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SYNTHESIS OF SUBSTANCES RELATED TO GIBBERELLINS—XXI*

TOTAL SYNTHESIS OF (±)-GIBBERELLINS A_2, A_4, A_9 AND A_{10}

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Abstract—The formal total synthesis of some of the C_{19}-gibberellins in their racemic forms is described in detail.

THE gibberellins, first discovered in 1938,[1] are plant growth hormones.[2] After extensive chemical studies by the Japanese[2a] and the British [2b], the structure of gibberellic acid (=gibberellin A_3), the most easily obtainable fungal gibberellin,[3] was determined as I.[4, 5, cf. 6] Its stereochemistry, which had been discussed by several workers,[7–10] was finally settled as shown in I by X-ray crystallography.[11, 12] The 24 gibberellins isolated from fungal and plant sources[13] can be classified into two groups—compounds with 19 carbon atoms (C_{19}-gibberellins) and those with 20 carbon atoms (C_{20}-gibberellins).

Gibberellins possess the gibbane skeleton (II)[14] and belong to the modified diterpenoids biogenetically related to (−)-kaur-16-en-19-oic acid (III)[15] and (−)-kaur-16-ene (IV).[16] The synthesis of the gibberellins has been attempted in many laboratories,[17–23] and we have worked on this subject since 1959[24] and recently announced the formal total synthesis of some C_{19}-gibberellins—A_2, A_4, A_9 and A_{10}—in their racemic forms.[25, 26] In this paper we describe in detail the work which has been reported in preliminary form.[24–27]

The synthesis can be divided into five stages: (i) synthesis of racemic epigibberic acid (V)‖ from *o*-xylene[28, 29] (ii) synthesis of a racemic dioxo ester (VI) from racemic epigibberic acid (V)[25, cf. 30] (iii) transformation of the optically active dioxo ester (VI) into a dienone (VII) (iv) partial synthesis of gibberellin C (VIII) from the dienone (VII)[27] and (v) conversion of gibberellin C (VIII) into gibberellin A_4 (IX).[26, 31] The British workers prepared gibberellins A_2 (X)[32] and A_9 (XI)[33, 34] from A_4 (IX). Transformation of gibberellin A_9 (XI) into A_{10} (XII)[35] was also reported. The present work, therefore, constitutes the formal total synthesis of these four gibberellins from *o*-xylene.

* Biochemical Studies on "Bakanae" Fungus—79. Part XX, K. Mori, T. Ogawa, N. Itaya, M. Matsui and Y. Sumiki, *Tetrahedron* **25**, 1281 (1969).

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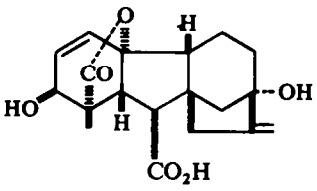
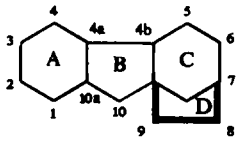
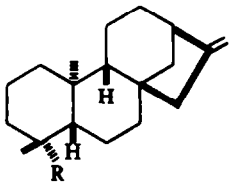
‖ Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the cases of totally synthetic products.



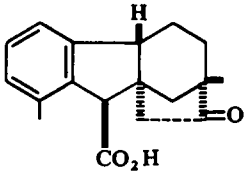
I



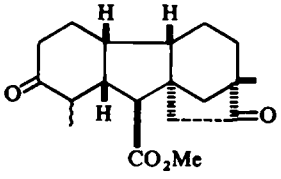
II



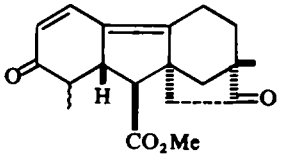
III: R = CO_2H
IV: R = Me



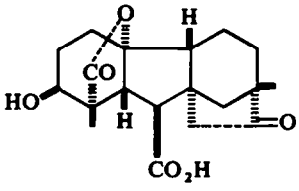
V



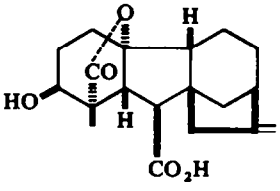
VI



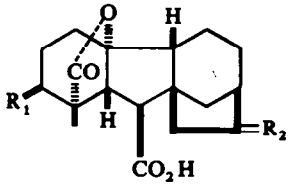
VII



VIII



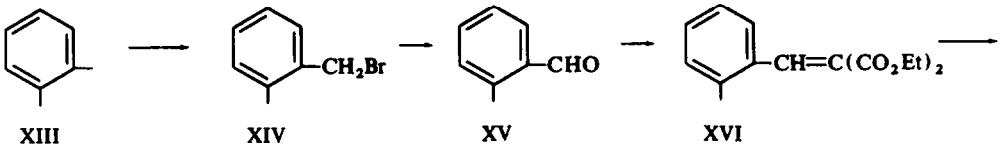
IX



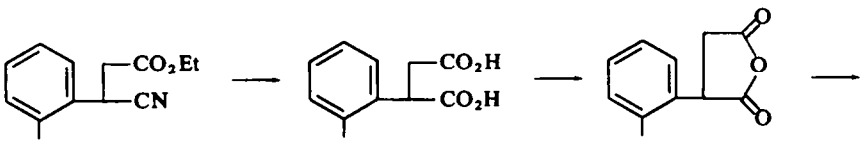
	R_1	R_2
X:	OH	Me, OH
XI:	H	$=CH_2$
XII:	H	Me, OH

Synthesis of the racemic epigibberic acid (V)

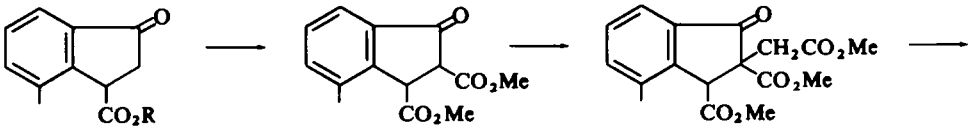
Treatment of gibberellic acid (I) with hot dilute mineral acid gave two isomeric 7α-gibbane carboxylic acids, gibberic (V, 4bHα) and epigibberic (V) acids.[3] We synthesized the latter from *o*-xylene in 21 steps.[28] Although this work has been published in detail,[29] it seems necessary to review it in order to comprehend all the steps involved in the present total synthesis. The earlier steps (XIII–XXV)[36] were recently reinvestigated by House *et al.*[19] who confirmed the higher over-all yield by our method than by other methods they tried. The major problem in building up the acid molecule (V) was the stereoselectivity required in generating the correct configurations at C-4b, 7 and 10. To this end a 7α,10α-compound (XXIX) was prepared *via* an anhydride (XXVIII). An unsaturated ketone (XXXI), obtained from XXIX by esterification and ketalization, was hydrogenated to give a compound (XXXII) with a β-oriented hydrogen atom at C-4b. Reduction of the corresponding



XIII XIV XV XVI

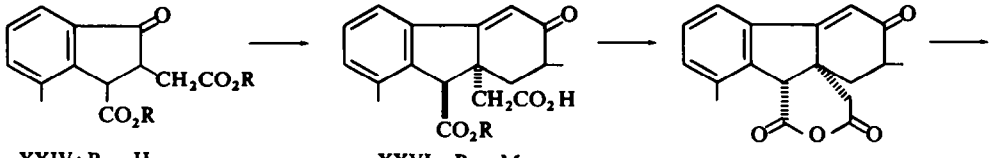


XVII XVIII XIX



XX: R = H
XXI: R = Me

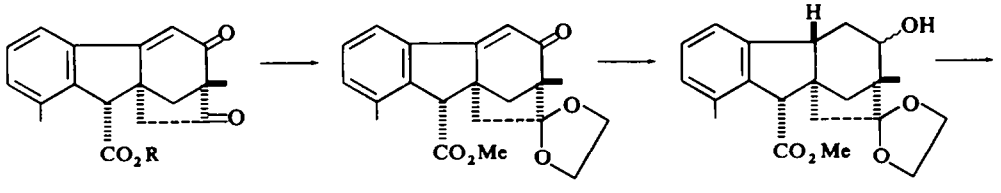
XXII XXIII



XXIV: R = H
XXV: R = Me

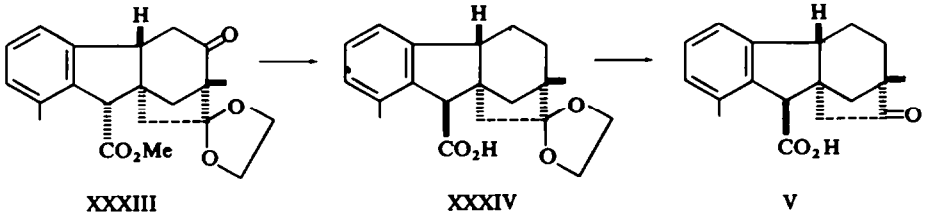
XXVI: R = Me
XXVII: R = H

XXVIII



XXIX: R = H
XXX: R = Me

XXXI XXXII



XXXIII XXXIV V

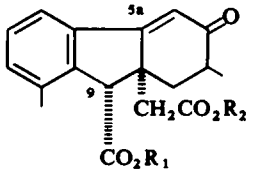
ketone (XXXIII) by the Huang Minlon procedure epimerized the C-10 carbomethoxyl group and finally led to an acid (XXXIV). This was treated with hot dilute hydrochloric acid to give the racemic epigibberic acid (V).* A few months prior to the completion of our work, Loewenthal and Malhotra[37,38] synthesized (±)-gibberic acid (V, 4bHα) employing the same intermediate (XXV) prepared in a different manner.

Synthesis of the racemic dioxo ester (VI)

On the basis of the results reported[30] we decided to employ epigibberic acid as the starting material. Since the yield of (+)-epigibberic acid (V) from gibberellic acid (I) was very low (about 6%) compared with that (about 70%) of (−)-gibberic acid (V, 4bHα), we had to secure the necessary amount of the racemate by total synthesis.

Methyl (±)-epigibberate (XXXV)[39] was nitrated to a nitro ester (XXXVI) as the major product. The minor product was a positional isomer (XXXVII) whose nitro group was thought to be at C-4, since signals from aromatic protons appeared as doublets at δ 7·12 (J = 8 Hz) and 7·64 (J = 8 Hz). The magnitude of the coupling constant definitely supported the structure XXXVII and was inconsistent with a C-3 nitro group. The nitro ester (XXXVI) was hydrogenated over Pd–C to yield an amino ester (XXXVIII). Its diazotization followed by hydrolysis afforded a hydroxy

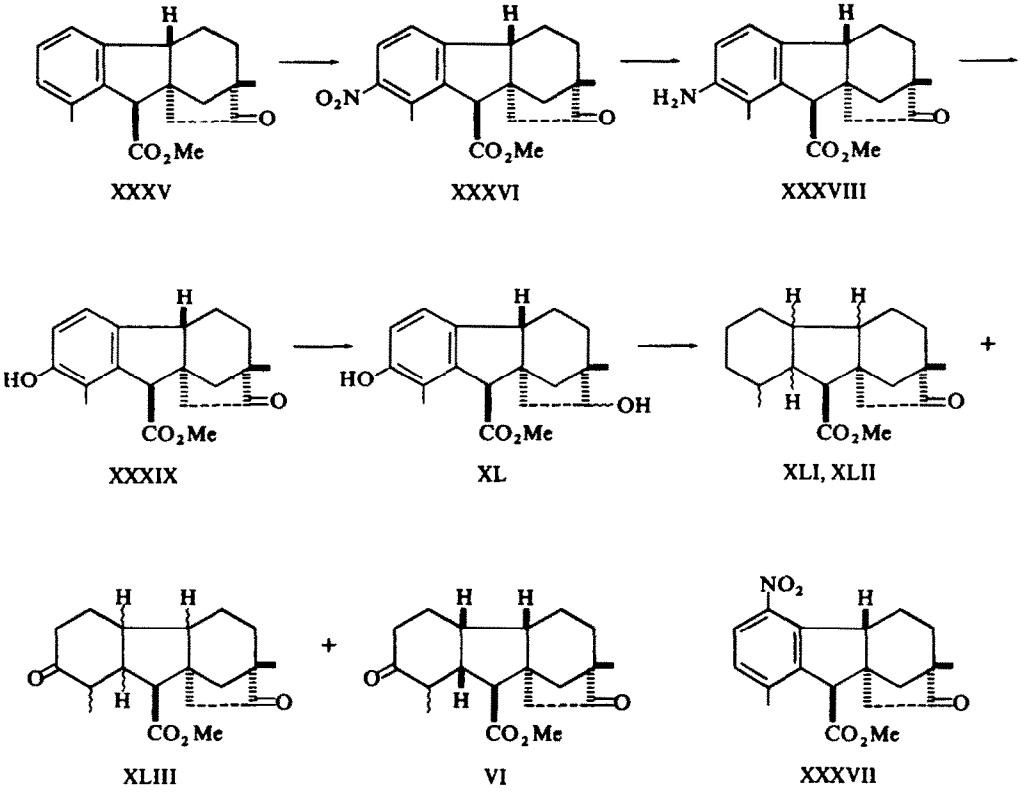
* During the course of a large scale preparation of (±)-epigibberic acid (V) we noticed several new facts (Experimental). (1) The Robinson annelation of the oxo diester (XXV) was believed to give only the thermodynamically more stable *trans*-half ester (XXVI)[29,38] However, when the reaction was carried out at low temperature, some *cis*-half ester (i) was obtained in addition to the normal product (XXVI). This means that the initial attack of methyl isopropenyl ketone takes place on the side opposite to the carbomethoxyl group at the benzylic position. After the kinetically-controlled addition, the carbomethoxyl



	R_1	R_2
i	Me	H
ii	H	H
iii	H	Me
iv	Me	CH_2CH_2OH
v	Me	Me

group epimerizes to give more stable *trans*-half ester (XXVI). As another by-product there was obtained the Na salt of *cis*-diacid (ii). It is difficult to rationalize the reason why the C-9 (hydrofluorene numbering) carbomethoxyl group was hydrolyzed without epimerization to give this diacid. One explanation was that lactone formation occurred between the C-9 carboxyl group and C-5a hydroxyl group of intermediary β-ketol prior to the elimination of the C-5a hydroxyl group to give a *cis*-half-ester (iii) which was hydrolysed to the diacid (ii). (2) Ketalization of the tetracyclic dioxo ester (XXX) was known to give an ester (iv) in 36% yield rather than the normal product (XXXI, 30% yield).[29] This ester (iv) was shown to afford either a *cis*-diester (v)[29] or the *cis*-half ester (i) by ester-exchange or controlled hydrolysis. (3) The *cis*-half ester (i) obtained as described above could be cyclized to yield the tetracyclic ester (XXX) in good yield. Thus the by-product (iv) could easily be put back on the main pathway of the synthesis. (4) The *cis*-diacid (ii) was found to give the anhydride (XXVIII) in very good yield.

ester (XXXIX). The position of the OH group was confirmed by conversion of the ester (XXXIX) into the known (±)-2-hydroxyepigibberic acid.[30] The over-all yield of these 3 steps was 37%.



XXXV XXXVI XXXVIII

XXXIX XL XLI, XLII

XLIII VI XXXVII

Hydrogenation of the phenol (XXXIX) over T-1 Raney nickel[40] resulted in the reduction of only the C-8 carbonyl group. The resulting dihydroxy ester (XL) was further hydrogenated over rhodium-platinum oxides[41] to give a complex mixture of esters with hydroaromatic A-ring. This was oxidized with Jones reagent[42] and the product was chromatographed on silica gel. Elution with petroleum ether–benzene (6:1) gave an oxo ester (XLI, unknown configurations at C-4a, 4b, 10a) in 8% yield. Petroleum ether–benzene (3:1) eluted another stereoisomeric oxo ester (XLII, unknown configurations at C-4a, 4b, 10a) in 2% yield. These two compounds were obviously generated by hydrogenolytic removal of the C-2 OH group. Subsequent elution with benzene afforded a dioxo ester (XLIII) in 12% yield. Its IR and NMR spectra were different from those of the desired product (VI). No definite stereochemistry could be assigned to this product. Successive elution with benzene gave a racemic dioxo ester (VI) in 4% yield. Its IR and NMR spectral properties in solution as well as gas chromatographic behaviour were indistinguishable from those of the

optically active dioxo ester (VI)*† derived from gibberellic acid (I). Another crystalline product absorbing at 1723 and 1662 cm^{-1} in IR spectrum was eluted with benzene in 2% yield but its structure remained unknown.

Synthesis of the dienone ester (VII).

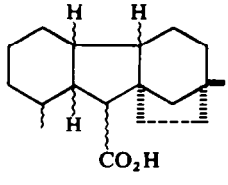
For the purpose of introducing a double bond at C-3 of the oxo ester (VI), we first attempted its direct bromination with pyridinium bromide perbromide in tetrahydrofuran. The product, however, was shown by its NMR spectrum to be a stereoisomeric mixture of 1-bromoketones (XLIV). This paralleled with the results obtained with 3-ketosteroids with A/B *cis* ring junction.[44]

The next attempt was bromination of an enamine[45] derived from the dioxo ester (VI). Unfortunately we could not prepare the necessary pyrrolidine enamine by commonly used methods.[46,47]

The third attempt was the DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) dehydrogenation[48] of an α-formyl ketone (XLV) followed by decarbonylation.[49] A recent report[50] on the successful preparation of a Δ^1-3-ketosteroid with A/B *cis* ring junction by this method was a stimulating factor. A crystalline formyl ketone (XLV) was prepared from the dioxo ester (VI) in 69% yield by treatment with methyl formate and sodium methoxide. The DDQ dehydrogenation, however, was unfruitful under conditions successfully applied in the steroid field[51] and only intractable gum was obtained.

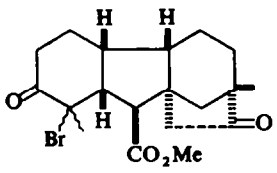
The final and successful method employed was that of Kühne[45] which involved the use of an α-formyl group as an activating group for introduction of a bromine atom. The formyl ketone (XLV) was dissolved in aqueous sodium hydroxide and treated with bromine to give a bromide (XLVI) as white foam. This, without purification, was hydrolysed with an equimolar amount of sodium hydroxide to give a bromoketone (XLVII) as a crude gum. Lithium bromide and lithium carbonate in hot dimethylformamide[52] was employed as a dehydrobromination agent to give a crude gummy product containing, an α,β-unsaturated ketone (XLVIII) and its $\Delta^{1(10a)}$-isomer. The NMR spectrum of the gum dissolved in $CDCl_3$ showed signals at δ ca. 6·1 and 7·1 due to two olefinic protons of the unsaturated ketone (XLVIII) and at 2·02 due to vinylic methyl protons of the $\Delta^{1(10a)}$-isomer. The IR spectrum (film) of

* This and related 2-oxogibbane compounds hereafter described possess the C-1 Me group in the thermodynamically more stable configuration, although it is difficult to decide whether it is α- or β-oriented.[cf. 43]

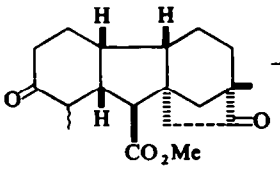


vi

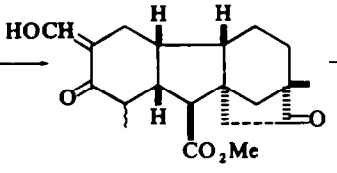
† Attempts were made to correlate the oxo ester (XLI) with XLIII or VI. The Huang Minlon reduction products (vi) of the ketones (XLI, XLIII, VI) were different from each other by IR comparisons and no useful informations on the configurations at C-4a, 4b, 10a could be obtained.



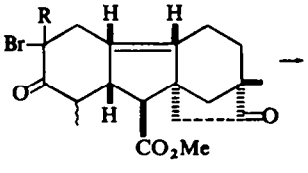
XLIV



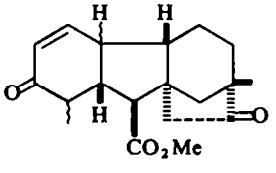
VI



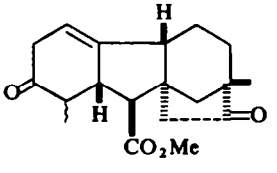
XLV



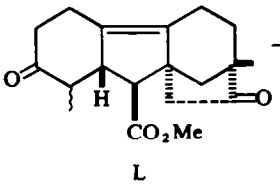
XLVI: R = CHO
XLVII: R = H



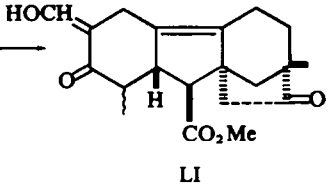
XLVIII



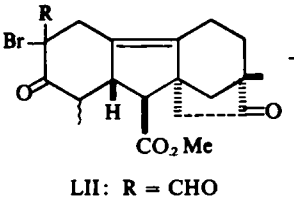
XLIX



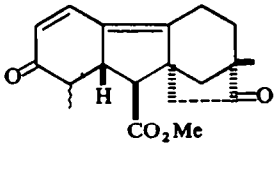
L



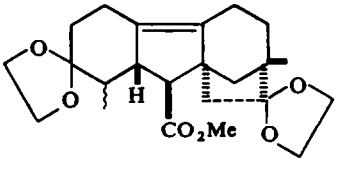
LI



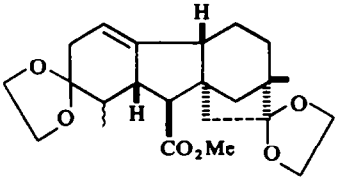
LII: R = CHO
LIII: R = H



VII



LIV



LV

the gum showed absorptions at 1730 (broad), 1670, 1650 (sh) cm^{-1} indicating the presence of the α,β-unsaturated carbonyl chromophore. In order to obtain the desired product (XLVIII) in a pure state, the mixture was boiled with dilute hydrochloric acid and separated into acid and neutral fractions. Since the $\Delta^{1(10a)}$ isomer was a β,γ-unsaturated δ-oxo ester, it was hydrolysed and decarboxylated under acidic condition to give a neutral diketone which was discarded after separation. The desired acid fraction was esterified with diazomethane and chromatographed on alumina. Surprisingly, the only crystalline product eluted by petroleum ether-ether (4:1) in 7% yield from XLV was not the expected α,β-unsaturated ketone (XLVIII) but a β,γ-unsaturated ketone (XLIX). This was identified by IR, NMR and mixed m.p. with an authentic sample (XLIX) prepared from gibberellic acid. A possibility that this ketone (XLIX) had been present in the original gummy mixture before acid treatment was excluded by inspection of the NMR spectrum of the gum which showed

no signal at δ 5·42. The NMR spectrum of the β,γ-unsaturated ketone (XLIX) contains a characteristic C-4 olefinic proton resonance at δ 5·42. This suggests that the non-conjugated enone (XLIX) is more stable than the conjugated isomer (XLVIII). The supporting two facts are as follows: (i) Attempted equilibration of the ketone (XLIX) with sodium methoxide in methanol did not afford the conjugated enone (XLVIII) and (ii) Equilibration of the ketone (XLIX) in boiling benzene in the presence of *p*-toluenesulfonic acid resulted in the complete recovery of the starting material. Inspection of a molecular model of XLVIII indicates steric inhibition of conjugation due to the non-coplanarity of the C-3 double bond and the C-2 carbonyl group. Therefore the migration of C-4 double bond to C-3 does not increase the stability of the molecule. The absorptions at 1670 and 1650 cm^{-1} observed in the IR spectrum of the crude gum obtained by dehydrobromination were perhaps entirely due to the $\Delta^{1(10a)}$-isomer.

The next task was the conversion of the enone (XLIX) into the dienone (VII). We first attempted to prepare a 4(4a)-epoxide which would yield the desired dienone (VII) by acid treatment. However, the epoxidation of the enone (XLIX) by monoperphthalic acid, perbenzoic acid or performic acid did not give useful results.

The second and successful scheme was to divide the conversion into two stages. The first stage was migration of the 4(4a) double bond to the 4a(4b) position. The second was the introduction of 3(4) double bond. For the first purpose we took advantage of the widely known ability of Pd–C to promote double bond migration.[53] The gibb-4(4a)-ene (XLIX) in ethanol was shaken under hydrogen atmosphere with 10% Pd-C. The oily product was next oxidized with the Jones reagent[42] and fractionally crystallized from ethyl acetate-petroleum ether. The first and the second crops (12% yield) were shown to be the desired gibb-4a(4b)-ene (L), identical with an authentic sample prepared from gibberellic acid by IR, NMR and mixed m.p. The third and the fourth crops (38% yield) were crystalline mixtures of the dioxo esters (VI, XLIX and L). Repeated experiments confirmed the reproducibility of this double bond migration.*

The introduction of the 3(4) double bond was carried out by a sequence of reactions similar to those described for the saturated ketone (VI). A formyl ketone (LI) was obtained in 92% yield as a gum. This was brominated to give an α-bromo-α-formyl ketone (LII). Removal of the formyl group with aqueous sodium hydroxide yielded a bromoketone (LIII). Dehydrobromination was carried out by heating the bromoketone with lithium bromide and lithium carbonate suspended in dimethylformamide. After treatment with boiling dilute hydrochloric acid and esterification of the acid fraction with diazomethane the product was chromatographed on alumina to afford the crystalline dienone ester (VII) in 3·4% yield from the formyl ketone (LI). No other crystalline product was obtained. The synthetic dienone (VII) was identical with an authentic sample prepared from gibberellic acid on the basis of IR and NMR spectral comparisons and mixed m.p.

In our preliminary communication,[25] we reported the conversion of the gibb-4(4a)-ene (XLIX) into a crystalline bis-ketal (LIV) with concomitant migration of the double bond into 4a(4b) position. After several attempts, it was found that the formation of the bis-ketal (LIV) could not be repeated. When the ketalization was

* This Pd-catalysed double bond migration did not occur under nitrogen atmosphere.

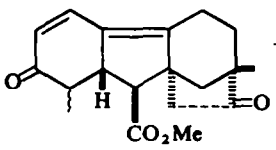
carried out in usual manner (ethylene glycol and *p*-toluenesulphonic acid in boiling dichloroethane), a chromatographically homogeneous oil was obtained which was shown to be the bis-ketal (LV) of the starting diketone (XLIX). When the diketone (XLIX) was heated with methanolic hydrogen chloride, a good yield of a crystalline compound with no olefinic proton was obtained. This was clearly different from the gibba-4a(4b)-ene (L) on the basis of IR, NMR and m.p., and its structure remained unknown. When the ketalization of the diketone (XLIX) was carried out under drastic condition (a large amount of *p*-toluenesulphonic acid and prolonged heating), a mixture of gummy bis-ketals were obtained which showed no signal due to olefinic protons in its NMR spectrum. Instead of the desired ketone (L), the mixture afforded two ketones after chromatographic purification and deketalization. One remained unidentified but the other was shown to be identical with the compound generated from the ketone (XLIX) by treatment with methanolic hydrogen chloride. These results forced us to abandon the study of acid-catalysed double bond migration.

Synthesis of gibberellin C (VIII).

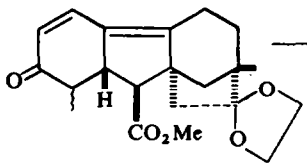
In order to construct the 1 → 4a lactone bridge which is characteristic of all the gibberellins, an α-oriented carboxyl group had to be attached to C-1 of the dienone (VII). Chronologically speaking, the experiments described in this section had been completed prior to the conversion of epigibberic acid (V) into the dienone (VII) and was the driving force to continue our efforts in the gibberellin field.

Ketalization of the dienone (VII) with an excess of ethylene glycol and *p*-toluenesulphonic acid in boiling dichloroethane* gave a monoketal (LVI). The assigned structure was supported by its IR (ν_{max} 1650, 1572 cm^{-1}) and UV (λ_{max} 308 mμ) spectra. Carbomethoxylation at C-1 of this ketone (LVI) was unsuccessful using several pairs of carbomethoxylating agent and base (i) methyl carbonate and sodium hydride (ii) methyl carbonate and sodium amide (iii) carbon dioxide and lithium amide (iv) methyl chloroformate and triphenylmethyl sodium. Finally, successful carboxylation was possible with ethereal triphenylmethyl sodium and carbon dioxide.[cf. 54] After acidification, the product was immediately treated with dizaomethane to give a mixture of esters which was chromatographed on alumina and divided into four fractions. Each fraction was treated with hot dioxan-dilute hydrochloric acid to effect deketalization. The four products corresponding to the four fractions were separately re-chromatographed on silica gel. The third fraction of the original alumina chromatography gave a crystalline dioxo diester (LVIII) in 11·4% yield after treatment. This was identified with an authentic sample prepared from gibberellic acid by IR, NMR and mixed m.p. The low yield of the diester (LVIII) and the stereoselective introduction of the α-oriented C-1 carbomethoxyl group could be due to the large steric hindrance caused by the β-oriented C-10 carbomethoxyl group. Failure to introduce a carbomethoxyl group at C-3 could be ascribed to the lack of enolizability of the C-2 carbonyl function to the direction of C-3 because of the extraordinary stability of the gibba-3,4a(4b)-diene system. The fact that a considerable amount (540 mg) of the diester (LVIII) was synthesized in crystalline form confirmed our preliminary work[27] in which the final separation of the product (LVIII, 0·5 mg) had been accomplished by preparative gas chromatography.

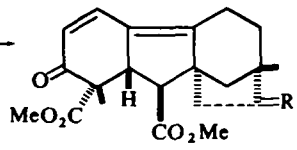
* In previous reports[27, 28, 29] we erroneously described this as dichloroethylene which should be read as 1,2-dichloroethane.



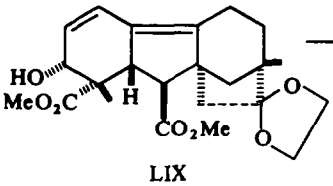
VII



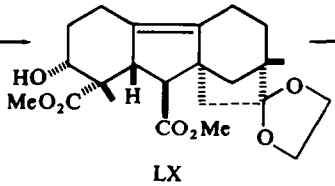
LVI



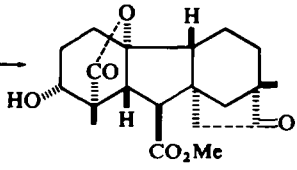
LVII: R = <O]
LVIII: R = O



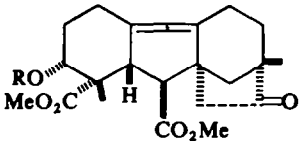
LIX



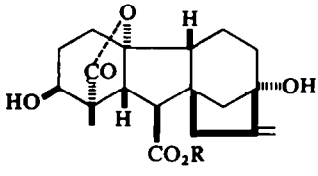
LX



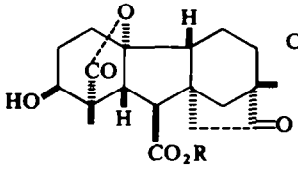
LXI



LXII: R = H
LXIII: R = Ac



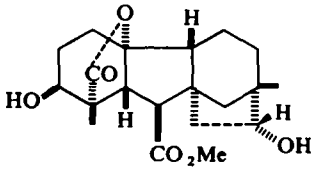
LXIV: R = Me
LXVI: R = H



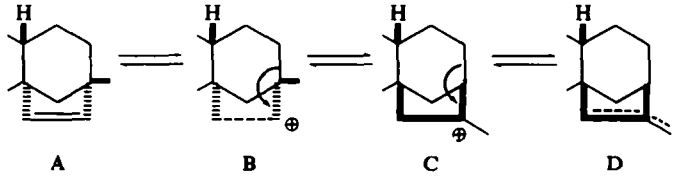
LXV: R = Me
VIII: R = H

Cross et al.

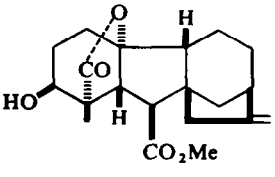
LXVIII



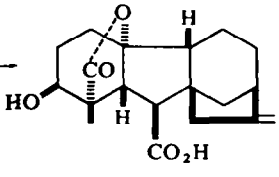
LXVII



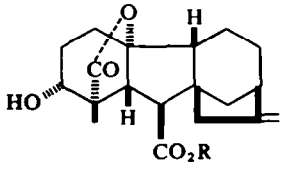
A B C D



LXVIII



IX



LXIX: R = Me
LXX: R = H

The remaining problem was the modification of the A-ring with special emphasis on the building up of the γ-lactone bridge. The dioxo diester (LVIII) was boiled with ethylene glycol and *p*-toluenesulphonic acid in dichloroethane to give back the gummy monoketal (LVII) initially present in the crude carbomethoxylation products. Reduction of the monoketal (LVII) with sodium borohydride yielded a hydroxy ester (LIX). The α-configuration was assigned to the C-2 OH group. This assignment was on the basis of the analogous result obtained by the British group on the reduction of the C-2 ketone derived from methyl 8-epitetrahydrogibberellate[55] and was supported by the later conversion of this ester (LIX) into 2 (eq)-hydroxy-epimer (LXI) of gibberellin C methyl ester. The 2-hydroxygibba-3,4a(4b)-diene (LIX) was hydrogenated over Pd–C to give a 2-hydroxygibb-4a(4b)-ene (LX) as a gum. The tetrasubstituted 4a(4b) double bond remained intact during the reduction.[cf. 55,56] The hydroxy ketal ester (LX) was boiled with dilute sulphuric acid to effect relactonization[56] and deketalization. The product was treated with diazomethane and chromatographed on alumina to give 2(eq)-hydroxy-epimer (LXI) of gibberellin C methyl ester in 20% yield from LX. This was identified with an authentic sample by IR spectrum and mixed m.p. The earlier fractions of the chromatographic separation yielded a hydroxy diester (LXII) which was characterized as its known crystalline acetate (LXIII).[57]

The reversible epimerization of 2 (ax)-hydroxygibbane 1 → 4a lactones such as gibberellin A_1 methyl ester (LXIV) or gibberellin C methyl ester (LXV), by dilute aqueous alkali at room temperature, is well established.[55,57,58] Conversion of the 2(eq)-hydroxy-epimer (LXI) into gibberellin C methyl ester (LXV) by this epimerization reaction and subsequent acid hydrolysis of the methyl ester (LXV) to gibberellin C (VIII) have already been published.[57] This completed the total synthesis of racemic gibberellin C (VIII)* which was first obtained by the Japanese group in 1941[59] and later more thoroughly studied by both the British[5] and the Japanese[60] groups. The keto acid (VIII) is now easily obtainable by acid-catalysed Wagner–Meerwein rearrangement of the C/D rings of gibberellin A_1 (LXVI) which can be prepared from gibberellic acid (X).[5]

Conversion of gibberellin C (VIII) *into gibberellin* A_4 (IX).

Rearrangement of the C/D rings of tetracyclic diterpenoids has received much attention,[61] and we also have published our work in this area.[15] The rearrangement can be shown by the sequence A ⇌ B ⇌ C ⇌ D. In gibberellin field, Cross *et al.*[31] carried out the successful conversion of 7α-gibbanes into gibbanes. They prepared a diol (LXVII) from gibberellin C methyl ester (LXV) by reduction with sodium borohydride. The diol (LXVII) was treated with phosphorus pentachloride to give gibberellin A_4 methyl ester (LXVIII) in 5% yield. In view of this successful transformation, our work can be regarded as the total synthesis of racemic gibberellin A_4 methyl ester (LXVIII).

The final problem was the conversion of the methyl ester (LXVIII) into gibberellin A_4 (IX).[26] Since the alkaline hydrolysis of gibberellin A_1 methyl ester (LXIV) was known to give a mixture of gibberellin A_1 (LXVI) and its 2 (eq)-hydroxy-epimer,[62]

* Since we did not try to resolve the racemic dioxo ester (VI), this total synthesis remained to be that of the racemate. However, by the use of relay compounds, what we actually synthesized was not the racemic but the optically active gibberellin C.

an analogous situation was expected in the case of gibberellin A_4 methyl ester (LXVIII). The ester (LXVIII) was prepared from crude gibberellin A_7 (IX, Δ^3)* as described[33,63] and purified by chromatography on alumina. The pure ester (LXVIII) was boiled with 0·1N NaOH for 40 min. The product was chromatographed on Celite buffered with phosphate buffer (pH 6·2).[64] Subsequent elution gave, (1) a mixture of the methyl esters (LXVIII and LXIX, 36% yield), (2) gibberellin A_4 (IX, 4% yield)[33,63,65] and (3) the 2 (eq)-hydroxy-epimer (LXX, 27% yield).[63] The IR spectrum of the gibberellin A_4 was identical with the authentic spectrum kindly provided by Professor N. Takahashi. The identity was also proved by TLC.[66] The mixture of the methyl esters was re-chromatographed on alumina to give gibberellin A_4 methyl ester (LXVIII) and its 2 (eq)-hydroxy-epimer (LXIX) in 1:14 ratio.

Since gibberellins A_2(X), A_9(XI) and A_{10}(XII) have been derived from gibberellin A_4 (IX)[32–35] as stated in the beginning of this paper, these four gibberellins are now firmly correlated to epigibberic acid (V).

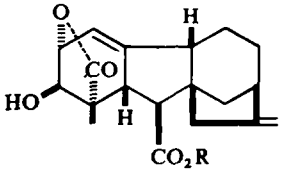
Preparation of relay compounds from gibberellic acid (I).

The total synthesis was made possible by the preparation of several new degradation products of gibberellic acid which were used as relay compounds. In this final section we will describe our degradation work on gibberellic acid which constitutes the essential part of our synthetic studies.

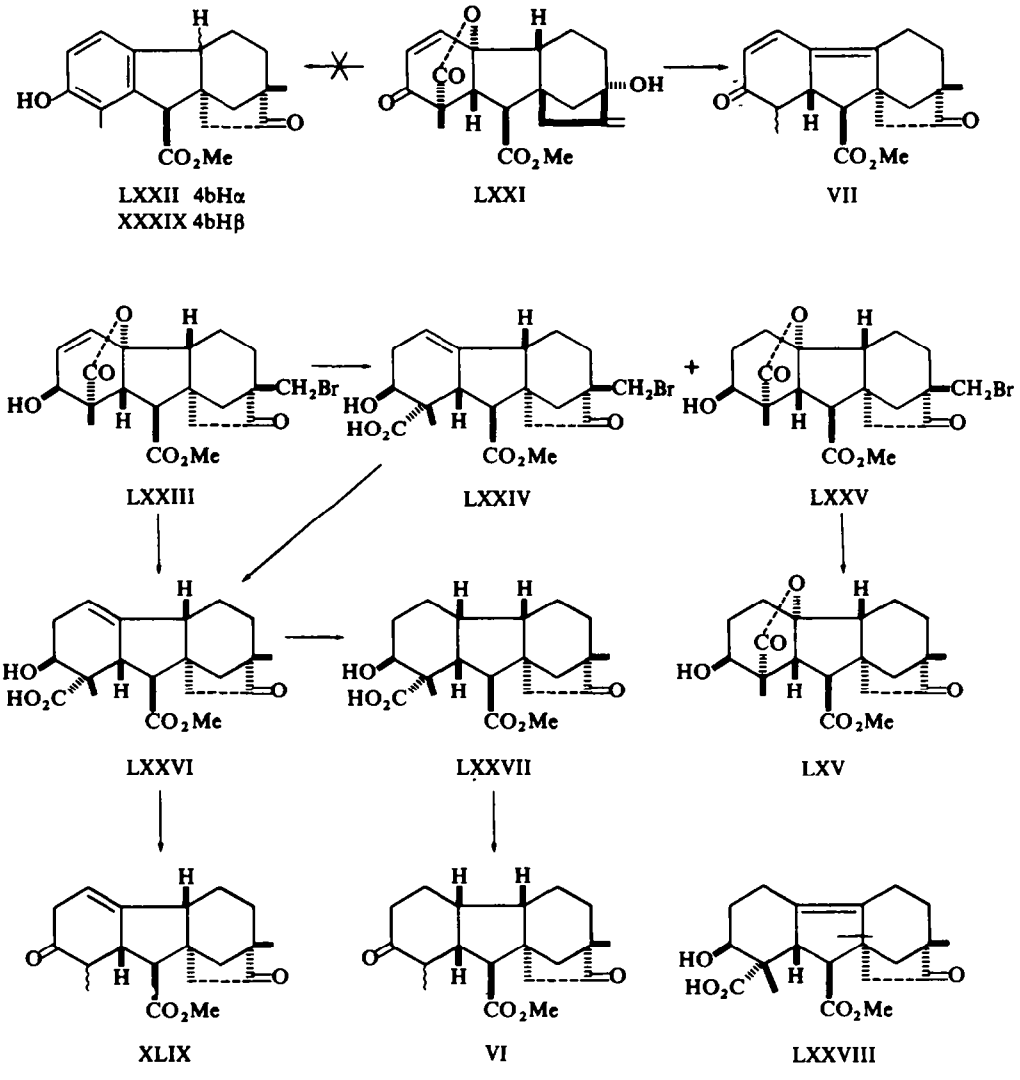
The most important degradation product (VII) which determined our synthetic route was prepared from an oxo lactone (LXXI) obtained from methyl gibberellate by oxidation.[5] Treatment of LXXI with hot mineral acid was expected to give a phenol like LXXII or its 4bHβ isomer (XXXIX). However, the product actually obtained in 48% yield after acid treatment, esterification and chromatographic purification on alumina was not a phenol but a crystalline ketone. The assigned structure (VII) was supported by elementary analysis and spectroscopic properties. Its IR spectrum showed characteristic absorptions at 1672, 1660 and 1547 cm^{-1}, while its UV showed a maximum at 302 mμ (ε 16,100), both due to the dienone chromophore. The genesis of this dienone (VII) may be ascribed to the extraordinary stability of the 2-oxogibba-3,4a(4b)-diene system.

Methyl bromogibberellate (LXXIII)[67,68] was the starting material for the first (VI) and the second (XLIX) relay compounds used in the course of conversion of epigibberic acid (V) into the dienone (VII). This bromide (LXXIII) was prepared from gibberellic acid (I) by the action of an equimolar amount of pyridinium bromide

* The crude gibberellin A_7, kindly given to us by Kyowa Fermentation Industry Co., contained A_4 (IX), A_7 (IX,Δ^3) and its Isomer (vii).

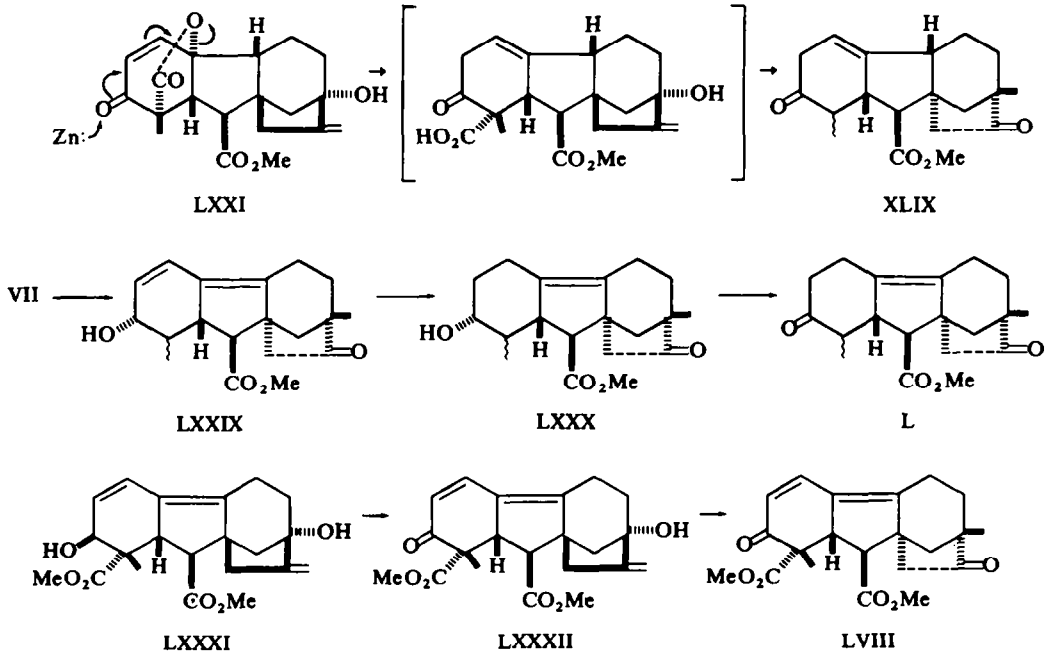


vii R = H
viii Me



perbromide in tetrahydrofuran in 71% yield.[cf. 68] It should be mentioned that this crystalline bromide was used in the X-ray work of the Glasgow group.[11] The bromide (LXXIII) in tetrahydrofuran-methanol (2:1) was hydrogenated over Adams PtO_2 to give a hydrogenolysis product (LXXIV) and bromogibberellin C methyl ester (LXXV) in 1:2·5 ratio. The structure (LXXIV) assigned to the hydrogenolysis product was supported by the NMR spectrum of the corresponding methyl ester which contained two 3H singlets at δ 3·61 and 3·76 (CO_2Me) and 1H signal at 5·14 (C=C<u>H</u>). The bromides (LXIV, LXXV) were debrominated with zinc dust in acetic acid to give an unsaturated acid (LXXVI) and gibberellin C methyl ester (LXV), respectively. The over-all yield of the acid (LXXVI), which was necessary in our synthetic work, from gibberellic acid (I) was only 12·5%. Later a better method was devised for the

preparation of this acid (LXXVI). Hydrogenation of methyl bromogibberellate (LXXIII) in tetrahydrofuran–methanol over Pd–C in the presence of pyridine[69] under high pressure at 80° gave directly the debrominated acid (LXXVI) in 82% yield. Gibberellin C methyl ester (LXV) was also obtained in 14% as a by-product. Under atmospheric pressure and at room temperature, even in the presence of pyridine, the Pd–C catalysed hydrogenation stopped at the stage of bromo compounds, LXXIV and LXXV. This high-pressure reduction improved the over-all yield of the acid (LXXVI) to 58%. Further hydrogenation of the acid (LXXVI) over Adams PtO_2 in acetic acid gave a crystalline saturated acid (LXXVII) in 62% yield after chromatography on silica gel. The saturation of the double bond was confirmed by disappearance of a signal due to the C-4 olefinic proton in the NMR spectrum of the corresponding methyl ester. The stereochemistry depicted in LXXVII was assigned by analogy with the established stereochemistry of the hydrogenolysis products of gibberellic acid.[43] Another expected product (LXXVIII), generated by double bond migration,[cf.43] could not be obtained in crystalline form. Jones oxidation[42] followed by decarboxylation of the saturated acid (LXXVII) gave the first relay compound (VI). More conveniently, the crude oily hydrogenation product obtained from the unsaturated acid (LXXVI) was directly oxidized, decarboxylated and equilibrated with methanolic socium methoxide to give the dioxo ester (VI) in 49% yield from LXXVI. The second relay compound (XLIX) was obtained in 37% yield from the unsaturated acid (LXXVI) by oxidation and decarboxylation. Alternatively, the oxo lactone (LXXI) was treated with zinc dust in hot acetic acid to effect reductive cleavage of the lactone ring. The product was heated with dilute hydrochloric acid, esterified with diazomethane and chromatographed on alumina to give the oxo ester (XLIX) in 44% yield. No C-1 methyl epimer of VI or XLIX was obtained in pure form.



The third relay compound (L) was prepared from the dienone (VII) in 73% yield. Reduction of the dienone (VII) with sodium borohydride gave a crude gummy dienol (LXXIX). This was hydrogenated over Pd–C to give a hydroxy ester (LXXX) and then oxidized with the Jones reagent to give the gibb-4a(4b)-ene (L).*

The last relay compound, the diester (LVIII), was prepared by heating gibberellic acid (I) with hydrazine hydrate to give gibberellenic acid (LXXXI, CO_2H instead of CO_2Me).[14,56] The corresponding dimethyl ester (LXXXI) was oxidized with manganese dioxide to give a ketone (LXXXII).[70] The acid-catalysed Wagner–Meerwein rearrangement of the C/D ring of the diester (LXXXII) gave the desired compound (LVIII).

Finally, the biological activity of gibberellin C (VIII) deserves a short comment. This 7α-gibbane compound was reported to elongate rice seedlings.[56] However, Brian *et al.*[71] recently questioned its activity on the basis of the possible contamination of a minute amount of some gibbane compounds, for the activity of gibberellin C was only about 1% of that of gibberellic acid in the bioassay system they used. At the same time Hashimoto *et al.*[72] reported the interesting anti-gibberellin activity of a closely related compound, 2-desoxygibberellin C. In order to clarify this point, pure crystalline gibberellin C was prepared from gibberellic acid *via* methyl bromogibberellate (LXXIII) and bromogibberellin C methyl ester (LXXV). These two compounds were crystalline and could be purified by recrystallization. After debromination and recrystallization, pure gibberellin C methyl ester (LXV) was obtained which was hydrolysed with boiling dilute hydrochloric acid. The pure gibberellin C was shown to elongate d-5 dwarf maizes and to be more active than (−)-kaur-16-en-19-ol.[15] It can thus be concluded that gibberellin C (VIII) is biologically active, although the activity is small.

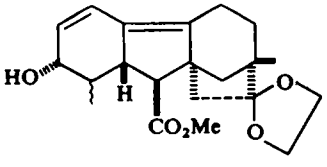
EXPERIMENTAL

All m.ps are uncorrected. IR spectra refer to Nujol mulls for solid samples and films for gums unless otherwise stated. UV spectra were determined in EtOH. NMR spectra were recorded at 100 MHz in $CDCl_3$ with TMS as an internal standard.

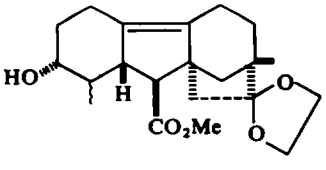
The Robinson annelation of XXV (*the acids* XXVI, i *and* ii).

The diester XXV (478 g) in MeOH (1 l) was added with stirring to a soln of NaOMe (from 54·6 g of Na) in MeOH (1 l) at −12–−10°. To this soln methyl isopropenyl ketone (273 g) was added dropwise at −12–−8°. The stirring was continued for 4 hr at −8–−5°. The mixture was poured into ice–water and acidified with dil HCl. The precipitated crystalline *trans*-half ester XXVI (200 g, 35% yield) was collected by filtration. The filtrate was extracted with $CHCl_3$. The extract was concentrated *in vacuo* and the residue was triturated with C_6H_6 to give crystalline *cis*-half ester *i* (78 g, 14% yield). Recrystallization from $CHCl_3$–C_6H_6 gave prisms, m.p. 177–178°; ν_{max} ~3200–~2600, 1718, 1690, 1650, 1628, 1210, 1170, 802 cm^{-1}. (Found: C, 68·89; H, 6·45. $C_{19}H_{20}O_5$ requires: C, 69·50; H, 6·14%). The residual gum after removal of *i*

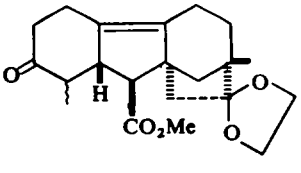
* Another compound (xi) was prepared from LVI *via* ix and x. Attempted carboxylation at C-1 of xi after protection of the C-3 methylene was unsuccessful.



ix



x



xi

weighed 340 g which was thought to be a mixture of XXVI and *i*. In order to obtain crystalline XXVI after equilibration, the gum was treated with NaOMe (from 34 g of Na) in MeOH (1·2 l.) at 27–30° for 4 hr. During that period white crystalline material precipitated. This was collected, dissolved in MeOH–water (1:1) and treated with dil HCl to give crystalline *cis*-diacid *ii* (38 g, 7% yield). No crystalline product was obtained from the MeOH soln. This annelation gave the *trans*-half ester XXVI in 95% yield when the reaction was carried out at 27°.[29] XXVI and ii were identified with authentic samples by IR spectra. Structure of the isomeric half-ester (*i*) was confirmed by its later conversion to XXX.

Ester-exchange of the diester iv (*dimethyl ester* v)

The diester *iv* (3 g) in MeOH (60 ml) containing conc HCl (20 ml) was heated under reflux for 2 hr. The mixture was concentrated *in vacuo*, diluted with water and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated to give 2·5 g of crystalline *v*, identified with an authentic sample by IR spectrum.

Controlled hydrolysis of the diester iv

The diester *iv* (47 g) in AcOH (150 ml) and dil HCl (1:2, 300 ml) was heated under reflux for 1 hr. The mixture was diluted with water and extracted with $CHCl_3$. The acid in the extract was taken into Na_2CO_3 aq and liberated by acidification to give 30 g (72%) of crystalline *cis*-half ester (*i*), identified with an authentic sample by IR spectrum.

Cyclization of the cis-*half ester* i

The *cis*-half ester *i* (43 g) in AcOH (500 ml) and Ac_2O (70 ml) was treated with BF_3-etherate (10 ml) at room temp for 24 hr. The dark coloured mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$ aq, dried (Na_2SO_4) and concentrated to give 34 g (84%) of crystalline tetracyclic ester XXX, identified with an authentic sample by IR spectrum, ν_{max} 1742, 1664, 1620, 1600 cm^{-1}.

The anhydride XXVIII *from the* cis-*diacid* ii

The *cis*-diacid *ii* (38 g) in Ac_2O (750 ml) was heated under reflux for 3 hr. The mixture was concentrated *in vacuo* and the residual crystalline mass was washed with a small amount of ether to give 33 g (92%) of pure XXVIII, identified with an authentic sample by IR spectrum, ν_{max} 1808, 1758, 1654, 1632, 1600 cm^{-1}.

Methyl (±)-2-*nitroepigibberate* (XXXVI)

To a stirred and cooled soln of XXXV (11·5 g) in Ac_2O (100 ml), a mixture of fuming HNO_3 (*d* 1·50; 9·6 ml), conc HNO_3 (*d* 1·38; 9·6 ml) and Ac_2O (60 ml) was added dropwise at −4 – −3° during 30 min. After the addition, the mixture was stirred for 1 hr at −1–4°. It was poured into ice-water (0·8 l.) and left to stand overnight to hydrolyse Ac_2O. The solid product was taken into EtOAc. The extract was washed with water, sat $NaHCO_3$ aq and brine. Concentration of the soln after drying ($MgSO_4$) gave semi-solid. The crystalline XXXVI (4·5 g) was collected on a filter and washed with a small amount of ether. The filtrate and the washings were combined and concentrated. The residual gum was chromatographed on silica gel (120 g) in C_6H_6. Elution with C_6H_6 (1·6 l.) gave 3·5 g of XXXVI, increasing the total amount of the desired product to 8·0 g (60·5%). Recrystallization from MeOH gave needles, m.p. 128–129°; ν_{max} 1735, 1720, 1600, 1590, 1515, 1350, 1160 cm^{-1}; δ 1·10 (3H, s), 2·42 (3H, s), 3·70 (3H, s), 7·09 (1H, d, J = 8Hz), 7·87 (1H, d, J = 8Hz) ppm. (Found: C, 66·63; H, 6·23; N, 4·03. $C_{19}H_{21}O_5N$ requires: C, 66·46; H, 6·16; N, 4·08%). Subsequent elution gave a gum from which 0·1 g of pure 4-nitro isomer XXXVII was obtained after repeated recrystallization from EtOAc–n-hexane. Recrystallization from EtOAc–n-hexane gave rods, m.p. 178–180°; ν_{max} 1738, 1720, 1590, 1520, 1215 cm^{-1}; δ 1·08 (3H, s), 2·30 (3H, s), 7·12 (1H, d, J = 8 Hz), 7·64 (1H, d, J = 8 Hz) ppm. (Found: C, 66·07; H, 6·15; N, 4·33. $C_{19}H_{21}O_5N$ requires: C, 66·46; H, 6·16; N, 4·08%). In another run 700 mg (58%) of XXXVI and 400 mg (33%) of XXXVII were obtained from 1·1 g of XXXV after repeated fractional crystallization from MeOH.

Methyl (±)-2-*aminoepigibberate* (XXXVIII)

The nitro ester XXXVI (6·5 g) suspended in 99% EtOH (200 ml) containing conc HCl (4 ml) was hydrogenated over 10% Pd–C (2 g) at room temp under atmospheric press until the H_2 uptake ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was neutralized with Na_2CO_3 aq and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 5·0 g (84·5%) of crystalline XXXVIII. Recrystallization from EtOAc–n-hexane gave prisms, m.p.

190–192°; ν_{max} 3460, 3370, 1730, 1712, 1630, 1605 cm^{-1}; δ 1·08 (3H, s), 2·05 (3H, s), 3·66 (3H, s), 6·58 (1H, d, J = 8 Hz), 6·80 (1H, d, J = 8 Hz) ppm. (Found: C, 72·79; H, 7·35; N, 4·46. $C_{19}H_{23}O_3N$ requires: C, 72·82; H, 7·40; N, 4·47%).

Methyl (±)-*2-hydroxyepigibberate* (XXXIX)

A soln of $NaNO_2$ in H_2SO_4 was prepared by portionwise addition of $NaNO_2$ (4 g) to 80% (v/v) H_2SO_4 (200 ml) under ice-cooling. The mixture was once warmed (30°) to dissolve $NaNO_2$ and then cooled to −5°. To this soln, the amino ester XXXVIII (4·8 g) in pyridine (80 ml) was added with stirring and cooling at −3–3° during 40 min. After stirring for 20 min, ice (60 g) was added during 30 min at 0°. Then urea (10 g) in water (50 ml) was added portionwise to the stirred mixture to destroy excess HNO_2. The soln was poured into boiling water (1 l.). After cooling, the product was extracted with ether. The extract was washed with water, $NaHCO_3$ aq and brine, dried (Na_2SO_4) and decolourized (activated charcoal). Concentration of the soln gave 3·5 g (73%) of crystalline XXXIX. Recrystallization from EtOAc–n-hexane gave needles, m.p. 169–169·5°; ν_{max} 3450, 1732, 1703, 1604 cm^{-1}; δ 1·09 (3H, s), 2·10 (3H, s), 3·68 (3H, s), 5·03 (1H, broad) 6·58 (1H, d, J = 8 Hz), 6·78 (1H, d, J = 8 Hz) ppm. (Found: C, 72·52; H, 7·16. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%).

(±)-*2-Hydroxyepigibberic acid* (XXXIX CO_2H *instead of* CO_2Me)

The ester XXXIX (0·3 g) in MeOH (10 ml) was heated under reflux with 40% KOH aq (4 ml) for 2·5 hr. After cooling, the mixture was acidified with HCl and extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4) and concentrated to give 0·2 g (65%) of the acid, identified with an authentic sample[30] by IR spectrum, ν_{max} 3430, ~3200–~2600, 1710, 1695 (sh), 1600 cm^{-1}.

Reduction of methyl (±)-*2-hydroxyepigibberate* (XXXIX) [*methyl* (±)-*1,3-dimethyl-2,8-dihydroxy-4bβ,7α-gibba-1,3,4a(10a)-triene-10β-carboxylate* (XL)]

The ester XXXIX (2·0 g) in 99% EtOH (100 ml) was hydrogenated over Raney nickel T-1 (10 g) at 180–190° and an initial press of 100 kg/cm^2 for 4 hr. The catalyst and the solvent were removed to give 2·0 g of crude crystalline diol XL. Recrystallization from EtOAc gave prisms, m.p. 216–220°; ν_{max} 3520, 3280, 1715, 1610, 1598, 1200, 1170, 1004, 845 cm^{-1}. (Found: C, 71·75; H, 7·52. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%).

Catalytic hydrogenation of XL (*gibbane compounds* XLI, XLII, XLIII *and* VI)

The phenol XL (1·95 g) dissolved in AcOH (110 ml) was hydrogenated over RhO_2–PtO_2 (prepared from 0·5 g of $RhCl_3$ and 0·16 g of H_2PtCl_6) at 70° and an initial press of 80 kg/cm^2 for 10 hr. Removal of the catalyst and the solvent gave an oil which was dissolved in acetone (120 ml) and treated with the Jones reagent (9 ml) under ice-cooling. After 30 min MeOH (30 ml) was added to the reaction mixture which was then concentrated *in vacuo*. The residue was diluted with water (100 ml) and extracted with EtOAc. The extract was washed with water, $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave an oil which was chromatographed on silica gel (50 g of SiO_2 and 15 ml of water) in pet. ether to give the following fractions (200 ml each). No. 1–15 (pet. ether–C_6H_6, 6:1): 165 mg (8% yield) of crystalline XLI at 4–15. No. 16–20 (pet. ether–C_6H_6, 3:1): 27 mg of crystalline XLII at 19, 20. No. 21–25 (pet. ether–C_6H_6, 1:1): 8 mg of XLII at 21. The total yield of XLII was 35 mg (2%). No. 26–43 (C_6H_6): 235 mg (12% yield) of XLIII at 28–32; 78 mg (4% yield) of racemic VI at 33–35; 31·3 mg (2% yield) of unidentified crystalline compound at 37–39. No. 44, 45 (EtOAc): 633 mg of gum.

XLI was recrystallized from ether–pet. ether as prisms, m.p. 110·5–111·5°; ν_{max} 1735, 1188, 1172, 1160, 1144 cm^{-1}; δ 0·98 (3H, d, J = 7 Hz) 1·03 (3H, s), 3·66 (3H, s) ppm. (Found: C, 74·99; H, 9·31. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%).

XLII was recrystallized from ether–pet. ether as prisms, m.p. 98·5–99·5°; ν_{max} 1740, 1720, 1155 cm^{-1}. (Found: C, 74·89; H, 9·12. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%). XLIII was recrystallized from ether as prisms, m.p. 178–179°; ν_{max} 1730, 1720, 1705, 1190, 1170, 1160; ($CHCl_3$) 1740, 1724, 1715 (sh), 1186, 1170, 1155 cm^{-1}; δ 0·95 (3H, d, J = 5 Hz), 1·05 (3H, s), 3·68 (3H, s) ppm. (Found: C, 71·57; H, 7·97. $C_{19}H_{26}O_4$ requires: C, 71·67; H, 8·23%).

(±)-VI was recrystallized from ether as prisms, m.p. 112–113°; ν_{max} 1730, 1705, 1230, 1184, 1160, 1140; ($CHCl_3$) 1744, 1736, 1716, 1190, 1163, 1153 (sh), 1145 (sh), 1100, 1080, 992, 966, 835 cm^{-1}; δ 1·06 (3H, s), 1·08 (3H, d, J = 5 Hz), 1·48, 1·56, 1·85, 2·25, 2·38, 2·58, 2·62, 2·72, 3·70 (3H, s) ppm. Gas chromatography: Shimadzu GC-4AP; 1·5% OV-17 on Shimalite W(100–120 mesh) 4 mm i.d. × 2 m; Column temp 220°;

Carrier gas N_2; Retention time 10·8 min (98%), Small peak (2%) at 8·4 min. (Found: C, 72·07; H, 8·38. $C_{19}H_{26}O_4$ requires: C, 71·69; H, 8·23%).

The unidentified compound melted at 155–160°; ν_{max} 1725, 1660 cm^{-1}.

Huang Minlon reduction of XLI

The ester XLI (80 mg) was mixed with 50% KOH aq (1 ml), 80% $N_2H_4 \cdot H_2O$ (1·2 ml) and diethylene glycol (10 ml). The mixture was heated under reflux for 30 min. Then water and excess hydrazine was distilled off from the mixture and the bath temp was gradually raised to 200° and was kept at this temp for 2·5 hr. After cooling, the mixture was diluted with water and extracted with ether to remove neutral impurities. The aqueous layer was acidified with HCl and extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4) and evaporated to give an oil. This was chromatographed on silica gel (5 g). Elution with C_6H_6 (300 ml) gave 40 mg of acid vi, m.p. 172–174°; ν_{max} 1688; ($CHCl_3$) 1705, 1467, 1453 cm^{-1}. (Found: C, 77·92; H, 9·75. $C_{18}H_{28}O_2$ requires: C, 78·21; H, 10·21%).

Huang Minlon reduction of XLIII

The ester XLIII (116 mg) was mixed with 50% KOH aq (1 ml), 80% $N_2H_4 \cdot H_2O$ (1·2 ml) and diethylene glycol (10 ml). Subsequent treatments as described above and silica gel chromatography gave 70 mg of acid vi, m.p. 131–132°; ν_{max} 1700 cm^{-1}. (Found: C, 77·73; H, 9·90. $C_{18}H_{28}O_2$ requires: C, 78·21; H, 10·21%).

Huang Minlon reduction of VI

The optically active ester VI (200 mg) was mixed with 50% KOH aq (2 ml), 80% $N_2H_4 \cdot H_2O$ (2·4 ml) and diethylene glycol (20 ml). Subsequent treatments as described for XLI and silica gel chromatography gave 100 mg of acid vi, m.p. 128–131°; ν_{max} 1694; ($CHCl_3$) 1705, 1458 cm^{-1}. (Found: C, 78·43; H, 10·37. $C_{18}H_{28}O_2$ requires: C, 78·21; H, 10·21%).

The IR spectrum of the acid derived from XLI was different from that of the acid from XLIII. The IR spectrum ($CHCl_3$) of the acid derived from XLI differed from that of the acid from VI.

Direct bromination of VI

The dioxo ester VI (103 mg) dissolved in THF (3 ml) was mixed with $C_5H_5N \cdot HBr \cdot Br_2$ (111 mg). The mixture was shaken at room temp for 10 min, poured into $NaHCO_3$ aq and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 111 mg (90%) of an oil, ν_{max} 1740 (broad), 1270, 1200, 1170 cm^{-1}; δ 1·02 (s), 1·06 (s); 1·68 (s), 1·75 (s); 3·72 (s), 3·74 (s) ppm. The duplicity of the major NMR signals suggests that this is a mixture of two possible epimers of XLIV.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-3-*formyl*-4aβ,4bβ,7α,10aβ-*gibbane*-10β-*carboxylate* (XLV)

The ester VI (2·0 g) in dry THF (10 ml) was added to a stirred suspension of powdered NaOMe (2·0 g) in dry C_6H_6 (40 ml). To the ice-cooled mixture HCO_2Me (7 ml) was added and the stirring was continued overnight at room temp under N_2. Within 30 min the mixture became gelatinous. It was poured into ice-water and the aqueous layer was separated. The organic layer was diluted with ether and extracted with 5% NaOH aq (15 ml × 3). The combined aqueous soln was acidified with dil HCl at 0–5° and rapidly extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give a gum. This was triturated with ether–pet. ether to give 1·5 g (69%) of crystalline XLV. Recrystallization from ether–pet. ether gave prisms, m.p. 129–130°; ν_{max} 1740, 1732, 1664, 1604, 1150 cm^{-1}; δ 1·06 (3H, s), 1·17 (3H, d, J = 5 Hz), 3·70 (3H, s), 7·21 (1H), 10·38 (1H, broad) ppm. (Found: C, 69·70; H, 7·62. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%).

Methyl 1,7-*dimethyl*-2,8-*dioxo*-3-*bromo*-4aβ,4bβ,7α,10aβ-*gibbane*-10β-*carboxylate* (XLVII)

The formyl ketone XLV (500 mg) was dissolved in 0·05N NaOH aq (44 ml) with stirring under N_2 at 0–5°. To this soln Br_2 (230 mg) in 10% KBr aq (5 ml) was added dropwise at 0–5°. A bromo formyl ketone XLVI immediately separated from the soln as white foams. To this suspension 0·05N NaOH aq (12·6 ml) and THF (80 ml) were added. The homogeneous clear soln was kept at 0–5° for 3 hr and then left to stand overnight at room temp. After removal of THF, the residue was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give ca. 500 mg of gummy XLVII, ν_{max} 1730 (broad), 1180, 1150 cm^{-1}. This was employed for the next step without further purification.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-4bβ,7α,10aβ-*gibb*-4 (4a)-*ene*-10β-*carboxylate* (XLIX).

(i) The ketone XLVII (500 mg) in dry DMF (15 ml) was mixed with LiBr (500 mg) and Li_2CO_3 (750 mg). The mixture was heated at 120–125° under N_2 for 75 min. After cooling, it was diluted with dil HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was dissolved in $CHCl_3$ and concentrated again to give a gum (300 mg) freed from EtOAc; ν_{max} 1730 (broad), 1670, 1650 (sh) cm^{-1}. δ 1·02, 1·05, (MeC—), 2·02 (MeC=C), 3·70, 3·73, 3·76 (CO_2Me) 6·1, 7·1 (CH=CH) ppm. The NMR spectrum indicated that this is a mixture of more than three compounds including XLVIII and its $\Delta^{1(10a)}$-isomer.

(ii) This gum in dil HCl (1:4, 20 ml) was heated under reflux for 2 hr under N_2. After cooling, the mixture was extracted with ether. The residue remaining after evaporation of ether was dissolved in EtOAc. The soln was extracted with $NaHCO_3$ aq. The aqueous layer was acidified with dil HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 160 mg of gum [δ 5·42, 6·10 (weak), 7·10 (weak)]. This was treated with ethereal CH_2N_2 and the resulting oil was chromatographed on alumina (12 × 1·5 cm) in pet. ether to give the following fractions (30 ml each). The eluant used were : (i) ether: pet. ether 1:4, No. 1-10; (ii) ether–pet. ether 1:1, No. 11–13; (iii) EtOAc, No. 14. No. 1–6: gum (37 mg). No. 7, 8: crystalline XLIX (50 mg). No. 9–14: gum (53 mg). Total: 139 mg. Crude XLIX was recrystallized from ether–pet. ether to give 30 mg (7%) of plates, m.p. 121–122°; ν_{max} 1744, 1732, 1724 cm^{-1}; δ 1·08 (3H, s), 1·12 (3H, d, J = 5 Hz), 3·73 (3H, s), 5·44 (1H, broad) ppm. This was identified with an authentic sample by IR, NMR and mixed m.p. (121°).

Methyl 1,7-*dimethyl*-2,8-*dioxo*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (L)

The gibb-4(4a)-ene XLIX (311 mg) dissolved in 95% EtOH (35 ml) was shaken under H_2 over 10% Pd–C (400 mg) at room temp for 4 hr. The catalyst and the solvent were removed *in vacuo* and the residue in acetone (20 ml) was treated with the Jones reagent (0·2 ml) for 3 min at room temp. MeOH was added to the reaction mixture which was then concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Fractional crystallization of the residue from EtOAc–pet. ether gave 36 mg (12%) of L as the first (21 mg) and the second (15 mg) crops. This was identified with an authentic sample of L by IR, NMR and mixed m.p. L crystallized from EtOAc–pet. ether as prisms, m.p. 166–167°; ν_{max} 1742, 1714, cm^{-1}; δ 0·98 (3H, s), 1·06 (3H, d, J = 5 Hz), 3·80 (3H, s) ppm. The third (95 mg) and the fourth (23 mg) crops were the mixture of VI, XLIX and L. As the mother liquor 133 mg of oil was obtained.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-3-*formyl*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (LI)

The ketone L (1 g) in dry C_6H_6 (35 ml) was mixed with HCO_2Me (5 ml) and NaOMe (1 g). The mixture was stirred under N_2 at room temp for 30 min. The solidified mixture was left to stand overnight at room temp. It was then poured into ice–water and the aqueous layer was separated. The organic layer was diluted with ether and extracted with 5% NaOH aq (20 ml × 2). The combined aqueous soln was acidified with dil HCl at 0–5° and rapidly extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1g (92%) of gummy LI, ν_{max} 1740, 1680, 1640, 1580, 1220, 1168 cm^{-1}; δ 1·06 (3H, s), 1·12 (3H, d, J = 5 Hz), 1·62, 3·10, 3·74 (3H, s), 8·45 (1H, broad s) ppm. This resisted crystallization and was used for the next step without further purification.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-3-*bromo*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (LII)

The ketone LI (800 mg) was dissolved in 0·05N NaOH (88 ml) with stirring under N_2 at 0–5°. To this soln Br_2 (370 mg) in 10% KBr aq (8 ml) was added dropwise under ice-cooling. A bromo formyl ketone LII immediately separated from the soln as white foams. To this suspension 0·05N NaOH (20 ml) and THF (90 ml) were added. The homogeneous clear soln was kept at 2–5° for 1 hr and then left to stand overnight at room temp. After removal of THF, the residue was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give ca 500 mg of crude LIII, ν_{max} 1730–1710 (broad), 1220, 1162 cm^{-1}, δ 1·06 (3H, s), 1·08 (3H, d), 1·25, 3·74 (3H, s), 5·70 (1H, q) ppm.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-7α,10aβ-*gibba*-3,4a(4b)-*diene*-10β-*carboxylate* (VII)

The ketone LIII (500 mg) in dry DMF (15 ml) was mixed with LiBr (500 mg) and Li_2CO_3 (750 mg). The mixture was heated at 120–125° under N_2 for 75 min. After cooling, it was diluted with dil HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a gum. This was heated under reflux with dil HCl (1:4, 20 ml) for 2 hr under N_2. After cooling, the

mixture was extracted with EtOAc. The soln was extracted with $NaHCO_3$aq. The aqueous layer was acidified with dil HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. This was treated with ethereal CH_2N_2 and the soln was concentrated to afford 150 mg of gum which was chromatographed on Al_2O_3 (7·2 × 1·5 cm) in pet. ether. Elution with ether–pet. ether (1:4) gave the following fractions (10 ml each). No. 1–9: none. No. 10, 11: crystalline VII (12 mg). No. 12, 13: semi-solid (crude VII, 35 mg). No. 14–19: gum (50 mg). Total: 97 mg.

Recrystallization of the crude VII from ether–pet. ether gave 25 mg (3·4% from LI) of pure dienone VII as needles, m.p. 105–106°; mixed m.p. 105–106°; ν_{max} 1736, 1672, 1660, 1574 cm^{-1}; δ 1·08 (3H, s), 1·10 (3H, d, J = 5 Hz), 3·80 (3H, s), 6·04 (1H, d, J = 10 Hz), 7·27 (1H, d, J = 10 Hz) ppm. The IR and NMR spectra was identical with that of an authentic VII.

Bis-ethyleneketal of methyl 1,7-*dimethyl*-2,8-*dioxo*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (LIV)

(a) *From* L. To a soln of L (53 mg) in dichloroethane (100 ml), ethylene glycol (3 ml) and *p*-TsOH (10 mg) were added and the mixture was stirred and heated under reflux for 2·5 hr. During that period anhyd dichloroethane (100 ml) was gradually added while an equal amount of the water-containing solvent was distilled off from it. After cooling, the soln was washed with K_2CO_3aq, dried (K_2CO_3) and concentrated *in vacuo* to give LIV (55 mg) which recrystallized from pet. ether as plates, m.p. 145–146°; ν_{max} 1738, 1706 (w), 1690 (w), 1155, 1086, 1078, 1055, 1034, 1005, 983, 937 cm^{-1}; δ 0·80 (3H, d, J = 6 Hz), 0·90 (3H, s), 1·26, 1·43, 2·11, 2·25, 2·40, 2·46, 3·68 (3H, s), 3·83–3·94 (8H, m) ppm. (Found: C, 67·79; H, 7·72. $C_{23}H_{32}O_6$ requires: C, 68·29; H, 7·97%).

(b) *From* XLIX. To a soln of XLIX (222 mg) in dichloroethane (300 ml), ethylene glycol (20 ml) and *p*-TsOH (250 mg) were added. The solvent was gradually distilled off with continuous addition of anhyd dichloroethane (300 ml) during 6 hr until the removed solvent amounted to 550 ml. After cooling, the soln was washed with K_2CO_3aq, dried (K_2CO_3) and concentrated *in vacuo* to give an oil. This was chromatographed on alumina (5 × 1·2 cm) in pet. ether. Elution with ether–pet. ether (2:3) gave the following fractions. No. 1,2: crystalline LIV (50 mg). No. 3–6: gum (200 mg). The obtained crystalline product was identified with an authentic sample of LIV by IR, NMR and mixed m.p. Unfortunately, this experiment was not reproducible.

Deketalization of the bis-ketal LIV

The bis-ketal LIV (50 mg) in dioxan (10 ml) was mixed with dil HCl (1:4, 10 ml) and the mixture was heated for 30 min on a boiling water bath. The solvent was removed *in vacuo* and the residue was extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 33 mg (86%) of the diketone L. This was identified with an authentic sample by IR spectrum.

The bis-ketal LV

To a soln of XLIX (580 mg) in dichloroethane (300 ml), ethylene glycol (30 ml) and *p*-TsOH (500 mg) were added. The solvent was gradually distilled off during 2 hr and the residue was heated at 130° (bath temp) for 15 min. After cooling, K_2CO_3aq was added to the residue and the mixture was extracted with EtOAc. The extract was dried (K_2CO_3) and concentrated *in vacuo* to give 620 mg of an oil. This was chromatographed on alumina (12·5 × 1·8 cm) in n-hexane. The column was eluted with ether–n-hexane (1:3) to give the following fractions (50 ml each). No. 1: oil (2 mg). No. 2: oil (96 mg). No. 3: oil (127 mg). No. 4: oil (95 mg). No. 5: oil (86 mg). No. 6: oil (63 mg), No. 7: oil (70 mg), No. 8–12: oil (47 mg). No. 13 (elution with ether): oil (20 mg). The IR spectrum of each fraction was essentially same. Total yield of the oily bis-ketal LV was 606 mg; ν_{max} 1730, 1240, 1170, 1110, 1080, 1045 cm^{-1}; δ 0·88 (3H, d, J = 5 Hz), 0·90 (3H, s), 3·66 (3H, s), 3·80–3·95 (8H, m), 5·20 (1H) ppm. This oil, upon deketalization, gave back XLIX quantitatively.

Action of methanolic hydrogen chloride upon XLIX

A soln of XLIX (206 mg) in MeOH (30 ml) was saturated with dry HCl gas and left to stand overnight at room temp. After removal of the solvent *in vacuo*, the residue was dissolved in EtOAc. The EtOAc soln was washed with water, $NaHCO_3$aq and brine. Concentration of the soln after drying ($MgSO_4$) gave 200 mg (97%) of a crystalline compound. Recrystallization from EtOAc–pet. ether gave needles, m.p. 195–197°. ν_{max} 1738, 1724, 1712, 1700, 1186, 1166, 1148, 1130, 1072; ($CHCl_3$) 1742 (sh), 1734, 1716, 1188, 1163 cm^{-1}; δ 0·95 (3H, d, J = 6 Hz), 1·04 (3H, s), 1·2–2·15 (8H), 2·15–3·05 (7H), 3·68 (3H, s) ppm. No

olefinic proton was detected. No UV maximum was observed. Beilstein halogen test was negative. (Found: C, 72·13; H, 7·65. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%). MW (mass spectrometry) 316.

Action of p-*toluenesulphonic acid* (p-TsOH) *upon* XLIX

A soln of XLIX (300 mg) in C_6H_6 (100 ml) containing *p*-TsOH (100 mg) was heated under reflux for 3 hr. After cooling, the soln was washed with $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give back the starting XLIX in quantitative yield. Identity was proved by IR measurements.

Ketalization of XLIX *under drastic condition*

To a soln of XLIX (220 mg) in dichloroethane (300 ml), ethylene glycol (20 ml) and *p*-TsOH (250 mg) were added. The solvent was gradually distilled off while continuously adding anhyd dichloroethane (300 ml). Then the bath temp was raised to 140° and kept at that temp for 30 min. After cooling K_2CO_3aq was added to the residue and the mixture was extracted with EtOAc. The extract was dried (K_2CO_3) and concentrated *in vacuo* to give an oil. This was chromatographed on alumina (5 × 1 cm). Elution with ether–pet. ether (1:3) gave two oily bis-ketals. Crystalline LIV could not be obtained. The more easily eluted bis-ketal was deketalized with dioxan-dil HCl to give a highly crystalline unidentified compound; ν_{max} 1725, 1703 cm^{-1}; δ (DMSO-d_6) 0·80 (3H, d, J = 6 Hz), 0·93 (3H, s), 3·60 (3H, s) ppm. No olefinic proton signal was observed. Since this was different from L, no further characterization was attempted. The less easily eluted bis-ketal was also deketalized to give a crystalline compound, m.p. 195–197°; ν_{max} 1740, 1725, 1713 (sh), 1700 cm^{-1}. The IR spectrum was identical with that of the unidentified compound obtained by the action of MeOH–HCl upon XLIX.

Attempted double bond migration of XLIX *under* N_2

The gibb-4(4a)-ene XLIX (300 mg) in 95% EtOH (35 ml) was stirred under N_2 with 10% Pd–C (150 mg) for 16 hr. Removal of the catalyst and the solvent gave back the unchanged XLIX in quantitative yield.

Action of sodium methoxide upon XLIX

The ester XLIX (247 mg) in MeOH (30 ml) containing NaOMe (100 mg) was left to stand at room temp for 4 hr. After neutralization with AcOH the mixture was concentrated *in vacuo*, diluted with water and extracted with EtOAc. The extract was washed with $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (230 mg). TLC analysis of this oil revealed the disappearance of the most of the starting material. TLC solvent system: n-hexane–ether–MeOH 10:10:1. R_f of XLIX 0·46; R_f of the products: 0·46 (trace), 0·31 (small amount), 0·18–0·13 (large amount). The oil showed the following spectral properties: ν_{max} ~3300, 1720 (broad), 1160 cm^{-1}; δ 1·04, 1·06, 1·10, 3·65, 3·68, 5·40 ppm. The NMR spectrum suggested the presence of a small amount of the starting material XLIX (a weak signal at δ 5·40). absence of any other olefinic proton denied the possible existence of an α,β-unsaturated ketone XLVIII.

Methyl 1,7-*dimethyl*-2-*oxo*-8-*ethylenedioxy*-7α-*gibba*-3,4a(4b)-*diene*-10β-*carboxylate* (LVI)

To a soln of VII (4·9 g) in 1,2-dichloroethane (200 ml), ethylene glycol (15 ml) and *p*-TsOH (0·6 g) were added and the mixture was stirred and heated. During 1·5 hr the water-containing solvent (1 l) was distilled off from the mixture with continuous addition of the anhyd solvent (1 l). After cooling, the mixture was washed with K_2CO_3aq, dried (K_2CO_3) and concentrated *in vacuo* to give 3·15 g (56%) of crystalline LVI. The mother-liquor was deketalized with hot dioxan–dil HCl and the product was ketalized again to give an additional amount of LVI. Repetition of this procedure raised the yield, for one instance, to 89% (11·15 g of LVI form 11·0 g of VII). Recrystallization from EtOAc–pet. ether gave needles, m.p. 180–181°; ν_{max} 1730, 1650, 1572 cm^{-1}; λ_{max} 308 mμ (ε 17,200); δ (60 Mc) 0·92 (3H, s), 1·03 (3H, d, J = 6 Hz), 3·78 (3H, s), 3·93 (4H, d, J = 2 Hz), 6·02 (1H, d, J = 10 Hz), 7·24 (1H, d, J = 10 Hz) ppm. (Found: C, 70·70; H, 7·20. $C_{21}H_{26}O_5$ requires: C, 70·37; H, 7·31%).

Carbomethoxylation at C-1 *of* LVI [*methyl* 1,7-*dimethyl*-2,8-*dioxo*-7α-*gibba*-3,4a(4b)-*diene*-1α,10β-*dicarboxylate* (LVIII)]

To a stirred (magnetic stirrer) soln of LVI (4·0 g) in dry THF (60 ml) under N_2, an ethereal soln of $(C_6H_5)_3CNa$ (ca. 0·13 mole/l; 105 ml) was added under ice-cooling during 30 min until the soln became faintly reddish. Then CO_2 (dried with conc H_2SO_4 and $CaCl_2$) was bubbled through the stirred soln for

1·5 hr. This mixture was poured into ice-dil HCl [conc HCl (10 ml) and ice-water (300 ml)] and immediately extracted with ether. The soln was combined with ethereal CH_2N_2, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (4·1 g). This was chromatographed on alumina (90 g) with the following eluants (500 ml fractions). No. 1–6: C_6H_6–n-hexane 1:3. No. 7–12: C_6H_6–n-hexane 1:1. No. 13–18: C_6H_6–n-hexane 2:1. No. 19: C_6H_6. No. 20: EtOAc. Total amount of the eluted oil was 3·37 g. Similar fractions (judged by IR comparison) were combined to give four products, A, B, C and D. Each products were deketalized and chromatographed.

Fraction A: No. 3, 4 (0·27 g). This was mixed with dioxan (15 ml) and dil HCl (1:4, 10 ml) and heated on a boiling water bath for 10 min. After removal of the solvent *in vacuo*, the product was extracted with EtOAc. The extract was washed with water, $NaHCO_3$ aq and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residual gum was chromatographed on silica gel (7 g). Elution with EtOAc–C_6H_6 (1:9) gave the following fractions (100 ml each). No. 1: crystalline $(C_6H_5)_3CCO_2Me$. No. 2–4: oil. No. 5, 6: crystalline VII (180 mg), identified by IR comparison. No. 7–9: oil.

Fraction B: No. 5–8 (1·36 g). This was mixed with dioxan (50 ml) and dil HCl (1:4, 50 ml). The mixture was heated on a boiling water bath for 20 min. Subsequent work-up gave an oil. This was chromatographed on silica gel (30 g) to give the following fractions (200 ml each). No. 1 (C_6H_6): $(C_6H_5)_3CCO_2Me$. No. 2, 3 (C_6H_6): oil (810 mg). No. 4 (C_6H_6–EtOAc 9:1): crystalline VII (80 mg). No. 5–7 (C_6H_6–EtOAc 9:1): oil (130 mg).

Fraction C: No. 9–13 (1·06 g). Deketalization of this oil was carried out as described for Fraction B and the obtained oil was chromatographed on silica gel (20 g) to give the following fractons (200 ml each). No. 1 (C_6H_6): $(C_6H_5)_3COH$ No. 2–4 (C_6H_6): oil (320 mg). No. 5–8 (C_6H_6–EtOAc 19:1)–crystalline diester LVIII (540 mg, 11·4% yield from VII). Recrstyallization from ether–pet. ether gave plates, m.p. 107–107·5°; mixed m.p. 107° ν_{max} 1738, 1698, 1602, 1560 cm^{-1}; λ_{max} 308 mμ (ε 14,800); δ 1·08 (3H, s), 1·35 (3H, s), 3·56 (3H, s), 3·75 (3H, s), 6·02 (1H, d, J = 10 Hz), 7·23 (1H, d, J = 10 Hz) ppm. The spectral data were identical with those of an authentic sample. No. 9–12 (C_6H_6–EtOAc 19:1): oil.

Fraction D: No. 14–16 (0·72 g). This was mixed with dioxan (40 ml) and dil HCl (1:4, 30 ml). The mixture was heated on a boiling water bath for 20 min. Subsequent workup gave an oil which was chromatographed on silica gel (15 g) to give the following fractions (150 ml each). No. 1 (C_6H_6): $(C_6H_5)_3COH$; No. 2, 3 (C_6H_6): oil; No. 4–6 (C_6H_6–EtOAc, 19:1): oil; No. 7–10 (C_6H_6–EtOAc, 9:1): oil.

TABLE 1. GAS CHROMATOGRAPHIC ANALYSIS OF VII AND LVIII

Compound	Retention times (min)[a]		
	1·5% SE-30[b]	2·0%QF-1[b]	2·0% CNSi[b]
VII	3·9	10·4	18·4
LVIII	5·8	16·2	29·5

[a] All retention times were determined on a Shimadzu Model GC-1B, hydrogen flame detector, stainless steel column, 150 cm × 4 mm i.d.

[b] Column temp: 220°. Carrier gas: N_2, 90 ml/min.

Ketalization of LVIII [*methyl* 1,7-*dimethyl*-2-*oxo*-8-*ethylenedioxy*-7α-*gibba*-3,4a(4b)-*diene*-1α,10β-*dicarboxylate* (LVII)]

To a soln of LVIII (380 mg) in dichloroethane (40 ml), ethylene glycol (4 ml) and *p*-TsOH (200 mg) were added. The mixture was stirred and heated for 1·25 hr. During this period the water containing solvent was distilled off from the mixture with concomitant addition of anhyd dichloroethane. After cooling, the soln was washed with K_2CO_3 aq, dried (K_2CO_3), and concentrated *in vacuo* to give 380 mg (90%) of gum, ν_{max} 1738 (sh), 1730, 1680, 1660, 1574 cm^{-1}. Evaporative distillation of the ketal at 200–210°/0·15 mm caused decomposition and satisfactory analytical data could not be obtained. (Found: C, 67·32; H, 6·94. $C_{23}H_{28}O_7$ requires: C, 66·33; H, 6·78%).

Reduction of LVII [*methyl* 1,7-*dimethyl*-2α-*hydroxy*-8-*ethylenedioxy*-7α-*gibba*-3,4a(4b)-*diene*-1α,10β-*dicarboxylate* (LIX)]

A soln of LVII (600 mg) in dioxan (15 ml) was mixed with a soln of $NaBH_4$ (200 mg) in MeOH (2 ml). After 17 hr at room temp the mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give LIX as an oil (600 mg), ν_{max} 3480, 1730, 1670 (sh) cm^{-1}. This was employed for the next step without further purification.

Hydrogenation of LIX [*methyl* 1,7-*dimethyl*-2α-*hydroxy*-8-*ethylenedioxy*-7α-*gibb*-4a(4b)-*ene*-1α,10β-*dicarboxylate* (LX)]

The dienol LIX (550 mg) in EtOAc (50 ml) was hydrogenated over 10% Pd–C (200 mg) under atmospheric press for 2 hr at room temp. The catalyst and the solvent were removed to give 500 mg (90%) of LX as foams, ν_{max} 3500, 1725 cm^{-1}. (Found: C, 65·38; H, 8·21. $C_{23}H_{32}O_7$ requires: C, 65·69; H, 7·67%). The corresponding acetate was also an oil.

Relactonization and deketalization of LX [2 (eq)-*hydroxy-epimer of gibberellin* C *methyl ester* (LXV)]

To a soln of LX (100 mg) in MeOH (2 ml), dil H_2SO_4 (3 ml conc H_2SO_4 in 10 ml water) was added and the mixture was heated under reflux for 4 hr. After cooling, it was extracted with EtOAc. Ethereal CH_2N_2 was added to the EtOAc soln. The excess CH_2N_2 was destroyed with AcOH. The soln was washed with water, $NaHCO_3$ aq and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was chromatographed on alumina (8·5 × 1·4 cm). Elution with C_6H_6–MeOH (150:1) afforded the following fractions (30 ml each). No. 1, 2: none. No. 3, 4: oil (40 mg), ν_{max} 3520, 1734, 1720 cm^{-1}; δ 1·04 (3H, s), 1·30 (3H, s), 3·10 (1H), 3·64 (3H, s), 3·72 (3H, s) ppm. This oil showed an identical IR spectrum with that of LXII and was characterized as its crystalline acetate LXIII. The oil LXII (38 mg) in pyridine (5 ml) was mixed with Ac_2O (5 ml). After 14 hr the mixture was concentrated *in vacuo*. The residual gum was chromatographed on alumina (6·5 × 1 cm). Elution with C_6H_6–ether (1:1, 50 ml) gave 10 mg of crystalline LXIII. Recrystallization from ether–pet. ether gave prisms, m.p. 136–138°; mixed m.p. 137°; ν_{max} 1738, 1718 cm^{-1}. The IR spectrum was identical with that of an authentic sample. No. 5–8: crystalline γ-lactone (LXV, 19 mg). Recrystallization from EtOAc–pet. ether gave needles, m.p. 220–225°; mixed m.p. 222–225°; ν_{max} 3560, 1757, 1730 cm^{-1}. The IR spectrum was completely identical with that of an authentic sample. δ 1·04 (3H, s), 1·25 (3H, s), 3·71 (3H, s) ppm.

Chromatographic purification of gibberellin A_4 *methyl ester* (LXVIII)

A crystalline mixture (5·0 g) of the methyl esters LXVIII, LXVIII (Δ^3) and *viii* in EtOAc (50 ml) was chromatographed on alumina (250 g) in C_6H_6. Elution with C_6H_6–EtOAc (4:1) gave the following fractions (300 ml each). No. 1–3: none. No. 4–8: gibberellin A_4 methyl ester (LXVIII, 1·56 g). Recrystallization from EtOAc–pet. ether gave needles, m.p. 173–175° (lit.[63] 178–180°; ν_{max} 3400, 1765, 1705, 1650, 1280, 1200, 1015, 990, 920, 870 cm^{-1}; δ 1·13 (3H, s), 3·66 (3H, s), 4·84, 4·96 (2H, $=CH_2$) ppm. (Found: C, 69·70; H, 7·39. Calcd. for $C_{20}H_{26}O_5$: C, 69·34; H, 7·57%). No. 9: a crystalline mixture of methyl esters of GA_4 and GA_7 (0·29 g). No. 10–30: a crystalline mixture of GA_7 methyl ester (LXVIII, Δ^3) and its isomer *viii* (2·68 g). Recrystallization of this mixture from EtOAc gave pure viii as prisms, m.p. 226–227° (lit.[63] m.p. 226–228°); ν_{max} 3400, 1760, 1700, 1660, 1650, 1300, 1280, 1250, 1110, 1100, 1070, 1060, 1020, 960, 880 cm^{-1}; δ 1·20 (3H, s). 2·52 (1H, d, J = 5 Hz C-10H), 3·27 (1H, q, C-10aH), 3·72 (3H, s), 4·72 (1H, t, C-3H), 4·90 (2H, $=CH_2$), 5·78 (1H, broad) ppm. (Found: C, 69·62; H, 6·97. Calcd. for $C_{20}H_{24}O_5$: C, 69·75; H, 7·02%). No. 31–33 (EtOAc elution): crystalline *viii* (0·39 g). The total yield of *viii* was 1·59 g. The fraction No. 8 and the mother liquor rich in GA_7 methyl ester were combined (1·7 g), dissolved in EtOAc (150 ml) containing pyridine (3 ml) and hydrogenated over 10% Pd–$BaCO_3$ (0·6 g) at room temp for 10 hr. The neutral fraction (0·8 g) was chromatographed on alumina (100 g) as described above to give LXVIII (0·55 g) and *viii* (0·2 g).

Alkaline hydrolysis of gibberellin A_4 *methyl ester* (LXVIII)

Finely powdered LXVIII (190 mg) was suspended in 0·1N NaOH (100 ml) and heated under reflux for 40 min. After cooling, the clear soln was acidified with conc HCl (1·5 ml) and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 185 mg of gum. This in acetone (4 ml) was mixed with Celite (1 g) and put on the top of a column of Celite (15 g) buffered with 2M-phosphate buffer (pH 6·2; 15 ml) and made up in $CHCl_3$–pet. ether (1:4). Elution of the column with 250-ml portions of solvents gave the following products on recovery. No. 1 ($CHCl_3$–pet. ether, 1:4): a

mixture of LXVIII and LXIX (69 mg). No. 2–5 ($CHCl_3$–pet. ether, 1:3): trace amount of gum. No. 6–12 ($CHCl_3$–pet. ether, 1:3): semi-solid (45 mg). No. 13 ($CHCl_3$–pet. ether, 1:3): gum (8 mg). No. 14–19 ($CHCl_3$–pet. ether, 1:1) and No. 20 ($CHCl_3$): crystalline solid (51 mg). Fractions No. 6–12 crystallized from EtOAc–pet. ether as rhombs, m.p. 213–216° (lit.[63] 217–225°); ν_{max} 3400, ~3000, 1730, 1710, 1655, 1190, 1050, 1010, 990, 910, 860 cm^{-1}. The IR spectrum was completely identical with that of gibberellin A_4 (IX). (Found: C, 68·52; H, 7·49. Calcd. for $C_{19}H_{24}O_5$: C, 68·25; H, 7·28%). TLC (solvent system[66]: C_6H_6–n-BuOH–AcOH, 80:15:5): R_f 0·40. This value was same as that of an authentic sample.

Fractions No. 14–19 crystallized from EtOAc–pet. ether as prisms, m.p. 220–223°. (lit.[63] 215–220°); ν_{max} ~3400, ~3000, 1730, 1710, 1650, 1175, 1150, 1080, 935, 865 cm^{-1}. This was 2 (eq)-hydroxy-epimer of gibberellin A_4 (LXX). (Found: C, 68·70; H, 7·53. Calcd. for $C_{19}H_{24}O_5$: C, 68·25; H, 7·28%).

Fraction No. 1 was re-chromatographed on alumina (16 × 1 cm). Elution with 50-ml portions of C_6H_6–MeOH (200:1) gave the following products on recovery. No. 1: gum. No. 2: GA_4 methyl ester (LXVIII, 4 mg). No. 3–6: 2 (eq)-hydroxy-epimer of GA_4 methyl ester (LXIX, 56 mg). This was recrystallized from EtOAc–pet. ether to give prisms, m.p. 144–146°; ν_{max} ~3440, 1760, 1705, 1650, 1200, 1180, 1170, 1130, 1100, 1080, 1060, 1020, 990, 870 cm^{-1}; δ 1·25 (3H, s), 3·70 (3H, s) 4·85 (1H, d) 4·97 (1H, d) ppm. (Found: C, 69·29; H, 7·87. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%).

Oxidation of methyl gibberellate with manganese dioxide. [*methyl 1-carboxy-4a,7-dihydroxy-1-methyl-8-methylene-2-oxo-gibb-3-en-10-carboxylate* 1 → 4a,*lactone* (LXXI)]

The yield of the oxo lactone was remarkably increased by raising the reaction temp. Methyl gibberellate (30 g) in $CHCl_3$ (2·2 l) was stirred and heated under reflux for 20 hr (or at 30° for 116 hr) in the presence of active MnO_2 (215 g). The mixture was filtered and the dioxide washed with $CHCl_3$. The filtrate and washings were concentrated *in vacuo* to give crystalline LXXI (27·7 g, 93%). Recrystallization from EtOAc–pet. ether gave plates, m.p. 182–184° (lit.[5] 186–187); ν_{max} 3540, 1770, 1725, 1672, 1650 cm^{-1}.

Methyl 1,7-dimethyl-2,8-dioxo-7α-gibba-3,4a(4b)-diene-10β-carboxylate (VII)

Finely powdered LXXI (11·3 g) suspended in dil HCl (1:5, 600 ml) was heated under reflux for 2·5 hr under N_2. After cooling, the mixture was extracted with EtOAc. The extract was washed with H_2O, dried (Na_2SO_4) and concentrated. To the residue, ethereal CH_2N_2 was added and the soln was concentrated *in vacuo*. The residual oil was chromatographed on alumina (16 × 3·5 cm) in benzene. Elution with C_6H_6–ether (1:1, 600 ml) gave 4·55 g of VII. Elution with ether (300 ml) afforded an additional amount (0·25 g) of VII increasing the total amount to 4·8 g (48%). Recrystallization from EtOAc–pet. ether gave needles, m.p. 107–108°; ν_{max} 1736, 1672, 1660, 1574 cm^{-1}; λ_{max} 302 mμ (ε 16,100); δ (60 MHz) 1·08 (3H, d, J = 6·5 Hz), 1·08 (3H, s), 3·80 (3H, s), 5·98 (1H, d, J = 10 Hz), 7·20 (1H, d, J = 10 Hz) ppm. (Found: C, 72·53; H, 7·01. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%).

Methyl bromogibberellate (LXXIII)

To a soln of methyl gibberellate (27·0 g) in THF (450 ml), $C_5H_5N \cdot HBr \cdot Br_2$ (22·8 g) was added portionwise with stirring and cooling at −15 ~ −10°. The stirring was continued for 1 hr at −10 ~ −5°. At the end of this period the red colour of bromine disappeared. The mixture was poured into $NaHCO_3$ aq and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual semi-solid was triturated with ether and filtered. The collected crystals were washed with a small amount of MeOH. The product (LXXIII, 23·3 g, 71%) was pure enough for the next step, m.p. 240–242° (lit.[67] 214–216°); ν_{max} 3560, 1760, 1740, 1732, 1170, 1045 cm^{-1}. (Found: C, 54·82; H, 5·58. Calcd. for $C_{20}H_{23}O_6Br$: C, 54·65; H, 5·24%).

Hydrogenation of LXXIII *over* PtO_2

The bromo lactone LXXIII (3·278 g) in THF–MeOH (2:1, 150 ml) was hydrogenated over Adams PtO_2 (70 mg) at 80° and an initial press of 80 kg/cm^2 for 2 hr. Removal of the catalyst and the solvents gave semi-solid. After trituration with EtOAc, crystalline LXXV was collected on a filter. The filtrate was separated into neutral and acid fractions in usual manner. The neutral fraction gave an additional amount of LXXV increasing the total amount to 1·784 g (54·1%). Recrystallization from EtOAc gave prisms, m.p. 285–286° (lit.[67] 264–266°); ν_{max} 3500, 1755, 1745, 1732, 1160, 1104, 1010, 930 cm^{-1}. (Found: C, 54·38; H, 5·73. Calcd. for $C_{20}H_{25}O_6Br$: C, 54·43; H, 5·71%). The acid fraction gave 740 mg (22·4%) of LXXIV by trituration with ether. Recrystallization from EtOAc gave prisms, m.p. 201–202°; ν_{max} 3560, 3200, 1745, 1730, 1265, 1232, 1195, 1160, 1074, 998, 908 cm^{-1}.

δ (as dimethyl ester at 60 MHz) 1·30 (3H, s), 3·15 (1H, s), 3·46 (1H, d, J = 5 Hz), 3·61 (3H, s), 3·76 (3H, s), 4·05 (1H, t), 5·14 (1H, broad) ppm. (Found: C, 54·85; H, 5·63. $C_{20}H_{25}O_6Br$ requires: C, 54·43; H, 5·71%).

Reductive debromination of LXXIV

To a soln of LXXIV (282 mg) in AcOH (15 ml) Zn dust (2 g) was added and the mixture was refluxed for 2·5 hr. The mixture was filtered and the solid was washed with EtOAc. The filtrate was concentrated *in vacuo*. After dilution with ether, Zn $(OAc)_2$ was filtered off. The filtrate was evaporated to give 182 mg (78·5%) of LXXVI. Recrystallization from EtOAc–pet. ether gave needles, m.p. 191–192°; ν_{max} 3380, 3200, 1745, 1730, 1697, 1195, 1160, 1132, 1070, 1035 cm^{-1}; δ 1·03 (3H, s), 1·34 (3H, s), 3·15 (1H), 3·72 (3H, s), 4·05 (1H, t), 5·15 (1H, broad) ppm. (Found: C, 65·60; H, 7·45. $C_{20}H_{26}O_6$ requires: C, 66·28; H, 7·23%). Sometimes an EtOAc–solvate, m.p. 188–189°, was obtained; ν_{max} 3380, 3100, 1740, 1734, 1724, 1240, 1155, 1124, 1028 cm^{-1}.

Reductive debromination of LXXV

The bromo lactone LXXV (302 mg) in AcOH (15 ml) was treated with Zn dust (2 g) as described above to give 180 mg (77%) of LXV. Recrystallization from EtOAc–pet. ether gave pure gibberellin C methyl ester LXV as needles, m.p. 225–226°; ν_{max} 3520, 1732 (broad), 1164, 1112, 1095, 1010, 996, 926 cm^{-1}. The IR spectrum was identical with that of an authentic sample.

Acid hydrolysis of LXV

The ester LXV (100 mg) in MeOH (4 ml) was heated under reflux with dil HCl (1:4, 20 ml) for 4 hr. The mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated to give 50 mg of VIII. Recrystallization from EtOAc with slow evaporation of the solvent gave prisms, m.p. 251–252°; ν_{max} 3520, 3470, 3325, 1756, 1718, 1700, 1640 cm^{-1}. The IR spectrum was identical with that of an authentic sample. This was used for the bioassay.

Hydrogenation of LXXIII *over* Pd–C

(a) *Under atmospheric press.* The bromo lactone LXXIII (850 mg) in THF–MeOH (2:1, 45 ml) containing pyridine (3 ml) was hydrogenated over 10% Pd–C (200 mg) under atmospheric press for 5·5 hr at room temp. The catalyst and the solvents were removed and the residue was separated into neutral and acid fractions in usual manner. The neutral fraction gave 100 mg of bromogibberellin C methyl ester. From the acid fraction 400 mg of the bromo acid LXXIV was obtained.

(b) *Under high press.* The bromo lactone LXXIII (7·0 g) suspended in THF–MeOH (2:1, 150 ml) containing pyridine (10 ml) was hydrogenated over 10% Pd–C (2 g) at 80° and an initial press of 80 kg/cm^2 for 1 hr. The catalyst and the solvents were removed and the residue was dissolved in EtOAc. The soln was extracted three times with $NaHCO_3$ aq. The EtOAc soln was washed with dil HCl and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2·7 g (14·0%) of gibberellin C methyl ester LXV, identified by IR spectrum. The $NaHCO_3$ aq was acidified with dil HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 14·3 g (73·2%) of LXXVI. The mother liquor was chromatographed on silica gel to give 1·6 g of LXXVI by elution with C_6H_6–EtOAc (1:1). The total yield of LXXVI was 15·9 g (82·0%). The identity was proved by its IR spectrum.

Hydrogenation of LXXVI *over* PtO_2 [*methyl* 1α-*carboxy*-2β-*hydroxy*-1,7-*dimethyl*-8-*oxo*-4aβ,4bβ,10aβ-*gibbane*-10β-*carboxylate* (LXXVII)]

The unsaturated acid LXXVI (5·0 g) in AcOH (150 ml) was hydrogenated over Adams PtO_2 (300 mg) under atmospheric press for 3·5 hr at room temp. The catalyst and the solvent was removed and the residual gum was chromatographed on silica gel (90 g) in benzene. Elution of the column with 300-ml portions of solvents gave the following products on recovery. No. 1 (C_6H_6): none. No. 2,3 (C_6H_6–EtOAc, 3:2): none. No. 4–9 (C_6H_6–EtOAc, 3:2): crystalline acid LXXVII (2·80 g). No. 10–12 (C_6H_6–EtOAc 2:3): crystalline LXXVII (0·2 g). No. 13: (C_6H_6–EtOAc, 2:3): polymorph or hydrated form of LXXVII (0·14 g). No. 14–16 (C_6H_6–EtOAc, 2:3): gum (0·62 g). Total amount of LXXVII was 3·14 g (62% yield).

Fractions No. 4–12 crystallized from MeOH as prisms, m.p. 274–276°; ν_{max} 3460, ~3100–~2600, 1740, 1702, 1152, 1110, 1037, 1020 cm^{-1}; δ (as dimethyl ester) 1·00 (3H, s), 1·38 (3H, s), 3·60 (3H, s), 3·70 (3H, s), 4·18 (1H) ppm. No olefinic proton signal was observed. (Found: C, 65·45; H, 7·77. $C_{20}H_{28}O_6$ requires: C, 65·91; H, 7·74%). Fraction No. 13 melted at 244–246°; ν_{max} 3480, 3250, 1736, 1692, 1645, 1170, 1160,

1073, 1060, 1040 cm^{-1}. Since both products gave VI upon oxidation and decarboxylation, the latter might by a polymorph or a hydrate of LXXVII.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-4aβ,4bβ,7α,10aβ-*gibbane*-10β-*carboxylate* (VI)

The unsaturated acid LXXVI (4·6 g) in AcOH (150 ml) was hydrogenated over PtO_2 (300 mg) as described above. The oily hydrogenation product obtained from 12·4 g of LXXVI was dissolved in acetone (500 ml). To this solution Jones chromic acid reagent (10 ml) was added under ice-cooling. After 10 min MeOH (20 ml) was added and the mixture was concentrated *in vacuo*. To the residue, water (200 ml) was added and the mixture was kept on a boiling water bath for 20 min to effect decarboxylation. After cooling, the mixture was extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give semi-solid product. Fractional crystallization of this from EtOAc–pet. ether gave 3·2 g of needles as the first crop and 3·0 g of powder as the second and third crops. The IR spectrum of the latter was slightly different from that of the former in finger-print region. The latter powder seemed to be a mixture of VI and its epimer at C-1. The powder (3·0 g) in MeOH (50 ml) containing NaOMe (250 mg) was heated under reflux for 30 min to effect equilibration at C-1. After cooling, the soln was acidified with AcOH (1 ml) and concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and evaporated to give semi-solid residue. Fractional crystallization of the residue from EtOAc–pet. ether gave 2·1 g of needles as the first and the second crops. A small amount (ca. 0·1 g) of L was obtained as the third crop. This suggested the presence of LXXVIII in the hydrogenation product. The total amount of the needles (VI) was 5·3 g (49%). Recrystallization from EtOAc–pet. ether gave needles, m.p. 128–129°; ν_{max} 1742, 1730, 1720, 1160, 1154, 1085, 965, 836; ($CHCl_3$) 1744, 1736, 1716, 1190, 1163, 1100, 1080, 992, 966, 835 cm^{-1}, δ 1·06 (3H, s), 1·08 (3H, d, J = 5 Hz), 3·70 (3H, s) ppm. The IR ($CHCl_3$) and NMR spectra were identical with that of the racemic product described earlier. The GLC retention time was also identical with that of the racemate. Oxidation of the pure acid LXXVII followed by decarboxylation gave the same ketone VI.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-4bβ,7α,10aβ-*gibb*-4-*ene*-10β-*carboxylate* (XLIX)

(a) *From the unsaturated acid* (LXXVI). The acid LXXVI (2·5 g) in acetone (100 ml) was treated with the Jones reagent (2·0 ml) at 0–5°. After 10 min MeOH (5 ml) was added and the mixture was concentrated *in vacuo*. To the residue, water (50 ml) was added and the mixture was heated on a boiling water bath for 20 min. After cooling, it was extracted with ether. The ether extract was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give semi-solid product. Trituration with ether–pet. ether gave 810 mg (37%) of crystalline XLIX. Recrystallization from MeOH gave plates, m.p. 122–123°; ν_{max} 1744, 1732, 1724, 1248, 1232, 1162, 992, 973, 840, 820; ($CHCl_3$) 1742, 1725 (sh), 1165, 992, 973, 840, 820 cm^{-1}; δ 1·08 (3H, s), 1·12 (3H, d, J = 5 Hz), 1·90, 1·98, 2·58, 2·60, 2·90, 3·73 (3H, s), 5·44 (1H, broad) ppm. (Found: C, 72·00; H, 7·69. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%).

(b) *From the oxo lactone* LXXI. To a soln of LXXI (10·0 g) in AcOH (600 ml), Zn dust (120 g) was added and the mixture was stirred and heated under reflux for 4·5 hr. The mixture was filtered and the solid washed with EtOAc. The filtrate and the washings were concentrated *in vacuo*. The ether soln of the residue was filtered to remove $Zn(OAc)_2$ and concentrated to give an oil. This was mixed with dil HCl (1:4, 600 ml) and heated under reflux for 2 hr under N_2. After cooling, the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), decolourized (activated charcoal) and concentrated to give an oil. This was treated with ethereal CH_2N_2 and the solvent was removed. The residue crystallized to give 4·5 g of XLIX. The gum recovered from the mother liquor was chromatographed on alumina (17 × 3·2 cm) to give 1·35 g of XLIX by elution with C_6H_6. Total amount of XLIX was 5·85 g (63%). The identity was proved by IR spectrum.

Methyl 1,7-*dimethyl*-2,8-*dioxo*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (L)

To a soln of VII (3·6 g) in dioxan (90 ml), a suspension of $NaBH_4$ (0·9 g) in MeOH (10 ml) was added. After 17 hr at room temp the mixture was diluted with water and extracted three times with EtOAc (90, 50 and 40 ml portions). The EtOAc soln was washed with water and brine. To this soln containing LXXIX 10% Pd–C (1 g) was added and the mixture was shaken under H_2 at room temp for 2·5 hr. The catalyst and the solvent were removed. The residue in acetone (100 ml) was oxidized with the Jones reagent (4 ml). After 10 min at room temp MeOH (10 ml) was added to the mixture which was concentrated *in vacuo*. To the residue EtOAc and water were added. The EtOAc layer was separated, washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2·65 g (73%) of crystalline L.

Recrystallization from EtOAc–pet. ether gave elongated prisms, m.p. 167–168°; ν_{max} 1742, 1714, 1220, 1162 cm^{-1}; δ 0·98 (3H, d, J = 5) 1·06 (3H, s), 1·63, 2·40, 2·54, 2·85, 2·92, 3·80 (3H, s) ppm. (Found: C, 72·32; H, 7·40. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%).

Methyl 1,7-*dimethyl*-2α-*hydroxy*-8-*ethylenedioxy*-7α,10β-*gibba*-3,4a(4b)-*diene*-10β-*carboxylate* (ix)

The ketal LVI (9 g) in dioxan (200 ml) was mixed with a suspension of $NaBH_4$ (2·2 g) in MeOH (35 ml). After 16 hr at room temp the mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The oily *ix* (8·5 g) was used for the next step without further purification. ν_{max} 3450, 1730, 1666, 1600 cm^{-1}.

Methyl 1,7-*dimethyl*-2α-*hydroxy*-8-*ethylenedioxy*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (x)

The dienol (*ix*, 8·4 g) in EtOAc (120 ml) was hydrogenated over 10% Pd–C (0·7 g) under atmospheric press for 1·5 hr at room temp. Removal of the catalyst and the solvent gave 8·2 g (90%) of crystalline x. Recrystallization from EtOAc–pet. ether gave elongated prisms, m.p. 147–148°; ν_{max} 3578, 1714, 1670 (sh) cm^{-1}. (Found: C, 69·39; H, 8·47. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%).

Methyl 1,7-*dimethyl*-2-*oxo*-8-*ethylenedioxy*-7α,10aβ-*gibb*-4a(4b)-*ene*-10β-*carboxylate* (xi)

A soln of *x* (8·0 g) in pyridine (60 ml) was added to the Sarett reagent prepared from CrO_3 (8 g) in pyridine (120 ml). After 3 days the mixture was diluted with water and extracted with EtOAc. The extract was washed with water, $NaHCO_3$aq and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue crystallized from EtOAc–pet. ether to give 6·0 g (76%) of *xi*. This was recrystallized from EtOAc–pet. ether as leaflets, m.p. 160–161°; ν_{max} 1732, 1702, 1650 cm^{-1}; δ (60 MHz) 0·90 (3H, s), 0·93 (3H, d, J = 6 Hz), 3·77 (3H, s), 3·92 (4H) ppm. No olefinic proton signal was observed. (Found: C, 69·99; H, 7·64. $C_{21}H_{28}O_5$ requires: C, 69·97; H, 7·83%).

Methyl 1,7-*dimethyl*-2,8-*dioxo*-7α,10aβ-*gibba*-3,4a(4b)-*diene*-1α,10β-*dicarboxylate* (LVIII)

The diester LXXXII (1·15 g) suspended in dil HCl (1:5, 180 ml) was heated under reflux for 40 min under N_2. After cooling, the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated to give an oil. This was treated with etheral CH_2N_2 and the soln was concentrated. The residual gum was chromatographed on alumina (18 × 1·8 cm) in C_6H_6. Benzene (300 ml) eluted a small amount of oil. Benzene–ether (4:1· 250 ml; 3:1, 500 ml; 1:1, 500 ml) eluted the desired product LVIII (320 mg, 28%). Recrystallization from ether–pet. ether gave leaflets, m.p. 107–108°; ν_{max} 1738, 1698, 1662, 1638 (sh), 1560, 1218, 1185, 1173, 1160, 1145, 1100, 1075, 838 cm^{-1}. λ_{max} 309 mμ (ε 14,200); δ 1·08 (3H, s), 1·35 (3H, s), 3·56 (3H, s), 3·75 (3H, s), 6·02 (1H, d, J = 10 Hz), 7·23 (1H, d, J = 10 Hz) ppm. (Found: C, 67·79; H, 6·41. $C_{21}H_{24}O_6$ requires: C, 67·73; H, 6·50%). Elution with ether (1 l.) gave 300 mg of the starting material LXXXII.

Bioassay.

Assay plants: dwarf maize (*Zea mays* L.) d_5 mutants.

Treatment: as a 10 μl drop of 90% ethanolic soln applied to the first leaf blade.

Measurement: 10 days after application. Lengths of the first and the second leaf sheath (average of 9 plants).

	(−)-Kaurenol	(±)-Kaurenol	(±)-Kaurenol acetate	Gibberellin C
Control	100 μg/plant	100 μg	100 μg	100 μg
45·9 mm	84·1	69·4	84·8	115·6

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