A Thesis

entitled

"Synthetic Studies on Gibberellins"

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for the degree of Doctor of Philosophy

in the Faculty of Science

by

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SUMMARY

A stereospecific synthesis of 3-methoxy-6,16-dioxo-9βH-gibb-A-triene has been achieved in good yield, starting from a Diels-Alder reaction of itaconic acid with methyl 5-(p-methoxyphenyl)-trans, trans-penta-2,4-dienoate, the major products from which violate the cis addition principle.

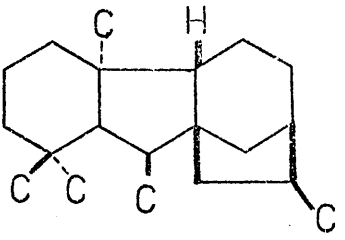
An efficient stereospecific synthesis of the multifunctional gibberellin synthon 3-methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4,6β-dicarboxylic acid from 3-methoxy-6,16-dioxo-9βH-gibb-A-triene is described.

Attempted elaboration of 3-methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4,6β-dicarboxylic acid to methyl 4α-carboxyl-10α-hydroxy-4β-methyl-3,16-dioxo-9βH-gibbane-6β-carboxylate 4α⟶10α-lactone, prepared from a mixture of gibberellin A_4 and A_7 as a relay compound to gibberellin A_4, has resulted in this synthesis of methyl 3-methoxy-4-methyl-16,16-ethylenedioxy-9βH-gibb-A-triene-6β-carboxylate.

A partial solution, by spectroscopic methods, of the problem of assignment of C-9 stereochemistry in gibbanes has been devised.

CONTENTS

Synthetic Studies on Gibberellins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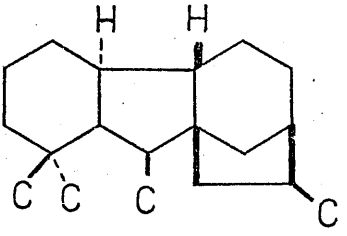
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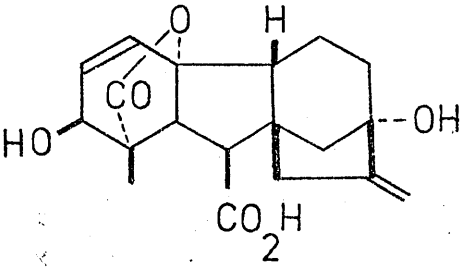
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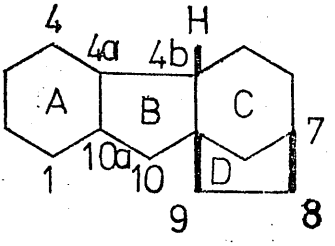
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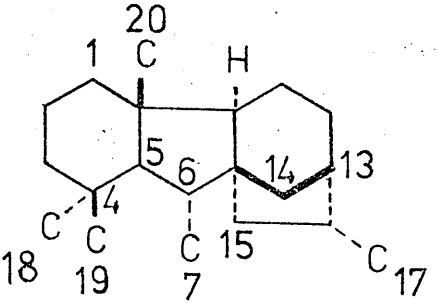
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(5)

INTRODUCTION

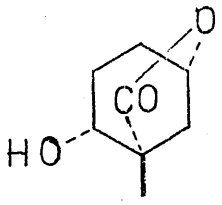
The gibberellins, first discovered in 1938,[1] are endogenous plant hormones.[2] They are diterpenoid acids and can be subdivided into two groups, namely C_{20}-(1) and C_{19}-(2) gibberellins.

The structure and correct stereochemistry of gibberellic acid (gibberellin A_3) (3), the most easily obtainable fungal gibberellin,[3] was finally confirmed by X-ray structure analysis.[4] The structures of the other gibberellins (of which there are thirty-seven known at present) have been elucidated by interconversion and correlation with the acid (3), its derivatives and degradation products.

Until recently, gibberellins, their derivatives and degradation products have been named as derivatives of gibbane,[5] numbered as shown in (4). A recent proposal[6] that nomenclature based on the hypothetical diterpene gibberellane (5) be used together with conventional diterpene numbering is finding support. However, both systems are still used. While diterpene numbering is desirable, 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.

Because of the structural and stereochemical complexity of the gibberellins, the ease with which they rearrange[7] and the potential commercial viability of any synthesis due to their remarkable biological activity, these molecules have long presented an intriguing synthetic challenge to the organic chemist.

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



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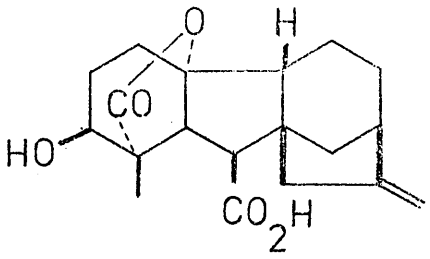

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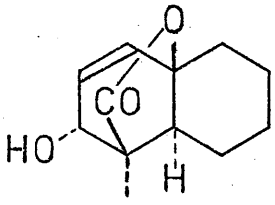

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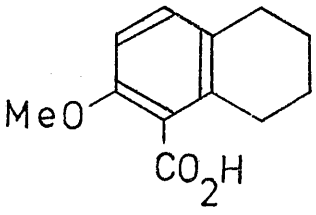

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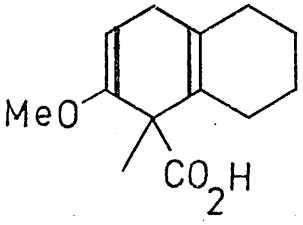

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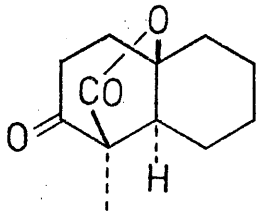

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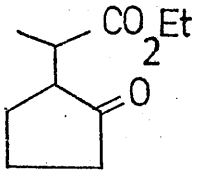

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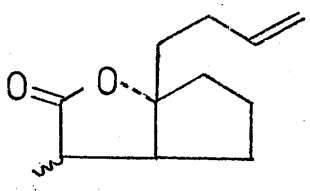

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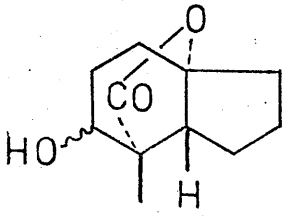

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Synthetic studies directed towards the gibberellins can be considered under three main categories:

a) Synthesis of the ring A system.

b) Construction of the CD ring system.

c) Synthesis of hydrofluorenes.

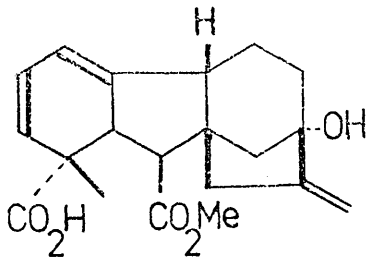
a) Synthesis of the ring A system.

The problem was first tackled by Mori[8] who, while attempting to define the structure of ring A of gibberellic acid (3), synthesised a series of thirteen cyclohexane γ- and δ-lactones. One of these lactones (6), synthesised from 1-methyl-2-hydroxy-5-keto-cyclohexan-1-oic acid, proved to be the C-3 epimer of ring A of gibberellin A_4 (7). A similar approach to this problem by Moffat[9] resulted in the synthesis of the ring A analogue of this natural product (7).

The lactone synthesised was shown to be epimeric at C-3 with the lactone (6) synthesised by Mori and epimerised to (6) in dilute aqueous alkali by what was suggested by Cornforth[10] to be a retro-aldol mechanism. This behaviour has also been observed in the gibberellins[11] and appears to occur by the same mechanism.[12]

A better model ring A analogue of gibberellic acid (3) was obtained by Loewenthal[13] in the formation of the lactone (8) from the readily available[14] 2-methoxy-5,6,7,8-tetrahydronaphth-1-oic acid (9) by the reaction sequence (9 $\longrightarrow$ 10 $\longrightarrow$ 11 $\longrightarrow$ 8).

Dolby[15] has also solved this problem by tackling it in a completely different manner. Reaction of the substituted cyclo-pentan-1-one (12) with homoallyl magnesium bromide yielded the olefinic lactone (13) after saponification. Oxidation and aldol condensation then afforded a mixture of epimeric alcohols (14) which were separated



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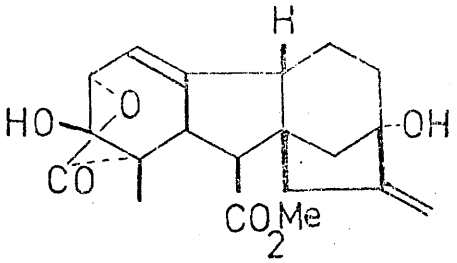

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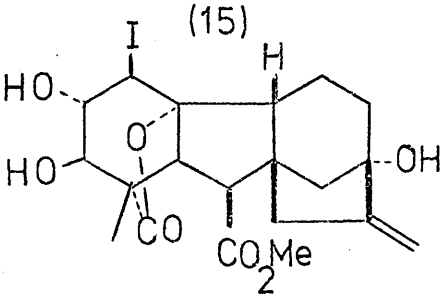

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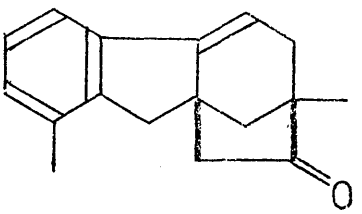

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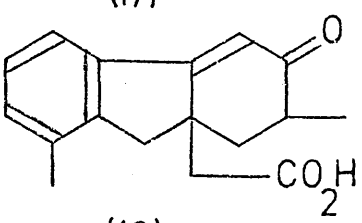

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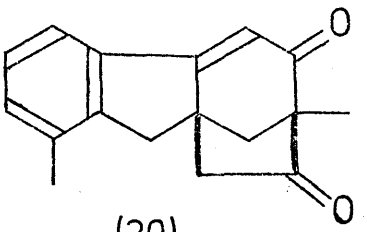

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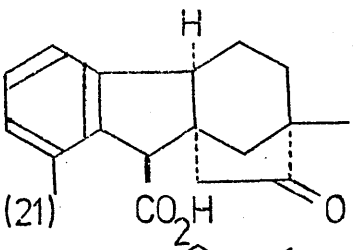

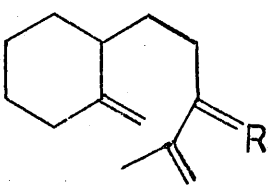

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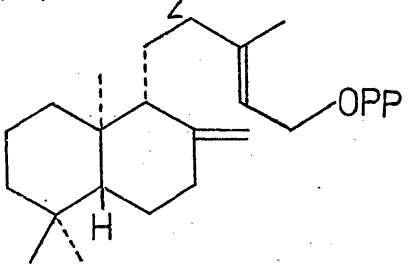

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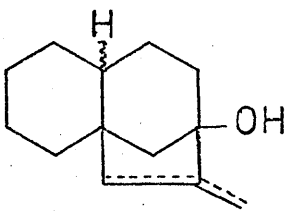

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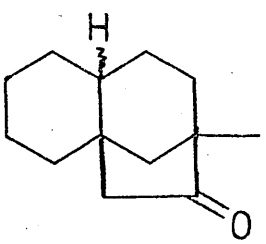

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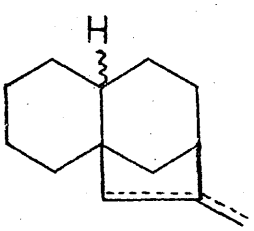

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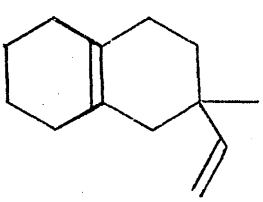


(27)

to yield the desired δ-hydroxylactone.

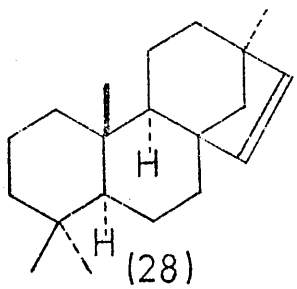
Corey[16] recently achieved a stereospecific elaboration of ring A of gibberellic acid (3) from the triene acid (15) derived from methyl gibberellate. Regioselective oxidation of (15) with m-chloroperbenzoic acid afforded the known dihydroxy δ-lactone ester (16), which on saponification of the lactonic function and subsequent treatment with iodine gave the lactone (17). Conversion of the latter to methyl gibberellate was achieved by (a) trifluoroacetylation, (b) elimination with zinc dust, and (c) detrifluoroacetylation with aqueous sodium bicarbonate.

b) Construction of the CD ring system.

1) Acid Catalysed Cyclisations.

Loewenthal[17] and Raphael[18] achieved the synthesis of gibberone (18), a degradation product of gibberellic acid (3), by constructing the bicyclo(3.2.1)octyl CD ring system on a suitably substituted indanone. The most interesting step in these syntheses was the use of boron trifluoride-acetic acid to form ring D by cyclodehydration (19 ⟶ 20), a method which Loewenthal later improved by using naphthalene-1-sulphonic acid.[19] Gibberic acid (21), also a degradation product of gibberellic acid, was synthesised by Loewenthal[20] using a similar approach.

A less successful attempt was made by Dolby and Iwomoto,[21] who attempted the acid catalysed cyclisation of the diene (22; R=O) and the allylic alcohol(22; R=CH_3, OH) both of which bear a formal relationship to the known[22] labdane biogenetic precursor (23). However, the desired products(22; R=O ⟶ 24,25) and (22; R=CH_3,OH ⟶ 26) were not isolated. The dienone (22; R=O) gave more than a dozen products on attempted cyclisation under a variety of conditions,



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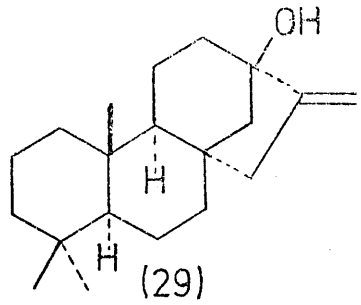

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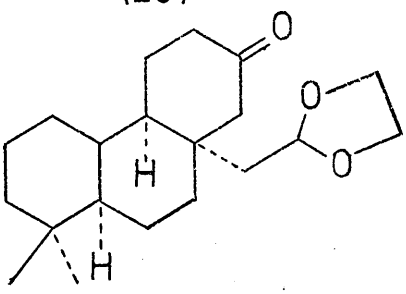

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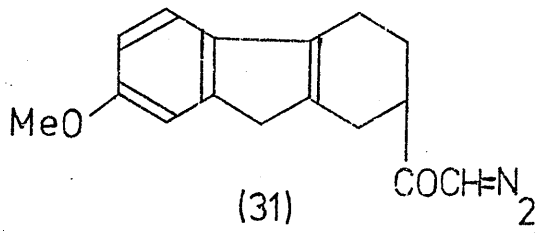

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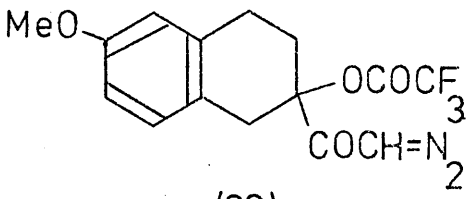

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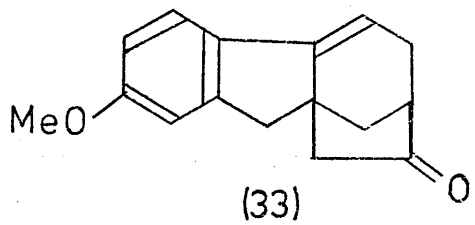

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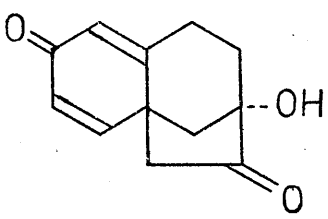

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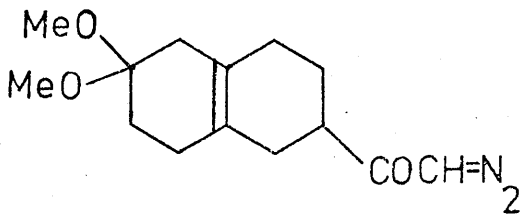

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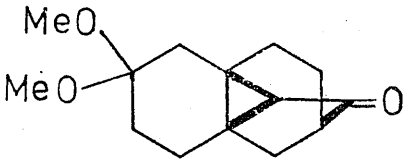

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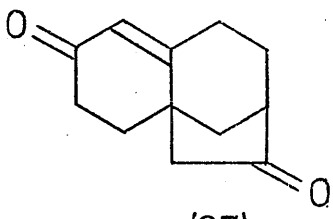

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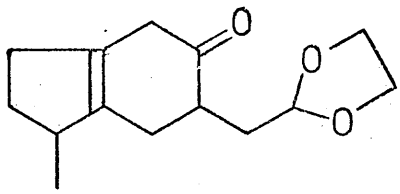

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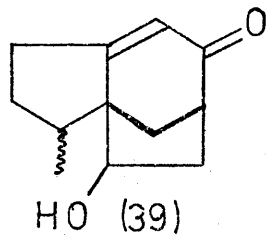

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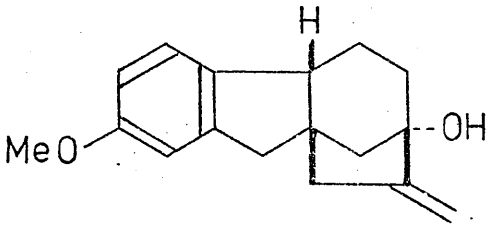

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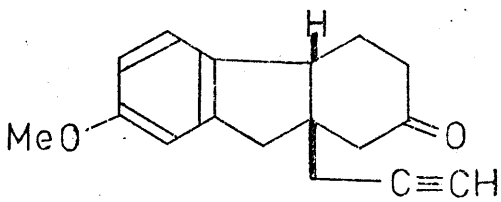


(41)

while the alcohol (22; R=CH_3, OH) yielded the substituted octalin (27).

In addition to these synthetic efforts directed towards the synthesis of gibberellins, mention should also be made of Ireland's masterly synthesis of hibaene (28),[23] in the course of which he synthesised a compound (29) from the tricyclic keto acetal (30) by a series of high yield transformations. The tetracyclic compound (29) contains the CD ring system of the gibberellins and was smoothly rearranged in a stereospecific manner by analogy with the well-known gibberellic acid (3)→ gibberic acid (21) transformation[24] to yield the expected product of defined stereochemistry.

Mander[25] achieved cyclisation of the diazo ketones (31) and (32) to the unsaturated ketones (33) and (34) respectively, using fluoroboric acid in nitromethane. In earlier work, Mander[26] described a copper catalysed decomposition of the diazo ketone (35) to the cyclopropyl ketone (36) which, on subsequent acid treatment, gave the bridged octalone (37). An identical synthesis of (33) via (31) had been reported by Ghatak.[27]

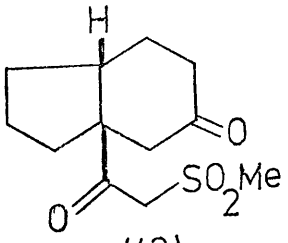
By a novel procedure, Wiesner[28] cyclised the unsaturated keto acetal (38) to a mixture of tricyclic epimers (39) in high yield by heating (38) in 80% acetic acid.

In general, the gibbene produced from acid catalysed cyclisation is hydrogenated largely to give the unnatural stereochemistry at C-9 unless a suitably orientated C-6 substituent is present.[20]

2) Base Catalysed Cyclisations.

One of the first to synthesise a molecule incorporating the gibberellin A_3 (3) CD ring system was Stork,[29] who achieved the synthesis of the gibbane alcohol (40) by the elegant reductive cyclisation of the ethynyl ketone (41).[30]

Another route to the bridgehead hydroxylated bicyclo (3.2.1)-



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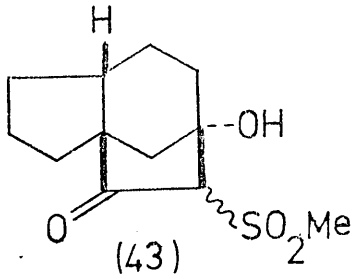

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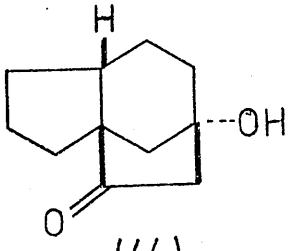

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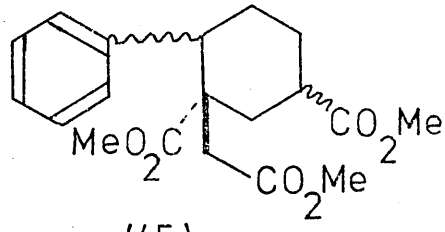

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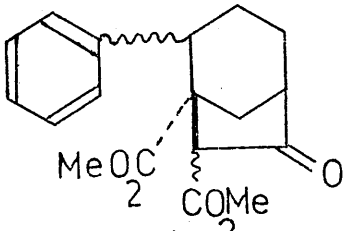

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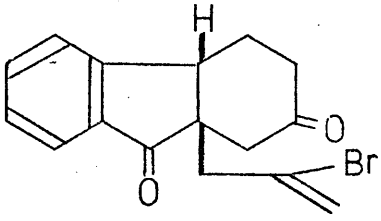

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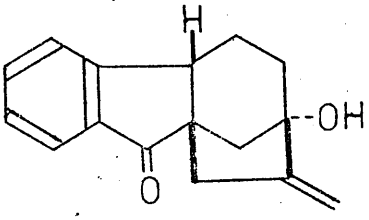

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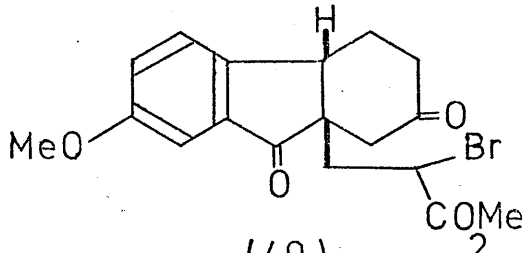

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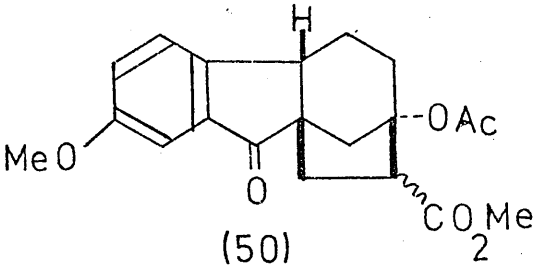

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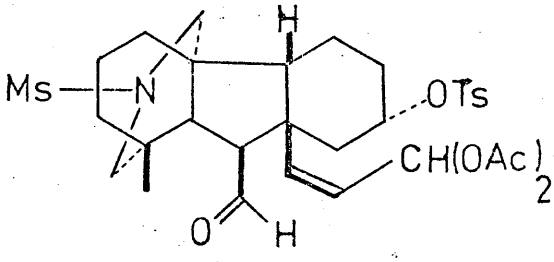

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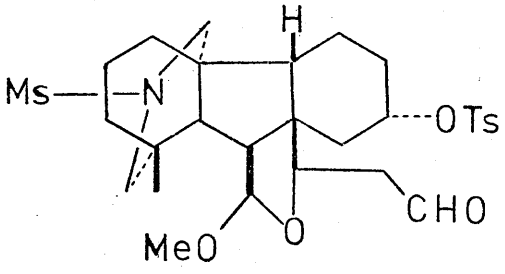

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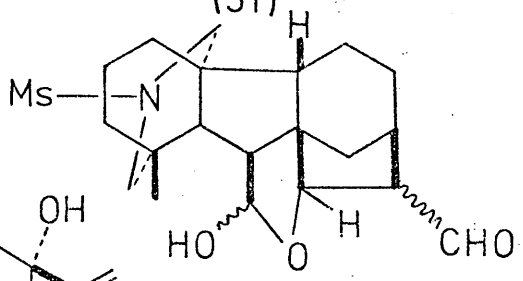

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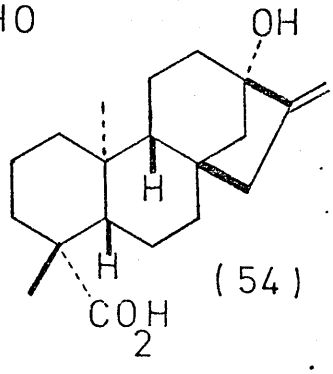


(54)

octane system was explored by House.[31]

Intramolecular aldol condensation of the diketo sulphone (42) using sodium tertiary amyloxide in benzene gave the tricyclic product (43), which was reductively cleaved with aluminium amalgam and water to the hydroxy ketone (44).

To obtain a CD ring structure without a bridgehead alcohol Gerber[32] used a Dieckmann reaction to convert the trimethyl ester (45) to the keto diester (46).

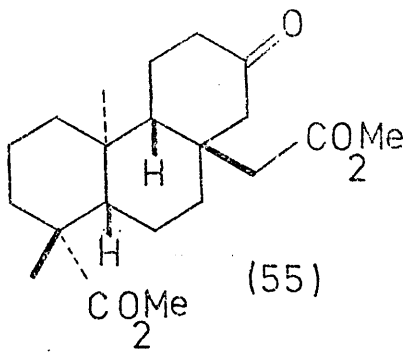
The importance of choice of the final cyclisation reaction can be illustrated by comparing the independent work of Ziegler[33] and Corey.[34] From the same bromo diketone (47), Ziegler was unable to obtain any of the tetracyclic hydroxy ketone (48) by an internal Grignard reaction, whereas Corey carried out a smooth conversion of (47) to (48) using di-n-butylcopper lithium in ether at -50°.

Ziegler, however, succeeded in cyclising the bromo ester (49) to the tetracyclic product (50) by an internal Reformatsky reaction, followed by quenching of the reaction mixture with acetic anhydride.

In his total synthesis of dl-gibberellin A_{15}, Nagata[35] described a unique cyclisation method devised for the BCD ring system. The aldehyde (51) was treated with potassium hydroxide in dry methanol and tetrahydrofuran to give the intermediate (52), which with pyrrolidine in methanol-N-methyl-pyrrolidone, followed by hydrolysis with 50% acetic acid, afforded a mixture of hexacyclic hemiacetals (53), epimeric at C_7 and C_{16}.

3) Radical-anion cyclisations.

The first use of an acyloin condensation to construct a bicyclo(3.2.1)octane system was in the synthesis of steviol (54)



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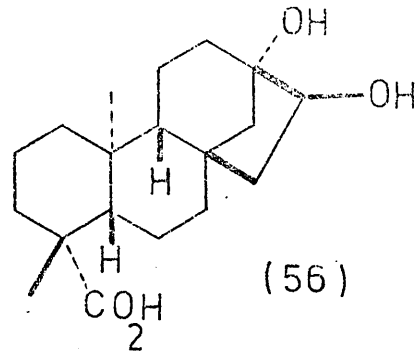

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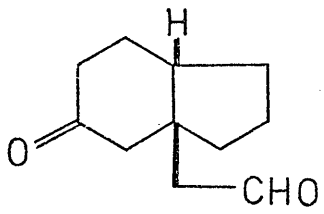

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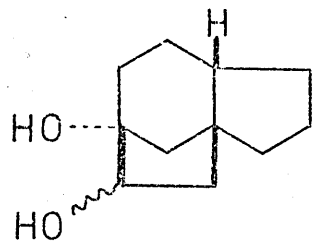

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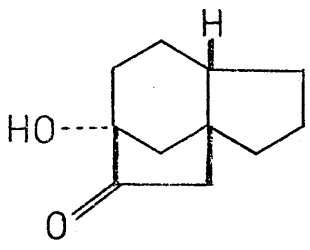

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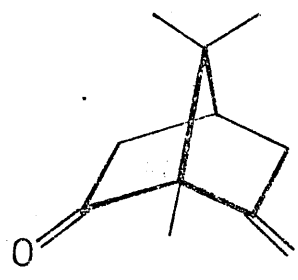

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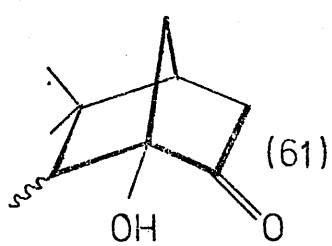

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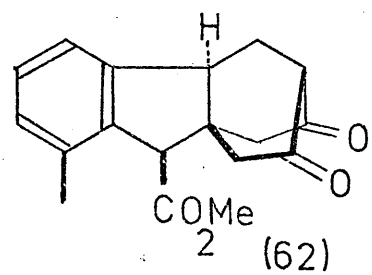

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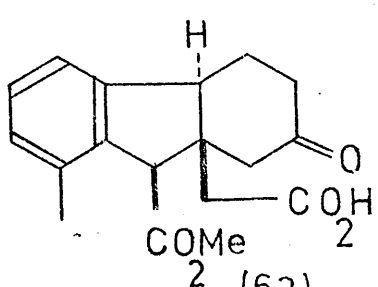

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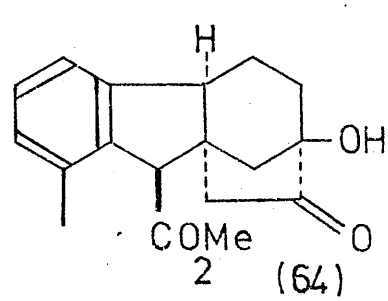

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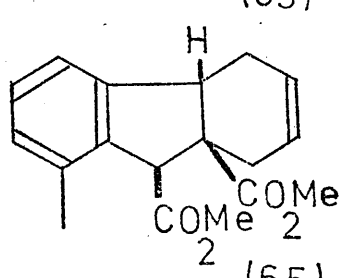

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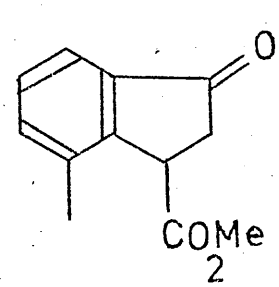

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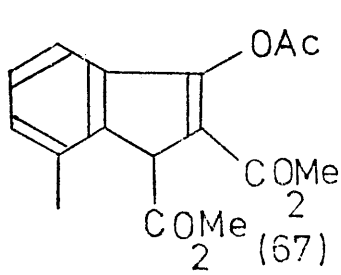

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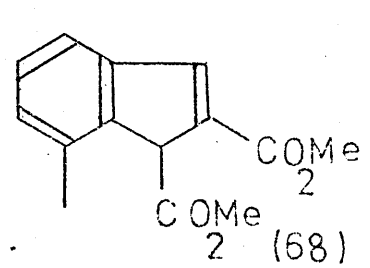


(68)

by Cook,[36] who converted the keto ester (55) to the diol (56).

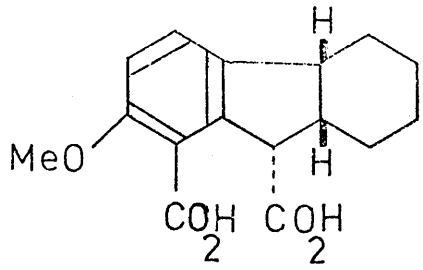
The first successful pinacol cyclisation of a cycloaliphatic keto aldehyde was achieved by Corey.[37] Keto aldehyde (57) was readily cyclised to the diol (58) using magnesium amalgam and dimethyldichlorosilane in tetrahydrofuran. The success of the conversion lay in the trapping of the intermediate as its silyl ether. The diol (58) was oxidised to the ketol (59) with tertiary butyl hypochlorite.

Following the observation[38] that pinacol reduction of diketone (60) gave ketol (61), Mori[39] applied the reaction to the bicyclo(2.2.2)octyl derivative (62), readily available from the keto acid (63), and obtained ketol (64). It is noteworthy that the reaction proceeded to give mainly the cis fused ketol thus providing a route from the BC trans fused intermediates. e.g. (63).

c) Preparation of hydrofluorenes.

An obvious route to the gibbane skeleton lies in the construction of suitably functionalised hydrofluorenes, e.g. (19), (31), (41), (47) and (63), which can then be further cyclised to the tetracyclic system as discussed above.

In a series of papers[40] investigating synthetic routes to the gibberellins and related compounds, House has used this approach in his synthesis of the epiallogibberic acid precursor (65). The indanone (66), prepared from o-tolualdehyde by standard procedures, was carbomethoxylated using dimethyl carbonate and sodium hydride and then converted to the related enol acetate (67) by reaction with acetic anhydride and perchloric acid. Hydrogenation followed by acid catalysed elimination of acetic acid from the acetoxy ester yielded (68) which afforded the desired adduct (65)



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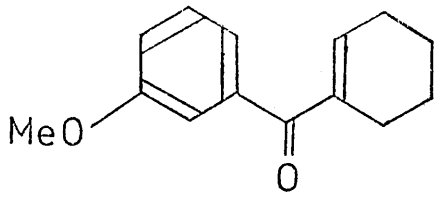

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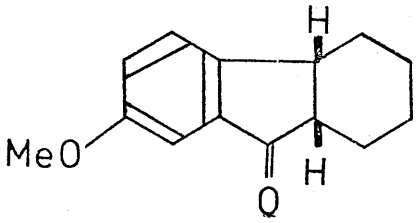

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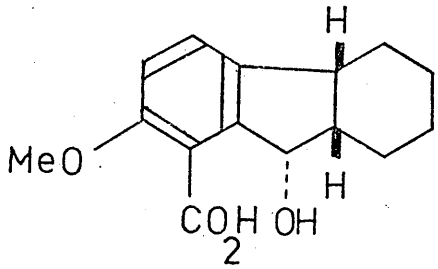

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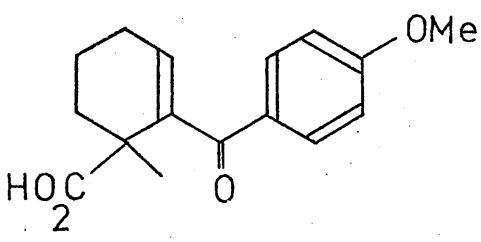

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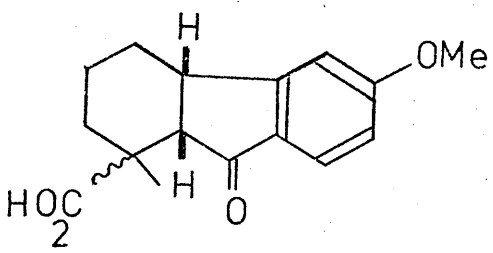

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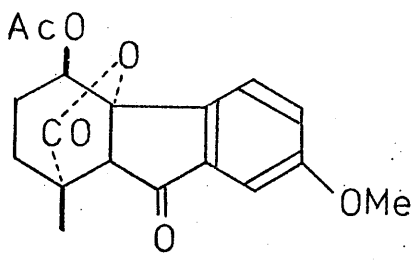

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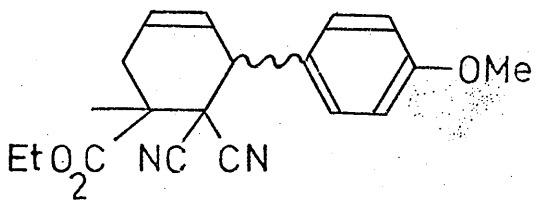

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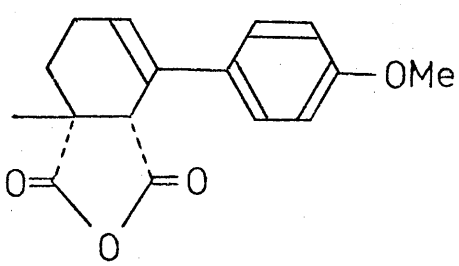

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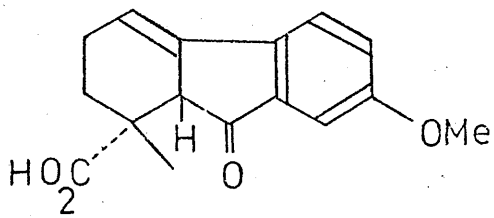


(78)

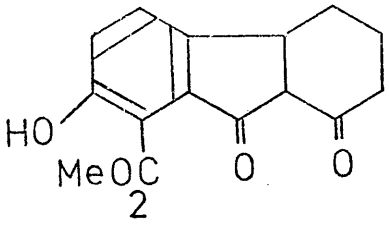
following a Diels-Alder reaction with 1,3 butadiene at elevated temperature and pressure.

Further investigation[41] on the general applicability of this reaction scheme showed, however, that a substituent at C_7 of the dienophile (68) was necessary to prevent thermal isomerisation to the less stable $\Delta^{1,2}$ compound before Diels-Alder addition took place.

Turning his attention next to the 7-methoxyhexahydrofluorene system, House[42] achieved an elegant synthesis of the diacid (69). Reaction of 1-cyanocyclohexene with m-methoxyphenylmagnesium bromide, followed by dilute acid treatment, produced the unsaturated ketone (70), which cyclised in concentrated sulphuric acid to the ketone (71). Reduction of this ketone with lithium aluminium hydride gave an alcohol which underwent regiospecific carboxylation to the acid (72) using butyl sodium and carbon dioxide. Sequential acid catalysed dehydration, carboxylation with methyl lithium and carbon dioxide, and hydrogenation converted the acid (72) to the diacid (69).

In a more recent paper,[43] Jackman photolysed the anisoyl-cyclohexene (73) to an epimeric mixture of acids (74) in nearly quantitative yield.

Another example of the hydrofluorene approach is the intermediate (75) synthesised by Nakanishi.[44] The initial Diels-Alder reaction of 1-(p-methoxyphenyl)butadiene with ethyl 2-methyl -3,3-dicyano acrylate yielded a mixture of the esters (76) which on saponification and anhydride formation afforded the substituted cyclohexene (77). Treatment of (77) with aluminium chloride yielded the hydrofluorene (78), easily converted to (75) with p-nitro-perbenzoic acid followed by acetylation.



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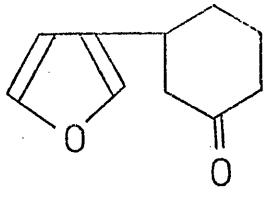

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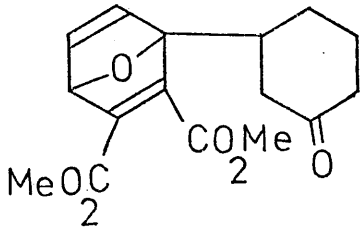

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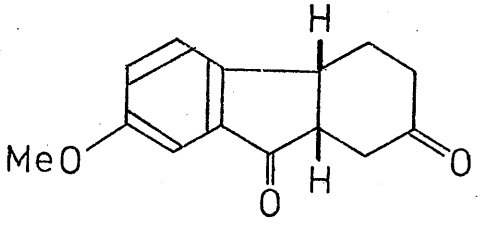

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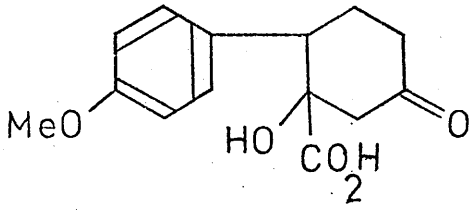

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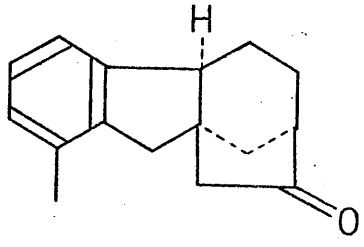

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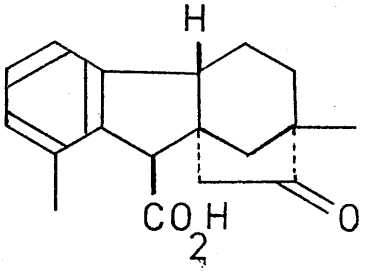

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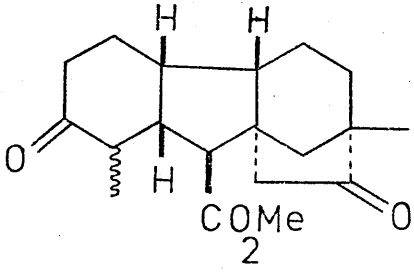

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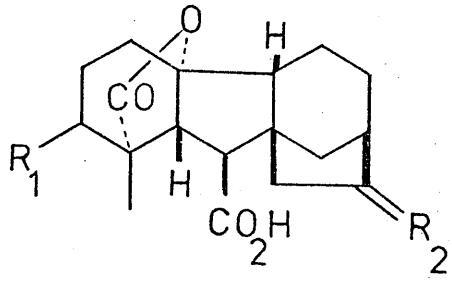
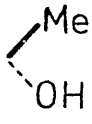
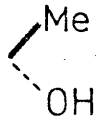


	R_1	R_2
(86)	OH	
(87)	H	CH_2
(88)	H	

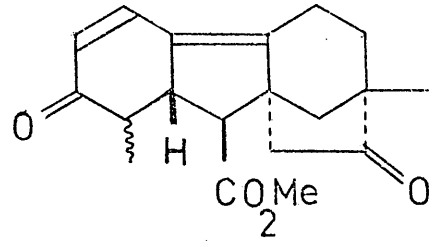
Kitahara[45] chose a novel approach to this problem in his synthesis of the hydrofluorene (79). The Diels-Alder reaction of dimethyl acetylenedicarboxylate with the diene (80) yielded the adduct (81), which cyclised in 80% yield to (79) using boron trifluoride etherate.

An efficient synthesis of 7-methoxyhexahydrofluorene-2,9-dione (82) was devised by Ziegler.[33] Condensation between p-methoxyphenylpyruvic acid and methyl vinyl ketone was achieved in aqueous methanolic sodium hydroxide, yielding the acid (83) as a single diastereomer in high yield. Thermal dehydration, reduction with zinc in refluxing acetic acid, and finally poly-phosphoric acid catalysed cyclisation converted the acid (83) to the desired diketone (82).

By far the most active group engaged in the synthesis of these secondary metabolites has been the Tokyo group headed by Matsui, Mori and Sumiki. These workers have synthesised a wide variety of hydrofluorene derivatives including 13-desmethyldihydro-gibberone (84)[46] and epigibberic acid (85).[47]

The culmination of their efforts was the total synthesis of gibberellins A_2 (86), A_4 (7), A_9 (87) and A_{10} (88) from o-xylene.[48] The synthesis was achieved in five stages by interrelating various degradation products of gibberellic acid (3) and then using the degradation products obtained from natural sources as relay compounds.

Firstly, epigibberic acid (85), a rearrangement product of gibberellic acid,[49] was synthesised from o-xylene in a twenty-one stage synthesis.[47] Epigibberic acid was in turn converted to the ester (89) by a standard five step synthesis[50] followed by separation of the epimeric products. This ester (89) was a new



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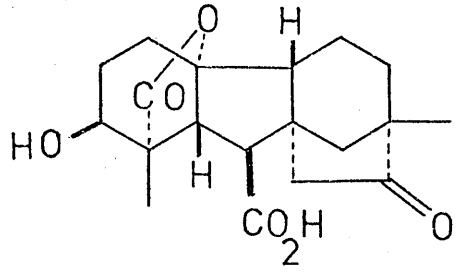

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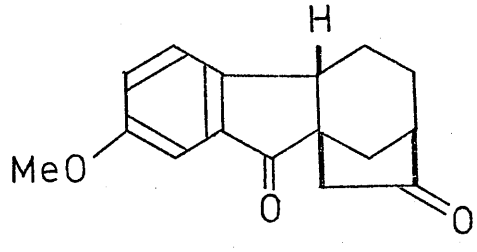

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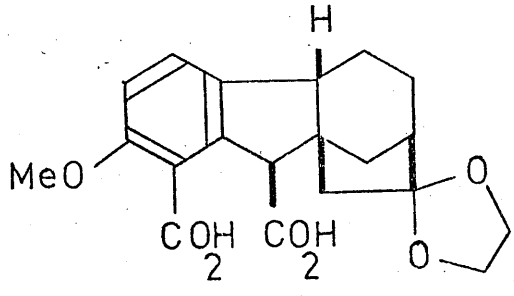

(93)

degradation product[50] of gibberellic acid (3) and served as the first relay compound. Transformation of (89) to the dienone (90) was achieved in ten stages utilising a bromination-dehydrobromination technique. Since a previous publication[51] by Mori had been concerned with the synthesis of gibberellin C (91), in eight stages from the dienone (90) using triphenyl sodium and carbon dioxide as carboxylating agents, reduction of the endocyclic ring A double bond being carried out with palladium/charcoal and hydrogen and lactonisation being effected by sulphuric acid, this completed the synthesis of gibberellin C (91). This in turn completed the total synthesis of the gibberellins since other authors[52] had converted gibberellin C (91) into gibberellin A_4 (7) in 5% yield using sodium borohydride and phosphorus pentachloride. Gibberellin A_4 (7) had itself been transformed into A_2 (86),[53] A_9 (87)[54] and A_{10}(88).[55]

Although the total synthesis of gibberellins C, A_2, A_4 and A_{10} and of gibberellin A_{15} reported by Mori and Nagata respectively are meritorious, they are of little practical value because of their many steps.

An understanding of the relationship between biological activity and chemical structure in the gibberellin group of plant hormones requires an adequate source of gibberellins and specifically labelled (e.g. ^{14}C) derivatives; this in turn could lead to the design and synthesis of compounds of less complex structure with similar activity in biological systems regulated by gibberellins.

This thesis is concerned with the development of an efficient and stereospecific route to gibberellin A_4 (7). The aims of this investigation were as follows:

a) The synthesis of a suitably functionalised gibbane (92).

b) The subsequent conversion of the gibbane (92) to the fully

substituted gibberellin intermediate (93).

c) The stereospecific elaboration of (93) to gibberellin A_4.

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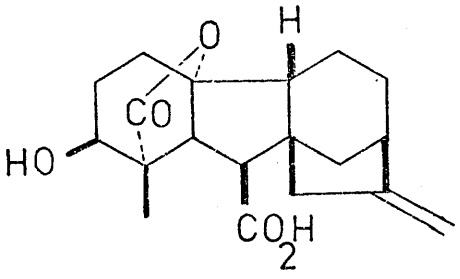

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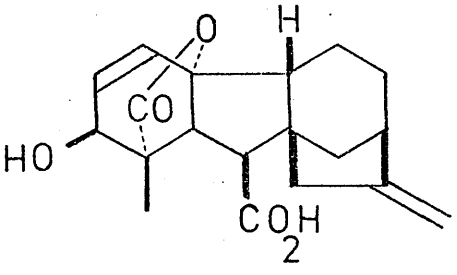

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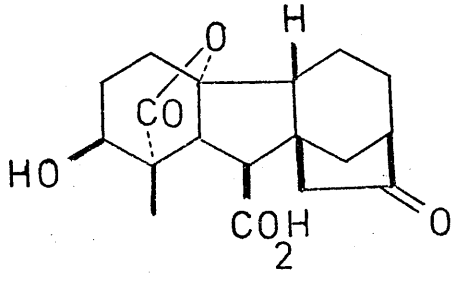

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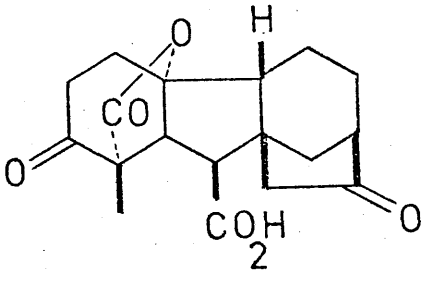


(55)

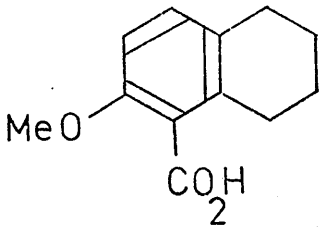
DISCUSSION

The total synthesis of gibberellin A_4 (52) presents the organic chemist with a logistical as well as a stereochemical challenge. The compound contains a complex carbon framework incorporating eight chiral centres 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 again stereospecifically elaborated.

In the planning of a projected synthesis of a complex molecule the cardinal rule is to work back from the goal breaking the problem down into a number of intermediate objectives and then to work forward to each objective in turn. The results of previous work in the field, both synthetic and degradative, should be borne in mind since they may have a bearing on the success of the project.

Since gibberellin A_4 (52) had already been partially synthesised from gibberellin A_7 (53) via ketol (54)[1], a relay approach to gibberellin A_4 (52) was envisaged, using the novel diketone (55), derived from ketol (54), as a key intermediate. As part of this investigation, diketone (55) was prepared by ozonolysis and oxidation of a mixture of gibberellin A_4 (52) and A_7 (53). Since the total synthesis of the diketone (55) and its transformation to the ketol (54) would constitute a total synthesis of gibberellin A_4, a stereocontrolled route to the diketone (55) was investigated in this thesis.

From the extensive literature on the degradative work[2] to determine the structure of the gibberellins, it was apparent that the ring A system was sensitive to hydrolytic conditions. Accordingly, this labile portion of the molecule is best constructed late in the



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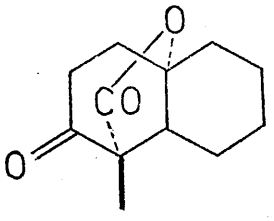

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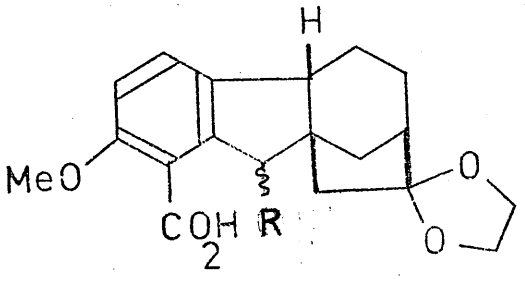
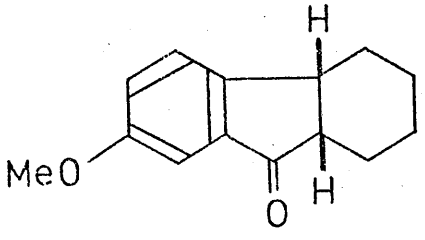
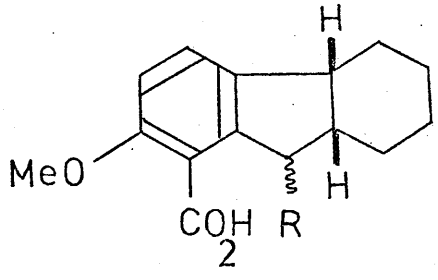


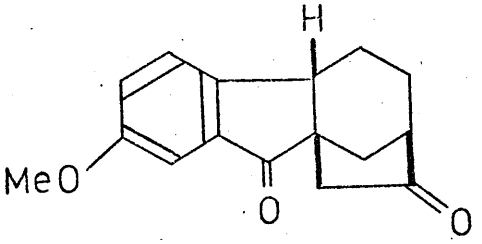
	R
(42)	β CO_2H
(28)	α OH



(58)



	R
(59)	α OH
(60)	β CO_2H

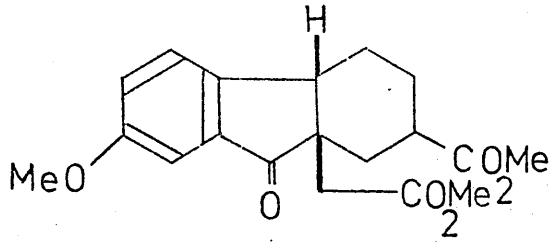


(19)

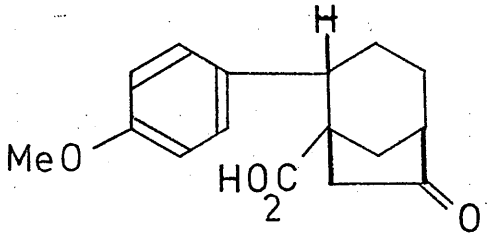
synthesis, preferably from an aromatic precursor. Such a precursor must possess functionality suitably disposed for conversion to ring A of gibberellin A_4 in perhaps the manner originally pioneered by Loewenthal[3] using 2-methoxy-5,6,7,8-tetrahydronaphth-1-oic acid (56) as a model. Reductive methylation and lactonisation of the acid (56) produced (57) in excellent yield. Accordingly, the aromatic diacid (42) was chosen as the keystone from which the diketone (55) and ultimately gibberellin A_4 might be derived.

Just before research on this project was undertaken, House[4] had elegantly converted the methoxyhexahydrofluorenone (58), via the hydroxy acid (59), to the diacid (60), obviously to be used as a model for the study of the transformations of the aromatic ring to the A ring of a gibberellin. Since the diacid (60) represented an excellent model for the synthesis of the diacid (42), the gibbane diketone (19)[5] was selected as the first main synthetic objective. Apart from possessing functionality suitable for elaboration to the hydroxy acid (28), the diketone (19) contains the basic carbon skeleton and stereochemistry of the diketone (55). However, since the methods used by House to convert the hydroxy acid (59) to the diacid (60), namely (a), introduction of the B ring carboxyl group via a Wittig reaction on the corresponding keto acid, or (b), carboxylation of a benzylic-allylic carbanion, were of doubtful applicability to the more sterically congested and less reactive gibbane system, a modified method of obtaining the diacid (42) from the hydroxy acid (28) would have to be investigated.

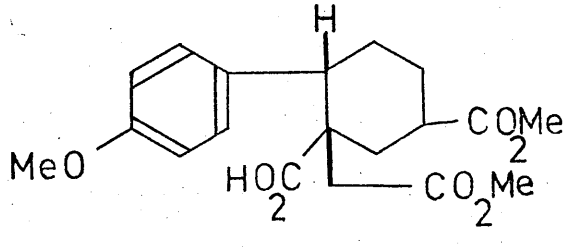
The two most recognisable sub-units of the diketone (19) are the hexahydrofluorenone comprising the A, B and C rings, and the bicyclo(3.2.1)octanone comprising the C and D rings. Through recognition of these two structural features of the diketone (19) the



(61a)



(16a)

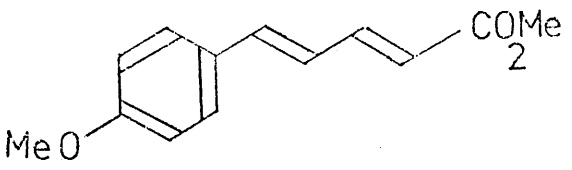


(13a)

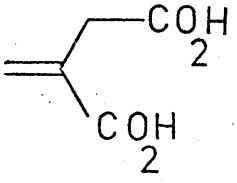
carbon skeleton complexity becomes much simpler and more amenable to synthetic design. In extant syntheses of gibbane systems it was known that routes dependent on a $\Delta^{9,11}$ gibbene intermediate[6,7,8] gave on reduction the unnatural BC trans fused system, in the absence of a C-6 keto group[9] or a suitably oriented C-6 substituent[10]. A similar fate befalls hydrofluorene precursors prepared by cyclodehyration of 1-benzyl cyclohexanones, although recent work[11] has shown that the stereochemical outcome is dependent on the nature of the 9a substituent of the hydrofluorene involved. The initial planning of our route required therefore a hydrofluorene, such as (61a), or an aryl bicyclo(3.2.1)octanone, such as (16a), from which this potential stereochemical weakness was eliminated. A Dieckmann cyclisation of the hexahydrofluorenone (61a), followed by hydrolysis and decarboxylation of the resulting β-keto ester, should afford the diketone (19). Alternatively, starting from the aryl bicyclo-(3.2.1)octanone (16a), the diketone (19) could be elaborated by a Friedel-Crafts reaction.

Both these synthons, (61a) and (16a), might be derived from a common precursor such as the acid (13a), the synthesis of which would introduce considerable latitude into subsequent planning. In this way, a Friedel-Crafts or a Dieckmann cyclisation carried out on the acid (13a) or its appropriate derivatives should lead to the synthons (61a) or (16a) respectively. Moreover, since ring B in each case would have been made by a Friedel-Crafts reaction, a preferred cis ring fusion[12] in the hydrofluorene intermediates (61a) and (19) might be expected even from a mixture of the acid (13a) and its C-2 epimer, affording the natural stereochemistry at C-9 in the final product.

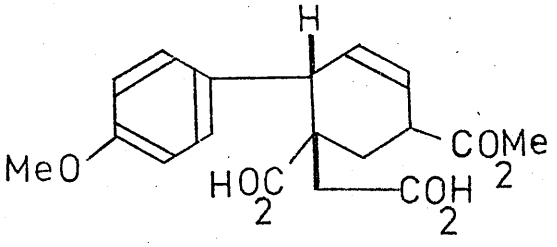
The method of choice for the construction of the cyclohexane


COMe
2
MeO

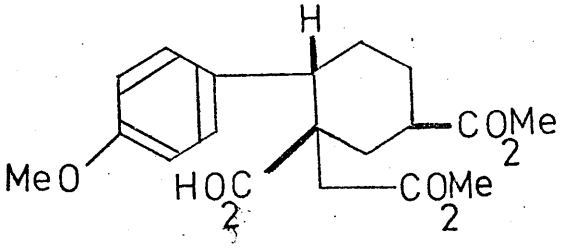
(2)


CO2H
CO2H

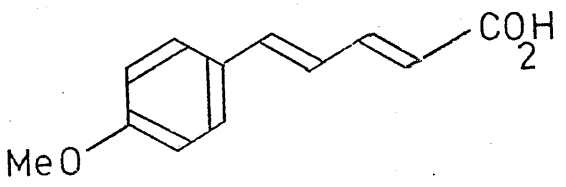
(4)


H
COMe
2
MeO
HOC
2
CO2H

(62)


H
COMe
2
MeO
HOC
2
COMe
2

(13c)

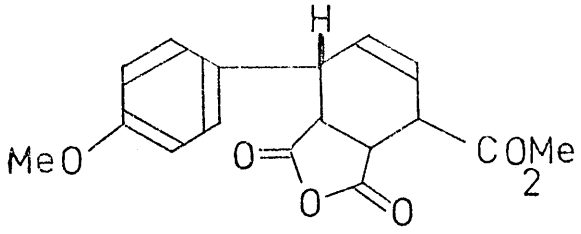

CO2H
MeO

(1)

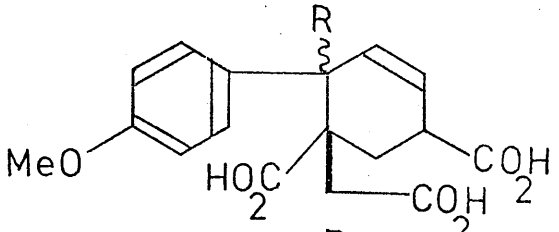
ring with stereochemical control over the pendant functionality in the acid (13a) is the Diels-Alder condensation.[13] If the "principle of maximum overlap of non-bonding orbitals" was obeyed, the diene ester (2) and itaconic acid (4) should align themselves as closely as possible with the anisyl group of the diene and the conjugated acid group of the dienophile overlapping each other. Since this orientation of the reactants leads to the thermodynamically most favoured transition state, conrotation of the diene (2) and itaconic acid (4) with concomitant bond formation should give the acid (62) as the predominant adduct in a regiospecific and stereoselective manner.[14] Hydogenation followed by selective esterification of the unhindered, primary acid group should then transform (62) into the desired acid (13a). Any epimeric acid (13c), with the anisyl group and the tertiary acid group trans to each other, would cyclise with much greater difficulty than (13a) in a Friedel-Crafts reaction.[12] A stereoselective preparation of the hydrofluorenone (61a) or the diketone (19) could therefore be accomplished from a mixture of (13a) and (13c).

Itaconic acid (4) is commercially available and inexpensive while the diene ester (2) should be readily accessible by the base catalysed condensation of p-methoxybenzaldehyde and methyl crotonate. By analogy with the known[15] reaction of m-methoxybenzaldehyde, the trans, trans diene should result, but prolonged exposure of the diene (2) to iodine in daylight[16] should guarantee this. Hence, with the starting materials at hand and a plan in mind, work could begin on the total synthesis of gibberellin A_4.

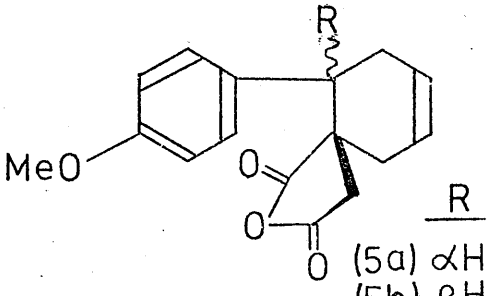
Condensation of p-methoxybenzaldehyde and methyl crotonate in t-butanol containing potassium t-butoxide produced a mixture of the diene acid (1) and the diene ester (2). When the mixture was



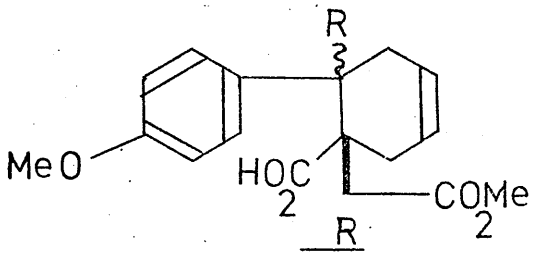
(3)



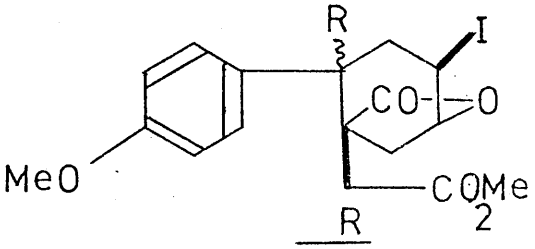
R
(63a) αH
(63b) βH



R
(5a) αH
(5b) βH



R
(6a) αH
(6b) βH



R
(7a) αH
(7b) βH

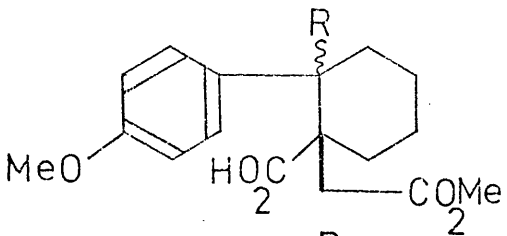
saponified and treated with iodine, 5-(p-methoxyphenyl)-trans, trans-penta-2,4-dienoic acid (1) was obtained in 84% yield as a single geometric isomer, as confirmed by n.m.r. spectroscopy.

Acid catalysed methanolysis of the mixture of dienes (1) and (2) gave, after iodine treatment, the pure methyl ester (2) in 88% yield. A Diels-Alder reaction of the diene ester (2) with maleic anhydride afforded a single crystalline adduct (3), homogeneous by g.l.c. and n.m.r. standards. Rigorous confirmation of the structure and purity of dienes (1) and (2) was thus achieved by physical and chemical means.

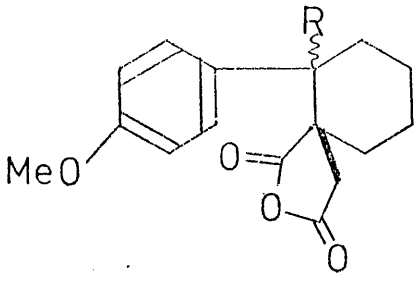
In this work all asymmetric synthetic products described are racemic mixtures. Only one enantiomer is drawn for each; nomenclature is for the enantiomer depicted.

When the Diels-Alder reaction of (1) with itaconic acid (4) was carried out at 160° in the absence of solvent, the initially formed adducts (63a) and (63b) underwent thermal dehydration of the succinic acid unit and decarboxylation of the βγ-unsaturated acid unit to give a 1:1 mixture (by g.l.c. analysis) of the two stereoisomeric anhydrides (5a) and (5b); carbonyl absorptions of 1845 and 1770 cm^{-1} in the i.r. spectrum of (5a) and (5b) confirmed the anhydride group in these adducts.

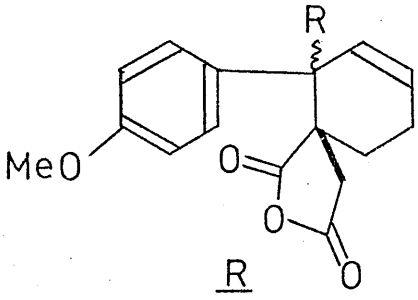
Regiospecific methanolysis at the primary carbonyl function of the anhydrides (5a) and (5b) yielded the acids (6a) and (6b), which were converted to the corresponding iodo lactones (7a) and (7b). The fact that (7a) and (7b) were γ-lactones (ν max 1779 cm^{-1}) proved that the anhydrides (5a) and (5b) had opened on methanolysis as expected to give the tertiary acids (6a) and (6b). The position of the double bond in the acids (6a) and (6b) was substantiated by a study of their n.m.r. spectrum. Since the benzylic proton in (6a)



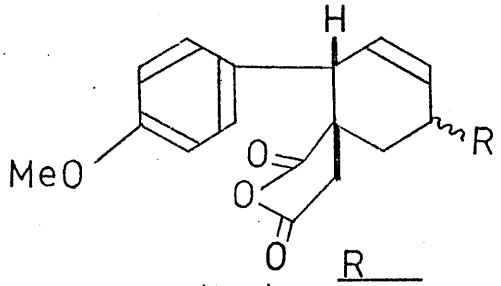
	R
(8a)	αH
(8b)	βH



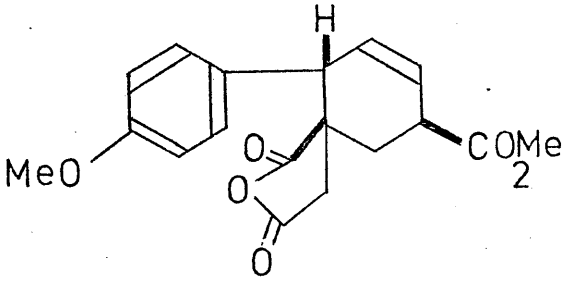
	R
(9a)	αH
(9b)	βH



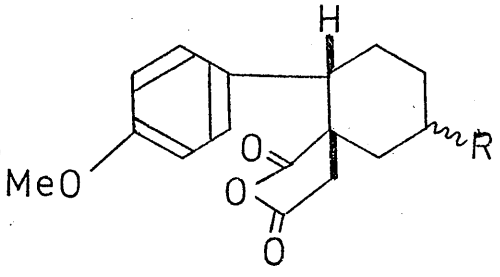
	R
(10a)	αH
(10b)	βH



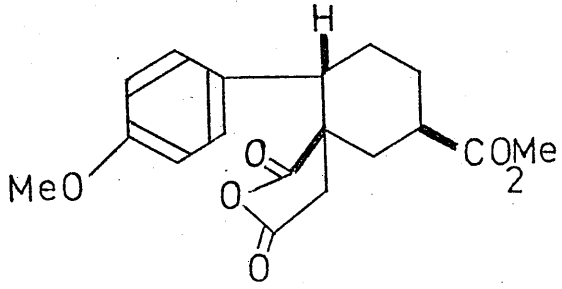
	R
(11a)	αCOMe 2
(11b)	βCOMe 2



(11c)



	R
(12a)	αCOMe 2
(12b)	βCOMe 2



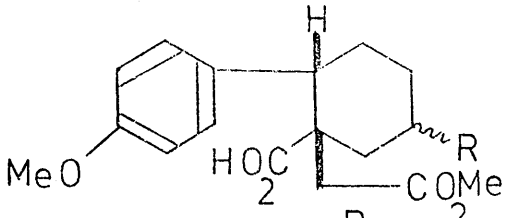
(12c)

or (6b) resonates at δ 3.5-3.2, as compared with δ 4.2-3.8 in the adduct (3), it can no longer be allylic to the double bond. This observation agrees with the fact that the double bond migrates during decarboxylation, and thereby lessens steric congestion caused by the quasi-axial C-5 carboxylic acid of the adducts (63a) and (63b).

Hydrogenation of the acids (6a) and (6b) afforded the corresponding cyclohexane derivatives (8a) and (8b), which on sublimation afforded the anhydrides (9a) and (9b). The latter compounds, (9a) and (9b), were synthesised by an alternative route, involving the condensation of 1-p-methoxyphenyl butadiene, prepared[17] by the reaction of p-methoxyphenyl magnesium bromide and crotonaldehyde, and itaconic acid (4). The 1:1 mixture (by g.l.c. analysis) of adducts (10a) and (10b) obtained was hydrogenated to the anhydrides (9a) and (9b), which were identical to the mixture prepared earlier.

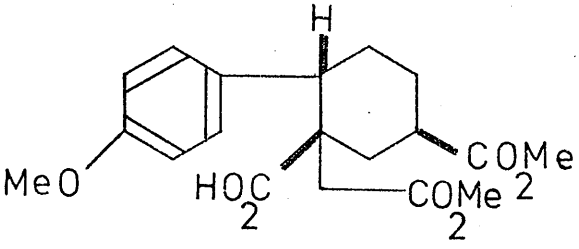
To prevent thermal decarboxylation of the initially formed Diels-Alder adducts the diene ester (2) was used and, with itaconic acid again as the dienophile, a mixture of three stereomeric adducts was produced in 80% yield. The major constituents (60% of the mixture) were the quasi-axial and quasi-equatorial esters (11a) and (11b) in the ratio 1:2.3 (by g.l.c. analysis); the third adduct was the quasi-equatorial ester (11c), epimeric with (11b) at C-1. This observation is contrary to the findings of Gerber[18], who reported the isolation of a single isomer, of undefined stereochemistry, derived from the reaction of 5-phenyl-trans,trans-penta-2,4-dienoic acid and itaconic acid. Assignment of stereochemistry to the adducts (11a), (11b) and (11c) was made as follows.

Hydrogenation to the corresponding cyclohexane derivatives (12a), (12b) and (12c) followed by methanolysis afforded a mixture

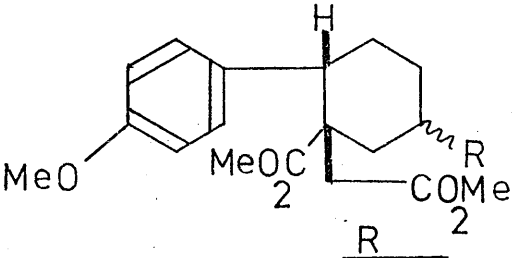


(13a) $\frac{R}{\alpha COMe_2}$

(13b) $\beta COMe_2$

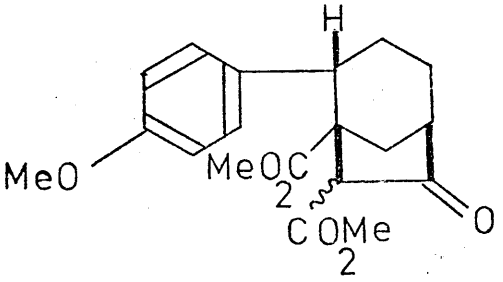


(13c)



(14a) $\frac{R}{\alpha CO_2Me}$

(14b) βCO_2Me



(15a)

of the acids (13a), (13b) and (13c) in the same isomer ratio as the initial adducts (by g.l.c. analysis). Since sublimation of the acids (13a), (13b) and (13c) gave the anhydrides (12a), (12b) and (12c) respectively, the acids could be injected directly on to a g.l.c. column at 225° and studied as their anhydrides.

The acid (13a) was separated readily from (13b) and (13c) due to its very low solubility in methanol, and shown to be axial at C-5 by its quantitative epimerisation in methanol containing sodium methoxide to the acid (13b) (by g.l.c. comparison).

Both acids (13a) and (13b) were esterified separately with diazomethane so that a comparison of the relative rates of Dieckmann cyclisation of their corresponding methyl esters could be made. The fact that the equatorial trimethyl ester (14b) underwent quantitative cyclisation with sodium methoxide in benzene - of necessity in the alternative chair diaxial conformation (figure 1, path 1) - to the

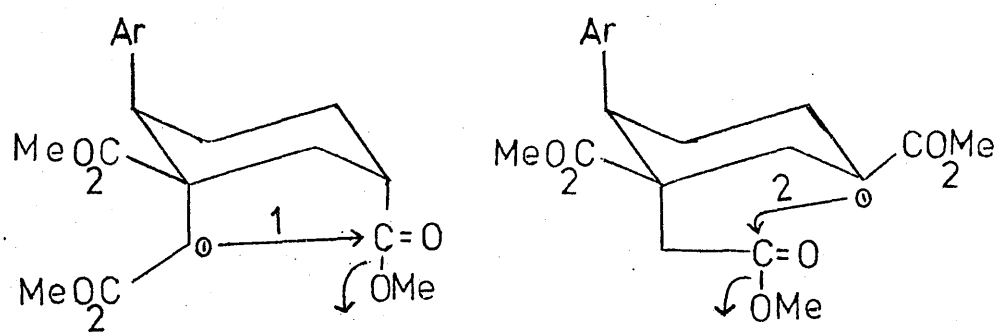
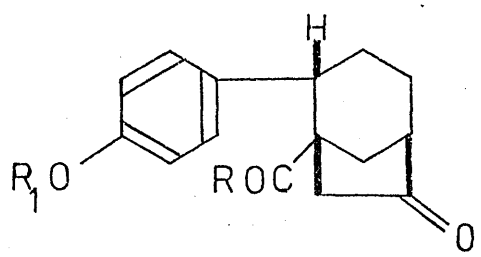
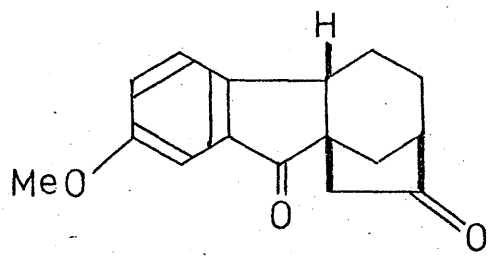


FIGURE 1

bicyclo(3.2.1)octanone (15a), whereas similar conversion of the axial trimethyl ester (14a) proceeded more slowly and via (14b), established the <u>cis</u> diequatorial relationship of the C-1 CH_2CO_2Me and the C-5 CO_2Me groups in (14b) and hence in (11b). An alternative Dieckmann cyclisation of (14a) involving the C-5 carbanion and the C-1 CH_2CO_2Me group (figure 1, path 2) is theoretically possible, but no



	R_1	R
(16a)	Me	OH
(17)	H	OH
(18a)	Me	Cl
(24a)	Me	OMe



(19)

example of such a closure leading to an unstable β-keto ester is reported in the literature.[19]

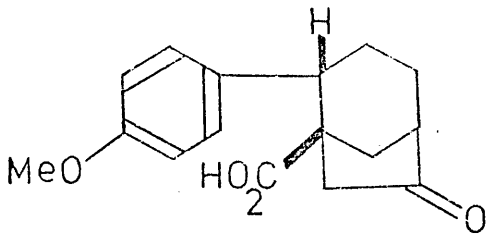
Although two configurations of the C-7 carbomethoxyl group in the bicyclo(3.2.1)octanone from the Dieckmann cyclisation were possible, the bicyclic β-keto ester (15a) was surprisingly highly crystalline and appeared homogeneous on g.l.c. and also by n.m.r. studies. The exact stereochemistry of this C-7 group was not investigated since it would be removed in the next step of the synthesis. The apparent strain in the bicyclic system was reflected in the high carbonyl frequency (1764 cm^{-1}) of (15a). The corresponding enolate form of (15a) was readily formed since (15a) gave a positive ferric chloride test and was soluble in aqueous sodium carbonate. The latter observation facilitated its separation from any unreacted trimethyl ester (14b) following the Dieckmann cyclisation.

The bicyclic β-keto ester (15a) was converted in 70% yield by acid hydrolysis to 1-carboxy-anti-2-(p-methoxyphenyl)bicyclo(3.2.1)-octan-6-one (16a). The stereochemistry of the anisyl group in this compound and in its precursors was uncertain until the later conversion of (16a) to the gibbane diketone (19). The intermediate β-keto acid had decarboxylated, as expected, on refluxing the aqueous acetic acid solution. During this reaction, however, about 5% of the phenolic acid (17) was produced due to acid catalysed cleavage of the methyl ether of (16a). Successive treatment of the over-reacted product (17) with dilute aqueous sodium hydroxide and dimethyl sulphate gave the methyl ester (24a), which was hydrolysed back to the required acid (16a) with dilute base.

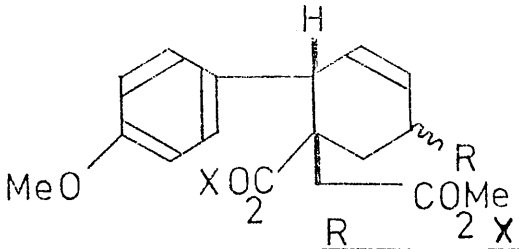
Oxalyl chloride reacted smoothly with the keto acid (16a) at room temperature but the resulting acid chloride (18a) (ν max1785 and

1740 cm^{-1}) failed to undergo an intramolecular Friedel-Crafts reaction using only one molar equivalent of aluminium trichloride in benzene. Only absorption at 276 and 283 nm due to the p-methoxyphenyl group of the acid chloride was visible in the u.v. spectrum. Addition of a second molar equivalent of aluminium trichloride, however, afforded in 90% yield 3-methoxy-6,16-dioxo-9βH-gibb-A-triene (19), thereby establishing the cis relationship of the C-1 carboxyl and the C-2 p-methoxyphenyl groups and therefore the equatorial configuration of the latter group in (11a), (11b) - (14a), (14b). The configuration at C-9 in (19) was confirmed later by independent correlations of derivatives of (19). The cyclopentanone and indanone carbonyl groups of (19) showed absorptions in the infrared at 1751 and 1711 cm^{-1} respectively, while the u.v. spectrum of (19) exhibited maxima at 251 and 321 nm, typical absorptions for a hexahydrofluorenone such as (19). When more than two molar equivalents of aluminium trichloride were used or added too quickly, the yield and purity of the diketone (19) were lowered. Apparently, the first molar equivalent of Lewis acid had become, for all practical purposes, bound to the sterically more accessible ketone group of (18a), thereby unaffecting the electrophilicity of the acid chloride and preventing cyclisation. On the other hand, excess reagent had complexed with the methyl ether of (18a),[20] with the result that the nucleophilicity of the aromatic ring was greatly reduced. In this case, since the acid chloride of (18a) was activated but the aromatic ring was deactivated, side reactions such as acylation of the solvent could occur, thereby lowering the yield and purity of the diketone (19).

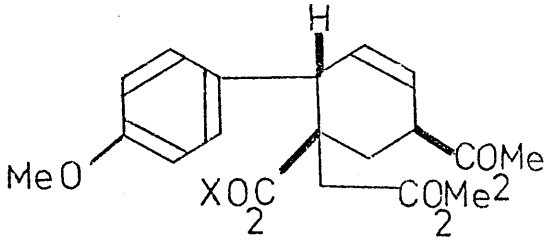
Having achieved the synthesis of the first objective, namely the diketone (19) from the single isomeric acid (13a) in good overall yield, it was considered that a similar sequence of reactions



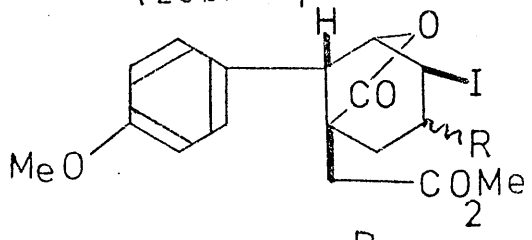
(16b)



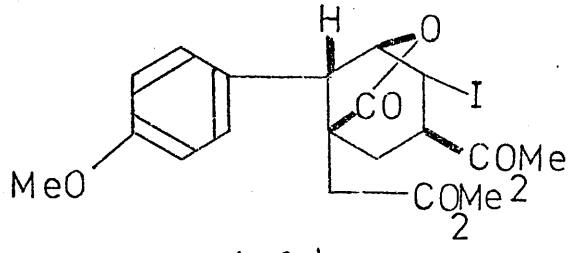
	R	X
(21a)	α $COMe_2$	Me
(20a)	α "	H
(21b)	β $COMe_2$	Me
(20b)	β "	H



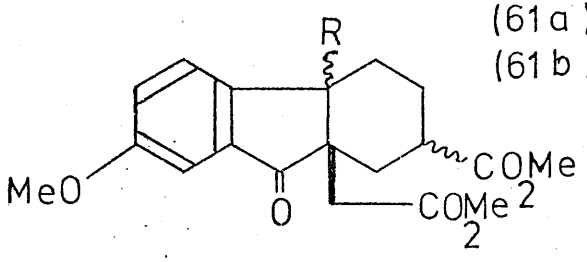
	X
(21c)	Me
(20c)	H



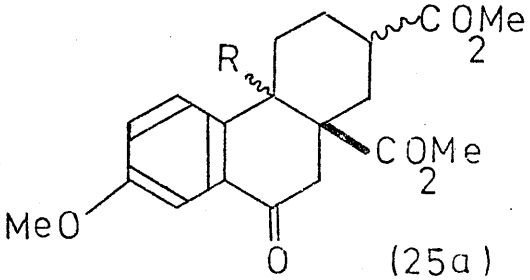
	R
(22a)	α $COMe_2$
(22b)	β $COMe_2$



(22c)



	R
(61a)	β H
(61b)	α H

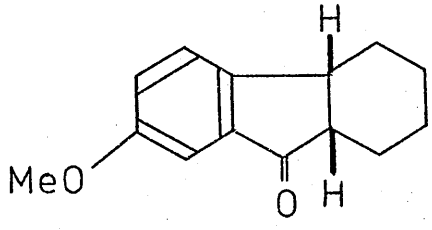


	R
(25a)	β H
(25b)	α H

applied to the mixture of the stereoisomeric acids (13a), (13b) and (13c) would afford the diketone (19) from (13a) and (13b); compound (13c), in which the C-2 anisyl and C-1 tertiary carboxyl groups are trans related, was not expected to undergo a Friedel-Crafts cyclisation when it was converted to the bicyclo(3.2.1)octanone (16b). However, before this investigation was carried out, attempts were made to effect the separation of any of the epimeric precursors of the keto acids (16a) and (16b). Since chromatography was neither effective nor desirable in separating the stereoisomers of type (11), (12), (14) or (21), a chemical separation was investigated.

Methanolysis of the initial Diels-Alder adducts (11a), (11b) and (11c) gave the unsaturated acids (20a), (20b) and (20c) respectively, in the same isomer ratio (by g.l.c. analysis) as before. Iodolactonisation of these unsaturated acids was attempted in the hope that the reaction might be selective because of the different steric congestion expected in the products. When the derived iodolactones (22a), (22b) and (22c) were treated with zinc and acetic acid, however, the starting acids were regenerated in almost the same isomer ratio (by g.l.c. analysis) as before.

Attention was also focussed on the behaviour of the acid chlorides of the acids (13a), (13b) and (13c) towards cyclisation, in the hope that (13a) and (13b), with the anisyl and the carboxyl groups cis related to each other, would cyclise preferentially to give the hydrofluorenone (61a). However, when the derived acid chlorides (ν max 1780 and 1730 cm^{-1}) were treated with aluminium trichloride, a 1:1 mixture (by g.l.c. analysis) of two hydrophenanthrenones (25a) and (25b) (ν max 1683 cm^{-1}) was obtained in high yield. Although no attempt to derive the stereochemistry of the hydrophenanthrenones was made, they were most likely the cis BC and trans BC



(58)

compounds respectively; one of the isomers could be isolated by fractional crystallisation.

Assignment of the structure (25a) or (25b), rather than (61a) or (61b), was made from spectroscopic observations. Firstly, a carbonyl frequency of 1683 cm^{-1} is indicative of a tetralone rather than an indanone (ν max normally of about 1705 cm^{-1}). Secondly, an absorption maximum in the u.v. at 255 nm is significantly different from 248 nm, as observed in a corresponding hydrofluorenone, such as (58).[4] Indeed, 1-tetralone and 1-indanone absorb at 248 and 243 nm respectively.[21] Thirdly, the $-CH_2CO-$ grouping in ring B was observed as an unperturbed AB quartet (J=16Hz) at δ3.26 and δ2.32. The large separation in the chemical shift position of H_A and H_B was indicative of the hydrophenanthrenone (25a) or (25b) rather than the hydrofluorenone structure (61a) or (61b) in which type of system[22] the C-10a CH_2CO_2R grouping appears as a fine doublet (in fact a distorted AB quartet) due to the small δ/J ratio.

A mechanism by which the hydrophenanthrenones (25a) and (25b) are produced is postulated as follows. The aluminium trichloride reacts with the tertiary acid chloride which is then attacked intramolecularly by the primary ester to give the complex as shown in figure 2. Friedel-Crafts cyclisation occurs to give the tetralone

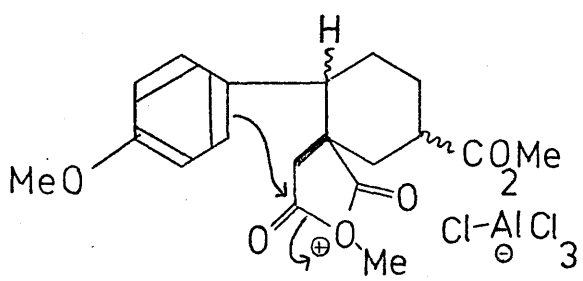
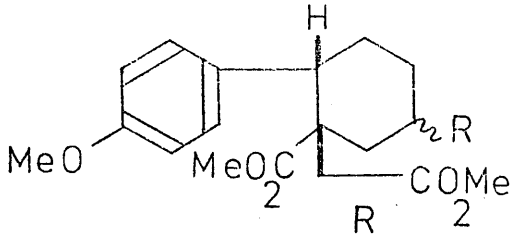


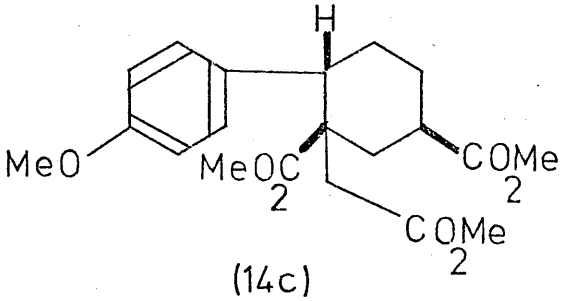
FIGURE 2

in preference to the indanone[23] and, at the same time, transester-

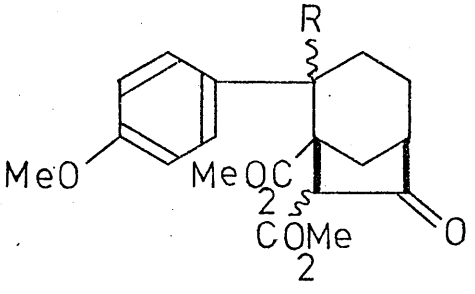


(14a) α R / CO_2Me

(14b) β CO_2Me

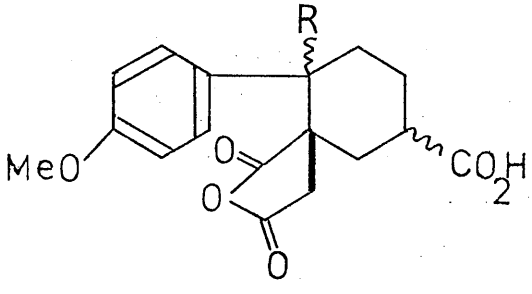


(14c)



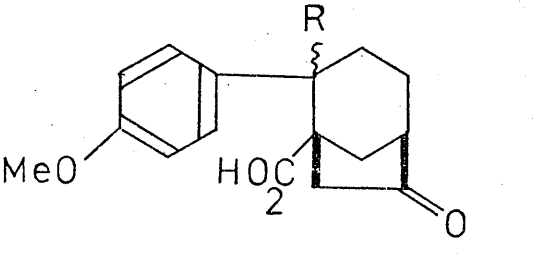
(15a) β R / H

(15b) α H



(23a) β R / H

(23b) α H



(16a) β R / H

(16b) α H

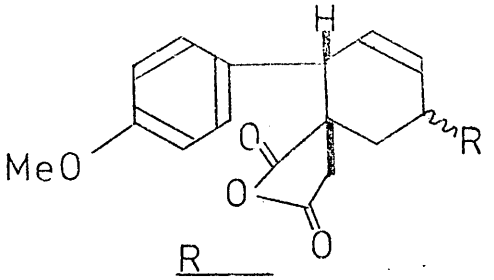
ification gives the tertiary ester at C-10a in (25a) or (25b). As a chemical substantiation of these observations, a mixture of the hydrophenanthrenones (25a) and (25b) was refluxed with sodium methoxide but no β-keto ester was produced.

Another attempt at a chemical separation was investigated at the Dieckmann reaction of the mixture of trimethyl esters (14a), (14b) and (14c). The relative rates of cyclisation of these epimers were insufficiently different, however, to enable separation of the resulting β-keto esters (15a) and (15b).

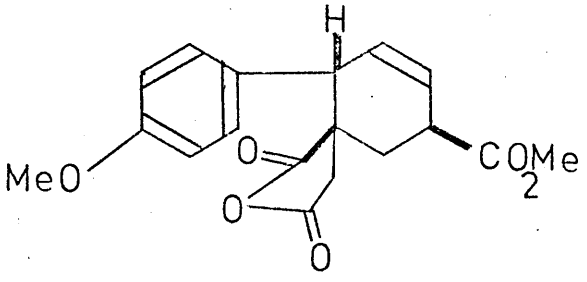
An attempt was also made to separate the β-keto esters (15a) and (15b) by preferential formation of a sodium enolate using dilute aqueous sodium carbonate or sodium hydroxide but this was unsuccessful. Prolonged exposure of the β-keto esters (15a) and (15b) to dilute aqueous sodium hydroxide caused a retro-Dieckmann reaction followed by ester hydrolysis to give the anhydride acids (23a) and (23b) on sublimation.

When the Friedel-Crafts reaction was applied to the mixture of the acid chlorides derived from the keto acids (16a) and (16b), prepared from the β-keto esters (15a) and (15b) by acid hydrolysis, a readily separable mixture of the gibbane diketone (19) and 1-carboxy-syn-2-(p-methoxyphenyl)bicyclo(3.2.1)octan-6-one (16b) was obtained. The success of this reaction is due partly to the preferred cis ring fusion in hydrofluorenones. In this case, however, the acid (16b) also requires substantially more activation energy than does (16a) to cyclise, due to the extra torsional strain required to bring the trans orientated C-1 carboxyl and C-2 p-methoxyphenyl groups into one plane.

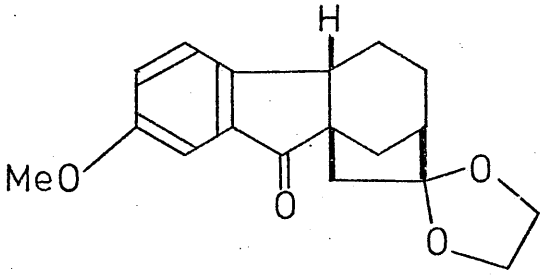
The conversion of the trimethyl ester (14c) to the keto acid (16b) and the stability of (14c) in admixture with (14a) and



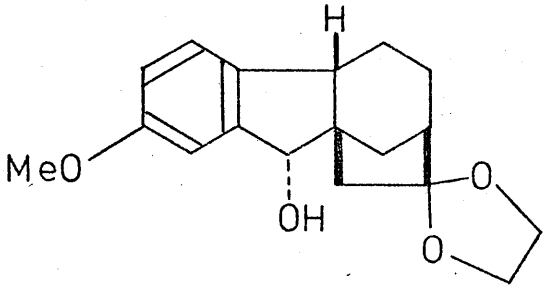
	R
(11a)	α CO_2Me
(11b)	β CO_2Me



(11c)



(26)



(27)

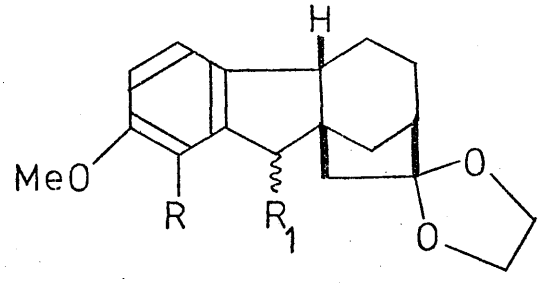
(14b) to epimerisation (as determined by g.l.c.) established the structure of (11c) as shown, i.e. trans diequatorial at C-2 and C-5.

The violation of the "cis addition principle"[24] in the production of the initial anhydride adducts (11b) and (11c) (82% of the total mixture) is considered to occur by a thermally catalysed process,[25] either in the transition state or after initial product formation to relieve the 1,3 quasi-diaxial interactions at C-1 and C-5 which result in the normal Diels-Alder product (11a).

With an efficient route to 3-methoxy-6,16-dioxo-9βH-gibb-A-triene (19) now available means whereby the C-4 carboxyl group could be introduced and the C-6 ketone function transformed into a C-6β carboxyl function were now investigated. Regiospecific C-4 carboxylation was effected as follows.

Selective acetalisation of the more reactive aliphatic carbonyl function in the diketone (19) with ethylene glycol produced the monoacetal (26) in 97% yield. The mother liquors from the crystallisation of the monoacetal (26) contained bis-acetal which could be hydrolysed readily to the diketone (19) and recycled to (26). Confirmation of the structure (26) assigned to the monoacetal was achieved spectroscopically. The hydrofluorenone chromophore of the diketone (19) in both the i.r. (1711 cm^{-1}) and u.v. (251 and 321 nm) spectra remained unchanged in the product, while the aliphatic cyclopentanone frequency at 1751 cm^{-1} was absent.

Reduction of the monoacetal (26) with lithium aluminium hydride in ether afforded a single alcohol, m.p. 138-139°, in 98% yield. The alcohol obtained was believed to have the C-6α configuration indicated in structure (27) as a result of attack of the complex metal hydride anion from the less hindered β-face of the molecule.[4]



	R	R_1
(28)	CO_2H	αOH
(29)	$COMe_2$	αOH
(30)	CO_2H	β CN
(31)	$COMe_2$	β Br
(32)	$COMe_2$	β CN
(35)	CO_2H	H

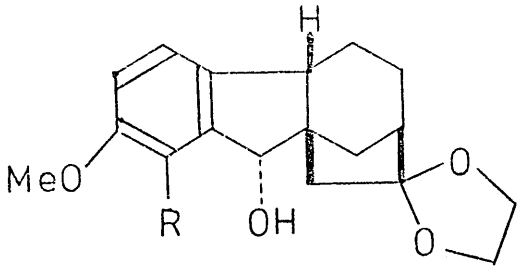
When the alcohol (27) was reacted with n-butyl lithium in tetrahydrofuran, no C-metallation resulted and the alcohol (27) was recovered unchanged.

The corresponding reaction, however, with a mixture of n-butyl lithium and sodium t-butoxide[4] in hexane, followed by carbonation and acidification, produced the desired carboxylic acid (28) in 90% yield. The n.m.r. spectrum of the acid (28) established that the substitution had occurred in the C-4 position, since the aromatic protons exhibited an AB pattern with J=9Hz, consistent with the presence of two ortho related protons.

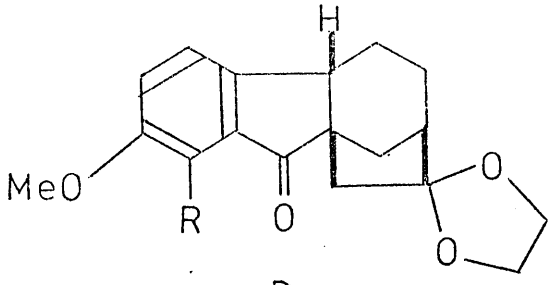
Several approaches were now made to the replacement of the C-6 hydroxyl function of (28) with a C-6β carboxyl group. It was considered that the most obvious and straightforward method would be the direct displacement of the derived tosylate of the hydroxy acid (28) by cyanide anion, resulting in the inversion of the configuration at C-6 to give the C-6β cyano acid (30). However, the desired tosylate failed to form, a result not entirely unexpected from steric and stability considerations, since the C-6 position of (28) is both benzylic and neopentylic.

As an alternative route to the cyano acid (30) the bromo ester (31) was synthesised. Reaction of the hydroxy ester (29), derived from the hydroxy acid (28) with ethereal diazomethane, with triphenylphosphine dibromide[26] produced the bromo ester (31), which with sodium cyanide in dimethyl sulphoxide afforded a mixture of unidentified products rather than the desired cyano ester (32).

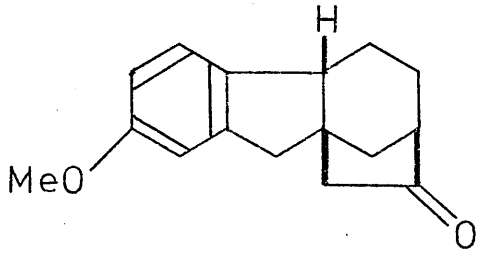
Since nucleophilic substitution by cyanide at C-6 in derivatives of (28) proved unsuccessful, attention was turned to the conversion of the hydroxy acid (28) to the C-6 desoxy acid (35), so that a C-6 benzylic carbanion might be generated using a sufficiently



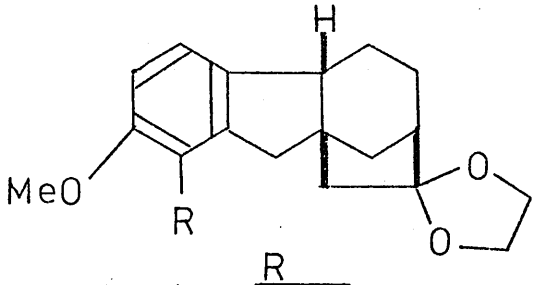
	R
(27)	H
(28)	CO_2H



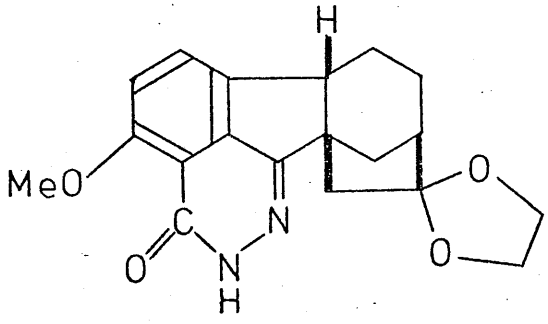
	R
(26)	H
(37)	CO_2H



(34)



	R
(33)	H
(35)	CO_2H



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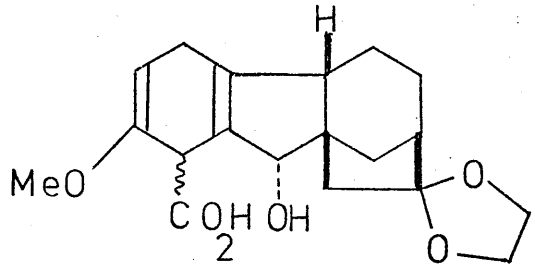

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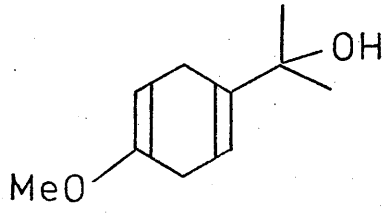


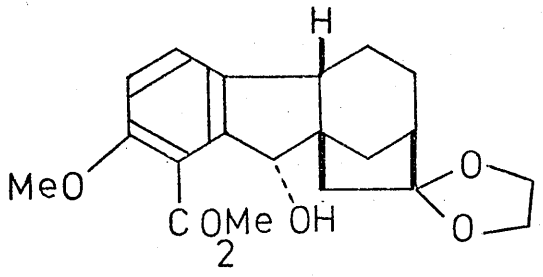
(64)

strong base. To conserve material, the hydroxy acetal (27) was used as a model for the hydroxy acid (28) in a series of experiments concerned with the elimination of the C-6 hydroxyl group.

Jones oxidation of the hydroxy acetal (27) gave the keto acetal (26) from which the monoketone (34) was prepared by Wolff-Kishner reduction and hydrolysis. By the same procedure, the hydroxy acid (28) was converted to the keto acid (37) but subsequent reduction of (37) to the C-6 desoxy acid (35) proved unsuccessful. Apparently, during the Wolff-Kishner reaction hydrazine had condensed with both the keto and carboxyl groups of (37) to form (38), which resisted reduction at C-6 and prevented the acid (35) from being formed.

When the hydroxy acetal (27) was treated with sodium in liquid ammonia, smooth hydrogenolysis of the C-6 hydroxyl group occurred to afford the desoxy acetal (33) as the sole product. The C-1 carbanion, produced in the Birch reduction, appears to be able to effect an intramolecular elimination of the allylic C-6 hydroxyl before being protonated by the liquid ammonia. This is in agreement with findings by Birch[27], who showed that 3-methoxyphenyldimethylcarbinol was hydrogenolysed to 3-methoxyisopropylbenzene whereas the 4-methoxyphenyldimethylcarbinol gave the dihydroaromatic alcohol (64). The structure of the desoxy acetal (33) was confirmed by its hydrolysis to the ketone (34), prepared previously.

The corresponding reaction of the hydroxy acid (28) with sodium and liquid ammonia, gave only the dihydroaromatic hydroxy acid (36) and not the desired C-6 desoxy acid (35). In this case, the C-4 carbanion can abstract the C-6 hydroxyl proton via the enolate anion of the C-4 carboxylic acid (figure 3). Since the C-6 hydroxyl group is now protected as its alkoxide anion,[28] ring reduction rather than hydroxyl elimination takes place to give the dihydroaromatic



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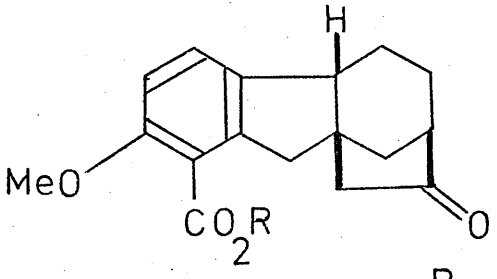


	R
(39)	H
(41)	Me

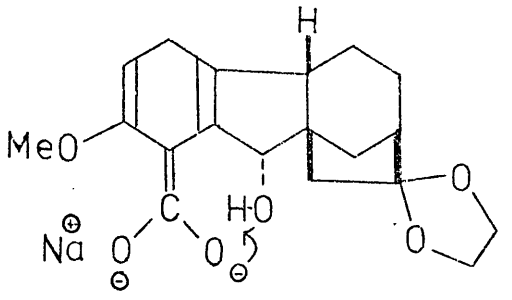


FIGURE 3

hydroxy acid (36). The structure of (36) was confirmed by its reoxidation to the hydroxy acid (28), using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Hydrogenolysis of the hydroxy acetal (27), using 10% palladium/charcoal and perchloric acid as catalyst in ethyl acetate, afforded, with concomitant deacetalisation, the ketone (34).

When the corresponding reaction was carried out in the absence of mineral acid, the hydroxy acetal (27) was recovered unchanged. Complete substitution in the α-position of an aryl alkyl ketone was reported[29] to inhibit hydrogenolysis e.g. pivalophenone, $C_6H_5COC(CH_3)_3$, is smoothly and quantitatively reduced to the carbinol but not to the hydrocarbon. It seems, therefore, that a sp^2 hybridised carbon, such as found in a ketone or in a carbonium ion, is necessary before hydrogenolysis can take place.

Application of the hydrogenolysis conditions to the hydroxy acid (28) or its derived methyl ester (29) produced the desoxy acid (39) or its methyl ester (41) in quantitative yields. In the reaction of the methyl ester (29) methyl acetate rather than ethyl acetate was used as solvent in order to prevent trans-esterification between the solvent and the reactant.

At this stage in the synthesis, an opportunity arose to confirm the stereochemistry at C-9 in the ketones (34) and (41), since their C-9 epimers, (34b)[7] and (41b)[30] respectively, had

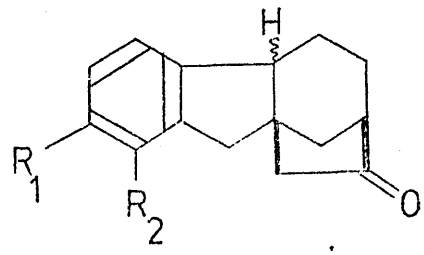
been synthesised by two entirely different methods from that used in this thesis. One of the problems encountered in the syntheses leading to gibberellins is the determination of the stereochemistry at C-9 in gibbane intermediates. Stereochemical assignment has hitherto been made on the basis of (1) preferred cis ring fusion in hydrofluorene intermediates,[12] and (2) the stereospecific reduction of $\Delta^{9,11}$ gibbenes governed by the orientation of a C-6 substituent.[10,31,32] Spectroscopic methods for the assignment of the C-9 sterochemistry in gibbanes lacking functionality at C-6 were developed in this investigation to offer, in part, a solution to this problem.[33]

In the C-9α gibbanes (34b), (41b) and (65b)[34] the respective C-6 methylene protons resonate at higher field than those of the isomeric C-9β gibbanes (34), (41) and (65)[34], as shown in Table 1. This effect may arise, in the C-9β isomers, by greater deshielding of the C-6 protons by the C-8, C-15 and C-8, C-14 σ-bonds with which they are separately coplanar.

TABLE 1

Compound	R_1	R_2	H-9	A	- C-6 -	B	J_{AB}
(34b)	MeO	H	α	2.53		2.23[a]	14
(34)	MeO	H	β	2.71		2.33[a]	16
(41b)	MeO	CO_2Me	α	3.06		2.85[b]	16
(41)	MeO	CO_2Me	β	3.18		2.88[b]	16
(65b)	H	Me	α	2.82		2.70[b]	16
(65)	H	Me	β	3.01		2.79[b]	16

a) In C_6D_6 at 100 MHz; b) In $CDCl_3$ at 60MHz.

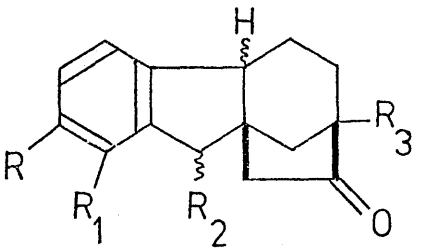


The small difference (1.5 Hz) in chemical shift of the methoxyl resonances in (34) and (34b) enables the isomer composition from the reduction of the corresponding $\Delta^{9,11}$ gibbene to be readily determined (61:39); so far (34) and (34b) have not been resolved on g.l.c..

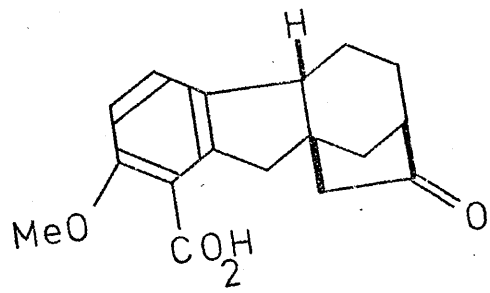
In gibban-16-ones having ester functionality at C-4 or C-6 it is apparent from this work, and from data extant in the literature,[32,35] that there is a tendency for C-9α isomers to exhibit C-16 carbonyl absorption in the infrared near 1740 cm^{-1} whereas C-9β isomers absorb nearer 1730 cm^{-1} (Table 2). This effect is best observed when spectra are recorded as KBr discs.

TABLE 2

H-9	R	R_1	R_2	R_3	C=O	Phase	Ref.
α	H	CH_3	β-CO_2Me	CH_3	1745	Nujol	32
α	MeO	CO_2Me	β-CH_3	H	1746	CCl_4	6
β	H	CH_3	α-CO_2Me	CH_3	1736	Nujol	32
β	H	CH_3	β-CO_2Me	CH_3	1735	Nujol	32
α	H	H	-CHO	CH_3	1745	CCl_4	35
α	MeO	CO_2Me	H	H	1742	KBr	36
β	MeO	CO_2Me	H	H	1735	KBr	



It would appear from a study of molecular models that the derivation of the stereochemistry at C-9 in C-9α and C-9β epimers (e.g. 41 and 41b) by n.m.r. spectroscopy would not be possible since H-9 in both epimers subtends similar dihedral angles with the C-11 protons.



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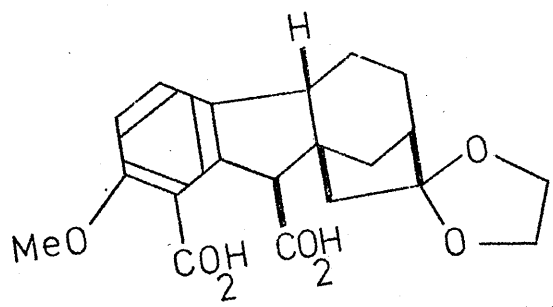


(42)

The H-9 proton in favourable cases e.g. (34b) is observed as a quartet (X part of a ABX system) but the respective couplings J_{AX} and J_{BX} are not derivable due to the complexity of the AB pattern hidden among other resonances. Moreover, there appears to be little if any difference in chemical shift for C-9α and C-9β isomers.

The problem of elucidating the stereochemistry at C-9 has been solved previously[6] by the observed deshielding effect of a C-16β acetoxy group on the C-11αH in a C-9αH gibbane derivative. This method is tedious and involves the rigorous establishment of the chemical shift (by solvent shift technique) of the protons under investigation. In C-9β gibbanes the 9βH proton is expected to undergo deshielding by the C-16 acetoxy function.

A method which also offers a solution to this problem is based on the fact that 9α C-16 methylene gibbanes undergo autoxidation at C-15 whereas 9β gibbanes do not.[37]

With the stereochemistry of the keto acid (39) firmly established as having the B and C rings cis fused, as found in the gibberellins, the further elaboration of (39) to the diacid (42) via carboxylation of the C-6 benzylic carbanion was investigated.

Creger[38] had recently demonstrated that o-toluic acid could be converted to its carboxyate-benzylic dianion by treatment with lithium diisopropylamide in tetrahydrofuran. The ready formation of the benzylic anion in the case is presumably due to the effective resonance stabilisation and oxygen lone pair stabilisation in the planar system as shown in figure 4. Reaction of

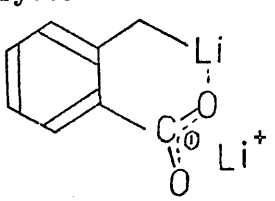
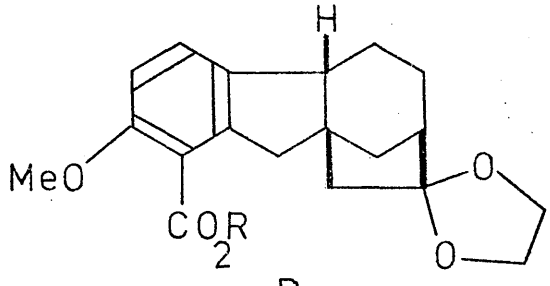
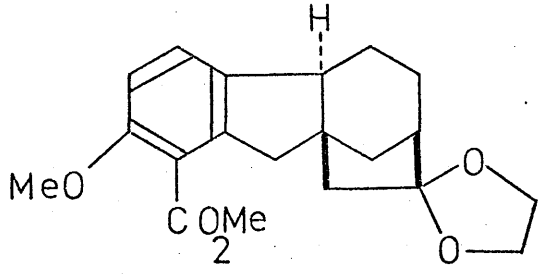


FIGURE 4



	R
(35)	H
(40)	CH_2CH_2OH



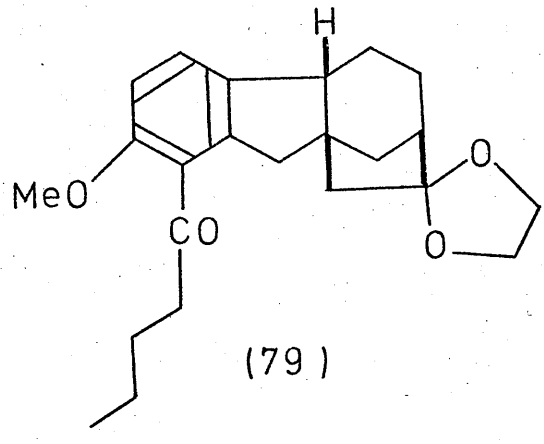
(66)

this dianion with various alkyl halides led to a series of o-alkyl benzoic acids.

Application of this method to the acetal acid (35) was now considered in the expectation that carbonation of the resulting benzylic anion would afford the required diacid. The acetal acid (35) was obtained from the keto acid (39) by acetalisation with ethylene glycol. In this preparation some esterification of the acid function by ethylene glycol also occurred, but the glycolate ester (40) produced could be saponified to the desired acetal acid (35).

Little if any C-6 metallation, however, resulted when the acetal acid (35) was treated with lithium diisopropylamide in tetrahydrofuran. The failure to generate the benzylic carbanion in this case cannot be due to steric hindrance to attack by the base, since Loewenthal has just recently shown[30] that the stronger base lithium N-cyclohexyl t-butylamide generated the benzylic carbanion of the C-9 epimeric gibbane ester (66). A more likely cause for the failure is the weaker acidity of the benzylic protons of (35) relative to o-toluic acid. In the acid (35) the C-6 protons are held at about 45° to the plane of the AB ring system with the result that the derived C-6 carbanion receives little stabilisation by way of orbital overlap with the aromatic ring. Consequently, a base stronger than lithium diisopropylamide was required to abstract the C-6 proton from the acetal acid (35).

The corresponding reaction of the acetal acid (35) with n-butyl lithium as base gave a mixture (70%) of the starting acid (35) and the desired diacid (42) in the ratio 2:1 (as determined by g.l.c. analysis of their corresponding methyl esters). The structure (42) for the diacid was confirmed at a later stage in the investigation. As well as these acidic compounds, 30% of the



(79)

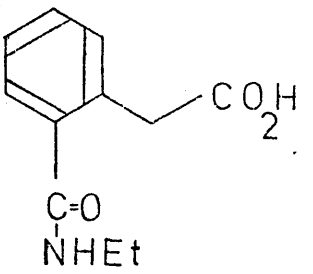
reaction mixture consisted of the aromatic n-butyl ketone (79), derived from nucleophilic attack on the lithium salt of the starting acetal acid (35) by the n-butyl lithium. Varying the reaction temperature or the rate of addition of the n-butyl lithium, or preforming the carboxylate anion of the acetal acid (35) with either lithium or sodium hydride, failed to increase the yield of the diacid (42) to any great extent.

The rate of abstraction of the C-6 proton and the rate of nucleophilic attack on the acid group seemed, therefore, to be quite competitive. Although bases such as sodium hydride and lithium diisopropylamide showed no tendency towards nucleophilic attack on the acid group of (35), they were nevertheless incapable of generating the C-6 carbanion.

A method was therefore sought to protect the acid function of (35) from nucleophilic attack while using n-butyl lithium as base to abstract the C-6 proton.

Hauser[39] has shown that, when N-methyl o-toluamide was heated under reflux with n-butyl lithium in tetrahydrofuran, the amide-benzylic dianion could be formed in excellent yield without any nucleophilic attack by the reagent on the amide carbonyl. Conversion of the acetal acid (35) into an N-alkyl amide should thus allow carboxylation at C-6 without concomitant ketone formation. Moreover, the isolation of the amido acid formed from such a reaction should be greatly facilitated using a neutral, rather than an acidic, starting material.

To test the feasibility of this proposal, the conversion of o-toluic acid, via N-ethyl o-toluamide, into homophthalic acid was investigated. The synthesis of N-ethyl o-toluamide from o-toluic acid was accomplished by refluxing the derived acid chloride



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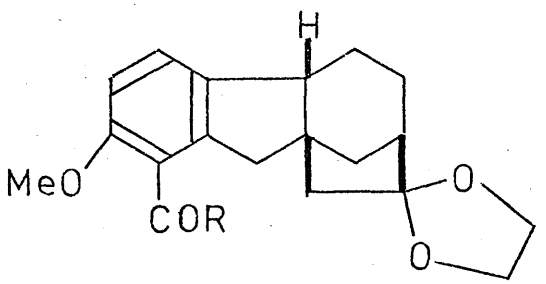
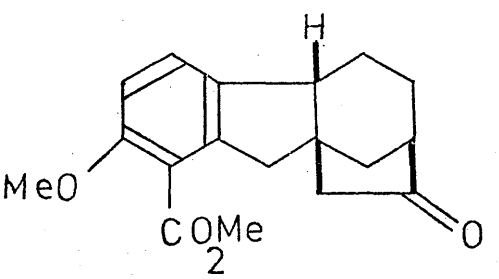


	R
(35)	OH
(40)	OCH_2CH_2OH
(45)	OMe
(46)	NHEt



(41)

with ethylamine, or alternatively, by treatment of methyl o-toluate at room temperature with lithium ethylamide. Subsequent conversion of N-ethyl o-toluamide to the amido acid (44) was achieved in high yield by the reaction of n-butyl lithium in tetrahydrofuran followed by carbonation and acidification. The amido acid (44) thus obtained was hydrolysed with dilute aqueous sodium hydroxide to homophthalic acid.

Since an acceptable overall yield (71%) had been achieved for the conversion of o-toluic acid to homophthalic acid, the same procedure was applied to the acid acetal (35).

Successive treatment of the acid acetal (35) with diazomethane and lithium ethylamide afforded the amide acetal (46) in almost quantitative yield. On a larger scale, the amide acetal (46) was more conveniently synthesised from the keto ester (41) in 94% overall yield as follows. Re-acetalisation of the keto ester (41) with ethylene glycol gave a 9:1 mixture (by g.l.c. analysis) of the methyl and glycolate ester acetals (45) and (40) respectively. Separation of the mixture of the ester acetals was unnecessary since lithium ethylamide quantitatively converted both to the amide acetal (46).

Regiospecific carboxylation of the amide acetal (46) at C-6 was accomplished in 82% yield via the amide-benzylic dianion of (46), as shown in figure 5, generated by n-butyl lithium in an

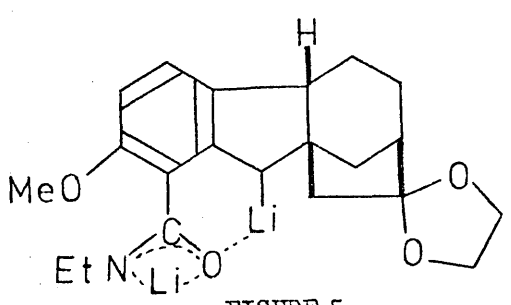
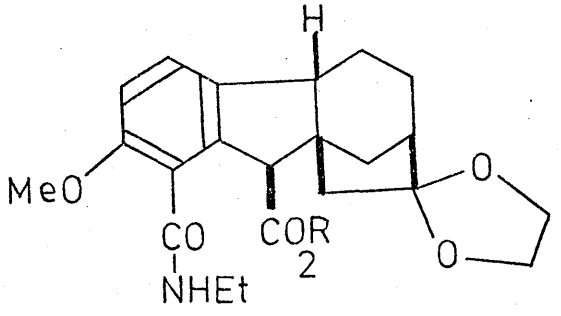
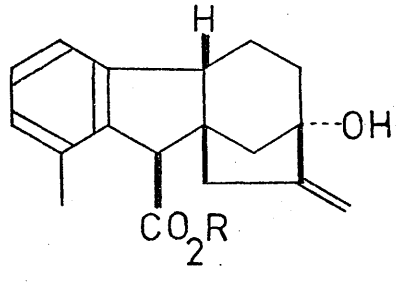


FIGURE 5



	R
(47)	H
(48)	Me



	R
(67)	Me
(69)	H

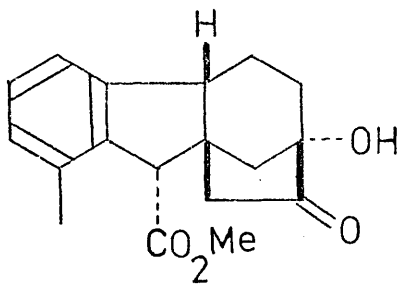
analogous procedure to that used for the model compound.

The fact that carboxylation of the acetal amide (46) had occurred at C-6 rather than C-2 or C-9 was evident from various spectroscopic measurements on the derived amido acid (47). Comparison of the n.m.r. spectra (deuteriochloroform) of the amide acetal (46) and the amido acid (47) showed that the C-6 benzylic protons of (46), which resonated as a quartet at $\delta 3.13$, had been replaced by a one proton singlet resonating at $\delta 4.03$. In the infrared spectrum the amide carbonyl of (46) appeared at 1650 cm^{-1} whereas the amido acid had absorptions at 1647 and 1607 cm^{-1}, the latter amide absorption being due to intramolecular hydrogen bonding with the C-6 acid grouping. When the amido acid (47) was heated at its melting point, the colourless crystals decomposed to a crude yellow oil, the infrared spectrum (carbon tetrachloride) of which exhibited absorptions at 1705 and 1665 cm^{-1}, consistent with it being a cyclic imide.

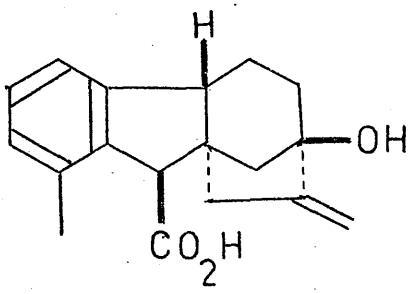
Apart from being regiospecific, the carboxylation of the amide acetal (46) appeared to be also stereospecific since the amido acid (47) obtained was a single stereoisomer, as determined by n.m.r. and g.l.c. analysis of its corresponding methyl ester (48). Also the amido methyl ester (48), prepared from (47) with ethereal diazomethane, was recovered unchanged after treatment with sodium methoxide in benzene under reflux and on hydrolysis with aqueous sodium hydroxide was reconverted to the amido acid (47).

The fact that (48) was not epimerised, or equilibrated, under the above conditions indicated that the amido acid (47) had the β-configuration at C-6 in keeping with the known[40,41,30] stability of this configuration in BC cis fused gibbane derivatives e.g. methyl epiallogibberate (67).

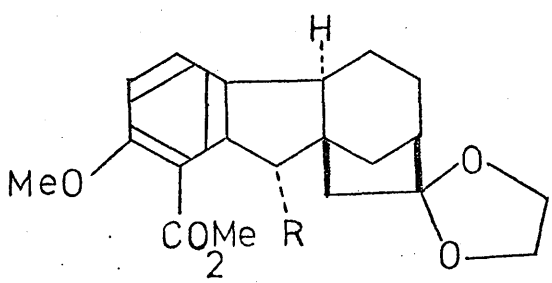
Methyl epiallogibberate (67),[40] to which (48) bears a



(68)



(70)



	R
(66)	H
(71)	CO_2Me

close resemblance, is stable to base whereas its C-9 epimer, methyl allogibberate, undergoes epimerisation at C-6 on base treatment.

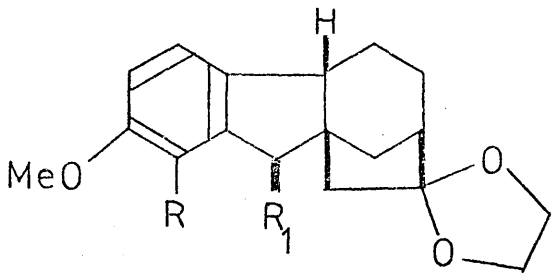
More pertinent to our case is the observation that the ketol (68),[41] with a C-6α carbomethoxyl group, on treatment with triphenylmethylene phosphorane followed by alkaline hydrolysis is converted to epiallogibberic acid (69). Epimerisation of the C-6 carboxyl group occurred during hydrolysis. When the ketol (68) was first hydrolysed with base and then treated with the Wittig reagent, inversion of the D ring[42] followed by epimerisation of the C-6 carboxyl group took place to afford the acid (70).

At the same time as this work was in progress, Loewenthal[30] converted the acetal ester (66), epimeric with (45) at C-9, into the single diester (71) using the lithio derivative of t-butyl cyclohexylamine as base, followed by carbonation and esterification. Lithium t-butyl cyclohexylamide is apparently too bulky to undergo nucleophilic attack at the carbomethoxyl group at C-4 but is a strong enough base to abstract the benzylic proton at C-6.

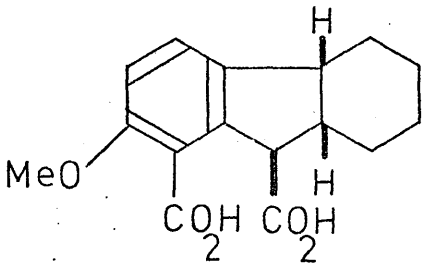
In all of the cases mentioned above the final stable stereoisomers (67), (69), (70) and (71) have the C-6 group <u>cis</u> to the C-9 proton, in agreement with that assigned for the amido acid (47).

Since the amido acid (47) was inert to basic hydrolysis, recourse was made to the mild method developed by White[43] for the conversion of amides to esters or to acids. This involves the conversion of an amide to its N-nitroso derivative, which can be thermally converted to an ester or readily hydrolysed to an acid.

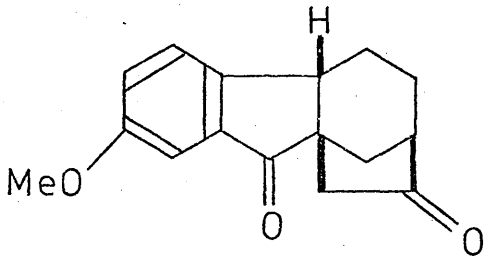
Treatment of the amido ester (48), derived from the amido acid (47) with diazomethane, with nitrogen dioxide and sodium acetate in methylene chloride readily afforded the N-nitroso



	R	R_1
(35)	CO_2H	H
(42)	CO_2H	CO_2H
(42b)	CO_2Me	CO_2Me
(48)	CONHEt	CO_2Me
(49)	CONEt NO	CO_2Me



(60)



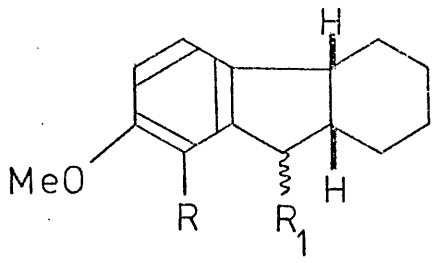
(19)

amide (49) as a yellow oil. Infrared spectroscopy showed that the amide bands of (48) at 1645 and 1532 cm^{-1} had been replaced by the nitroso absorption of (49) at 1505 cm^{-1}. Conversion of the N-nitroso amide (49) to the required diacid (42) was achieved by hydrolysis in dilute sodium hydroxide solution, giving an overall yield from the monoacid (35) to the diacid (42) of about 80%.

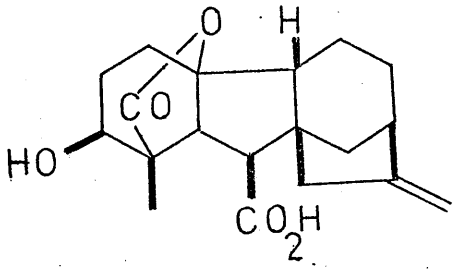
From the foregoing discussion, the diacid (42) was assumed to maintain the β-configuration of the carboxyl group at C-6. The n.m.r. spectrum of the diacid (42) was consistent with it being one stereoisomer, while the corresponding dimethyl ester (42b) was homogeneous on g.l.c. analysis. The u.v. and i.r. spectroscopic characteristics of the diacid (42) agreed very closely with those of the model diacid (60), synthesised by House.[4] Indeed, both diacids showed double carboxyl absorptions in the infrared spectrum, the model diacid (60) at 1735 and 1690 cm^{-1} and the diacid (42) at 1731 and 1692 cm^{-1}.

The synthesis of the diacid (42) represented a major objective in the projected synthesis of gibberellin A_4. Moreover its synthesis constitutes, in our opinion, the best route yet devised to a multifunctional gibberellin synthon from which an attack on the gibberellin hormones may be launched. The overall yield from the diketone (19) was about 43% and apart from the reactions employed being efficient, tedisome isolation and purification of the intermediate stages by chromatography had been avoided. The high yields and specificity at each stage is a necessary requisite for a synthesis based on a linear approach.

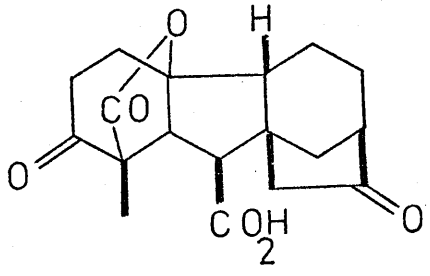
Although the synthesis of the model diacid (60) by House[4] had inspired the conversion of the diketone (19) to the diacid (42), the actual approach had required considerable modification. Shortly



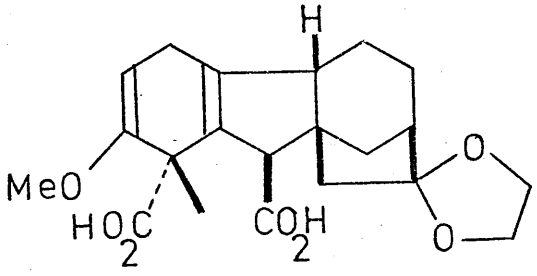
	R	R_1
(72)	CONHMe	H
(73a)	"	αCO_2H
(73b)	"	β "
(74)	"	βCO_2Me
(75)	CO_2Me	β "



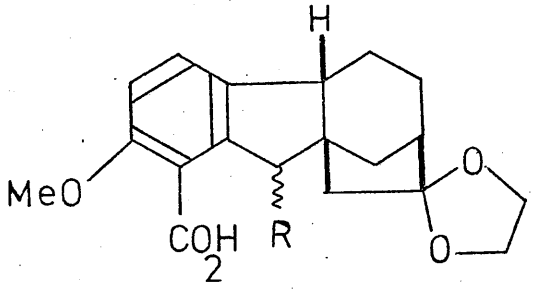
(52)



(55b)



(50b)

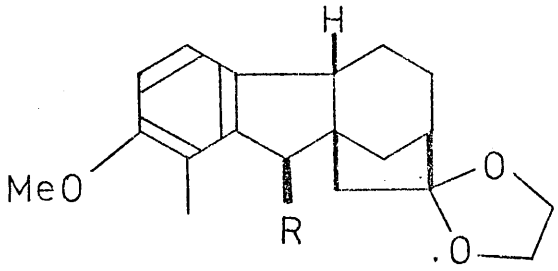


	R
(28)	αOH
(42)	βCO_2H

after the diacid (42) had been synthesised, therefore, it was interesting to see that House[44] had constructed his model diacid (60) again, but in this case, he had used a similar route to that developed in this thesis. Regiospecific metallation of the N-methyl amide (72) with n-butyl lithium followed by carbonation and acidification gave the epimeric amido acids (73a) and (73b). Reaction of one of the derived methyl esters (74) with nitrogen dioxide and subsequent thermal decomposition produced the diester (75), which was saponified to the model diacid (60).

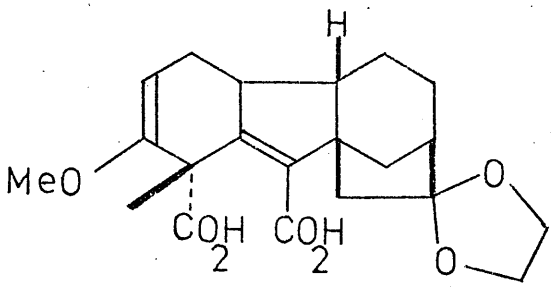
Since the diacid (42) possessed the correct stereochemistry at both C-6 and C-9, it was felt that gibberellin A_4 (52) could be synthesised from the diacid (42) provided that stereochemical control could be exercised during the final elaboration of ring A. Application of the ring A elaborative sequence, recently described by Loewenthal,[3] to the diacid (42) would be expected to furnish the lactonic acid (55b) via the dihydroaromatic diacid (50b). Since the carboxyl group at C-6 might be expected to maintain its β-configuration during the Birch reduction of the diacid (42), this should induce an α-configuration of the carboxyl group at C-4 in (50b), in order to minimise steric interactions between these two groups. Accordingly, methylation of the intermediate carbanion at C-4 should then lock the dihydroaromatic diacid in the relative and required stereochemistry shown in structure (50b).

The di-lithium salt or the di-sodium salt of the diacid (42) was formed prior to effecting the Birch reduction in order to prevent the carbanion, which would be produced at C-4, from being internally protonated by the carboxyl group at C-6. A similar intramolecular protonation had occurred during the Birch reduction of the hydroxy acid (28) (page 28).

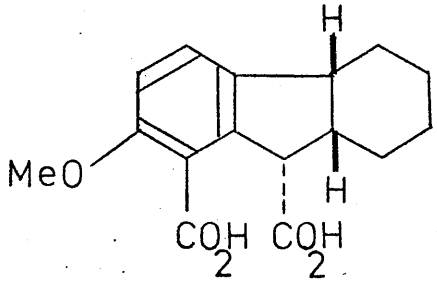


(51b) R / CO_2H

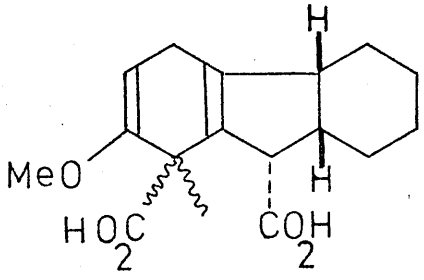
(51) CO_2Me



(76)



(77)



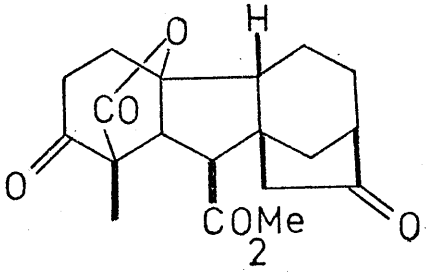
(78)

However, reductive methylation of the di-sodium salt of the diacid (42), followed by careful acidification (pH 4) with sodium dihydrogen phosphate, afforded surprisingly the aromatic monoacid (51b) instead of the desired diacid (50b).

The structure of the monoacid (51b) was elucidated as its methyl ester (51), which gave the following spectral data. Only one carbonyl absorption at 1730 cm^{-1} was present in the infrared spectrum, while the u.v. spectrum, with maxima at 282 and 287 nm, was consistent with the chromophore expected for an indane such as (51). In the absence of the carboxyl function in ring A, the aromatic protons at C-1 and C-2 of (51) had shifted up-field to δ6.93 and 6.70 from the typical values of δ7.32 and 6.94 exhibited by the diacid (42). Also present in the n.m.r. spectrum of the ester (51) was a series of singlet resonances, two at δ3.80 and 3.62 for the methoxyl groups, one at 3.66 for the proton at C-6, and one at 2.33 for the methyl group at C-4. From previous considerations, the more stable β-configuration was assigned to the carbomethoxyl group at C-6 of (51).

Although the dihydroaromatic diacid (50b) was not in fact isolated during the reaction sequence, it must, nevertheless, have been present as a precursor of the aromatic monoacid (51b). After the dihydroaromatic diacid (50b) had been formed by the reductive methylation of the diacid (42), base or acid catalysis could have isomerised (50b) to the vinylogous β-dicarboxylic acid (76). To relieve steric interactions between the C-4 and C-6 centres and possibly strain in the gibbane system decarboxylation and oxidation of the diacid intermediate (76) would give the aromatic acid (51b).

In the model system, House[45] has just recently achieved the reductive methylation of the diacid (77) to the dihydroaromatic diacid (78), of as yet undefined stereochemistry. The success in



(55)

this case may be due to the fact that the relatively strain free hydrofluorene system can accommodate the bulky substituents at C-8 and C-9 of the dihydroaromatic diacid (78).

Since the formation of the aromatic monoacid (51b) by decarboxylation of the vinylogous malonic acid (76) was presumed to occur after acidification of the di-sodium salt of either (50b) or (76), an attempt to trap the latter in situ by iodolactonisation was made. Accordingly, the crude product from the reductive methylation of the diacid (42) was treated with a solution of potassium iodide and iodine in sodium carbonate solution. After 24 hours the mixture was carefully acidified (pH 4) and methylated with diazomethane but the product was again the aromatic monoester (51).

In this case, the dihydroaromatic diacid (50b) probably underwent simultaneous decarboxylation and oxidation by iodine as shown in figure 6.

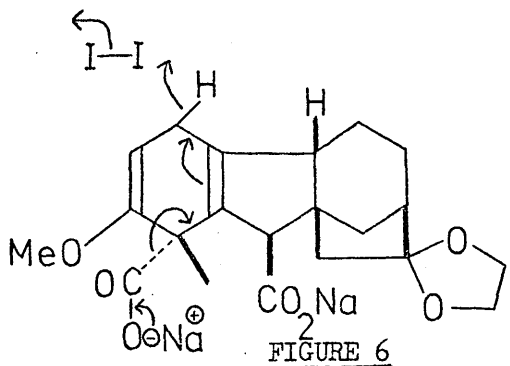
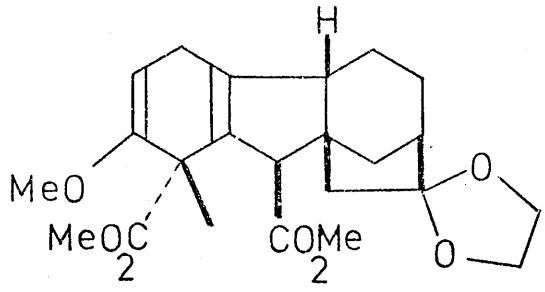


FIGURE 6

With the failure to produce the dihydroaromatic diacid (50b), the penultimate goal of the synthesis, the relay diketolactone (55) could not be reached at this time. Since the diacid (42) can now be made in sufficient quantities as a result of this work, it is felt that a detailed study of the reductive methylation sequence from (42) is worthwhile, particularly with respect to the work up



(50)

procedure. To this end, the intermediate di-sodium salt of the dihydroaromatic diacid (50b) could be converted to the corresponding dimethyl ester (50), which should then prove less susceptible to aromatisation.

Moreover, the simplicity of the approach, the high overall yield in the steps leading to the diacid (42), and the potential adaptability of the route for the synthesis of gibberellins more complex than A_4 makes this investigation more than just academically interesting.

EXPERIMENTAL

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

Routine infrared spectra (liquid films and Nujol mulls) were recorded on Pye Unicam S.P. 200 or Perkin-Elmer 257 spectrophotometers; solution infrared spectra were recorded by Mrs. F. Lawrie on either a Perkin-Elmer 257 spectrophotometer or a Unicam S.P. 100 double beam spectrophotometer, equiped with an S.P. 130 sodium chloride prism grating double monochromator operated under vacuum. High resolution infrared spectra (at high dilution, i.e. approximately at 0.003M concentration, in carbon tetrachloride) were recorded on this latter spectrophotometer.

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

Nuclear magnetic resonance (n.m.r.) spectra were obtained on Varian T-60 and H.A. 100 spectrometers, using approximately 0.3M solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard. Coupling constants (J) were measured in hertz (Hz).

Analytical gas-liquid chromatography (g.l.c.) was carried out on a Pye Argon Chromatograph equiped with a β-ionisation detector. All compounds were analysed on a 5% QF-1 column at 225° and the data obtained is recorded in Table 3 (page 80). R_t and R_i are the retention time and the retention index respectively of the compounds analysed.

Light petroleum refers to the petroleum fraction with boiling range 60-80°.

Thin layer chromatoplates were spread with Merck Kieselgel G and developed in ethyl acetate-light petroleum. Preparative chromatoplates were spread with Merck Kieselgel HF 254.

Mass spectra were determined on a G.E.C.-A.E.I. M.S. 12 spectrometer. The figure quoted for the molecular ion (M) in the mass spectrum refers to the m/e value.

Microanalyses were by Mr. J.M.L. Cameron, Miss F. Cowan and their staff.

All solutions were dried over anhydrous sodium sulphate.

5-(p-methoxyphenyl)-trans, trans-penta-2,4-dienoic acid (1)

A mixture of p-anisaldehyde (38.8g; 0.285mol) and methyl crotonate (43g; 0.43mol) in tertiary butanol (100ml) was added, over a period of 1 hour, to a solution of potassium (23g; 0.59mol) in tertiary butanol (400ml), while the reaction mixture was kept at approximately 30°. After stirring for a further 3 hours at 30°, the resulting solution was acidified with aqueous HCl and then extracted with chloroform. The organic extract was dried and concentrated to leave a clear oil consisting of acidic and ester material.

This mixture was heated under reflux with potassium hydroxide (16g; 0.29mol) in water (300ml) and ethanol (100ml). Acidification and work up of the solution, as before, gave crude acid (52.4g), which was allowed to stand in chloroform for 3 days under a visible lamp with a few crystals of iodine.[16] Recrystallisation from chloroform gave the pure acid (1) (48g; 84%), m.p.182-183°, ν max. (KBr) 1673 cm^{-1} (carboxyl C=O), λ max. 330 nm (ε 35,000), δ 15.5-14.5 (1H, COOH), 7.41 and 6.86 (4H, q, J=9, aryl H), 7.6-6.6 (3H, m, vinyl H), 5.92 (1H, d, J=14Hz, 1-H) and 3.80 (3H, s, OMe) (Found: C, 70.44; H, 6.06%. $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%).

Methyl 5-(p-methoxyphenyl)-trans, trans-penta-2,4-dienoate (2)

A mixture of the acid and the ester (10g), from the previous preparation, in dry methanol (100ml) and 98% sulphuric acid (0.5ml) was refluxed for 4 hours, cooled and the crystals

which separated collected. Recrystallisation from methanol gave the pure ester (2) (9.8 g; 88%), m.p. 126-127°, ν max. (KBr) 1711 cm^{-1} (ester C=O), λ max. 333 nm (ε 36,000), δ 7.37 and 6.84 (4H, q, J=9Hz, aryl H), 7.6-6.6 (3H, m, vinyl H), 5.92 (1H, d, J=14Hz, 1-H), 3.80 (3H, s, OMe) and 3.77 (3H, s, OMe).

All cis-3-(p-methoxyphenyl)-6-carbomethoxy-cyclohex-4-enyl-1,2-dicarboxylic acid anhydride (3)

Condensation of methyl 5-(p-methoxyphenyl)-trans, trans-penta-2,4-dienoate (2) (218 mg; 1 mmol) with maleic anhydride (260 mg; 2 mmol) without solvent at 160° gave a crystalline adduct (250 mg) after trituration with acetonitrile. Recrystallisation from acetonitrile afforded the pure anhydride (3) (205 mg), m.p. 149-150°, ν max. (KBr) 1840 and 1775 cm^{-1} (anhydride C=O) and 1730 cm^{-1} (ester C=O), δ 7.14 and 6.90 (4H, aryl H), 6.63 and 6.27 (2H, q with additional fine coupling to 3-H and 6-H, J=10Hz, 4-H and 5-H), 4.2-3.8 (1H, m, 3-H), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3) and 3.7-3.1 (3H, m, aliphatic H) (Found: C, 64.69; H, 5.09%. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10%).

Methyl 1-carboxy-2-(p-methoxyphenyl)-cyclohex-4-enyl acetates (6a) and (6b)

An intimate mixture of powdered 5-(p-methoxyphenyl)-trans-trans-penta-2,4-dienoic acid (10 g; 0.046 mol) and itaconic acid (4) (13 g; 0.10 mol) was heated (bath temperature 156°) for 9 hours in a

flask fitted with an air condenser. The semi-solid mass was stirred occasionally and after 5 hours the condenser was removed. Excess itaconic acid was removed by heating in vacuum, leaving a 1:1 mixture (by g.l.c. analysis) of the adducts (5a) and (5b) as a colourless oil (10.9 g), ν max. (film) 1845 and 1770 cm^{-1} (anhydride C=O).

The crude reaction product was refluxed for 16 hours in dry methanol (50 ml). The solvent was removed under vacuum to leave a mixture of the acids (6a) and (6b) as a colourless oil (11.2 g; 80%). Repeated crystallisation from methanol afforded a single isomer, (6a) or (6b), m.p. 148-150°, ν max. (Nujol) 1727 (ester C=O) and 1708 cm^{-1} (acid C=O), λ max. 276 and 283 nm, δ 9.6-8.8 (1H, COOH), 7.11 and 6.74 (4H, q, J=9Hz, aryl H), 6.2-5.4 (2H, m, vinyl H), 3.77 (3H, s, OMe), 3.66 (3H, s, OMe), 3.5-3.3 (1H, m, 2-H) and 3.2-1.6 (6H, m, aliphatic H). The n.m.r. spectrum of the mixture of the acids (6a) and (6b) had additional signals at δ 10.3-9.8 (COOH), 3.80 (OMe) and 3.60 (OMe) (Found: C, 66.96; H, 6.63%; M, 304. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%; M, 304).

Methyl 1-(2-p-methoxyphenyl-4-exo-iodo-7-oxo-6-oxabicyclo[3.2.1]-octyl) acetates (7a) and (7b)

To a solution of the acids (6a) and (6b) (290 mg; 1 mmol) in 0.5N sodium bicarbonate (10 ml) was added a solution of iodine (510 mg; 2.01 mmol) and potassium iodide (1 g; 6 mmol) in water (3 ml). The mixture was left overnight in the dark, after which an excess of sodium thiosulphate solution was added and the product extracted with

ethyl acetate. The extracts were washed with brine, dried, and the solvent removed, giving (7a) and (7b) as a crystalline residue (150 mg). Preparative t.l.c., using 40% (by volume) of ethyl acetate in light petroleum, gave one crystalline iodo lactone (7a) or (7b), m.p. 177-179°, ν max. (KBr) 1779 (lactone C=O) and 1720 cm^{-1} (ester C=O), δ 7.21 and 6.84 (4H, q, J=9Hz, aryl H), 4.95-4.3 (3H, m, 2-H, 4-H and 6-H), 3.8 (3H, s, OMe), 3.66 (3H, s, OMe) and 2.8-1.4 (6H, m, aliphatic H) (Found: C, 47.45; H, 4.38%. $C_{17}H_{19}IO_5$ requires C, 47.43; H, 4.41%).

1-carboxy-2-(p-methoxyphenyl)-cyclohexyl acetic acid anhydrides (9a) and (9b)

A mixture of the acids (6a) and (6b) (580 mg) and platinic oxide (46 mg) absorbed hydrogen (39 cc) in 1 hour at room temperature and pressure. Removal of the catalyst and the solvent gave the acids (8a) and (8b) (560 mg; 96%), m.p. 140-150°, ν max. (KBr) 1730 (ester C=O) and 1695 cm^{-1} (acid C=O), δ 7.8-7.4 (1H, COOH), AB overlapping patterns (J=9Hz) with estimated line positions at 7.04, 6.86 and 6.71 (aryl H), 3.75, 3.58, 3.53 (OMe), 3.2-2.8 (1H, m, 2-H) and 2.8-1.2 (aliphatic H).

Sublimation (150°; 1 mm) gave a 1:1 mixture (by g.l.c. analysis) of the epimeric anhydrides (9a) and (9b), m.p. 80-86°, ν max. (film) 1840 and 1775 cm^{-1}, n.m.r., AB overlapping patterns (J=9Hz) with estimated line positions at δ 7.10, 7.07 and 6.77 (aryl H), 3.76 (3H, s, OMe), 2.97 and 2.93 (1H, overlapping doublets, J=19Hz, CHC=O), 2.59 and 2.49 (1H, overlapping doublets, J=19Hz, CHC=O) and 2.6-1.2 (aliphatic H) (Found: C, 70.34; H,

6.59%. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%).

1-(p-methoxyphenyl)-trans-butadiene

This was prepared, as described in the literature,[17] by the reaction of p-methoxyphenyl magnesium bromide and crotonaldehyde giving, after dehydration, a white solid, m.p. 44-46° (lit.[17] 45-46°), λ max. 284 (ε 35,000) and 291 (35,000), δ 7.38 and 6.85 (4H, q, J=9Hz, aryl H), 8.0-6.1 (3H, m, vinyl H), 5.51-4.92 (2H, m, 4-H) and 3.80 (3H, s, OMe).

An alternative preparation of the anhydrides (9a) and (9b)

A mixture of 1-(p-methoxyphenyl)-trans-butadiene (160 mg; 1 mmol) and itaconic acid (260 mg; 2 mmol) was heated at 160°, without solvent, until the diene chromophore in the u.v. disappeared. The adduct was dissolved in ether, washed with aqueous sodium bicarbonate, dried and concentrated, giving a clear oil, which consisted of a 1:1 mixture (by g.l.c. analysis) of the anhydrides (10a) and (10b) (230 mg; 85%). A solution of this oil (60 mg) in ethyl acetate (5 ml) took up hydrogen (5 cc) at room temperature and pressure, using platinic oxide (6 mg) as catalyst. Removal of the catalyst and the solvent gave the anhydrides (9a) and (9b) (58 mg), m.p. 81-87°, which were shown by g.l.c. analysis to be a 1:1 mixture and to be identical to the mixture prepared earlier.

1-carboxy-2-(p-methoxyphenyl)-5-carbomethoxy-cyclohex-3-enyl acetic acid anhydrides (11a), (11b) and (11c)

A powdered mixture of the diene ester (2) (124 g; 0.57 mol) and itaconic acid (4) (149.5 g; 1.15 mol) was heated without solvent at 160° for 8 hours. The adduct formed was dissolved in benzene, washed with aqueous sodium bicarbonate, dried and concentrated, leaving an oil (150 g; 80%) containing a mixture of the three stereoisomeric adducts (11a), (11b) and (11c) in the ratio of 1:2.3:2.2 (by g.l.c. analysis), ν max. (film) 1850 and 1775 (anhydride C=O) and 1725 cm^{-1} (ester C=O), λ max. 277 and 283 nm, δ 7.11 and 6.84 (4H, q, J=9Hz, aryl H), 6.4-5.6 (2H, m, vinyl H), 3.8 (3H, s, OMe) and 4.2-2.0 (6H, m, aliphatic H) (Found: C, 65.45; H, 5.46%. $C_{18}H_{18}O_6$ requires C, 65.44; H, 5.49%).

1-carboxy-2-(p-methoxyphenyl)-5-carbomethoxy-cyclohexyl acetic acid anhydrides (12a), (12b) and (12c)

Hydrogenation of the above adducts (11a), (11b) and (11c) (125 g) in ethyl acetate with platinic oxide (2 g) as catalyst proceeded quantitatively at room temperature and pressure. Removal of the catalyst and the solvent gave a mixture of the isomeric anhydrides (12a), (12b) and (12c) as a clear oil (122 g) in the same ratio as before (by g.l.c. analysis). ν max. (Nujol) 1855 and 1777 (anhydride C=O) and 1725 cm^{-1} (ester C=O), λ max. 277 and 283 nm, δ 7.4-6.6 (4H, m, aryl H), 3.8 (3H, s, OMe) and 4.2-1.2 (10H, m, aliphatic H) (Found: C, 64.80; H, 6.16%. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.07%).

Methyl 1-carboxy-*trans*-2-(p-methoxyphenyl)-*trans*-5-carbomethoxy-cyclohexyl acetate (13a)

A mixture of the anhydrides (12a), (12b) and (12c) (122 g) and dry methanol (500 ml) was refluxed overnight, whereby quantitative methanolysis occurred. After the solution had been reduced to half its volume and left for 3 days at -10°, acid (13a) (6.95 g) separated as colourless crystals, m.p. 150-152° (ethyl acetate), ν max. (CCl_4) 1741 (ester C=O) and 1707 cm^{-1} (acid C=O), λ max. 227nm (ε 8520), 277 (1770) and 283 (1550), δ 10.2-9.8 (1H, COOH), 7.17 and 6.78 (4H, q, J=9Hz, aryl H), 3.78 (3H, s, OMe), 3.67 (3H, s, OMe), 3.62 (3H, s, OMe) and 3.2-1.4 (10H, m, aliphatic H) (Found: C, 62.43; H, 6.76%. $C_{19}H_{22}O_7$ requires C, 62.62; H, 6.64%).

Sublimation (210°; 0.7 mm) of the acid (13a) gave the anhydride (12a). Such a transformation occurred when all similar ester acids were subjected to g.l.c. analysis (Table 3).

Methyl 1-*trans*-5-dicarbomethoxy-*trans*-2-(p-methoxyphenyl)-cyclohexyl acetate (14a)

Excess ethereal diazomethane was added to the acid (13a) (6.69 g) in ether and the solution was left overnight. Removal of the polymer and the solvent, followed by recrystallisation of the crude product from aqueous methanol, yielded the trimethyl ester (14a) (6.87 g; 96%) as colourless needles, m.p. 98-99°, ν max. (CCl_4) 1730 cm^{-1} (ester C=O), λ max. 226 nm (ε 11040), 276 (1390) and 283 (1190), δ 7.14 and 6.74 (4H, q, J=9Hz, aryl H),

3.78 (3H, s, OMe), 3.73 (3H, s, OMe), 3.65 (3H, s, OMe), 3.37 (3H, s, OMe) and 3.0-1.5 (10H, m, aliphatic H) (Found: C, 63.46; H, 6.91%. $C_{20}H_{24}O_7$ requires C, 63.48; H, 6.93%).

Methyl 1-cis-5-dicarbomethoxy-trans-2-(p-methoxyphenyl)-cyclohexyl acetate (14b)

A solution of the acid (13a) (250 mg) in dry methanol (25 ml), to which sodium (35 mg) had been added, was refluxed under nitrogen overnight. The resulting suspension was cooled, acidified with dilute aqueous sulphuric acid, and extracted with ether. The ether extract was washed with brine, dried and concentrated, leaving the crude acid (13b) (235 mg). Complete epimerisation of the C-5 carbomethoxyl group had occurred, as determined by g.l.c. comparison of (13b) with (13a).

Treatment of the acid (13b) (96 mg) with excess ethereal diazomethane gave, after the usual manipulations, the ester (14b) (101 mg), m.p. 102-103° (ethyl acetate/light petroleum), ν max. (CCl_4) 1735 cm^{-1} (ester C=O), λ max. 227 nm (ε 11510), 277 (1630) and 283 (1390), δ 6.94 and 6.71 (4H, q, J=9Hz, aryl H), 3.77 (3H, s, OMe), 3.66 (3H, s, OMe), 3.55 (3H, s, OMe), 3.50 (3H, s, OMe) and 3.1-1.2 (10H, m, aliphatic H) (Found: C, 63.54; H, 6.84%. $C_{20}H_{24}O_7$ requires C, 63.48; H, 6.93%).

1,7-dicarbomethoxy-anti-2-(p-methoxyphenyl)-bicyclo(3.2.1)octan-6-one (15a)

a) Preparation from the trimethyl ester (14a).

To methanol-free sodium methoxide (from 0.84 g of sodium) under nitrogen was added a solution of the trimethyl ester (14a) (6.7 g) in benzene (60 ml). The mixture was refluxed for 20 hours, cooled, then added to a solution of cold, dilute sulphuric acid, and extracted with ether. The β-keto ester (15a) was removed from the ether extract by washing with a solution of cold, dilute sodium hydroxide. The ether extract on work up afforded the trimethyl ester (14b) (2.14 g; 32%). Acidification of the aqueous sodium hydroxide extract with dilute sulphuric acid followed by ether extraction gave, after drying and evaporation, the crude β-keto ester (15a). Recrystallisation from ether afforded the pure β-keto ester (15a) (3.67 g; 60%) as colourless crystals, m.p. 112-114°, ν max. (CCl_4) 1764 (ketone C=O) and 1739 cm^{-1} (ester C=O), λ max. 227 nm (ε 11020), 277 (1550) and 283 (1350), δ 7.19 and 6.79 (4H, q, J=9Hz, aryl H), 4.1-3.8 (1H, m, 2-H), 3.85 (3H, s, OMe), 3.75 (3H, s, OMe), 3.55 (3H, s, OMe), 3.42 (1H, s, 7-H) and 3.0-1.5 (7H, m, aliphatic H) (Found: C, 65.72; H 6.38%. $C_{19}H_{20}O_6$ requires C, 65.88; H, 6.40%).

b) Preparation from the trimethyl ester (14b).

To methanol-free sodium methoxide (from 0.24 g of sodium) under nitrogen was added a solution of the trimethyl ester (14b) (2 g) in benzene (25 ml). The mixture was refluxed overnight, cooled, added to a solution of cold, dilute sulphuric acid and extracted with ether. The ether was washed with brine, dried and concentrated.

Recrystallisation from ether gave the β-keto ester (15a) (1.48 g; 82%), m.p. 112-114°. No starting material was present in the mother liquors (by g.l.c. analysis).

1-carboxy-anti-2-(p-methoxyphenyl)-bicyclo(3.2.1)octan-6-one (16a)

A solution of the β-keto ester (15a) (2.7 g) in acetic acid (30 ml) and 50% sulphuric acid (40 ml) was refluxed for 20 hours, cooled and poured onto crushed ice (50 g). The white precipitate was filtered, washed with water and dried, yielding the crude keto acid (16a) (1.76 g; 82%). From the u.v. spectrum, a small amount of the phenol (17) was detected by noting a λ max. shift on addition of a drop of dilute aqueous sodium hydroxide solution.

Consequently, a mixture of the crude keto acid (16a), sodium hydroxide (0.53 g), water (15 ml) and ethanol (30 ml) was treated with dimethyl sulphate (1.5 ml) until no phenol remained. After the addition of dilute sodium hydroxide solution (40 ml), the resulting mixture was refluxed overnight under nitrogen, cooled to 0°, and acidified to pH 1 with 50% sulphuric acid. The white solid was collected by filtration, washed with water, dried, and recrystallised from ethyl acetate to give the keto acid (16a) (1.48 g; 70%), m.p. 192-194°, ν max. (CCl_4) 1751 (ketone C=O) and 1708 cm^{-1} (carboxyl C=O), λ max. 227 nm (ε 10380), 276 (1609) and 283 (1418), δ (CF_3COOH) 10.6-10.0 (1H, COOH), 7.37 and 6.93 (4H, q, J=9Hz, aryl H), 3.97 (3H, s, OMe), 3.7-3.4 (1H, m, 2-H), 3.1-2.8 (3H, m, 5-H and 7-H_2) and 2.8-1.7 (6H, m, aliphatic H) (Found: C, 69.90; H, 6.72%. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%).

3-Methoxy-6,16-dioxo-9βH-gibba-A-triene (19)

A suspension of the keto acid (16a) (1.17 g; 4.45 mmol) in oxalyl chloride (0.7 ml; 8.4 mmol) and dry benzene (50 ml) was stirred at room temperature for 1 hour and at 60° for 30 minutes, whereupon the resulting solution became homogeneous. The benzene and excess oxalyl chloride were removed at water pump pressure, leaving the acid chloride (18a) as a clear oil, ν max. (film) 1785 (acid chloride C=O) and 1740 cm^{-1} (ketone C=O).

To a stirred solution of the acid chloride (18a) (1.29 g) in dry benzene (50 ml) was added, slowly over 1 hour, aluminium trichloride (1.12 g; 9.0 mmol). The cyclisation was monitored by u.v. spectroscopy and after 6 hours the mixture was poured onto crushed ice and extracted with ether. The organic extract was washed successively with water, aqueous sodium bicarbonate and brine, dried and concentrated. Recrystallisation of the product from ethyl acetate gave the diketone (19) (0.96 g; 88%), m.p. 184-185°, ν max. (CCl_4) 1751 and 1711 cm^{-1} (cyclopentanone and indanone respectively), λ max. 220 (ε 25,100), 251 (10,000) and 321 nm (3,800), δ 7.5-7.2 (3H, m, aryl H), 3.90 (3H, s, OMe) and 3.3-1.2 (10H, m, aliphatic H) (Found: C, 75.10; H, 6.52%. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%).

Methyl 1-carboxy-2-(p-methoxyphenyl)-5-carbomethoxy-cyclohex-3-enyl acetic acids (20a), (20b) and (20c)

A mixture of the anhydride adducts (11a), (11b) and (11c) (24 g) and dry methanol (125 ml) was refluxed overnight, whereby

quantitative methanolysis occurred. After removal of the solvent, recrystallisation of the crude product from ethyl acetate/light petroleum gave the acids (20a), (20b) and (20c) as colourless crystals, m.p. 132-160°, ν max. (KBr) 1728 and 1702 (ester C=O) and 1680 cm^{-1} (acid C=O), λ max. 277 and 283 nm, δ 8.45-7.90 (1H, COOH), 7.33-6.66 (4H, overlapping quartets, aryl H), 6.05-5.70 (2H, m, vinyl H), 3.82, 3.80, 3.70, 3.65 (9H, overlapping OMe groups) and 4.1-1.9 (6H, m, aliphatic H) (Found: C, 62.87; H, 6.08%. $C_{19}H_{20}O_7$ requires C, 62.97; H, 6.12%).

Methyl 1,5-dicarbomethoxy-2-(p-methoxyphenyl)-cyclohex-3-enyl acetates (21a), (21b) and (21c)

The above acids (26 g) in ether were treated with a large excess of ethereal diazomethane. After 24 hours excess diazomethane was destroyed with acetic acid and the solution was evaporated to dryness, leaving a colourless oil containing a mixture of the three stereoisomeric adducts (21a), (21b) and (21c) in the ratio of 1:2.2:2.1 respectively (by g.l.c. analysis), ν max. (film) 1725 cm^{-1} (ester C=O), λ max. 277 and 283 nm, δ 7.10, 6.79 and 6.76 (4H, overlapping quartets, J=9Hz, aryl H), 6.20-5.60 (2H, m, vinyl H), 3.78, 3.73, 3.63, 3.57 and 3.37 (12H, overlapping OMe groups) and 4.1-1.9 (6H, m, aliphatic H) (Found: C, 63.66; H, 6.40%. $C_{20}H_{22}O_7$ requires C, 63.82; H, 6.42%).

Methyl 1-(3-carbomethoxy-4-exo-iodo-7-oxo-8-p-methoxyphenyl-6-oxa-bicyclo[3.2.1]octyl) acetates (22a), (22b) and (22c)

The acids (20a), (20b) and (20c) (300 mg) were dissolved in sodium bicarbonate solution (0.5 M; 10 ml), and a solution of iodine (0.51 g) and potassium iodide (1.0 g) in water (3 ml) was added. The mixture was left overnight in the dark, whereupon an excess of a solution of sodium thiosulphate was added, and the precipitate collected by filtration. The crude product was recrystallised from ethyl acetate/light petroleum to yield a mixture of the iodo lactones (22a), (22b) and (22c) (106 mg), m.p. 145-160°, ν max. (KBr) 1783 (lactone C=O) and 1725 cm^{-1} (ester C=O), λ max. 277 and 283 nm, δ 7.17 and 6.81 (4H, q, J=9Hz, aryl H), 5.05-4.0 (3H, m, 4-H, 6-H and 8-H), 3.80 (6H, s, two superimposed OMe groups), 3.66 (3H, s, OMe) and 3.25-1.80 (4H, m, aliphatic H).

The above iodo lactones (100 mg) in glacial acetic acid (1 ml) were stirred with zinc dust (20 mg) for 4 hours. The acetic acid was removed under vacuum and the residue in ether was washed with sodium bicarbonate solution, dried and concentrated to give unreacted iodo lactone (25 mg). Acidification of the aqueous washings gave, after the usual work-up, acids (20a), (20b) and (20c) in almost the same ratio as before (by g.l.c. analysis).

Preparation of 3-Methoxy-6,16-dioxo-9βH-gibb-A-triene (19) from a mixture of the acids (13a), (13b) and (13c)

A mixture of the acids (13a), (13b) and (13c) (18.7 g)

and excess diazomethane in ether was left overnight. After the usual manipulations a clear oil was obtained consisting of a mixture of the trimethyl esters (14a), (14b) and (14c) (18.9 g). Analytical, i.r. and u.v. data corresponded to that for the single isomer (14a). The n.m.r. spectrum contained a complex pattern of similar groups of signals, as expected for three stereoisomers.

The above mixture of trimethyl esters (17.5 g) was refluxed under nitrogen for 20 hours with sodium methoxide (from 2.18 g of sodium) in benzene (100 ml). Using the work up described previously (page 53), the neutral material (5.74 g) consisted of the unreacted esters (14b) and (14c) (by g.l.c. analysis) and the base soluble material (10.6 g) was the expected β-keto esters (15a) and (15b) in the ratio 1:1 (by g.l.c. analysis). Analytical, i.r. and u.v. data of these β-keto esters corresponded to that for the single isomer (15a). The n.m.r. spectrum was identical to (15a) with additional peaks at δ 6.72, 3.52 and 3.40.

The above mixture of β-keto esters (15a) and (15b) (8.7 g) in glacial acetic acid (120 ml) and 50% sulphuric acid (150 ml) was refluxed for 20 hours. After the usual manipulations a white crystalline solid (5.3 g) was obtained containing the keto acids (16a) and (16b), m.p. 178-192°.

A solution of the keto acids (16a) and (16b) (5.3 g), oxalyl chloride (3 ml) and benzene (50 ml) was stirred overnight at room temperature. Excess oxalyl chloride and benzene were then removed and replaced by pure methylene chloride (125 ml) and to the resulting solution was added, over 1 hour, aluminium trichloride (5 g) in small portions. The reaction was carefully monitored by g.l.c., samples being obtained by refluxing aliquots of the solution with dry methanol. In this way a check was made on the formation

of the diketone (19) as well as the corresponding decrease in concentration of the keto ester (24a) relative to the keto ester (24b). After 4 hours the solution was poured onto crushed ice (150 g) and worked up as before (page 55) to give the diketone (19) (1.34 g), identical to that obtained from the single isomer (16a).

The sodium bicarbonate washings were cooled in an ice bath and then acidified with dilute hydrochloric acid. The white solid was collected by filtration, washed with water, dried and recrystallised from ethyl acetate/light petroleum to give 1-carboxy-syn-2-(p-methoxyphenyl)-bicyclo(3.2.1)octan-6-one (16b) (1.82 g), m.p. 203-205°, ν max. (CCl_4) 1750 (ketone C=O) and 1707 cm^{-1} (carboxyl C=O), λ max. 227 (ε 11,050), 276 (1650) and 283 nm (1430), δ (CF_3COOH) 10.6-10.1 (1H, COOH), 7.24 and 6.91 (4H, q, J=9Hz, aryl H), 3.93 (3H, s, OMe), 3.75-3.35 (1H, m, 2-H), 3.1-2.8 (3H, m, 5-H and 7-H_2) and 2.6-1.7 (6H, m, aliphatic H) (Found: C, 69.90; H, 6.72%. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%).

For comparative purposes, the mixture of the keto acids (16a) and (16b), the keto acid (16a) and the keto acid (16b) were methylated with diazomethane to give the corresponding esters (24a) and (24b). ν max. (24a) or (24b) (CCl_4) 1746 (ketone C=O) and 1734 cm^{-1} (ester C=O), n.m.r. (24a), δ 7.27 and 6.83 (4H, q, J=9Hz, aryl H), 3.80 (3H, s, OMe), 3.58 (3H, s, OMe), 3.60-3.30 (1H, m, 2-H), 2.77-2.33 (3H, m, 5-H and 7-H_2) and 2.32-1.75 (6H, m, aliphatic H). n.m.r. (24b), δ 7.10 and 6.77 (4H, q, J=9Hz, aryl H), 3.77 (3H, s, OMe), 3.51 (3H, s, OMe), 3.60-3.20 (1H, m, 2-H), 2.77-2.33 (3H, m, 5-H and 7-H_2) and 2.33-1.60 (6H, m, aliphatic H) (Found: C, 71.04; H, 7.08%. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%).

1,5-Dicarboxy-2-(p-methoxyphenyl)-cyclohexyl acetic acid anhydrides (23a) and (23b)

A 1:1 mixture of the β-keto esters (15a) and (15b) (356 mg) in dilute aqueous sodium hydroxide (15 ml) and methanol (10 ml) was refluxed for 14 hours under nitrogen. The resulting solution was cooled, acidified with dilute hydrochloric acid solution and extracted with ether. The organic extracts were washed with brine, dried and concentrated to leave a clear oil (242 mg). Distillation (180^{o}; 1 mm) of the crude product gave an oil, which contained a mixture of the anhydride acids (23a) and (23b), ν max. (film) 1850 and 1780 (anhydride C=O) and 1700 cm^{-1} (acid C=O), δ 9.0-8.3 (1H, COOH), 7.3-6.6 (4H, m, aryl H), 3.87 (3H, s, OMe) and 3.4-1.4 (10H, m, aliphatic H) (Found: C, 64.23; H, 5.77%. $C_{17}H_{18}O_6$ requires C, 64.14; H, 5.70%).

7-Methoxy-9-oxo-2,10a-dicarbomethoxy-1,2,3,4,9,10-hexahydrophenanthrenes (25a) and (25b)

A mixture of the acids (13a), (13b) and (13c) (1.82 g) and thionyl chloride (0.5 ml) was stirred in benzene (50 ml) for 6 hours at room temperature. The benzene and excess thionyl chloride were removed at water pump pressure leaving the acid chloride as an oil, ν max. (film) 1780 (acid chloride C=O) and 1730 cm^{-1} (ester C=O).

To a vigorously stirred solution of the acid chloride in benzene (20 ml) at 10^{o} was added slowly aluminium trichloride (0.72 g). After 12 hours at room temperature the mixture was poured onto dilute

hydrochloric acid (20 ml) and extracted with ether. The organic extract was washed with water, 2% potassium hydroxide solution and brine, dried and concentrated to give a 1:1 mixture (by g.l.c. analysis) of the hydrophenanthrenones (25a) and (25b) (0.81 g), m.p. 138-152°, ν max. (Nujol) 1725 (ester C=O) and 1683 cm^{-1} (ketone C=O), λ max. 225, 255 and 323 nm. Recrystallisation from aqueous methanol gave a single stereoisomer, m.p. 158-160°, ν max. (Nujol) 1725 (ester C=O) and 1683 (ketone C=O), λ max. 224, 255 and 323 nm, δ 7.48 (1H, d, J=3Hz, 8-H), 7.30 (1H, d, J=8Hz, 5-H), 7.06 (1H, q, J=3 and 8Hz, 6-H), 3.79 (3H, s, OMe), 3.60 (3H, s, OMe), 3.36 (3H, s, OMe), 3.9-3.5 (1H, m, 4a-H), 3.26 (1H, d, J=16Hz, 10-H), 2.32 (1H, d, J=16Hz, 10-H) and 3.0-1.4 (7H, m, aliphatic H) (Found: C, 65.68; H, 6.50%. $C_{19}H_{20}O_6$ requires C, 65.88; H, 6.40%).

When the above mixture of ketones (25a) and (25b) (383 mg) was refluxed with sodium methoxide (from 46 mg of sodium) in benzene (5 ml), no β-keto ester was observed.

3-Methoxy-6-oxo-16,16-ethylenedioxy-9βH-gibb-A-triene (26)

A solution of the diketone (19) (5.85 g), ethylene glycol (40 ml) and p-toluenesulphonic acid monohydrate (0.25 g) in benzene (250 ml) was refluxed for 8 hours with constant separation of water (Dean-Stark trap). The solution was cooled to room temperature, washed with dilute sodium bicarbonate, dried, and concentrated. Recrystallisation from ethyl acetate/light petroleum afforded the desired monoacetal (6.62 g; 97%) as colourless crystals, m.p. 82-83°, ν max. (CCl_4) 1712 cm^{-1} (ketone C=O), λ max. 250

(ε 8340) and 321 nm (6670), δ 7.47-7.07 (3H, m, aryl H), 3.90 (4H, m, acetal H), 3.83 (3H, s, OMe) and 3.3-1.2 (10H, m, aliphatic H) (Found: C, 71.71; H, 6.77%. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%).

3-Methoxy-6α-hydroxy-16,16-ethylenedioxy-9βH-gibb-A-triene (27)

To a cold (0°) suspension of lithium aluminium hydride (500 mg) in ether (100 ml) was added, dropwise with stirring, a solution of the ketone (26) (6.62 g) in ether (300 ml). After the solution had been stirred at room temperature for 4 hours, it was cooled (ice bath), treated successively with water (0.5 ml), aqueous 15% sodium hydroxide solution (0.5 ml), and water (1.5 ml) and then filtered to remove the inorganic salts. The residue was washed with methylene chloride and the combined organic filtrates were concentrated. Recrystallisation of the residual solid from ether separated the alcohol (27) (6.55 g; 98%) as colourless crystals, m.p. 138-139°, ν max. (CCl_4) 3630 (free OH) and 3605 cm^{-1} (bonded OH), λ max. 282 (ε 2580) and 289 nm (2290), δ 7.18 (1H, d, J=8Hz, 4-H), 6.93 (1H, d, J=2Hz, 2-H), 6.73 (1H, q, J=2 and 8Hz, 1-H), 5.07-4.77 (1H, s, 6-H), 3.90 (4H, m, acetal H), 3.80 (3H, s, OMe), 3.03-2.66 (1H, m, 9-H) and 2.66-1.0 (10H, m, aliphatic H and OH) (Found: C, 71.44; H, 7.42%. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

3-Methoxy-6α-hydroxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxylic acid (28)

To a vigorously stirred mixture of sublimed (220-250°; 0.05 mm), powdered sodium t-butoxide (389 mg), alcohol (27) (590 mg), and hexane (30 ml) was added, dropwise over a 15 minute period, 15% n-butyl lithium in hexane (3.2 ml), while the reaction mixture was kept at 25° under nitrogen. The resulting dark red solution was stirred at 30° for 2 hours and then poured, still under nitrogen, into a flask containing solid carbon dioxide and ether. The reaction mixture was diluted with water (5 ml) and then sodium carbonate (0.5 g) was added with stirring and the resulting mixture allowed to stand overnight. From the organic layer crude unchanged alcohol (27) was recovered.

The aqueous layer was acidified at 0° with dilute sulphuric acid and extracted with chloroform. After the chloroform extract had been washed free of mineral acid with brine, dried and concentrated, the residual acid (419 mg) was recrystallised from ethyl acetate to separate the acid (28) (389 mg; 90%, based on recovered alcohol), m.p. 201-209°, ν max. (KBr) 3440 (bonded OH) and 1702 cm^{-1} (acid C=O), λ max. 291 nm (ε 2370) with intense end absorption, δ 7.5-6.4 (2H, broad singlet, OH and COOH), 7.36 and 7.01 (2H, q, J=9Hz, aryl H), 5.30 (1H, s, 6-H), 4.07 (3H, s, OMe), 3.92 (4H, m, acetal H) and 3.1-1.0 (10H, m, aliphatic H) (Found: C, 65.64; H, 6.47%. $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40%).

Methyl 3-Methoxy-6α-hydroxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxylate (29)

Reaction of the acid (28) (160 mg) with excess ethereal diazomethane yielded the methyl ester (29) (162 mg) as colourless crystals (ethyl acetate/light petroleum), m.p. 166-167°, ν max. (CCl_4) 3597 (intra-bonded OH), 3475 (inter-bonded OH), 1742 and 1700 cm^{-1} (ester C=O), λ max. 291 nm (ε 3035), δ 7.15 and 6.81 (2H, q, J=9Hz, aryl H), 5.10 (1H, s, 6-H), 3.92 (3H, s, OMe), 3.87 (4H, m, acetal H), 3.82 (3H, s, OMe) and 3.0-1.0 (11H, m, aliphatic H and OH) (Found: C, 66.86; H, 6.79%. $C_{20}H_{24}O_6$ requires C, 66.65; H, 6.71%).

3-Methoxy-6β-cyano-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxylic acid (30)

Attempted preparation from the hydroxy acid (28).

To a cold (-5°), stirred suspension of the hydroxy acid (28) (142 mg) in dry ether (25 ml) was added, dropwise over 10 minutes under nitrogen, a solution of 15% n-butyl lithium in hexane (0.54 ml) and the mixture was then stirred for a further 20 minutes. Pure p-toluenesulphonyl chloride (80 mg) was added slowly over 5 minutes and the resulting suspension was left overnight at 0°. Ether was removed at 0° under vacuum and the residual colourless solid was dissolved in dimethyl sulphoxide (15 ml) and treated with sodium cyanide (45 mg). After stirring for 3 days at room temperature, the resulting solution was diluted with water, acidified at 0° with dilute sulphuric acid, and extracted with methylene chloride.

The organic extract was washed with brine, dried and concentrated to afford the crude hydroxy acid (28) (130 mg) as the sole product.

Methyl 3-Methoxy-6β-cyano-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxylate (32)

Attempted preparation from the hydroxy ester (29).

A mixture of the hydroxy ester (29) (35 mg), triphenylphosphine (39 mg) and carbon tetrachloride (5 ml) was heated for 1 hour at 60°. The reaction was monitored by i.r. spectroscopy and t.l.c. but only starting materials were present.

A mixture of the ester (20mg), triphenylphosphine (19 mg) and carbon tetrachloride (5 ml) was refluxed with excess bromine for 1 hour, the reaction again being monitored by t.l.c. and i.r. spectroscopy. The solution was cooled, filtered and concentrated to leave the crude bromide (31) (25 mg) as a pale yellow oil, less polar than the starting material, exhibiting no hydroxyl absorption in the i.r. spectrum, which had ν max. (CCl_4) 1735 cm^{-1} (ester C=O). The n.m.r. spectrum showed that the C-6 benzylic proton had shifted from δ 5.1 to 5.3, consistent with the conversion of ArCHOH to ArCHBr.

The crude bromide (31) (20 mg) and excess sodium cyanide were heated at 60° overnight in dimethyl sulphoxide (5 ml). The resulting solution was cooled to 0°, poured on to a solution of ferrous sulphate and extracted with methylene chloride. The organic extract was washed with water, dried and concentrated to give an unidentified mixture of products (12 mg), exhibiting no nitrile absorption in the i.r. spectrum.

3-Methoxy-16-oxo-9βH-gibb-A-triene (34)

a) Preparation from the alcohol (27) by sodium/ammonia hydrogenolysis followed by hydrolysis.

After reacting the alcohol (27) (76 mg) with sodium (10 mg) in liquid ammonia (15 ml) for 3 minutes, ammonium chloride (74 mg) was added to quench the resulting blue solution. The ammonia was allowed to evaporate, cold (5°) water (10 ml) added to the residue and the mixture was then extracted with ether. The organic extract was washed with brine, dried and concentrated. The residual crude product (68 mg) was subjected to preparative t.l.c. (ethyl acetate/light petroleum, 1:1), which gave the starting alcohol (27) (31 mg) with R_F=0.27 and the acetal (33) (32 mg) with R_F=0.57; i.r. (33), no hydroxyl absorption; n.m.r. (33), δ 6.87-6.33 (3H, m, aryl H), 3.73 (4H, m, acetal H), 3.63 (3H, s, OMe), 3.13-2.47 (3H, m, 6-H_2 and 9-H) and 2.45-1.0 (9H, m, aliphatic H).

After the acetal (33) had been refluxed in 75% acetic acid for 1 hour, the solution was cooled, neutralised with sodium carbonate and extracted with ether. The crude product (26 mg) was recrystallised (ethyl acetate/light petroleum) to give the pure ketone (34), m.p. 111-113°, ν max.(KBr) 1746 cm^{-1} (ketone C=O), λ max. 282 (ε1870) and 288 nm (1690), δ 7.06-6.58 (3H, m, aryl H), 3.80 (3H, s, OMe), 3.17 and 2.75 (2H, q, J=16Hz, 6-H_2), 3.20-2.80 (1H, m, 9-H) and 2.5-1.0 (9H, m, aliphatic H) (Found: C, 79.10; H, 7.46%. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%).

b) Preparation from the ketone (26) by Wolff-Kishner reduction followed by hydrolysis.

To a vigorously stirred solution of the alcohol (27) (60 mg)

in acetone (10 ml) at -5° was added dropwise excess Jones reagent. After 5 minutes at 5°, excess oxidant was destroyed with isopropyl alcohol and the solution was concentrated and partitioned between water and methylene chloride. The organic layer was dried and concentrated to leave keto acetal (26) (56 mg; 92%), m.p. 81-83°, identical to the authentic sample.

A mixture of the above keto acetal (26) (50 mg), ethylene glycol (1 ml), 100% hydrazine (0.25 ml) and potassium hydroxide (35 mg) was heated at 150° overnight. The solution was cooled, diluted with water and extracted with methylene chloride. The organic extract was washed with water, dried and concentrated to give the crude acetal (33) (41 mg), which lacked any carbonyl absorption in its i.r. spectrum. Hydrolysis of this material, as before, gave the ketone (34) (30 mg; 74%), m.p. 111-113°, after recrystallisation.

c) Preparation from the alcohol (27) by catalytic hydrogenolysis.

A mixture of the alcohol (27) (45 mg), 10% palladium/charcoal (15 mg), 60% perchloric acid (1 drop) and ethyl acetate (5 ml) was stirred for 4 hours under hydrogen. The solution was filtered, washed with water, dried and concentrated to leave the ketone (34) (36 mg; 99%), m.p. 111-113°, after recrystallisation.

3-Methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxylic acid (35)

a) Attempted preparation from the hydroxy acid (28) by sodium/ammonia hydrogenolysis.

A solution of the acid (28) (113 mg) in liquid ammonia (30 ml)

was treated with sodium (17 mg) until a blue colour persisted. After 15 minutes, ethanol was added to quench the reaction and the ammonia was then allowed to evaporate. The residue was dissolved in cold water, carefully acidified at 0° with dilute sulphuric acid, and extracted several times with methylene chloride. The organic extract was washed with brine, dried and concentrated to leave the crude dihydroaromatic acid (36) (110 mg), ν max. (CCl_4) 1740 and shoulder at 1720 (acid C=O) and 1662 cm^{-1} (C=C), λ max. end absorption only, δ 6.8-6.0 (2H, broad singlet, OH and COOH), 4.77 (1H, t, J=4Hz, 2-H), 4.57 (1H, m, 4-H), 3.83 (5H, m, acetal H and 6-H), 3.53 (3H, s, OMe) and 3.0-1.0 (12H, m, aliphatic H).

To a stirred solution of the dihydroaromatic acid (36) (95 mg) in benzene (20 ml) under nitrogen was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (65 mg) until a faint yellow colour persisted. The acidic product (70 mg) from this reaction was identical to the hydroxy acid (28).

b) Attempted preparation from the hydroxy acid (28) by oxidation followed by Wolff-Kishner reduction.

After oxidation of the hydroxy acid (28) (34 mg) with Jones reagent (0.04 ml) in acetone (5 ml) at 0° for 5 minutes, the excess oxidant was destroyed with isopropyl alcohol and the solution was concentrated and partitioned between water and methylene chloride. The organic layer was dried and concentrated to leave the crude keto acid (37) (26 mg), ν max. ($CHCl_3$) 1710 cm^{-1} (acid and ketone C=O), λ max. 255 and 323 nm.

A mixture of the keto acid (37) (21 mg), ethylene glycol (2 ml), 100% hydrazine (0.2 ml) and potassium hydroxide (20 mg)

was heated at 150° overnight. After the usual manipulations, there was isolated a crude, unidentified product (14 mg), which had neither u.v. nor i.r. characteristics of the expected compound but which indicated a structure such as (38).

c) Preparation from the hydroxy acid (28) by catalytic hydrogenolysis followed by re-acetalisation.

Hydrogenolysis of the hydroxy acid (28) (427 mg) in ethyl acetate (120 ml) occurred overnight using 10% palladium/charcoal (120 mg) and 60% perchloric acid (3 drops) as catalyst. The solution was filtered, washed with water, dried and concentrated to give the keto acid (39) (407 mg), ν max. (CCl_4) 1735 (ketone C=O) and 1695 cm^{-1} (acid C=O), δ 8.8-8.4 (1H, COOH), 7.23 and 6.90 (2H, q, J=8Hz, aryl H), 4.01 (3H, s, OMe), 3.38 (2H, s, 6-H_2), 3.25-2.80 (1H, m, 9-H) and 2.6-1.0 (9H, m, aliphatic H).

A mixture of the above keto acid (39), ethylene glycol (10 ml), p-toluenesulphonic acid monohydrate (20 mg) and benzene (140 ml) was refluxed for 20 hours with constant separation of water. The solution was cooled, diluted with water and extracted with ethyl acetate. The organic extract was washed with water, dried and concentrated. Recrystallisation (ethyl acetate) of the crude product (443 mg) separated the acid (35) (393 mg), m.p. 213-217°, ν max. (CCl_4) 1690 cm^{-1} (acid C=O), λ max. 294 nm (ε 2440), δ 9.3-8.2 (1H, COOH), 7.23 and 6.87 (2H, q, J=8Hz, aryl H), 4.03 (3H, s, OMe), 3.92 (4H, m, acetal H), 3.30 (2H, s, 6-H_2), 3.20-2.80 (1H, m, 9-H) and 2.5-1.1 (9H, m, aliphatic H) (Found: C, 68.89; H, 6.57%. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%).

The mother liquors (50 mg), which contained the glycolate ester (40) and the acid (35), were left at room temperature in 15% sodium hydroxide solution for 60 hours. The resulting solution was cooled to 0°, acidified with dilute sulphuric acid, and extracted with ethyl acetate. From the dried, organic extract was obtained the acid (35) (32 mg), identical to the authentic sample.

Methyl 3-Methoxy-16-oxo-9βH-gibb-A-triene-4-carboxylate (41)

A mixture of the hydroxy ester (29) (45 mg), 10% palladium/charcoal (15 mg), 60% perchloric acid (1 drop) and methyl acetate (5ml) was stirred overnight under hydrogen. The solution was filtered, washed with water, dried and concentrated. Recrystallisation (ether) of the residual solid gave the keto ester (41) (37 mg; 99%), m.p. 113-114°, ν max. (KBr) 1735 (ketone C=O) and 1690 cm^{-1} (ester C=O), λ max. 294 nm (ε 2480), δ 7.17 and 6.80 (2H, q, J=8Hz, aryl H), 3.92 (3H, s, OMe), 3.87 (3H, s, OMe), 3.18 and 2.88 (2H, q, J=16Hz, 6-H_2), 3.30-2.90 (1H, m, 9-H) and 2.7-1.1 (9H, m, aliphatic H) (Found: C, 71.82; H, 6.80%. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%).

3-Methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4,6β-dicarboxylic acid (42)

Attempted preparation from the acid (35) by direct C-6 carboxylation.

To a suspension of the acid (35) (33 mg) and lithium hydride (1 mg) in tetrahydrofuran (5 ml) was added, dropwise over

10 minutes, a solution of 2.1M n-butyl lithium in hexane (0.1 ml). After the resulting red solution had been left stirring for 1 hour at room temperature, it was poured on to a solution of solid carbon dioxide in ether. The resulting mixture was partitioned between water and ether. Concentration of the ether layer gave an oil (10 mg), containing the n-butyl ketone (79), ν max. (film) 1690 cm^{-1} (ketone C=O), λ max. 255 and 305 nm, mass spectrum, M=370. $C_{23}H_{30}O_4$ requires M=370.

The aqueous layer was cooled in an ice bath, acidified with dilute sulphuric acid and extracted with chloroform. The acidic material obtained (29 mg) was a mixture of the acid (35) and the diacid (42) in the ratio 2:1 (by g.l.c. analysis of the corresponding methyl esters).

N-Ethyl o-toluamide (43)

a) Preparation from o-toluoyl chloride.

A mixture of o-toluic acid (1.36 g), oxalyl chloride (2 ml) and benzene (25 ml) was stirred for 1 hour at room temperature. Excess oxalyl chloride and benzene were removed and the resulting acid chloride in ether (10 ml) was added slowly to a stirred solution of ethylamine (3 ml) in ether (10 ml) at 0°. After 30 minutes the solution was washed with water, dried and concentrated. Recrystallisation (cyclohexane) of the product gave the amide (43) (1.4 g; 86%) as white needles, m.p. 63-64°, ν max. (KBr) 3285 (NH), 1633 and 1536 cm^{-1} (amide C=O), λ max. 270 nm (ε 600), δ 7.50-6.93 (4H, m, aryl H), 6.4-5.6 (1H, broad singlet, CONH), 3.45 and 3.37 (2H, overlapping quartets, J=8Hz, CH_2N), 2.42 (3H, s, aryl CH_3) and 1.20 (3H, t,

J=8Hz, aliphatic CH_3) (Found: C, 73.47; H, 7.99; N, 8.66%. $C_{10}H_{13}NO$ requires C, 73.59; H, 8.03; N, 8.58%).

b) Preparation from methyl o-toluate.

To a stirred solution (0°) of ethylamine (1 ml) in tetrahydrofuran (5 ml) was added dropwise 2.1M n-butyl lithium in hexane (0.5 ml) under nitrogen. After 10 minutes a solution of methyl o-toluate (150 mg) in tetrahydrofuran (2 ml) was added slowly and the resulting mixture was then stirred at room temperature for a further hour. The solution was diluted with water (1 ml), concentrated under vacuum, and extracted with ether. The product from the organic extract consisted entirely of amide (43) (155 mg; 95%), m.p. 62-64°, identical to the authentic sample.

o-(N-ethyl carboxamido)phenyl acetic acid (44)

To a solution of the amide (43) (320 mg) in tetrahydrofuran (10 ml) under nitrogen was added, dropwise over 10 minutes, 2.1M n-butyl lithium in hexane (2.4 ml) and the resulting dark red solution was refluxed for 15 minutes. After cooling to room temperature, the solution was injected on to solid carbon dioxide in ether and left for 2 hours. The resulting mixture was partitioned between water and ether. Concentration of the ether layer and crystallisation of the residue separated the starting amide (43) (140 mg), m.p. 63-64°.

The aqueous layer was cooled in an ice bath, acidified with dilute sulphuric acid, and extracted with ethyl acetate. The organic extract was washed with brine, dried and concentrated

to leave the crude amido acid (44) (194 mg; 88%, based on recovered amide), m.p. 144-146°. Recrystallisation from benzene separated the pure amido acid (44), m.p. 147-148°, ν max. (KBr) 3240 (NH), 1715 acid C=O), 1582 and 1555 cm^{-1} (amide C=O), λ max. 270 nm (ε 565), δ 9.4-8.8 (1H, COOH), 7.60-7.10 (4H, m, aryl H), 7.0-6.3 (1H, broad singlet, CONH), 3.73 (2H, s, 1-H_2), 3.50 and 3.47 (2H, overlapping quartets, J=6Hz, CH_2N) and 1.30 (3H, t, J=8Hz, CH_3) (Found: C, 63.50; H, 6.41; N, 6.86%. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.32; N, 6.76%).

A solution of the amido acid (44) (44 mg) in aqueous sodium hydroxide (4 ml) was refluxed overnight under nitrogen. The usual manipulations gave a colourless solid (29 mg; 82%), identical to homophthalic acid.

N-Ethyl 3-Methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxamide (46)

A mixture of the keto ester (41) (2.18 g), ethylene glycol (20 ml), p-toluenesulphonic acid monohydrate (100 mg) and benzene (100 ml) was refluxed for 20 hours with constant separation of water. The solution was cooled, diluted with ethyl acetate, washed with dilute sodium bicarbonate, dried and concentrated to leave the acetals as a clear oil (2.04 g), consisting of a mixture of the methyl ester (45) and the glycolate ester (40) in the ratio 9:1 (by g.l.c. analysis).

A solution of the above esters (2.04 g) in tetrahydrofuran (50 ml) was added slowly to a mixture of lithium ethylamide, prepared from ethylamine (25 ml) and 2.1M n-butyl lithium in hexane (6 ml),

in tetrahydrofuran (35 ml) at 0°. The reaction was followed by t.l.c. (ethyl acetate/light petroleum in the ratio 1:1; methyl ester (45), R_F=0.54; glycolate ester (40), R_F=0.25; amide (46), R_F=0.16) until quantitative amidation had occurred (3 hours at 30°). Excess ethylamine and tetrahydrofuran were removed under vacuum and the residue was dissolved in cold water and extracted with ethyl acetate. The organic extract was dried and concentrated to leave the amide (46) (2.02 g; 94%) as colourless crystals (chloroform/isopropyl ether), m.p. 185-186°, ν max. (KBr) 3372 (NH), 1650 and 1519 cm^{-1} (amide C=O), λ max. 289 nm (ε 2820), δ 7.2-6.8 (1H, broad singlet, CONH), 7.07 and 6.73 (2H, q, J=8Hz, aryl H), 3.92 (4H, m, acetal H), 3.85 (3H, s, OMe), 3.52 and 3.42 (2H, overlapping quartets, J=8Hz, NCH_2), 3.13 (2H, s, 6-H_2), 3.2-2.8 (1H, m, 9-H), 2.4-1.3 (9H, m, aliphatic H) and 1.22 (3H, t, J=8Hz, CH_3) (Found: C, 70.41; H, 7.81; N, 3.88%. $C_{21}H_{27}NO_4$ requires C, 70.56; H, 7.61; N, 3.92%).

N-Ethyl 3-Methoxy-6β-carboxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4-carboxamide (47)

To a cold (0°) suspension of the amide (46) (538 mg) in tetrahydrofuran (10 ml) was added dropwise 2.1M n-butyl lithium in hexane (1.5 ml). The resulting dark red solution was stirred at 50° for 2 hours, cooled and poured onto a slurry of solid carbon dioxide in ether. The resulting mixture was left for 1 hour and then partitioned between water and ether. Concentration of the ether layer gave the starting amide (46) (185 mg), m.p. 183-186°. The aqueous layer was cooled in an ice bath, acidified with dilute

sulphuric acid and extracted with chloroform and ethyl acetate. The organic extracts were washed with brine, dried and concentrated to leave the acid (47) (337 mg; 82%, based on recovered amide) as colourless crystals (ethyl acetate), m.p. 190-199° (decomposition), ν max. (KBr) 3370 (NH), 1731 and shoulder at 1705 (acid C=O), 1647 and 1607 cm^{-1} (amide C=O), λ max. 292 nm (ε 2810), δ (d_5 pyridine) 11.0-9.3 (1H, COOH), 8.9-8.1 (1H, broad singlet, CONH), 7.22 and 6.83 (2H, q, J=8Hz, aryl H), 4.51 (1H, s, 6-H), 3.80 (4H, m, acetal H), 3.65 (3H, s, OMe), 3.53 and 3.50 (2H, overlapping quartets, J=7Hz, CH_2N), 3.1-1.2 (10H, m, aliphatic H) and 1.18 (3H, t, J=7Hz, CH_3) (Found: C, 65.62; H, 6.98; N, 3.49%. $C_{22}H_{27}NO_6$ requires C, 65.82; H, 6.98; N, 3.44%).

3-Methoxy-16,16-ethylenedioxy-9βH-gibb-A-triene-4,6β-dicarboxylic acid (42)

A sample of the amido acid (47) (600 mg) in ethyl acetate (50 ml) was esterified with excess diazomethane in ether to yield the amido ester (48) (620 mg), ν max. (film) 3420 (NH), 1728 (ester C=O), 1645 and 1532 cm^{-1} (amide C=O), δ (d_5 pyridine) 8.6-8.1 (1H, broad singlet, CONH), 7.20 and 6.85 (2H, q, J=8Hz, aryl H), 4.43 (1H, s, 6-H), 3.80 (4H, m, acetal H), 3.66 (6H, s, superimposed OMe groups), 3.50 and 3.47 (2H, overlapping quartets, J=7Hz, CH_2N), 3.1-1.2 (10H, m, aliphatic H) and 1.18 (3H, t, J=7Hz, CH_3).

A mixture of the amido ester (48) (30 mg), sodium methoxide (5 mg) and benzene (5 ml) was refluxed under nitrogen for 1 hour. The solution was cooled and partitioned between water and

ether. The organic layer was dried and concentrated to give the amido ester (48) (28 mg), identical to the starting material by g.l.c. and n.m.r. standards.

A solution of the amido ester (48) (30 mg) in dilute aqueous sodium hydroxide was refluxed for 6 hours under nitrogen. The solution was cooled (0°), acidified with dilute sulphuric acid, and extracted with ethyl acetate. The organic extract was washed with brine, dried and concentrated to give the amido acid (47) (22 mg), identical to an authentic sample.

A solution of the amido ester (48) (610 mg) in methylene chloride (5 ml) was added slowly to a suspension of sodium acetate (550 mg) and sodium sulphate (250 mg) in methylene chloride (10 ml) containing nitrogen dioxide (280 mg) at 0°. After the mixture had been left overnight at 0°, it was washed with water, dried and concentrated to leave the N-nitroso amide (49) as a yellow oil, ν max. (film) 1725 (ester C=0) and 1505 cm^{-1} (N=0).

A mixture of the N-nitroso amide (49) (605 mg), methanol (10 ml) and 15% sodium hydroxide solution (5 ml) was refluxed under nitrogen for 4 hours and then partitioned between ether and water. After the aqueous phase had been acidified at 0° with dilute sulphuric acid and extracted with chloroform and ethyl acetate, the organic extract was dried and concentrated. The residual crude product was recrystallised from ethyl acetate to separate the diacid (42) (451 mg; 80%) as colourless crystals, m.p. 207-215°, ν max. (KBr) 1731 and 1692 cm^{-1} (carboxyl C=0), λ max. 300 nm (ε 2170), δ 8.2-7.5 (2H, COOH), 7.32 and 6.94 (2H, q, J=9Hz, aryl H), 4.17 (1H, s, 6-H), 4.00 (3H, s, OMe), 3.90 (4H, m, acetal H) and 3.45-1.0 (10H, m, aliphatic H) (Found: C, 64.43; H, 6.17%. $C_{20}H_{22}O_7$ requires C, 64.16; H, 5.92%).

For comparative purposes the diacid (42) was esterified with diazomethane to the corresponding dimethyl ester (42b).

Methyl 3-Methoxy-4-methyl-16,16-ethylenedioxy-9βH-gibb-A-triene-6β-carboxylate (51)

a) To a mixture of the diacid (42) (38 mg), sodium hydride (5 mg) and freshly distilled liquid ammonia (10 ml) was added sodium (8 mg) in small portions until the blue colour of the solution persisted for 1 hour. Excess methyl iodide was then added over a period of 5 minutes, whereupon the colour turned through yellow to white. After the ammonia had been removed in a slow stream of nitrogen, the remaining material was dissolved in water, and the solution washed with ether. The aqueous layer was cooled to -5°, acidified (pH 4) with 1N sodium dihydrogen phosphate, and extracted with chloroform and ethyl acetate. The organic extracts were washed with brine, dried and immediately treated with excess ethereal diazomethane to yield the crude mono-ester (51) (33 mg) instead of the expected diester (50). Preparative t.l.c. (ethyl acetate/light petroleum in the ratio of 1:1) gave the pure mono-ester (51) (23 mg; 64%), m.p. 120-122° (ether/light petroleum), ν max. (CCl_4) 1730 cm^{-1} (ester C=0), λ max. 282 and 287 nm, δ 6.93 and 6.70 (2H, q, J=8Hz, aryl H), 3.90 (4H, m, acetal H), 3.80 (3H, s, OMe) and 3.3-1.1 (13H, m, aliphatic H including the CH_3 singlet at 2.33) (Found: C, 70.58; H, 7.42%; M, 358. $C_{21}H_{26}O_5$ requires C, 70.37; H, 7.31%; M, 358).

b) To a mixture of the diacid (42) (38 mg) and freshly distilled

liquid ammonia was added lithium (4 mg) until the blue colour of the solution persisted. After 1 hour lithium amide (5 mg) was added to the mixture which was then allowed to reflux for a further 4 hours. Excess methyl iodide was added and the ammonia-free product was dissolved in dilute sodium carbonate solution and washed with ether. The aqueous layer was treated with iodine (50 mg) and potassium iodide (100 mg) and left overnight in the dark. After addition of excess sodium thiosulphate solution the resulting mixture was acidified at 0° and worked up as before. The residual crude product (25 mg) afforded, on crystallisation, the ester (51), identical to an authentic sample.

Methyl 4α-Carboxy-10α-hydroxy-4β-methyl-3,16-dioxo-9βH-gibbane-6β-carboxylate 4α⟶10α-Lactone (55)

A mixture of gibberellin A_4 (52) and A_7 (53) (60 mg; in the ratio of 45:55 respectively, by n.m.r. analysis) was esterified with excess ethereal diazomethane at 0°. The crude esters were ozonised in ethyl acetate/acetic acid (4:1) and treated with excess zinc dust and water. The crude product containing the hydroxy ketone (54) was extracted, dried and oxidised with excess Jones reagent in acetone (10 ml) at 0°. Excess oxidant was destroyed with isopropyl alcohol and the solution was concentrated and partitioned between water/chloroform. The organic layer was washed with dilute sodium bicarbonate solution, dried and concentrated to leave a neutral product(20 mg). Preparative t.l.c. (ethyl acetate/light petroleum in the ratio of 1:1) of this material yielded the lactonic ester (55) (14 mg), m.p. 200.5-201° (ether), ν max. (KBr) 1780

(lactone C=O) and 1732 cm^{-1} (ketone and ester C=O), δ 3.73 (3H, s, OMe), 3.8-1.3 (16H, m, aliphatic H) and 1.20 (3H, s, CH_3) (Found: C, 65.63; H, 6.42%. $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40%).

TABLE 3

G.L.C. DATA

Compound	Flow Rate (ml/min)	R_t (min)	R_i
5a (or 5b)	65	8.5	3200
5b (or 5a)	65	9.5	3250
6a (or 6b)	65	8.5	3200
6b (or 6a)	65	9.5	3250
7a and 7b	61	11.0	3415
8a (or 8b)	62	6.3	3080
8b (or 8a)	62	8.0	3170
9a (or 9b)	62	6.3	3080
9b (or 9a)	62	8.0	3170
10a (or 10b)	65	8.4	3190
10b (or 10a)	65	9.4	3240
11a	60	21.9	3620
11b	60	20.8	3605
11c	60	27.0	3705
12a	60	20.7	3600
12b	60	19.5	3575
12c	60	26.5	3700
13a	60	20.7	3600
13b	60	19.5	3575
13c	60	26.5	3700
14a	63	9.1	3400
14b	63	7.9	3330
14c	63	10.9	3470
15a	63	4.5	3085
15b	63	5.1	3090
16b (200°)	62	9.3	3025

Compound	Flow Rate (ml/min)	R_t (min)	R_i
16b (200°)	62	9.8	3030
19	45	8.1	3270
20a	60	21.9	3620
20b	60	20.8	3605
20c	60	27.0	3705
21a	70	9.0	3330
21b	70	8.1	3295
21c	70	12.2	3380
22a,22b,22c	61	29.0	3740
25a and 25b	55	12.9	3515
26	45	9.2	3320
27 (200°)	55	7.0	3270
29	50	16.0	3430
33	40	6.1	2790
34	40	7.5	2840
40	39	13.0	3390
41	36	7.3	3365
42b	60	10.8	3480
45	39	10.5	3310
46	60	14.6	3810
48	60	29.7	4120
51	60	3.8	3220
55	60	26.2	4070

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