preparation of aldehyde 137 is outlined in Scheme 34.* Tetralone 133, a logical precursor, has been prepared by a Friedel Crafts cyclization of acid 131 (in 65% yield)[133]. When the cyclization was performed with polyphosphoric acid, acid 131 gave a 75% yield of tetralone 133 and ester 132 gave an 87% yield. The methylene compound 134 was formed from the tetralone by reaction with the ylide generated from triphenylmethylphosphonium iodide and n-butyl lithium. The reaction reached equilibrium at approximately 85% conversion and was not affected by an increase in the concentration of the ylide. The unreacted tetralone, however, was separated by chromatography and was recycled.

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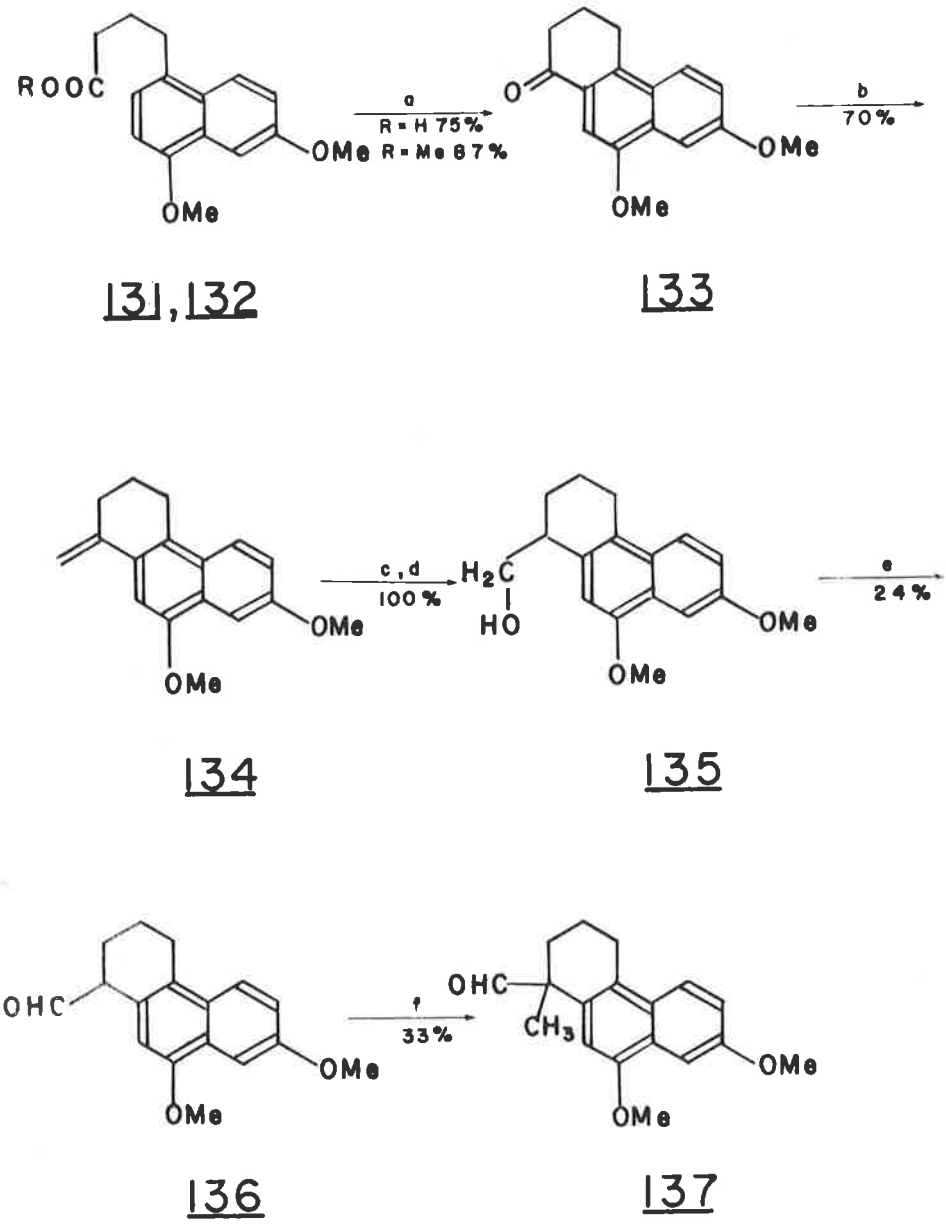
* Compounds of this type containing what will become the Δ^1 double bond and the C3-hydroxyl group of the gibberellins are being made by another worker[128] in this Department.

Hydroboration[126] (and subsequent oxidation) of the methylene compound 134 afforded alcohol 135.

A mild method of oxidation was sought to convert alcohol 135 to aldehyde 136 since it was realized that the aldehyde would be particularly prone to over oxidation. A Collins oxidation[71] afforded aldehyde 136 in 81% crude yield but this dropped to 24% after chromatography.

Alkylation of aldehyde 136 with potassium t-butoxide and methyl iodide[127] was then tried. All solvents were purged with argon and there was a constant flow of that gas above the reaction. Aldehyde 137 was isolated in 33% yield from the mixture. The remainder of the material was tetralone 133 which had presumably arisen from attack by the anion of aldehyde 136 on oxygen and subsequent displacement of the formyl group. The poor yields of this and of the previous step forced the abandonment of this route, and a reconsideration of the strategy.

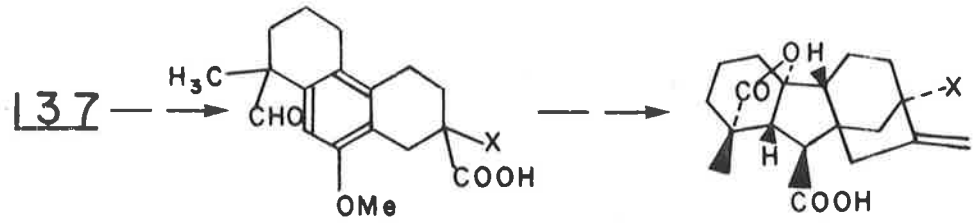
Clearly the aldehyde group is not essential as long as another group is present which can be elaborated to it at a later stage. Alcohol 135 was chosen, accordingly, as a substrate in lieu of aldehyde 137. A Birch-Dryden reduction of alcohol 135 was expected to afford alcohol 141. It gave, instead, the hydrogenolysis product, tetralone 140 (Scheme 36.). Variations in the conditions of the reduction, which included preforming the sodium salt of the alcohol and omitting the proton source, also failed to give alcohol 141. When the reaction was quenched within fifteen minutes, the nmr spectrum of the product indicated that a further compound, suspected to be the methylene tetralone 142, had formed. The



Scheme 34. Reagents: (a)PPA; (b)$\emptyset_3PCH_3Br$, BuLi; (c) B_2H_6; (d)H_2O_2, NaOH; (e)CrO_3, py; (f)t-BuOK, MeI.

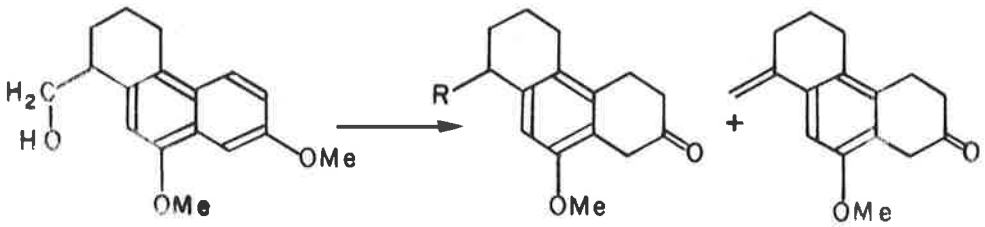
presence of this compound suggested that elimination of the alcohol had occured to give the methylene compound which was then reduced to tetralone 140. Under the same conditions, the bicyclic analogue, alcohol 143 gave no hydrogenolysis product (see Scheme 37.).

No further studies along the route outlined in Scheme 35. were carried out.



138 139

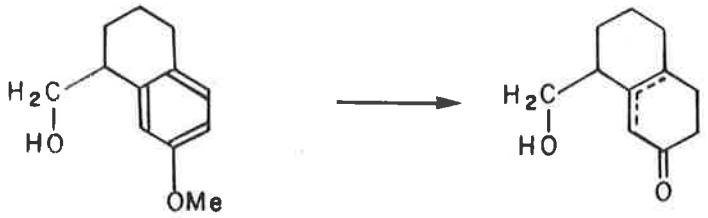
Scheme 35.



135 140 R = CH_3 142

141 R = CH_2OH

Scheme 36.



143

Scheme 37.

CHAPTER 6

A DISCUSSION OF THE ACID CATALYSED

CYCLIZATION OF TETRAHYDRONAPHTHYL DIAZOKETONES

(a) Mechanism

(b) Scope

(c) Limitations

The results of the acid catalysed cyclizations of diazoacetyl-tetrahydronaphthalenes, described in Chapters 1-4, are summarized in this Chapter in terms of the mechanism, the scope and the limitations of the reaction.

(a) The mechanism

In aqueous, acidic solution diazoketones react with nucleophiles by one of two accepted mechanisms. Diazomethyl-ketones generally undergo a fast and reversible protonation prior to a rate determining substitution step[129,130]. This "A2" mechanism (Scheme 38.) is characterised by a solvent isotope effect of $k_{H_2O}/k_{D_2O} \sim 0.3$.

$$RCOCHN_2 \rightleftharpoons RCOCH_2N_2^+ \xrightarrow{Nu^-} RCOCH_2Nu + N_2$$

Scheme 38.

In contrast, more highly substituted diazoketones are characterised by an initial rate determining protonation before the substitution step[129]. The solvent isotope effect for this "A-S_E 2" mechanism (Scheme 39.) is $k_{H_2O}/k_{D_2O} > 1$.

$$RCOC(R')N_2^+ \xrightarrow{H^+} RCOCH(R')N_2^+ \xrightarrow{Nu^-} RCOCH(R')Nu + N_2$$

Scheme 39.

These two mechanisms were clearly distinguished in the cyclization of a number of cyclopentenyl diazoketones by Dahn[131,132]. The various rate and thermodynamic constants for some of these cyclizations (at T=25°) are summarized in

Table 1. The cyclization of diazoketone S which involved intermolecular substitution had a similar solvent isotope effect, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to those from the cyclizations of diazoketones T - V, which involved intramolecular substitution. An "A2" mechanism is therefore evident in both the intermolecular and intramolecular reactions. The large solvent isotope effect (1.74) and the substantial rate enhancement for the cyclization of diazoketone W indicated that an "A-S_E2" mechanism had operated in this case. Intramolecular cyclization of this diazoketone competed effectively with intermolecular substitution by an added nucleophile (e.g. bromide ion) even when the concentration of this nucleophile was ten times greater than that of the diazoketone. The change in mechanism was no doubt due to the rigid norbornene molecule holding the diazoketone group in close to the optimum position for cyclization.* The other cyclopentenyl diazoketones, S - V, are considerably more flexible.

Although these cyclizations were carried out in aqueous media, Dahn's results should be applicable to the non-aqueous system which was used to cyclize the diazoketones discussed in Chapters 1-4. The yield of cyclized products

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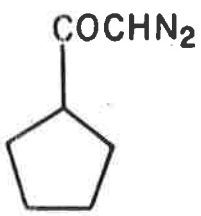
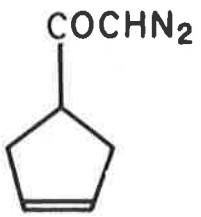
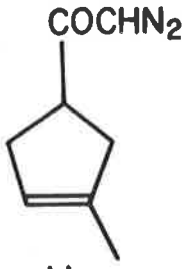
* It is difficult to account for the large rate enhancement for the cyclization of diazoketone W by an entropy effect alone and it is likely that there is a "non-classical" type assistance to the cyclization, similar to that observed in the solvolysis of exo-tosyl norbornanes, which results in a smaller enthalpy of activation.



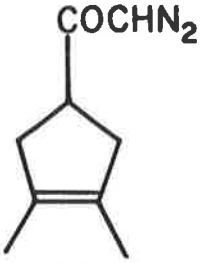
S



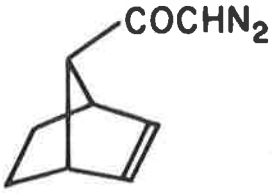
T



U



V



W

	K_{rel}	K_H/K_D	% cyclization	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
S	1.00	0.27	0	21.3	-0.9
T	0.90	0.26	60	20.9	-2.4
U	2.32	0.29	90	20.7	-1.4
V	10.4	0.29	100	19.2	-3.2
W	570	1.74	100		

Table 1.

in these reactions was 60 - 100% which would indicate that the aryl ring of the tetrahydronaphthyl diazoketones provides a similar degree of activation to that of a disubstituted (60% yield*) or perhaps a trisubstituted (90% yield*) double bond. Consequently, an "A2" mechanism with its fast initial protonation could be assumed.

---

* The yields of cyclized products from the appropriate cyclopentenyl diazoketone in Table 1.

(b) Scope of the reaction

In the conversion of phenolic diazoketones to spirodienone ketones (Scheme 40.)[130] those cyclizations which gave other than a cyclobutanone or a cyclopentanone (i.e. n=4,5) were unfavourable presumably because there were too many degrees of freedom in the longer chain diazoketones (greater entropy of activation). Where the flexibility of the reacting diazoketone was reduced as in the tetrahydronaphthyl diazoketones[46] higher overall yields were obtained and the formation of cyclohexanone rings was a viable process (e.g. the preparations of dienone ketones 49 and 115). Cyclizations to give both five and six membered ring products were undertaken in Chapters 1-4. Five membered ring formation was found to be favoured kinetically over six membered ring formation as expected[133]. Under thermodynamic conditions this was reversed. For example, it has been demonstrated[134] that in the presence of methanolic sulphuric acid, dienone ketone 6 rearranged cleanly to dienone ketone 49 (Scheme 41.).*

The yield of cyclized products was dependent on the activity of the participating aryl ring. The nature and position of substituents on this aryl ring determined the degree of activation. A single methoxyl group led to

---

* The acid catalysed rearrangement of a cyclobutanone to a cyclopentanone has been previously observed in the cyclization of a tetrahydronaphthyl diazoketone[46].

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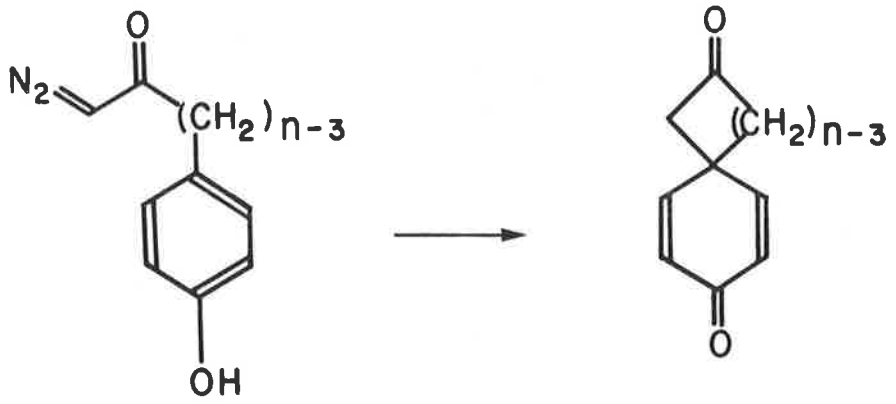
approximately a 70% yield of cyclized material (e.g. the cyclization of diazoketone 47) whereas a phenolic group was usually responsible for a >95% yield. When optimal overlap of the lone pair electrons of the oxygen atom of these groups with the pi system of the aromatic ring was prevented, with, for example, the methylenedioxy group of diazoketone 94, there was a reduced yield of cyclized products. Other examples of this effect, this time due to buttressing, were observed in the cyclizations of diazoketones 117 and 144[135]. An acetate group, in which the oxygen lone pair electrons are further delocalized over other atoms has been found[134] to completely deactivate the ring to cyclization (e.g. the acetate derived from diazoketone 5).

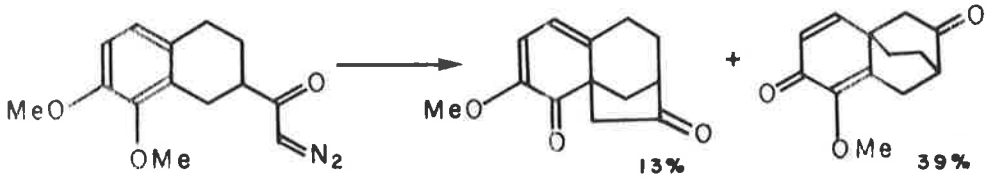
The directing effects of two substituents, one ortho and the other para to the ring junction were cumulative (see for example the cyclization of dimethoxydiazoketone 130) and a >95% yield of cyclized product was obtained.



Scheme 40.

6 49

Scheme 41.



144 145

Scheme 42.

(c) Limitations

When a second oxygen substituent (with the exception of OH) was present on the aryl ring of the diazoketone, which did not assist the cyclization, rearrangement to a trienone was usually observed (e.g. the formation of trienone 66, Scheme 19.). It was concluded that an alkyl shift of the initial cyclized intermediate to give an intermediate which led to the rearrangement product was faster than dealkylation to give the dienone ketone. This rearrangement was avoided by cyclizing a phenolic diazoketone rather than its O-alkylated derivative (e.g. the cyclizations of diazoketones 117 and 114).

EXPERIMENTAL

General Topics

(i) Melting points were determined on a Reichert hot-stage apparatus and are uncorrected.

(ii) Infra red spectra, unless otherwise indicated, were measured as Nujol mulls on Unicam SP200 and Jasco IRA-1 spectrophotometers.

(iii) Ultraviolet spectra were recorded in 95% ethanol on a Perkin-Elmer 137 instrument.

(iv) Mass spectra were measured on a Hitachi-Perkin Elmer RMU-6D instrument operating at 70 eV and with an inlet temperature of 200°.

(v) The nuclear magnetic resonance spectra were recorded on Varian DA-60-IL and T60 spectrometers operating at 60 MHz. The spectra were measured in deuterochloroform solution relative to tetramethylsilane (δ 0.00 p.p.m.) unless otherwise stated; each signal is described in terms of chemical shift in p.p.m. from tetramethylsilane, multiplicity, intensity, coupling constants in Hz and assignment in that order with the use of the following abbreviations : s,singlet ;d,doublet ; t,triplet ; q,quartet ;m,multiplet; and $W_{h/2}$, width of peak at half height.

(vi) The carbon magnetic resonance spectrum was measured on a Bruker HX90 instrument by H.B. Selby & Co., Melbourne.

(vii) Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

(viii) Accurate molecular weight determinations were performed

on an AEI MS902 high resolution mass spectrometer using Heptacosa as a reference compound.

(ix) Chromatographic absorbents used were Spence type H alumina and Sorbsil silica gel. Analytical and preparative thin layer chromatography were carried out on layers containing an equal mixture of Merck Kieselgel G and HF254.

(x) All solvent extracts were dried over anhydrous sodium sulphate.

(xi) Light petroleum refers to the fraction b.p. 40-60^{o}.

General method for the preparation of diazomethylketones from carboxylic acids.

Diazoketones were prepared by the following two-step sequence.

(a) Preparation of the acid chloride

A solution of the acid (0.01 mol) in dry benzene (10 ml) was added during 1h to a stirred solution of oxalyl chloride (0.08 mol) in benzene (20 ml) (with the exclusion of moisture). The mixture was stirred at room temperature for 2h and at 50° for 30 min. The solvents were removed under reduced pressure. The residual oxalyl chloride was removed by adding two further portions of benzene, and separately re-evaporating under reduced pressure. The crude acid chloride was used immediately in the next step.

(b) Reaction of the acid chloride with diazomethane

The crude acid chloride (0.01 mol) in benzene was added during 1h to a stirred, ice-cold solution of ethereal diazomethane[136] (0.05 mol). The solution was allowed to warm to room temperature and stirred for a further 6-14h. The excess of diazomethane was driven off by warming the solution and it was gravity filtered. The solvents were removed by distillation under reduced pressure to afford the (usually) yellow diazoketone.

CHAPTER 1

3,4-Dihydro-8-hydroxynaphthalen-2(1H)-one 18

To a solution of naphthalene-1,7-diol (8.0g, 0.05 mol) in a mixture of tetrahydrofuran (20 ml), t-butyl alcohol (9.5 ml) and liquid ammonia (100 ml) under an atmosphere of nitrogen, were added small pieces of lithium metal (1.1g, 0.15 g-atom) during 10 min. After a further 1h, methanol (30 ml) was added and the ammonia was removed in a stream of nitrogen. The residue was rendered acidic by the addition of hydrochloric acid (10% aqueous) and extracted with ethyl acetate (2x150 ml). The organic extracts were combined, washed with water and dried. The residue, after removal of the solvent under reduced pressure was chromatographed on Sorbsil (150g) under an atmosphere of nitrogen. Elution with ether-light petroleum (1:4) yielded the phenolic ketone 18 (3.8g, 44%) as white crystals, m.p. 156-157°. A sample crystallized from ether as white needles, m.p. 156-157° (Found : C, 74.4; H, 6.4. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%). ν_{max} 3170 (OH), 1680 cm^{-1} (CO). δ 7.1 (t, 1H, J 7.5 Hz, Ar H), 6.6-6.9 (m, 2H, Ar H), 5.5 (s, 1H, OH), 3.5 (s, 2H, $ArCH_2CO$). M^+, m/e 162 (7%).

5,6,7,8-Tetrahydronaphthalene-1,7-diol 20

Naphthalene-1,7-diol was reduced with five equivalents of lithium metal under otherwise identical conditions for the preparation of tetralone 18 to give a quantitative yield of the diol 20. A sample was crystallized twice from chloroform as pale brown needles, m.p. 154-155° (Found : C, 73.4; H,

7.4. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%). ν_{max} 3410 (aliphatic OH), 3050 cm^{-1} (phenolic OH). δ ($CDCl_3$/$(CD_3)_2SO$) 6.4-7.1 (m, 3H, Ar H), 4.4(br s, 1H, phenolic OH), 4.1 (m, 1H, CHOH), 3.5 (br s, 1H, aliphatic OH). M^+, m/e 164 (54%).

1,2,3,4-Tetrahydro-8-methoxy-2-naphthol 21

Methylation of diol 20 with dimethyl sulphate gave naphthol 21 in 93% yield as a brown solid, m.p. 99-100°. An analytical sample crystallized from ether-light petroleum as pale brown needles, m.p. 105.5-106.5° (Found : C, 74.1; H, 8.2. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%). ν_{max} 3300 (OH), 1255, 1040 cm^{-1} (CO). δ 6.6-7.3 (m, 3H, Ar H), 4.2 (m, 1H, CHOH), 3.8 (s, 3H, OMe), 1.7 (s, 1H, OH). M^+, m/e 176 (100%).

3,4-Dihydro-8-methoxynaphthalen-2(1H)-one 19

(A) To a solution of 1,7-dimethoxynaphthalene (15.8g, 0.084 mol) in a mixture of tetrahydrofuran (150 ml), ethanol (215 ml) and liquid ammonia (600 ml) was added sodium (23.0g, 1.0 g-atom) during 15 min. The ammonia was removed in a stream of nitrogen and the residue was diluted with water and extracted with ether. The ethereal solution was washed with water and 3N hydrochloric acid (10 ml) was added, followed by sufficient methanol to make the solution homogenous. After 5 min, the solution was diluted with water, benzene was added and the organic layer was separated. The organic extract was washed with water, sodium bicarbonate solution and dried. The residue (14.4g), after removal of the solvent under reduced pressure, was shown to contain tetralone 19

75% yield. A sample was distilled as a colourless liquid, b.p. 94-96^{o} (0.3 mm) which crystallized as white needles, m.p. 55-56.5^{o} (Found : C, 75.0; H, 6.9. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9%). ν_{max} 1705 (CO), 1585 cm^{-1} (aromatic C=C). δ 7.1 (t, 1H, J 7.5 Hz, Ar H), 6.5-6.8 (m, 3H, Ar H), 3.8 (s, 3H, OMe), 3.4 (s, 2H, $COCH_2Ar$). M^+, m/e 176 (100%).

(B) Chromium trioxide (600mg, 6 mmol) was added to a stirred solution of pyridine (950mg, 12 mmol) in dichloromethane (15 ml). The red solution was stirred at room temperature for 15 min (with exclusion of moisture) and a solution of naphthol 21 (178mg, 1 mmol) in dichloromethane (2 ml) was added all at once. The suspension was stirred for 15 min and the solution decanted from the tarry residue. Ether (50 ml) was added to precipitate the remaining chromium salts which were then separated by filtration. The solution was washed with water, hydrochloric acid (5% aqueous), water and dried. Removal of the solvent under reduced pressure gave tetralone 19 (150mg, 85%) as a yellow semi-solid which gave an identical infrared spectrum to that of a sample prepared by Method A.

1,2,3,4-Tetrahydro-2,8-dihydroxy-2-naphthonitrile 22

Hydroxytetralone 18 (1.0g, 0.0062 mol) in ether (50 ml) and water (35ml) was stirred vigorously while a stream of nitrogen was passed through the solution. Sodium cyanide (1.0g) was added and the solution was treated dropwise with concentrated hydrochloric acid over a 1h period. The organic layer was separated, washed with water and dried.

Removal of the solvent under reduced pressure gave cyanohydrin 22 (1.1g, 95% crude yield) as a pale brown solid, m.p. 130-135°. A sample crystallized from ether-light petroleum as white rhombohedral crystals, m.p. 157-158.5° (Found : C, 69.9; H, 6.0; N, 7.1. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%). ν_{max} 3340 (OH), 2250 cm^{-1} (CN). δ 7.9 (s, 1H, OH), 6.5-7.1 (m, 3H, Ar H), 5.5 (s, 1H, OH). M^+, m/e 162 (M^+-HCN, 69%).

1,2,3,4-Tetrahydro-2-hydroxy-8-methoxy-2-naphthonitrile 23

Hydrocyanation of tetralone 19 by the method described for the preparation of the phenolic cyanohydrin 22 gave a quantitative yield of cyanohydrin 23 as a brown solid. A sample crystallized from ether-light petroleum as white crystals, m.p. 118-119° (Found : C, 71.1; H, 6.7; N, 7.2. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%). ν_{max} 3390 (OH), 2240 cm^{-1} (CN). δ 6.6-7.3 (m, 3H, Ar H), 3.8 (s, 3H, OMe). M^+, m/e 203 (8%).

1,2,3,4-Tetrahydro-2,8-dihydroxy-2-naphthoic Acid 16

Cyanohydrin 22 (500mg, 2.7 mmol) was added portion-wise to stirred, concentrated hydrochloric acid (10 ml) during 15 min. This solution was stirred at room temperature for 30 min, at 70° for 4h, then poured onto ice (100g) and extracted with ethyl acetate (3x50 ml). The extracts were washed with water, dried, and evaporated under reduced pressure to yield hydroxy acid 16 (450mg, 82%) as a brown solid, m.p. 142-145°. An analytical sample crystallized

from ether-light petroleum as white crystals, m.p. 162-163° (Found : C, 63.3; H, 6.1. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.8%). ν_{max} 3400 (tertiary OH), 3150 (phenolic OH), 1705 cm^{-1} (CO_2H). δ ($CDCl_3$/$(CD_3)_2SO$) 7.6 (br s, 3H, phenolic, tertiary and acid OH), 6.6-7.2 (m, 3H, Ar H). M^+, m/e 208 (33%).

1,2,3,4-Tetrahydro-2-hydroxy-8-methoxy-2-naphthoic Acid 17

Hydrolysis of cyanohydrin 23 in an analogous manner to the preparation of the phenolic acid 16 gave a 79% yield of methoxy acid 17 as a brown solid. A sample crystallized from chloroform as thin, white platelets, m.p. 164-165° (Found : C, 65.0; H, 6.1. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.4%). ν_{max} 3350 (OH), 2600-2800, 1700 (CO_2H), 1250, 1100, 1090 cm^{-1} (CO). δ 6.5-7.4 (m, 3H, Ar H), 5.7 (br s, 1H, OH), 3.8 (s, 3H, OMe). M^+, m/e 222 (42%).

2-Acetoxy-1,2,3,4-tetrahydro-8-methoxy-2-naphthoic Acid 24

Methoxy acid 17 (1.0g, 0.0045 mol), acetic anhydride (20 ml) and pyridine (0.6 ml) were stirred together at room temperature for 3h and at 90° for 2h. Sufficient water was added to hydrolyse the acetic anhydride and the aqueous solution was extracted with dichloromethane (2x50 ml). The dichloromethane solution was washed repeatedly with water and dried. Removal of the solvent under reduced pressure yielded the acetoxy acid 24 (1.0g, 84%) as a brown solid. An analytical sample crystallized from ether-light petroleum as long, white needles, m.p. 159-159.5° (Found : C, 63.9;

H, 6.3. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%). ν_{max} 2600-2800, 1700 (CO_2H), 1725 cm^{-1} (acetate C=O). δ 6.6-7.1 (m, 3H, Ar H), 4.5 (br s, 1H, CO_2H), 3.8 (s, 3H, OAc). M^+, m/e 204 (M-HOAC, 98%).

Lithium and Liquid Ammonia Reduction of 2-Acetoxy-1,2,3,4-tetrahydro-8-methoxy-2-naphthoic Acid 24

A solution of acetoxy acid (132mg, 0.5 mmol) in tetrahydrofuran (2 ml), liquid ammonia (5 ml) and t-butyl alcohol (0.15 ml) was reduced by the addition of lithium metal (14mg, 2.0mg-atom). The solution was stirred for 1h and methanol (1 ml) was added. The solution was poured into a mixture of ice (10g) and concentrated hydrochloric acid (10 ml) and extracted with ether (3x20 ml). The ether was removed under reduced pressure to give 120mg of a brown solid, which was shown from its spectra to be methoxy acid 17.

Methyl 2-Acetoxy-1,2,3,4-tetrahydro-8-methoxy-2-naphthoate 25

This compound was prepared from the acid by treatment with diazomethane. A sample crystallized from ether-light petroleum as pale yellow crystals, m.p. 121.5-122.5° (Found : C, 64.7; H, 6.6. $C_{15}H_{18}O_3$ requires C, 64.7; H, 6.5%). ν_{max} 1725 (ester and acetate C=O), 1275, 1265, 1210 cm^{-1} (CO). δ 3.8 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.0 (s, 3H, OAc). M^+, m/e 278 (1%). The α-hydroxy ester was obtained from treatment with lithium in ammonia as described above.

3,4-Dihydro-8-hydroxy-2-naphthonitrile 26

A solution of cyanohydrin 22 (2.0g, 0.0108 mol) in pyridine (50 ml) at 0^{o} was treated dropwise with thionyl chloride (2 ml) and the solution was stirred for 18h at room temperature and under nitrogen. An equivalent volume of water was added, followed by sufficient concentrated hydrochloric acid to neutralize the pyridine. The solution was extracted with ether (4x50 ml) and the extracts were combined, washed and dried. Removal of the ether under reduced pressure gave the unsaturated nitrile 26 (1.5g, 83%) as a brown solid, m.p. 202-205^{o}. A sample was crystallized twice from ether-light petroleum as pale yellow platelets, m.p. 217-219^{o} (dec.) (Found : C, 77.4; H, 5.5; N, 8.1. $C_{11}H_9NO$ requires C, 77.2; H, 5.3; N, 8.2%). ν_{max} 3300 (OH), 2200 (CN), 1615 cm^{-1} (C=C). δ ($CDCl_3$/ $(CD_3)_2SO$) 7.6 (br s, 1H, OH), 6.5-7.2 (m, 3H, Ar H), 6.4 (br s, 1H, (CN)C=CH). M^+, m/e 171 (100%).

3,4-Dihydro-8-methoxy-2-naphthonitrile 27

Dehydration of cyanohydrin 23 by the method described above, afforded the unsaturated nitrile 27 as a yellow-brown solid, m.p. 55-60^{o} in 85% yield. An analytical sample was crystallized from light petroleum as poorly formed, yellow crystals, m.p. 73-74^{o} (Found : C, 77.5; H, 5.8; N, 7.3. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%). ν_{max} 2250 (CN), 1655, 1620 (C=C), 1595, 1580 cm^{-1} (aromatic C=C). δ 6.7-7.7 (m, 4H, Ar H, and C=CH), 3.8 (s, 3H, OMe). M^+, m/e 185 (100%).

3,4-Dihydro-8-hydroxy-2-naphthoic Acid 28

A solution of nitrile 26 (300mg, 0.0018 mol) in aqueous sodium hydroxide solution (30 ml, 10%) was boiled under reflux for 2h. The solution was cooled, made acidic with concentrated hydrochloric acid and extracted with ethyl acetate (3x25 ml). The extracts were combined, washed and dried. The ethyl acetate was removed under reduced pressure and the residue was chromatographed on Sorbsil (20g). Elution with ether yielded the unsaturated acid 28 (230mg, 69%) as a brown solid, m.p. 146-149°. A sample crystallized from ether-light petroleum as white crystals, m.p. 149-151° (Found : C, 69.1; H, 5.5. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%). ν_{max} 3400 (OH), 2600-2800, 1665 (CO_2H), 1600 cm^{-1} (C=C). δ ($CDCl_3$/$(CD_3)_2$ SO) 8.0 (s, 1H, OH), 6.6-7.2 (m, 4H, Ar H and $HC{=}CCO_2H$), 5.0 (br s, 1H, CO_2H). M^+, m/e 190 (55%).

3,4-Dihydro-8-methoxy-2-naphthoic Acid 29

Hydrolysis of nitrile 27 by an identical procedure to that described above gave the unsaturated acid 29 in 67% yield as a brown solid, m.p. 176-178°. A sample was crystallized from ether-light petroleum as white rhombohedra, m.p. 205-207° (Found : C, 70.5; H, 6.1. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%). ν_{max} 1675 (CO_2H), 1620 cm^{-1} (C=C). δ 8.2 (s, 1H, C=CH), 6.7-7.5 (m, 3H, Ar H), 3.8 (s, 3H, OMe). M^+, m/e 204 (100%).

1,2,3,4-Tetrahydro-8-hydroxy-2-naphthoic Acid 14

(A) To a solution of naphthoic acid 28 (950mg, 0.005 mol)

in a mixture of tetrahydrofuran (20 ml), liquid ammonia (25 ml), and t-butyl alcohol (1.9 ml) were added small pieces of sodium metal (575mg, 0.025g-atom) during 15 min. The solution was stirred for 60 min whilst immersed in ethanol and dry ice, poured into ice and concentrated hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate extract was washed and dried and the solvent was removed under reduced pressure to yield acid 14 (880mg, 93% crude yield) as a brown solid. A sample crystallized from ether-light petroleum as white needles, m.p. 138-139° (Found : C, 69.0; H, 6.3. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν_{max} 3340 (OH), 1680 cm^{-1} (CO_2H). δ ($CDCl_3$/$(CD_3)_2$SO) 8.8 (br s, 2H, phenol and acid OH). M^+, m/e 192 (54%). (B) This compound was also made by a pyridine hydrochloride demethylation[65] of acid 15.

1,2,3,4-Tetrahydro-8-methoxy-2-naphthoic Acid 15

Reduction of unsaturated acid 29 by the same method described in Section A of the previous preparation gave methoxy acid 15 in 82% yield. A sample was recrystallized from ether-light petroleum as yellow needles, m.p. 140-142° (lit.[137] m.p. 141-143°) (Found : C, 69.6; H, 7.2. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν_{max} 1690 cm^{-1} (CO_2H). δ 11.4 (br s, 1H, CO_2H), 7.1 (t, 1H, Ar H), 6.5-6.8 (m, 2H, Ar H), 3.8 (s, 3H, OMe). M^+, m/e 206 (68%).

5,6,7,8-Tetrahydro-1-methoxy-7-tosyloxy-naphthalene 35

A solution of tetralol 21 (8.9g, 0.05 mol) in

pyridine (100 ml) at 0° was treated with p-toluenesulphonyl chloride (16.0g, 0.1 mol) and the resultant solution was stirred at room temperature, with the exclusion of moisture, for 16h. It was poured into ice-hydrochloric acid and extracted with dichloromethane. The dichloromethane solution was washed with water, dried and evaporated under reduced pressure to give a red oil which on trituration with light petroleum afforded tosylate 35 (15.45g, 93%) as a yellow solid, m.p. 88-90°. A sample was recrystallized from dichloromethane-light petroleum as orange crystals, m.p. 95-95.5° (Found : C, 64.9; H, 6.0; S, 9.4. $C_{18}H_{20}SO_4$ requires C, 65.1; H, 6.1; S, 9.6%). ν_{max} 1590 (aromatic C=C), 1345, 1170 cm^{-1} (OSO_2). δ 7.5 (AB_q, 4H, J_{AB}8Hz, SO_2Ar H), 6.5-7.2 (m, 3H, Ar H), 4.9 (m, 1H, $CHOSO_2$), 3.8 (s, 3H, OMe), 2.5 (s, 3H, $ArCH_3$).

5,6,7,8-Tetrahydro-1-methoxy-7-mesyloxy-naphthalene 30

This compound was prepared in an analogous manner to tosylate 35 from tetralol 21, as yellow needles, m.p. 85-86.5° (Found : C, 56.2; H, 6.0; S, 12.4. $C_{12}H_{16}SO_4$ requires C, 56.2; H, 6.3; S, 12.5%). ν_{max} 1345, 1160 cm^{-1} (OSO_2). δ 6.7-7.4 (m, 3H, Ar H), 5.2 (m, 1H, CHOMs), 3.8 (s, 3H, OMe), 3.0 (s, 3H, SO_2 CH_3).

5,6-Dihydro-1-methoxy-naphthalene 31

A solution of tosylate 35 (10.0g, 0.03 mol) in dimethylformamide (200 ml) was treated with potassium t-butoxide (6.6g, 0.059 mol) and the mixture was stirred at

75° for 16h under a nitrogen atmosphere. The mixture was cooled, diluted with water (200 ml), acidified with concentrated hydrochloric acid and extracted with light petroleum (3x100 ml). The organic extract was washed with concentrated hydrochloric acid and with water and dried. The solvent was removed by distillation under reduced pressure to give olefin 31 (4.65g, 97%) as a colourless liquid, b.p. 73° (0.05mm) (Found : C, 82.2; H, 7.3. $C_{11}H_{12}O$ requires C, 82.5; H, 7.6%). ν_{max} 1628 (C=C), 1595, 1585 aromatic C=C), 1265 cm^{-1} (C-O). δ 6.5-7.1 (m, 4H, Ar H, ArCH=C), 5.9 (dt, 1H, $J_1$10Hz, $J_2$4Hz, ArC=CH), (s, 3H, OMe). M^+, m/e 160 (100%).

3-(2'-Carboxy-3'-methoxyphenyl) propionic Acid 33

A solution of olefin 31 (300mg) and tetra-n-butylammonium bromide (100mg) in benzene (5 ml) was added to a solution of potassium permanganate (720mg) in water (7.5 ml) and the mixture was stirred at room temperature for 2h. The suspension was filtered through Celite and washed with sodium hydroxide solution (5 ml, 10% aqueous). The filtrate was separated into an aqueous and an organic layer. The organic layer was washed, dried and evaporated under reduced pressure to afford starting material (106mg). The aqueous layer was acidified with concentrated hydrochloric acid and was extracted with ethyl acetate. The ethyl acetate solution was washed, dried and evaporated under reduced pressure to give diacid 33 (254mg, 60%) as a yellow oil. This oil resisted all attempts to crystallize it (lit.[22]

double m.p. 98,110°). ν_{max} 1680-1705 cm^{-1} (CO_2H). δ10.5 (s, 2H, CO_2H), 6.7-7.4 (m, 3H, Ar H), 3.8 (s, 3H, OMe), 2.8 (sym m, 4H, $(CH_2)_2$).

1,2,3,4-Tetrahydro-6-methoxy-2-naphthoic Acid 40

To a solution of olefin 38 (0.8g, 0.005 mol) in ether (15 ml) at 0° was added chlorosulphonylisocyanate (1.06g, 0.0075 mol) in ether (5 ml) and the mixture was allowed to warm to room temperature, with the exclusion of moisture, during 2h. Concentrated hydrochloric acid (1 ml) was added dropwise to the solution and it was stirred at room temperature for a further 2.5 days. The off-white precipitate which formed was collected by filtration, washed repeatedly with cold water and dried, to give the unsaturated amide 39 (350 mg, 35%) as a yellow solid, m.p. 135-140°. A sample was recrystallized from acetone-light petroleum as white needles, m.p. 150-152°. ν_{max} 3340, 3130(NH_2), 1645, 1630, 1590 ($C=CCONH_2$), 1585 cm^{-1} (aromatic C=C). δ 7.3 (br s, 1H, C=CH), 6.6-7.2 (m, 3H, Ar H), 6.3 (br s, 2H, NH_2), 3.8 (s, 3H, OMe). M^+, m/e 203 (3%).

To a stirred solution of unsaturated amide 39 (0.32g, 1.5 mmol), tetrahydrofuran (10 ml), liquid ammonia (40 ml) and t-butyl alcohol (2.4 ml) was added sodium metal (0.28g, 12mg-atom). The blue solution was stirred for 2h and the excess of sodium was destroyed by the addition of methanol. The ammonia was removed in a stream of nitrogen and the residue was made acidic by the addition of hydrochloric acid (10% aqueous). The solution was extracted with ethyl acetate, washed with water and dried. The solvent was removed by distillation under reduced pressure to give

1,2,3,4-Tetrahydro-6-methoxy-naphthalene-2-carboxamide (317mg, 98%) as an off-white solid, m.p. 137-138° (lit.[138] m.p. 141°).

Hydrolysis of this amide by the method of Price and Kaplan[138] afforded an 85% yield of acid 40 as white crystals, m.p. 150-151° (lit.[138] 151°).

8-Methoxy-3,4-dihydro-naphthalene-2-carboxamide 41

Treatment of olefin 31 with chlorosulphonylisocyanate followed by hydrolysis with concentrated hydrochloric acid under the same conditions described for the preparation of unsaturated amide 39, gave unsaturated amide 41 in 92% yield as a green solid, m.p. 192-193.5°. An analytical sample was recrystallized from acetone as white, tetragonal crystals, m.p. 197-198° (Found : C, 70.9; H,6.5 ; N, 7.2. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%). ν_{max} 3320,3160 (NH_2), 1650 ,1600 ($CONH_2$), 1630 (C=C), 1590, 1572 cm^{-1} (aromatic C=C). δ ($CDCl_3$/$(CD_3)_2SO$) 7.6 (s, 1H, C=CH), 5.6-7.3 (m, 3H, Ar H), 3.8 (s, 3H, OMe), 3.3(br s, 2H, NH_2). M^+, m/e 203 (84%).

Reduction of unsaturated amide 41 by the same method described for the reduction of unsaturated amide 39 afforded 1,2,3,4-Tetrahyro-8-methoxy-naphthalene-2-carboxamide in 96% yield as a white solid, m.p. 184-185°. A sample crystallized from dichloromethane as white, tetragonal crystals, m.p. 203-205°. ν_{max} 3300,3150 (NH_2), 1660, 1625 ($CONH_2$), 1585 cm^{-1} (aromatic C=C). δ 6.6-7.3 (m, 3H, Ar H), 5.5 (br s, 2H, NH_2), 3.8 (s, 3H, OMe). M^+, m/e 205 (29%).

Hydrolysis of this amide by the method of Price and Kaplan[138] afforded an 86% yield of acid 15 as a yellow solid, m.p. 90-100°. It gave identical spectra to those of a sample

of acid 15 prepared by another method.

8-Acetoxy-1,2,3,4-tetrahydro-2-naphthoic Acid 43

A solution of hydroxy acid 14 (9.6g, 0.05 mol) and anhydrous sodium acetate (4.5g, 0.055 mol) in acetic anhydride (100 ml) was stirred at room temperature overnight. Water (20 ml) was added slowly to hydrolyse the acetic anhydride and after a further 2h, water (150 ml) and dichloromethane (150 ml) were added. The dichloromethane layer was separated, washed with water and dried and chromatographed on Sorbsil (200g). Elution with ether-light petroleum (1:3) yielded the acetoxy-acid 43 (8.8g, 75%) as an off-white solid. A sample crystallized from ether-light petroleum as white crystals, m.p. 93-93.5° (Found : C, 66.9; H, 6.2. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%). ν_{max} 1755(ArOAc), 1695 cm^{-1} (CO_2H). δ 10.4 (br s, 1H, CO_2H), 6.8-7.3 (m, 3H, Ar H), 2.3 (s, 3H, $OCOCH_3$). M^+, m/e 234 (2.5%).

7-Diazoacetyl-5,6,7,8-tetrahydro-naphthyl Acetate 44

Acetoxy acid 43 was converted to its acid chloride and treated with diazomethane to give the crude diazoketone 44 in 96% yield as an orange solid. An analytical sample crystallized from ether-light petroleum as pale yellow crystals, m.p. 70-71.5° (Found : C, 65.3; H, 5.6; N, 10.7. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.9%). ν_{max}3050, 2100,1640 ($COCHN_2$), 1740 cm^{-1} ($OCOCH_3$). δ 6.7-7.2(m, 3H, Ar H), 5.3 (s, 1H, $COCHN_2$), 2.3 (s, 3H, $OCOCH_3$). M^+(direct insertion, inlet temperature 70°), m/e 258 (5%).

7-Diazoacetyl-5,6,7,8-tetrahydro-1-naphthol 45

A solution of acetoxy diazoketone 44 (1.03g, 0.004 mol) in methanol (25 ml) was treated with sodium carbonate solution (5 ml, 20% aqueous) and the resultant suspension was stirred at room temperature for 4h. Oxalic acid (10% aqueous) was added to neutralize the solution, which was extracted repeatedly with dichloromethane. The dichloromethane extracts were washed, dried and evaporated in vacuum to yield the phenolic diazoketone 45 (760mg, 89%) as a yellow solid. An analytical sample crystallized from ether-light petroleum as yellow plates, m.p. 141-142° (Found : C, 66.4; H, 5.9; N, 13.0. $C_{12}H_{12}N_2O_2$ requires C, 66.7; H, 5.6; N, 13.0%). ν_{max} 3280 (OH) ,3060, 2100, 1620 cm^{-1} ($COCHN_2$). δ ($CDCl_3$/$(CD_3)_2SO$) 8.3 (br s, 1H, OH), 6.5-7.1 (m, 3H, Ar H), 5.4 (s, 1H, $COCHN_2$). M^+, m/e 188 ($M-N_2$, 53%).

7-Diazoacetyl -5,6,7,8-tetrahydro-1-methoxy-naphthalene 47

Treatment of the acid chloride of acid 15 with diazomethane gave a 76% yield of diazoketone 47. An analytical sample was recrystallized from ether-light petroleum as yellow needles, m.p. 73-74° (Found : C, 67.9; H, 6.3; N, 12.4. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%). ν_{max}3050, 2120 , 1625 cm^{-1} ($COCHN_2$). δ 5.4 (s, 1H, $COCHN_2$). M^+-N_2, m/e 202 (89%).

1,2,3,4-Tetrahydro-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 6

(A)A solution of diazoketone 45 (100mg, 0.53 mmol) in dichloromethane (5 ml) was added dropwise during 15 min to vigorously stirred, ice-cold trifluoroacetic acid (10 ml). The orange fluorescent solution was stirred for a further 15 min

and diluted successively with dichloromethane (10 ml) and water (50 ml). The organic layer was separated and washed with sodium hydroxide solution (10% aqueous) and water and dried. Removal of the dichloromethane under reduced pressure yielded the dienone ketone 6 (83mg, 96% crude yield) as a yellow oil. A sample crystallized from ether-light petroleum as pale yellow plates, m.p. 57-58° (Found : C, 76.7; H, 6.6. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%). ν_{max} 1725 (CO), 1655, 1625, 1560 cm^{-1} (dienone). δ 7.1 (ABq, 1H, $J_{AX}+J_{BX}$ 16.5Hz, C7-H), 6.0-6.3 (m, 2H, C6-H and C8-H), 1.7-3.3 (m, 9H). λ_{max} 208 (ε 4600), 327 (ε4500). M^+, m/e 188 (100%). ^{13}C.m.r. spectrum δ ($CDCl_3$,$SiMe_4$,0.0 p.p.m.) 214.47 (s, C=O, cyclopentanone), 201.53 (s, C=O, dienone), 156.64 (s, C=CH, C8a), 142.84 (d, CH=CHCO, C7), 124.5 (d, CH=CHCO, C6), 115.33 (d, C=CHCH=CHCO, C8), 55.88 (s, C4a), 48.76 (t, C9 or C1), 47.42 (t, C1 or C9), 30.75 (t, C4 or C2), 29.34 (t, C2 or C4).

(B) This compound was also prepared from diazoketone 47, in 68% yield, by treatment with trifluoroacetic acid at -30° and chromatography of the product on Sorbsil.

Methyl 1,2,3,4-Tetrahydro-5-methoxy-1-oxo-2-naphthoate 51

To a suspension of sodium hydride (4.8g, 0.2 mol) in a boiling solution of dimethyl carbonate (17.6g, 0.14 mol) and tetrahydrofuran (80 ml) under a nitrogen atmosphere, was added a solution of 3,4-dihydro-5-methoxy-naphthalen-1(2H)-one 50 in tetrahydrofuran (35 ml) during 60 min. The solution was boiled under reflux for a further 90 min, cooled to room temperature, and acidified with glacial acetic acid (12 ml). Sufficient water was added to dissolve the pasty precipitate which formed, and the mixture was extracted with ether several times.

The ethereal extracts were washed with water, dried and evaporated under reduced pressure to yield the ketoester 51 (13.1g, 100% crude yield) as a pale brown solid, m.p. 48-51°. An analytical sample crystallized from ether-light petroleum as yellow needles, m.p. 55-56° (Found : C, 66.8, H, 6.1. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%) ν_{max} 1725 (CO_2Me), 1680 (CO), 1590, 1580 cm^{-1} (aromatic C=C). δ 6.9-7.8 (m, 3H, Ar H), 3.8 (s, 6H, OMe and CO_2Me). M^+, m/e 234 (74%).

1,2,3,4-Tetrahydro-5-methoxy-2-naphthoic Acid

A solution of ketoester 51 (12.0g, 0.051 mol) in glacial acetic acid (100 ml) containing palladium on carbon (1.0g, 5%) and perchloric acid (0.2 ml) was hydrogenated overnight at a maximum hydrogen pressure of 4 atm. Chloroform (100 ml) was added and the mixture was filtered through Celite. The filtrate was washed repeatedly with water and dried; the chloroform was removed by distillation under reduced pressure to yield the deoxy ester (11.5g) as a brown liquid. ν_{max} 1725 cm^{-1} (ester). This ester was dissolved in methanol (20 ml) and added to an aqueous methanolic solution of potassium hydroxide (20g) and boiled under reflux for 1h. The cooled solution was acidified with concentrated hydrochloric acid (10% aqueous) and extracted with ether. The ethereal extracts were washed with water, dried, and evaporated under reduced pressure to yield 1,2,3,4-tetrahydro-5-methoxy-2-naphthoic acid (10.3g, 99%) as a yellow solid, m.p. 146-148°. A sample crystallized from ether-light petroleum as colourless needles, m.p. 150-151° (Found : C, 69.6; H, 6.8. $C_{14}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν_{max} 1690 cm^{-1} (CO_2H). δ 9.4 (br s, 1H, CO_2H), 6.6-7.3

(m, 3H, Ar H), 3.8 (s, 3H, OMe). M^+, m/e 266 (12%).

1,2,3,4-Tetrahydro-5-hydroxy-2-naphthoic Acid 52

A mixture of 5-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid(8.0g, 0.039 mol) and pyridine hydrochloride (40g) was heated at 220-240° for 18h under an atmosphere of nitrogen. The cooled reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and dried; the ethyl acetate was removed by distillation under reduced pressure to yield the hydroxy acid 52 (7.0g, 93%) as a pale brown solid, m.p. 120-122°. An analytical sample crystallized from ether-light petroleum as small white crystals , m.p. 149-150° (Found : C,68.9; H, 6.5. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν_{max} 3340 (OH), 1690 cm^{-1} (CO_2H). δ ($CDCl_3$/ $(CD_3)_2SO$) 9.3 (br s, 2H, OH and CO_2H). M^+, m/e 192 (48%).

5-Acetoxy-1,2,3,4-tetrahydro-2-naphthoic Acid

Acetylation of hydroxy acid 52, by the same method which was used to prepare acetoxy acid 43, gave the acetoxy acid in 73% yield as colourless needles, m.p. 128-129° (Found : C, 66.9; H, 5.9. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%). ν_{max} 1750 ($OCOCH_3$), 1695 cm^{-1} (CO_2H).

6-Diazoacetyl-5,6,7,8-tetrahydro-1-naphthyl Acetate

Treatment of the acid chloride of the acetoxy acid above, with diazomethane gave the acetoxy diazoketone in 100% crude yield. A sample crystallized from ether-light petroleum as yellow crystals, m.p. 87-88.5° (Found : C, 65.3; H, 5.6; N, 10.6. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.9%). ν_{max}

3050, 2100,1620 ($COCHN_2$), 1750 cm^{-1} ($OCOCH_3$).

6-Diazoacetyl-5,6,7,8-tetrahydro-1-naphthol 48

Hydrolysis of the acetoxy diazoketone by the procedure described for the 1,7-isomer 45 gave the phenolic diazoketone 48 in 99% crude yield. A sample crystallized from dichloromethane-light petroleum as yellow prismatic needles, m.p. 129-130° (dec.) (Found : C, 66.6; H, 6.1; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.7; H, 5.6; N, 13.0%). ν_{max} 3160 (OH), 3050, 2100, 1620 cm^{-1} ($COCHN_2$).

1,2-Dihydro-2,4a-ethanonaphthalene-3,5(4H,4aH)-dione 49

Cyclization of phenolic diazoketone 48 by the method described for the preparation of the dienone ketone 6 gave dienone ketone 49 as a yellow liquid, b.p. 128-131° (0.8 mm). ν_{max} (film) 1715 (C=O), 1655, 1625, 1555 cm^{-1} (dienone). δ 7.1 (ABq, 1H, $J_{AX}+J_{BX}$15.5Hz, C7-H), 5.6-6.3 (m, 2H, C6-H and C8-H), 1.6-3.1 (m, 9H). λ_{max} 205 (ε5000), 324 nm (ε2800). The dienone ketone proved too labile for satisfactory elemental analysis results to be obtained.

1,2,3,4,6,7,8,8a-Octahydro-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 54

A solution of dienone ketone 6 (235mg, 1.25 mmol) in ethanol (20 ml) containing palladium on carbon (20 mg, 5%) was hydrogenated at atmospheric pressure and at room temperature. The consumption of hydrogen ceased after 1h and the suspension was filtered through Celite. The ethanol was removed by distillation under reduced pressure to give diketone 54 (224mg, 95%)

as a colourless liquid, b.p. 85-88° (0.1 mm) (Found : C,75.2; H, 8.7. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%). ν_{max} (film) 1735 (cyclopentanone), 1700 cm^{-1} (cyclohexanone). M^+, m/e 192 (40%).

1,2,3,4,6,7-Hexahydro-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 55

Dienone ketone 6 (300mg, 1.62 mmol) in ethanol (4 ml) was added to a stirred suspension of sodium borohydride (62mg, 1.65 mmol) in ethanol (3 ml) at 0° during 15 min. The solution was stirred at room temperature overnight, water was added, followed by dilute hydrochloric acid, and the aqueous solution was extracted with ethyl acetate. The ethyl acetate solution was washed and dried and the solvent was removed under reduced pressure to yield 255mg of a yellow-brown oil. This was dissolved in acetone (20 ml) and treated dropwise with Jones reagent until an orange colour persisted. Chloroform, followed by water, was added and the organic layer was separated, washed and dried. Removal of the chloroform gave the enone ketone 55 (220mg, 73%) as a viscous yellow oil, b.p. 110-112° (2.0 mm) (Found : C, 75.5; H, 7.7. $C_{12}H_{14}O_2$ requires C,75.8; H, 7.4%). ν_{max} (film) 1730 (cyclopentanone), 1700 cm^{-1} (cyclohexanone).

1,2,3,4-Tetrahydro-7-methyl-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 56

A solution of dimethyl copper lithium was prepared by mixing CuI (267mg, 1.4 mmol) and methyl lithium (2.8 mmol) in ether (3 ml) at 0° under nitrogen. Dienone ketone 6 (130mg, 0.69 mmol) dissolved in ether (1 ml), was added to the above

stirred solution during 5 min. A deep yellow colour developed. The solution was stirred at 0^{o} for 3h, water was added, followed by dilute sulphuric acid until the solution was neutral. This solution was extracted with ether, and the ether solution was washed and dried. Evaporation of the ether under reduced pressure gave the methyl diketone 56 (110mg, 78%) as a pale yellow liquid, b.p. $87-90^{o}$ (0.1 mm) (Found : C,76.6; H, 8.1. $C_{13}H_{16}O_2$ requires C, 76.4; H, 7.9%). ν_{max} (film) 1735 (cyclopentanone), 1700 cm^{-1} (cyclohexanone). δ 5.5 (br s, 1H, olefinic H), 1.5-3.0 (m, 11H, aliphatic H), 1.2 (d, 1.5H, J5Hz, axial Me), 1.1 (d, 1.5H, J5Hz, equatorial Me). M^{+}, m/e 204 (100%).

1,2,3,4-Tetrahydro-10-oxo-7-propen-2'-yl-3,4a-ethanonaphthalen-5(4aH)-one 57

Dienone ketone 6 was treated with a solution of di-isopropenyl copper lithium in the same manner as above to give the isopropenyl diketone 57 in 89% yield as a pale yellow liquid, b.p. $100-104^{o}$ (0.1 mm). ν_{max} (film) 3030, 1635, 895 ($C=CH_2$), 1735 (cyclopentanone), 1700 cm^{-1} (cyclohexanone). δ 5.2-5.5 (m, 1H, trisubstituted double bond), 4.5-4.8 (m, 2H, disubstituted double bond). M^{+}, m/e 230 (100%).

CHAPTER 2

Methyl 1,2,3,4-Tetrahydro-5,8-dimethoxy-1-oxo-2-naphthoate

This compound was prepared from tetralone 60[96], by the procedure which was used to prepare ketoester 51, in 100% crude yield as a yellow oil. A sample crystallized from ether-light petroleum as a yellow solid, m.p. 50-53° (Found : C, 63.4 ; H, 6.2. $C_{14}H_{16}O_3$ requires C, 63.6; H, 6.1%). ν_{max} 1730 (ester), 1680 cm^{-1} (tetralone). δ 12.7 (s, 0.5H, enol H), 6.8 (ABq, 2H, J_{AB} 8Hz, Ar H), 3.8 (s, 6H, OMe), 3.7 (s, 3H, CO_2Me). M^+, m/e 264 (10%).

3,4-Dihydro-5,8-dimethoxy-2-naphthoic Acid 62

A solution of the ketoester (prepared above) (13.5g, 0.053 mol) in dry isopropyl alcohol (50 ml) was added during 15 min to a stirred suspension of sodium borohydride (2.0g, 0.053 mol) at 0°. The mixture was allowed to warm to room temperature and was stirred for a total of 6h. The solution was made neutral by the addition of hydrochloric acid (10% aqueous) and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried and evaporated under reduced pressure to give the hydroxy ester 61 (12.6g, 93%) as a viscous brown oil. ν_{max} 3450 (OH), 1725 cm^{-1} (CO_2Me).

A solution of hydroxy ester 61 (12.6g) in glacial acetic acid (150 ml) was treated with p-toluenesulphonic acid (200mg) and the mixture was boiled under reflux for 2.5h. The dichloromethane extracts (3x50 ml) of the cooled solution were combined, washed with water until the washings were neutral and dried. Removal of the solvent under reduced pressure gave

methyl 1,4-dihydro-5,8-dimethoxy-2-naphthoate (11.65g, 92%) as a brown, low m.p. solid. A sample was recrystallized from ether-light petroleum as white crystals, m.p. 75-76° (Found : C, 68.0; H, 6.7. $C_{14}H_{16}O_4$ requires C,67.7; H, 6.5%). ν_{max} 1705 (ester), 1630 cm^{-1} (C=C). δ 7.9 (br s, 1H, C=CH), 6.8 (ABq, 2H, J_{AB}8Hz, Ar H), 3.8 (br s, 9H, OMe). M^+, m/e 262 (64%).

To a solution of methyl 1,4-dihydro-5,8-dimethoxy-2-naphthoate (11.6g, 0.048 mol) in methanol (150 ml) was added a solution of potassium hydroxide (24.0g) in methanol-water (50 ml, 1:1) and the mixture was boiled under reflux for 1h. The cooled solution was diluted with an equal volume of water and acidified to pH2 with concentrated hydrochloric acid. Unsaturated acid 62 (10.25g, 93%) precipitated as a yellow solid, m.p. 197-200° and was collected by vacuum filtration, washed with water and dried at 110°. Recrystallization from ethyl acetate afforded yellow crystals, m.p. 230-232° (Found ; C, 66.7; H, 6.1. $C_{18}H_{14}O_4$ requires C, 66.7; H, 6.0%). ν_{max} 1675 (CO_2H), 1620 cm^{-1} (C=C). δ ($CDCl_3$/$(CD_3)_2SO$) 7.9 (br s, 1H, C=CH), 7.0 (ABq, 2H, Ar H), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe). M^+, m/e 254 (100%).

1,2,3,4-Tetrahydro-5,8-dimethoxy-2-naphthoic Acid 63

A solution of unsaturated acid 62 (10.0g, 0.043 mol) in a mixture of tetrahydrofuran (50 ml), liquid ammonia (150 ml) and t-butyl alcohol (20.3 ml) was reduced by the addition of sodium metal (4.9g, 0.21g-atom) during 5 min. The solution was stirred for a further 3h while immersed in a bath of ethanol-dry ice. Methanol was added to destroy the excess of

sodium and the ammonia was driven off in a stream of nitrogen. The mixture was poured into a mixture of ice-concentrated hydrochloric acid and the resultant aqueous solution was extracted three times with ethyl acetate. The ethyl acetate solution was washed with water, dried and evaporated under reduced pressure to give acid 63 (8.5g, 85%) as a grey-brown solid , m.p. 163-165°. A sample crystallized from ether as yellow needles, m.p. 174-175° (Found : C,66.4; H, 6.7. $C_{13}H_{16}O_4$ requires C,66.1; H, 6.8%). ν_{max} 1690 (CO_2H), 1600 cm^{-1} (aromatic C=C). δ 6.6 (s, 2H, Ar H), 5.9 (br s, 1H, CO_2H), 3.7 (s, 6H, OMe). M^+, m/e 236 (100%).

6-Diazoacetyl-1,2,3,4-tetrahydro-1,4-dimethoxy-naphthalene 64

Treatment of the acid chloride of acid 63 with diazomethane followed by chromatography on a preparative thick layer plate gave diazoketone 64 in 73% yield as a yellow solid, m.p. 94-95.5°. An analytical sample was recrystallized from ether-light petroleum as yellow needles, m.p. 104-105° (Found : C, 64.9; H, 6.3; N, 10.7. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.8%). ν_{max} 3040, 2100, 1625 cm^{-1} ($COCHN_2$). δ 6.5 (s, 2H, Ar H), 5.3 (s,1H, $COCHN_2$), 3.7 (s, 6H, OMe). M^+, m/e 232 (100%).

3,4-Dihydro-5,8-dimethoxy-3,4a-ethanonaphthalene-2(4aH)-one 66

Diazoketone 64 (100mg) was added portionwise during 5min to stirred trifluoroacetic acid (10 ml) at 0°. The resultant maroon solution was stirred at 0° for 10min and an equal volume of dichloromethane was added. The dichloromethane solution was washed with water, sodium hydroxide solution (10%

aqueous) and water and dried. A yellow oil (119mg) was obtained upon removal of the dichloromethane from the solution. An nmr spectrum obtained of this oil indicated the presence of trienone 66 (42%) and aromatic material. Despite repeated chromatography the trienone was not completely separated from uncyclized impurities. (Accurate mass : Found : 232.1101. $C_{14}H_{16}O_3$ requires 232.1099). ν_{max} 1650, 1640, 1550 cm^{-1} (trienone). δ 6.0 (s, 1H, C=CHCO), 5.4 (d, 1H, J7.5Hz, HC=COMe), 5.0 (d, 1H, J7.5Hz, HC=COMe), 3.65 (s, 3H, OMe), 3.60 (s, 3H, OMe). M^+, m/e 232 (100%).

1,2,3,4-Tetrahydro-8-methoxy-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 65

Diazoketone 64 (210mg) was added portionwise during 5min to stirred trifluoroacetic acid at -15°. The red solution was stirred at -15° for a further 10min and worked up in the same manner described for the preparation of trienone 66. A yellow oil (197mg) was isolated and the nmr spectrum obtained from it indicated a mixture of dienone ketone 65 (43%), trienone 66 (14%) and uncyclized material. A pale yellow solid, m.p. 91.5-94.5° was obtained from chromatography of the mixture (twice) on a preparative thick layer plate. Recrystallization from ether-light petrolecm gave dienone ketone 65 as pale yellow needles, m.p. 110-110.5° (Accurate mass : Found : 218.0941. $C_{13}H_{14}O_3$ requires 218.0943). ν_{max} 1730 (cyclopentanone), 1670, 1630, 1565 cm^{-1} (2,4-dienone). δ 7.1 (d, 1H, J10Hz, HC=CCO), 6.1 (dd, 1H, $J_1$10Hz, $J_2$1Hz, C=CHCO), 3.6 (s, 3H, OMe). λ_{max} 342 nm (ε2100). M^+, m/e 218 (100%).

2,3,4,5-Tetrahydro-1-benzoxepin-2-one 76

A solution of 6-methoxy-1-tetralone 75 (16.8g, 0.1 mol) and m-chloroperbenzoic acid (38.0g, 0.2 mol) in dichloromethane (500 ml) was boiled under reflux for 72h. The dichloromethane solution was washed with sodium bisulphite solution (10% aqueous), sodium bicarbonate solution (5% aqueous) and water and dried. Removal of the solvent under reduced pressure gave lactone 76 (16.2g,88%) as a brown liquid, b.p. 112-115° (0.1 mm) (Found : C, 69.1; H, 6.4. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν_{max} (film) 1755 (lactone), 1595 cm^{-1} (aromatic C=C). δ 6.5-7.0 (m,3H, Ar H), 3.7 (s, 3H, OMe). M^+, m/e 192 (64%).

2-Ethoxy-5-methoxy-phenyl-γ-butyric Acid 77

A mixture of lactone 76 (10.9g,0.057 mol), concentrated hydrochloric acid (40 ml) and water (150 ml) was boiled under reflux for 1h. The solution was made basic by the addition of sodium carbonate solution (10% aqueous) and extracted with ether (2x100 ml). The aqueous solution was acidified with concentrated hydrochloric acid and was extracted with ethyl acetate (3x50 ml). The combined ethyl acetate extracts were washed with water, dried and evaporated under reduced pressure to give 2-hydroxy-5-methoxy-phenyl-γ-butyric acid (10.65g, 90%) as a red-brown solid, m.p. 60-62°. An analytical sample crystallized from ether-light petroleum as white tabular crystals, m.p. 63-64° (Found : C, 62.6; H, 6.7. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%). ν_{max} 3500 (OH), 1710 cm^{-1} (CO_2H). δ ($CDCl_3$/$(CD_3)_2SO$) 6.6-6.8 (m, 3H, Ar H), 5.2 (br s, 2H, ArOH and CO_2H), 3.8 (s, 3H, OMe). M^+, m/e 210 (23%).

To a stirred suspension of sodium hydride (3.2g, 0.134 mol) in tetrahydrofuran (150 ml) was added the hydroxy acid (13.5g, 0.061 mol) in tetrahydrofuran (20 ml) during 1h. The solution was stirred for 15min and ethyl iodide (19.05g, 0.15 mol) was added during 30min. The mixture was stirred at room temperature for 16h and boiled under reflux for 5h. The solution was acidified to pH2 by the addition of hydrochloric acid (10% aqueous) and extracted with dichloromethane. The dichloromethane extract was washed with water, dried and evaporated under reduced pressure to give acid 77 (14.4g, 94%) as a dark oil, b.p. 140-150^{o} (0.1 mm). A sample crystallized from ether-light petroleum as white needles, m.p. 50-51^{o} (Found : C, 65.6; H, 7.7. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%) ν_{max} 1705 cm^{-1} (CO_2H). δ 11.9 (br s, 1H, CO_2H), 6.7 (s, 3H, Ar H), 4.0 (q, 2H, OCH_2), 1.4 (t, 3H, CH_3). M^+, m/e 238 (100%).

3,4-Dihydro-5-ethoxy-8-methoxy-naphthalen-1(2H)-one 78

Acid 77 (13.0g, 0.055 mol) dissolved in polyphosphoric acid (300 ml) was heated at 70-90^{o} for 1.5h. The cooled mixture was poured onto ice (2kg) and the resultant solution was extracted with ether. The ethereal extract was washed with sodium carbonate solution (400 ml, 10% aqueous) and with water and dried. The solvent was removed by distillation under reduced pressure to give tetralone 78 (8.0g,67%) as a yellow solid, m.p. 88.5-90.5^{o}. An analytical sample was recrystallized from ether-light petroleum as yellow needles, m.p. 96-97^{o} (Found : C, 70.9; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). ν_{max} 1675 (C=O), 1590 cm^{-1} (aromatic C=C).

δ 6.9 (ABq, 2H, J_{AB}9Hz, Ar H), 4.0 (q, 2H, J7Hz, OCH_2), 3.9 (s, 3H, OMe), 1.4 (t, 3H, J7Hz, CH_3). M^+, m/e 220 (100%).

Methyl 1,2,3,4-Tetrahydro-5-ethoxy-8-methoxy-1-oxo-2-naphthoate

This compound was prepared from tetralone 78, by the same method which was used to convert tetralone 60 to its keto-ester, in 100% crude yield as an orange semi-solid. A sample was crystallized from ether-light petroleum as orange tetragonal crystals, m.p. 88.5-90.5° (Found : C, 65.0; H, 6.5. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%). ν_{max} 1745 (ester), 1680 (tetralone), 1640, 1620 cm^{-1} (C=C(OH)). δ 12.9 (s, 0.7H, C=C(OH)), 6.7-7.1 (m, 2H, Ar H), 4.0 (q, 2H, J7Hz, OCH_2), 3.8 (s, 3H, OMe), 3.75 (s, 2.1H, keto OMe), 3.7 (s, 0.9H, enol OMe), 1.4 (t, 3H, J7Hz, CH_3). M^+, m/e 278 (2%).

Methyl 1,2,3,4-Tetrahydro-5-ethoxy-8-methoxy-1-hydroxy-2-naphthoate

Reduction of the ketoester (prepared above) with sodium borohydride in isopropyl alcohol by the same method which was used to prepare hydroxy ester 61 gave the hydroxy ester in 100% crude yield as a pale brown oil. ν_{max} 3460 (OH), 1725 cm^{-1} (ester). The compound was used in the next preparation without purification.

3,4-Dihydro-5-ethoxy-8-methoxy-2-naphthoic Acid

Dehydration of the hydroxy ester (prepared above) followed by basic hydrolysis, by the same procedure which was used to prepare unsaturated acid 62 gave a 97% yield of 1,2-dihydro-5-ethoxy-8-methoxy-2-naphthoic acid as a yellow solid,

m.p. 203-205°. An analytical sample was recrystallized from dichloromethane-light petroleum as yellow needles, m.p. 218-219.5° (Found : C, 67.6; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). ν_{max} 1670 (CO_2H), 1620 cm^{-1} (C=C). δ 8.1 (s, 1H, C=CH), 6.7 (ABq, 2H, J8Hz, Ar H), 4.0 (q, 2H, J7Hz, OCH_2), 3.8 (s, 3H, OMe), 1.4 (t, 3H, CH_3). M^+, m/e 248 (100%).

1,2,3,4-Tetrahydro-5-ethoxy-8-methoxy-2-naphthoic Acid 72

The unsaturated acid (prepared above) was reduced with sodium in liquid ammonia, by the same method which was used to prepare acid 63, to give acid 72 in 95% yield as a brown solid, m.p. 159-160.5°. A sample crystallized from dichloromethane-light petroleum as pale brown, rhombohedral crystals, m.p. 173-174.5° (Found : C, 66.9; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%). ν_{max} 1685 cm^{-1} (CO_2H). δ 6.6 (s, 2H, Ar H), 4.0 (q, 2H, OCH_2), 3.8 (s, 3H, OMe), 1.4 (t, 3H, CH_3). M^+, m/e 250 (100%).

1,2,3,4-Tetrahydro-5-ethoxy-8-hydroxy-2-naphthoic Acid 71

To a solution of acid 72 (800mg, 3.2 mmol) in tetrahydrofuran (30 ml) was added a suspension of lithium hydride (32mg, 4 mmol) in tetrahydrofuran (10 ml). The resultant mixture was stirred at room temperature for 3h. A solution of phenyl lithium and lithium diphenylphosphide was prepared by adding lithium metal (320mg, 4.8mg-atom) to a solution of triphenylphosphine (2.4g, 4.54 mmol) in tetrahydrofuran (30 ml) with stirring at room temperature, and under a nitrogen atmosphere, for 3h. Diphenylphosphine (4.5 ml, 1M solution in

tetrahydrofuran) was added to this solution, and one half of the resultant solution was added to the lithium salt prepared above. The red mixture was boiled under reflux for 3h and the second half of the basic solution was added. The mixture was boiled under reflux for a further 4h; it was cooled to room temperature and poured into hydrochloric acid (20 ml, 10% aqueous). The acidic solution was extracted with chloroform (6x30 ml) and the combined chloroform extracts were washed with water and dried. Evaporation of the solvent under reduced pressure gave 7.5g of a brown oil. This oil was chromatographed on Sorbsil (200g) with chloroform and eluted with ethyl acetate, after all of the phosphorous compounds had been eluted with chloroform, to give 524mg (71%) of acid 71 as a white solid, m.p. 194-196°. A sample was recrystallized from acetone-light petroleum as white needles, m.p. 203-204.5° (Found : C, 65.9; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). ν_{max} 3100-3150 (OH), 1695 cm^{-1} (CO_2H). δ 7.5 (br s, 1H, ArOH), 6.6 (s, 2H, Ar H), 4.0 (q, 2H, J7Hz, OCH_2), 1.4 (t, 3H, J7Hz, CH_3). M^+, m/e 236 (100%).

1,2,3,4-Tetrahydro-5-ethoxy-8-acetoxy-2-naphthoic Acid

Acetylation of acid 71 with acetic anhydride and sodium acetate gave the acetoxy acid in 87% crude yield. A sample was recrystallized from ether-light petroleum as white, rhombohedral crystals, m.p. 175-176° (Found : C, 64.4; H, 6.5. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%). ν_{max} 1745 (acetate), 1700 cm^{-1} (CO_2H). δ 7.9 (br s, 1H, CO_2H), 6.7 (ABq, 2H, J_{AB}9Hz, Ar H), 2.3 (s, 3H, $OCOCH_3$). M^+, m/e 278 (15%).

6-Diazoacetyl-5,6,7,8-tetrahydro-1-ethoxy-4-naphthyl Acetate

Treatment of the acid chloride of the acid prepared above with diazomethane gave the acetoxy diazoketone, m.p. 128 -130° in 84% yield. An analytical sample was recrystallized from ether-light petroleum as yellow needles, m.p. 131-132.5° (Found : C, 63.7; H, 6.1; N, 9.1. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%). ν_{max} 3090, 2100, 1640 ($COCHN_2$), 1750 cm^{-1} ($OCOCH_3$). δ 6.8 (ABq, 2H, J9Hz, Ar H), 5.4 (s, 1H, $COCHN_2$), 4.0 (q, 2H, J7Hz, OCH_2), 2.3 (s, 3H, $OCOCH_3$), 1.3 (t, 3H, J7Hz, CH_3). M^+, m/e 270 (60%).

6-Diazoacetyl-5,6,7,8-tetrahydro-1-ethoxy-4-naphthol 70

The acetoxy diazoketone (prepared above) was deacetylated with sodium carbonate in methanol, by the same method used to prepare phenolic diazoketone 45, to give the phenolic diazoketone 70 in 99% yield as a brown solid, m.p. 120-124°. A sample was recrystallized from dichloromethane-light petroleum as yellow orthorhombic crystals, m.p. 130-131.5° (dec.) ν_{max} 3300 (OH), 3040, 2100, 1630 cm^{-1} ($COCHN_2$). δ 6.6 (s, 2H, Ar H), 5.4 (s, 1H, $COCHN_2$), 4.9 (s, 1H, OH), 3.9 (q, 2H, OCH_2), 1.4 (t, 3H, CH_3). M^+, m/e 232 ($M-N_2$, 62%).

6-Diazoacetyl-5,6,7,8-tetrahydro-1-ethoxy-4-methoxy-naphthalene 79

Treatment of the acid chloride of acid 72 with diazo-methane gave a 100% crude yield of diazoketone 79 as a yellow solid, m.p. 99-101°. Crystallization from ether-light petroleum afforded yellow needles, m.p. 108-109° (Found : C, 65.8;

H, 6.6; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%). ν_{max} 3090, 2120, 1630 cm^{-1} ($COCHN_2$). δ 5.4 (s, 1H, $COCHN_2$). M^+, m/e 217 ($M-N_2$, 100%).

1,2,3,4-Tetrahydro-8-ethoxy-10-oxo-3,4a-ethanonaphthalen-5(4aH)-one 80

(A) Treatment of phenolic diazoketone 70 with trifluoroacetic acid at 0° for 10min afforded dienone ketone 80 in quantitative yield as a red solid, m.p. 58-61°. A sample was recrystallized from ether-light petroleum as yellow flakes, m.p. 72-73.5° (Accurate mass : Found : 232.1106. $C_{14}H_{16}O_3$ requires 232.1099). ν_{max} 1730 (cyclopentanone), 1665, 1630, 1565 cm^{-1} (2,4-dienone). δ 7.0 (d, 1H, J10Hz, HC=CCO), 6.0, (d, 1H, J10Hz, C=CHCO), 3.8 (q, 2H, OCH_2), 1.3 (t, 3H, CH_3). λ_{max} 211 (ε4700), 341 nm (ε2700). M^+, m/e 233 (100%).

(B) A solution of diazoketone 79 (60mg, 0.22 mmol) in dichloromethane (1 ml) was added to stirred trifluoroacetic acid-dichloromethane (4:1) at -30° during 5min. The solution was stirred at -30° for 10min and an equal volume of water was added. The organic layer was separated, washed with sodium hydroxide solution (10% aqueous) and with water and dried. A yellow oil (51mg) was obtained on removal of the solvent under reduced pressure. The nmr spectrum afforded by this oil indicated that it contained dienone ketone 80 (63%). The yellow oil was chromatographed on a preparative thick layer plate with ether and dienone ketone 80 (24mg) was isolated as a yellow solid, m.p. 76.5-77.5°. It gave identical infra red and nmr spectra to those of a sample prepared by method A.

1,2,3,4,6,7-Hexahydro-10-oxo-3,4a-ethanonaphthalene-5,8 (4aH, 8aH)-dione 82

Treatment of phenolic diazoketone 70 with trifluoroacetic acid at 0° for 10min followed by removal of the trifluoroacetic acid under reduced pressure at 20° gave a black liquid. This liquid was extracted with ether to give the enetrione 81 as an unstable yellow liquid. ν_{max} 3020, 1685, 1675, 1595 (enedione), 1730 cm^{-1} (cyclopentanone). δ 6.8 (br s, 2H, HC=CH). λ_{max} 226 (ε8000), 368 nm(ε40). M^+, m/e 204 (98%).

Freshly chromatographed enetrione 81 (70mg) dissolved in acetic acid (30 ml, 50% aqueous) was treated with zinc powder (100mg) and stirred at 40-50° for 1h. The solution was filtered, diluted with water and extracted with dichloromethane. The colourless dichloromethane solution was washed with water, dried, and the solvent was removed by distillation under reduced pressure to give a colourless oil. This oil was chromatographed on a preparative thick layer plate with ether and trione 82 (52mg) was isolated as a white solid. It was recrystallized from dichloromethane-light petroleum as white flakes, m.p. 96-98° (Found : C, 69.6; H, 6.8. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν_{max} 1735 (cyclopentanone), 1695 cm^{-1} (cyclohexanone). M^+, m/e 206 (94%).

CHAPTER 3

The reaction of 6-Diazoacetyl-1,2,3,4-tetrahydro-2,3-dimethoxy-naphthalene with trifluoroacetic Acid

(A) Diazoketone 88 (100mg) was added portionwise during 5min to stirred trifluoroacetic acid-dichloromethane (10 ml, 3:1) which was maintained at -30° by a mixture of acetone, water and dry ice. The green fluorescent solution was stirred at -30° for a further 10min and equal volumes of both water and dichloromethane were added. The organic layer was separated and washed with water, sodium hydroxide solution (10% aqueous) and water and dried. Removal of the solvent by distillation under reduced pressure gave a yellow solid (103mg). The nmr spectrum afforded by this solid indicated that it contained a mixture of dienone ketone 85 (71%) and trienone 90 (23%). The mixture was chromatographed on a preparative thick layer plate with ether-dichloromethane (3:1). The band of rf 0.15 was eluted with ethyl acetate and 1,2,3,4-Tetrahydro-6-methoxy-10-oxo-3,4a-ethanonaphthalen-7(4aH)-one 85 was obtained as a yellow solid (plates), m.p. 179-181° after recrystallization from dichloromethane-light petroleum (Found : C, 71.3, H, 6.4. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%). ν_{max} 1730 (cyclopentanone), 1650, 1625, 1610 cm^{-1} (2,5-dienone). δ 6.2 (d, 1H, J1.5 Hz, MeOC=CH), 5.7(s, 1H, HC=CCO), 3.7 (s, 3H, OMe). λ_{max} 252 nm (ε9100). M^+, m/e 218 (100%).

Elution of the region rf 0.4 of the above preparative thick layer plate afforded 3,4-dihydro-6,7-dimethoxy-3,4a-ethanonaphthalene-2(4aH)-one 90 as a yellow gel, b.p. 140-142° (0.1 mm) (Accurate mass : Found : 232.1098. $C_{14}H_{16}O_3$ requires

232.1099). ν_{max} 3020, 1640, 1575, 1565 cm^{-1} (trienone). δ 5.7 (br s, 1H, $J_{Wh/2}$3Hz, MeOC=CH), 5.55 (s, 1H, MeOC=CH), 5.05 (s, 1H, C=CHCO), 3.8 (s, 3H, OMe), 3.7 (s, 3H, OMe). λ_{max} 385 nm (ε6500). M^+, m/e 232 (100%).

(B) Diazoketone 88 (100mg) was added portionwise during 5min to stirred trifluoroacetic acid-water (9:1) at 0°. The solution was allowed to warm to room temperature and stirred for a total of 2h. Water was added and the yellow solution was extracted with dichloromethane. The dichloromethane solution was washed with water, sodium hydroxide solution (10% aqueous) and with water and dried. Evaporation of the solvent under reduced pressure gave a yellow solid, the nmr spectrum of which indicated that it contained a mixture of dienone ketone 85 (32%) and dienedione 91 (52%). This mixture was chromatographed on a preparative thick layer plate with ether-ethyl acetate (1:4). Elution of the band of rf 0.25 afforded 3,4-Dihydro-7-methoxy-3,4a-ethanonaphthalene-2,6(4aH,5)-dione 91 as pale yellow, rhombohedral crystals, m.p. 179-180° after recrystallization from dichloromethane-light petroleum (Found : C, 71.2; H, 6.2. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%). ν_{max} 1685, 1650, 1590 cm^{-1} (dienone). δ 6.2 (s, 1H, MeOC=CH), 5.9 (d, 1H, J1Hz, C=CHCO), 3.8 (s, 3H, OMe). λ_{max} 324 nm (ε27000). λ_{max} (EtOH-NaOH) 212, 276, 454 nm. M^+, m/e 218 (94%).

3,4-Dihydro-7-hydroxy-3,4a-ethanonaphthalene-2,6(4aH,5H)-dione 92

A solution of dienone ketone 85 (30mg) in hydro-

chloric acid (20 ml, 50% aqueous) was stirred at room temperature for 3 days. Water was added and the solution was extracted with dichloromethane. The dichloromethane solution was washed with water, dried and evaporated under reduced pressure to give hydroxy dienedione 92 (22mg, 78%) as a yellow solid, m.p. 190-194°. This was recrystallized from methyl acetate-light petroleum as a yellow powder, m.p. 230-232° (Accurate mass : Found : 204.0785. $C_{12}H_{12}O_3$ requires 204.0786). ν_{max} 3180 (OH), 1675, 1650, 1620, 1570 cm^{-1} (dienone). δ 6.4 (s, 1H, C=CHCO), 5.9 (d, 1H, J1Hz, (HO)C=CH). λ_{max} 272 (s, ε2500), 285 (s, ε2900), 331 (ε7400), 415 nm (ε1900). M^+, m/e 204 (79%).

1,2,3,4-Tetrahydro-6,7-methylenedioxy-2-naphthoic Acid

This compound was prepared by catalytic hydrogenation of ketoacid 93[110]. An analytical sample was recrystallized from dichloromethane-light petroleum as white flakes, m.p. 185-187° (Found : C, 65.1; H, 5.4. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%). ν_{max} 1695 cm^{-1} (CO_2H). δ ($CDCl_3$/$(CD_3)_2SO$) 6.5 (s, 2H, Ar H), 5.8 (s, 3H, OCH_2O), 3.7 (br s, 1H, CO_2H). M^+, m/e 220 (100%).

6-Diazoacetyl-5,6,7,8-tetrahydro-2,3-methylenedioxy-naphthalene 94

Treatment of the acid chloride of the acid prepared above with diazomethane gave diazoketone 94 in 94% yield as a yellow solid, m.p. 105-110°. A sample crystallized from dichloromethane-light petroleum as pale yellow needles, m.p. 118-119° (dec.) (Found : C, 63.7; H, 4.8; N, 11.3. $C_{13}H_{12}N_2O_3$

requires C, 63.9; H, 5.0; N, 11.5%). ν_{max} 3060, 2130, 1630 cm^{-1} ($COCHN_2$). δ 6.6 (s, 2H, Ar H), 5.9 (s, 2H, OCH_2O), 5.4 (s, 1H, $COCHN_2$). M^+, m/e 218 ($M-N_2$, 100%).

The reaction of 6-Diazoacetyl-5,6,7,8-tetrahydro-2,3- methylenedioxy-naphthalene with Trifluoroacetic Acid

Diazoketone 94 (100mg) was added portionwise during 5min to stirred trifluoroacetic acid-dichloromethane (3:1) at -30°. The green fluorescent solution was stirred at -30° for 10min and an equal volume of dichloromethane was added. The dichloromethane solution was washed three times with water, dried and evaporated under reduced pressure to give a yellow solid (87mg). An nmr spectrum obtained of this solid indicated that it contained dienone ketone 95 (42%) and trienone 96 (22%). Recrystallization of this mixture from ether-light petroleum gave 7,8-dihydro-3-hydroxy-4a,7-ethanonaphthalene-2,6(4aH,5H)-dione 95 as pale yellow crystals, m.p. 164-166° (Accurate mass : Found : 204.0786. $C_{12}H_{12}O_3$ requires 204.0786). ν_{max} 3340 (OH), 1730 (cyclopentanone), 1645, 1615 cm^{-1} (2,5-dienone). δ 6.3 (s, 1H, OH), 6.2 (d, 1H, J1.5Hz, (HO)C=CH), 5.9 (s, 1H, C=CHCO). M^+, m/e 204 (100%).

The recrystallization liquors were concentrated and chromatographed on a preparative thick layer plate with ether. Elution of the band of rf 0.5 afforded 3,4-dihydro-6,7-methylenedioxy-3,4a-ethanonaphthalen-2(4aH)-one 96 as yellow crystals, m.p. 143.5-144.5°, after recrystallization from ether-light petroleum (Found : C, 71.9; H, 5.5. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.6%). ν_{max} 1620, 1560 cm^{-1} (trienone). δ 5.7 (

s, 4H, C=CH and OCH_2O), 5.2 (s, 1H, C=CHCO). λ_{max} 249 (ε14700), 257 (ε17800), 366 nm (ε9200). M^+, m/e 216 (100%).

CHAPTER 4

1-(2',3',4'-Trimethoxy-phenyl)-propane-2,2,3-tricarboxylic Acid 104

To a stirred solution of lithium aluminium hydride (0.88g, 0.01 mol) in ether (10 ml) at 0° was added a solution of 2,3,4-trimethoxybenzaldehyde (1.96g, 0.01 mol) in ether (10 ml) during 15min. The mixture was stirred at 20° for 1h and an excess of sulphuric acid (10% aqueous) was added. The ethereal solution was separated, washed with water and dried. The ether was removed by distillation under reduced pressure to afford the alcohol (1.91g, 96%) as a colourless liquid. ν_{max} 3370 cm^{-1} (OH).

A solution of the alcohol (1.85g, 0.0093 mol) in ether (10 ml) at -10° was treated with a solution of phosphorous tribromide (2.7g, 0.01 mol) in ether (10 ml) during 30min. The mixture was stirred at -10° for a further 1h, washed with ice cold water and dried. The ether was removed by distillation under reduced pressure (the temperature of the solution was maintained below 0°) to give bromide 102 as a colourless liquid. It was used immediately in the next step.

A solution of sodium ethoxide (from sodium (0.31g, 0.0135g-atom)) in ethanol (10 ml) was added to a vigorously stirred mixture of the bromide and triethyl ethane-1,1,2-tricarboxylate (2.2g, 0.009 mol) at 0°. The resultant mixture was stirred at 20° for 1h and water (50 ml) was added. The aqueous layer was acidified with hydrochloric acid (10% aqueous) and extracted three times with ether. The ethereal extracts were washed with water and dried and evaporated under reduced

pressure to give the crude triester 103 (3.45g, 90%) as a yellow liquid. ν_{max} 1725 (ester), 1600 cm^{-1} (aromatic C=C). δ 6.6 (ABq, 2H, Ar H), 3.9-4.4 (m, 6H, CO_2CH_2), 3.85 (s, 6H, OMe), 3.8 (s, 3H, OMe), 3.5 (s, 2H, $ArCH_2$), 2.9 (s, 2H, CH_2-CO_2Et), 1.3 (t, 9H, CH_3).

A mixture of the triester 103 (3.4g), potassium hydroxide (2.24g, 0.04 mol) and ethanol (50 ml) were boiled under reflux, with stirring, for 20h. The mixture was cooled, made acidic by the addition of concentrated hydrochloric acid , and the ethanol was removed by distillation under reduced pressure. The residue was extracted with acetone, and the acetone was evaporated under reduced pressure to give triacid 104 (2.2g, 66% overall) as a pale brown solid, m.p. 157-160°. A sample was crystallized from acetone-light petroleum as white needles, m.p. 168-170° (dec.). This compound would not give a satisfactory elemental analysis result. ν_{max} 1700 cm^{-1} (CO_2H). δ 10.0 (br s, 3H, CO_2H), 6.7 (ABq, 2H, Ar H), 3.8 (s, 9H, OMe), 3.2 (s, 2H, $ArCH_2$), 3.0 (s, 2H, $CH_2(CO_2H)$).

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-3-naphthoic Acid 105

Triacid 104 (1.0g, 0.0029 mol) was heated at 180-190° until the evolution of carbon dioxide had ceased. The resultant brown liquid was cooled to 90° and polyphosphoric acid (10 ml) was added. The mixture was maintained at 90° for 1h, with occasional stirring, cooled, and poured into water (50 ml). The yellow solid which precipitated was collected by filtration, dissolved in methanol and treated with charcoal. The mixture was filtered and the methanol was removed by distillation under reduced pressure to give ketoacid 105 (0.65g,

80%) as an off-white solid, m.p. 149-153°. A sample was recrystallized from acetone-light petroleum as white needles, m.p. 160-161°. ν_{max} 1725 (CO_2H), 1640 cm^{-1} (C=O). δ 10.1 (br s, 1H, CO_2H), 7.3 (s, 1H, Ar H), 3.95 (s, 3H, OMe), 3.9 (s, 6H, OMe). M^+, m/e 280 (78%).

1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-naphthoic Acid 106

A Clemmenson reduction of ketoacid 105 afforded acid 106 in 90% yield as a yellow solid, m.p. 111-115°. An analytical sample was recrystallized from dichloromethane-light petroleum as pale yellow crystals, m.p. 121-122° (Found : C, 62.9; H, 6.9. $C_{14}H_{18}O_5$ requires C, 63.1; H, 6.8%). ν_{max} 1690 (CO_2H), 1600, 1580 cm^{-1} (aromatic C=C). δ 10.4 (br s, 1H, CO_2H), 6.4 (s, 1H, Ar H), 3.8-3.9 (br s, 9H, OMe). M^+, m/e 266 (100%).

7-Diazoacetyl-5,6,7,8-tetrahydro-1,2,3-trimethoxy-naphthalene 107

Treatment of the acid chloride of acid 106 with diazomethane gave diazoketone 107 in 95% yield as a yellow oil (which was not crystallizable). ν_{max} 3060, 2120, 1635 cm^{-1} ($COCHN_2$). δ 6.4 (s, 1H, Ar H), 5.4 (s, 1H, $COCHN_2$), 3.8 (br s, 9H, OMe).

1,2,3,4-Tetrahydro-10-oxo-5,6-dimethoxy-3,4a-ethanonaphthalen-7(4aH)-one 110

A solution of diazoketone 107 (75mg, 0.3 mmol) in dichloromethane (1 ml) was added during 5min to a stirred solution of trifluoroacetic acid (7.5 ml) and dichloromethane (2 ml) at -30°. The mixture was stirred at -30° for a further

5min and equal volumes of both dichloromethane and water were added. The organic layer was separated and washed with water, sodium carbonate solution (10% aqueous) and water and dried. An nmr spectrum, obtained of the yellow oil after evaporation of the solvent, indicated that it contained a mixture of dienone ketone 110 (77%) and aromatic material. The mixture was chromatographed on a preparative thick layer plate with ether and the fraction of rf 0.3 was eluted with ethyl acetate. Removal of the ethyl acetate by distillation under pressure gave a pale yellow solid (37mg, 55%). This was recrystallized from light petroleum to give dienone ketone 110 as white prisms, m.p. 112-113° (Found : C, 67.6; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). ν_{max} 1730 (cyclopentanone), 1675, 1640, 1605 cm^{-1} (2,5-dienone). δ 6.0 (br s, 1H, C=CH), 4.1 (s, 3H, OMe), 3.7 (s, 3H, OMe). λ_{max} 245 (ε11000), 291 nm (ε3900). M^+, m/e 248 (100%).

1,2,3,4-Tetrahydro-6,7-dimethoxy-8-hydroxy-1-oxo-3-naphthoic Acid 112

To a solution of ketoacid 111 (1.6g, 0.0057 mol) in dichloromethane (15 ml) at -78° was added a solution of boron trichloride (1.06g, 0.009 mol) in dichloromethane (4.5 ml) also at -78°. The mixture was allowed to warm to 20° and was quenched with water 30min after the addition. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, washed repeatedly with water and dried. The solvent was removed by distillation under reduced pressure to give phenolic acid 112 (1.3g, 86%) as a white solid, m.p. 212-215°. An analytical sample was recrystallized from acetone-light petrol-

eum as pale yellow crystals, m.p. 217-218° (Found : C, 54.7; H, 5.6. $C_{13}H_{14}O_6^*$ requires C, 54.9; H, 5.7%). ν_{max} 3500 (OH), 1720 (CO_2H), 1630 (C=O), 1605, 1585 cm^{-1} (aromatic C=C). δ ($CDCl_3/(CD_3)_2SO$) 12.7 (s, 1H, OH), 6.4 (s, 1H, Ar H), 6.1 (br s, 3H, CO_2H and H_2O), 3.9 (s, 3H, OMe), 3.8 (s, 3H, OMe). M^+, m/e 266 (17%). * As monohydrate

1,2,3,4-Tetrahydro-5-hydroxy-6,7-dimethoxy-2-naphthoic Acid 113

(A)A Clemmenson reduction of phenolic ketone 112 afforded phenol 113 as a white solid in 76% yield. A sample was recrystallized from dichloromethane-light petroleum as red orthorhombic crystals, m.p. 164-165.5°. ν_{max} 1705 (CO_2H), 1620, 1590 cm^{-1} (aromatic C=C). δ 6.2 (s, 1H, Ar H), 3.8 (d, 6H, OMe). M^+, m/e 252 (100%). This compound became red on exposure to air and would not give satisfactory elemental analysis results.

(B)A mixture of acid 116 (1.33g, 0.005 mol) and concentrated hydrochloric acid (100 ml, 20% aqueous) was boiled under reflux (and under an atmosphere of nitrogen) for 2h. The mixture was cooled and was treated with sodium hydroxide solution (20% aqueous) to give a solution of pH3. This solution was extracted three times with ethyl acetate and the combined ethyl acetate layers were washed with water and dried. The solvent was removed by distillation under reduced pressure to give phenol 113 (1.2g, 95%) as a red solid, m.p. 120-125°. A sample was crystallized from dichloromethane-light petroleum as red, orthorhombic crystals, m.p. 162-164°, which afforded identical infra red and nmr spectra to those given by a sample

prepared by Method A.

6-Diazoacetyl-5,6,7,8-tetrahydro-2,3-dimethoxy-1-naphthol 114

Acetylation of phenol 113 with acetic anhydride and sodium acetate gave the acetate as white needles, m.p. 149-150° after crystallization from dichloromethane-light petroleum. The acid chloride of this compound was treated with diazomethane to give the acetoxydiazoketone as a pale yellow liquid. δ 6.6 (s, 1H, Ar H), 5.4 (s, 1H, $COCHN_2$), 3.8 (s, 3H, OMe), 2.3 (s, 3H, $OCOCH_3$). The acetoxydiazoketone was deacetylated by treatment with pyridine in benzene to give phenolic diazoketone 114 (62% overall) as a pale yellow solid. A sample was crystallized from dichloromethane-light petroleum as yellow needles, m.p. 118.5-119.5° (dec.). ν_{max} 3350 (OH), 3100, 2120, 1640 ($COCHN_2$), 1625, 1590 cm^{-1} (aromatic C=C). δ 6.1 (s, 1H, ArOH), 6.0 (s, 1H, Ar H), 5.2 (s, 1H, $COCHN_2$), 3.7 (d, 6H, OMe). M^+, m/e 248 ($M-N_2$, 100%).

1,2-Dihydro-2,4a-ethanonaphthalene-6,7-dimethoxy-3,5(4H,4aH)-dione 115

A solution of diazoketone 114 (140mg, 0.51 mmol) in dichloromethane (1 ml) was added to vigorously stirred trifluoroacetic acid (14 ml) containing dichloromethane (3 ml) at -30°. The mixture was stirred at -30° for 5min and equal volumes of both dichloromethane and water were added. The organic layer was separated, washed with sodium hydroxide solution (5% aqueous) and with water and dried. The solvent was removed by distillation under reduced pressure to give a yellow solid (106mg). The nmr spectrum given by this product indicated that

it contained dienone ketone 115 (74%) and uncyclized material. The mixture was chromatographed on a preparative thick layer plate with ethyl acetate. Elution of the region of rf 0.4 afforded dienone ketone 115 as yellow needles, m.p. 138-139° after crystallization from dichloromethane-light petroleum (Found : C, 67.5; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). ν_{max} 1740 (cyclohexanone), 1650, 1620, 1550 cm^{-1} (2,4-dienone). δ 6.1 (t, 1H, J2.3Hz, C=CH), 4.0 (s, 3H, OMe), 3.6 (s, 3H, OMe). λ_{max} 344 nm (ε3700). M^+, m/e 248 (26%).

1-(3',4',5'-Trimethoxy-phenyl)-propane-2,2,3-tricarboxylic Acid

This compound was prepared from 3,4,5-trimethoxybenzaldehyde, by the same procedure which was used to prepare triacid 104, in 80% yield as a white powder, m.p. 147-150° (dec.). ν_{max} 1725 cm^{-1}(CO_2H). δ ($CDCl_3$/$(CD_3)_2SO$) 9.5 (br s, 3H, CO_2H), 6.4 (s, 2H, Ar H), 3.8 (s, 9H, OMe), 3.3 (s, 2H, $ArCH_2$), 3.0 (s, 2H, CH_2).

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-3-oxo-2-naphthoic Acid 111

This compound was prepared from the triacid, by an identical procedure to that used to make ketoacid 105, in 82% yield. A sample was recrystallized from dichloromethane-light petroleum as white, rhombohedral crystals, m.p. 218-219°. ν_{max} 1700 (CO_2H), 1675 (C=O), 1590, 1585 cm^{-1} (aromatic C=C). δ 10.3 (br s, 1H, CO_2H), 6.6 (s, 1H, Ar H), 3.8-3.9 (3s, 9H, OMe). M^+, m/e 280 (79%).

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-naphthoic Acid 116

A Clemmenson reduction of ketoacid 111 afforded

acid 116 as a pink solid in 88% yield. An analytical sample was recrystallized from ether-light petroleum as white needles, m.p. 111-112° (Found : C, 63.3; H, 7.1. $C_{14}H_{18}O_5$ requires C, 63.1; H, 6.8%). ν_{max} 1695 (CO_2H), 1610, 1590 cm^{-1} (aromatic C=C). δ 10.3 (br s, 1H, CO_2H), 6.3 (s, 1H, Ar H), 3.8-3.9 (3s, 9H, OMe). M^+, m/e 266 (100%).

2-Diazoacetyl-1,2,3,4-tetrahydro-5,6,7-trimethoxy-naphthalene 117

Treatment of the acid chloride of acid 116 with diazomethane gave diazoketone 117 as a yellow oil (which was not crystallizable) in 95% yield. ν_{max} (film) 3060, 2120, 1640 cm^{-1} ($COCHN_2$). δ 6.3 (s, 1H, Ar H), 5.3 (s, 1H, $COCHN_2$), 3.8 (s, 3H, OMe), 3.7 (s, 6H, OMe).

The reaction of 2-Diazoacetyl-1,2,3,4-tetrahydro-5,6,7-trimethoxy-naphthalene with Trifluoroacetic Acid

A solution of diazoketone 117 (100mg) in dichloromethane (0.5 ml) was added to vigorously stirred trifluoroacetic acid (10 ml) containing dichloromethane (2 ml) at -30° during 5min. The mixture was stirred at -30° for a further 5min and equal volumes of both dichloromethane and water were added. The dichloromethane layer was separated and washed with sodium hydroxide solution (5% aqueous) and water and dried. The solvent was removed by distillation under reduced pressure to give a yellow oil (126mg). The nmr spectrum obtained of this oil indicated that it contained a mixture of dienone ketone 118 (24%), dienone ketone 119 (17%) and uncyclized material. The mixture was chromatographed on a preparative thick layer plate

with ether-ethyl acetate (1:1). Elution of the band of rf 0.3 afforded the dienone ketone 118 as white needles, m.p. 123-124° after recrystallization from dichloromethane-light petroleum (Found : C, 68.0; H, 6.4. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). ν_{max} 1745 (cyclopentanone), 1650, 1620, 1605 cm^{-1} (2,5-dienone) δ 5.6 (s, 1H, Ar H), 3.7 (d, 6H, OMe). λ_{max} 264 nm (ε6000). M^+, m/e 248 (76%).

Elution of the band of rf 0.4 afforded dienone ketone 119 as white needles, m.p. 89-90° after recrystallization from dichloromethane-light petroleum (Accurate mass : Found : 248.1044. $C_{14}H_{16}O_4$ requires 248.1048). ν_{max} 1745 (cyclohexanone), 1680,1645, 1615 cm^{-1} (2,5-dienone). δ 6.1 (t, 1H, J1.9Hz, C=CH), 4.1 (s, 3H, OMe), 3.7 (s, 3H, OMe). λ_{max} 245 (ε8000), 290 nm (ε3100). M^+, m/e 248 (17%).

1,2,3,4-Tetrahydro-6,8-dimethoxy-2-naphthoic Acid 129

To a solution of ketoacid 105 (1.23g, 5 mmole) in tetrahydrofuran (20 ml) and liquid ammonia (100 ml) was added small pieces of sodium (0.98g, 42.5mg-atom). The reaction was allowed to proceed for 10min and the excess of sodium was destroyed by the addition of ammonium chloride solution (20% aqueous). The ammonia was removed in a stream of nitrogen and the residue was dissolved in water. The aqueous solution was extracted with ether and acidified to pH3 by the addition of concentrated hydrochloric acid. The solution was extracted with ethyl acetate and the ethyl acetate extract was washed with water, dried and evaporated under reduced pressure to give a yellow oil (1.26g). The oil was subjected immediately to a Clemmenson reduction and the crude product was chromat-

ographed on Sorbsil (20g) and eluted with ether-light petroleum (1:1) to give acid 129 (549mg, 47% overall) as a white solid. A sample was recrystallized from ether-light petroleum as white, monoclinic crystals, m.p. 121-122° (Found : C, 66.2; H, 6.7. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). ν_{max} 1700 (CO_2H), 1605, 1590 cm^{-1} (aromatic C=C). δ 9.6 (br s, 1H, CO_2H), 6.3 (br s, 2H, Ar H), 3.8 (s, 6H, OMe). M^+, m/e 236 (100%).

2-Diazoacetyl-1,2,3,4-tetrahydro-6,8-dimethoxy-naphthalene 130

Treatment of the acid chloride of acid 129 with diazomethane afforded diazoketone 130 in 97% yield as a yellow oil. This was recrystallized from ether-light petroleum as pale yellow needles, m.p. 84-85° (dec.) (Found : C, 64.4; H, 6.2; N, 10.9. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.8%). ν_{max} 3040, 2135, 1640 ($COCHN_2$), 1620, 1600 cm^{-1} (aromatic C=C). δ 6.0 (br s, 2H, Ar H), 5.2 (s, 1H, $COCHN_2$), 3.6 (d, 6H, OMe). M^+, m/e 222 ($M-N_2$, 73%).

1,2,3,4-Tetrahydro-5-methoxy-10-oxo-3,4a-ethanonaphthalen-7(4aH)-one 123

Diazoketone 130 (40mg, 0.18 mmol) was added portionwise during 5min to a stirred mixture of trifluoroacetic acid (5 ml) and dichloromethane (1 ml) at -30°. The red solution was stirred at -30° for a further 5min and equal volumes of both dichloromethane and water were added. The organic layer was separated and washed with water, sodium hydroxide solution (5% aqueous) and water and dried. The solvent was removed by distillation under reduced pressure to give dienone ketone 123 (37mg, 96%) as a yellow solid. This was recrystallized from

dichloromethane-light petroleum as pale yellow, rhombohedral crystals, m.p. 181-182° (Found : C, 71.3; H, 6.5. $C_{13}H_{14}O_3$ requires C, 71.5: H, 6.5%). ν_{max} 1740 (cyclopentanone), 1660, 1620, 1610, 1600 cm^{-1} (2,5-dienone). δ 6.0 (br s, 1H, HC=COMe), 5.7 (d, 1H, J1.5Hz, C=CH). λ_{max} 242 (ε11000), 270 nm (ε3700). M^+, 218 (72%).

1,2,3,4-Tetrahydro-5-hydroxy-10-oxo-3,4a-ethanonaphthalen-7(4aH)-one 124

Dienone ketone 123 (20mg, 0.092 mmol) was added to concentrated hydrochloric acid (5 ml) and was allowed to stand at room temperature for two days. The hydrochloric acid was removed by careful distillation under vacuum and the residue was dissolved in dichloromethane, treated with charcoal, filtered and evaporated. Dienone ketone 124 (14.0mg, 73%) was obtained as a yellow solid, m.p. 194-196° (dec.) (Accurate mass : Found : 204.0786. $C_{12}H_{12}O_3$ requires 204.0786). ν_{max} 1745 (cyclopentanone), 1665, 1590,1565 cm^{-1} (dienone). δ 9.0 (s, 1H, OH), 7.1 (s, 1H, C=CH), 6.5 (s, 1H, C=CH). M^+, m/e 204 (100%).

CHAPTER 5

Amendments to General Topics

(ii) Infra red spectra, unless otherwise indicated, were measured as Nujol mulls on Jasco IRA-1 and Perkin Elmer 257 spectrophotometers.

(iv) Mass Spectra (including accurate mass measurements) were measured on an AEI MS902 high resolution mass spectrometer

(v) The nuclear magnetic resonance spectra were recorded on Varian HA100 and Jeol "Minimar 100" spectrometers operating at 100MHz.

(vii) Microanalyses were performed by the Australian National University Analytical Services Unit, Canberra.

Methyl γ-(1,7-dimethoxy-4-naphthyl)-butyrate 132

Methylation of acid 131 with diazomethane gave methyl ester 132 in 97% yield as a white solid, m.p. 42-45°. A sample was recrystallized from dichloromethane as white needles, m.p. 46-47° (Found : C, 70.8; H, 7.1. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%). ν_{max} 1740 (ester), 1630, 1610, 1590 cm^{-1} (aromatic C=C). δ 6.4-7.9 (m, 5H, Ar H), 3.9 (d, 6H, OMe), 3.6 (s, 3H, CO_2Me). M^+, m/e 288 (52%).

1-Keto-7,9-dimethoxy-1,2,3,4-tetrahydro-phenanthrene 133

(A) Treatment of acid 131 with polyphosphoric acid at 90° for 1h afforded tetralone 133 in 75% yield as a yellow solid, m.p. 130-132°. A sample was recrystallized from di-

chloromethane as yellow crystals, m.p. 134-135° (lit.[125] 134-135°). ν_{max} 1670 (C=O), 1620, 1600 cm^{-1} (aromatic C=C). δ 8.1 (d, 1H, J10Hz, Ar H), 7.7 (d, 1H, J3Hz, Ar H), 7.5 (s, 1H, Ar H), 7.3 (dd, 1H, $J_1$10Hz, $J_2$3Hz, Ar H), 4.0 (d, 6H, OMe).

(B)Under the same conditions (described above), ester 132 gave tetralone 133 in 87% yield as a yellow solid, m.p. 125-128°. The spectra afforded by this compound were identical with those obtained from a sample prepared by Method A.

1,2,3,4-Tetrahydro-1-methylene-7,9-dimethoxy-phenanthrene 134

A suspension of methyl triphenylphosphonium bromide (33.6g, 0.088 mol) in dry tetrahydrofuran (170 ml) at 0° and under an atmosphere of nitrogen was treated with a solution of n-butyl lithium (0.086 mol) in hexane (65 ml). The mixture was allowed to warm to room temperature, and after 15min, it was treated with a solution of tetralone 133 (7.0g, 0.027 mol) in tetrahydrofuran (50 ml). The resultant solution was stirred overnight and the tetrahydrofuran was removed by distillation under reduced pressure. The residue was partitioned between hexane (150 ml) and methanol (100 ml, 50% aqueous). The methanolic extract was washed in turn with two portions (100 ml) of hexane and all of the hexane layers were washed in turn with aqueous methanol (2x100 ml portions). The hexane layers were combined, dried and evaporated under reduced pressure to afford olefin 134 (4.8g, 70%) as white flakes, m.p. 99-100° after chromatography on Fluorisil (60-100 mesh) (160g) followed by recrystallization from methanol-water. An analytical sample was recrystallized from methanol as white flakes, m.p. 102-103° (Found C, 80.3; H, 7.0. $C_{17}H_{18}O_2$ requires C, 80.3;

H, 7.1%). ν_{max} 1625 ($C=CH_2$), 1600 cm^{-1} (aromatic C=C). δ 7.70 (d, 1H, J9Hz, C5-H), 7.44 (d, 1H, J3Hz, C8-H), 7.02 (dd, 1H, $J_1$9Hz, $J_2$3Hz, C6-H), 6.90 (s, 1H, C10-H), 5.36 (s, 1H, $C=CH_2$), 4.90 (s, 1H, $C=CH_2$), 3.96 (s, 3H, OMe), 3.88 (s, 3H, OMe). M^+, m/e 254 (100%).

1,2,3,4-Tetrahydro-1-hydroxymethyl-7,9-dimethoxy-phenanthrene 135

A suspension of sodium borohydride (380mg, 10 mmol) in tetrahydrofuran (20 ml) at 0° and under an atmosphere of nitrogen was treated with boron trifluoride etherate (1.4 ml) and the mixture was stirred at 0° for 2h. A portion (2.0 ml) of this diborane solution was diluted with tetrahydrofuran (5 ml) and was treated dropwise with a solution of olefin 134 (500mg, 2.0 mmol) in tetrahydrofuran (5 ml) at room temperature. The mixture was stirred at room temperature for 1h and water (0.5 ml) was added to hydrolyse the excess of sodium borohydride. Hydrogen peroxide (0.5 ml, 30%) was added dropwise with stirring and the solution was kept basic by the addition of sodium hydroxide solution (10% aqueous). The mixture was poured into water (50 ml) and was extracted with dichloromethane. The dichloromethane solution was washed and dried and evaporated under reduced pressure to give alcohol 135 (0.56g, 100%) as an off-white solid, m.p. 130-132°. An analytical sample crystallized from dichloromethane-light petroleum as white flakes, m.p. 149.5-150.5° (Found : C, 74.7; H, 7.3. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%). ν_{max} 3350 (OH), 1630, 1610 cm^{-1} (aromatic C=C). δ 7.82 (d, 1H, J9Hz, C5-H), 7.53 (d, 1H, J3Hz, C8-H), 7.14 (dd, 1H, $J_1$9Hz, $J_2$3Hz, C6-H), 6.66 (s, 1H, C10-H),

3.96 (s, 3H, OMe), 3.90 (s, 3H, OMe). M^+, m/e 272 (43%).

1,2,3,4-Tetrahydro-7,9-dimethoxy-1-phenanthraldehyde 136

Chromium trioxide (0.6g, 6 mmol) was added to a stirred solution of pyridine(0.95g, 12 mmol) in dichloromethane (15 ml). The red solution was stirred at room temperature with the exclusion of moisture for 15min and a solution of alcohol 135 (272mg, 1 mmol) in dichloromethane (2 ml) was added. The suspension was stirred for 15min and decanted from the residue which had formed. Ether was added to this solution to precipitate the chromium salts, and the mixture was filtered. The ethereal filtrate was washed with sulphuric acid (10% aqueous) and dried. Removal of the solvent under reduced pressure gave a yellow oil (29mg). This oil was chromatographed on a preparative thick layer plate with ether-light petroleum (1:3) and the fraction of rf 0.4 was eluted. Evaporation of the elutant afforded aldehyde 136 (65mg, 24%) as white flakes, m.p. 99-102° (dec.). ν_{max} 1725 (C=O), 1630, 1610 cm^{-1} (aromatic C=C). δ 9.66 (s, 1H, CHO), 7.80 (d, 1H, J7Hz, C5-H), 7.55 (d, J2Hz, C8-H), 7.19 (dd, 1H, $J_1$7Hz, $J_2$2Hz, C6-H) ,6.50 (s, 1H, C10-H), 3.96 (s, 3H, OMe), 3.91 (s, 3H, OMe). This compound was too labile to be characterized further.

1,2,3,4-Tetrahydro-1-methyl-7,9-dimethoxy-1-phenanthraldehyde 137

A solution of aldehyde 136 (62mg, 0.23 mmol) in benzene (5 ml; all solvents used in this preparation were purged with argon for 15min before use) under argon was treated with a solution of potassium t-butoxide(162mg, 1.45

mmol) in t-butyl alcohol (5 ml), and the mixture was stirred at room temperature for 10min. Methyl iodide (207mg, 2.9 mmol) was added and the mixture was stirred at room temperature for 16h. A further portion of potassium t-butoxide (81mg, 0.073 mmol) was added, followed by methyl iodide (104mg, 1.45 mmol). The mixture was stirred for 2h and water(30 ml) and ether (30 ml) were added. The organic layer was separated, washed and dried and evaporated under reduced pressure, to give a yellow solid (66mg). This solid was chromatographed on a preparative thick layer plate with ether-light petroleum (2:3). Elution of the region of rf 0.4 afforded tetralone 133 (21mg). Elution of the region of rf 0.6 gave the aldehyde 137 (22mg, 34%) as a white solid. This was recrystallized from ether-light petroleum as white flakes, m.p. 95-96° (Accurate mass : Found : 284.1414. $C_{18}H_{20}O_3$ requires 284.1412). ν_{max} 1720 (C=O), 1600 cm^{-1} (aromatic C=C). δ 9.46 (s, 1H, CHO), 7.83 (d, 1H, J7Hz, C5-H), 7.55 (d, 1H, J2Hz, C8-H), 7.17 (dd, 1H, $J_1$7Hz, $J_2$2Hz, C6-H), 6.38 (s, 1H, C10-H), 3.96 (s, 3H, OMe), 3.92 (s, 3H, OMe). M^+, m/e 284 (33%).

1,2,3,4,5,6-Hexahydro-1-methyl-9-methoxy-7(8H)-phenanthrone 140

A solution of alcohol 135 (272mg, 1 mmol) in dry tetrahydrofuran (5 ml) was added to a mixture of liquid ammonia (50 ml) and t-butyl alcohol (0.33 ml). Small pieces of freshly cut lithium (32mg, 4.4mg-atom) were added, and the solution was stirred in a bath of ethanol and dry ice for 2h. The ammonia was removed in a stream of nitrogen and the residue was acidified with dilute hydrochloric acid. The aqueous sol-

ution was extracted with dichloromethane and the dichloromethane extract was washed with water and with brine and dried. The solvent was removed by distillation under reduced pressure and the resultant oil was chromatographed on a preparative thick layer plate with ether-light petroleum (3:1). The fraction of rf 0.9 was eluted and evaporation of the elutant afforded tetralone 140 (80mg, 33%) as a colourless oil. This was crystallized from light petroleum as white flakes, m.p. 70-71^{o} (Accurate mass : Found : 244.1463. $C_{16}H_{20}O_2$ requires 244.1463). ν_{max} 1725 (C=O), 1600 cm^{-1} (aromatic C=C). δ 6.72 (s, 1H, Ar H), 3.86 (s, 3H, OMe), 3.55 (s, 2H, $ArCH_2CO$), 1.35 (d, 3H, J5Hz, CH_3). M^+, m/e 244 (100%).

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