# Synthesis of Compounds related to Gibberellic Acid. Part IV.[1] Construction of a Tetracyclic System containing Functional Elements of Rings A, C, and D

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The synthesis from suitable indane derivatives of methyl 16,16-ethylenedioxy-3-methoxy-9α*H*-gibba-1(10),2,4-triene-4-carboxylate (27b) and the corresponding 1(10),2,4,9(11)-tetraene (34b), possible intermediates for the total synthesis of gibberellin $A_4$ (1b), is described.

FOLLOWING our previous work describing the partial construction of ring A[1] (Scheme 1) and of rings C and D [2,3] (Scheme 2) of a compound such as the nor-ketone (1a),† which has been reconverted into gibberellin $A_4$ (1b),[5] this paper describes the first steps towards combining these synthetic results.

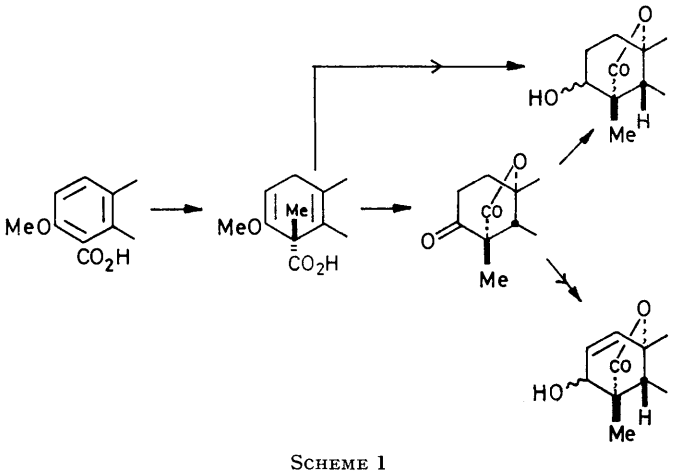
Ideally an oxo-triester such as (2) would represent a logical starting point, but no satisfactory route to such a compound was apparent. The preparation of an oxo-diester such as (3) was comparatively simple, but its reaction with methyl vinyl ketone in the presence of sodium methoxide led not to the normal cyclisation to give a hydrofluorene skeleton but, unexpectedly, to a product (4) of little further interest in this connection; this result will be described separately. Our work therefore concentrated on finding a simple route to the oxo-ester (12b) and thence to the oxo-diester (18), leaving the problem of the introduction of the carboxy-group in ring B to a later stage.

Initially this approach was based on the finding that chloromethylation of 5-methoxyindan-1-one (5) was highly regiospecific, giving the 4-chloromethyl derivative (6) and the 6-isomer (7) in the ratio 6 : 1. Delobelle and Fetizon [6] have reported a similar specificity in the chloromethylation of 6-methoxy-1-tetralone. On the other hand the nitration of (5) appears to be much less specific. Such differences in selectivity with different types of aromatic substitution have been reported in similar

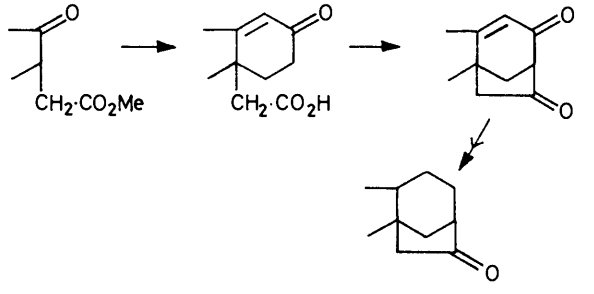
† In conformity with Raphael and his co-workers,[4] this paper retains the gibbane nomenclature,[2] while employing the numbering based on '*ent*-gibberellane' proposed by J. W. Rowe ('The Common and Systematic Nomenclature of Cyclic Diterpenes,' 3rd revision, October 1968) which differs from that currently used by *Chemical Abstracts*. We agree with the Editor on the need for resolving this situation as soon as possible by international agreement and hope that a reasonable solution will be found after consultation with workers active in this field.

[1] Part III, M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, 1969, **34**, 126.
[2] H. J. E. Loewenthal and Y. Kos, *J. Chem. Soc.*, 1963, 605.
[3] H. J. E. Loewenthal and S. K. Malhotra, *J. Chem. Soc.*, 1965, 990.
[4] A. J. Baker, J. Brown, and R. A. Raphael, *J.C.S. Perkin I*, 1972, 1256.
[5] D. C. Aldridge, J. R. Hanson, and T. P. C. Mulholland, *J. Chem. Soc.*, 1965, 3539.
[6] J. Delobelle and M. Fetizon, *Bull. Soc. chim. France*, 1961, 1900.

cases,[7,8] but our result of predominant ' ar.-α-substitution ' does not appear to be the one predicted by the latter authors' interpretation of this ' Mills–Nixon ' effect.



SCHEME 1



SCHEME 2

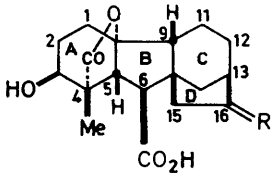
Conversion of compound (6) into the alcohol (9) was simple, but oxidation of the latter with chromic acid in acetone went no further than the aldehyde stage to give compound (10). In practice the crude chloromethylation product obtained from (5) could be subjected to this transformation and pure (10) isolated by elution from Florisil, which retained all products derived from the isomer (7). Further oxidation of (10) to the oxo-acid (12a) was then found possible by repeating the oxidation with chromic acid in the presence of a trace of cerium(IV).[9]

A better preparative route followed upon the observation[10] that oxidation of a 2-hydroxymethylenecyclopentanone with hydrogen peroxide in t-butyl gives an adipic acid, and not a glutaric acid as is formed in the presence of alkali. A large-scale preparative method for 7-methoxyindan-1-one was developed (see Experimental section); and this type of ring cleavage, whose mechanism has been elucidated,[11] was applied to its hydroxymethylene derivative (14), giving in excellent yield the dicarboxylic acid (15a). Cyclisation of the latter or of the derived half-ester (15c) afforded the oxo-ester (12b), again in excellent yield.

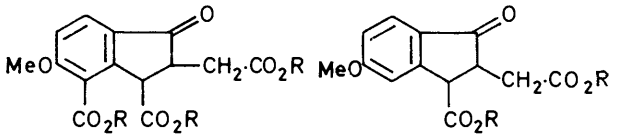
Attachment of the acetic acid side chain was accomplished by acid-catalysed condensation with n-butyl glyoxylate to give compound (16), followed by catalytic hydrogenation and methanolysis leading to the desired oxo-diester (18).

In parallel experiments we studied the chloromethylation of the oxo-ester (20) and of the oxo-lactone (23). In both these cases, likewise, aromatic substitution occurred mainly at the 4-position, giving products (21) (formed by additional attack α to the ketone group) and (24), respectively. Neither of these could be transformed into the oxo-diester (18); in particular all attempts to remove the unwanted side-chain carbon atom in the lactone (21) by a retro-aldol type of reaction were abortive.

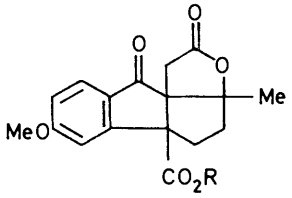
Fusion of a six-membered ring to the oxo-diester (18) by use of methyl vinyl ketone in methanolic sodium methoxide proceeded in high yield to give the half-ester (25). Cyclisation of similar compounds to bridged-ring diketones has previously been achieved under a variety of conditions;[2-4,12,13] in the present case the use of a mixture of trifluoroacetic acid and its anhydride at room temperature led to the tetracyclic dioxo-ester (26a) in nearly theoretical yield.



(1) a; R = O
b; R = $CH_2$



(2) (3)

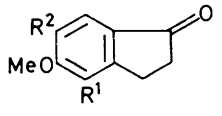


(4)

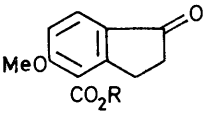
It was now necessary to remove the conjugated ketone group, and to saturate the double bond, preferably so as

[7] R. Granger and H. Orzalesi, *Compt. rend.*, 1961, **252**, 1478, 1971.
[8] J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 1965, **21**, 1665.
[9] *Cf.*, M. Doyle, R. J. Swedo, and J. Rocek, *J. Amer. Chem. Soc.*, 1973, **95**, 8352.
[10] S. I. Zavialov, L. P. Vinogradova, and G. V. Kondratieva, *Tetrahedron*, 1964, **20**, 2745.
[11] G. Payne, *J. Org. Chem.*, 1961, **26**, 4793.
[12] H. J. E. Loewenthal and Z. Neuwirth, *J. Org. Chem.*, 1967, **32**, 517.
[13] K. Mori, M. Matsui, and Y. Sumuki, *Agric. and Biol. Chem. (Japan)*, 1962, **26**, 783.

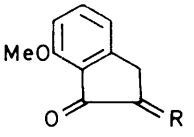
to give the hydrogen atom at C-9 *cis* to the two-carbon bridge as in compound (1a). Previous efforts towards this end [2-4,13] have involved a multi-step sequence such as that based on preferential acetalisation of the ring D oxo-group which is complicated by the sensitivity of the non-enolisable β-diketone system. The monoacetal (26b) could be obtained in fair yield, but, contrary to previous experience,[2,3] removal of the free oxo-group was not found possible. As an alternative the hydrogenation of compound (26a) was investigated. This led to mixtures of at least six of the possible expected twelve



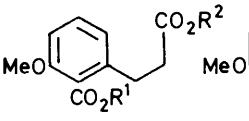
(5) $R^1=R^2=H$
(6) $R^1=CH_2Cl, R^2=H$
(7) $R^1=H, R^2=CH_2Cl$
(8) $R^1=CH_2\cdot OAc, R^2=H$
(9) $R^1=CH_2\cdot OH, R^2=H$
(10) $R^1=CHO, R^2=H$
(11) $R^1=H, R^2=CHO$



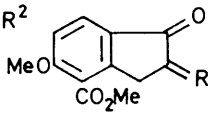
(12) a; R = H
b; R = Me



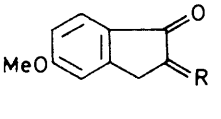
(13) $R=H_2$
(14) R = CH·OH



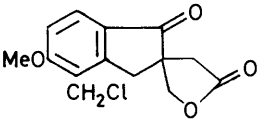
(15) a; $R^1=R^2=H$
b; $R^1=R^2=Me$
c; $R^1=Me, R^2=H$



(16) R = CH·$CO_2$Bu
(17) R = H, $CH_2\cdot CO_2$Bu
(18) R = H, $CH_2\cdot CO_2$Me



(19) R = CH·$CO_2$Bu
(20) R = H, $CH_2\cdot CO_2$Me



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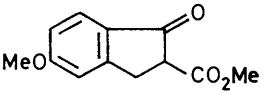
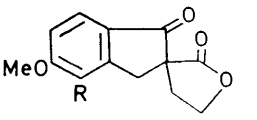
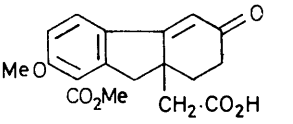


(22)

products, depending on conditions (solvent, temperature, and pressure) and catalyst (platinum or palladium in various forms). Eventually the use of a catalyst prepared *in situ* from palladium chloride and charcoal in acetic acid was found to give directly and in acceptable yield the oxo-ester (27a), convertible into its acetal (27b) by the usual methods.[14] A minor product of this hydrogenolysis was the epimer (28a), identical with the product obtained by Baker [15] by an entirely different route.



(23) R = H
(24) R = $CH_2Cl$



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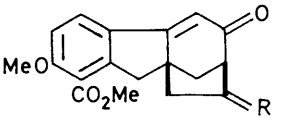
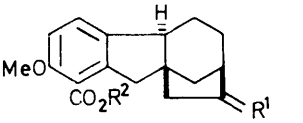
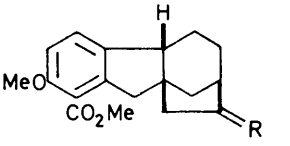


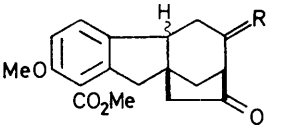
(26) a; R = O
b; R = ·O·$CH_2\cdot CH_2$·O·



(27) a; $R^1=O, R^2=Me$
b; $R^1$ = ·O·$CH_2\cdot CH_2$·O·, $R^2=Me$
c; $R^1$ = ·O·$CH_2\cdot CH_2$·O·, $R^2=H$

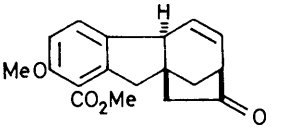


(28) a; R = O
b; R = ·O·$CH_2\cdot CH_2$·O·

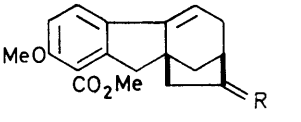


(29) R = β-OH, α-H; 9α-H
(30) R = O; 9α-H
(31) R = α-OH, β-H; 9β-H
(32) R = β-O·CS·O·$C_6H_4Me$-*p*
α-H; 9α-H

This result provided a one-step removal of functional groups that had served their purpose; but it gave the wrong stereochemistry at C-9. We were hopeful that this could be corrected at a penultimate stage through the intermediacy of a carbocation at this position or at C-10,[16] but nevertheless considered an option such as the unsaturated oxo-ester (34). The double bond of the latter could conceivably be hydrogenated to give the correct 9β-stereochemistry at a later stage subsequent to the introduction of, and directed by, a ring B carboxy-group *trans* to the two-carbon bridge.[17] For this the



(33)



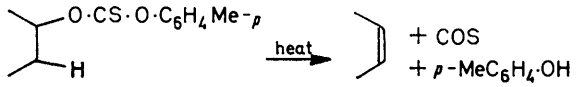
(34) a; R = O
b; R = ·O·$CH_2CH_2$·O·

hydroxy-oxo-ester (29), the main product of hydrogenation of (26a) in methanol over palladium hydroxide,[18]

[14] H. J. E. Loewenthal, in 'Protective Groups in Organic Chemistry,' ed. J. F. W. McOmie, Plenum Press, London, 1973, p. 309.
[15] A. J. Baker and A. C. Goudie, *J.C.S. Chem. Comm.*, 1972, 951.
[16] D. C. Aldridge, J. F. Grove, R. N. Speake, B. K. Tidd, and W. Klyne, *J. Chem. Soc.*, 1963, 143.
[17] J. F. Grove, J. MacMillan, T. P. C. Mulholland, and W. B. Turner, *J. Chem. Soc.*, 1960, 3049.
[18] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. I, p. 782.

appeared to be a likely intermediate. Various substituted sulphonate derivatives of this alcohol were prepared, but all were remarkably resistant to attempted elimination even with potassium t-butyloxide in toluene. A similar result has been observed [2] with an analogous chloro-compound.

Gerlach and Mueller [19] have recently described a method for dehydrating secondary alcohols involving the pyrolysis of derived *p*-tolyl thioncarbonates (35). The attractiveness of this method lies in the ease of




(35)

preparation of these derivatives in comparison with that of the *S*-methyl xanthates used in the Chugaeff elimination.[20] Indeed, the thioncarbonate (32) was found to undergo elimination smoothly at 230—260 °C and 0.1 mmHg; and rearrangement of the resulting olefin (33) by using palladium in boiling *p*-xylene gave the unsaturated oxo-ester (34a) in high overall yield. Unexpectedly, acetalisation of this product by both azeotropic and exchange methods [14] was unsatisfactory, but this problem was eventually solved by using ethanediol containing boron trifluoride at room temperature without solvent, a method which we have since found satisfactory for other ketones containing functional groups susceptible to cleavage or transesterification when different methods are used.

Some experiments were also conducted on the reintroduction of the conjugated double bond by dehydrogenation [21] of either the oxo-ester (27a) or its acetal (27b). These were partly successful but provided no good practical alternative to the dehydration approach described above in that separation of dehydrogenation product from starting material was difficult owing to only slight differences in polarity between the two; this difference was slightly greater in the case of the acetal than of the ketone.

The $^1$H n.m.r. spectra and assignments of most of the tetracyclic compounds mentioned in this paper are given in the Table; they are in accord with those reported.[4,16,22-24] Of particular interest is our confirmation of the dependence of the chemical shifts of the C-6 protons upon the stereochemistry at C-9 relative to the two-carbon bridge.[22]

## EXPERIMENTAL

Thin-layer chromatoplates (0.25 mm) were either of alumina G or of silica gel G and were developed with ethyl acetate–cyclohexane mixtures unless otherwise indicated. N.m.r. spectra were measured for solutions in $CDCl_3$ at 60 MHz, u.v. spectra for solutions in MeOH, and i.r. spectra for solutions in $CHCl_3$ unless stated otherwise.

100 MHz $^1$H N.m.r. spectra and assignments for gibbane derivatives (ring A aromatic) [δ values; in $CDCl_3$ except for (30)]

| Compd. | H-1 [a] | H-2 [a] | MeO-3 | $CO_2$Me-4 | $H_2$-6 [b] | H-9 | H-11 | H-12 | H-13 | H-15 | Acetal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (26a) | 7.0 | 7.67 | 3.94 | 3.93 | 3.28, 3.35 | | 6.08 [c] (d, *J* 2 Hz) | | 3.5—3.6 (m) | | |
| (26b) | 6.95 | 7.63 | 3.90 | 3.90 | 3.14, 3.27 | | 6.08 [c] (d, *J* 2 Hz) | | 2.9—3.0 (m) | | 3.90 |
| (27a) | 6.77 | 7.10 | 3.90 | 3.82 | 2.82, 3.02 | *ca.* 3.0 (m) | | | | | |
| (27b) | 6.70 | 7.08 | 3.82 | 3.78 | 2.68, 2.89 | *ca.* 2.75 (m) | | | | 2.13br (d, *J* 7 Hz) | 3.83 |
| (28a) | 6.81 | 7.15 | 3.90 | 3.83 | 2.80, 3.20 | *ca.* 3.0 (m) | | | | 2.39 (d, *J* 2 Hz) | |
| (28b) [d] | 6.78 | 7.11 | 3.88 | 3.83 | 2.79, 3.05 | | | | | 2.11 (split d, *J* 2 Hz) | 3.88—3.92 |
| (29) | 6.75 | 7.07 | 3.86 | 3.80 | 2.82, 2.98 | 3—3.2 (m) | | 4.0—4.2 (m) | | 2.13 (d, *J* 5 Hz) | |
| (30) [e] | 6.96 | 7.20 | 3.82 | 3.78 | *f* | *f* | | *f* | *f* | 2.55 (d, *J* 2 Hz) | |
| (31) | 6.82 | 7.20 | 3.90 | 3.83 | 2.89, 3.15 | | | *ca.* 4.0 (m) | | | |
| (34a) | 6.80 | 7.37 | 3.86 | 3.81 | 3.04, 3.16 | | 5.68 (t, *J* 4 Hz) | | | | |
| (34b) | 6.80 | 7.40 | 3.87 | 3.81 | 2.92, 3.10 | | 5.72 (m) | | | | 3.87 |

[a] Doublets, *J* 8—9 Hz. [b] AB quartets, *J* 16—18 Hz. [c] W-coupling with H-13. [d] To be published. [e] In $(CD_3)_2SO$. [f] Considerable overlap of all these signals.

*Chloromethylation of 5-Methoxyindan-1-one.*—Hydrogen chloride was passed at 45 °C for 8 h, and then at room temperature overnight, through a mixture of the ketone (16.0 g), paraformaldehyde (6.0 g), and zinc chloride (5.0 g) in concentrated hydrochloric acid (15 ml) and acetic acid (50 ml). Water was then added and the product isolated with dichloromethane. The crude neutral product (11.0 g) was chromatographed on Florisil (250 g); elution with light petroleum (b.p. 40—60°)–chloroform with increasing proportions of the latter gave, in order of elution, starting material (2.0 g), *4-chloromethyl-5-methoxyindan-1-one* (6) (4.3 g), m.p. 126.5—127° (from dichloromethane–hexane), $\nu_{max.}$ 1 710, 1 600, 1 260, and 1 150 cm$^{-1}$, δ 4.00 (3 H, s, OMe), 4.75 (2 H, s, $CH_2Cl$), 7.02 (1 H, d, *J* 10 Hz, H-7), and 7.78 (1 H, d, *J* 10 Hz, H-6) (Found: C, 62.6; H, 5.4; Cl, 16.7.

[19] H. Gerlach and W. Mueller, *Helv. Chim. Acta*, 1972, **55**, 2277, 2962.
[20] R. Nace, *Org. Reactions*, 1962, **12**, 57.
[21] B. E. Cross, J. F. Grove, J. MacMillan, and T. P. C. Mulholland, *J. Chem. Soc.*, 1958, 2520.
[22] A. J. Baker, A. C. Goudie, U. R. Ghatak, and R. Dasgutpa, *Tetrahedron Letters*, 1972, 1103.
[23] U. R. Ghatak, P. C. Chakrabarti, B. C. Ranu, and B. Samyal, *J.C.S. Chem. Comm.*, 1973, 548.
[24] R. Evans, J. R. Hanson, and L. J. Mulheirn, *J.C.S. Perkin I*, 1973, 753.

$C_{11}H_{11}ClO_2$ requires C, 62.7; H, 5.25; Cl, 16.85%); and the isomeric *6-chloromethyl-5-methoxyindan-1-one* (7) (0.8 g), m.p. 130—131° (from dichloromethane–hexane), δ 4.00 (3 H, s, OMe), 4.65 (2 H, s, $CH_2Cl$), 7.00 (1 H, s, H-7), and 7.80 (1 H, s, H-6) (Found: Cl, 16.95%).

The n.m.r. spectrum of the crude chloromethylation product showed the two isomers to be present in a 6 : 1 ratio in accord with chromatographic separation.

*Nitration of 5-Methoxyindan-1-one.*—A sample of the ketone was added with cooling in ice to an excess of fuming nitric acid; the stirred mixture was kept at −5 °C for 25 min, then poured on ice, and the products were isolated with dichloromethane. The mixture was shown by t.l.c. to contain two mononitration products and no starting material; its n.m.r. spectrum showed in the aromatic region δ 7.20 and 7.86 (0.8 H, q, *J* 8 Hz), 7.04 (0.6 H, s), and 8.06 (0.6 H, s), indicating the 4- and 6-nitro-isomers to be present in the ratio 3 : 2, but no attempt at separation was made.

*4-Acetoxymethyl-5-methoxyindan-1-one* (8).—A solution of the 4-chloromethyl derivative (15.0 g) and anhydrous sodium acetate (45 g) in acetic acid (300 ml) was heated under reflux for 3.5 h, after which ice–water was added and the product isolated with chloroform. The neutral residue was distilled and the product, b.p. 150—160° at 0.01 mmHg, was crystallised from dichloromethane–hexane to give the *ester* (10.0 g), m.p. 110—111°, $\nu_{max.}$ 1 730, 1 700, 1 600, and 1 100 $cm^{-1}$ (Found: C, 66.65; H, 5.95. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%).

*5-Methoxy-1-oxoindane-4-carbaldehyde* (10).—The crude chloromethylation product from 5-methoxyindan-1-one was converted into the isomeric mixture of acetoxymethyl compounds as described above, and after distillation this (25.0 g) was hydrolysed in methanol (250 ml) containing sodium hydroxide (10%; 15 ml) at room temperature for 15 min. After addition of water, neutralisation, and removal of methanol *in vacuo* the product was isolated with chloroform to give a mixture of hydroxymethyl isomers [(9) + isomer] (17 g, 85%), which was used directly for the next step.

This mixture (14.0 g) in acetone (300 ml) was added with stirring to acetone (100 ml) in portions alternately with 8N-chromic oxide in 4.3M-sulphuric acid (18.3 ml), with the temperature kept below 8 °C, after which an excess of oxidising agent was maintained for 10 min and then removed with propan-2-ol. After removal of acetone *in vacuo* and isolation with dichloromethane–ethyl acetate a neutral product was obtained which was shown by g.l.c. (10% silicone XE-30 on Chromosorb W; 200 °C) to be a mixture of two products in the ratio 7.3 : 1. Chromatography on Florisil (150 g) and elution with light petroleum–chloroform gave the *oxo-aldehyde* [8.4 g, 72% based on content of isomer (6) in the chloromethylation product], m.p. 152—152.5° (from dichloromethane–hexane), $\nu_{max.}$ 2 870, 1 710, and 1 690 $cm^{-1}$, δ 4.05 (3 H, s, OMe), 7.08 (1 H, d, *J* 8 Hz, H-7), 7.92 (1 H, d, *J* 8 Hz, H-6), and 10.50 (1 H, s, CHO) (Found: C, 69.05; H, 5.35. $C_{11}H_{10}O_3$ requires C, 69.45; H, 5.3%). The other isomer (11) was retained strongly on the column and was not obtained pure.

*7-Methoxyindan-1-one* (13).—Chroman-4-one [25] (90 g; melted by warming to 60 °C) was added dropwise with stirring to a partial melt obtained from aluminium trichloride (500 g) and sodium chloride (50 g) in a 1 l resin flask at 150—160 °C during 10 min, after which the temperature was raised to 200 °C during 20 min. The dark red mixture was then allowed to cool to room temperature, and the resulting semisolid was added in portions with stirring to concentrated hydrochloric acid (250 ml) and ice. During the decomposition the temperature was allowed to rise to 60 °C; and on cooling the brown product was filtered off. The crude product from four such runs was suspended in concentrated sodium chloride solution (1 l) and steam distilled (total 25 l). Most of the product crystallised in the receiver; the supernatant distillate was removed periodically, saturated with salt, and extracted with chloroform. The solid was dissolved in the combined extracts and, after drying, the solution was concentrated to 500 ml and an equal volume of hot cyclohexane was added. On cooling, *7-hydroxyindan-1-one* (207 g) crystallised; m.p. 111—112° (lit.,[26] 111°). From the mother liquor a second crop (35 g) was obtained (total 65.5%).

This phenolic ketone (33 g) was suspended in tetrahydrofuran (60 ml) and aqueous sodium hydroxide (10% w/v; 80 ml), and with stirring dimethyl sulphate (17 ml) was added during 5 min, with the temperature kept at 50—60 °C. Two more additions of the sodium hydroxide solution (50 ml) and of dimethyl sulphate (9 ml) were made, finally at 70 °C, and this was followed by heating under reflux for 10 min. After cooling, isolation with chloroform gave a residue which was distilled (110 °C and 0.1 mmHg) and then recrystallised from cyclohexane to give the *methoxy-ketone* (28 g, 85%), m.p. 108—109° (lit.,[27] 106°).

*2-Hydroxymethylene-7-methoxyindan-1-one* (14).—The ketone (13) (52 g) in benzene (300 ml) was added under nitrogen with vigorous stirring to a suspension of sodium methoxide (32.25 g) in benzene (100 ml) and ethyl formate (52 ml) at 5—10 °C during 0.5 h. The mixture was stirred at room temperature for 4 h, cooled again to 4 °C, and acidified with concentrated hydrochloric acid (60 ml) and ice. After stirring for another 4 h to ensure complete acidification (both the product and its sodium salt are sparingly soluble) the yellowish solid was filtered off, washed with water and with benzene, then air-dried, and slurried with warm acetic acid (75 ml); water was added and the product was filtered off and dried at 80 °C to give the *hydroxymethylene ketone* (56.5 g, 93%), m.p. 157°, suitable for the next step. A sample recrystallised from ethyl acetate had m.p. 158.5—159° (recrystallisation from methanol gave a product of double m.p. 120—125° and 157—159°), $\nu_{max.}$ (KBr) 3 430br, 1 690, 1 620, and 1 600 $cm^{-1}$ (Found: C, 69.35; H, 5.4. $C_{11}H_{10}O_3$ requires C, 69.45; H, 5.3%). It gave a green-black colour with methanolic iron(III) chloride.

*3-(2-Carboxy-3-methoxyphenyl)propionic Acid* (15a).—The hydroxymethylene ketone (14) (68.1 g) was added in portions during 1 h to a refluxing mixture of t-butyl alcohol (161 ml) and hydrogen peroxide (30%; 50 ml). After heating under reflux for another 1 h more t-butyl alcohol (15 ml) and hydrogen peroxide (8 ml) were added and thereafter heating was continued (total 8.5 h). The mixture was cooled in ice and the excess of peroxide decomposed overnight after addition of a trace of platinum black. Most of the solvents were removed *in vacuo*, after which sodium hydroxide (20 w/v) was added until the colour of the sodium salt of starting material was evident (*ca.* 130 ml). This was then discharged by addition of

[25] W. E. Parham and L. D. Huestis, *J. Amer. Chem. Soc.*, 1962, **84**, 813.

[26] J. D. Loudon and R. D. Razdan, *J. Chem. Soc.*, 1954, 4299.

[27] V. C. Farmer, N. F. Hayes, and R. H. Thomson, *J. Chem. Soc.*, 1956, 3600.

sodium dihydrogen phosphate (5M; 22 ml). The solution was then shaken with benzene (200 ml) and filtered from starting material (2.5 g), and the aqueous layer was separated from the benzene phase, which was extracted several times with dilute aqueous sodium hydrogen carbonate. The combined alkaline phases were adjusted to pH 8, treated with charcoal, filtered, and acidified to pH 2. After saturation with ammonium sulphate the product was isolated with chloroform to give a gum which crystallised after prolonged trituration with boiling carbon tetrachloride to give, after cooling, the *dicarboxylic acid* (57.4 g, 71.5%), m.p. 105° (some samples showed double m.p. 88—89° and 105°),* $\nu_{max.}$ 1 705sh, 1 695, and 1 585 $cm^{-1}$ (Found: C, 58.9; H, 5.75. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%). The neutral product from this reaction (after removal of benzene) was shown to be the crude methoxy-ketone (13) (6.4 g).

The dicarboxylic acid (44.8 g) was converted into its half-ester (15c) as follows: it was dissolved in dioxan (160 ml), and dimethyl sulphate (42 ml) and then sodium hydroxide (6.12N; 72 ml) were added dropwise at 40—50 °C during 15 min, after which the mixture was heated to 70 °C. After cooling, two more such additions were made, each with half quantities of the above reagents; and the mixture was then heated to 100 °C for 30 min. Cooling, concentration *in vacuo*, and isolation with dichloromethane gave a neutral residue (41.3 g) of the diester (15b) and an acidic portion (8.4 g) which after recrystallisation gave the half-ester (6.95 g), m.p. 107—108° (see below). The crude diester was dissolved in methanol (60 ml) and with stirring a solution of sodium hydroxide (6.8 g) in water (170 ml) was added with cooling during 1 h. After stirring at room temperature overnight, work-up gave an acidic portion which afforded the *half-ester* (35.2 g), m.p. 108—108.5° (from carbon tetrachloride) (Found: C, 60.5; H, 5.9. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

*Methyl 5-Methoxy-1-oxoindane-4-carboxylate* (12b).—(*a*) The half-ester (15c) (30 g) was added to polyphosphoric acid [from phosphoric acid (*d* 1.84; 120 ml) and phosphoric oxide (240 g)] and the solution was stirred at 75—78 °C for 1.5 h. After cooling, ice was added and the mixture was stirred until the complex had decomposed, after which the solid was filtered off and the filtrate extracted with benzene–ether–chloroform. The solid was dissolved in the extract, which was washed with aqueous potassium carbonate (9%), acidification of which gave acidic material (3.7 g) which was esterified with ethereal diazomethane. The combined neutral product was passed in benzene–dichloromethane through Florisil (30 g) and distilled (180 °C and 1 mmHg); it was then recrystallised from dichloromethane–hexane to give the *oxo-ester* (23.7 g, 85.7%), m.p. 109.5—110°, $\nu_{max.}$ 1 730sh, 1 715, and 1 600 $cm^{-1}$, δ 2.68 (2 H, m, $H_2$-2), 3.20 (2 H, m, $H_2$-3), 3.92 (3 H, s, $CO_2Me$), 3.98 (3 H, s, OMe), 7.00 (1 H, d, *J* 9 Hz, H-7), and 7.82 (1 H, d, *J* 9 Hz, H-6) (Found: C, 65.35; H, 5.35. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.5%).

(*b*) The dicarboxylic acid (15a) (37.8 g) was cyclised with polyphosphoric acid exactly as for its half-ester, after which the mixture was decomposed with ice–water (total volume 750 ml). The brown solid was filtered off and dried; more was obtained after saturation of the filtrate with ammonium sulphate. The total crude product (33.3 g) was esterified and remethylated in dioxan with dimethyl sulphate and sodium hydroxide as described for the dicarboxylic acid (15a), by using half molar quantities, after which the product was isolated with ethyl acetate and separated into acidic (1.35 g) and neutral portions; the latter was passed in benzene–dichloromethane through Florisil (25 g) and then recrystallised to give the oxo-ester (12b) (27 g, 72.6%), identical (m.p. and mixed m.p.) with the product obtained in (*a*).

(*c*) The oxo-aldehyde (10) (10.0 g) in acetone (250 ml) was added with stirring to acetone (20 ml) containing cerium(IV) ammonium sulphate (100 mg) in portions alternately with 8N-chromic oxide in 4.3M-sulphuric acid (13.0 ml) at room temperature. Stirring was continued overnight, after which propan-2-ol was added and most of the acetone was removed *in vacuo*. Isolation with chloroform–tetrahydrofuran (7 : 3) and crystallisation from chloroform gave *5-methoxy-1-oxoindane-4-carboxylic acid* (12a) (8.1 g, 75%), m.p. 207—208° (Found: C, 63.75; H, 5.1. $C_{11}H_{10}O_4$ requires C, 64.05; H, 4.9%). Esterification with diazomethane gave the oxo-ester (12b), identified by m.p. and mixed m.p.

*Methyl 5-Methoxy-4-methoxycarbonyl-1-oxoindan-2-ylacetate* (18).—The oxo-ester (12b) (16.9 g), n-butyl glyoxylate (20 g), and toluene-*p*-sulphonic acid (0.1 g) were refluxed in benzene (200 ml) overnight with azeotropic removal of water. On cooling, chloroform (50 ml) was added; and work-up gave a crystalline residue which afforded the *unsaturated oxo-ester* (16) (23.0 g), m.p. 95—96° (from cyclohexane), $\nu_{max.}$ 1 820, 1 730sh, 1 710, and 1 600 $cm^{-1}$, $\lambda_{max.}$ 257 (ε 12 600) and 332 nm (11 000), δ 3.95 (3 H, s, $CO_2Me$), 4.00 (3 H, s, OMe), 4.23 (2 H, t, *J* 6 Hz, $CO_2{\cdot}CH_2$), 6.80 (1 H, t, *J* 2 Hz, =CH–), 7.21 (1 H, d, *J* 9 Hz, H-7), and 8.00 (1 H, d, *J* 9 Hz, H-6) (Found: C, 65.45; H, 6.15. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.05%). Another 1.0 g of material isolated from the mother liquors raised the yield to 94%.

A suspension of this product (23.0 g) and palladium–calcium carbonate (5%; 2.2 g) in methanol (70 ml) and tetrahydrofuran (30 ml) was shaken in hydrogen at 42—34 lb $in^{-2}$; the theoretical amount was absorbed in 20 min. Filtration and removal of solvents left a crude product which was used directly for the next step; a sample crystallised from hexane at 0 °C gave the *n-butyl ester* (17), m.p. 45—47° (Found: C, 64.4; H, 6.4. $C_{18}H_{22}O_6$ requires C, 64.65; H, 6.05%). This product was dissolved in dry methanol (400 ml), and with cooling to 0 °C acetyl chloride (18 ml) was added dropwise during 15 min, after which the solution was left at room temperature overnight. Removal of solvents *in vacuo* and recrystallisation from isopropyl ether and then from methanol gave the *oxo-diester* (14.2 g), m.p. 98—99°, $\nu_{max.}$ 1 741, 1 730, 1 710, and 1 590 $cm^{-1}$, δ 3.70 (3 H, s, $CH_2{\cdot}CO_2Me$), 3.93 (3 H, s, $ArCO_2Me$), 3.98 (3 H, s, OMe), 7.08 (1 H, d, *J* 9 Hz, H-7), and 7.88 (1 H, d, *J* 9 Hz, H-6) (Found: C, 61.45; H, 5.15. $C_{15}H_{16}O_6$ requires C, 61.65; H, 5.5%). A second crop (0.76 g) from the mother liquors raised the yield to 81%.

*Methyl 5-Methoxy-1-oxoindan-2-yl acetate* (20).—5-Methoxyindan-1-one was subjected to acid-catalysed condensation with n-butyl glyoxylate as described for the oxo-ester (12b), to give the *unsaturated butyl ester* (19) (70%), m.p. 44—45° (from pentane), $\nu_{max.}$ 1 700 and 1 100 $cm^{-1}$, $\lambda_{max.}$ 257 (ε 10 500) and 336 nm (11 400) (Found: C, 69.85; H, 6.75.

* This compound has been mentioned without details by E. Adler, R. Magnussen, and R. Berggren (*Acta Chem., Scand.* 1960, **14**, 539) as having been obtained by them from Professor J. F. Eastham as the product of ozonolysis of 1,2-dihydro-5-methoxynaphthalene (J. F. Eastham and D. R. Larkin, *J. Amer. Chem. Soc.*, 1958, **80**, 2887), but the latter paper makes no mention of it. We are grateful to Professor E. Adler for establishing the identity of our dicarboxylic acid with the sample in his possession.

$C_{16}H_{18}O_4$ requires C, 70.05; H, 6.6%). Hydrogenation, followed by transesterification as described for (16) gave the *oxo-ester* (60—70%), m.p. 77—78°, $\nu_{max.}$ 1 735, 1 700, and 1 150 $cm^{-1}$ (Found: C, 66.75; H, 5.9. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%).

*Chloromethylation of the Oxo-ester* (20).—Hydrogen chloride was passed through a mixture of the oxo-ester (18.0 g), paraformaldehyde (10 g), and zinc chloride (10 g) in concentrated hydrochloric acid (12 ml) and acetic acid (50 ml) at 40—45 °C for 5 h. Addition of water and isolation with chloroform gave a neutral product which was passed in chloroform–hexane through Florisil (200 g) to remove a dark impurity, and was then recrystallised three times from dichloromethane–hexane to give the *4-chloromethyl-2-hydroxymethyl-5-methoxy-1-oxoindan-2-ylacetic acid γ-lactone* (21) (10.0 g, 46%), m.p. 160—161°, $\nu_{max.}$ 1 770 (lactone), 1 710 (aryl ketone), and 1 600 $cm^{-1}$, δ 4.02 (3 H, s, OMe), 4.75 (2 H, s, C·$CH_2$·O·CO), 7.08 (1 H, d, *J* 9 Hz, H-7), and 7.82 (1 H, d, *J* 9 Hz, H-6) (Found: Cl, 13.0. $C_{14}H_{13}ClO_4$ requires Cl, 12.65%). All attempts to convert this compound into the oxo-diester (18) were unsuccessful.

*Methyl 5-Methoxy-1-oxoindane-2-carboxylate* (22).—A solution of the ketone (5) (30 g) in benzene (150 ml) was added under nitrogen with stirring to a suspension of sodium hydride (9.12 g) in benzene (70 ml) and dimethyl carbonate (77 ml) at 60 °C during 0.5 h. After a further 1 h at 70 °C the mixture was cooled and acidified with acetic acid. The product obtained from the organic layer was distilled (155—160 °C and 1 mmHg) and crystallised from dichloromethane–hexane to give the *β-oxo-ester* (69%), m.p. 77—78°, $\nu_{max.}$ 1 750, 1 710, and 1 150 $cm^{-1}$ (Found: C, 64.95; H, 5.75. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.5%).

*2-(2-Hydroxyethyl)-5-methoxy-1-oxoindane-2-carboxylic Acid γ-Lactone* (23).—The foregoing β-oxo-ester (11 g) in dimethylformamide (150 ml) was added with stirring under nitrogen to a suspension of sodium hydride (1.20 g) in dimethylformamide at 15 °C. After evolution of hydrogen had ceased, 1,2-dibromoethane (20 ml) was added and the mixture was heated to reflux for 10 min, cooled, and acidified with acetic acid. Water was added, and isolation with dichloromethane followed by distillation of the neutral portion gave (*a*) (up to 180 °C and 0.1 mmHg) 5-methoxyindan-1-one (3.0 g), and (*b*) (220—225° and 0.01 mmHg) the *oxo-lactone* (5.5 g, 43%), m.p. 85—86° (from dichloromethane–hexane), $\nu_{max.}$ 1 770 (lactone), 1 700 (aryl ketone), and 1 170 $cm^{-1}$, δ 3.90 (3 H, s, OMe) and 4.25—4.95 (2 H, m, lactone $CH_2$) (Found: C, 67.35; H, 5.2. $C_{13}H_{12}O_4$ requires C, 67.25; H, 5.2%).

*Chloromethylation of the Oxo-lactone* (23).—The oxo-lactone (18.0 g) was subjected to chloromethylation as for the oxo-ester (20), and the crude product chromatographed on Florisil (400 g) in chloroform–hexane. After elution of early fractions (6.35 g) showing no lactone i.r. absorption there was obtained the *4-chloromethyl-2-(2-hydroxyethyl)-5-methoxy-1-oxoindane-2-carboxylic acid γ-lactone* (24) (5.7 g, 38%), m.p. 76—77° (from dichloromethane–hexane), $\nu_{max.}$ 1 775 (lactone), 1 720, and 1 600 $cm^{-1}$, δ 3.98 (3 H, s, OMe), 7.00 (1 H, d, *J* 8 Hz, H-7), and 7.72 (1 H, d, *J* 8 Hz, H-6) (Found: C, 59.6; H, 4.4; Cl, 13.05. $C_{14}H_{13}ClO_4$ requires C, 59.6; H, 4.65; Cl, 12.65%). This compound could not be converted into the oxo-diester (18).

*7,8,8a,9-Tetrahydro-2-methoxy-1-methoxycarbonyl-6-oxo-6H-fluoren-8a-ylacetic Acid* (25).—The oxo-diester (18) (12.92 g) was added at room temperature with stirring under nitrogen to a solution of sodium methoxide [from sodium (4.44 g)] in methanol (150 ml). The suspension was cooled to 5 °C, and redistilled methyl vinyl ketone (11.0 ml) was added dropwise during 45 min at 5—7 °C. Towards the end of the addition most of the solid dissolved, and a dense cream precipitate of the sodium salt of the product formed. After stirring at room temperature for 4 h the suspension was cooled to 5 °C and acidified with acetic acid (15 ml), and water (110 ml) was added. On removal of methanol (110 ml) *in vacuo* most of the product crystallised; washing with water and then with benzene gave the *half-ester* (11.29 g), m.p. 235—238°, unchanged after recrystallisation from methanol–benzene, $\nu_{max.}$ (KBr) 1 710—1 735, 1 655, 1 635, and 1 600 $cm^{-1}$, $\lambda_{max.}$ 260 (ε 9 000) and 340 nm (18 000) δ ($C_5D_5N$) 3.81 (3 H, s, $CO_2Me$), 3.88 (3 H, s, OMe), 6.5 (1 H, s, –CH=C–), 7.05 (1 H, d, *J* 8 Hz, H-4), and 7.75 (1 H, d, *J* 8 Hz, H-3) (Found: C, 65.55; H, 5.55. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%). Extraction of the filtrates from this product with chloroform, removal of solvent, and trituration with hot benzene gave another crop (1.97 g, total yield 90%) of product with the same m.p.

*Methyl 12,16-Dioxo-3-methoxygibba-1(10),2,4,9(11)-tetraene-4-carboxylate* (26a).—The half-ester (25) (5.90 g) in trifluoroacetic acid (25 ml) was treated with stirring under nitrogen at 0 °C with trifluoroacetic anhydride (5 ml). After 12 h at room temperature the red-brown solution was concentrated *in vacuo* at room temperature and the residue, dissolved in chloroform (50 ml), was added to ice (100 g) and sodium acetate (5 g). After shaking until the ice had melted the chloroform layer was separated and again washed with ice-cold saturated sodium hydrogen carbonate solution (10 ml) until there was no further fading of colour. The dried solution was passed through Florisil (10 g) and the product recrystallised from chloroform–cyclohexane giving the *dioxo-ester* (5.22 g, 92%), double m.p. 200—201° and 214—215°, $\nu_{max.}$ 1 755, 1 730, 1 670, 1 635, and 1 600 $cm^{-1}$, $\lambda_{max.}$ 254 (ε 8 200), 308 (11 400), and 348 nm (16 400) (Found: C, 69.1; H, 5.1. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.15%).

*Selective Acetalisation of the Dioxo-ester* (26a).—The product (26a) (100 mg) was dissolved in benzene (7 ml) and the stirred solution was cooled rapidly to 0 °C and treated with 2-ethyl-2-methyl-1,3-dioxolan (0.41 ml) and then with boron trifluoride–ether complex (0.30 ml). The fluorescent suspension was stirred at room temperature while the reaction was followed by t.l.c. (alumina; ethyl acetate–cyclohexane, 1 : 1; the starting material remains stationary on the plate). After 3 h ice and dilute sodium hydrogen carbonate solution were added, and the crude product (128 mg) was passed in benzene–dichloromethane through alumina (basic, activity II; 1.5 g) which completely retained unchanged material. Recrystallisation from dichloromethane–cyclohexane gave the *monoacetal* (26b) (64 mg, 56%), m.p. 223—223.5°, $\nu_{max.}$ 1 721, 1 653, 1 618, and 1 593 $cm^{-1}$, $\lambda_{max.}$ 250 (ε 10 100), 303 (16 000), and 333 nm (21 000) (Found: C, 67.45; H, 5.65. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.65%). On t.l.c. on silica this was more polar than the diketone. All attempts at reduction of the ketone group in this compound with sodium borohydride were unsuccessful, and attempts to perform a Wolff–Kishner reduction gave an intractable product. No derivative of the free ketone group (semicarbazone or methoxycarbonylhydrazone) could be prepared.

*Hydrogenation of the Dioxo-ester* (26a).—(*a*) A suspension of the dioxo-ester (6.74 g), palladium chloride (2.4 g), and activated carbon (purified by treatment with dilute nitric acid; 4.8 g) in acetic acid (210 ml) was shaken in hydrogen

at 50—35 lb $in^{-2}$ until uptake (3—3.1 mol. equiv.) was complete (20—35 min.). The residue obtained after filtration and removal of solvent *in vacuo* was taken up in benzene, washed with dilute sodium carbonate solution, and recrystallised after solvent removal, twice from a limited amount of methanol and then from dichloromethane–di-isopropyl ether, to give *methyl* 3-*methoxy*-16-*oxo*-9αH-*gibba*-1(10),2,4-*triene*-4-*carboxylate* (27a) (3.70 g), double m.p. 144—145 and 154° (differential scanning calorimetry revealed an addition change of phase at *ca.* 135°), $\nu_{max.}$ 1 740 and 1 721 $cm^{-1}$ (Found: C, 71.5; H, 6.5. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%). The mother liquors were combined and chromatographed on alumina (basic, activity II; 40 g) in dichloromethane–hexane; all initial fractions showing a single spot on t.l.c. were combined, digested with hot hexane (60 ml), and seeded with the above oxo-ester. Cooling and further recrystallisation gave a further amount of the latter (0.45 g, total yield 64.5%). The hexane mother liquor was concentrated to 20 ml; on cooling, the 9βH-*oxo-ester* (28a) separated (0.37 g); m.p. 108—113°, raised to 113.5—114° by another recrystallisation from methanol. This epimer was identical (m.p., mixed m.p., and i.r. spectrum) with a sample prepared by Baker [15] by a different route. The two epimers were indistinguishable by t.l.c. Elution of the above chromatogram with chloroform–methanol (95 : 5) gave the hydroxy-oxo-ester (29) (see below) (0.61 g).

(*b*) A suspension of the dioxo-ester (5.00 g) and palladium hydroxide–carbon (20%; 1 g) [18] in methanol (100 ml) was shaken in hydrogen at 50—38 lb $in^{-2}$ until uptake (2.0—2.1 mol. equiv.) was complete (20—30 min). The residue obtained after filtration and removal of solvent was twice recrystallised by dissolution in dichloromethane and displacement of the latter with boiling benzene–cyclohexane (1 : 1; 35 ml) and then from dichloromethane–cyclohexane to give *methyl* 12β-*hydroxy*-3-*methoxy*-16-*oxo*-9αH-*gibba*-1(10),2,4-*triene*-4-*carboxylate* (29) (2.80 g), m.p. 171—171.5°, $\nu_{max.}$ (KBr) 3 520, 3 430, 1 728—1 738, and 1 065 $cm^{-1}$ (Found: C, 68.35; H, 6.4. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%). From the mother liquors, fractional crystallisation and chromatography on silica and alumina gave more of the above hydroxy-oxo-ester (total yield 3.20 g); an *isomeric hydroxy-oxo-ester* [probably (31)], m.p. 157—159°, $\nu_{max.}$ 3 550, 1 730—1 741, and 1 065 $cm^{-1}$ (Found: C, 68.0; H, 6.35%); and the *dioxo-ester* (30), m.p. 217—220°, $\nu_{max.}$ (KBr) 1 715, 1 745, and 1 260 $cm^{-1}$ (Found: C, 68.85; H, 5.9. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.75%). Prolonged adsorption of the hydroxy-oxo-ester (29) and subsequent elution gave a non-crystalline epimeric mixture (by t.l.c.), presumably owing to a retro-aldol–aldol isomerisation.

*Methyl* 3-*Methoxy*-16-*oxogibba*-1(10),2,4,9(11)-*tetraene*-4-*carboxylate* (34a).—The hydroxy-oxo-ester (29) (2.65 g) in dry pyridine (12 ml) was treated at 10 °C with *p*-tolyl chlorothioformate [19] (1.675 g, 1.425 ml) with vigorous stirring which was continued at room temperature overnight. Ice and an excess of concentrated hydrochloric acid were added, the product was extracted with chloroform, and the dried extract was passed through Florisil (10 g). Removal of solvent and recrystallisation from dichloromethane–methanol gave the p-*tolyl thioncarbonate* (32) (3.75 g, 95%), m.p. 222—223° (decomp.) (Found: C, 67.05; H, 5.45. $C_{26}H_{26}O_6S$ requires C, 66.95; H, 5.6%).

This derivative (4.01 g) was pyrolysed in a Kugelrohr tube (three 50 ml bulbs) at 230—260 °C and 0.05 mmHg during 20 min. Most of the *p*-cresol formed escaped into the liquid nitrogen trap, and some of the product ketone sublimed into the middle bulb, from which it was washed back with ether. After removal of residual *p*-cresol (at up to 120° and 0.05 mmHg) the product was evaporatively distilled at 210—220° and 0.05 mmHg to give a product (33) which crystallised spontaneously (2.35 g); its n.m.r. spectrum showed the expected two multiplets centred at δ 5.88 and 6.43 (–CH–CH=CH–CH–), but no satisfactory analysis could be obtained. This was dissolved in the minimum of *p*-xylene, and the solution was added to a suspension prepared by prehydrogenation of palladium hydroxide–carbon (20%; 300 mg) in *p*-xylene followed by distillation of part of the solvent in a stream of argon to remove adsorbed hydrogen and water. The suspension (total volume 30 ml) was heated under reflux in argon until t.l.c. (silica; ethyl acetate–cyclohexane, 1 : 1) showed isomerisation to be complete (3.5 h; the product shows a higher $R_F$ value than the starting material). Filtration, removal of solvent *in vacuo*, evaporative distillation (Kugelrohr) at 210—220° and 0.05 mmHg, and crystallisation from dichloromethane–hexane gave the *unsaturated oxo-ester* (1.97 g, 75% overall yield from the *p*-tolyl thioncarbonate), m.p. 105—105.5° (some samples showed double m.p. 93—95 and 105°), $\lambda_{max.}$ 233 (ε 17 500), 265 (16 000), and 317 nm (4 600), $\nu_{max.}$ 1 718—1 738, 1 599, and 1 488 $cm^{-1}$ (Found: C, 72.0; H, 6.15. $C_{18}H_{18}O_4$ requires C, 72.45: H, 6.1%). This compound was sensitive to air and light, being changed to a yellow insoluble gum.

*Methyl* 16,16-*Ethylenedioxy*-3-*methoxy*-9αH-*gibba*-1(10),2,4-*triene*-4-*carboxylate* (27b).—The oxo-ester (27a) (2.84 g) was dissolved in benzene (60 ml) and 2-ethyl-2-methyl-1,3-dioxolan (17 ml); naphtnalene-2-sulphonic acid (150 mg) was added and the solution was refluxed through a short column with a partial take-off head for 8 h during which 35 ml of distillate was removed. After cooling, washing with dilute sodium hydroxide solution, and drying, the solution was passed through basic alumina (12 g). Recrystallisation from dichloromethane–methanol gave the *acetal ester* (2.96 g, 91%), m.p. 159.5—160°, $\nu_{max.}$ 1 725, 1 595, and 1 070 $cm^{-1}$ (Found: C, 69.7; H, 7.05. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%).

Prolonged alkaline hydrolysis of this product (N-KOH containing 10% dioxan; reflux overnight), followed by acidification to pH 5 and isolation with chloroform containing 7% tetrahydrofuran gave the corresponding *acetal acid* (27c), m.p. 199—200° (Found: C, 68.9; H, 6.8. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.7%).

*Methyl* 16,16-*Ethylenedioxy*-3-*methoxygibba*-1(10),2,4,9(11)-*tetraene*-4-*carboxylate* (34b).—The unsaturated oxo-ester (34a) (3.435 g) was dissolved at 100 °C in dry ethanediol (28 ml); the solution was cooled with rapid stirring to 0 °C and boron trifluoride–ether complex (4.48 ml) was added. The resulting suspension was stirred at room temperature overnight after which ice and an excess of dilute sodium carbonate solution were added. The solid was filtered off and dissolved in benzene, and the dried solution was passed through basic alumina (10 g). Crystallisation from dichloromethane–hexane gave the *unsaturated acetal ester* (3.68 g, 93.5%), m.p. 133—133.5°, $\lambda_{max.}$ 235 (ε 16 700), 303 (17 000), and 318 nm (3 950), $\nu_{max.}$ 1 713 $cm^{-1}$ (Found: C, 69.95; H, 6.5. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%). Other methods of acetalisation (ethanediol, benzene, toluene-*p*-sulphonic acid; transacetalisation with ethylmethyldioxolan) gave yields of less than 50%.

Catalytic hydrogenation of this product (116 mg) in

methanol–tetrahydrofuran (1 : 1) over palladium–carbon (20%; 50 mg) proceeded rapidly (5 min). Two recrystallisations of the product from methanol gave the acetal ester (27b) (61 mg), m.p. and mixed m.p. 157—158°.

*Experiments on the Dehydrogenation of the Oxo-ester* (27a) *and the Acetal Ester* (27b).—(*a*) Either compound was mixed with half its weight of commercial palladium–carbon (30%) and the mixture was heated in a Kugelrohr tube under argon at 200—230 °C for 1—3 h, after which the product was evaporatively distilled and examined by t.l.c. (ethyl acetate–cyclohexane; 1 : 3 for the former, and 1 : 5 for the latter). Three to five developments were necessary to separate the product (strong light blue fluorescence in u.v. light) from the starting material in either case, but less than 40% conversion was indicated under a variety of conditions.

(*b*) Similar results were obtained by using boiling *p*-cymene as solvent, even with a reflux time of 36 h.

(*c*) Palladium hydroxide–carbon [18] (20%; 0.48 g) was prehydrogenated in methanol, which was then displaced by boiling bis-(2,2-diethoxyethyl) ether (25 ml) under argon. The acetal ester (27b) (1.00 g) and dimethyl maleate (freshly distilled; 1.0 ml) were then added, and the mixture was then heated under reflux for 14 h. Filtration and removal of solvents, finally at 100° and 0.1 mmHg, gave a gum, which was subjected to careful dry-column chromatography [28] on silica (activity II: 50 g) in ethyl acetate–cyclohexane (1 : 4). After repeated chromatography of intermediate fractions a total of 0.56 g of the unsaturated acetal-ester (34b) was obtained, identified by m.p. and mixed m.p. The use of alumina or of silica impregnated with up to 20% its weight of silver nitrate [29] did not appreciably improve separation.

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