SYNTHETIC STUDIES ON GIBBERELLINS

THESIS

presented to the University of
Glasgow for the degree of
Doctor of Philosophy

by

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To my loving wife Heyam

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. A.J.Baker for his advice,guidance and enthusiasm,which has been a constant source of encouragment throughout the duration of this work.

I would also like to thank all members of the technical staff for services rendered.

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CONTENTS

SUMMARY

As part of a programme directed towards the total synthesis of the plant hormones - the gibberellins - efficient synthesis of 4-carboxy-5,6-dimethoxyindanone and related compounds were required.

This thesis describes the synthesis of 4-4-carboxy-5,6-dimethoxyindanone and related compounds from methyl β-(2-hydroxymethyl-3-hydroxy-4-methoxyphenyl)propionate which was derived from isovanillin using a regiospecific benzeneboronic acid catalysed hydroxymethylation reaction.

The same indanone was synthesised by an independent route from opianic acid, a degradation product of the alkaloid narcotine.

4-Methyl-5-hydroxy-6-methoxyindanone and related compounds were synthesised in a related fashion from isovanillin. An efficient route to a monoprotected derivative of 4-methylindane-5,6-quinone - 3-oxo-4,4-oxoethylenedioxy-5-methylbicyclo [4.3.0] nona-1,5-diene is described together with its facile Diels-Alder reaction with methyl vinyl ketone.

The stability of the phenylboronate derivative of an ortho-hydroxybenzyl alcohol towards poly - phosphoric acid cyclisation conditions is also recorded.

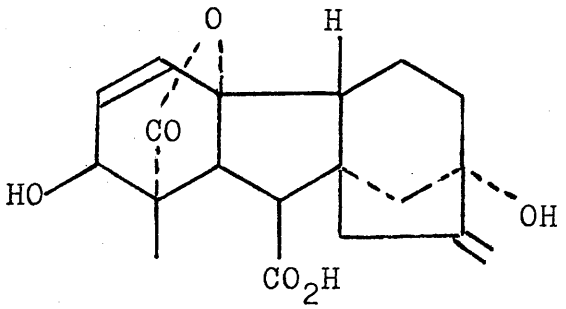
INTRODUCTION

The gibberellins were discovered as a result of studies by Japanese chemists into a soil borne disease of rice, Bakanae disease, caused by the fungus gibberella fujikoroi.[1]

From cell-free extracts of the fungus Yabuta and Hayashi isolated,in 1939, a crystalline active principle which they named gibberellin[1a].To date some fifty two gibberellins have been isolated and their structures assigned by correlation with that of gibberellic acid(GA3) (1).

The gibberellins,which are diterpenoid acids, are endogenous plant hormones associated with plant growth and can be divided into two groups, namely C_{19} (2) and C_{20} (3) gibberellins.Further investigation by Grove[2] have shown that they are natural constituents of green plants. Studies[3,4]have shown that the gibberellins are able to control growth and developmental processes in plant by stimulating cell division and elongation.They promote stem extension and fruit growth; they can also stimulate flowering in some plants and overcome dormancy of certain seeds[5].

The first gibberellin to be obtained in a pure form (by Cross and Curtis[6]) was gibberellic acid (GA3)(1). Final confirmation concerning the structure and absolute stereochemistry of the



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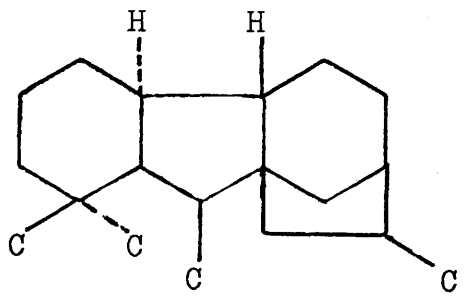

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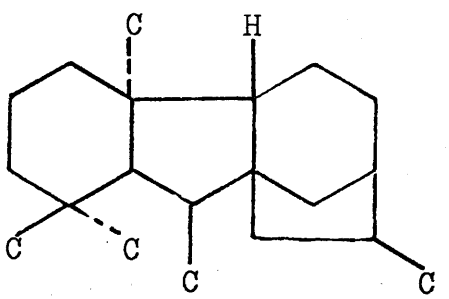


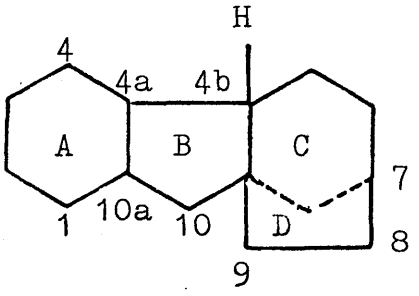
(3)

gibberellins was not achieved until Scott and Sim,[7] carried out an x-ray structure analysis.

Formerly, the gibberellins, their derivatives and degradation products were named as derivatives of the hypothetical gibbane[8] (4) and numbered as shown. A more recent proposal [9,10] that nomenclature based on the hypothetical diterpene gibberelline(5) be used together with conventional diterpenoid numbering. However, both systems are still used. The use of gibberellane nomenclature, especially for synthetic intermediates, is clumsy when they lack C_7, C_{17}, C_{18}, C_{19} and C_{20} functionality. In this thesis gibbane nomenclature and gibberellane numbering will be used.

Due to their remarkable biological activity, the synthesis of gibberellins is of pivotal importance. Because these molecules possess structural and stereochemical complexity, the ease with which they rearrange these compounds have only presented an intriguing synthetic challenge to the organic chemist. However the number of steps which would be involved in such a synthesis will inevitably reduce their commercial viability. This leaves the way open for the field of partial synthesis which has attracted interest at the expense of total synthesis in recent years.

This introduction will cover the synthesis of gibberellins and related synthons;the biosynthesis has been comprehensively reviewed by MacMillan[2,11] and is not discussed here.



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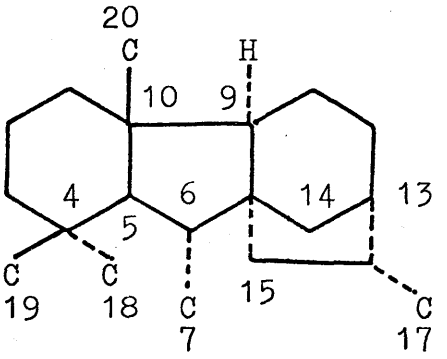

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Synthetic studies directed towards the gibberellins can be considered under three main categories:

a- Construction of the CD ring system.

b- Synthesis of hydrofluorenes.

C- Synthesis of the ring A system.

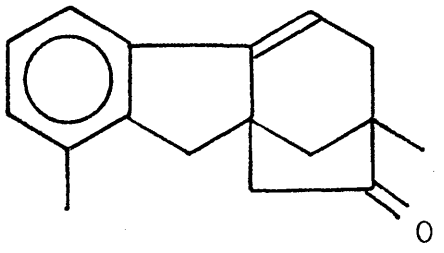
a- Construction of the CD ring system.

1- Acid catalysed cyclization.

Loewenthal[12] and Raphael[13] achieved the synthesis of gibberone (6), a degradation product of gibberellic acid (3) by constructing the bicyclo(3.2.1) octyl CD ring system on a suitably substituted indanone, using boron trifluoride-acetic acid to form ring D by cyclodehydration (7→ 8), a method which Loewenthal later improved by using naphthalene -1- sulphonic acid[14]. Gibberic acid (9) also a degradation product of gibberellic was synthesised by Loewenthal[15] using a similar approach.

Wiesner[16] cyclized the unsaturated keto-acetal (10) by heating in 80% acetic acid to give a mixture of tricyclic epimers (11) in excellent yield.

Ghatak[18,19] has synthesised the endo-2-aryl-6-oxobicyclo (3.2.1) octane derivatives (12) by the Diels Alder cyclization of the diene derived from the carbinol (13) and either methyl acrylate (14: R=H) or methyl methacrylate (14:R=CH_3), followed by



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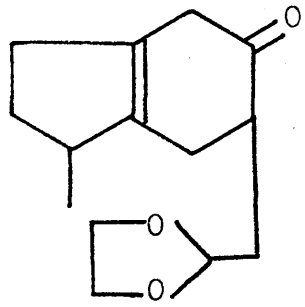

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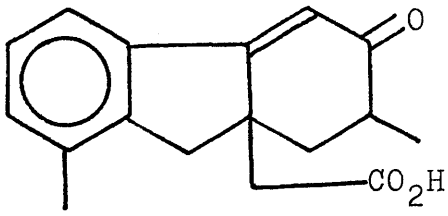

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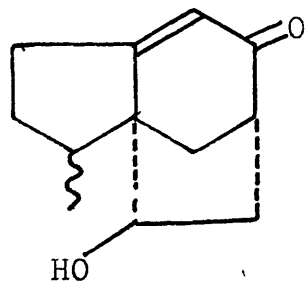

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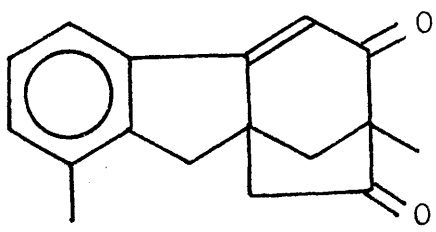

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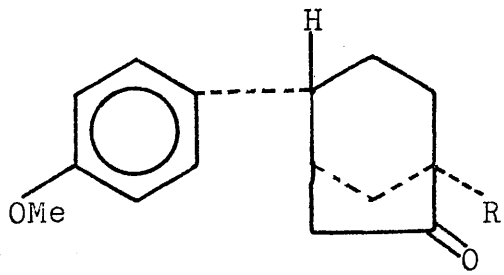
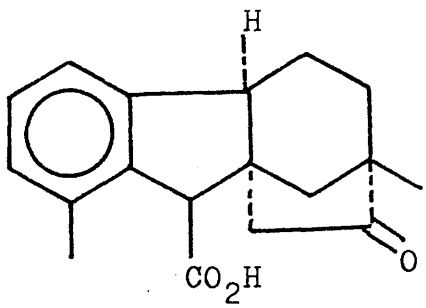


(12) R=CH_3,H



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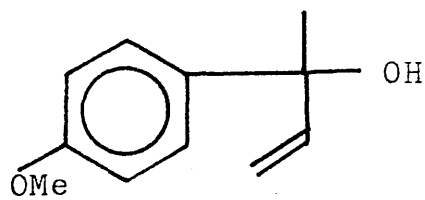


(13)

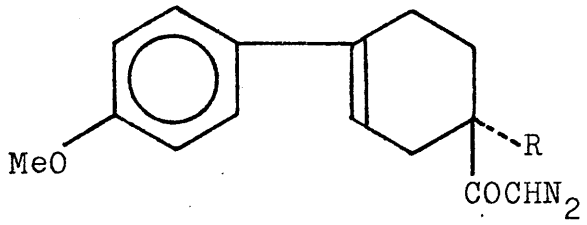
saponification and conversion of the resulting acid to its diazomethyl ketone (14). Boron trifluoride etherate catalysed cyclization afforded the bicyclo (3.2.1) octanones(12) in high yields.

Lately[17], he has also investigated the cyclization of tricyclics to tetracyclics by similar procedures as exemplified by the conversion of the tricyclic acid (15) to the tetracyclic ketone (16) in 50% yield.

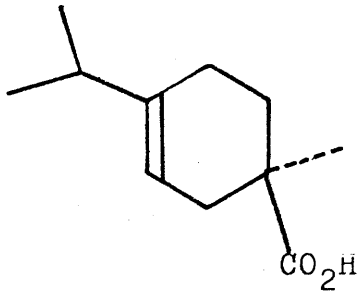
Mander[20,21] has published two papers on the synthesis of the 14-norhelminthosporic acid analogue (17),which snows gibberellin-like properties. The key step in a multistage synthesis involved the cyclization of the acid (18), via its diazoketone, to ketone (19) using boron trifluoride etherate in nitromethane (Helminthsporic acid = (20)). He[22,23,24] improved the cyclization product yield of the diazoketones (21), (22) and (23) prepared from the corresponding acid by successive treatment with oxalyl chloride and diazomethane. Treatment of the resulting diazoketones, with trifluoroacetic acid and dichloromethane afforded the tricyclic ketones (24), (25) and (26) respectively. The trichloroacetoxy derivatives gave the best yields of tricylic ketones.

2- Base catalysed cyclizations.

Gerber[25] synthesised gibbane (27) using a Dieckmann cyclization to construct the CD ring system



(14) R= CH_3, H



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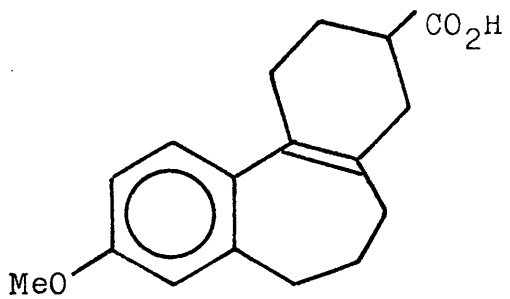

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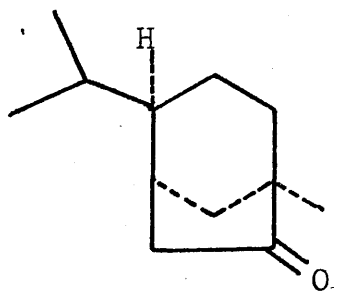

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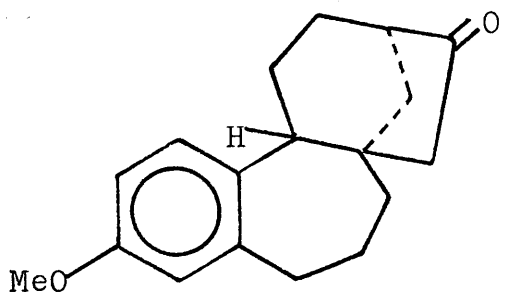

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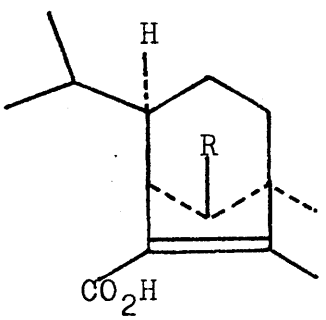
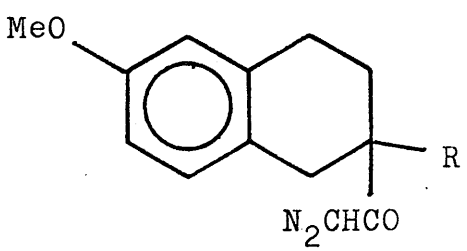


(17) R= H

(20) R= CH_2OH

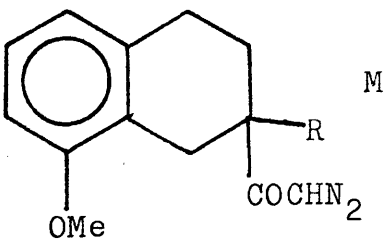


(21)

a. R=$OCOCF_3$

b. R=$OCOCCl_3$

c. R=$OCOCHCl_2$



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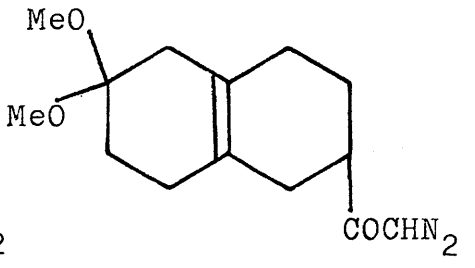
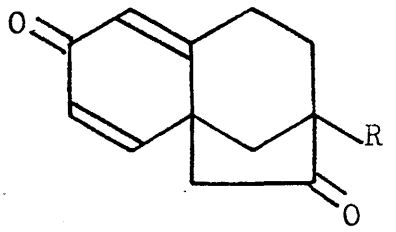


(23)

a.R= $OCOCF_3$

b.R= $OCOCCl_3$

c.R= $OCOCHCl_2$



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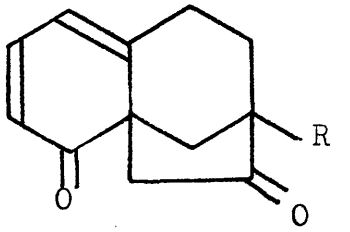
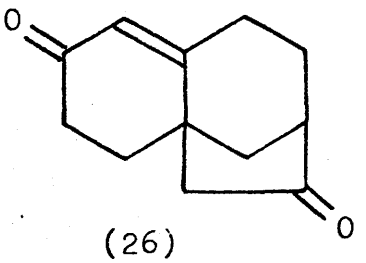


(25)

a.R= OH

b.R= $OCOCCl_3$

c.R= $OCOCHCl_2$



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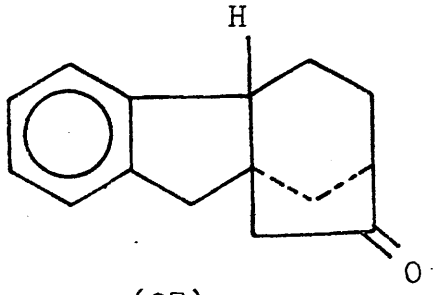


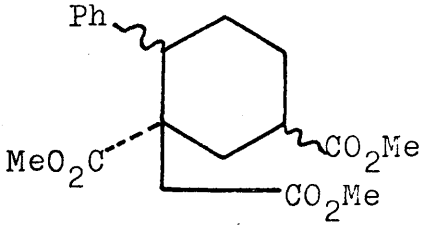
(27)

(29) from (28). This approach was taken up by Baker[26,27] in his synthesis of the advanced gibberellin synthon (30).

Recently, Kato[28,29] utilised this approach in his synthetic approach to the gibberellin- like metabolite fujenoic acid (31). Diels Alder reation between methyl furfurylidenecrotonate and methyl itaconate, followed by sequential catalytic hydrogenation, Dieckmann cyclization and decarbomethoxylation produced the keto-ester(32).

Bicyclooctanone (33) was synthesised [30] from 3-carboethoxycyclohexanone, which, under Knoevenagel condensation conditions in the presence of ethyl cyanoacetate, followed by treatment with potassium cyanide, gave the ester (34) in 60% yield. Dieckmann like cyclization followed by basic hydrolysis and decarboxylation yielded the acid (33).

Independent work by Corey[31] and Ziegler[32], utilised bromo-diketone (35). Corey prepared the hydroxy ketone (36), using di-n-butyl copper lithium in ether at -50°C. A similar cyclization of the bromodiketone (37), via an intramolecular Grignard reaction carried out by Ziegler was unsuccessful due to internal protonation, presumably from enolization of the aliphatic carbonyl. However, he succeeded in cyclizing the bromo ester(38) to the tetracyclic product (39) by an internal Reformatsky reaction, followed by quenching of the reaction with acetic



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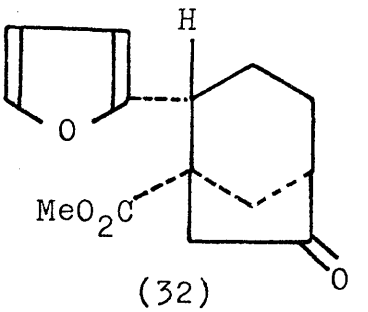

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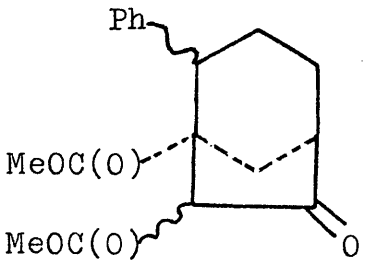

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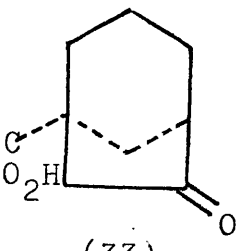

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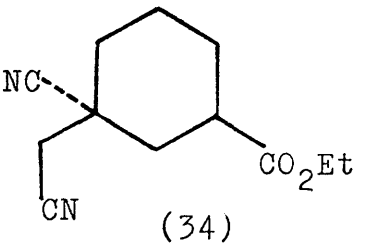

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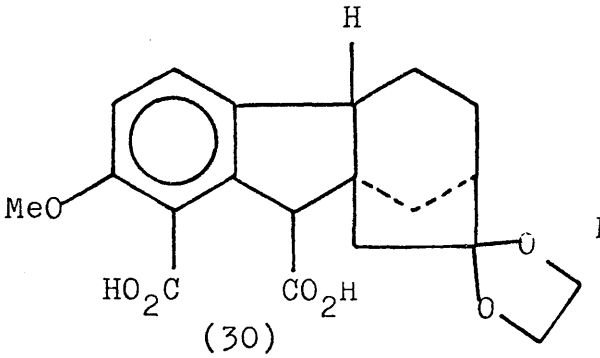

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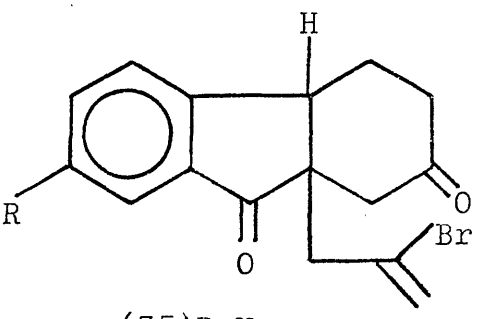
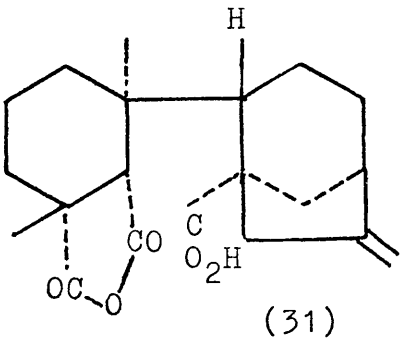


(35)R=H
(37)R=MeO



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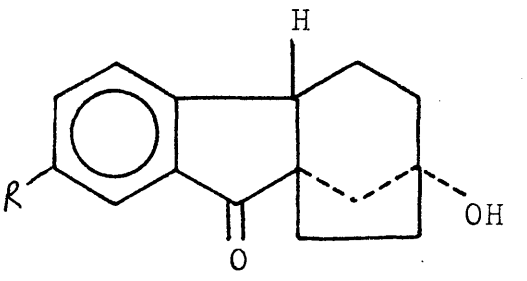

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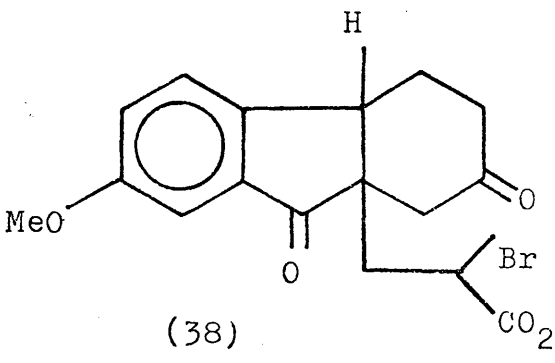

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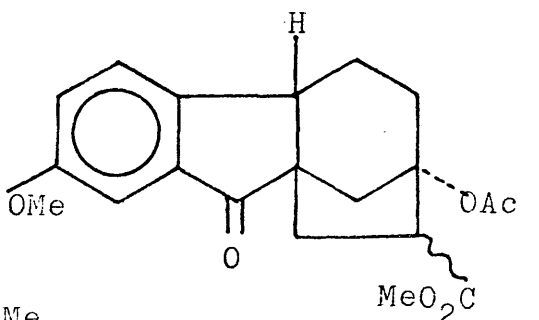


(39)

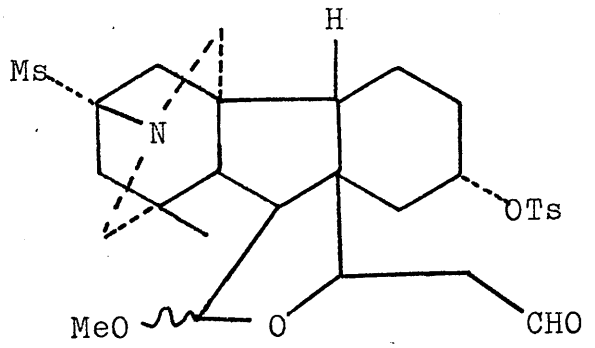
anhydride.

In his total synthesis of gibberllin A15. Nagata[33] effected the ring D closure of the complex synthon (40) to the bicyclooctane derivative (41) using pyrrolidine in methanol/N-methyl pyrrolidine, followed by hydrolysis with 50% acetic acid.

Stork[34] achieved the synthesis of gibbane alcohol (42) by an elegant reductive cyclization of the ethynyl ketone (43)[35] . Trost[36] reported a new approach to the stereo-controlled production of the BCD fragment by a BD→ C sequence. Cyclopentanone (44) treated with DBN in DMF-THF gave the tricyclic ketone (45) in 55% yield. Cyclopentanone (44) was prepared by treatment of (46) with methyl-p-tolylsulfinate/sodium hydride to give a sulfoxide (47), which on reaction with stannous chloride in acetic anhydride and acetonitrile gave the sulfide and also replaced the trityl group by acetyl. The resulting acetoxy-sulphide(48) was then converted into the mesylate(44).

3- Pericyclic reactions

Yamada[37] produced the olefins(49) by Diels Alder reaction of the dihydroindane (51) with 2-chloroacrylonitrile at 120°C ,isolable from an epimeric mixture. Treatment with m-chloroperbenzoic acid afforded the corresponding ∝- epoxide (50) which underwent skeletal rearrangment to produce the polyfunctional tetracyclic compound(52). This provided an alternative



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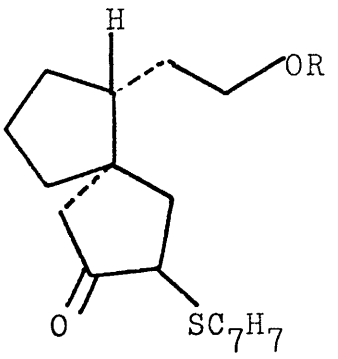
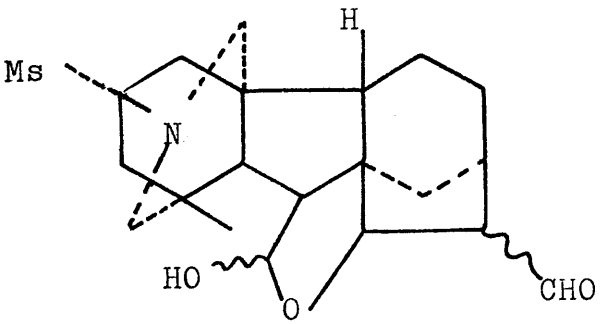


(44) R= Ms

(48) R= Ac



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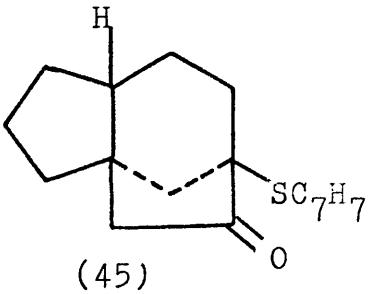

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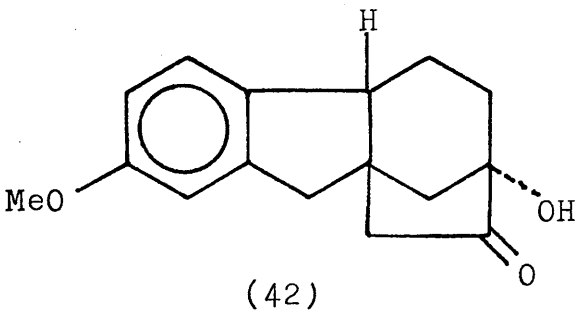

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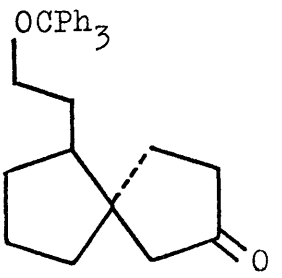

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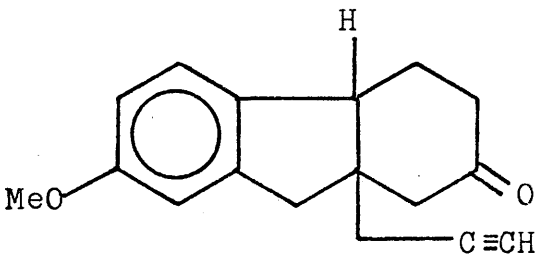

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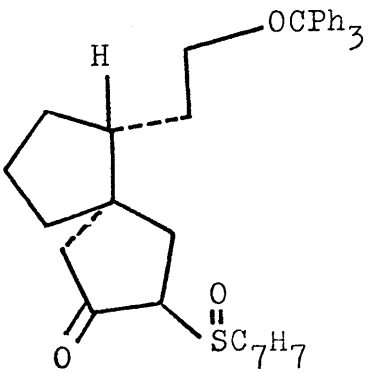

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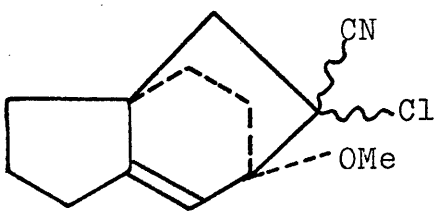

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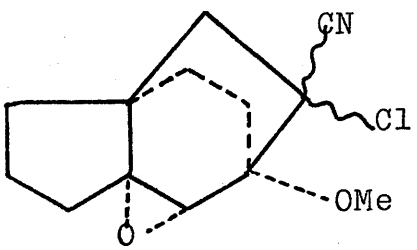

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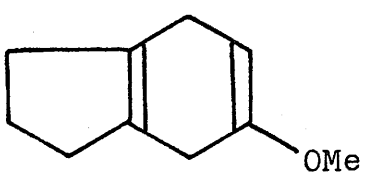
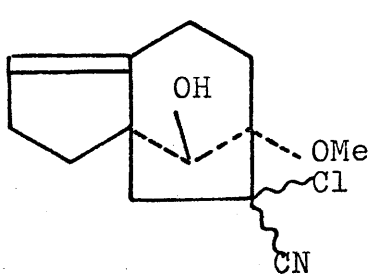


(51)



(52)

to his earlier work in which rings ABC were constructed from a suitable aromatic precursor serving as a protected ring C equivalent.[38,39]

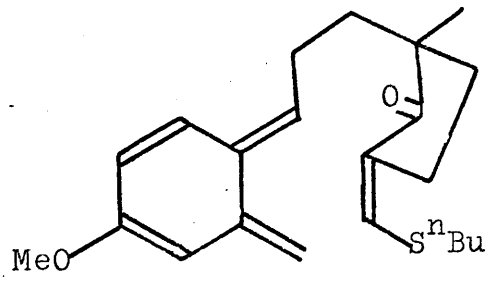
Kametani [40,41, 42] synthesised a more attractive potential intermediate for tetracyclic diterpenoids by an intramolecular cycloaddition of *o*-quinodimethane (53), which on subsequent desulphurization afforded the ethano-octahydromethoxyphenanthrenone(54).

4- Ring contraction of kauranes.

In a series of papers investigating routes to the gibberellins, Galt and Hanson[43] converted the 7-hydroxykaurenolide(55) to the tricarboxylic acid (56). Treatment with refluxing acetic anhydride produced the internal 6,7-anhydride which on pyrolysis at 280°C gave the diketone(57).

Utilising the procedure, MacMillan,[44] prepared GA14-aldehyde (58) from the 3β,7β-dihydroxykaurenolide (59). He later improved upon this sequence by adopting the method employed by Cross[45] by selectively protecting the 3-hydroxy group of the alcohol (59) as its tetrahydropyranyl ether, epimerising the 7β-hydroxy group to its 7α-analogue, followed by the formation of the 7α-p-toluenesulphonate, which on treatment with potassium hydroxide in t-butanol , afforded the 3β- tetrahydropyranyl ether(60) in excellent yield.

More recently Gonzalez[46] has synthesised



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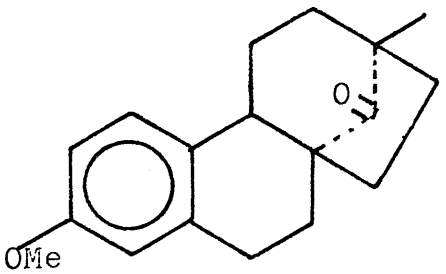

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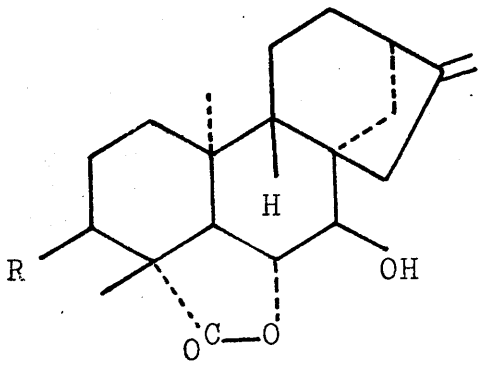
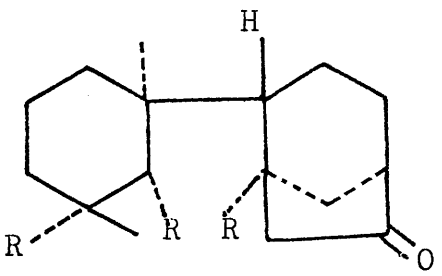
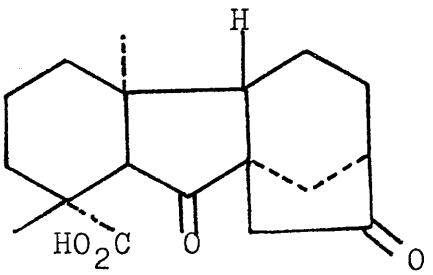


(55) R= H

(59) R= OH



(56) R= CO_2H



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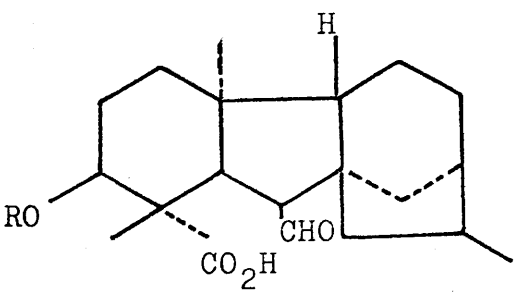
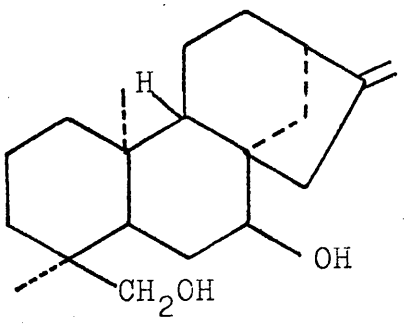


(58) R= H

(60) R= THP

4-epi-gibberellin A12 from the kaurene diol (61) as follows. Oxidation followed by esterification gave the keto-ester (62) which with oxygen in the presence of butoxide gave the keto lactone in 85% yield. The derived chloro lactone (62a) underwent a Favorskii rearrangment in the presence of sodium methoxide to give 4-epi-gibberellin A12 dimethyl ester in high yield.

Mori and Matsui,have synthesised a wide variety of hydrofluorene derivatives. As an alternative mode of approach, Mori[47] employed a sequence involving the ring contraction of the kaurene(63) by ozonolysis and a reductive work up,which resulted in the formation of a keto-aldehyde(64)which underwent an intramolecular aldol condensation when chromatographed on alumina to give the gibbane(65). This work was followed by his total synthesis of gibberellin A12(66),[48] in which he employed methyl-7,16-dioxo-17-norkauran-19-oate as a relay compound. He then synthesised the lactone(55)which underwent ring contraction to afford gibberellin A12(66).Since this lactone could be synthesised from ethyl-1-methyl cyclohexan-2-one-1-carboxylate,[49] via methyl-7-oxopodocarp-8-en-16-oate(67) in many steps,formal total synthesis of gibberellin A12 was completed.



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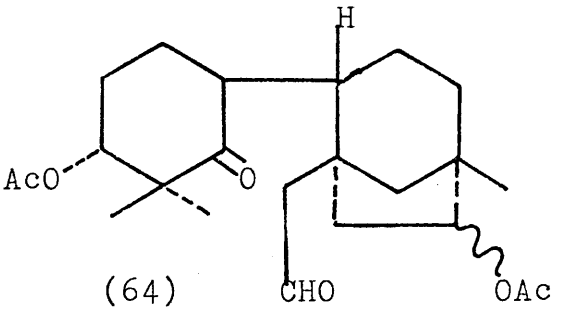

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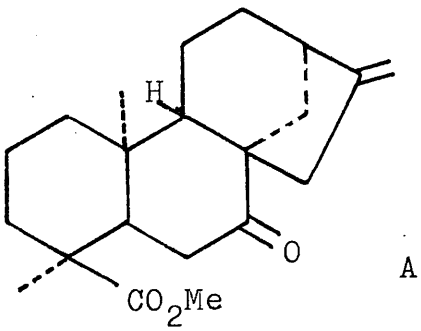
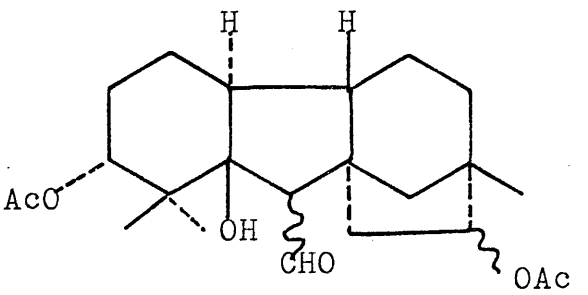


(62)



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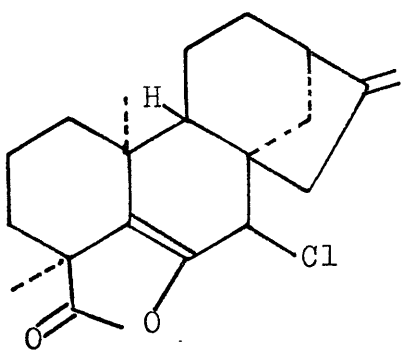
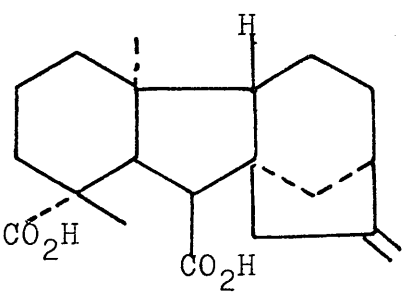


(62a)



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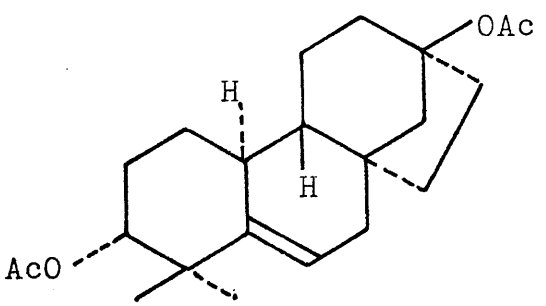
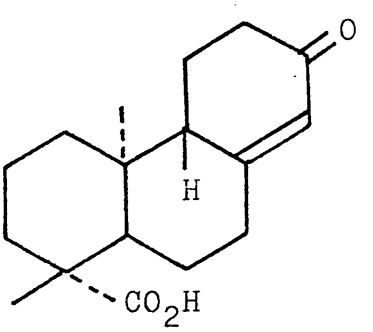


(63)



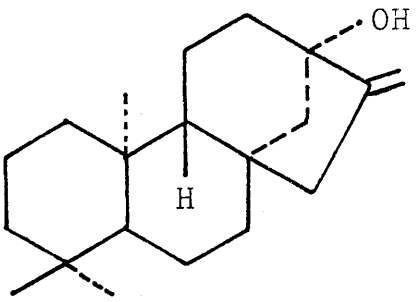
(67)

5- Radical anion cyclization

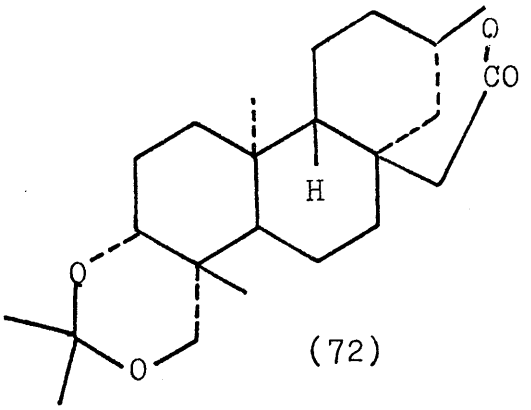
Cook[50] has used an acyloin condensation to construct the bicyclo (3.2.1) octane system in his synthesis of steviol (68). Keto-ester (69) was converted to the diol (70) using the liquid ammonia, sodium, THF reduction medium. He later modified this reaction[51] in such a manner that an hydroxyl group could be introduced into a 7-methylenebicyclo (3.2.1) octane system. Thus treatment of the natural endiol (71) by a Lemieux-Johnson oxidation, followed by Baeyer-Villiger oxidation and subsequent protection of the diol by ketalisation resulted in the ketal (72). Acid hydrolysis followed by esterification, afforded the keto-ester (73), which on treatment with sodium in naphthalene, afforded , after a Wittig reaction and acid catalysed diol reformation, the required triol (74).

A method of transforming a trans-fused BC ring system into a cis-fused BCD ring system was demonstrated by Mori.[52] The keto-acid (75) was converted into the bicyclo (2.2.2) octane derivative (76) which on subjection to pinacol reduction conditions, yielded the cis-fused BC ring gibbane(77).

The pinacol type cyclisation has also been studied by Corey and is a key step in his synthesis of the gibberellic acid precursor (78) In earlier studies [53] on model compounds, the keto aldehyde(79)



(68)



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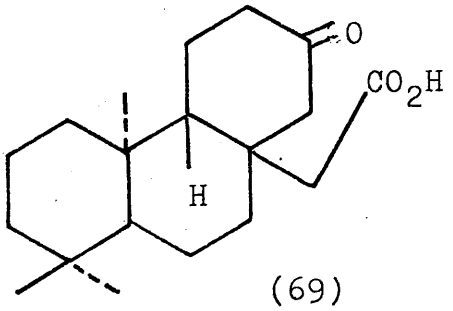

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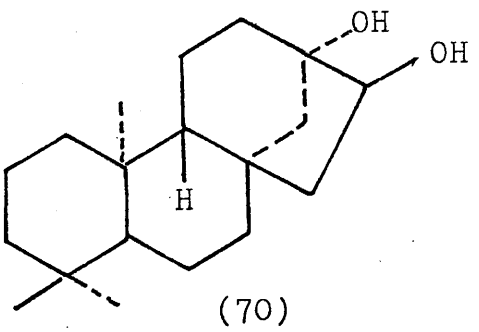

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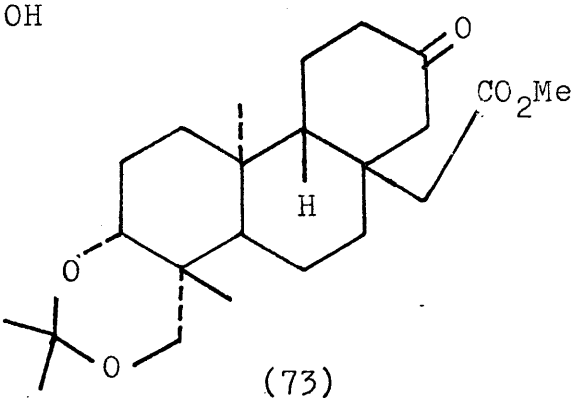
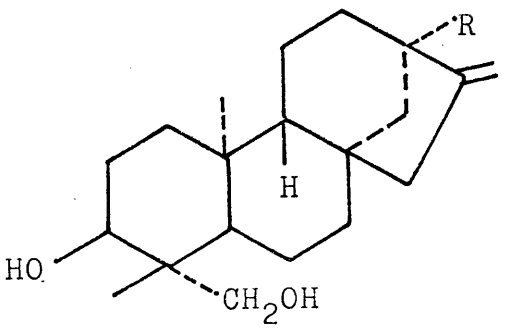
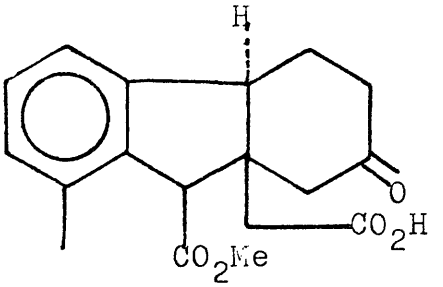


(73)



(71) R= H

(74) R= OH



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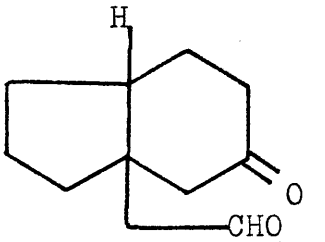

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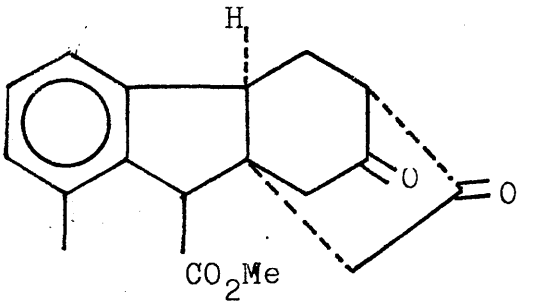

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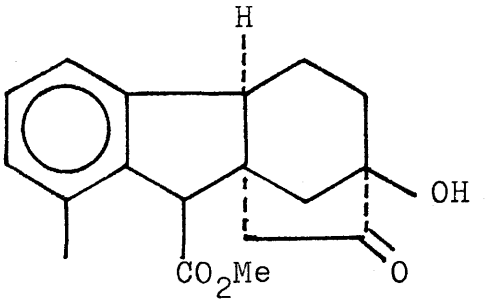

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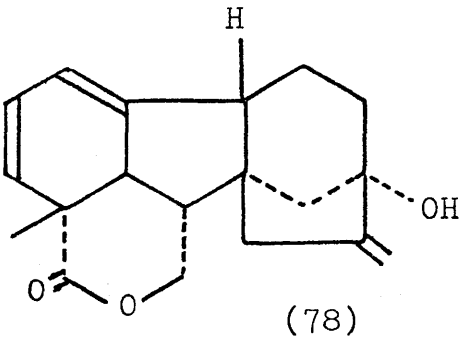


(78)

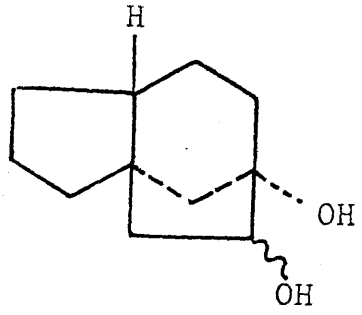
was cyclised to the diol (80) on treatment with magnesium amalgam and dimethyl dichlorosilane in tetrahydrofuran, with the yield of crude diol being 75%. This reaction was improved upon by reduction with the complex formed on addition six equivalents of cyclopentadienyltitanium trichloride to four and one half equivalents of lithium aluminium hydride at 50°C in tetrahydrofuran, followed by the rapid addition of the keto-aldehyde. This resulted in a 90% yield of isolated diol. This was the final study on model compounds prior to the embarkation into a synthetic route to gibberellic acid (3), which is discussed in the section dealing with the construction of the ring A functionality .

b- Hydrofluorene derived routes.

An obvious route to the gibbane skeleton lies in the construction of suitably functionalised hydrofluorenes, which can then be further elaborated to the tetracyclic system as discussed above.

In a series of papers[54] investigating synthetic routes to the gibberellins and related compounds, House has used this approach in his synthesis of the epiallogibberic acid (81) precursor (82).

The indanone (83), prepared from o-tolualdehyde by standard procedure, was carbomethoxylated using dimetnyl carbonate and sodium hydride and then



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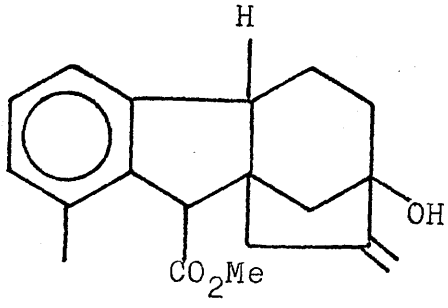
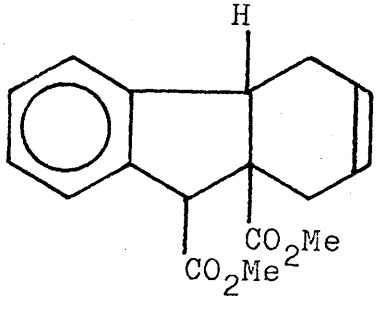
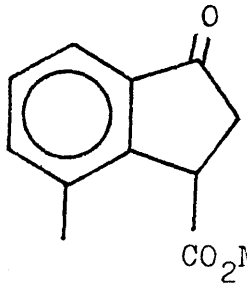


(81)

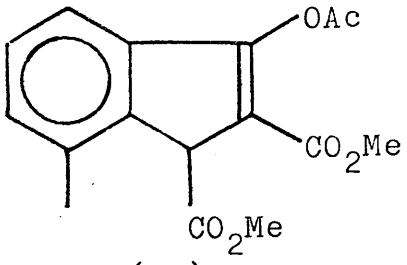


(82)



(83)

converted to the related enol acetate (84) by reaction with acetic anhydride and perchloric acid. Hydrogenation followed by acid catalysed elimination of acetic acid from the acetoxy ester yielded (85), which afforded the desired adduct (82) following a Diels Alder reaction with butadiene at elevated temperature and pressure. Another intermediate was then pursued. The compound chosen was the ester[55] (86) which had the appropriate functionality and stereochemistry to serve as a precursor for epiallogibberic acid (81) . Saponification of the diester (82) followed by iodolactonisation, reductive removal of iodide by tri-n-butyltin hydride and then treatment with an equimolar mixture of dimethyl sulphoxide and methyl lithium , followed by Jones oxidation, produced the intermediate (87) which underwent an intramolecular aldol condensation to afford the sulphone (88) . This reaction was unfavorable in polar, protic solvent but was forced to completion by the formation of the covalent magnesium alkoxide (89) in non polar, aprotic solvents by treatment of (87) with two equivalents of t-butylmagnesium chloride. Reaction of the aldol adduct (88) with diazomethane followed by acid catalysed hydrolysis and reductive cleavage with aluminium amalgam, formed the hydroxy ketone (90) which was converted to the acetoxy olefin (86) by the scheme devised by Nagata.[56] This involved the formation of the acetate, reduction with sodium borohydride, quenching of the alkoxide with methyl



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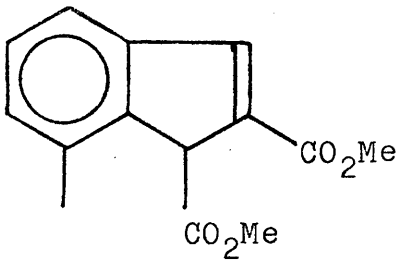

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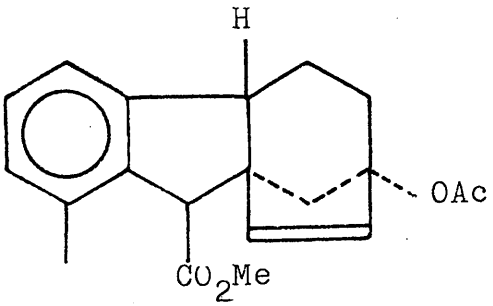

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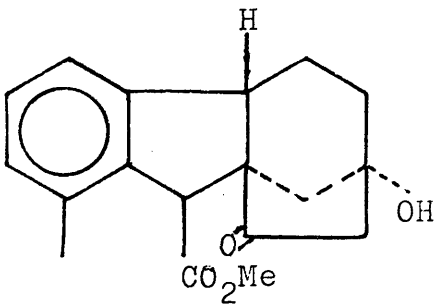

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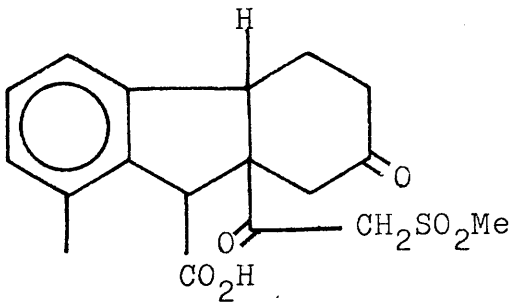

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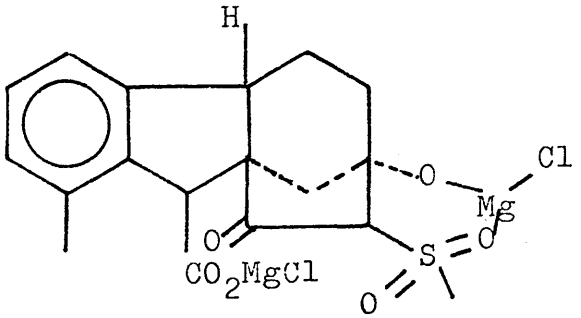

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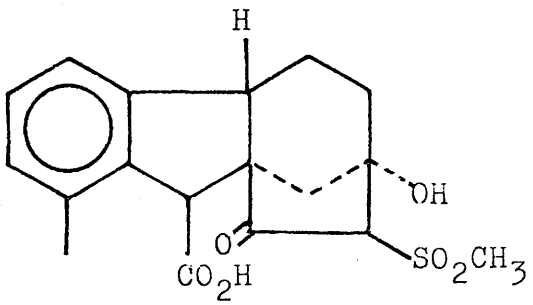
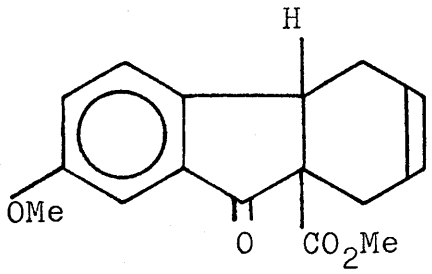


(88)

sulphonyl chloride and then refluxing the product in collidine. In conjunction with this work, and noting the high degree of stereoselectivity for the Diels Alder reaction, House[57] synthesised the hydrofluorenone (91)..Previous studies of the reaction between butadiene and the unsaturated ester (92),[58,59] established that the rather vigorous conditions required for a successful reaction resulted in the concurrent isomerisation of the double bond to afford the olefin (93). The problem was overcome by using the non-isomerisable indenone-ketal (94) prepared from 7-methoxyindane -1-one. Monobromination, ketalisation and exchange with n-butyl lithium on the indanone produced the β-alkoxy organolithium compound (95) which was unusually stable due to the fact that elimination of lithium alkoxide would produced a highly strained, cyclic allene.Carbonation of the lithio derivative, followed by esterification, produced the indene ketal (94) , Diels Alder reaction of which at relativly low temperature, with butadiene, followed by acid hydrolysis produced the desired hydrofluorene (91).

Continuing his study on the 7-methoxyhexahydrofluorene system, House[60] achieved the synthesis of the diacid (96). Reaction of 1-cyanocyclohexene with m-methoxyphenyl magnesium bromide followed by dilute acid treatment produced the unsaturated ketone (97), which cyclised to ketone (98) in concentrated H_2SO_4.Reduction of this ketone with lithium aluminium



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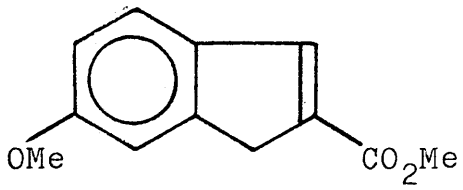

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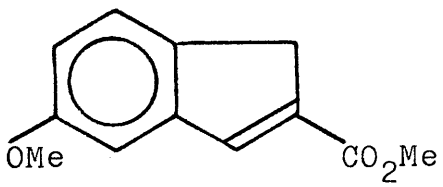

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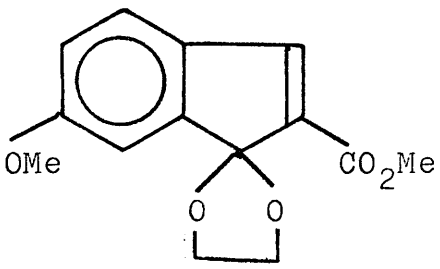

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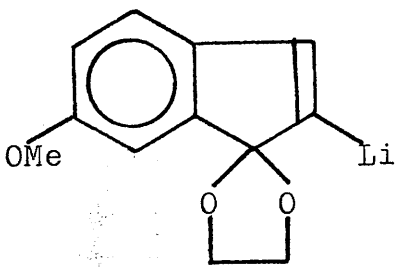

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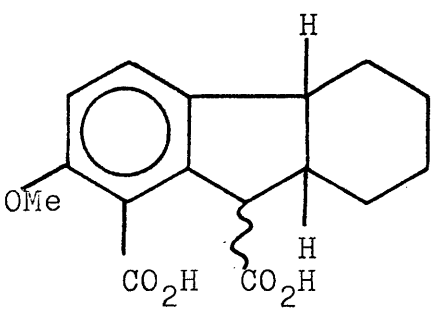
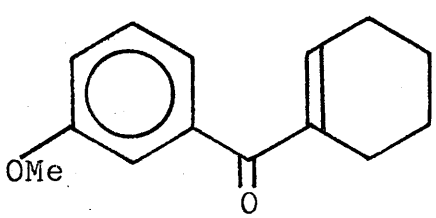


(96) α- CO_2H

(102) β- CO_2H



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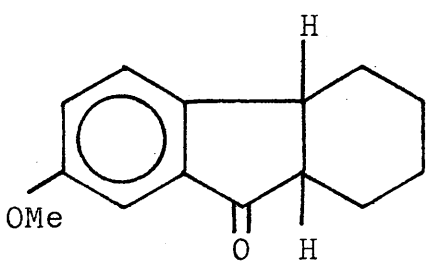
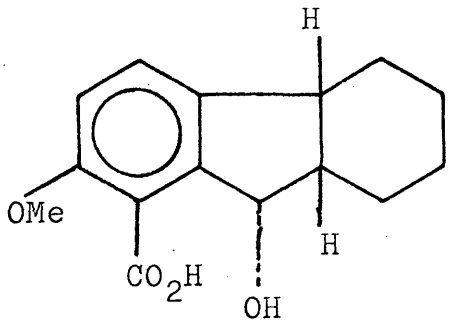


(98)

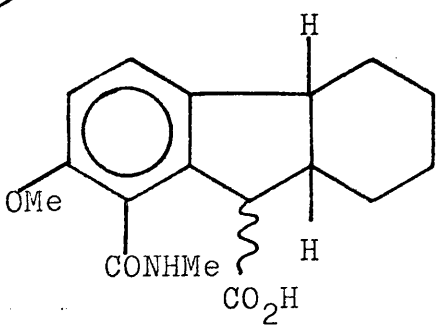
hydride gave the α-alcohol which underwent regiospecific carboxylation to the acid (99) using t-butyl sodium and carbon dioxide . Sequential acid catalysed dehydration, carboxylation with methyl lithium and carbon dioxide, and hydrogenation converted the acid (99) to the diacid(96).

A similar sequence was successfully applied to the gibbane (100) by Baker[26] to afford the acid (101) .

House[61,62] has now synthesised the β-epimer(102) of the acid (99). The amide (103), obtained from hydroxy acid (99) by hydrogenolysis followed by the reaction of the corresponding acid chloride with methylamine, was converted to an easily separable mixture of amide-acids (104) by the reaction with carbon dioxide and n-butyllithium. Hydrolysis of the β-epimer, via its N-nitroso analogue, with dilute sodium hydroxide produced the β-diacid (102). In this investigation it was also found that the less thermodynamically stable α-epimer could be converted to the more stable β-diacid via the formation of the anhydride (105) which was formed on treatment of the diacid with dicyclohexylcarbodiimide and subsequent aqueous hydrolysis. In connection with the modification of ring A, reductive methylation of each epimer (96) and (102) respectively with lithium, liquid ammonia and methyl iodide produced the keto-diacids(106) and (107) respectively .



(99)



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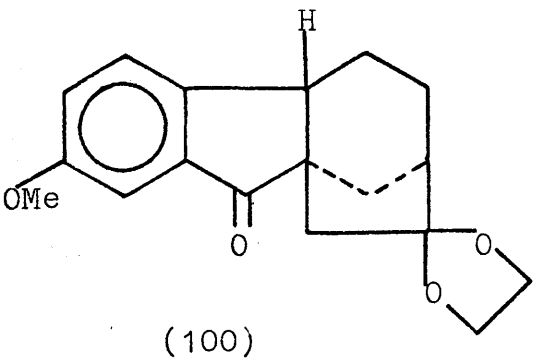

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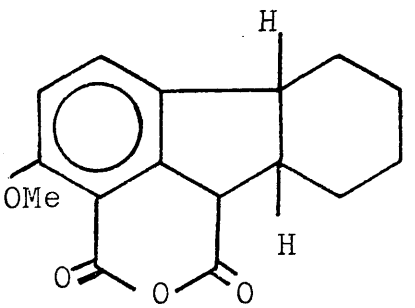

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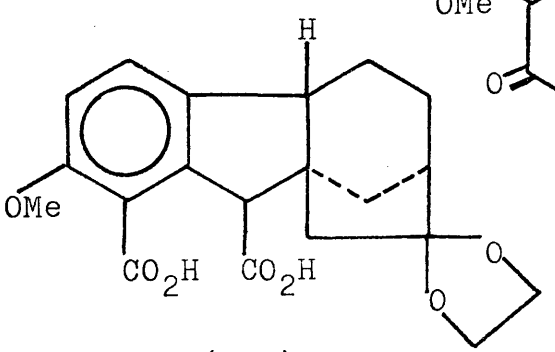
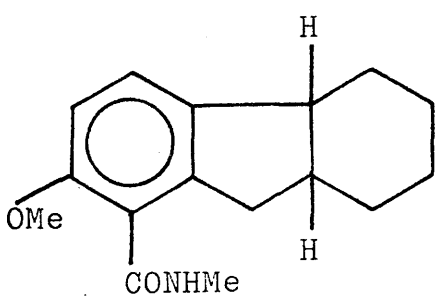


(101)



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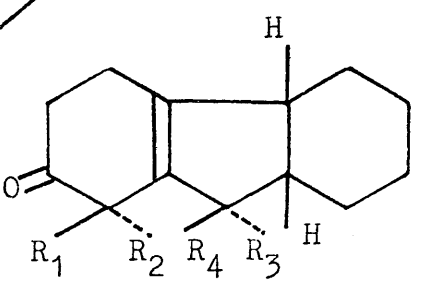
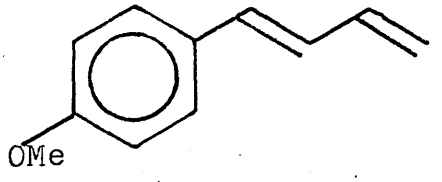


(106) R_1=Me, R_4=H, R_2=R_3=CO_2H

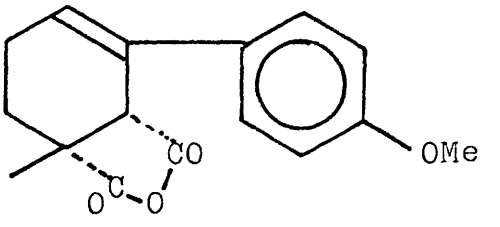
(107) R_2=Me, R_3=H, R_1=R_4=CO_2H

Utilising the hydrofluorene approach, Nakanishi[63] prepared the lactone (108) . Diels Alder addition of ethyl-3,3-dicyano-2-methylprop -2-enoate (readily available from the knoevenagel condensation between ethyl pyruvate and malononitrile) and diene (109), followed by base hydrolysis and concomitant shift of the double bond, decarboxylation and dehydration afforded the anhydride (110). Treatment with aluminium chloride gave the hydrofluorenone (111) which was readily converted to lactone (108) , by hydroxy lactonisation with p-nitroperbenzoic acid followed by acetylation. This approach has been extended[38] to produce the ring B carboxylic acid (112) stereoselectively by reaction of the corresponding trimethylsilyl ether (113) with dimethylsulphonium-methylide in a binary solution, tetrahydrofuran and hexamethylphosphorus triamide, to afford the β-epoxide (114) Rearrangment of the epoxide with boron trifluoride etherate afforded the β-aldehyde (115), mild Jones oxidation of which and subsequent methylation and treatment with p-toluenesulphonic acid yielded the 9β-methoxycarbonyl derivative (116) in 90% overall yield.

Having modified rings A and B, ring C was functionalised by Yamada[39]. Starting from the ketal (117) , saponification followed by Birch reduction and acetic acid assisted lactonisation produced the diene acetal (118), a molecule which shows appreciable



(109)



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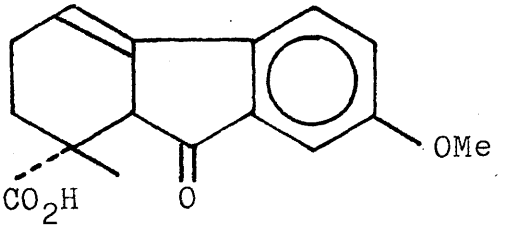

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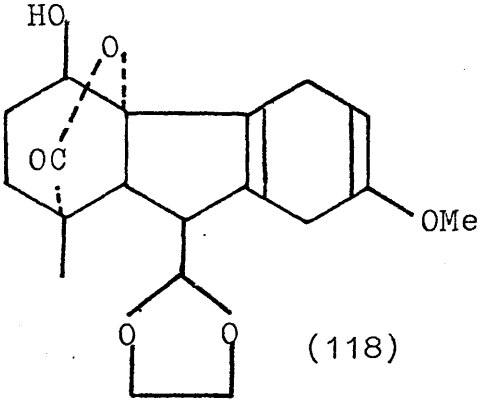
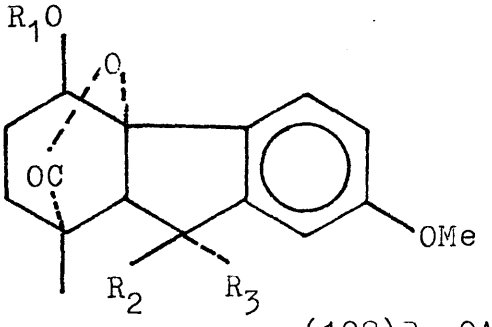
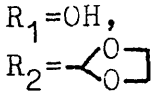


(118)



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

(108) R_1=OAc, R_2R_3=O

(112) R_1=OH, R_2=CO_2H, R_3=H

(113) R_1=Me_3SiO, R_2R_3=O

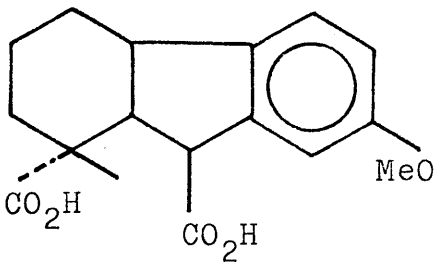
(114) R_1=Me_3SiO, R_2R_3=β- 

(115) R_1=Me_3SiO, R_2=CHO, R_3=H

(116) R_1=OH, R_2=CO_2Me, R_3=H

possibilities in the future formation of ring D. Curiously, if Birch reduction was applied to the lactone acid (112) , ring C remained aromatic and high yields of diacid (119) were obtained, possibly explained by the formation of a styrene type intermediate (120) which might be formed by the initial hydrogenolysis of the C-O bond at the benzylic position. In the previous case, cleavage of C-O bond at the benzylic position was presumably prevented by the conversion of the free hydroxy group to an alkoxide ion during the reaction.

Since his earlier success [12,15] Loewenthal has tried to synthesise gibberellin A4 and suitable tetracyclic synthons based on his gibberone pathway. He formed the tetracyclic ketones[64] (121) and (122) with the former having the unuatural C-9 configuration Acid catalysed aldol condensation of indanone (123) with n-butylglyoxalate, followed by catalytic hydrogenation and methanolysis, led to diester (124) in 76% yield. Treatment of the diester with methyl vinyl ketone in methanolic sodium methoxide gave the half ester (125) which was cyclised with trifluoroacetic anhydride to the diketo-ester (122) which afforded the ketone (121) after a lengthy process. Unfortunately this synthon showed no biological giberellin-like activity . To combat this he[65] synthesised the ketone (127) by treatment of the diketone (122) with freshly prepared palladium hydroxide in methanol to yield the hydroxy ketone



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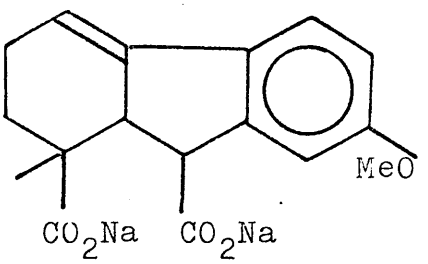

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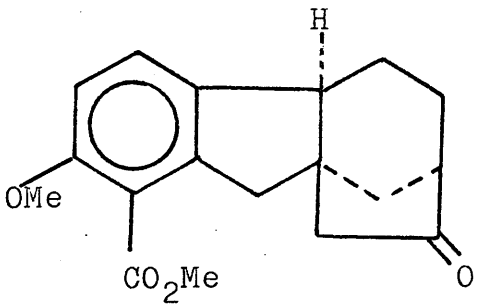

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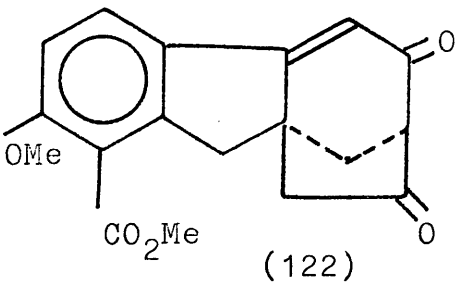

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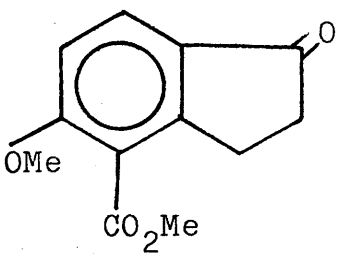

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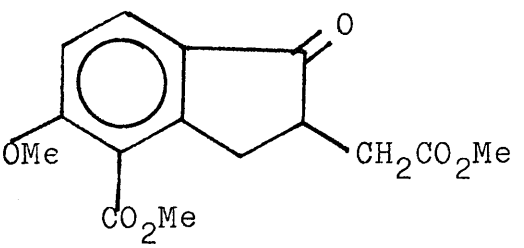
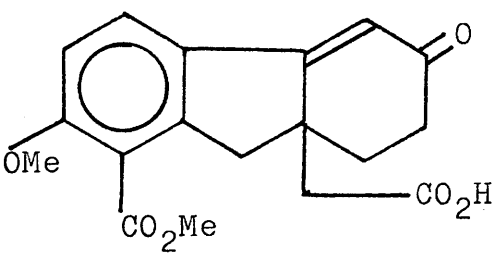
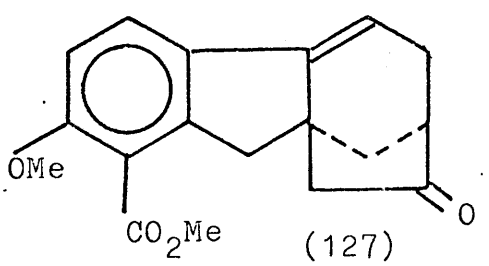


(124)



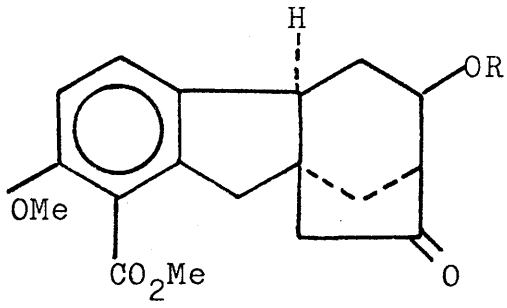
(125)



(127)

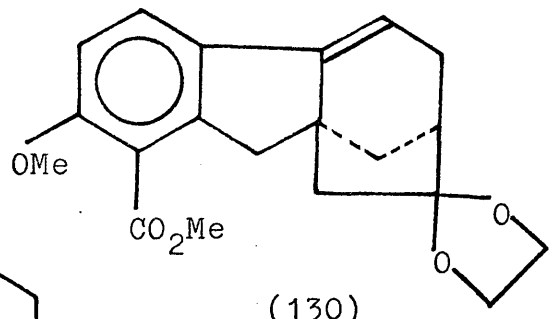
(128) which was dehydrated by pyrolysing the derived p-tolylthiocarbonate (129) at 250°C and 0.1 mm. The resulting olefinic ketone was refluxed in p-xylene with palladium to afford the desired isomeric enone (127), catalytic hydrogenation of which produced the unnatural BC ring fused ketone (121).

Ring B was functionalised[66] by treatment of the ketal (130) with N-cyclohexyl-N-t-butylamide and carbon dioxide to afford the diacid (131) stereoselectively . Hydrogenation of the diacid (131) gave the cis BC ring fused diacid (132). Earlier he had synthesised gibberone (133), starting from 4-methoxyindan-1-one by reacting the corresponding α-bromo-ketone with di-t-butyl sodiomalonate followed by acid hydrolysis and decarboxylation which gave the keto-acid (134) in good yield. Its methyl ester was converted to the unsaturated keto-acid (135) by reaction with isopropenyl methyl ketone and excess sodium methoxide in methanol. Cyclisation of the keto-acid (135) with boron trifluoride-ether complex in acetic acid-acetic anhydride gave the diketone (136), Wolff Kishner reduction of its monoketal (137) followed by acid treatment gave gibberone (133). In his gibberic acid (9) synthesis, the key intermediate, 3-carboxy-4-methyl-1-oxoindan -2-ylacetic acid (138) was obtained from the reaction of β-keto-ester (139) with ethyl bromoacetate, followed by acid hydrolysis and decarboxylation.



(128) R= H

(129) R= COC_6H_4-p-Me
‖
S



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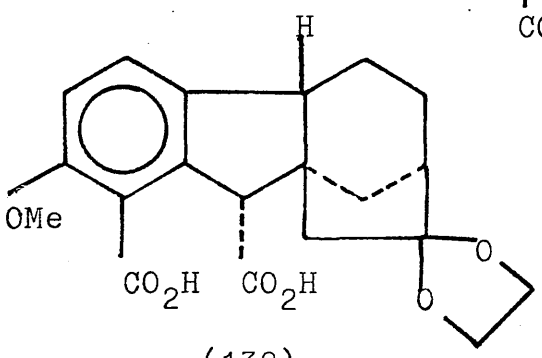

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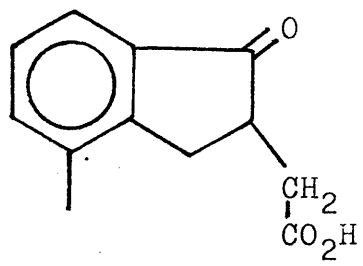

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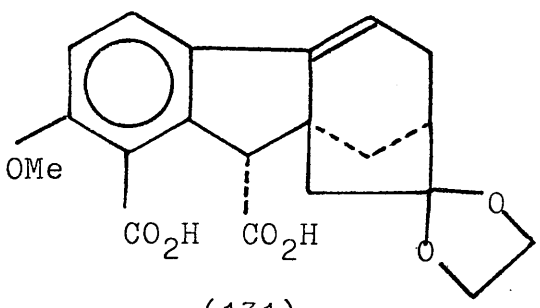
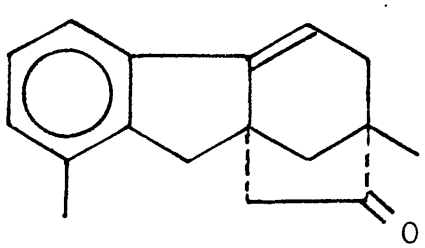
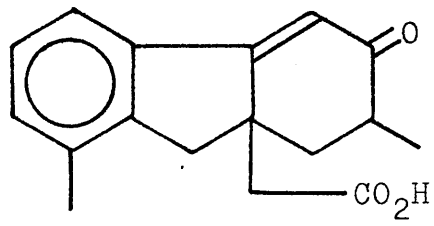


(131)

(133)





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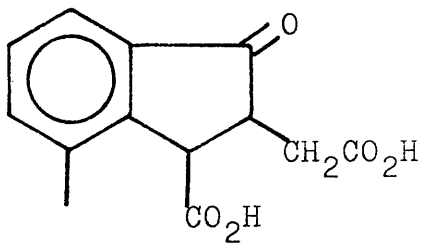

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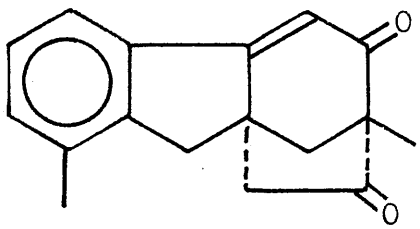

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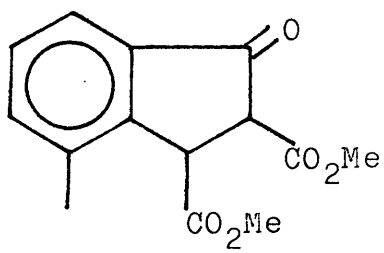

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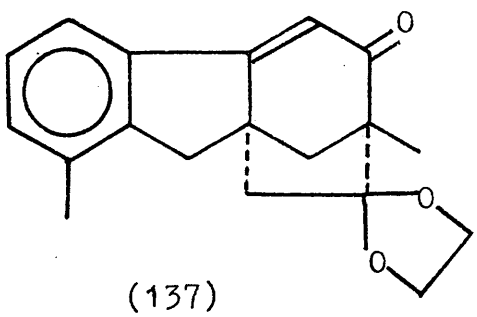
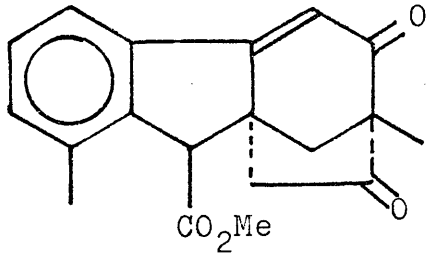


(137)

Its dimethyl ester was then converted to diketone (140)via (141) using the procedure described above. Huang-Minlon reduction of the mono ketal (142) followed by catalytic hydrogenation furnished gibberic acid (9).

The trans stereochemistry of keto-acid (141) and subsequent products has been confirmed by Mori[67] in his synthesis of epigibberic acid (143). Trans-diacid (141) was converted to a cis anhydride (144) in refluxing acetic anhydride.Cyclisation of the anhydride in acetic acid with boron trifluoride etherate then afforded the diketo-acid (145), which was converted to the monoketal which was hydrogenated over Raney nickel to afford a hydroxy ester (146) , Chromic anhydride - pyridine complex oxidation of the hydroxy ester gave keto-ester (147) from which epigibberic acid (143) was obtained after Huang-Minlon reduction[8] followed by hydrolysis.

Matsui[68] has also synthesised epiallogibberic acid (81). Ketodiester (148) was transformed into the trans-dibasic acid (149) in 54% yield by condensation with methyl vinyl ketone using sodium methoxide as a base and by subsequent treatment with aqueous sodium hydroxide. Treatment of the dibasic acid (149) in acetic acid-acetic anhydride with borontrifluoride etherate under reflux afforded in 70% yield the tetracyclic diketone (150), which was esterified with diazomethane followed by ketalisation to the monoketal



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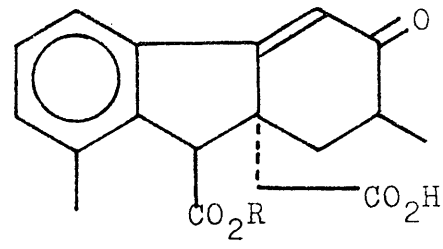
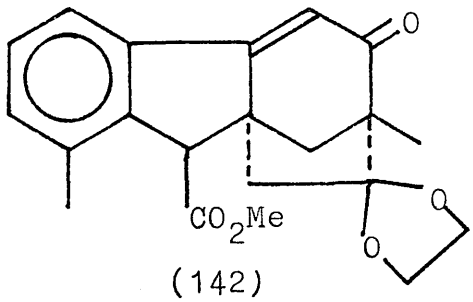


(141) R= Me, H



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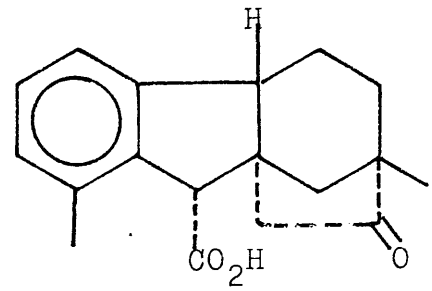

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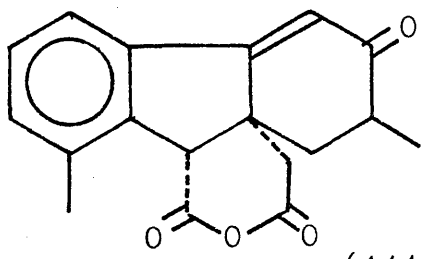

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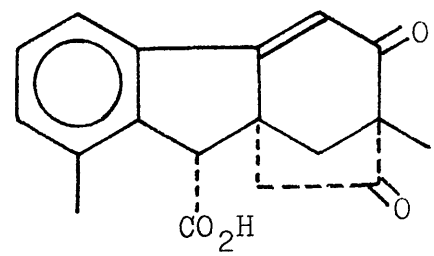

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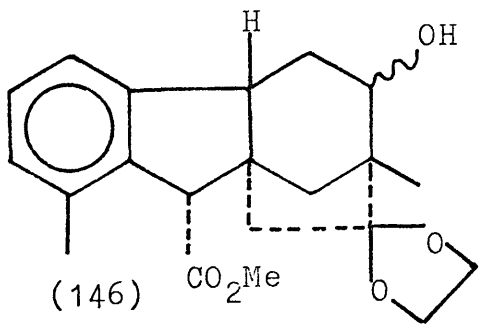

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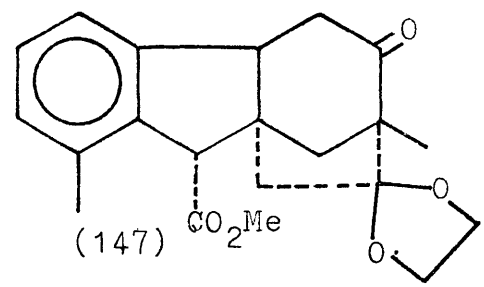

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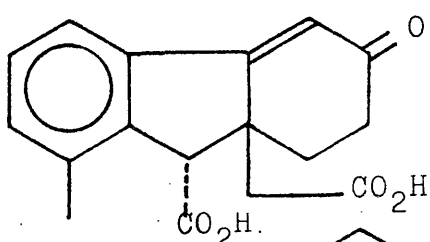

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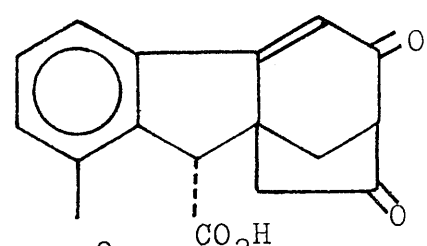

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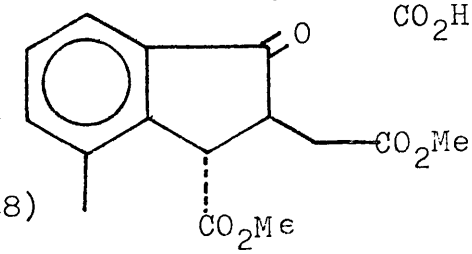
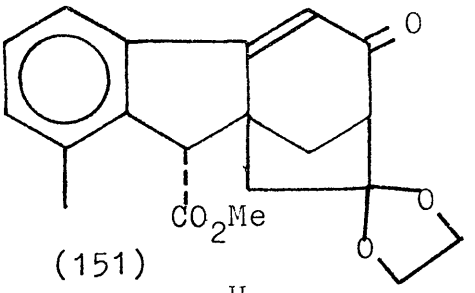


(148)

(151). Wolff-Kishner reduction of monoketal (151) and subsequent treatment with hydrochloric acid gave the keto acid (152) in 39% yield . The (±) -7-demethyl-gibberic acid (153) was obtained quantitatively from (152) by catalytic hydrogenation using palladium on charcoal in ethyl acetate. The stereochemistry at C-9 was determined as 9-βH relative to the C-6 α-carboxyl group. The hydrogenation of these systems is stereoselective from the anti direction to the C-6 carboxyl group. The acid (153) was converted to its methyl ester with diazomethane then epimerised with methanolic sodium methoxide under reflux for 15 minutes to afford the (±) -7-deoxyepiallogibberic acid methyl ester norketone (154) having the same relative B,C,D ring stereochemistry as gibberellin A7 (155). The norketone (154) was subsequently transformed to epiallogibberic acid (81). The gibbane compound (156) had already been obtained by Cross[69] by the acid treatment of gibberellin A7 methyl ester norketone (157) but the stereochemistry at C-9 remained to be determined. Matsui[70] described the synthesis and unusual alkylation of indanone diester (158),which was obtained from indanone (159) by acylation with dimethyl carbonate and sodium amide in benzene-ether followed by alkylation with methyl bromoacetate and methanolic sodium methoxide in benzene.

Attempts to convert diester (158) to the keto-acid (160) with methyl vinyl ketone under basic condition gave an unexpected product isolated in 36%, the structure of which was (161) or (162) . It is known that



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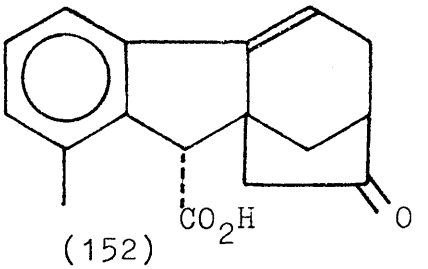

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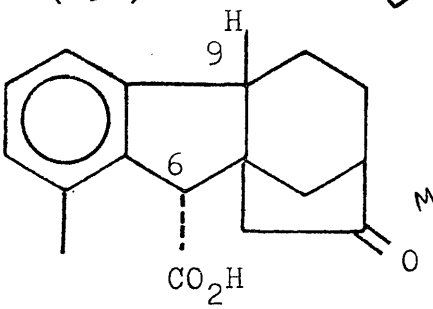
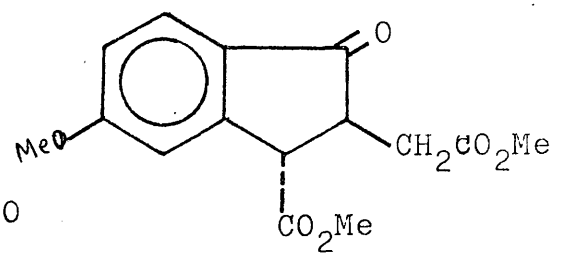
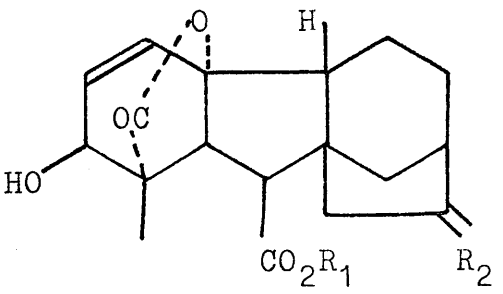


(153)

(154) 6β-CO_2H

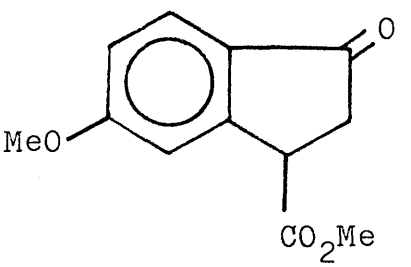


(158)



(155) R_1=H, R_2=CH_2

(157) R_1=Me, R_2=O



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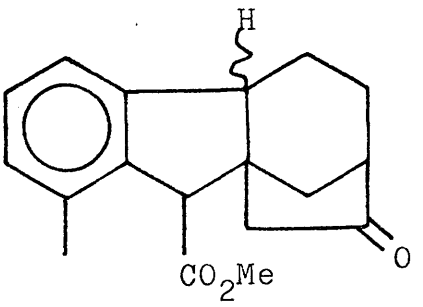

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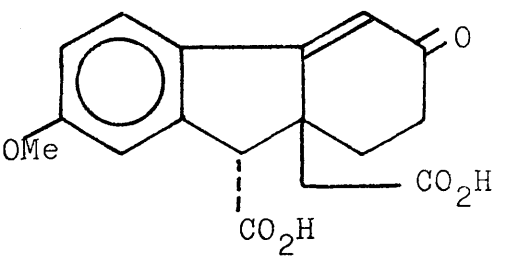

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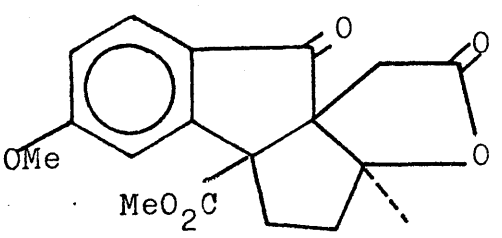
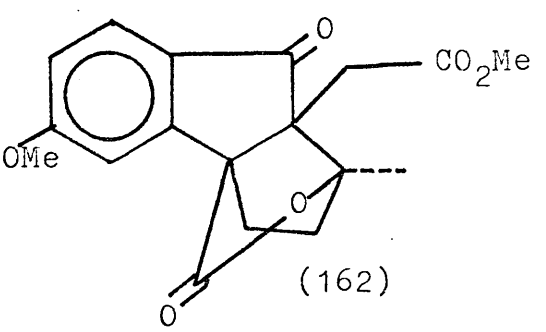


(161)

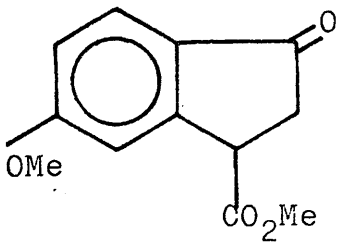


(162)

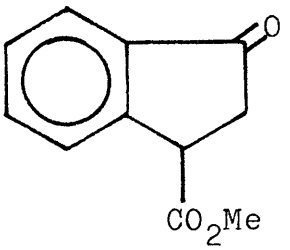
the diester (148) gave the expected keto acid (149) under the same reaction conditions.In the case of diester (148) and (158) , the carbanion was developed at C-2 and C-3 respectively, the different in reactivity is due to the steric repulsion between the methyl group at C-4 and the methoxycarbonyl group at C-3 in (148). In further studies on the effect of the methyl group at C-4 on the alkylation of indanones esters, the indanones (163) and (164) were alkylated with methyl bromoacetate, and transformed into the diester (165) and (166) respectively .

In a novel procedure, Martens[71] produced the diketone (167) which has the desired cis-fused BC ring junction. The starting material was the indanone (168) , Diels Alder reaction of which with butadiene, followed by base hydrolysis produced the hydrofluorene (169) in high yield. Polyphosphoric acid treatment followed by catalytic hydrogenation afforded the diketone (167) .

This provided an alternative route to the diketone from that executed earlier by Baker[27] who starting from Diels Alder cyclisation between itaconic acid and methyl -5-(p-methoxyphenyl)-trans, trans-2,4-dienoate, followed by catalytic hydrogenation esterification with diazomethane, and Dieckmaun cyclisation, produced the keto-ester (170). Base hydrolysis of the decarboxylated keto-diester, followed by interconversion of the resulting acid to its acid chloride produced, after an intramolecular Friedel-



(163)



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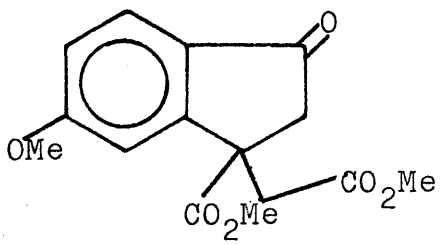

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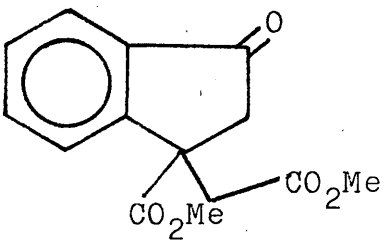
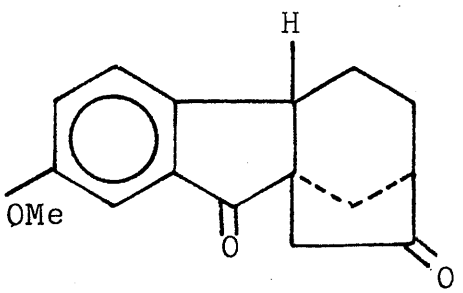


(166)



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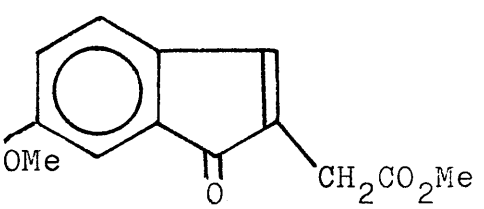

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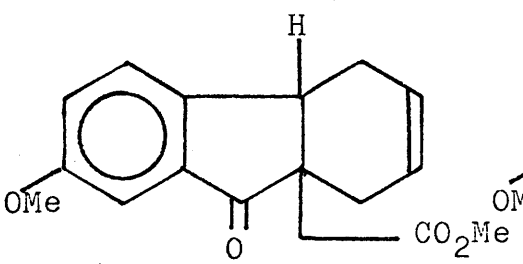

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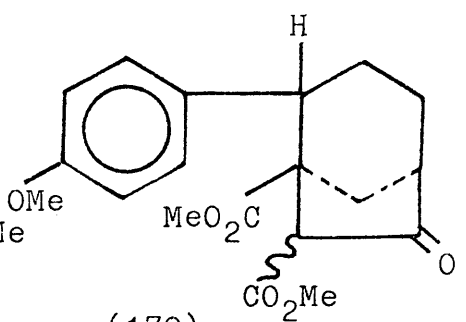


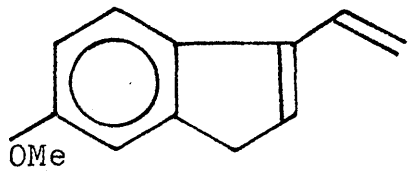
(170)

Crafts acylation, the diketone (167).

Mander[72] approached the problem of synthesising the gibbane skeleton by preforming diazomethylketo-hydrofluorenes. The precursor chosen for the gibbane synthesis was the diazoketone (171), which had the added advantage of being a potential 13-hydroxylated gibbane precursor. The diazoketone was formed from the vinyl indene (172),obtained from 6-methoxyindanone, which underwent a Diels Alder cyclisation with ethyl α-acetoxyacrylate in boiling benzene to form the hydrofluorene (173). Base hydrolysis, protection of the resulting hydroxyl group as its trifluoroacetate, conversion of the acid to its acid chloride, followed by reaction with excess diazomethane , produced the diazoketone (174). On stirring in trifluoroacetic acid, followed by base hydrolysis, the tetracyclic ketone (175) was obtained almost quantitatively. Repeating the procedure with acrylonitrile as a dienophile produced excellent yield of ketone (176).

An independent approach to diazomethylketo - hydrofluorenes was made by Ghatak[73,74,75] who also prepared the keto olefin (176) from the reaction of 2,4-dicarboethoxycyclohexanone, m-methoxybenzyl chloride and sodium hydride followed by saponification, decarboxylation and polyphosphoric acid promoted cyclization to give hydrofluorene (177) which was cyclized to the keto-olefin (176) via its diazoketone.

Mander[72] has claimed that in his hands the reaction afforded a mixture of acid (177) and its



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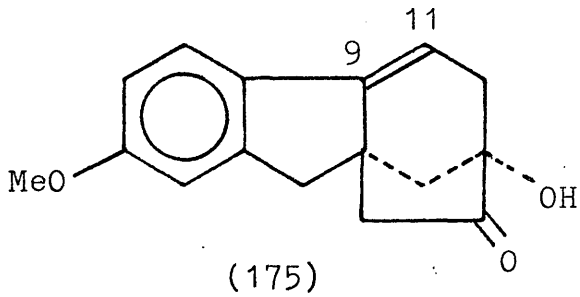

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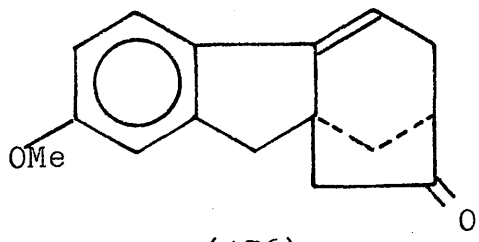

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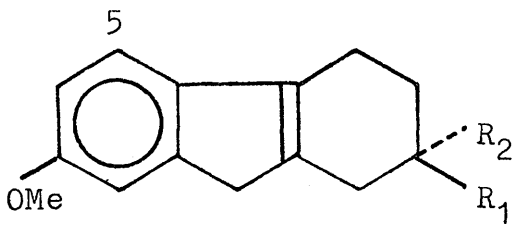


(171) R_1=$COCHN_2$, R_2=CF_3CO_2

(173) R_1=CO_2Et, R_2=OAc

(174) R_1=$COCHN_2$, R_2=CF_3CO_2

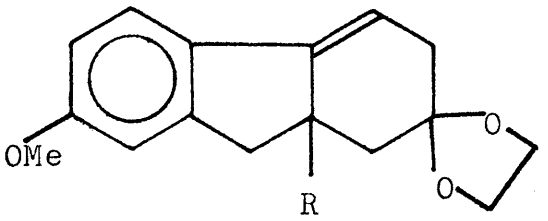
(177) R_1=CO_2H, R_2=H

5-methoxy isomer.

Ghatak also studied the stereochemistry of the hydrogenation of the cyclopropanes and olefins produced from such keto-carbenoid addition, and in general found that the $\Delta^{9,11}$ gibbenes are hydrogenated to give the unnatural configuration at C-9 unless a suitably orientated C-6 substituent is present, as discovered by Loewenthal.[65,66]

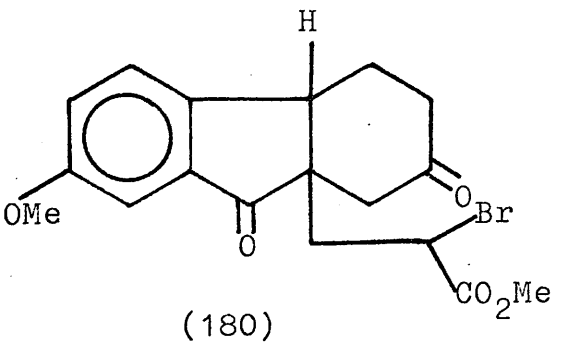
The same criteria hold for the hydrogenation of certain hydrofluorenes, which have been comprehensibly studied by Thompson[76] ketals of type (178) were synthesised from 2-carboethoxy-4,4-ethylenedioxycyclohexanone, m-methoxybenzyl chloride and sodium hydride, and then cyclised to give the 9a-carboethoxy derivative (179). It was then found when R=CH_2OH or CO_2H then a 4aβ- hydrogen was produced on catalytic hydrogenation; when R was CO_2alkyl then the natural 4aα-hydrogen resulted.

Ziegler[32] has used an efficient method for the preparation of the diketone (180) by condensing methyl vinyl ketone and p-methoxyphenylpyruvic acid to afford the acid (181) in high yield. Dehydration, catalytic hydrogenation and cyclodehydration with polyphosphoric acid afforded 7-methoxyhexahydrofluoren-2,9-dione. Selective ketalisation of the 2-oxo grouping followed by Michael addition of methyl α-bromoacrylate and deketalisation produced the desired diketone (180) an internal Reformatsky reaction on which gave the polyfunctional gibb-A-triene (182).

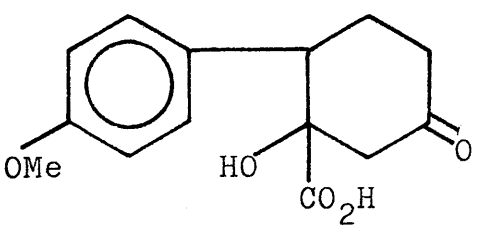


(178)

(179) R=CO_2Et



(180)



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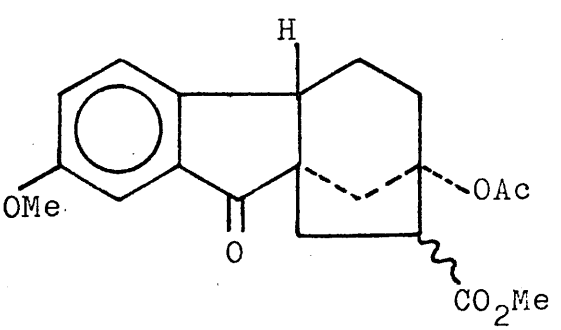
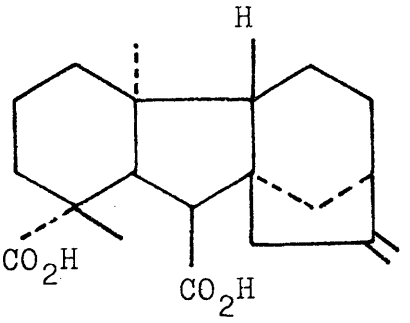


(182)

A novel approach to the problem was recorded by Tahara[77,78] who synthesised gibberellin A12 (183) from ℓ-abietic acid (184). Dehydrogenation of ℓ-abietic acid followed by chromic oxidation and esterification produced the diketo-ester (185), which was converted to the hydroxy-diacid (186); dehydration and hydrogenation of the acid produced after esterification the diester (187). Friedel-Crafts acylation with acetyl chloride, Baeyer Villiger oxidation, and hydrolysis with concentrated sulphuric acid gave the phenolic diester (188) regioselectively. Hydrogenation over ruthenium dioxide in ethanol at 100 atmospheres afforded the α-hydroxy diester (189). Jones oxidation, followed by Wittig reaction with methyl triphenylphosphonium iodide and sodium hydride, gave the 13-methylene diester(190). Hydroboration with diborane, followed by Jones oxidation gave two separable, isomeric acids(191) and (192) from which the β-isomer (192) was isolated and converted to its diazoketone which underwent an intramolecular carbenoid insertion (performed in benzene with copper sulphate under irradiation by a 300 watt tungsten lamp) to afford the tetracyclic diester (193). Ketalisation and partial hydrolysis afforded the keto ester (194). Deketalisation followed by Wittig reaction with triphenylmethylphosphonium iodide and sodium hydride gave pure gibberellin A12 (183) on demethylation .



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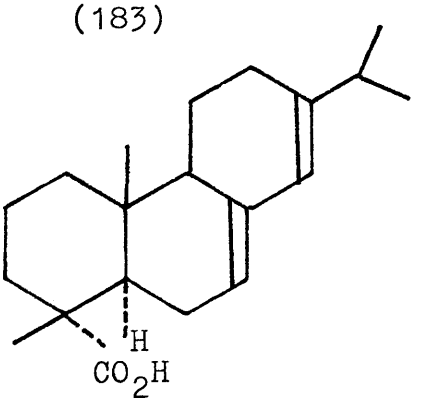

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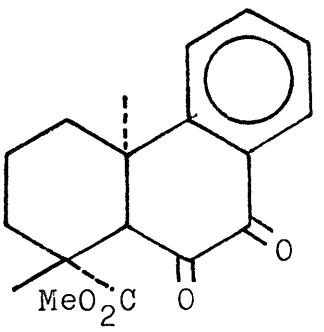

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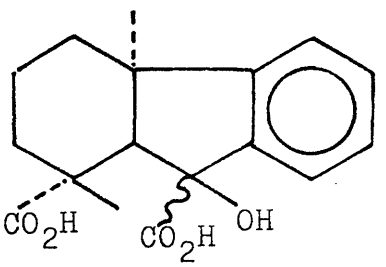

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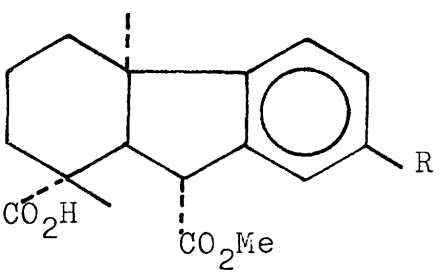
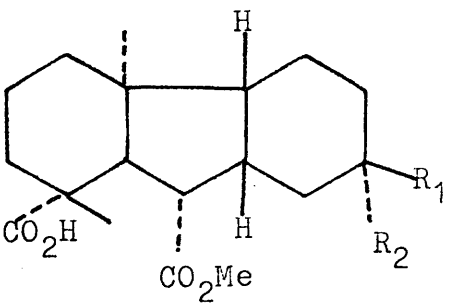


(187) R=H

(188) R=OH

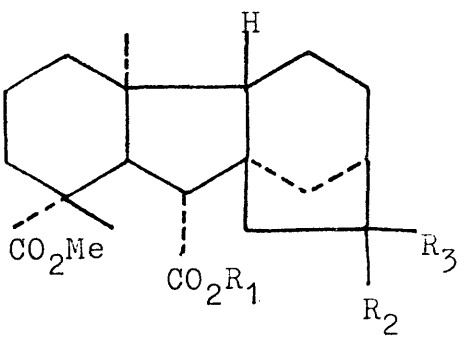


(189) R_1=H, R_2=OH

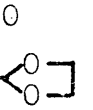
(190) R_1R_2=CH_2

(191) R_1=H, R_2=CO_2H

(192) R_1=CO_2H, R_2=H



(193) R_1=Me, R_2R_3=O

(194) R_1=H, R_2R_3= 

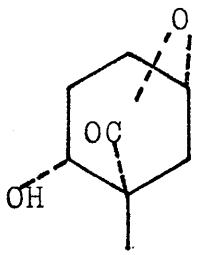
c- Synthesis of the ring A system

The problem was first tackled by Mori[79] who, while attempting to define the structure of ring A of gibberellic acid (1) , synthesised a series of cyclohexane γ-and δ-Lactones. One of these lactones (195), synthesised from 1-methyl-2-hydroxy-5-ketocyclohexan-1-carboxylic acid, proved to be the C-3 epimer of ring A of gibberellin A4 (196). A similar approach to this problem by Moffat[80] resulted in the synthesis of the ring A analogue of (196).

The lactone synthesised was shown to be epimeric at C-3 with the lactone (195) synthesised by Mori and epimerised to (195) in dilute aqueous alkali by what was suggested by Cornforth[81] to be a retro-aldol mechanism. This behaviour has also been observed in the gibberellins[82] and appears to occur by the same mechanism[83].

A model ring A analogue of gibberellic acid (1) was obtained by Loewenthal[84] in formation of lactone (197) from the readily available[85] 2-methoxy-5,6,7,8-tetrahydronaphth-1-oic acid (198) by the reaction sequence (198 $\longrightarrow$ 199 $\longrightarrow$ 200 $\longrightarrow$ 197)

Dolby[86] has also solved this problem by tackling it in a different manner. Reaction of the substituted cyclopentan -1- one (201) with homoallylmagnesium bromide yielded the olefinic lactone (202) after saponification. Oxidation and aldol condensation afforded a mixture of epimeric



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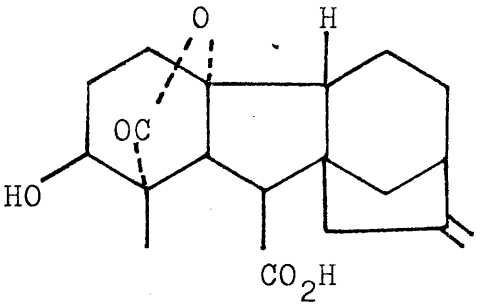

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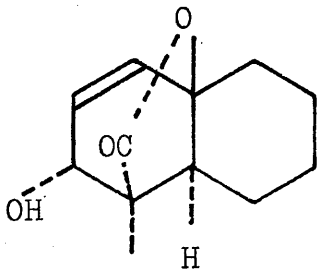

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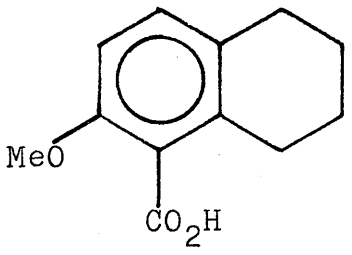

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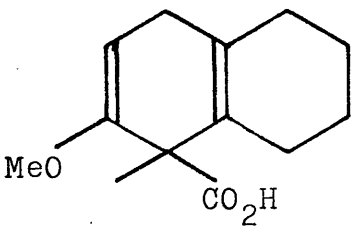

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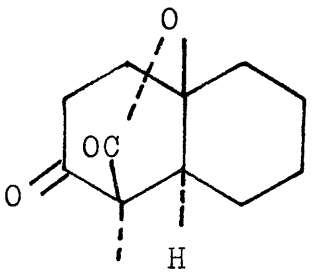

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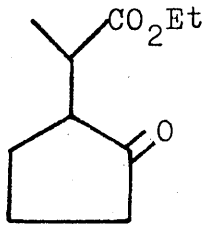

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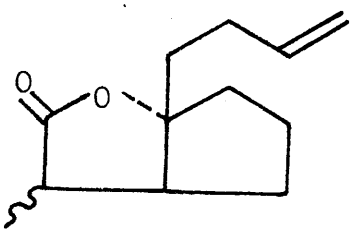


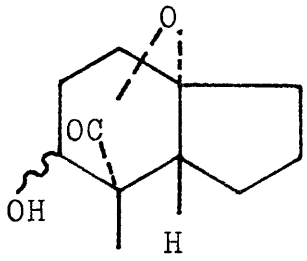
(202)

alcohols (203) which were separated to yield the desired α-hydroxy lactone.

Corey [87] achieved a stereospecific elaboration of ring A of gibberellic acid (1). The triene acid (204) was readily available from gibberellic acid by successive treatment with p-toluenesulphonyl chloride and sodium bromide followed by elimination of hydrogen bromide. He established that it could be readily converted back to gibberellic acid by the regioselective oxidation with m-chloroperbenzoic acid to afford, after saponification and iodine treatment the lactone (205). Conversion of lactone (205) to the desired product was achieved by trifluoroacetylation , elimination with zinc dust and detrifluoroacetylation with aqueous sodium bicarbonate.

Model studies on the formation of rings A and B of the triene (204) were successfully completed[88]. The key step involved the intramolecular Diels Alder cyclisation of the readily prepared diene-ester (206), (from 2,5-diethyl-1-cyclopentanonedicarboxylate) to form the lactone (207) which was alkylated to afford the corresponding diene-lactone (208). Hydrolysis and oxidation gave the required diene acid (209), after a selective methylation via an iodolactone intermediate.

Thus model studies had fully functionalised rings A and B into one segment of the target molecule (204) and rings C and D into another. Claisen rearrangment of guaiacol allyl ether, followed



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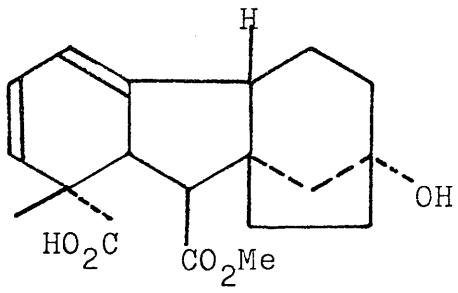

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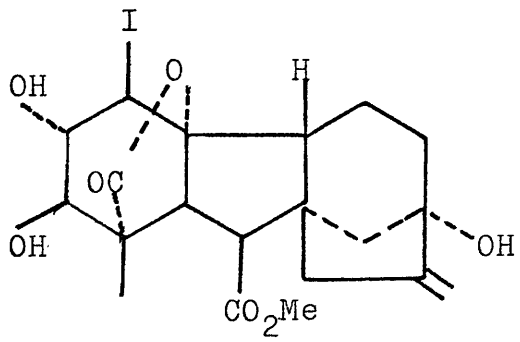

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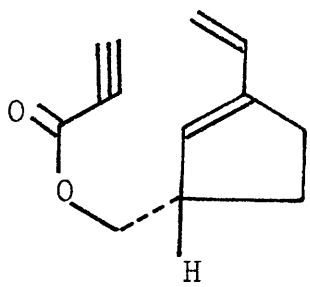

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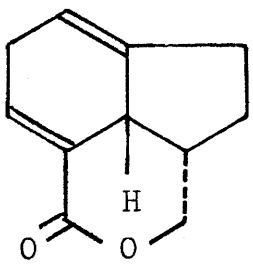

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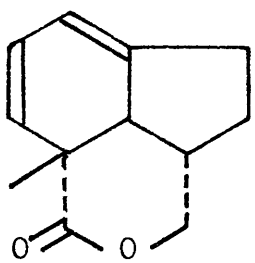
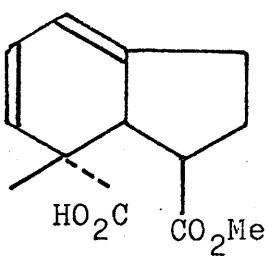


(208)



(209)

by β-methoxyethoxymethyl ether formation and Lemieux-Johnson oxidation afforded the aldehyde (210) which was converted into quinone (211) in four steps. Diels Alder reaction with penta-2,4-dienol afforded the adduct (212) stereospecifically , which was converted into the keto-aldehyde (213) in seven steps. Pinacol cyclisation, oxidation of the resulting secondary alcohol to the corresponding ketone, β-methoxy ethoxymethyl ether protection of the newly formed t-alcohol, Lemieux-Johnson oxidation and an intramolecular aldol condensation formed the tricyclic keto-aldehyde (214). Wittig reaction, removal of the tetrahydropyranyl ether protecting the primary alcohol group which has to orientate the incoming dienophile, and reaction with β-chloroacrylyl chloride furnished the triene (215). Diels Alder cyclisation in benzene removal of β- hydroxy protecting group afforded the target molecule (216). Unfortunately, this molecule refused to undergo an oxidative hydrolysis, thus preventing the formation of his original goal (204) despite the ease of hydrolysis of the model compound (208). Corey succeded in performing every reaction sequence in greater than 85% yield of isolated product.

The foregoing review indicates that many diverse synthetic routes to the gibberellin framework exist. Also, the problems associated with the introduction of the necessary functionality e.g. the C-6 carboxyl group, the C-13 hydroxyl group have been successfully surmounted in so far as rings B,C

and D are concerned.

There remains the challenge of assembling the functionality of ring A in the presence of rings B,C and D such that the correct stereochemical relationships pertain.

It has been shown that a suitably substituted aromatic ring A generates the incorrect relative stereochemistry at C-4 . The only attractive solution to the problem to date which has been demonstrated by Corey[88] in model systems has so far resisted completion in the tetracyclic system.[89]

An alternative projected solution to this problem is outlined in the discussion section of this thesis. However the work described in this thesis is concerned only with the synthesis of hitherto unaccessible indanones which are required for this project.

REFERENCES

1) E.Kurosawa,J.Nat.Hist.Soc.Formosa,1926,16,213.

1a) T.Yabuta and T.Hayashi,J.Agric.Chem.Soc.,Japan, 1939,15,257.

2) J.F.Grove,Quart,Rev.,1961,15,56.

3) N.Ya Grigor eva and N.F.Kucherov,Russ.Chem.Rev., 1966,35,850.

4) J.Van Oerbeek,Science,1966,152,72.

5) R.L.Wain,Chemical Society Reviews,1977,6,261.

6) B.E.Cross and P.J.Curtis,Chem.And Ind.,1954,1066.

7) F.McCapra,A.I.Scott,G.A.Sim and D.W.Young,Proc. Chem.Soc.,1962,185.

8) J.F.Grove and T.P.C.Mulholland,J.Chem.Soc.,1960, 3007.

9) J.W.Rowe,The Common and Systematic Nomenclature of Cyclic Diterpene,3rd.revision,October,1968.

10) J.MacMillan,M.F.Barnes and R.C.Durley,J.Chem. Soc.(C),1970,1341.

11) J.MacMillan in Recent Advances In Phytochemistry, 1974,7,1.

12) Y.Kos and H.J.E.Loewenthal,J.Chem.Soc.,1963,605.

13) R.A.Raphael et al.,J.Chem.Soc.,1961,3958.

14) H.J.E.Loewenthal and Z.Neuwirth,J.Org.Chem.,1967, 32,517.

15) H.J.E.Loewenthal and S.Malhotra,J.Chem.Soc.,1965, 990.

16) K.Weisner,W.D.Mackay,K.J.Weisner,A.Deljac, and L.S.J.Pan,Can.J.Chem.,1972,50,726.

17) U.R.Ghatak and J.Krai,J.C.S.Perkin 1,1977,518.

18) U.R.Ghatak,S.K.Alam,B.C.Ranu,and P.C.Chakraborti, J.C.S.Perkin 1,1976,1669.

19) U.R.Ghatak and J.Krai,J.Org.Chem.,1976,41,1089.

20) L.N.Mander,J.V.Turner and B.G.Coombe,Aust.J.Chem., 1974,27,1985.

21) L.N.Mander,R.H.Prager and J.V.Turner,Aust.J.Chem., 1974,27,2645.

22) D.J.Beames and L.N.Mander,Chem.Comm.,1971,773.

23) D.J.Beames,J.A.Halliday and L.N.Mander,Aust.J. Chem.,1972,25,137.

24) I.A.Blair,A.Ellis,D.W.Johnson and L.N.Mamder, Aust.J.Chem.,1978,31,405.

25) N.N.Gerber,J.Amer.Chem.Soc.,1960,82,5216.

26) A.J.Baker and A.C.Goudie,J.C.S.Chem.Comm.,1972, 951.

27) A.J.Baker and Goudie,J.C.S. Chem.Comm.,1971,181.

28) T.Kato,T.Suzuki,N.Ototani,H.Maeda,K.Yamada and Y.Kitahara,J.C.S.Perkin 1,1977,206.

29) T.Kato,T.Suzuki,N.Ototani and Y.Kitahara,Chem. Letters,1976,887.

30) J.P.Nallet,R.Barret,C.Arnaud and J.Huet, Tetrahedron Letters,1975,1843.

31) E.J.Corey,M.Norisada,T.Hiraoka and R.A.Ellison, J.Amer.Chem.Soc.,1970,92,396.

32) F.E.Ziegler and M.E.Condon,J.Org.Chem.,1971,3707.

33) W.Nagata,T.Wakabayashi,M.Narisada,Y.Hayase and

S.Kamata, J.Amer.Chem.Soc., 1971, 93, 5740.

34) G.Stork, ~~et al.~~ S.Malhotra, H.Thompson and M.Uchibayashi, J.Amer.Chem.Soc., 1965, 87, 1148.

35) H.W.Thompson, J.Org.Chem., 1967, 32, 3712.

36) B.M.Trost and L.H.Latimer, J.Org.Chem., 1978, 43, 1031.

37) Y.Yamada, H.Nagaoka and M.Kimura, Synthesis, 1977, 581.

38) Y.Yamada, K.Hosaka, H.Nagoka and K.Iguchi, J.C.S. Chem.Comm., 1974, 519.

39) Y.Yamada and H.Nagoka, Synthesis, 1977, 577.

40) T.Kametani, H.Nemoto and K.Fukumoto, J.C.S.Chem. Comm., 1976, 400.

41) T.Kametani, K.Ogasawara and T.Takashi, Tetrahedron, 1973, 29, 73.

42) T.Kametani, K.Fukumoto and M.Kajiwara, Tetrahedron, 1974, 30, 1053.

43) R.H.B.Galt and J.R.Hanson, J.Chem.Soc., 1965, 1565.

44) P.Heddon and J.MacMillan, J.C.S.Perkin 1, 1974, 587.

45) B.E.Cross and K.Norton, J.C.Stewart, J.Chem.Soc.(C), 1968, 1054.

46) A.G.Gonzalez, B.M.Fraga, M.G.Hernandez and J.G.Luis, Tetrahedron Letters, 1978, 37, 3499.

47) T.Ogawa, K.Mori, M.Matsui and Y.Sumiki, Tetrahedron Letters, 1967, 4483.

48) K.Mori, I.Takemoto and M.Matsui, Tetrahedron, 1976, 32, 1497.

49) K.Mori and M.Matsui, Tetrahedron, 1966, 22, 879.

50) I.F.Cook and J.R.Knox, Tetrahedron Letters, 1970, 4091.

51) I.F.Cook and J.R.Knox,Tetrahedron,1976,32,363,369.

52) K.Mori,M.Matsui and Y.Sumiki,Tetrahedron Letters, 1970,429.

53) E.J.Corey and R.L.Carney,J.Amer.Chem.Soc.,1971, 93,7318.

54) H.O.House, ~~et al.~~, F.J. Sauter, W.G. Kenyon and Jean-Jacques Riehl, J.Org.Chem.,1968,33,957 and refs. therein.

55) H.O.House,D.G.Melillo and F.J.Santer,J.Org.Chem., 1973,38,741.

56) W.Nagata,T.Sugasawa,M.Naisada,T.Wakabayashi and Y.Hayase,J.Amer.Chem.Soc.,1967,89,1483.

57) H.O.House and W.C.McDani,J.Org.Chem.,1976,42,2155.

58) H.O.House,J.K.Larson and H.C.Muller,J.Org.Chem., 1968,33,961.

59) H.O.House,C.B.Hudson and E.J.Racah,J.Org.Chem., 1972,37,989.

60) H.O.House,T.M.Bare and W.E.Hanners,J.Org.Chem., 1969,34,2209.

61) H.O.House,W.E.Hanners and E.J.Racah,J.Org.Chem., 1972,37,985.

62) H.O.House,E.J.Zaico and R.C.Strickland,J.Org. Chem.,1976,41,2401.

63) T.Hori and K.Nakanishi,Chem.Comm.,1969,528.

64) H.J.E.Loewenthal and S.Schatzmiller,Tetrahedron Letters,1972,3115.

65) H.J.E.Loewenthal and S.Schatzmiller,J.C.S. Perkin 1,1975,2149.

66) H.J.E.Loewenthal and S.Schatzmiller,J.C.S.Perkin 1,1976,944.

67) K.Mori,M.Matsui and Y.Sumiki,Agr.Biol.Chem., 1962,26,783.

68) T.Ogawa and M.Matsui,Agr.Biol.Chem.,1967,31,1327.

69) B.E.Cross,R.H.B.Galt and J.R.Hanson,Tetrahedron, 1962,18,451.

70) T.Ogawa and M.Matsui,Agr.Biol.Chem.,1967,31,1332.

71) G.Jammaer,H.Martens and G.Hournaert,Tetrahedron, 1975,31,2293.

72) D.J.Beames,L.N.Mander and J.V.Turner,Aust.J.Chem., 1974,27,1977.

73) U.R.Ghatak,P.C.Chakrabori,B.Sanyal and B.C.Ranu, J.C.S.Chem.Comm.,1973,548.

74) S.K.Dasgupta,R.Dasgupta,S.R.Ghosh and U.R.Ghatak, Chem.Comm.,1969,1253.

75) P.C.Chakraborti,R.Dasgupta,S.K.Dasgupta,S.R.Ghosh and U.R.Ghatak,Tetrahedron,1972,28,4653.

76) H.W.Thompson,J.Org.Chem.,1971,36,2577.

77) A.Tahara and Y.Ohtsuka,J.C.S.Perkin 1,1972,320.

78) A.Tahara and T.Nagata,Tetrahedron Letters,1976, 1515.

79) K.Mori,M.Matsui and Y.Sumiki,Agr.Biol.Chem., 1961,25,205.

80) J.S.Moffat,J.Chem.Soc.,1963,2595.

81) J.W.Cornforth,Chem. and Ind.,1959,184.

82) B.E.Cross,J.F.Grove and A.Morrison,J.Chem.Soc., 1961,2498.

83) J.MacMillan and R.J.Puyce,J.Chem.Soc.(C),1967, 740.

84) H.J.E.Loewenthal, ~~etal.~~ M.D.Bachi, J.W.Epstein, and Y.Herzberg-Minzly, J.Org.Chem.,1969,34,126.

85) R.T.Arnold,H.E.Zaugg and J.Sprung,J.Amer.Chem. Soc.,1941,63,1314.

86) L.J.Dolby and R.J.Milligan,J.Amer.Chem.Soc., 1966,88,4536.

87) E.J.Corey,T.M.Brennan and R.L.Carney,J.Amer.Chem. Soc.,1971,93,7316.

88) E.J.Corey and R.L.Danheiser,Tetrahedron Letters, 1973,4477.

89) E.J.Corey,Fifth International Symposium On Synthesis In Organic Chemistry. To be published.

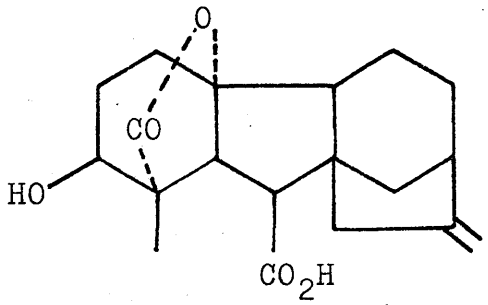
DISCUSSION

The total synthesis of gibberellin A4 (1) presents the organic chemist with a structural as well as a stereochemical challenge. The compound -one of the less complex gibberellins- has a carbon framework incorporating eight chiral centers and four different functional groups. The synthesis of such a molecule necessitates an efficient route to the carbon skeleton from which the functional group array may be elaborated in a stereospecific manner.

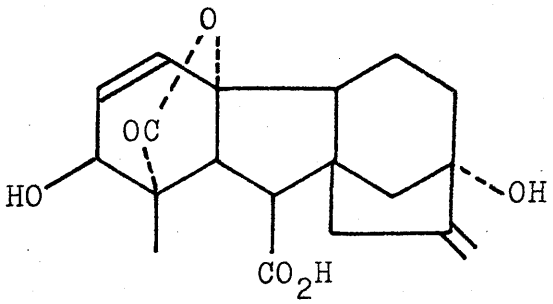
From the extensive literature on synthetic work in this field (see introduction) it is apparent that the construction of rings B C and D present no major difficulty and one would highlight the work on model compounds by Corey[1] and Mander[2] in this respect.

Less attention has been paid to the elaboration of ring A of gibberellins, the reason being that the ring A system is extremely sensitive to hydrolytic conditions and would therefore be developed late in the synthetic strategy. Thus the 3β (axial) hydroxyl group is epimerised to the more stable 3α (equatorial) configuration by the retro-aldol mechanism. In gibberellic acid (2) and the ring A identical gibberellin A7, ring A undergoes ready aromatisation.

The elaboration of ring A from a stable precursor requires that the precursor must possess suitable functionality , stable during the construction of the rest of the molecule but readily



(1)



(2)

transformed to ring A of gibberellins.

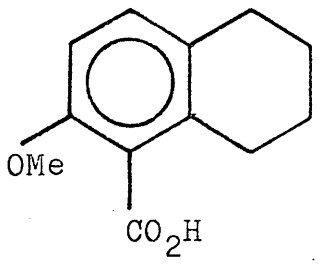
Loewenthal[3] achieved such a conversion of an aromatic ring by Birch reduction and further elaboration of the naphthoic acid(3) to the keto-lactone(4) .

Corey[4] has shown that the ring A diene acid (5) derived from gibberellic acid (2) can be readily reconverted to gibberellic acid (2). He has also synthesised from (6) the lactone (7), incorporating this diene feature, which has the correct stereochemistry at C-4 relative to C-9 and the ethano bridge. However, to date, the synthesis has not been completed owing to the unusual stability of the lactone to hydrolytic cleavage.

Loewenthal[5] and Baker[6] have extended the aromatic ring A approach of the former author to the synthesis of the two epimeric gibbanes (8) and (9). However Loewenthal has shown(unpublished work) that on Birch reduction followed by alkylation at C-4, all possible isomers give the unnatural stereochemistry at C-4 viz (10). This approach is therefore rendered useless unless some means of correcting the C-4 stereochemistry can be found.

A route to the Corey type intermediate (5) based on an aromatic ring A precursor , the synthesis of which will follow the well defined work of Loewenthal[5] and Baker[6] appeared to be feasible if the aromatic ring A could generate an o-quinone.

Ansell[7] has shown that o-quinones (11) readily undergo a Diels-Alder as the dienophile to give adducts



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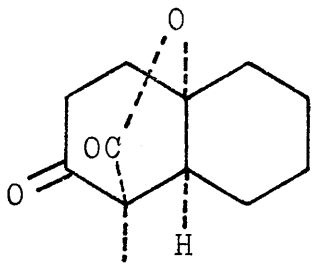

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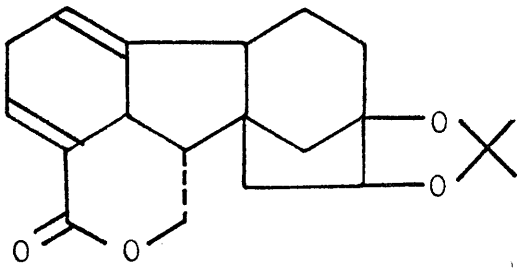

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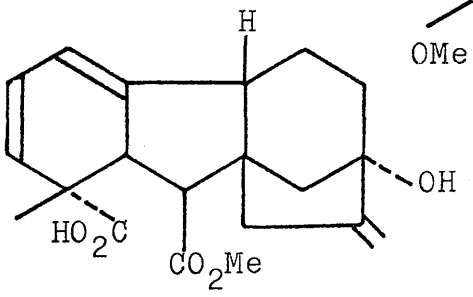

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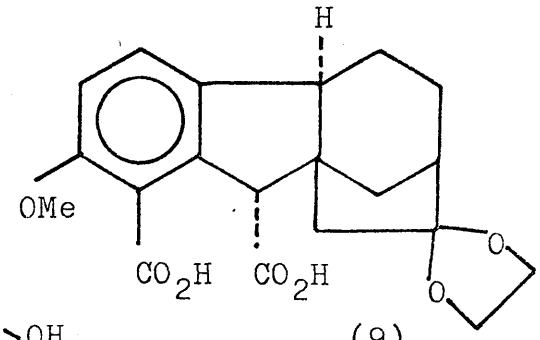

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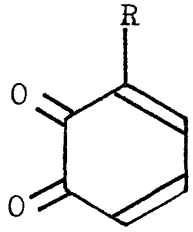

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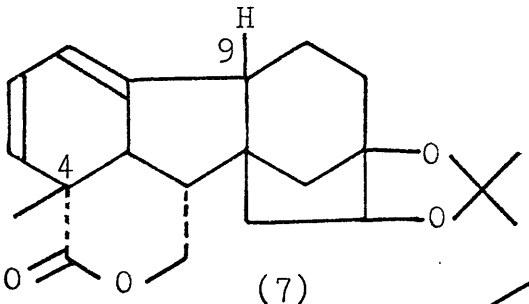

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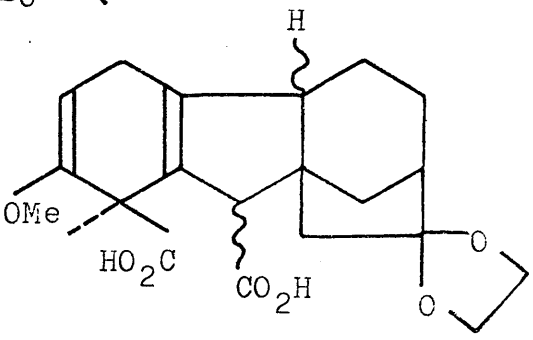

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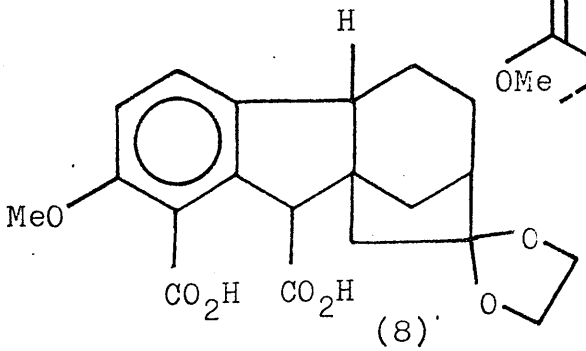
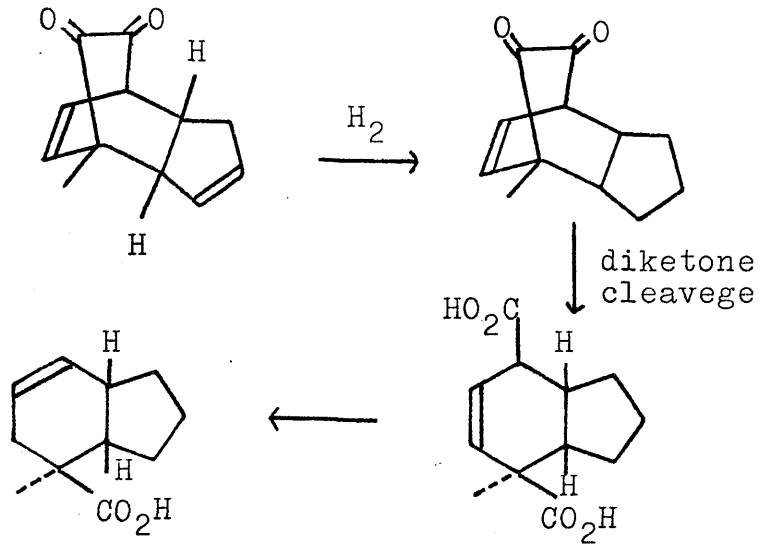


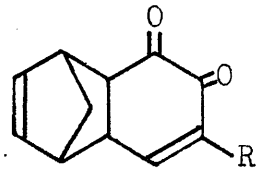
(8)

(12) which on heating undergoes a (3,3) sigmatropic rearrangment to give (13), in which the quinone appears to have reacted as a diene. The intermediate (13) can, on paper, be converted to a ring A analogue of gibberellins as shown below.



However, this model does not allow for the construction of the tetracyclic system, and is at the wrong oxidation level to permit lactonisation and the introduction of the alcohol function (at C-3).

A better model would be a tetracyclic o-quinone (14), or its equivalent, which would act as the diene component in the Diels-Alder reaction as outlined in scheme I . The adduct (15) should be amenable to conversion to the Corey ring A system (16) as outlined, provided the initial addition is regiospecific and stereospecific as shown .



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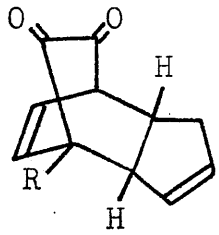
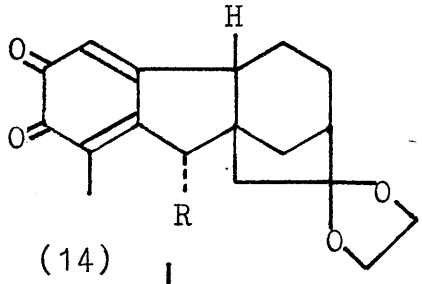


(13)

Scheme 1

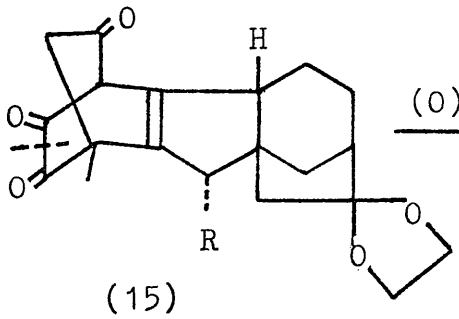


(14)

$R' = CO_2H$

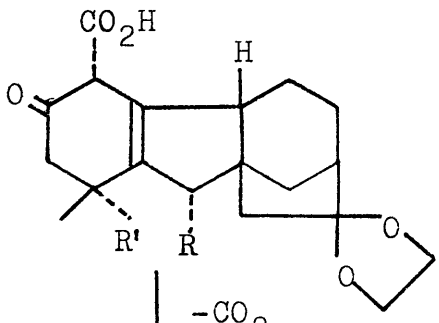
(O)= Oxidation

$H_2C=C=O$

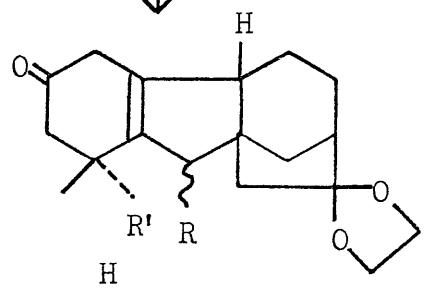


(15)

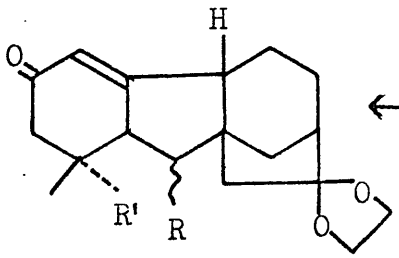
(O)

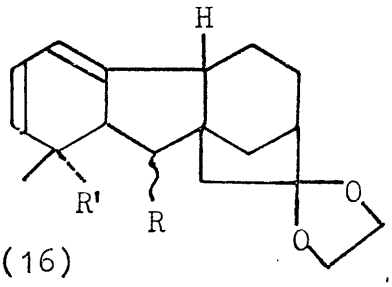


$-CO_2$



H^+





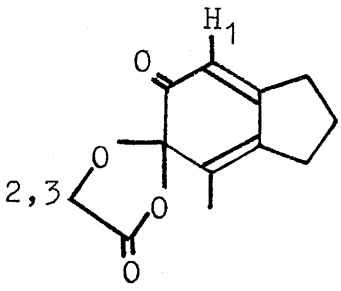
(16)

Deslongchamps[8,9] has shown that the spirolactone group in the indane o-quinone monoketal (17) controls the regiospecificity in the Diels-Alder reaction of (17) with methyl vinyl ketone which affords the adduct (18) as a mixture of epimers in high yield. This particular indanequinone used in the projected synthesis of ryanodin required the protection of the more hindered phenolic group in the diphenol precursor (19).

Wiesner[10,11] has recently made use of similarly protected o-quinone(20) and (21) in synthesis of the diterpene alkaloids denudatine and chasmanine and found that they are extremely reactive dienes, adding vinyl ethers and vinyl sulphides readily and regioselectively.

In all three examples cited the o-quinone spirolactone was generated from the corresponding phenoxyacetic acid by the reaction with sodium acetate and N-bromosuccinimide and required the selective formation of the required phenoxyacetic acid, which involved a number of stages.

The protected o-quinone required for the projected gibberellin synthesis has structure (22) in which the spirolactone, at least, would control the regiospecificity of the Diels-Alder reaction. It was hoped that the C-6 carboxyl group would control the stereospecificity in the reaction. However in case it or the C-6 -epimer did not, we considered that the alternative o-quinone derivative (23) should



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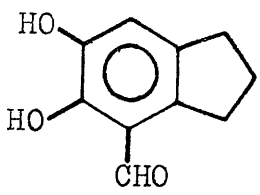

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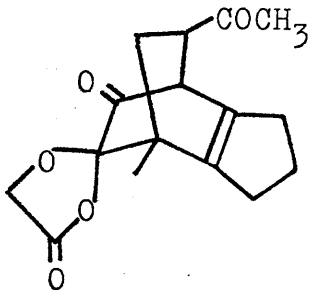

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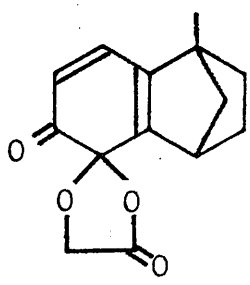

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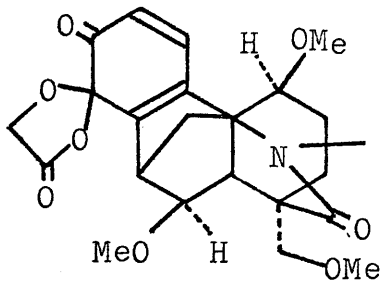

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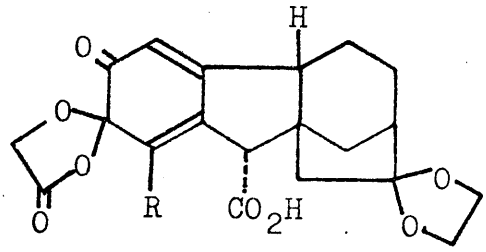


(22)

(23) R= CO_2H

also be considered although difficulties with the chemistry of such o-quinone were envisaged .

Both quinones (22) and (23) required the ready availability of the heavily substituted indanones (24),(25), (26)and (27), suitable for elaboration to the tetracyclic diphenol precursor (28) of the desired o-quinone.

This thesis in concerned with the initial phase of this project viz, the synthesis of the novel indanones (29),(30) and related compounds and for convenience is divided into two parts :

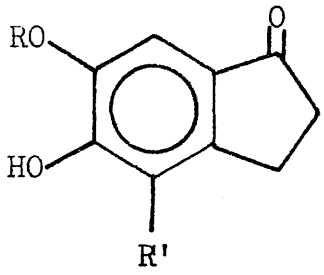
Part I - The synthesis of 4-carboxy-5,6-dimethoxyindanone (29) and related compounds.

Part II- The synthesis of 4-methyl -5-hydroxy -6- methoxyindanone (30) and its conversion to o-quinone spirolactone (17) by a modified procedure.

Part I - The synthesis of 4-carboxy-5-hydroxy -6-methoxyindanone (29)and related compounds.

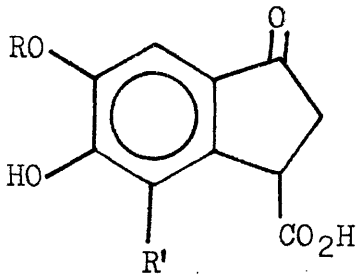
The need for indanones substituted at C-4 and C-5 as gibberellin synthons and as intermediates for other work has attracted attention during the last ten years.

Direct electrophilic substitution of a 5-substituted indanone at C-4 is not regioselective and results in a mixture of C-4 and C-6 substituted products



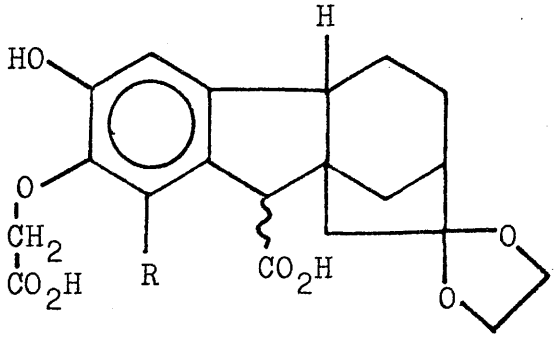
(24) $R' = CH_3$

(26) $R' = CO_2H$



(25) $R' = CH_3$

(27) $R' = CO_2H$



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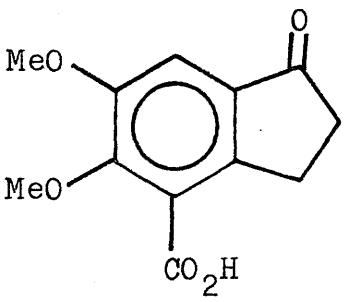

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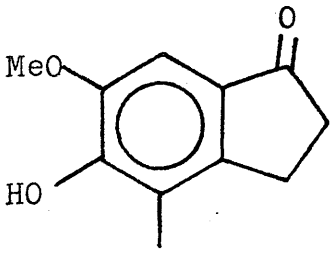
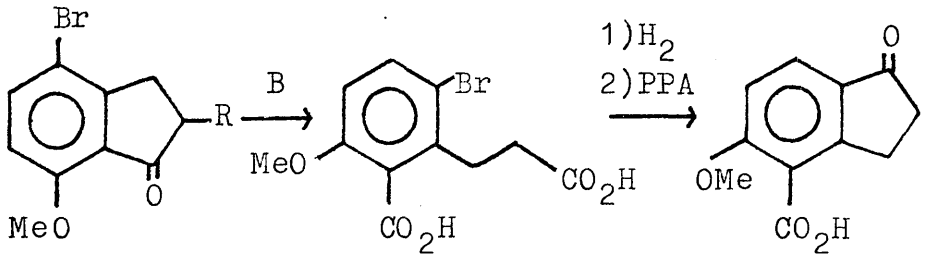


(30)

(e.g. nitration and chloromethylation) which necessitates a separation procedure.

Although the synthesis of 4-carboxy-5-methoxyindanone can be achieved in this way, via chloromethylation,[12] it has proved to be unsuccessful in the case of 5,6-dimethoxyindanone(see later).

The alternative synthetic route to 4-carboxyindanones[12,13] involves the ring cleavage of a suitable 2-cyano(or formyl)-7-methoxyindanone and subsequent cyclisation of the resulting arylpropionic acid as shown below



R=CN,CHO;B=Base or H_2O_2

This approach requires that the position para to the methoxy group be blocked(by bromine) in the synthesis of the 7- methoxyindanone and unblocked prior to the final cyclisation.

Although such an approach should be applicable to the synthesis of 4-carboxy-5,6-dimethoxyindanone (29) we decided to look for a more direct route to this compound which would also be applicable to the synthesis of 4-methyl-5-hydroxy-6-methoxyindanone (30).

The most suitable compound which would serve both purposes would be 4-hydroxymethyl-5-hydroxy-6-

methoxyindanone(31). This hopefully would afford(29) by methylation and oxidation and(30) by reduction.

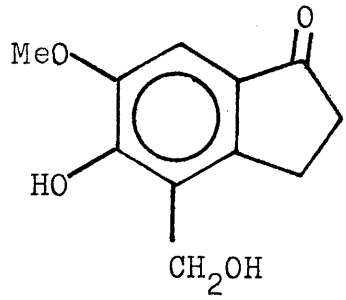
In view of the fact that(a) o-hydroxybenzyl-alcohols undergo ready polymerisation to form resins and (b) the hydroxymethylation reaction works efficiently only with reactive phenols to give often mixtures of ortho and para products the following synthetic scheme was devised for the reasons stated.

The hydroxymethylation reaction would have to be performed on the arylpropionic acid(32) rather than the much less reactive indanone(33) and in such a way that regiospecific attachment of the hydroxy-methyl group took place ortho to the phenolic group.

β(3-Hydroxy-4-methoxyphenyl) propionic acid (32) was prepared essentially as described in the literature. Isovanillin (34) was condensed with malonic acid to give the cinnamic acid(35) in high yield[14]. The conversion of the cinnamic acid(35) to the arylpropionic acid(32) had formerly been accomplished in 31% yield by sodium amalgam reduction. We have found that hydrogenation of (35) over 5%Pd/C was more convenient and gave, consistently, yields of about 65%.

It has been shown[15] that in the presence of boric acid, phenol is converted to o-hydroxybenzyl-alcohol exclusively on reaction with paraformaldehyde, but in very low yield(~ 5%).

Battersby[16] applied the Reimer-Tiemann reaction to 3-hydroxy-4-methoxyphenylacetic acid(36) and



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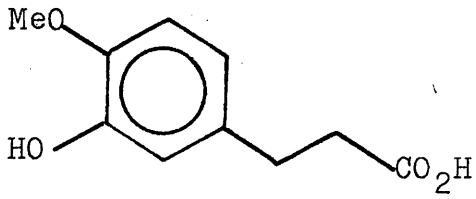

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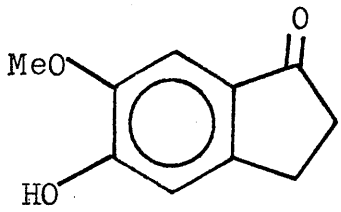

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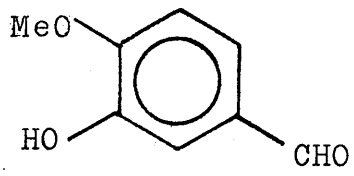
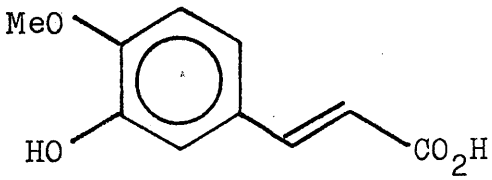


(34)



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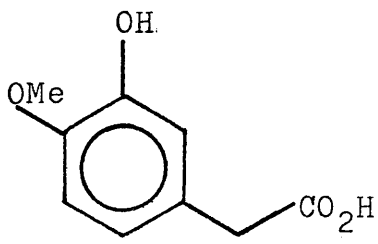


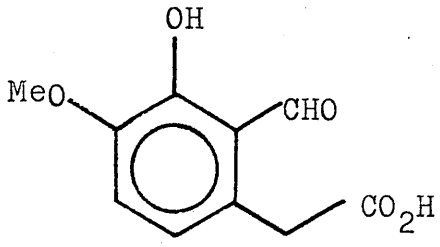
(36)

obtained a mixture of products from which 2-formyl-3-hydroxy-4-methoxyphenylacetic acid (37) was isolated in 15% yield. The latter compound on reduction with sodiumborohydride gave the lactone(38) which is formally the product of hydroxymethylation of (36).

Recently Nagata,[17] concerned with the synthesis of protoberberine alkaloids reinvestigated the hydroxymethylation reaction with boric acid in refluxing benzene. o-Hydroxybenzyl alcohol was the sole product(4%) but the absence of other products reinforced Peer's suggestion[15] that the reaction proceeds via the chelated transition state(39) to the intermediate borate(40) and finally to the product.

When applied to homoisovanillic acid(36) the yield of lactone(38) was 15%, the best yield being obtained in toluene. The use of benzeneboronic acid (with its greater solubility in aromatic hydrocarbons and its higher Lewis acidity) and a catalytic amount of propionic acid gave the isolable borin(41) in high yield when applied to phenol and the borin(42) when applied to homoisovanillic acid. The borin(41) afforded o-hydroxybenzyl alcohol on exchange with propylene glycol. Borin(42) with warm water gave lactone(38) in 83% overall yield.

This hydroxymethylation procedure was therefore applied to β-(3-hydroxy-4-methoxyphenyl) propionic acid with disappointing results. The product after many attempts was a complex mixture from which the



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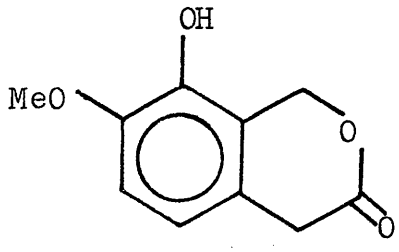

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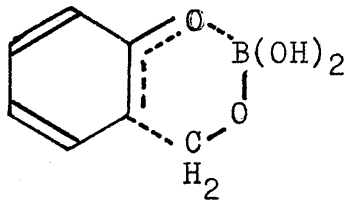

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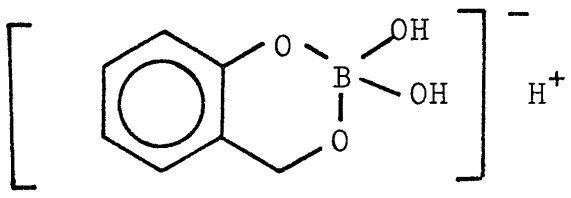

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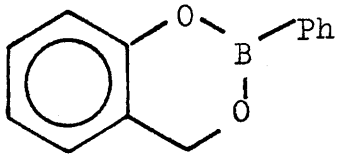

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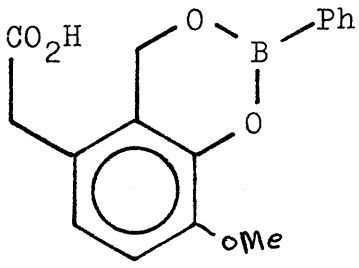
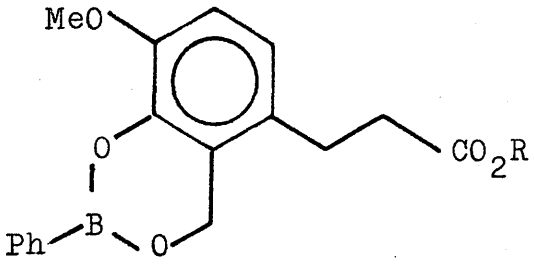


(42)

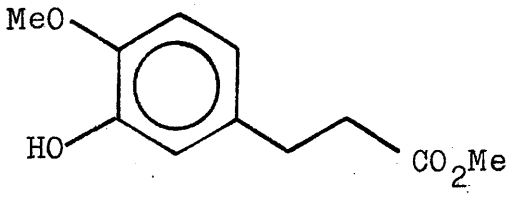
desired borin(43) could not be separated. In part II the successful hydroxymethylation of (32) is described.

When applied to the corresponding methyl ester (44) - obtained by acid catalysed reaction of acid (32) with methanol[14]- a quantitative yield of borin (45) was obtained. A singlet in NMR spectrum of(45) for the C-5,C-6 protons failed to confirm the assigned structure due to the equivalence of the two protons . The methylene protons appeared as a singlet at δ 5.23 while the phenyl protons were two groups of signalsat 8.03 and 7.47 in the ratio 2:3.[18] With propylene glycol the borin (45) was cleanly converted to methyl-β- (2-hydroxymethyl -3- hydroxy -4- methoxy-phenyl) propionate (46) in 96.6% yield . This hydroxyester showed no tendency to lactonise. Again the NMR spectrum of (46) shown a singlet for the C-5, C-6 protons . However the mass spectrum revealed a ready loss of water consistent with the o-hydroxy-benzyl alcohol structure .[18a] On Jones oxidation the phenolic benzyl alcohol(46) gave a complex mixture of products from which no carboxylic acid (47) could be isolated. It is well known [19] that phenols are extremely sensitive to oxidising agents. To circumvent this problem the phenolic group in (46) was converted to its methyl ether by reaction with methyl iodide and potassium carbonate in acetone. It was expected [20] and later realised that this methoxyl group being ortho to a carbonyl group of the

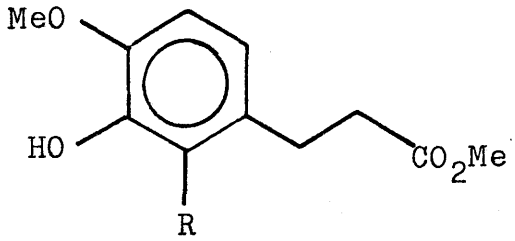


(43) R= H

(45) R= Me



(44)



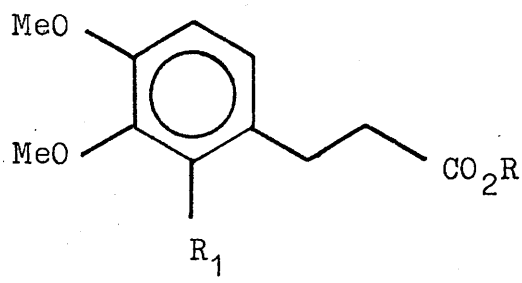
(46) R= CH_2OH

(47) R= CO_2H

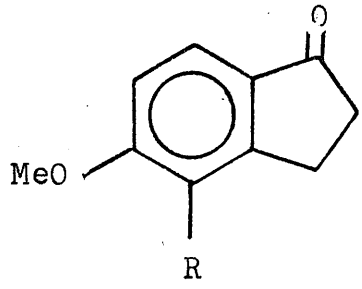
expected acid (or ester) could be selectively reconverted to the phenol. Jones oxidation of the dimethoxy-benzyl alchol (48) gave the acid (49) in good yield after maintaining the excess reagent for three hours. When the oxidation was interrupted after ten minutes the product was a mixture of the acid (49) and the corresponding aldehyde. The catalytic effect of adding Ce (1V)ion had no effect on the rate of oxidation . Loewenthal[12] had found that the benzyl alcohol (50) was oxidised only to the aldehyde (51) with Jones reagent, but that oxidation of the aldehyde (51) to the acid (52) could be effected by Jones reagent in the presence of Ce(1V) ion.

On basic hydrolysis ester (49) gave the desired β(2-carboxy-3,4-dimethoxyphenyl) propionic acid (53) as a nicely crystalline solid.

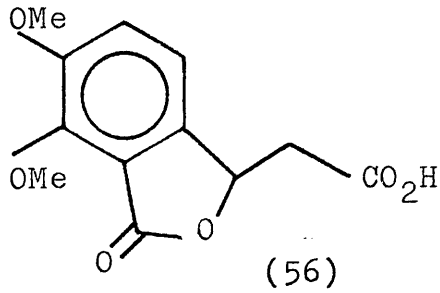
An alternative route to diacid(53) was also studied starting from opianic acid, 2-carboxy-3,4-dimethoxybenzaldehyde(54) ,which exists as the hydroxy-lactone tautomer. Opianic acid(54) was obtained from the alkaloid narcotine(55) by oxidative degradation with manganese dioxide in boiling dilute sulphuric acid.[21] Condensation of opianic acid(54) with malonic acid in sodium acetate buffered acetic acid gave the phthalide-3-acetic acid(56) in good yield as described in the literature[22]. The same product could also be obtained in high yield by conducting the condensation in pyridine with piperidine as catalyst. Somewhat surprisingly when the Perkin reaction was applied to



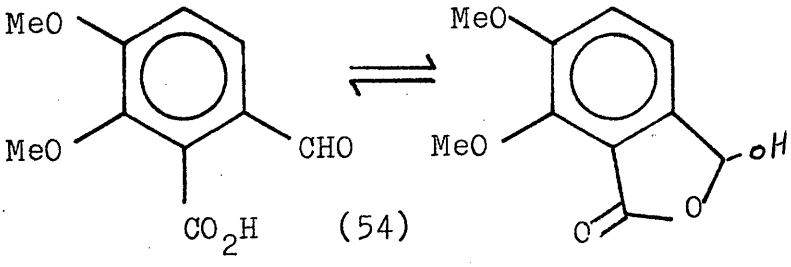
(48) R=Me, $R_1=CH_2OH$
(49) R=Me, $R_1=CO_2H$
(53) R=H , $R_1=CO_2H$



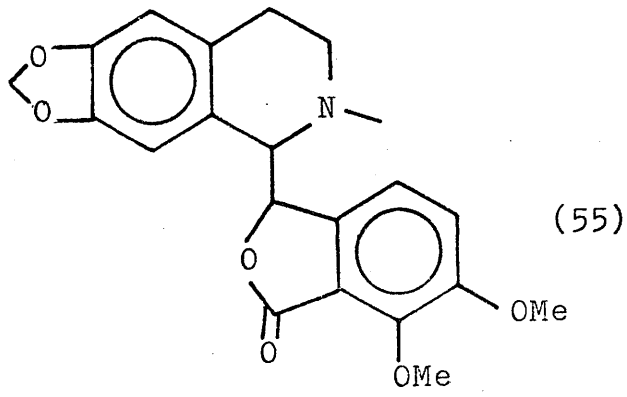
(50) $R=CH_2OH$
(51) R=CHO
(52) $R=CO_2H$



(56)



(54)



(55)

opianic acid the sole product obtained in high yield was the acetate(57).

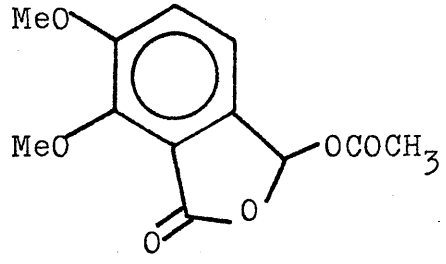
Attempts to convert 6,7-dimethoxyphthalide-3-acetic acid(56) directly to β-(2-carboxy-3,4-dimethoxy-phenyl) propionic acid(53) by hydrogenolysis of the benzylic C-O bond were totally unsuccessful;a variety of catalysts,solvents and conditions were tried.Zinc amalgam reduction was also unsuccessful.

The conversion of phthalide(56) to the diacid (53) was finally accomplished by first converting the phthalide to the cinnamic acid(58) using potassium hydroxide and then hydrogenating the latter compound in sodium carbonate solution to prevent re-lactonisation.[23] It was later found that the phthalide (56) could be converted directly to diacid (53) in higher yield without isolating the cinnamic acid(58) by catalytic hydrogenation in potassium hydroxide solution.

The diacid(53) prepared as described from opianic acid was identical in all respects with that prepared from isovanillin.

Cyclisation of β-(2-carboxy-3,4-dimethoxy) phenylpropionic acid(53)with freshly prepared poly-phosphoric acid gave the crystalline 4-carboxy-5,6-dimethoxyindanone (29) in 71.8% yield. The sole aromatic proton resonated at δ 7.30 in its NMR spectrum.

This indanone(29) would provide the starting point for the synthesis of the gibbane(59) by the annelation sequence pioneered by Loewenthal.The ring



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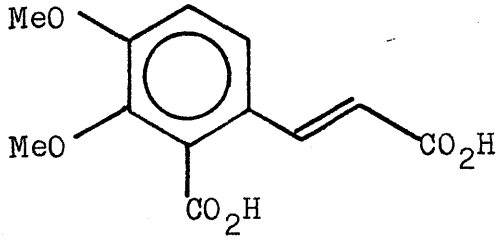
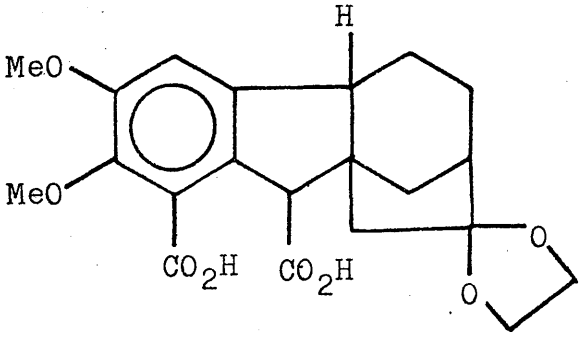


(58)



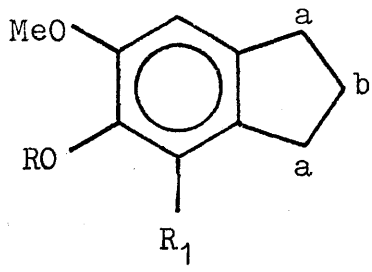
(59)

B carboxyl group would be attached, after rings C and D had been formed, by the methods of Loewenthal[5] or Baker.[6]

In order to pursue model studies leading to ring A of gibberellins, indanone(29) was hydrogenated over 30% Pd/C to give the indane(60) in 99% yield. Selective demethylation[20] of indane (60) with boron trichloride proceeded smoothly to give 4-carboxy-5-hydroxy-6-methoxyindane (61) in 86% yield. The infrared spectrum of this compound confirmed that selective demethylation had indeed occurred by the presence of the characteristic " salicyclic hydroxyl band " at 3400 cm^{-1} due to the strong hydrogen bonding. This band was more readily apparent in the infrared spectrum of the corresponding methyl ester (62)prepared by refluxing indane acid (61) in methanol containing concentrated hydrochloric acid .

Attempts to form the oxyacetic acid (63) from the phenolic ester using chloroacetic acid in sodium hydroxide solution[25] or in pyridine solution were uniformly unsuccessful in our hands. Under the former conditions hydrolysis of the ester to give acid (61) occurred.

Attempts were also made to synthesise the indanone -3,4-diacid (64) from 3-carboxy-5,6-dimethoxyindanone (65) via chloromethylation ; (65) was prepared as described [26,27] in the literature from veratraldehyde via (66), (67) and (68). It was found that higher yields of indanone (65) were obtained

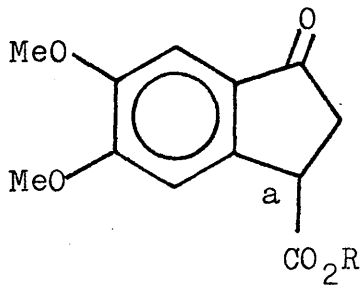


(60) R=Me, $R_1=CO_2H$

(61) R=H , $R_1=CO_2H$

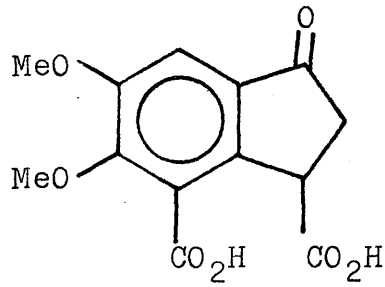
(62) R=H , $R_1=CO_2Me$

(63) $R=CH_2CO_2H$, $R_1=CO_2Me$

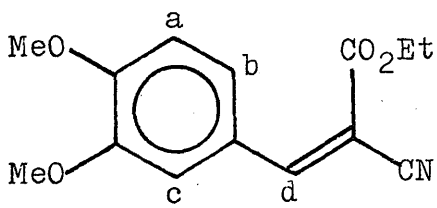


(65) R=H

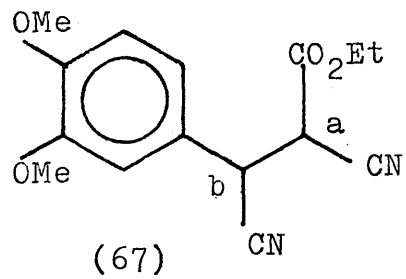
(65a) R=Me



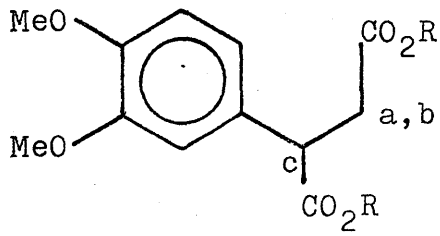
(64)



(66)



(67)



(68) R=H

(68a) R=Me

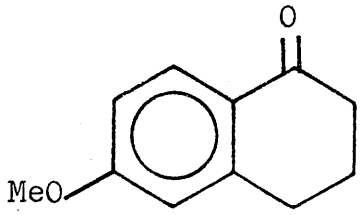
when the cyclisation of the diacid (68) was effected with polyphosphoric acid rather than by using the literature method [28] employing aluminium trichloride.

Chloromethylation of 3-carboxy-5,6-dimethoxyindanone (65) under a variety of conditions gave unreacted starting material in all cases. This was rather surprising in view of the fact that 6-methoxytetralone (69)[29], and more pertinent to our case, 5-methoxyindanone (70) [12] had been successfully chloromethylated using paraformaldehyde in acetic acid containing hydrochloric acid . The latter compound gave a mixture of C-4 and C-6 isomers in the ratio 6:1.

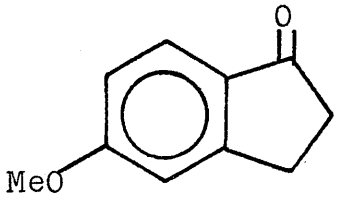
Although 3-carboxy-5,6-dimethoxyindanone(65) was considered to be more reactive towards electrophilic substitution at C-4 it was felt that the adjacent carboxyl group at C-3 was sterically hindering the C-4 position.

An attempts was also made to selectively demethylate 3-carboxy-5,6-dimethoxyindanone and 5,6-dimethoxyindanone (71) with boron trichloride to give the 5-hydroxy compound in each case. It has been reported [30] that (72) on treatment with boron trichloride gave (73) in which the methoxy group para to the aldehyde function was cleaved rather than the methoxy group which was flanked by the aldehyde and ester functions. Indanones (65) and (71) were totally unreactive towards boron trichloride even after seven days reaction.

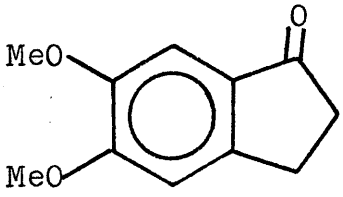
In the synthesis of 5,6-dimethoxy-indanone


O
MeO

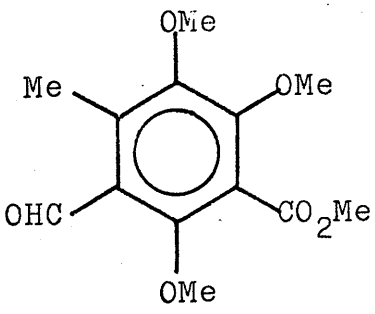
(69)


O
MeO

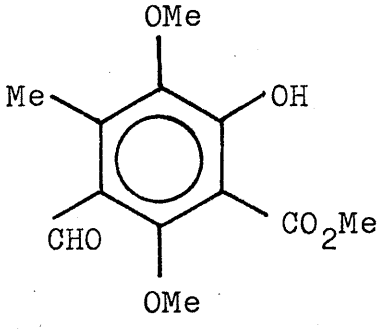
(70)


O
MeO
MeO

(71)


OMe
Me
OMe
OHC
CO2Me
OMe

(72)


OMe
Me
OH
CHO
CO2Me
OMe

(73)

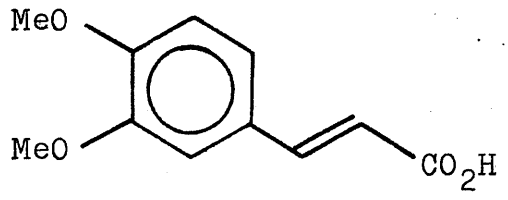
(71) from 3,4-dimethoxycinnamic acid (74) it was found that the latter compound could be hydrogenated easily to propionic acid (75) at room temperature and atmospheric pressure rathar than following the literature method[31] which employed hydrogenation at 60°C and two-three atmospheres of pressure.

Part II - The synthesis of 4-Methyl -5-hydroxy-6-methoxyindanone (30) and 4-methylindane-5,6-quinone-5,5-spirolactone (17) 3-Oxo-4,4-oxoethylenedioxy-5-methylbicyclo [4,3,0] nona-1,5-diene.

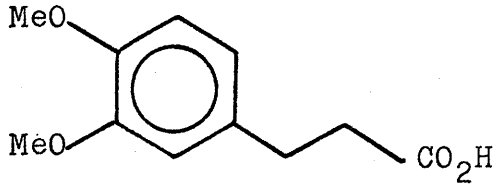
With a practicable synthesis of 4-carboxy-5,6-dimethoxyindanone (29) available from isovanillin and also from opianic acid, attention was focussed on a synthesis of 4-methyl-5-hydroxy-6-methoxyindanone (30) and its conversion to the o-quinonespirolactone (17) the desired model precursor for gibberellin ring A elaboration.

The starting material for this synthesis was β-(3-hydroxy-4-methoxyphenyl) propionic acid (32) the synthesis of which has already been described.

A further investigation of the benzeneboronic acid mediated hydroxymethylation reaction of (32) with paraformaldehyde revealed that by using excess benzeneboronic acid (3equivalents) in the reaction an 89% yield of the borin (43) of β-(2-hydroxymethyl-3-hydroxy-4-methoxyphenyl)propionic acid was obtained.



(74)



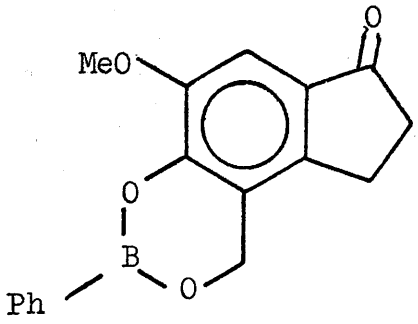
(75)

Although not directly relevant to this work it was of interest to see if the phenylboronate(43) would stand up to the conditions of a polyphosphoric acid cyclisation. It is, of course, well known that phenylboronates are thermally stable being used to derivatise 1,3-diols for gas-chromatographic work.[32]

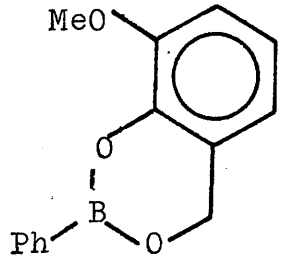
With polyphosphoric acid at 90°C the borin(43) cyclised to the indanone(76) in 79% yield. This result indicates that the phenylboronate of o-hydroxybenzyl alcohols of type (77) prepared from catechol monomethyl ether(78) may survive in other non-aqueous electrophilic reactions to give e.g.(79; R=H, alkyl, or aryl) in which the methoxy group would be expected to direct the course of substitution. Such reactions are worthy of further investigation.

The indanone borin(76) provides an alternative route to 4-carboxy-5,6-dimethoxyindanone(29) by borin exchange with propylene glycol, methylation,and oxidation. Because a good synthesis of (29) was already available this latter route has not been studied.

On a practical point it was found that the use of ferric chloride to monitor the course of the hydroxymethylation reaction was misleading since the borins (41),(43),(45) and(76) themselves gave a positive reaction (blue-grey colour) due possibly to complex formation with the borin or even ferric chloride catalysed hydrolysis of the borin and subsequent complexation.



(76)



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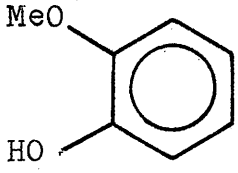

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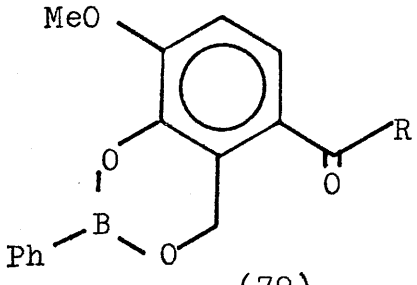
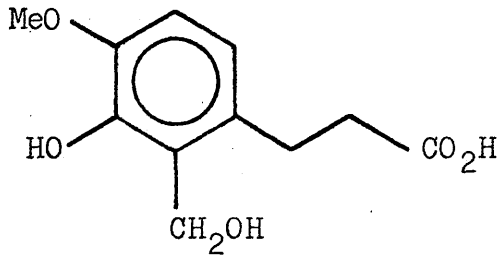


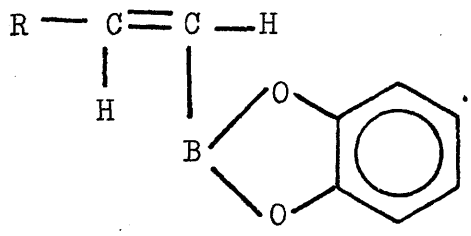
(79)

The borin(43) of β-(2-hydroxymethyl-3-hydroxy-4-methoxyphenyl) propionic acid (80) was converted to the latter compound in 96% yield by exchange with propylene glycol and with water in 41.3% yield. the aqueous hydrolysis of the boronate(81) to catechol and the vinylboronic acid(82) has been reported.[33]

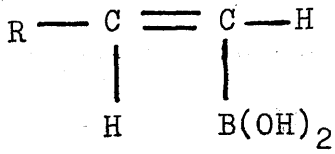
In an attempt to prepare the propionic acid (80) from the corresponding methyl ester(46) in a one-pot reaction borin ester(45) was first reacted with propylene glycol to effect exchange of the boronate grouping. The mixture was then subjected to alkaline hydrolysis with aqueous sodium hydroxide to effect the hydrolysis of the ester to the acid(80) . The products from this reaction were benzeneboronic acid, borin acid(43) and the desired acid(80). Also present was a trace of 3-hydroxy-4-methoxyphenylpropionic acid(32) formed by a retro-aldol reaction. Since the mixture before the hydrolysis stage showed only the presence of propyleneglycol phenylboronate and ester(46), it must be assumed that the presence of the borin acid (43) in the final product mixture must have arisen by base catalysed exchange of the boronate group from the propyleneglycol phenylboronate to the acid(80). It was found to be more practical to extract the propyleneglycol phenylboronate from the reaction mixture(using n-pentane) prior to the basic hydrolysis. In this way β-(2-hydroxymethyl-3-hydroxy-4-methoxy - phenyl) propionic acid(80) was readily obtained.The traces of retro-aldol product β-(3-hydroxy-4-methoxy-



(80)



(81)



(82)

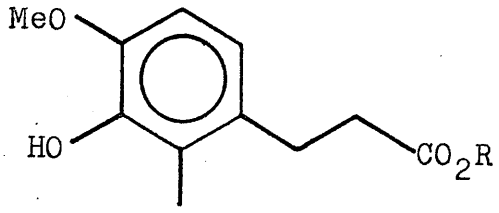
phenyl) propionic acid(32) were easily removed on recrystallization of (80) from ethyl acetate-petroleum ether.

On subjecting(80) to hydrogenation using 10% Pd/C in ethyl acetate containing 60% perchloric acid, the benzylic hydroxyl group was smoothly replaced by hydrogen to give β-(2-methyl-3-hydroxy-4-methoxyphenyl) propionic acid(83) in 40% yield. Varying amounts of the corresponding ethyl ester were also formed by trans-esterification catalysed by the perchloric acid when the hydrogenation was allowed to proceed for 45 hours. The acid(83) was best obtained(in 83.5% yield) by prolonged hydrogenolysis of the methyl ester(46) followed by subjecting the product to hydrolysis in tetrahydrofuran containing 15% aqueous hydrochloric acid. Tetrahydrofuran was used because of the low solubility of the starting ester and the desired acid in water.

Attempted hydrolysis of the ester using aqueous sodium hydroxide solution gave a less pure product which was pink in colour presumably due to air oxidation of the phenol in the basic conditions.

Cyclization of acid(83) with preformed poly-phosphoric acid gave 4-methyl-5-hydroxy-6-methoxy-indanone(30) in 51.4% yield. The cyclization of esters with excess polyphosphoric acid has been reported by Gilmore[34] who effected the cyclization of methyl δ-phenylvalerate(84) to benzsuberone(85).

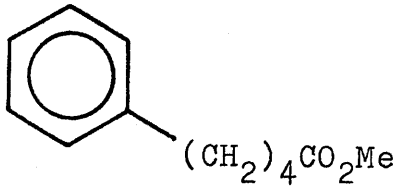
When applied to ester (86) the yield of indanone(30)



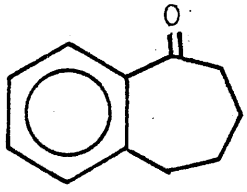
(83) R=H

(83a) R=Et

(86) R=Me



(84)



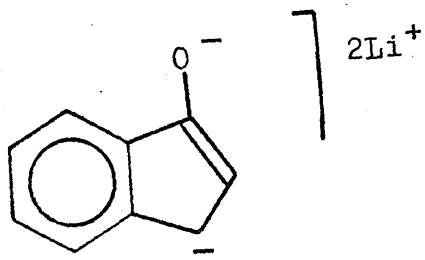
(85)

was only 21%.

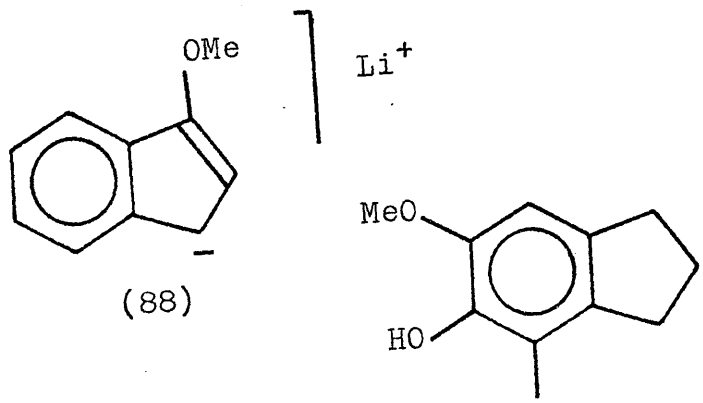
Although procedures exist in the literature[24,35,36] for converting indanone to a 3-alkylindanone which involve the formation of cyclopentadienyl anions such as (87),(88) and(89) it was considered that protection of the phenolic group as its benzyl ether would have to be done prior to introducing a carboxyl group at C-3 by the above procedures. This further extension of the synthesis leading to the gibbane derivative(90) was not pursued. Instead attention was focussed on the possible conversion of indanone (30) to the protected indane-o-quinone derivative (17) .

Deslongchamps [8] has reported a synthesis of the spirolactone (17) from 4-formyl-5,6-dihydroxyindane (92a) by the sequence shown in scheme 2 , which is an extension of a reaction reported earlier by Corey[37]. We felt that it might be possible to elaborate such a system from the indanone (30) which had been specifically constructed to allow differentiation between the two oxygen functions in the proposed gibbane intermediate (90) consequently 4-methyl-5-hydroxy-6-methoxyindanone (30) was converted to the corresponding indane (91). This was accomplished either by catalytic reduction over Pd/C or more conveniently, in 84% yield , by reduction with sodium borohydride in a reaction which is specific for o-or p-hydroxyaryl ketones.[38]

In Deslongchamps synthesis of spirolactone (17) from 4-formyl-5,6-dihydroxyindane(92a)(scheme 2) selective bromoacetylation occurred at the C-6 hydroxyl

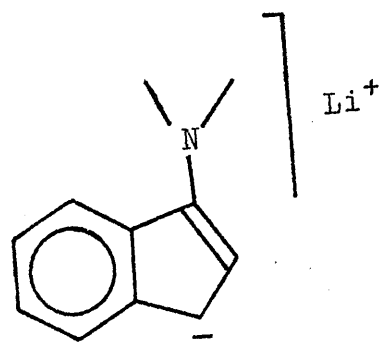


(87)

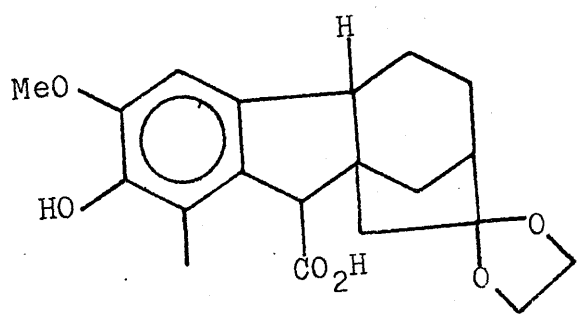


(88)

(91)

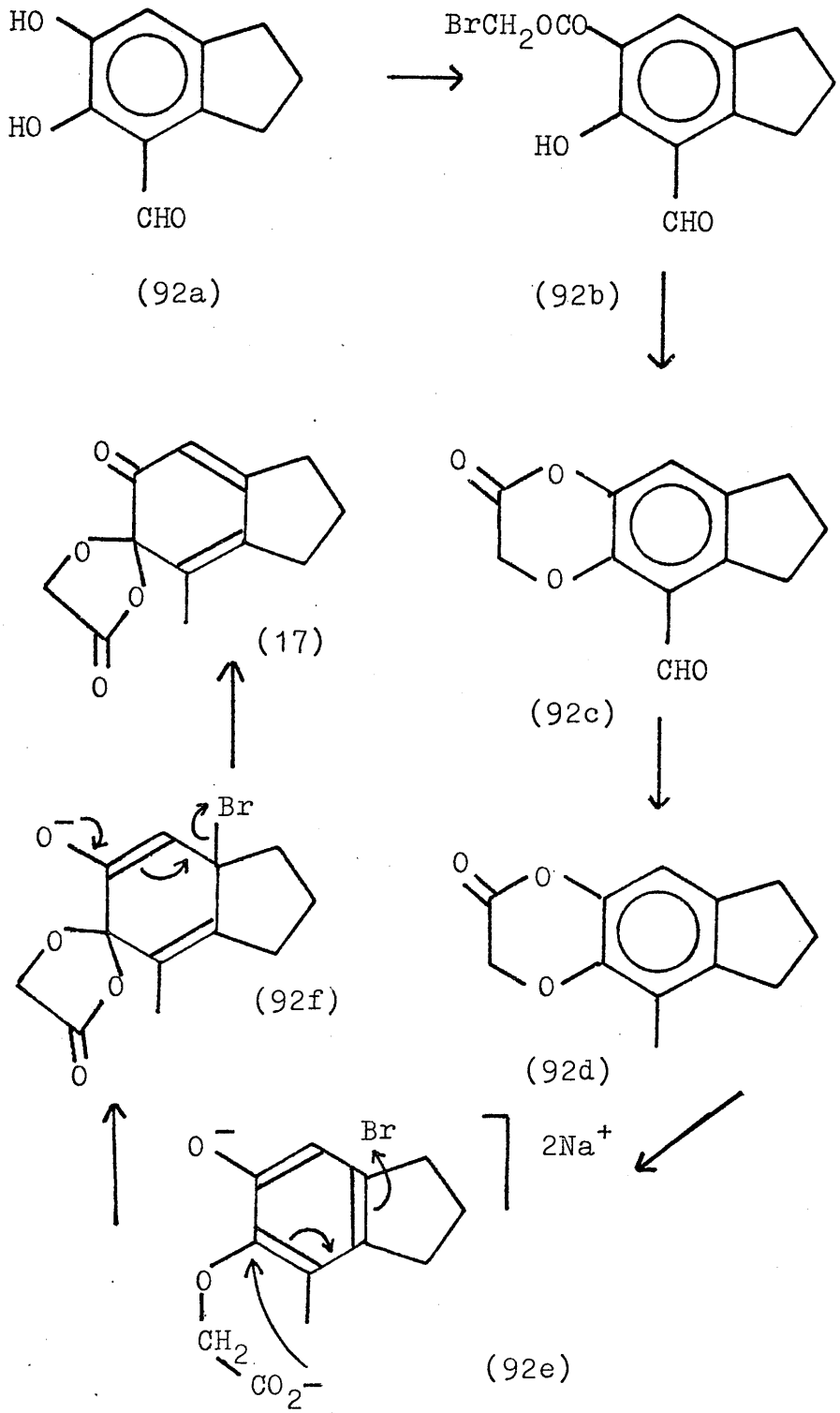


(89)



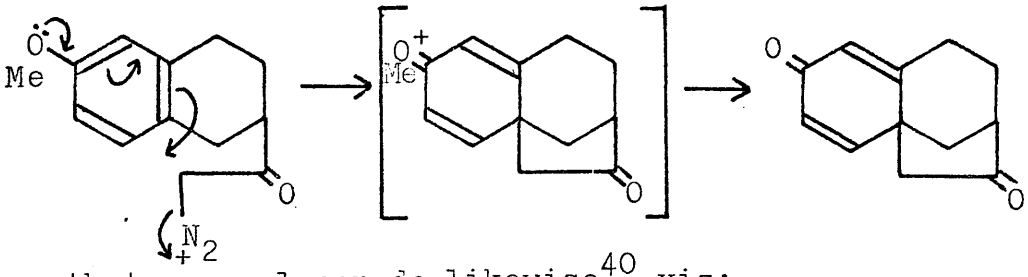
(90)

Scheme 2

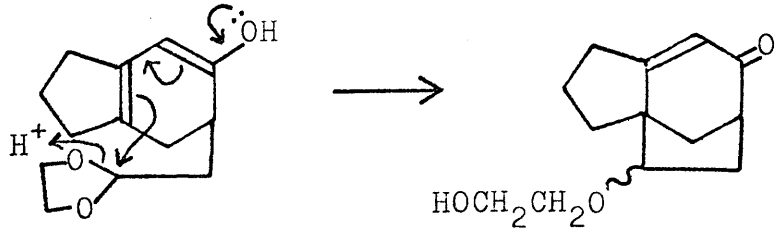

HO
HO
CHO
(92a)
BrCH2OCO
HO
CHO
(92b)
O
O
O
O
CHO
(92c)
O
O
O
(92d)
2Na+
O
Br
O
CH2
CO2−
(92e)
O
O
O
O
Br
(92f)
O
O
O
O
(17)

group due to the fact that the C-5 hydroxyl group is chelated to the aldehyde function. Etherification of this intermediate at C-5 was then effected in an intramolecular process to give the oxoethylenedioxy-indane(92c), the aldehyde function in which was then reduced to a methyl group affording(92d). Base treatment of the latter compound generated the phenoxide carboxylate dianion(92e) which in the presence of N-bromosuccinimide underwent bromospiro-lactonisation to give the spirolactone(17) via participation by the phenoxide anion as shown.

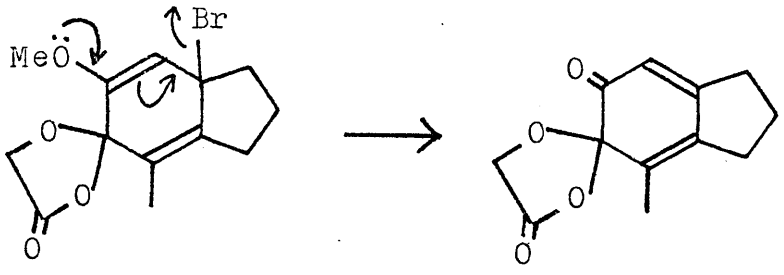
With evidence to hand that a methoxy group[39] can assist in expelling an electrophilic group in a ring forming reaction viz:



or that an enol can do likewise[40] viz:



it was felt that replacement of the phenoxide anion by a methoxy group in the mechanistic intermediate (92f) viz:



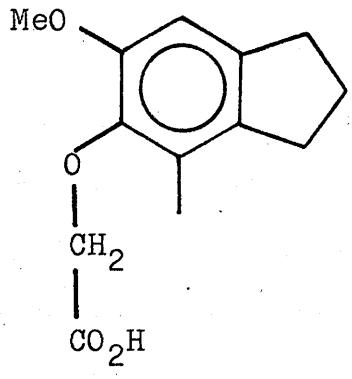
should bring about the same displacement of bromide ion to generate the monoprotected o-quinone(17), thus obviating the need to demethylate the oxyacetic acid derivative(93) prior to spirolactonisation.

4-Methyl-5-hydroxy-6-methoxyindane(91) was converted to its oxyacetic acid derivative(93). When this compound in a two phase system of aqueous sodium acetate and methylene chloride was treated with N-bromosuccinimide the spirolactone(17) was indeed produced in very good yield. The compound was relatively unstable and attempts to isolate it from its pale yellow solution in methylene chloride led to the formation of a cherry red oil . The NMR spectrum of the spirolactone thus prepared was was identical to that reported by Deslongchamps but the ultraviolet and infrared spectra were slightly different to those reported. viz:

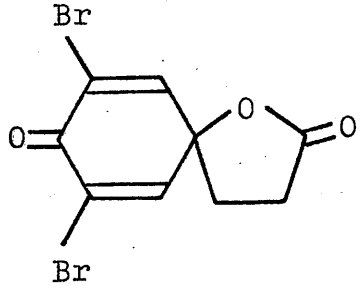
This work; λ_{max} 340nm; ν_{max} 1825, 1690, 1670 and 1610cm^{-1}

Deslongchamps: λ_{max} 355nm; ν_{max} 1790, 1665, 1640and 1600cm^{-1}

However, it was felt that this lack of identity could well due to an instrumental error on the part of Deslongchamps since the values reported for the infrared spectrum of(94)[41] were in close agreement



(93)



(94)

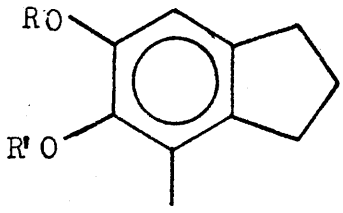
with our findings, viz: ν_{max} 1818,1701 and 1608cm^{-1}.

At this point it was felt that confirmation of the identity of the spirolactone (17) produced in this work should be made by synthesising the spirolactone (17) by Deslongchamp's method[8,9] which had also been applied by Wiesner,[11] very recently, to diterpenoid alkaloid syntheses.

Accordingly an attempt was made to demethylate 4-methyl-6-methoxy-5-indanyloxyacetic acid(93) using boron tribromide. The reaction was totally unselective and gave 4-methyl-5,6-dihydroxyindane(95) in good yield, identical with the product obtained by the similar demethylation of 4-methyl-5-hydroxy-6-methoxyindane (91).

Since (96) could not be obtained by this method selective bromoacetylation of 4-methyl-5,6-dihydroxyindane was investigated in the expectation that the less hindered C-6 hydroxyl group would react preperentially. The products of this reaction were starting indane(95),mono-esters(95a) and(97) and diester(98), which were not separated. This reaction contrasts with the similar reaction of 4-formyl-5,6-dihydroxyindane(92a) which affords the 6-bromoacetyl derivative(92b) cleanly.

In an attempt to repeat Deslongchamp's synthesis of 4-formyl-5,6-dihydroxyindane from 5,6-dimethoxyindane by bromination, and Grignard formation followed by reaction with ethyl orthoformate it was found that bromination of 5,6-dimethoxyindane(99)

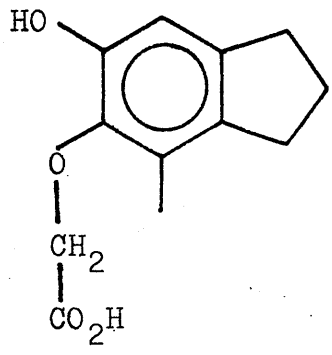


(95) R=R'=H

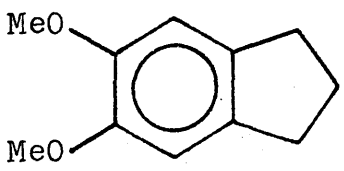
(95a) R=$BrCH_2CO$, R'=H

(97) R=H, R'=$BrCH_2CO$

(98) R=R'=$BrCH_2CO$



(96)

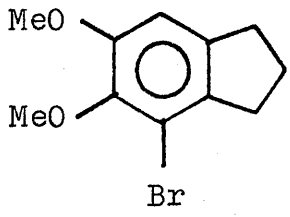


(99)

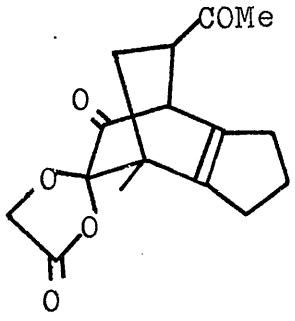
(obtained from the corresponding indanone(71) by catalytic hydrogenation or by zinc-amalgam reduction[42]) in carbon tetrachloride[8] led to a 1:1 mixture of 4-bromo-5,6-dimethoxyindane(100) and starting material. When chloroform was used as solvent in the presence of sodium acetate trihydrate[13] the yield of 4-bromo-5,6-dimethoxyindane was improved. However, difficulties in separating the two compounds at such an early stage of the synthesis led us to look for less arduous method for proving the formation of the protected o-quinone(17) .

Diels-Alder reaction of a freshly generated solution of the protected o-quinone(17) in methylene chloride with excess methyl vinyl ketone led to the formation of an adduct in good yield as a mixture of two stereoisomers (101) and (102) which were separated by TLC. Each isomer gave an identical infrared spectrum ($\nu_{max}(CCl_4)$ 1825,1740, and 1720 cm^{-1}, lit.[8] 1810,1740, and 1720 cm^{-1}) and lacked absorption in the ultraviolet spectrum as expected ; mass spectrometric analysis showed that both isomers had the same and correct molecular weight (290). From these findings the structure of the protected o-quinone (17) was substantiated.

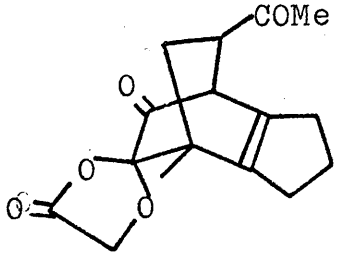
The result from this work show that 4-alkyl or 4-carboxyindanones bearing 5-hydroxy and 6-methoxy groups can be conveniently prepared by a modified hydroxymethylation procedure. It has also been shown that the 5,5-protected indane 5,6-quinone system can



(100)



(101)



(102)

be readily synthesised by a shorter and more efficient procedure than previously reported. It should now be possible to extend this work to the synthesis of gibbanes suitably functionalised to attempt the total synthesis of gibberellic acid.

EXPERIMENTAL

All melting points were determined on a kofler microscope hot-stage and are uncorrected.

Liquid film and KBr discs infrared spectra (IR) were recorded on a Perkin-Elmer 257 spectrophotometer.

Ultra -violet spectra were measured on a Pye-Unicam S.P. 800 spectrophotometer as solutions in 95% ethanol .

Nuclear magnetic resonance (NMR)spectra were obtained on a Varian T-60 spectrometer, using approximately 0.3M solution in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard. Coupling constants (J) were measured in hertz (Hz).

Thin layer chromoplates were spread with Merck Kieselgel G and preparative chromoplate were spread with Merck Kieselgel HF 254.

Mass spectra were determined on a G.E.C.-A.E.I.M.S.12 spectrometer, where figures quoted for molecular ions (M^+) refers to the m/e value.

All reactions were conducted in either Analar or purified technical solvents.[44]

Petroleum ether refers to the petroleum fraction with boiling range 60-80^{o}C .

Microanalyses were by Mrs Harkness and her staff.

Commercial polyphosphoric acid (PPA) was used unless otherwise stated.

3- Hydroxy -4- methoxy cinnamic acid (35)

It was prepared as described in the literature.[14,45]

A mixture of isovanillin (25g; 0.1644 mole), malonic acid (25g; 0.2403 mole) in pyridine (100ml) and piperidine (1ml) was heated at 80°C for 30 minute and at 100°C for 3 hour then heated under reflux for 30 minutes.The cold reaction mixture was poured into cold water (500ml) and acidified slowly with stirring with concentrated hydrochloric acid. The white crystalline product which precipitated was collected, washed with cold water (5X15ml) and dried to give (27g, 84.6%) m.p,233-235°C (lit.[14] 224-225°C for crude product).ν max. (KBr) 3405 (OH), 2540(OMe), 1665(acid C=O) and 1625cm^{-1} (C=C). δ (DMSO) 7.5 and 6.24 (1H,d,J=16Hz, olefinic H), 7.03 (3H,m, aromatic H) and 3.8 (3H,s, OMe).

β- (3-Hydroxy -4- methoxyphenyl) propionic acid(32)

A mixture of cinnamic acid (35) (10g), 5% Pd-C (1g)in acetic acid (250ml) was stirred under hydrogen at room temperature and atmospheric pressure for 5 hours. Removal of the catalyst by filtration and most of the acetic acid by evaporation under reduced

pressure allowed the dihydro acid to crystallise out on cooling . This was collected and dried to afford a (7.7g, 76.2%) m.p. 146°C (lit.[14] 146°C).
νmax. (KBr) 3400 (OH) (broad) and 1695 cm^{-1} (acid C=O)
δ(DMSO) 6.7(3H,m, aromatic H), 3.73 (3H,S,OMe) and 2.58 (4H,dt,methylenic H).

Methyl β (3-hydroxy-4-methoxyphenyl) propionate(44)

Prepared as described in the literature,[14] by refluxing a mixture of propionic acid(32)(7.8g) in 5% HCl/methanol (80ml) for 6 hours, After cooling to room temperature, ether (250ml) was added to the reaction mixture. The ether extract was washed with dilute sodium bicarbonate solution, and the bicarbonate layer further extracted with ether, the combined ether extracts were washed with brine, dried over magnesium sulphate and evaporated to give a white solid, recrystallization from ethyl acetate - petroleum ether gave the crystalline ester (6.95g, 82.4%) m.p. 94°C (lit.[14] 94°C).
νmax.(KBr) 3420 (OH), 2840 (OMe) and 1730 cm^{-1} (ester C=O). δ (DMSO) 6.65 (3H,m,aromatic H),5.59 (1H,s,OH),3.8(3H,s,OMe), 3.63 (3H,s,OMe) and 2.71 (4H,dt, methylene H).

Methyl β (2-hydroxymethyl -3-hydroxy -4- methoxy) propionate-phenyl boronate.(45)

A mixture of the ester (44) (10g; 0.0476 mole) benzeneboromic acid (14.16g; 0.1166mole) and propionic acid (500mg) in dry benzene (500ml) was stirred and refluxed under nitrogen with azeotropic removal of water for 1.5 hours.

The azeotropic removal of water was continued for a total period of 32 hours while paraformaldehyde portion (1.5g) was added at interval of 2 hours (reaction was followed by TLC; (silica gel/CH_2Cl_2: $(CH_3)_2CO$: AcOH = 7:2: 0.25). The cold reaction mixture was concentrated in vacuum and extracted with CH_2Cl_2, the CH_2Cl_2 extract was washed with water, dried over sodium sulphate, and evaporated to give quantitatively a white crystalline product (15.5g). A sample of it recrystallized from benzene/n-pentane had m.p.110-111°C. ν max (KBr) 2830 (OMe), 1730 (ester C=O), 800 and 700 cm^{-1} (aromatic C-H). δ ($CDCl_3$) 8.03 (2H, m, H_o), 7.47 (3H, m, $H_{m,p}$),6.81 (2H,s, aromatic H),5.23(2H,s, methylenic H)3.9(3H,s,OMe),3.68(3H,s,CO_2Me) and 2.65 (4H,m,methylenic H).λmax(ethanol)284 (ϵ4486) and 225nm (ϵ15090). (Found;C,66.44;H,6.00% ;M^+,326.$C_{18}H_{19}O_5B$ requires C,66.28;H,5.87%;M^+, 326).

(The excess benzene boronic acid recovered by salting the water from washing CH_2Cl_2 layer with

sodium chloride followed by ether extraction, ether extract was washed with brine, dried and evaporated).

Methyl β(2-hydroxymethyl-3-hydroxy-4-methoxyphenyl) propionate. (46)

A mixture of the borin ester (45) (10g), propylene glycol (50ml) and dry benzene (120ml) was refluxed for 3 hours. The benzene was evaporated and the resulting residue was extracted with n-pentane(toremove the boronic ester). water was added to glycol layer which was salted with sodium chloride and extracted with ether. The ether extract was washed with brine, dried over sodium sulphate and evaporated to give a pale yellow oil which crystalized on cooling (7.1g, 96.6%) m.p. 56-59°C . ν max.(CCl_4) 3618 (CH_2OH),3540(OH), and 1740cm^{-1}(ester C=O). δ ($CDCl_3$) 6.70(2H,s,aromatic H), 4.77(2H,s,methylenic H), 3.80(3H,s,OMe),3.62(3H, s,CO_2Me),and 2.75(4H,m,methylenic H).
(Found:C,59.75; H,6.79%; M^+,240. $C_{12}H_{16}O_5$ requries C,59.99; H,6.71% ; M^+,240).

The boronic ester in n-pentane was washed twice with 3N sodium hydroxide.The sodium hydroxide washes were acidified with concentrated hydrochloric acid,salted with sodium chloride and extracted with ether .

The ether extract was washed with brine dried over magnesium sulphate and evaporated to give benzeneboronic acid as shown by NMR and IR, total benzeneboronic acid recovered was 90% .

Methyl β-(2-hydroxy methyl -3,4-dimethoxyphenyl) propionate. (48)

A mixture of the benzyl alcohol (46) (250mg), methyl iodide (1ml) and K_2CO_3 (0.25g) in acetone (20ml), was heated under reflux. Methyl iodide portions (1ml) were added after 2 and 5 hours, the reflux was continued for 10 hours, (reaction was followed by TLC). After filtration to remove K_2CO_3 the acetone solution was evaporated under vacuum, water (20ml)was added and the mixture extracted with ether. The ether layer was washed with brine, dried over magnesium sulphate and evaporated to give a pale yellow oil (200 mg,75.7%). TLC showed one compound to be present .
νmax (CCl_4) 3620 (CH_2OH), 2840 (OMe) and 1740 cm^{-1} (ester C=O). δ ($CDCl_3$) 6.87 (2H,s, aromatic H), 4.72 (2H,s, methylenic H)3.85 (3H,s,OMe) 3.67(3H,s, CO_2Me) and 2.83 (4H,dt, methylenic H).
(Found: C, 61.55; H, 7.32% ;M^+254. $C_{13}H_{18}O5$ requires C, 61.40 ;H, 7.14% ;M^+, 254).

Methyl β-(2-carboxy -3,4- dimethoxyphenyl) propionate (49)

a- A solution of benzyl alcohol (48) (130mg) in acetone (2ml was added dropwise with stirring alternatively with 8N Jones reagent (20drops), to acetone (1ml), over a period of 1¼ hours,keeping the temperature below 8°C. The excess reagent was maintained for a further 3.5 hours after which time it was removed by the addition of isopropanol. Water was added and the solution was salted with sodium chloride and extracted with ethyl acetate. The ethyl acetate extract , was washed with brine, dried over magnesium sulphate and evaporated to give the acid as a yellow oil (106mg, 77%). TLC was showed one spot. ν max (CCl_4) 2845 (OMe), 1730cm^{-1} (broad)(acid and ester C=O). δ($CDCl_3$) 7.03 (2H,s, aromatic H), 3.97 (3H,s, OMe), 3.90 (3H,s, OMe), 3.70 (3H,s,CO_2Me) and 2.87(4H,m,methylenic H).
(Found: C,58.38;H, 6.19% ;M^+, 268. $C_{13}H_{16}O_6$ requries C, 58.20; H,6.01% ;M^+ 268)

8N Jones reagent.[46,47]

It was prepared by dissolving chromium trioxide (26.72g) in dilute sulfuric acid (40ml water + 23ml concentrated sulfuric acid) and then made up to 100ml with water.

b- Oxidation using Jones reagent + Ce(1V)ion.

A solution of alcohol (48) (.25mg) in acetone (3ml) was added to ammonium ceric sulphate (12.5mg). in acetone (1ml) alternatively with Jones reagent, keeping the temperature below 8°C over a period of one hour then the excess reagent was maintained for 3 hours the time at which the oxidation was completed (reaction tested by TLC after 30 minutes, 1½, and 2½ hours during the three hour period, which showed two comounds). On work up as in the previous experiment, the acid (49) was obtained.

Attempted oxidation of benzyl alcohol (46)

A solution of benzyl alcohol (46)(100mg) in acetone (2ml) was added with stirring to acetone (1ml) alternatively with 8N Jones reagent (10 drops) over a 45 minute, period, keeping the temperature below 8°C after which the excess reagent was maintained for 10 minutes. The excess reagent was destroyed with isopropanol, water was added and the aqueous solution was extracted with ether. The ether extract was washed with water, dried over sodium sulphate and evaporated to give a yellow residue (10mg). The aqueous layer was salted and reextracted with ethyl acetate then with chloroform. Both solvents were washed, dried and evaporated to give a yellow oil (33mg). The total product (43mg), was shown by TLC to be a complex mixture, ν max (CCl_4) 3540,1740,1715,1640 and 1610cm^{-1}

Opianic acid (3-Hydroxy-6,7-dimethoxyphthalide(54)[21]

Narcotine (20g) was dissolved in dilute sulphuric acid (water (300ml), concentrated sulphuric acid(17ml)) by heating and manganese dioxide (30g was added in portions with stirring over a period of 30 minutes. After filtration while it was hot, the filtrate was allowed to cool when , opianic acid crystalized out of the solution. The acid was filtered,washed with water and dried, the filtrate and the washes were extracted with ether, the ether extract washed with brine, dried over sodium sulphate and evaporated to give more opianic acid residue which was recrystallized from water. Total crystalline acid (5.75gm,52.8%) m.p.146-147°C. (lit.[48] 146-147°C). ν max.(KBr 3445 (OH),2848 (OMe) 1755(C=O) and 830 cm^{-1} (aromatic C-H). δ(DMSO) 7.38 (2H,s,aromatic H),6.57(1H,broad, OH), 3.87 and 3.80 (3H,s,OMe).

3- Acetoxy-6,7-dimethoxyphthalide(57)

A mixture of opianic acid (700mg), sodium acetate (300mg) and acetic anhydride (3ml), was stirred and heated at 150°C for 6.5 hours. The cold reaction mixture was poured into water, and the crystalline product which precipitated, was collected, washed with water and dried. Recrystalization from water gave white

crystals (350mg, 41.6%) m.p. 119-120°C (lit.[22] 120-121°C) ν max. (KBr) 2835 (OMe), 1787 (Lactone C=O) 1760 (C=O) and 830 cm^{-1} (aromatic c-H). δ ($CDCl_3$) 7.26 (1H,s,Ha), 7.10 (2H,s,aromatic H),4.12 and 4.12 and 3.93 (3H,s,OMe) and 2.17 (3H,s,CH_3).

Meconin acid (6,7-dimethoxyphthalide-3-acetic acid) (56)

1- It was prepared as described in literature.[22] A mixture of opianic acid (4g, 0.0190 mole),malonic acid (5g, 0.0480 mole), sodium acetate (2g)and acetic acid (30ml) was stirred and heated at 90°C and 140°C for 4 hours and 2 hours respectively.The reaction mixture was cooled to 80°C, malonic acid (2g) added and mixture stirred overnight . The reaction mixture was poured into cold water (80ml), and the white crystalline product which precipitated was collected, washed with water and dried. The filtrate was extracted with ethyl acetate,the ethyl acetate extract washed with brine, dried over sodium sulphate and evaporated to give crude lactone, recrystallization of which from water gave pure lactone (4.16g, 86%). m.p. 167-168°C (lit.[22], 167°C). ν max. (KBr) 2840 (OMe) , 1760 (lactone C=O), 1700 (acid C=O) and 835 cm^{-1} (aromatic C-H). δ (DMSO) 7.50, 7.30 (2H,AB,aromatic H),5.75(1H, m,Ha), 3.86 and 3.81 (3H,s, OMe) and 2.92 (2H,m,

methylenic H).

2- A mixture of opianic acid (0.4g, 0.0019 mole) and malonic acid (0.4g, 0.0038 mole) was dissolved in pyridine (5ml)and piperidine (0.2ml) added to reaction mixture, which was stirred and heated at 90°C for one hour, 100°C for one hour, and refluxed for 2½ hour. The cold reaction mixture was poured into ice water, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract, was washed with brine, dried over magnesium sulphate and evaporated to give a yellow oil (0.41g, 85%)which crystalized from water to give crystalline lactone (56) identical to a sample prepares as in (1)

Attempted reduction of lactone (56)

Unreacted lactone was shown by m.p. and IR

1- A mixture of lactone (56)(250mg) and 5% Pd/BaSO4 (60mg) in methanol (40ml), was stirred under hydrogen at room temperature and atmospheric pressure for 4 hours. The catalyst was removed by filtration and the methanol by evaporation to give unreacted lactone.

2- A mixture of lactone (56) (240mg) and 10% Pd/C (35mg) in acetic acid (30ml) was shaken under hydrogen at room temperature and 50lb/in^2 for 18 hours. Removal

of the catalyst by filtration and acetic acid by evaporation gave unreacted lactone.

3- A mixture of lactone (56) (240mg), 10%Pd/C (100mg) and 60% perchloric acid (12 drops) in acetic acid (30ml), was shaken under hydrogen at room temperature and 50lb/in^2 for 27 hours, catalyst was removed by filtration and the reaction mixture was poured into water, then extracted with ethyl acetate. The ethyl acetate extract was washed with brine , dried over sodium sulphate and evaporated to give unreacted starting material.

4- A mixture of lactone (56) (60mg), 10% Pd/C (30mg) and 60% perchloric acid (4 drops) in ethyl acetate (30ml), was shaken under hydrogen at 50lb/in^2 for 40 hours, catalyst was removed by filtration, and the ethyl acetate washed with brine, dried over sodium sulphate and evaporated to give unreacted lactone.

5- A mixture of lactone(56) (100mg) and Zn/Hg (prepared from a mixture of zinc wool (2g) and mercuric chloride (200mg), stirred with concentrated hydrochloric acid (0.25ml) and water (5ml)for 45 minutes. The acid was decanted and Zn/Hg washed with water), in toluene (2ml), concentrated hydrochloric acid (4ml) and water (2ml) was refluxed for 72 hours , concentrated hydrochloric acid portions (0.3ml)

were added after 5,20,26,45,50 and 54 hours, Zn/Hg (prepared as above from 1g zinc) and concentrated hydrochloric acid (2ml) was added after 30 hours. The reaction mixture was filtered while hot, and zinc residue washed with hot water. The filtrate was cooled to room temperature and extracted with ethyl acetate. The ethyl acetate extract, washed with brine, dried over sodium sulphate and evaporated. The residue was unreacted starting material

2- Carboxy-3,4- dimethoxy cinnamic acid (58)

It was prepared as described in literature.[23]

Lactone (56)(3g) and 50% potassium hydroxide (20ml) were mixed in a porcelain dish, and evaporated to dryness on a boiling water bath. The residue was dissolved in water (20ml) and evaporated again to dryness and the residue taken up in water (40ml). This was acidified with cold 20% hydrochloric acid with cooling. The white solid which precipitated was collected, washed with water and dried to give (2.4g, 80%). Recrystalization from water gave needles m.p. 183-185°C (lit.[23] 178-180°C).

νmax (KBr) 1720 and 1685 (acid C=O), 1625(C=C), 970 (HC=CH) and 812 cm^{-1} (aromatic C-H).

δ(DMSO) 7.60 and 6.23(1H,d,5=16H2,olefinic H)7.50

and 6.97 (1H,d,J=8Hz, aromatic H), 3.85 and 3.73 (3H,s, OMe).

λmax.(EtOH) 221 (ϵ 12881), 240 (ϵ 11695) and 305nm (ϵ 16610).

β-(2-Carboxy-3,4-dimethoxyphenyl) propionic acid (53)

a- From cinnamic acid (58)

(1)It was prepared as described in the literature by stirring a mixture of cinnamic acid (58)(300mg),10% Pd/$CaCO_3$ (150mg) and sodium bicarbonate solution (0.8g) 10ml water), under hydrogen at room temperature and atmospheric pressure for 30 hours. The catalyst was removed by filtration, and washed with water, the aqueous solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulphate and evaporated to give the acid as a colourless oil which solidified to a white crystalline mass (280mg , 92%), m.p. 125-127^{o}C (lit.,[23] 85^{o}C, after keeping in desiccator 125-127^{o}C) ν max(KBr) 1700(broad) (acid C=O) and 830 cm^{-1} (aromatic C-H). $\delta(CDCl_3)$ 11.30 (2H,s,CO_2H), 6.98(2H,s,aromatic H)3.92 and 3.85(3H,s, OMe) and 2.87(4H,m,methylene H).λ max. (EtOH) 219(ϵ 8559) and 281nm(ϵ 1949).

(2) A mixture of cinnamic acid (58)(1.2g), 5% Pd/C (120mg) in sodium carbonate solution (3.2g/ 40ml water) was stirred under hydrogen at room temperature and atmospheric pressure for 5 hours. On work up as in (1) acid (53) was obtained (1.06g,88%).

b- From the lactone (56)

A mixture of lactone (56)(0.5g) and 50% potassium hydroxide solution (3ml) in a porcelain dish was heated and evaporated to dryness.The residue was dissolved in water (3ml) and evaporated again to dryness on a boiling water bath,and the residue was taken up with water(15ml), 5% Pd/C (60mg) was added and the mixture was stirred under hydrogen at room temperature and atmospheric pressure for 5 hours. Work up as in (a) gave product (410mg, 81.3%)which was identical to the above preparation.

c- From the ester (49).

A mixture of the ester (49)(70mg) and 1N sodium hydroxide (25ml),was refluxed for one hour, and stirred at room temperature overnight. The reaction mixture was poured into water,and acidified with concentrated hydrochloric acid with cooling. The aqueous solution was extracted with ethyl acetate, the ethyl acetate extract was washed with brine,dried

over magnesium sulphate and evaporated to give the diacid (53) (45mg, 67.8%).

4-Carboxy-5,6-dimethoxyindanone (29)

A mixture of the acid (53)(1.8g) and poly-phosphoric acid (prepared from a mixture of phosphoric oxide (16g) and phosphoric acid (8ml), the mixture was stirred at 150°C for 1¼ hour, then was cooled to the reaction temperature) was stirred and heated at 75-80°C for 2 hours. The reaction mixture was poured into ice water, stirred for one hour and left to stand overnight, then extracted with (ether:benzene:chloroform, 8:1:1). The solvent mixture was washed with brine, dried over sodium sulphate and evaporated to give yellow crystalline indanone (1.2g,71.8%),m.p. 169-170°C . ν max. (KBr) 1720 (ketone C=0), 1675 (acidC=0) and 830cm^{-1} (aromatic C-H). δ (DMSO)7.30(1H,s,aromatic H),3.90 and 3.87(3H,s,OMe),3.10 and 2.60(2H,m,methylenic H). λ max (EtOH) 227 (ϵ 14882), 249(ϵ 8425) and 322 nm (ϵ 5984). (Found: C,60.80;H,5.00%;M^+ 236. $C_{12}H_{12}O_5$ requires C, 61.01; H,5.12% ; M^+ 236)

4-Carboxy -5,6-dimethoxyindane (60).

A mixture of indanone(29) (600mg),30%Pd/C (300mg)and 60% perchloric acid (0.24ml) in acetic acid (36ml), was stirred under hydrogen for 8 hours. The catalyst was removed by filtration and washed with ethyl acetate, brine was added to the resulting solution and the ethyl acetate layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined ethyl acetate extract was washed with brine, dried over sodium sulphate and evaporated to give a pale yellow oil (560mg, 99%) which solidified slowly. A sample of it, sublimed at 75-80°C (0.1mm), had m.p. 86-88°C. ν max. (KBr) 1685 (acid C=O) and 840cm^{-1} (aromatic C-H). δ(acetone) 7.1 (1H,s, aromatic H), 3.88 and 3.87 (3H,s,OMe) 2.92 (4H,m,methylenic H_a) and 2.0(2H,m,methylenic H_b). λmax. (EtOH) 222 (ϵ 12444) and 293 nm(ϵ 2888). (Found: C, 64.70;H,6.59% ;M^+,222. $C_{12}H_{14}O_4$ requires C, 64.85;H, 6.35%; M^+, 222).

4-Carboxy-5-hydroxy-6-methoxyindane (61)

To a solution of dimethoxy indane (60)(250mg) in methylene chloride(50ml) cooled to -76°C, boron trichloride (3ml) was added dropwise with stirring and the reaction mixture was stirred at this temperature

for 3 hours and at room temperature for 2 hours, then left to stand overnight. The reaction mixture was poured into ice water, stirred for 30 minute and the methylene choride layer separated. The aqueous layer was extracted with ether, the combined extracts were washed with brine, dried over sodium sulphate and evaporated to give the phenol (205mg,86%). m.p. 195-197°C. ν max(KBr)3400(OH)1640(acid C=O)and 850cm^{-1}(aromatic C-H).δ(acetone)7.12(1H,s,aromatic H), 3.83(3H,s,OMe) 3.03(4H,m,methylenic H_a) and 2.05 (2H,m,methylenic H_b) (Found:C,62.96;H,5.53%; M^+,208 $C_{11}H_{12}O_4$ requires C, 63.45; H,5.81%; M^+, 208).

4- Methoxycarbonyl-5-hydroxy-6-methoxyindane (62)

The acid (61) (160mg) in 5% HCl/methanol (10ml) was refluxed overnight. To the cold reaction mixture ether was added and the mixture was washed with sodium bicarbonate solution, the aqueous layer was extracted with ether. The combined ether extracts were washed with brine, dried over sodium sulphate and evaporated to afford the crystalline ester (145mg,84.9%)m.p.76-78°C. νmax.(CCl_4) 3560 (OH) and 1675 cm^{-1} (esterC=O). δ($CDCl_3$) 6.98(1H,s,aromatic H),3.95 and 3.88(3H,s,OMe), 2.97(4H,m,methylenic H_a) and 2.10 (2H,m,methylenic H_b). (Found;C,64.61;H, 6.51%; M^+, 222. $C_{12}H_{14}O_4$ requires C, 64.85;H, 6.35% ;M^+222).

Attempted preparation of oxyacetic acid (63) from phenol (62).

a- A mixture of indane (62) (30mg, 0.00013 mole)in pyridine(10ml)was stirred at room temperature for 30 minutes while chloroacetic acid (38mg, 0.000395 mole) was added and stirring continued overnight. Water (30 ml) was added and reaction mixture acidified with concentrated hydrochloric acid with cooling, more water was added and extracted with ether. The ether extract was washed with brine, dried over sodium sulphate and evaporated to give an oily residue NMR and IR showed that it was a mixture of starting indane and chloroacetic acid. The crude oil was redissolved in ether, and washed with dilute sodium bicarbonate solution then with water and dried over sodium sulphate. Evaporation of solvent gave unreacted starting material.

b- A mixture of indane (62) (30mg, 0.00013 mole), chloroacetic acid (38mg, 0.00039 mole) in water (2ml) was stirred at room temperature, 0.5% NaOH(2ml) was added dropwise, more water(4ml) was added and the reaction mixture was heated at 90°C for one hour, then cooled to room temperature. The reaction mixture was poured into water (8ml) and acidified with 20% hydrochloric acid , and extracted with ether. The ether extract was washed with water, dried over sodium

sulphate and evaporated to give acid of starting ester as shown by NMR.

Ethyl α- cyano-β- veratrylacrylate(66)

This was prepared as described in the literature

To veratraldehyde (50g, 0.3012 mole)dissolved in ethyl cyano-acetate (34 g, 0.4197 mole), piperidine (1ml) was added, and the mixture was heated on a water bath for 30 minutes by which time a solid mass of the product was obtained. After filtration and recrystalization from ethanol, the compound was obtained as needles (69g, 87.8%), m.p. 153-155°C. (lit.[26] 153-155), ν max.(KBr) 2840(OCH_3), 2220(CN) and 1715cm^{-1} (ester C=O), δ($CDCl_3$) 8.2 (1H,s, Hd), 7.85(1H, d, J=2 H 2,Hc) 7.53(1H,q,J=8 and 2H2,H_b)7.0 (1H,d,J=8H2,H_a), 4.4(2H,q,J=7Hz,methylene He),4(6H, s,overlapping OMe groups), 1.4 (3H,t,J=7 Hz, methyl Hf), λ max.244(ε 8772) and 360 nm (ε 20000).

Ethyl α ,β-dicyano -β- veraltrylacrylate(67)

A mixture of ethyl α-cyano -β-veraltrylacylate (30g), and KCN (17.5g) in methanol (100ml) was heated on a steam bath for 40 minutes with occasional shaking to get a clear red solution. The cold solution was

acidified (with cooling) with 50% hydrochloric acid,more water was added (15 ml) and the reaction mixture left to stand overnight. The white solid was collected,washed with cold aqueous ethanol (2:8, methanol:water)4X20ml and dried to give crystalline product (29.5g,89%). Recrystalliztion from methanol-water, m.p.88-90°C(lit.[27] 93-95°C) νmax.(KBr) 2840 (OMe) 2240(CN) and 1750cm^{-1} ester (C=O).λmax. (EtOH) 231(ϵ 8640)and 279 (ϵ 3398). δ($CDCl_3$) 6.95(3H,s,aromatic H)4.53 and 3.86(1H,d,$H_{a,b}$) 4.35 (2H,q,J=7Hz, CH_2CH_3),3.90 and 3.87(3H,s,OCH_3). and 1.32 (3H,t,J=7Hz, - CH_2CH_3).

3,4-Dimethoxyphenyl succinic acid (68)

This was prepared as described in the literature[27] by refluxing a mixture of ethyl α,β-dicyano-β- veratrylacrylate(15g) with concentrated hydrochloric acid (80ml) for 4 hours to give on cooling crystalline product (11g, 83.1%). Recrystalization from aqueous methanol gave product, m.p. 126-128°C ,which after keeping in a vacuum desiccator over sulphuric acid gave m.p. 173°C (lit.[27] 126 -128°, 172 - 174°C).νmax.(KBr) 2840(OMe) ,1710cm^{-1} (acid C=O). δ(acetone) 6.95(3H,m,aromatic H), 4.10 (1H,t,H_c), 3.84(3H,s,OMe), 3.80(3H,s,OMe), 3.20(1H, q,H_a) and 2.65(1H,q,H_b) λmax. 233(ϵ 1822) and 281nm

(ε 4576).

5,6-Dimethoxy-3-oxoindane-1-carboxylic acid (65)

A mixture of 3,4-dimethoxyphenyl succinic acid(68)(10g) polyphosphoric acid (100g) was stirred and heated at 80 - 85°C for 2 hours after which time the reaction mixture was poured into ice water and stirred for one hour and extracted with ethyl acetate. The ethyl acetate extract was washed with brine,dried over magnesium sulphate, and evaporated to give the indanone (65)(7.2g, 78%) . Recrystallization from methanol gave white needles m.p. 189 - 190°C (lit.[28] 190 - 190.5°C) . ν max.(KBr) 2840 (OMe), 1730 (acid C=O),and 1650cm^{-1} (C=O).δ(DMSO) 7.20(1H,s,aromatic H), 7.10(1H,s, aromatic H), 4.20(1H,t,H_a), 3.96(3H,s,OMe), 3.90(3H, s,OMe) and 2.83(2H,d,methylenic H).λ max.(EtOH) 233 (ε 12142), 270(ε 6571) and 312nm(ε 5500).

When a mixture of acid (68) and polyphosphoric acid was stirred at 85°C for one hour,work up gave a mixture of indanone (65) and starting acid (68). The mixture was identified as follow , excess diazomethane in ether was added to the product mixture in ether:dioxane over 20minutes and the reaction mixture was stirred at room temperature overnight, washed with 2% sodium bicarbonate and water, dried

over magnesium sulphate and evaporated to give a mixture of the esters (65a) and (68a), which were separated by TLC (silica, ethyl acetate : petroleum ether, 1:1) to give 2:3 (yellow oil)indanone (65a): (pale yellow oil) ester (68a). Indanone (65a) νmax. (CCl_4) 2840(OMe), 1740(ester C=O), 1715(C=O) and 860cm^{-1}(aromatic H). δ($CDCl_3$) 7.18,7.08(1H,s,aromatic H), 4.22(1H,m,H_a), 3.98(3H,s,OMe), 3.91(3H,s,OMe), 3.80(3H,s,OMe) and 2.97(2H,d,methylenic H). Ester (68a) ν max.(CCl_4) 2835(OMe) and 1745cm^{-1}(ester C=O). δ($CDCl_3$) 6.80(3H,s,aromatic H), 4.08(1H,m,H_a) 3.85(6H,s,OMe), 3.65(6H,s,CO_2Me) and3.17, 2.63(1H, m,$H_{b,c}$).

The acid (68)(0.5g) was esterified with diazomethane in dioxane:ether, using the procedure above, to give the ester (68a) (0.462g, 83.7%), identical with the ester which was obtained from the separation of the esterified product mixture, as shows by NMR and IR.

Preparation of diazomethane [49]

A mixture of ether (150ml), ethyl digol (25ml) and 30% sodium hydroxide (30ml) was cooled to 0^{o}C, and nitrosan(9g) was added in one portion, shaked gently and distilled into ice cold receiver containing dry ether to cover the tip of the adapter,

about 100ml of ether was distilled giving 0.03-0.05 mole diazomethane.

Attempted chloromethylation of indanone(65)[12,50,51]

a- To a mixture of indanone (1g,0.0042 mole), paraformaldehyde., and zine chloride in concentrated hydrochloric acid and acetic acid, hydrogen chloride gas was passed through the reaction mixture with heating, then at room temperature. Cold water (60ml) was added and the mixture extracted with chloroform. The chloroform extract was washed with brine, dried over magnesium sulphate and evaporated to give unreacted indanone as shown by m.p. and NMR.

	$(CH_2O)_n$ g/mole	Z_nCl_2 (g)	HCl/AcOH (ml)	temp.°C	time (hr)	room temp. (hr)
1-	0.27, 0.009	0.23	0.7/2.5	40-45	8	overnight
2-	0.27, 0.009	0.4	2/3	40-45	8	40
3-	0.5/ 0.0168	0.52	1.5/3	40-45	8	—
4-	0.27	0.4	2/3	65-70	40	—

b- A mixture of indanone (0,5g) and paraformaldehyde (0.13g) in concentrated hydrochloric acid (1.5ml),

acetic acid (1ml) and phosphoric acid (0.5ml) was stirred and heated at 60°C for 18 hours, the reaction mixture was then poured into cold water (100ml) and extracted with chloroform. The extract was washed with brine, dried over magnesium sulphate. Removal of the solvent gave unreacted starting material.

c- Indanone (0.5g, 0.021 mole) and paraformaldehyde (78mg, 0.0025 mole) in concentrated hydrochloric acid(5ml), was shaken on a mechanical shaker at R.T for 72 hours then stirred at 50°C for 115 hours after which time the reaction mixture was poured into cold water and extracted with chloroform. The $CHCl_3$ extract was washed with brine dried over magnesium sulphate and evaporated to give starting material.

d- A mixture of indanone was (0.5g, 0.0021 mole), monochloromethyl ether (0.425g, 0.00525 mole) and acetic acid (3ml) was stirred and heated at 50-52°C for 24hours and at R.T. overnight. The reaction mixture was poured into ice water stirred for 30 minutes and extracted with ethyl acetate. The extract was washed with brine and dried.Removal of the solvent gave starting material . There was no reaction when the reaction mixture was heated for 40 hours.

Monochloromethyl ether [52]

To formalin (100.9ml, 37.8g, 1.26 mole) and methanol (66.3 ml) , a rapid stream of HCl gas (generated from concentrated hydrochloric acid and concentrated sulphuric acid)[53,54] was passed into the mixture which was cooled with running water for 6 hours. The chloromethylether was separated from the aqueous layer, which was salted with $CaCl_2$, to give more ether which was separated. The combined ether was dried over $CaCl_2$, and distilled at 57-59°C.

Attempted selective demethylation of indanone (65)

A mixture of indanone(65) (400mg) in dry methylene chloride(60ml) was cooled to -76°C, and excess boron trichloride(5ml) added dropwise with stirring. The stirring was continued at this temperature for 4 hours and at room temperature overnight. The reaction mixture was then left to stand at room temperature for one week. The reaction mixture was poured into ice water then stirred for one hour, after which the methylene chloride layer was separated and the aqueous layer extracted with ether . The combined solvents, were washed with brine, dried over sodium sulphate, and evaporated to give

unreacted indanone as shown by NMR, and m.p.

β-(3,4-dimethoxyphenyl)-propionic acid (75)

A mixture of 3,4-dimethoxy cinnamic acid (20g) and 5% Pd/C (2g) in acetic acid (500ml) was stirred under hydrogen at room temperature and atmospheric pressure for 4 hours. The catalyst was removed by filtration and the acetic acid by evaporation to give colourless crystalline acid (75) (18.8g, 93%), m.p. 97°C (lit,[42] 97°C) ν max.(KBr) 2330(OMe), 1695(acid C=O), 840 and 805cm^{-1} (aromatic C-H). $\delta(CDCl_3)$ 6.65 (3H,s,aromatic H), 3.78(6H,s,OMe) and 2.93(4H,m, methylenic H).

5,6-dimethoxyindanone (71).

It was prepared as described in literature[55] A mixture of propionic acid (75)(20g) and polyphosphoric acid (prepared from 160g P_2O_5 and 100ml phosphoric acid), was stirred and heated at 65°C for 35 minutes. The reaction mixture was poured into ice-water, stirred for one hour and extracted with ether. The ether extract was washed with sodium bicarbonate, and water , and dried over sodium sulphate and

evaporated to give yellow crystalline indanone(71) (16.9g, 92.5%) m.p. 118-120°C (lit. 117-119°C,[55] 118.8-119.5°C[56]) νmax. (KBr) 2840(OMe), 1700(ketone C=O)and 850cm^{-1} (aromatic C-H). δ ($CDCl_3$) 7.17, 6.90 (1H,s,aromatic H), 3.97,3.90(3H,s,OMe)and 3.10,2.70 (2H,t,methylenic H).

Attempted selective demethylation of indanone(71)

A mixture of indanone (71)(80mg) in dry methylene chloride(20ml) was cooled to -76°C. BCl_3 (1ml) was added dropwise with stirring, and mixture was stirred for 2 hours at this temperature, then left to stand overnight. The reaction mixture was poured into ice-water and stirred for one hour. The methylene chloride layer was separated, and the aqueous layer extracted with methylene chloride. The combined solvent was washed with brine , dried over sodium sulphate and evaporated to give unreacted indanone as shown by NMR, IR, and m.p.

β(2-Hydroxymethyl-3-hydroxy-4-methoxypheny) propionic acid - phenyl boronate(43)

A mixture of the acid (32) (1g, 0.0051mole), benzeneboronic acid (1.55g, 0.013mole) and propionic acid (37mg, 0.0005mole) in dry benzene (50ml), was stirred and refluxed under nitrogen with azeotropic removal of water for 1 hour.

Paraformaldehyde portions(1.3g) was added at interval of 2 hours, benzeneboronic acid (0.31g) was added after 23 hours, and the reflux was continued for 32 hours (reaction followed by TLC). The cold reaction mixture was concentrated and extracted with CH_2Cl_2, CH_2Cl_2solution was washed with water (exess benzeneboronic acid recovered by ether extraction of the salted water from washing CH_2Cl_2), dried over sodium sulphate and evaporated to give a white crystalline residue (1.4g,88.6%). A sample of the product recrystalized from ethyl acetate-petroleum ether had m.p. 161-162°C.

νmax. 2840(OMe), 1710(acid C=O), and 805, 705 cm^{-1} (aromatic C-H). δ(DMSO) 7.80(2H,m,aromatic H_o), 7.35 (2H,m, aromatic $H_{m,p}$), 6.80(2H,s,aromatic H), 5.17 (2H,s,methylenic H)3.8(3H,s,OMe) and 2.54 (4H,m, 2methylenic H). λmax (ethanol) 282 (ϵ 3229), 223nm (ϵ 17604).

(Found; C, 65.67 ; H,5.31% ;M^+, 312. $C_{17}H_{17}O_5B$ requires C,65.41;H,5.49% ; M^+, 312).

4-Hydroxymethyl-5-hydroxy-6-methoxyindane-1-one - phenyl boronate (76)

A mixture of acid (43)(200mg) and poly-phosphoric acid (12g) was stirred and heated at 90°C for 1.5 hours after which the reaction mixture was poured into ice-water and stirred for one hour. The reaction mixture was extracted with chloroform, the extract was washed with sodium bicarbonate, and brine, then dried over sodium sulphate and evaporated to give a yellow oil (148mg,79%) which crystalised on leaving overnight , recrystalization from ethyl acetate-Pt. 60-80°C afforded the indanone as pale yellow crystals m.p. 126-128°C . ν max(CCl_4) 2840 (OMe), 1700 (ketone C=O), 855 and 695cm^{-1}(aromatic C-H). δ($CDCl_3$) 7.15 (5H,m , aromatic H), 6.87 (1H,s, aromatic H,), 3.97(2H,s, methylenic H_a),3.80 (3H,s, OMe) and 2.73 (4H,m, methylenic H_b). λ max (EtOH) 233 (ϵ 22 205), 276 (ϵ 10588) and 313 nm (ϵ 10514). (Found: C,69.16; H, 5.38% $C_{17}H_{15}O_4B$ requires C, 69.42, H,5.14%).

o-hydroxymethylphenol - phenyl boronate(77)

It was prepared as described in the literature[17]

A mixture of phenol (1.88g;0.02 mole),

benzeneboronic acid (2.43g, 0.02mole) and propionic acid (148mg, 0.002mole) in dry benzene (50ml)was refluxed with separation of water for 10 hours.Paraformaldehyde portions(1g) were added every 1.5 hours and benzeneboronic acid (0.488g) after 3 hours. The reaction mixture was cooled to room temperature,concentrated under vacuum and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulphate and evaporated to give a colourless oil (77) (3.9g,92.8%)which crystalized slowly m.p. 35-37°C(lit.[17] 36-38°C).νmax(KBr) 755 and 700cm^{-1} (aromatic C-H) δ($CDCl_3$)7.97 (2H,m,o-aromatic H), 7.43 (3H,m,m,P-aromatic H),7.05(4H,m,aromatic H) and 5.14(2H,s,methylenic H).

(2-Hydroxymethyl-3-hydroxy-4-methoxyphenyl) propionic acid (80)

a. From borin (43)

(1) A mixture of borin (43)(200mg)and propylene glycol (1ml) in dry benzene (4ml) was refluxed for 3 hours. The benzene was removed by distillation and the residual glycol was extracted with n-pentane, water was added to the glycol layer, which was then salted with NaCl and extracted with ether. The ether extract was washed with brine, dried over magnesium sulphate and evaporated to give a crystalline residue (145 mg).

which on recrystalization from ethyl acetate - petroleum ether afforded colourless crystals (139mg, 96%) m.p. 147-148°C νmax (KBr) 3550 (CH_2OH) 3430 (OH)(broad) 2830(OMe)and 1705cm^{-1} (acid C=O). δ(DMSO) 6.83 and 6.83 and 6.61 (2H, q, J=8Hz, aromatic H) 4.75(2H,s,methylenic H) 3.77 (3H,s,OMe) and 2.65 (4H,m, methylenic H) λmax. (EtOH) 223 (ϵ6136) and 286nm (ϵ2803). (Found: C,58.60; H,6.32% M^+, 226. $C_{11}H_{14}O_5$ requires C,58.40;H.6.24%; M^+,226).

(2) A solution of borin (43) (1g) in water (60ml) was stirred and refluxed for 2 hours, then cooled to room temperature and extracted with ether. The ether extract was washed with sodium bicarbonate and brine and dried over magnesium sulphate and evaporated to give benzene boronic acid (0.15g) as shown by NMR and IR The bicarbonate layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with brine dried over magnesium sulphate and evaporated to give benzyl alcohol(80), (0.3g, 41.3%)

b. From borin (45).

(1) A mixture of borin ester (45) (450mg) and propyylene glycol (1.8ml) in dry benzene (15ml) was refluxed for 3 hours . The benzene was removed by distillation, and the residual glycol was washed with n-pentane.Methanol (10ml) and 3 N aqueous NaOH(5ml)

was added and the reaction mixture was refluxed for 4 hours, and left to stand at room temperature overnight. Methanol was removed under vacuum, and the aqueous layer was washed with ether, water(5ml) was added to the aqueous layer which was then acidified with concentrated hydrochloric acid with cooling, then salted and extracted with ether.The ether extract was a mixture of two compounds.The major one was the desired benzyl alcohol (80) as shown by TLC. The ether extract was wshed with 5% sodium bicarbonate solution, the bicarbonate washes, were acidified with concentrated hydrochloric acid with cooling and extracted with ether. The ether extract was washed with brine,dried over magnesium sulphate and evaporated to give a crude oil (180mg), shown by TLC to be a mixture of benzyl alcohol(80),and traces of acid(32). The oil solidified slowly,and was recrystalized from ethyl acetate-petroleum ether, to give crystalline alcohol (80).

(2) A mixture of borin (45)(5g),and propylene glycol (24.5ml) in dry benzene (50ml) was refluxed for 2.5 hours,after which time the reaction mixture was cooled to room temperature ,and water(20ml) and benzene(250ml) were added. The benzene layer was separated,and the aqueous layer was further extracted with benzene.(The benzene extract contained the hydroxymethyl ester(46) and the propylene glycol

boronic ester as was shown by TLC). The combined benzene extract was washed with 3N sodium hydroxide solution(2x50ml). The sodium hydroxide layer on acidification(with cooling) afforded a white crystalline material which was filtered off,washed with water and dried .After recrystalization from methanol, this material was shown to be identical to the borin acid (43)(2.5g) by NMR,m.p.and IR. The filtrate was extracted with ether, which was then washed with sodium bicarbonate solution,and brine and dried over sodium sulphate. Evaporation gave benzeneboronic acid (0.94g) as shown by NMR, IR and TLC. The bicarbonate washing was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with brine and dried . TLC showed the presence of the hydroxymethyl acid (80) and traces of acid (32).

β(2-Methyl-3-hydroxy-4-methoxyphenyl) propionic acid (83).

a. From benzyl alcohol (46).

A mixture of benzyl alcohol(46)(11.63g), 10% Pd/C (3.5g) and 60% perchloric acid (3.2ml) in ethyl acetate (500ml) was stirred under hydrogen at room temperature and atmospheric pressure. When the

hydrogen absorption stopped, the catalyst was removed by filteration and the ethyl acetate solution was washed with brine, dried over sodium sulphate, and evaporated to give a yellow oil shown by TLC to be a mixture of the ester (86) and the corresponding acid.

The crude product from the hydrogenolysis was stirred and heated on a oil bath at 75-80°C for 4.5 hours with 15% hydrochloric acid (350 ml) and tetrahydrofuran , ratio 1:1. The tetrahydrofuran was removed under vacuum and the aqueous solution extracted with ethyl acetate. The ethyl acetate extract was extracted with dilute sodium bicarbonate solution , the bicarbonate solution acidified with concentrated hydrochloric acid , salted with sodium chloride and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulphate and evaporated to give a yellow reddish oil which solidified on cooling to a yellow solid (8.5g,83.5%) . Recrystalization from methanol-water , gave pale yellow crystalline acid (83),m.p. 134-136°C. ν max(KBr)3540 (OH), 2835 (OMe) and 1705cm^{-1} (acid C=O). δ(acetone) 6.68 (2H,s,aromatic H),3.80 (3H,s,OMe), 2.70 (4H,m,methylenic H) and 2.20(3H,s, CH_3). λmax(EtOH) 225 (ϵ 9895) and 280 nm (ϵ 2658). (Found: C,62.60;H,6.53%. $C_{11}H_{14}O_4$ requires C,62.84; H,6.71%).

b. From benzyl alchol (80)

(1) A mixture of benzyl alcohol (80) (140mg), 10% Pd/C (60mg) and 60% perchloric acid (5 drops) in ethyl acetate (30 ml) was shaken under hydrogen at 50 lb/in^2 overnight. The catalyst was removed by filtration and the ethyl acetate washed with brine, dried over magnesium sulphate and evaporated to give an oily residue, TLC indicated that the oil was mainly desired product contaminated with some starting material.

(2) A mixture of benzyl alcohol (80) (280 mg),10% Pd/C (120mg)and 60% perchloric acid (10 drops) in ethyl acetate (80ml) was shaken under hydrogen at 50 lb/in^2 for 45 hours. On work up as in (1), a yellow oil was obtained which was a mixture of two compounds as shown by TLC. The product mixture was separated by TLC (silica,10:3: 0.35; CH_2Cl_2: $(CH_3)_2CO$: AcOH) to give 1:1 ratio of the acid (83) and its ethyl ester (83a) . Ethyl ester, as yellow oil, ν max.(CCl_4) 3558 (OH)2840 (OMe) and 1735 cm^{-1} (ester C=O); δ(DMSO) 6.73 and 6.54(2H,d,J=8Hz, aromatic H), 4.05(2H,q,$\underline{CH_2}CH_3$),3.75(3H,s,OMe), 2.63 (4H,m,methylenic H), 2.08(3H,s,CH_3) and 1.15(3H,t, $CH_2\underline{CH_3}$). (Found: M^+, 238. $C_{13}H_{18}O_4$ requires M^+, 238).

(3) The acid (83) was obtained (40%) under the same conditions above after 22 hours.

4-Methyl -5-hydroxy-6-methoxyindane-1-one(30)

a. From acid (83)

A mixture of the acid (83)(850mg) and polyphosphoric acid (20g) was stirred and heated at 80°C for 2 hours. The reaction mixture was poured into ice water and stirred for one hour, salted with sodium chloride and extracted with ether. The ether extract was washed with sodium bicarbonate and brine, dried over sodium sulphate and evaporated to give the indanone (30) (0.4g, 51.4%), as pale yellow crystals which, on recrystalization from methanol had m.p . 214-215°C. ν max(KBr) 3200(OH)(broad),1675cm^{-1} (ketone), δ(acetone)6.92(1H,s,aromatic H),3.87(3H, s,OMe), 2.83(4H,m,methylenic H), 2.18(3H,s,CH_3) λmax. (EtOH) 232 (ϵ 11154), 280 (ϵ 8013) and 312nm (ϵ 7051).
(Found: $C_1$68.45;H,6.42%. $C_{11}H_{12}O_3$ requires C,68.73; H,6.29%).

b. From ester (86)

A mixture of the ester (200mg) and polyphosphoric (11g) was stirred and heated at 80°C for 2¼ hours. The reaction mixture was poured into ice-water stirred for one hour, salted and extracted with ether . The ether extract was washed with brine, dried over magnesium sulphate and evaporated to give the indanone (40mg,21.8%), TLC showed one compound, the U.V. and R_f ,were identical to the indanone obtained from the acid.

4-Methyl -5-hydroxy-6-methoxyindane (91).

a. A mixture of indanone (30)(400mg), 30% Pd/C (200mg) and 60% perchloric acid (0.16ml) in acetic acid (24ml), was stirred under hydrogen at room temperature and atmospheric pressure for 8 hours. The catalyst was removed by filtration, and washed with ether several times. To the filterate (acetic acid+ ether) brine was added, the ether layer was separated and the aqueous layer was extracted with ether. The combined solvents, were washed with brine, dried over sodium sulphate, and evaporated to give white crystalline indane (347 mg, 93.7%). A sample of it sublimed at 70-75°C (0.1mm), had m.p. 94-95°C. νmax.(KBr) 3440(OH), 2850(OMe) and 828cm^{-1}(aromatic C-H). δ($CDCl_3$) 6.67 (1H,s,aromatic H), 5.57(1H,broad, OH),3.86(3H,s,OMe), 2.83(4H,m,methylenic H_a), 2.18 (3H,s,CH_3) and 2.10 (2H,m, methylenic H_b) λmax.(EtOH) 220(ϵ 6338) and 288nm (ϵ 2997).
(Found: C, 73.90; H,7.87% ; M^+, 178. $C_{11}H_{14}O_2$ requires C, 74.13; H,7.92% ; M^+, 178).

b. To a solution of indanone (30)(100mg) in water (5ml) and 1.22M sodium hydroxide (1ml), sodium borohydride (75mg) was added and the reaction mixture refluxed for 2 hours. The solution was poured into cold water, acidified with 10% hydrochloric acid and extracted with ether. The ether extract was washed with brine , dried over sodium sulphate and evaporated

to give crystalline indane (91) (78mg, 84%) identical to that obtained from hydrogenation.

4-Methyl-6-methoxy-5-indanyloxy acetic acid (93)

To a solution of indane (91)(0.245g, 0.0013 mole) in sodium hydroxide solution (0.5g/1ml water), a solution of chloroacetic acid in water (0.375g, 0.0039 mole/1ml water) was added and more water(3ml) was added to dissolve the reaction mixture. The reaction mixture was heated and stirred at 90-100°C for 1¼ hours. It was then cooled to room temperature poured into water (8ml), acidified with 20% hydrochloric acid and extracted with ether . The ether extract was washed with water, sodium bicarbonate solution and water, dried over sodium sulphate and evaporated to give unreacted phenol (50mg) . The bicarbonate layer was acidified with 20% hydrochloric acid and extracted with ether, ether extract was washed with water, dried over sodium sulphate and evaporated to give white crystalline oxyacetic acid (130mg,39.9%) . A sample of it sublimed at 80-85°C (0.1mm), had m.p. 100-105°C. νmax (KBr) 2840 (OMe),1730 (acid C=O) and 825cm^{-1} (aromatic C-H). δ($CDCl_3$) 9.1 (1H,broad,CO_2H), 6.71 (1H,s,aromatic H), 4.53(2H,s,methylenic H) ,3.85(3H, s,OMe), 2.85 (3H,m,methylenic H_a), 2.20 (3H,s,CH_3) and 2.06 2H,m,methylenic H_b).

(Found: C,65.94;H, 7.06%. $C_{13}H_{16}O_4$ requires C,66.08; H,6.83%).

4-Methylindane -5,6- quinone-5,5 -spirolactone(17)

To a stirred solution of the acid (93)(80mg, 0.00034 mole) in CH_2Cl_2 (7ml), and 14% sodium acetate solution (2ml) at 10°C , N-bromosuccimide in sodium acetate solution (70 mg,0.00039 mole/5ml) was added and the stirring continued for 3 hours, then stirred at room temperature overnight, (total 24 hours). The methylene chloride layer was separated and the aqueous layer extracted with methylene chloride. The combined solvent extract was washed with sodium bicarbonate solution and water then dried over sodium sulphate and evaporated to give oily spirolactone (17)(67mg, 90.5%). ν max.(CCl_4) 1825, 1690,1670 and 1610cm^{-1} δ($CDCl_3$) 5.97 (1H,s,H_1) , 4.73 and 4.38 (2H,d ,d, J=15 Hz, H_2 and H_3) 2.7 (4H,m,methylenic H_a), 2.10 (2H,m,methylenic H_b) and 1.89 (3H,s,CH_3). λmax. (EtOH) 340nm.

4-Methyl-5,6-dihydroxyindane (95).

a. A solution of indane (91) (1.12g,0.00629 mole) in methlene chloride (85ml) was cooled to -76°C, while boron tribromide (3.46g,1.38ml,0.01384 mole) was added dropwise with stirring . The reaction mixture was stirred for 4 hours, at -76° and at room temperature , overnight . The reaction mixture was poured into ice-water, and stirred for one hour after which time the methylene chloride layer was separated and the aqueous layer extracted with ether.The combined extract were washed with brine, dried over sodium sulphate and evaporate to give the dihydroxyindane (95)(0.94g,91.4%), as an oil shown by TLC to be one compound. On sublimation the dihydroxyindane solidified m.p. 88-93°. ν max.(CCl_4) 3620, 3560 (OH) and 850cm^{-1}(aromatic C-H) δ($CDCl_3$) 6.52 (1H,s,aromatic H), 5.12 (2H,s,OH), 2.73(4H,m, methylenic H_a), 2.15 (3H,s,CH_3) and 2.0 (2H,m,methylenic H_b). (Found: C, 73.20; H,7.30%; M^+, 164 $C_{10}H_{12}O_2$ requires C, 73.14;H,7.37% ;M^+, 164).

b. To solution of indane (93)(100mg,0.00042mole) in methylene chloride (5ml) cooled to -76°C, boron tribromide (0.462g,0.00185 mole)was added dropwise with stirring. The reaction mixture was stirred for 4 hours, then kept overnight at room temperature. The reaction mixture was poured into ice-water,

stirred for one hours and then extracted with ether . The ether extract was washed with brine, dried over sodium sulphate and evaporated to give the dihydroxyindane (95)(64 mg, 92%), indentical with the product from (a).

Attempted preparation of monoester (95a).

a. A mixture of dihydroxyindane (95)(100mg, 0.000609 mole in dry benzene (7ml) and dry pyridine (0.1ml) was stirred at room temperature for 30 minutes. Then bromoacetyl bromide (0.123g, 0.053ml, 0.000609 mole) was added and the reaction mixture was stirred overnight. The reaction mixture was washed with brine, dried over sodium sulphate and evaporated to give a red oil . It was shown by mass spectrometry that the crude product was a mixture of starting dihydroxyindane, monoester (95a,97) and the diester (98).

b. The procedure as in (a) was used, but the reaction mixture was cooled to 10-15^{o}C before the addition of bromoacetyl bromide .The reaction mixture was stirred at this temperature for 3 hours and at room temperature overnight .Work up gave a product mixture as in (a).

c. A mixture of dihydroxyindane (95)(66mg, 0.00040

mole), in dry benzene (6ml) and dry pyridine (0.04ml) was stirred at room temperature for 15 minutes ,then cooled with ice-water to 10-15°C, before bromoacetyl bromide (0.02ml) was added and, the reaction mixture stirred for 45 minutes and at room temperature for 1.5 hours. The reaction mixture was again cooled to 10-15°C and bromoacetyl bromide (0.015 ml) was added (total 0.035ml , 1 equivalent). Stirring was continued for 3 hours with cooling and overnight at room temperature . The reaction was worked up as in (a) . The crude product was a mixture of starting dihydroxyindane,monoester and the diester as shown by mass spectra.

d. The procedure as in (c) was used; bromoacetyl bromide in benzene (2ml) was added dropwise over a period of 1.5 hours to the dihydroxyindane in benzene and pyridine with cooling and stirring, stirring was continued for 2 hours, then overnight at room temperature. The reaction was worked up to give a crude product which was a mixture as in (c) .

5,6-dimethoxyindane (99)

a. A mixture of indanone (71)(7g), 30% Pd/C (3.5g) in acetic acid (250ml) and perchloric acid (1.6ml) was stirred under hydrogen at room temperature, and

atmospheric pressure for 10 hours. The catalyst was removed by filtration and washed with ethyl acetate. Brine and more ethyl acetate was added to the filtrate. The ethyl acetate layer was separated and aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated to leave an oily residue which gave the crystalline indane (99)m.p.54°C (lit.[42] 54°C ,55°C after recrystalization from aqueous ethanol), (5g, 77%) on cooling in a fridge. νmax.(KBr) 2830 (OMe) , 850 and 830 cm^{-1}(aromatic C-H) δ($CDCl_3$) 6.80(2H,s,aromatic H), 3.82(6H,s, OMe), 2.85 (4H,m,methylenic H_a) and 2.05 (2H,m, methylenic H_b)

b. It was prepared as described in the literature[42]

To Zn/Hg in dilute hydrochloric acid)2; 1,water HCl) (60ml), indanone (71)(5g) was added and the reaction mixture refluxed with further addition of dilute hydrochloric acid (2:1)(25ml)over a period of one hour , then concentrated hydrochloric acid (20ml) was added during 3 hours and refluxed was continued for 4.5 hours. The aqueous layer was removed by decantation and the zinc residue washed with ether. The aqueous layer was salted and extracted with ether. The combined extracts were washed with brine, dried over sodium sulphate and evaporated to give crystalline indane (4.18g, 90.2%)m.p.54°C (lit[42] 54°C ,55°C

after recrystalization from aqueous ethanol).

Preparation of Zn/Hg [43]

A mixture of zinc wool (50g) and mercuric chloride (3g) in dilute hydrochloric acid (3ml HCl/ 60ml water) was shaken for 30-45 minutes, the dilute hydrochloric acid was decanted and the Zn/Hg washed once with water.

4-Bromo -5,6-dimethoxyindane (100)

a. To a solution of indane (99) (0.5g,0.0028 mole) in CCl_4 (20ml) at 30-35°C, bromine (0.14ml,0.0028 mole) in CCl_4 (10ml) was added dropwise over a period of 30 minutes with stirring. The reaction mixture was stirred for a further 30 minutes and then at room temperature overnight. The carbon tetrachloride solution was washed with sodium bisulphite solution and with water, dried over sodium sulphate and evaporated to give an oil (0.44g). Mass spectra showed that the product was a 1:1 mixture of starting indane and 4-bromoindane (100).

b. To a mixture of indane (99)(1g,0.0056 mole), and sodium acetate trihydrate (1g) in chloroform

(25 ml), bromine (0.28 ml, 0.0056 mole)in chloroform (10 ml) was added dropwise with stirring over a period of 1.5 hours . The reaction mixture was refluxed for 30 minutes and left to stand at room temperature overnight. The chloroform solution was washed with 5% sodium bisulphite solution and water, dried over sodium sulphate and evaporated to give an oil (0.986 g). This product was shown to be a mixture by MS consisting mainly 4-bromoindane (100) with some starting indane.

Diels - Alder reaction of spirolactone (17) with methyl vinyl ketone

A solution of acid (93) (132 mg) in methylene chloride (8ml) was stirred with 14% sodium acetate (4 ml), at $< 10^{o}C$. The N-bromosuccinimide (120mg) in sodium acetate solution (9ml) was added to the stirred reaction mixture. More methylene chloride(10 ml) was added and the reaction mixture was stirred at this temperature, for three hours and at room temperature overnight. The methylene chloride layer was separated, and the equeous layer extracted with methylene chloride. The combined methylene chloride extracts were washed with brine, dried over sodium sulphate and concentrated to about (15 ml)·Excess

methyl vinyl ketone (~ 10 ml) was added to the spirolactone solution and the reaction mixture was left to stand overnight at room temperature. The methylene chloride was removed by distillation and the residue was refluxed for 30 minutes. The excess methyl vinyl ketone was removed under reduced pressure and the residue which was shown to be a mixture of three components was separated by TLC (silica, ethyl acetate:petroleum ether, 1:1). One of the components was a self condensation product of methyl vinyl ketone . The two other components (32mg,75.4%) which had identical infrared spectra (showing the presence of the spirolactone function)were the stereoisomeric Diels-Alder adducts (101) and(102). ν max.(CCl_4) 1825, 1740 and 1720cm^{-1}.(Found: M^+, 290. $C_{16}H_{18}O_5$ requires M^+, 290).

REFERENCES

1) E.J.Corey,M.Norisada,T.Hiraoka and R.A.Allison, J.Amer.Chem.Soc.,1970,92,396.

2) D.J.Beames,L.N.Mander and J.V.Turner,Aust.J.Chem ., 1974,27,1977.

3) a- M.D.Bachi,J.W.Epstein and H.J.E.Loewenthal, Tetrahedron Lettres,1966,43,5333.
b-M.D.Bachi,J.W.Epstein,Y.Herzberg-Minzly and H.J.E.Loewenthal,J.Org.Chem.,1969,34,127.

4) E.J.Corey,R.L.Carney and J.M.Brennan,J.Amer.Chem. Soc.,1971,93,7316.

5) H.J.E.Loewenthal and S.Schatzmiller,J.C.S.Perkin 1, 1976,944.

6) A.J.Baker and A.C.Goudie,J.C.S.Chem.Comm.,1972,951.

7) M.F.Ansell,A.F.Gosden and V.J.Leslie,Tetrahedron Letters,1967,4537.

8) D.Berney and P.Deslongchamps,Can.J.Chem.,1969,47, 515.

9) P.Deslongchamps,Pure and Appl. Chem.,1977,49,1329.

10) a-K.Wiesner,T.Y.R.Tsai,G.I.Dmitrienko and K.P. Nambiar,Can.J.Chem.,1976,54,3307.
b-K.S.Atwal,R.Marini-Betto,I.H.Sanchez,T.Y.R.Tasi and K.Wiesner,Can.J.Chem.,1978,56,1102.

11) K.Wiesner,T.Y.R.Tsai and K.P.Nambiar,Can.J.Chem. , 1978,56,1451.

12) H.J.E.Loewenthal and S.Schafzmiller,J.C.S.Perkin 1, 1975,2148.

13) T.Kametani,Y.Hirai,M.Kajiwara,T.Takahashi and

K.Fukumoto,Chem.Pharm.Bull.,1975,23,2634.

14) R.Robinson and S.Sugasawa,J.Chem.Soc.,1931,3163-3169.

15) H.G.Peer,Rec.Trav.Chim.,1960,79,825.

16) A.R.Battersby,R.Staunton and M.Hirst,J.Chem.Soc. (C),1966,1052.

17) W.Nagata,H.Itazaki,K.Okada,T.Wakabayashi,K. Shibata and N.Tokutake,Chem.Pharm.Bull.,1975, 23,2867.

18) F.C.Nahm,E.F.Rothergy and K.Niedenzn,J.Organo-metallic Chem.,1972,35,9.

18a) J.S.Shannon,Aust.J.Chem.,1962,15,265.

19) Y.Yamada,K.Hosaka,H.Sanjoh and M.Suzuki,J.C.S. Chem.Comm.,1974,661.

20) F.M.Dean,J.Goodchild,L.Houghton,J.A.Martin,R.B. Morton,B.Parton,A.W.Price and N.Somvichien, Tetrahedron Letters,1966,35,4153.

21) J.Liebig and F.Wohler,Annalen Der Chemie,1842, 44,126.

22) C.Liebermann and S.Kleemann,Berichte Der Chemischen,1886,2287-2290.

23) C.Schopf etal.,Annalen Der Chemie,1940,544,77.

24) K.Wiesner etal.,Can.J.Chem.,1976,54,1039.

25) C.F.Koelsch,J.Amer.Chem.Soc.,1931,53,304.

26) Piccinini,Centr.,1904,11,903.

27) T.Richardson,R.Robinson and E.Seijo,J.Chem.Soc., 1937,835.

28) V.Askam and W.H.Linnell,J.Chem.Soc.,1954,2435.

29) J.Delobelle and M.Fetizon,Bull.Soc.Chim.(France),

1961,1900.

30) D.H.Barton,L.Bould,D.L.Jclive,P.D.Magnus,(in part) T.Hase,J.Chem.Soc.(C),1971,2204.

31) H.C.Horning,J.Koo and G.N.Walker,J.Amer.Chem.Soc., 1951,73,2826.

32) C.J.W.Brooks and J.Watson,Chem.Comm.,1967,952.

33) H.C.Brown and S.K.Gupta,J.Amer.Chem.Soc.,1972, 94,4370.

34) R.C.Gilmore,J.Amer.Chem.Soc.,1951,73,5879.

35) a-H.W.Thompson and B.S.Huegi,Chem.Comm.,1973,636. b-H.W.Thompson and B.S.Huegi,J.C.S.Perkin 1, 1976,1603.

36) B.M.Trost and L.H.Latimer,J.Org.Chem.,1977,42,3212.

37) E.J.Corey,S.Barcza and G.Klotmann,J.Amer.Chem.Soc., 1969,4782.

38) K.H.Bell,Aust.J.Chem.,1969,22,601.

39) I.A.Blair,A.Ellis,D.W.Johnson and L.N.Mander,Aust. J.Chem.,1978,405.

40) K.Wiesner,W.D.MacKay,K.J.Wiesner,A.Deljac and L.S.J.Pan,Can.J.Chem.,1972,50,726.

41) Schmir,J.Amer.Chem.Soc.,1959,81,2228.

42) W.H.Mills and I.G.Nixon,J.Chem.Soc.,1930,2510.

43) E.L.Martin,Org.Reactions,1,155.

44) "Purification of Laboratory Chemicals"Perrin,Arn Arego and Perrin,Pergammon Press,1966.

45) J.Koo,M.S.Fish,G.N.Walker and Blake,Org.Syn.Coll. Vol. 4,1963,327.

46) A.Bowers,T.G.Halsall,E.R.H.Jones and(in part) A.J.Lemin,J.Chem.Soc.,1953,2548.

47) C.Djerassi, R.R.Engle and A.Bowers, J.Org.Chem., 1956, 21, 1547.

48) W.M.Rodionow and S.J.Kanewskaia, Bull.Soc.Chim. (France), 1934, 653.

49) J.A.Moore and D.E.Reed, Org.Syn.Coll.Vol.5, 351.

50) R.C.Fuson and C.H.McKeever, J.Amer.Chem.Soc., 1940, 62, 784.

51) E.D.Hornbaker and A.Burger, J.Amer.Chem.Soc., 1955, 77, 5314.

52) C.S.Marvel and P.K.Porter, Org.Syn.Coll.Vol.1, 1941, 377.

53) J.B.Conant and O.R.Quayle, Org.Syn.Coll.Vol.1, 292.

54) O.R.Sweeney, J.Amer.Chem.Soc., 1917, 39, 2186.

55) J.Koo, J.Amer.Chem.Soc., 1953, 75, 1891.

56) W.S.Johnson and H.J.Glenn, J.Amer.Chem.Soc., 1949, 71, 1092.