The Stereochemistry of Tri-n-butyltin Hydride Reductions in the Preparation of Ring A Desoxygibberellins

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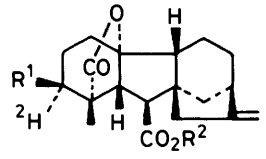
The hydrogenolysis of gibberellin 1- and 3-chlorides with tri-n-butyltin hydride has been shown by deuterium labelling combined with ^1H and ^2H n.m.r. analysis, to proceed with the introduction of the label from the less hindered β-face of the molecule. The hydrogenolysis reaction when applied to the preparation of 3-desoxygibberellins in the C-20 series, proceeds most satisfactorily with the thiocarbonylimidazole derivatives of gibberellins A_{13} and A_{14} methyl esters to afford the methyl esters of gibberellins A_{25} and A_{12} respectively.

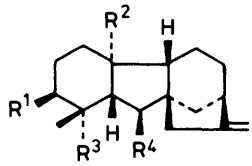
The hydrogenolysis of alkyl halides with tri-n-butyltin hydride [1] has proved to be a useful reaction in the partial synthesis of gibberellin plant hormones.[2,3] Despite the sparsity of stereochemical information on these reductions, the availability of tri-n-butyltin deuteride affords a means of labelling these hormones for metabolic studies. Beale *et al.* have examined the stereochemistry of reduction in the gibberellin series by a combination of chemical and metabolic studies.[3] [3α-^{2}H]Gibberellin A_9 (**1**) was prepared by the reduction of 3β-chloro[3α-^{2}H]gibberellin A_9 methyl ester (**2**) with tri-n-butyltin hydride and hydrolysis. It was shown to be hydroxylated by a cell-free enzyme preparation from *Cucurbita maxima* to afford [3α-^{2}H]gibberellin A_4 (**3**). On the assumption that this enzymatic hydroxylation takes place with retention of configuration, it followed that the reduction with tri-n-butyltin hydride had also taken place with retention of configuration. We have used tri-n-butyltin deuteride to introduce labels at C-1, C-3, and C-13 in the gibberellins.[4] In this paper we present our evidence for the stereochemistry of these reductions based on n.m.r. studies together with applications of the reagent in preparing 3-desoxygibberellins from their more readily accessible 3-hydroxy counterparts.

In studies on the conversion of gibberellin A_{13} trimethyl ester (**4**) into δ-lactones related to gibberellin A_{15}, Cross observed[5] long-range couplings on both the 19-H proton n.m.r. resonances of the lactone (**8**) and suggested that these involved coupling to the 3β- and 5β-protons. We have utilized the long-range coupling between a 19-H and 5β-H resonance in stereochemical studies involving reactions at C-19.[6] In a saturated desoxy ring A in which the 3-H resonances lie within the methylene envelope, this long-range coupling provides a probe for the stereochemistry of a proton (deuteron) at C-3. This coupled with ^{2}H n.m.r. studies, formed the basis of our stereochemical analysis.

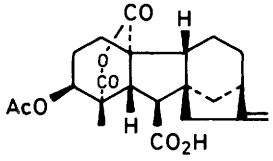
The reduction of gibberellin A_{13} trimethyl ester (**4**) and its relatives with lithium aluminium hydride has been described on a number of occasions.[5,7,8] The tetraol (**5**) is obtained under vigorous conditions in refluxing dioxane.[7] Under controlled conditions (tetrahydrofuran, −55 °C) reduction of the acetoxy anhydride (**7**) gave the 3-hydroxy 20-19-lactone (**9**).[5] In boiling ether reduction of gibberellin A_{13} trimethyl ester gave two products which were isolated as their acetates (**6**) and (**10**).[8] Thus the C-20 ester is much less reactive than the C-7 and C-19 esters. In our hands reduction of the trimethyl ester in tetrahydrofuran gave the dihydroxy-lactone (**11**). Treatment of the dihydroxy lactone (**11**) with triphenylphosphine–carbon tetrachloride gave the 3α,7-dichloride (**12**). The stereochemistry of the chloride was based on the following evidence. Spin-



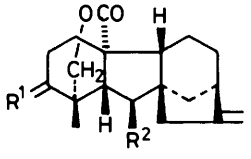
(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = Cl, R^2 = Me$
(**3**) $R^1 = OH, R^2 = H$



(**4**) $R^1 = OH, R^2 = R^3 = R^4 = CO_2Me$
(**5**) $R^1 = OH, R^2 = R^3 = R^4 = CH_2OH$
(**6**) $R^1 = OAc, R^2 = CO_2Me$, $R^3 = R^4 = CH_2OAc$



(**7**)



(**8**) $R^1 = \alpha$-OH, β-H, $R^2 = CO_2Me$
(**9**) $R^1 = \beta$-OH, α-H, $R^2 = CO_2H$
(**10**) $R^1 = \beta$-OAc, α-H, $R^2 = CH_2OAc$
(**11**) $R^1 = \beta$-OH, α-H, $R^2 = CH_2OH$
(**12**) $R^1 = \alpha$-Cl, β-H, $R^2 = CH_2Cl$
(**13**) $R^1 = H_2, R^2 = CH_3$

decoupling experiments based on irradiation at δ 4.64 and 4.16 (19-H) and δ 3.76 and 3.64 (7-H) and δ 1.84 (5-H) established the relationships and assignments shown in Figure 1(a). In particular, the presence of a long-range coupling (*J* 1.3 Hz) to one of the 19-H protons (δ 4.16) together with an axial,equatorial (6 Hz) coupling to a multiplet at δ 2.3 and an axial,axial coupling (12.5 Hz) to a multiplet at δ 1.95, established that 3-H was β and axial. Furthermore, whilst the 5-H signal (δ 1.84) appeared at higher field than in the parent dihydroxylactone (δ 2.03), the *pro-H* 19-H was shifted to lower field (δ 3.97 ⟶ 4.64) thus implying that the C-3 halogen had the α-configuration.

Reduction of the dichloride with tri-n-butyltin hydride gave the lactone (**13**). Spin-decoupling experiments based on irradiations at δ 1.00 (7-H), 1.40 (3-H), 1.70 (3-H), and 4.05 and 4.30 (19-H) established the assignments and coupling pattern shown in Figure 1(b). In this case the axial 3β-H proton (δ 1.40) showed a long-range coupling (*J* 2.3 Hz) to the *pro-S* 19-H (δ 4.30) and a geminal coupling (*J* 14 Hz) to the equatorial 3α-H (δ 1.71). Repetition of the reduction with tri-n-butyltin deuteride

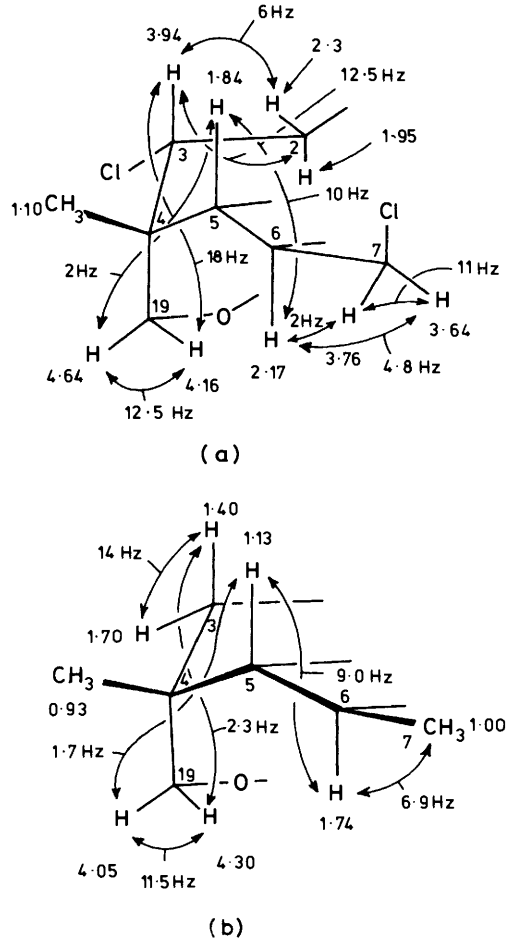
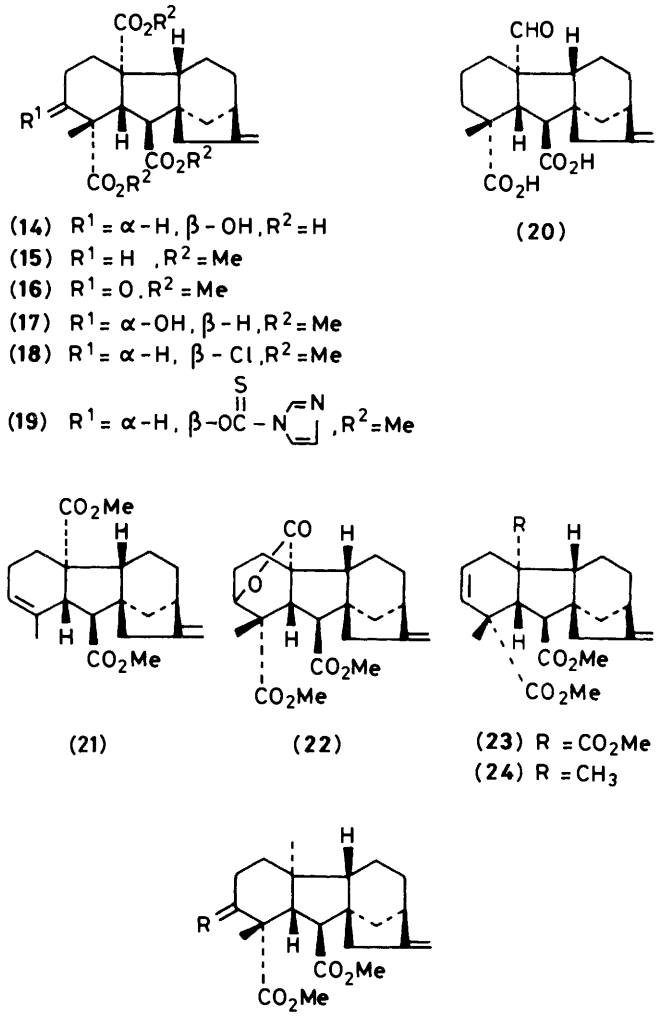


Figure 1. Coupling pattern and proton assignments in (**12**) and (**13**)



gave *ent*-19-hydroxy[3,7-$^2H_2$]gibberell-16-en-20-oic acid 20,19-lactone (**13**). The ^2H n.m.r. spectrum, determined at 55.3 MHz, contained three resonances [δ 1.01 (relative integral 1), 1.4 (0.77) and 1.7 (0.09)] showing that the deuterium had been introduced with 88% stereospecificity at 3β-H. Furthermore, in the ^1H n.m.r. spectrum the 19-H resonance (δ 4.30) lacked the long-range coupling to the 3β-H proton confirming that the deuterium had been introduced at the 3β-axial site. Hence in this case the reduction of the α-oriented chloride had proceeded predominantly with an overall inversion of configuration at C-3.

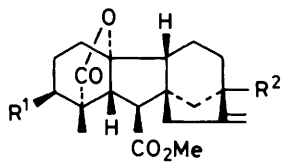
Gibberellin A_{13} (**14**) is the most abundant of the C_{20} gibberellins.[9] The corresponding 3-desoxygibberellin, gibberellin A_{25}, has been prepared as its trimethyl ester (**15**) from both gibberellin A_{13} (**14**) and gibberellin A_{24} (**20**).[10] However, insufficient material makes the latter unsuitable for synthetic use. The previous method which was used for the preparation of gibberellin A_{25} trimethyl ester (**15**) from gibberellin A_{13} (**14**) involved elimination of the corresponding 3β-toluene-*p*-sulphonate with collidine to form the Δ^2-olefin. Unfortunately this elimination can be accompanied, as revealed by one set of experiments,[9] by the formation of the 20,3α-lactone (**22**) and in another,[10] by the Δ^3-19-norolefin (**21**). Thus there are various ways in which an incipient C-3 carbocation, generated by an axial leaving group, may react and this is reflected in our eventual choice of a successful deoxygenation sequence.

As in the C_{19} series[4] reaction of the axial hydroxy group of gibberellin A_{13} trimethyl ester (**14**) with triphenylphosphine–carbon tetrachloride in pyridine led to smooth elimination rather than substitution. Consequently the 3-hydroxy group was oxidized under carefully controlled conditions to the 3-ketone (**16**).[9] Reduction of the latter with sodium borohydride at low temperatures gave the epimeric 3α-alcohol (**17**).[8] If the reduction was carried out at room temperature varying amounts of the δ-lactone (**22**) were obtained.[8,9] The implication of this ready lactonization is that, as in 3-oxo-4,4-dimethylsteroids,[11] ring A of this ketone may exist in a flattened or even boat conformation. Treatment of the 3α-equatorial alcohol (**17**) with triphenylphosphine and carbon tetrachloride although affording the required 3β-chlorogibberellin A_{13} trimethyl ester (**18**) nevertheless gave substantial amounts of the Δ^2-olefin (**23**) in contrast to the behaviour of the C_{19} gibberellins.[4] The stereochemistry of the 3-substituent was reflected in the position of the 5β-H proton resonance. The 1,3 interaction between an axial 3β-electronegative substituent and the 5β-H produces a significant deshielding of the latter. Thus, 5β-H resonates at δ 2.67 in the chloro compound (**18**) and at δ 2.12 in gibberellin A_{25} trimethyl ester (**15**). Reduction of the 3β-

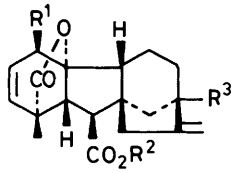
chlorogibberellin A_{13} trimethyl ester (**18**) with tri-n-butyltin hydride gave gibberellin A_{25} trimethyl ester (**15**).

The same sequence of oxidation, reduction, and attempted halogenation of the equatorial alcohol was applied to gibberellin A_{14} dimethyl ester (**25**).[12] Although the formation of the ketone (**26**)[12] and the 3α-alcohol (**27**) were uneventful, the halogenation reaction, even when conducted in the absence of pyridine, led almost entirely to elimination and the formation of Δ^2-dehydrogibberellin A_{12} dimethyl ester (**24**). It was not possible to obtain useful quantities of the 3β-chloro compound. The reduction of thiocarbonylimidazole derivatives of secondary alcohols by tri-n-butyltin hydride has recently been developed as a facile means of deoxygenation[13] particularly in situations where other reactions compete with substitution. In this case the problems of competing elimination were overcome by making the 3-thiocarbonylimidazole derivatives (**19**) and (**28**) which were readily reduced by tri-n-butyltin hydride to afford gibberellin A_{25} trimethyl ester (**15**)[10] and gibberellin A_{12} dimethyl ester (**29**).[14] The availability of tri-n-butyltin deuteride makes this an attractive route for labelling C-20 desoxygibberellins at the 3-position. The contrast in ease of elimination of a 3-substituent between the C_{19} and C_{20} series may in part be a reflection of the different geometry of ring A imposed by the lactone ring on the one hand and on the other by the repulsive interaction between C-19 and C-20.[15]

We have previously prepared[4] [3,13-$^2H_2$]gibberellin A_9 methyl ester (**30**) by the tri-n-butyltin deuteride reduction of the 3β,13-dichloride (**31**). Although the site of the labels was determined by carbon-13 n.m.r. spectroscopy, the stereochemistry at C-3 was not established in our previous work. The ^2H n.m.r. spectrum of the product contained signals at δ 2.57 (relative integral 1) (13-H), 1.66 (0.15) (3α-H), and 1.51 (0.77) (3β-H). The signal at δ 1.51 was assigned to the 3β-axial deuteron since irradiation at this centre in unlabelled gibberellin A_9 methyl ester produced a significant (12.5%) n.O.e. effect on the 5β-H proton resonance (δ 2.50). Thus the reaction with the β-chloride has proceeded with predominant retention of configuration as in the example recorded by MacMillan and his co-workers.[3]



(**30**) $R^1 = R^2 = H$
(**31**) $R^1 = R^2 = Cl$



(**32**) $R^1 = R^2 = H, R^3 = OH$
(**33**) $R^1 = H, R^2 = Me, R^3 = OH$
(**34**) $R^1 = R^3 = H, R^2 = Me$
(**35**) $R^1 = Cl, R^2 = Me, R^3 = OH$
(**36**) $R^1 = R^3 = Cl, R^2 = Me$
(**37**) $R^1 = {}^2H, R^2 = Me, R^3 = OH$
(**38**) $R^1 = R^3 = {}^2H, R^2 = Me$

Tri-n-butyltin deuteride has been used to introduce a label at C-1 in both gibberellin A_5 (**32**),[16] its methyl ester (**33**), and in Δ^2-dehydrogibberellin A_9 methyl ester (**34**) by hydrogenolysis of the corresponding 1β-chloro compounds (**35**) and (**36**).[17] The stereochemistry of the label followed from an analysis of the ^1H n.m.r. spectrum of gibberellin A_5 methyl ester. The ring A olefinic proton resonances appeared as two doublets of triplets at δ 5.66 and 5.79. Irradiation at δ 5.73 collapsed two multiplets (δ 2.57 and 2.31) to doublets (J_{gem} 18.5 Hz) which were assigned to the equatorial 1α-H and the axial 1β-H respectively. The assignments were made on the following basis. Separate irradiation at δ 5.66 and 5.79 established the coupling pattern shown in Figure 2. It is known from the Karplus equation that as the dihedral angle approaches 90° the vicinal coupling constant tends to 0. On the other hand the allylic coupling constant is at a maximum.[18] The coupling constant data indicate that the resonance at δ 2.31 possesses the greater dihedral angle (*i.e.* it has the smaller vicinal coupling and the larger allylic coupling). Examination of molecular models shows that the 1β(axial)-proton fulfils this condition whilst the 1α(equatorial)-proton subtends a smaller angle. Hence the δ 2.31 resonance is assigned to the 1β(axial)-proton. Furthermore this assignment agrees with the generalization that an axial proton resonates at higher field than its equatorial epimer.[19] The same pattern of signals were observed in the spectrum of Δ^2-dehydrogibberellin A_9 methyl ester (**34**) although, unfortunately, the signal assigned to 13-H appeared at δ 2.65 partly obscuring the resonance assigned to the 1α-proton.

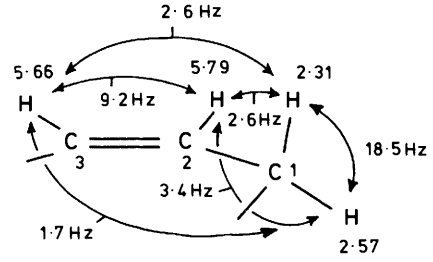


Figure 2. Coupling pattern and proton assignments in (**33**)

Reduction of the 1β-chlorogibberellin A_5 methyl ester (**35**) and 1β,13-dichlorodehydrogibberellin A_9 methyl ester (**36**) with tri-n-butyltin deuteride gave predominantly [1-^2H]gibberellin A_5 methyl ester (**37**) and [1,13-$^2H_2$]dehydrogibberellin A_9 methyl ester (**38**) containing some of the Δ^1-isomer (^1H n.m.r. signals at δ 6.18 and 5.86). The latter were substantially removed by repeated recrystallization. (An alternative procedure is given in ref. 16.) Based on both the integrals of the residual ^1H signals in the ^1H n.m.r. spectra and on the integrals of the ^2H n.m.r. signals there was 0.7 ^2H at δ 2.31 and 0.3 ^2H at δ 2.57. Hence in these cases the reduction has proceeded predominantly with retention of configuration. The common feature which runs through these reductions is that irrespective of the configuration of the initial halide, the label is introduced by the bulky tri-n-butyltin deuteride predominantly on the less hindered β-face of the molecule.

Experimental

^1H and ^2H N.m.r. spectra were determined for solutions in chloroform on a Bruker WH 360 spectrometer.

Reduction of Gibberellin A_{13} Trimethyl Ester (**4**).—The ester (**4**) (1 g) in tetrahydrofuran (100 ml) was heated with lithium aluminium hydride (2 g) under reflux for 3 days. Excess of reagent was destroyed with ethyl acetate, the solution acidified with dilute hydrochloric acid, and the product recovered in ethyl acetate and chromatographed on silica. Elution with 50% ethyl acetate–light petroleum gave *ent*-3α,7,19-trihydroxygibberell-16-en-20-oic acid 20,19-lactone (**11**) (680 mg) which crystallized as needles, m.p. 164—166 °C (lit.,[8] gum) (Found: C, 72.4; H, 8.4. Calc. for $C_{20}H_{28}O_4$: C, 72.3; H, 8.4%); $\nu_{max.}$ 3 425, 1 710, 1 660, 910, and 730 cm^{-1}; δ 1.04 (3 H, s, 18-H), 1.92 (1 H, octet, *J* 2.5, 6.5, and 12 Hz, 6-H), 2.03 (1 H, dd, *J* 1.5 and 12 Hz, 5-H), 3.63 (1 H, dd, *J* 4.8 and 11.5 Hz, 7-H), 3.7 (1 H, br m, 3-H),

3.88 (1 H, dd, *J* 2.5 and 11.5 Hz, 7-H), 3.97 (1 H, dd, *J* 1.5 and 12.5 Hz, 19-H), 4.35 (1 H, d, *J* 12.5 Hz, 19-H), and 4.9 (2 H, m, 17-H).

ent-3β,7-*Dichloro*-19-*hydroxygibberell*-16-*en*-20-*oic Acid* 20,19-*Lactone*.—The above diol (400 mg) in pyridine (10 ml) was heated with triphenylphosphine (1.6 g) and carbon tetrachloride (30 ml) under reflux for 2 h. The solvents were evaporated and the residue chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave ent-3β,7-*dichloro*-19-*hydroxygibberell*-16-*en*-20-*oic acid* 20,19-*lactone* (**12**) (380 mg) which crystallized as plates, m.p. 142—144 °C (Found: C, 65.3; H, 7.0. $C_{20}H_{26}Cl_2O_2$ requires C, 65.2; H, 7.1%); $\nu_{max.}$ 1 733, 1 660, 890, and 740 cm^{-1}; δ 1.1 (3 H, s, 18-H), 1.84 (1 H, dd, *J* 2 and 10 Hz, 5-H), 2.17 (1 H, octet, *J* 2, 4.8, and 10 Hz, 6-H), 3.64 (1 H, dd, *J* 4.8 and 11.5 Hz, 7-H), 3.76 (1 H, dd, *J* 2 and 11.5 Hz, 7-H), 3.94 (1 H, octet, *J* 1.8, 6 and 12.5 Hz, 3-H), 4.16 (1 H, dd, *J* 1.8 and 12.5 Hz, 19-H), 4.64 (1 H, dd, *J* 2 and 12.5 Hz, 19-H), 4.64 (1 H, dd, *J* 2 and 12.5 Hz, 19-H), and 4.92 (2 H, m, 17-H).

ent-19-*Hydroxygibberell*-16-*en*-20-*oic Acid* 20,19-*Lactone* (**13**).—The dichlorolactone (**12**) (180 mg) in benzene (10 ml) was heated with tri-n-butyltin hydride (0.35 ml) and azobisisobutyronitrile (5 mg) under reflux for 1 h. The solvent was evaporated and the residue chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave ent-19-*hydroxygibberell*-16-*en*-20-*oic acid* 20,19-*lactone* (**13**) (80 mg) which crystallized as plates, m.p. 99—101 °C (Found: C, 79.7; H, 9.4. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.7%); $\nu_{max.}$ 1 725, 1 660, and 880 cm^{-1}; δ 0.95 (3 H, s, 18-H), 1.02 (3 H, d, *J* 7 Hz, 7-H), 4.05 (1 H, dd, *J* 1.7 and 11.5 Hz, 19-H), 4.30 (1 H, dd, *J* 2.3 and 11.5 Hz, 19-H), 4.90 (2 H, m, 17-H) [for other assignments see Figure 1(b)]. Repetition with tri-n-butyltin deuteride gave ent-19-hydroxy[3,7-$^2H_2$]-gibberell-16-en-20-oic acid 20,19-lactone, M^+, *m/z* 302.

ent-10-Hydroxy[3,13-$^2H_2$]-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-methyl ester (**30**) was prepared as described previously.[4]

[1-^{2}H]*Gibberellin* A_5 *Methyl Ester* (**33**).—*ent*-1α-Chloro-10β,13-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**35**) (550 mg)[17] in benzene (10 ml) was heated under reflux with tri-n-butyltin deuteride (1.5 ml) and azobisisobutyronitrile (300 mg) for 45 min. The solvent was evaporated and the residue chromatographed in silica. Elution with 25% ethyl acetate–light petroleum and repeated recrystalliztion from ethyl acetate–light petroleum afforded [1-^{2}H]gibberellin A_5 methyl ester (200 mg) which crystallized as prisms, m.p. 188—189 °C (lit.,[20] 190—191 °C); M^+, *m/z* 345, identified by its n.m.r. spectrum.

Δ^2-*Dehydrogibberellin* A_9 *Methyl Ester* (**34**).—*ent*-1α,13-Dichloro-10β-hydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**36**) (100 mg)[17] in benzene 12 ml) was heated with tri-n-butyltin hydride (0.4 ml) and azobisisobutyronitrile (15 mg) under reflux for 45 min. The solvent was evaporated and the residue chromatographed on silica. Elution with 5% ethyl acetate–light petroleum and repeated recrystallization gave Δ^2-dehydrogibberellin A_9 methyl ester (**34**) (56 mg) which crystallized as plates, m.p. 78—80 °C (Found: C, 73.4; H, 7.4. $C_{20}H_{24}O_4$ requires C, 73.2; H, 7.3%), $\nu_{max.}$ 1 775, 1 710, 1 665, and 885 cm^{-1}; δ 1.19 (3 H, s, 18-H), 2.31 (1 H, dt, *J* 2.6 and 18.5 Hz, 1-H), 2.57 (1 H, *J* 1.7, 3.4, and 18.5 Hz, 1-H), 2.63 (1 H, d, *J* 10.3 Hz, 5-H), 2.65 (1 H, m, 13-H), 2.77 (1 H, d, *J* 10.3 Hz, 6-H), 3.68 (3 H, s, OMe), 4.82 and 4.94 (each 1 H, m, 17-H), 5.66 (1 H, *J* 1.7, 2.6, and 9.2 Hz, 3-H), and 5.79 (1 H, *J* 2.6, 3.4, and 9.2 Hz, 2-H).

[1,13-$^2H_2$]-Dehydrogibberellin A_9 methyl ester was prepared as above using tri-n-butyltin deuteride; M^+, *m/z* 330.

Chlorination of 3-epi-*Gibberellin* A_{13} *Trimethyl Ester*.—*ent*-3β-Hydroxygibberell-16-ene-7,19,20-trioic acid 7,19,20-trimethyl ester (**17**)[8] (1 g) in pyridine (3 ml) was heated under reflux with triphenylphosphine (2 g) in carbon tetrachloride (20 ml) for 2 h. The reaction progress was followed carefully by t.l.c. The solvent was evaporated and the residue chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave ent-3α-*chlorogibberell*-16-*ene*-7,19,20-*trioic acid* 7,19,20-*trimethyl ester* (**18**) (500 mg) which crystallized as needles, m.p. 86—87 °C (Found: C, 63.2; H, 7.1. $C_{23}H_{31}ClO_6$ requires C, 63.0; H, 7.1%), $\nu_{max.}$ 1 730, 1 720, 1 710, 1 655, and 870 cm^{-1}; δ 1.32 (3 H, s, 18-H), 2.67 (1 H, d, *J* 13 Hz, 5-H), 3.58, 3.67, and 3.70 (each 3 H, s, OMe), 3.90 (1 H, d, *J* 13 Hz, 6-H), 4.52 (1 H, m, 3-H), and 4.84 and 4.92 (each 1 H, m, 17-H). Elution with 10% ethyl acetate–light petroleum gave *ent*-gibberella-2,16-diene-7,19,20-trioic acid 7,19,20-trimethyl ester (**23**) (300 mg)[9] identified by its n.m.r. spectrum.

Gibberellin A_{25} *Trimethyl Ester*.—The above chloro compound (**18**) (250 mg) in benzene (5 ml) was heated under reflux with tri-n-butyltin hydride (1 ml) in the presence of the initiator, azobisisobutyronitrile (50 mg) for 1 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave gibberellin A_{25} trimethyl ester (**15**) (150 mg) as a gum (lit.,[10] gum) (M^+, *m/z* 422), $\nu_{max.}$ 1 735, 1 716, 1 660, and 870 cm^{-1}; δ 1.12 (3 H, s, 18-H), 2.12 (1 H, d, *J* 13 Hz, 5-H), 3.57, 3.62, and 3.69 (3 H each, s, OMe), 3.84 (1 H, d, *J* 13 Hz, 6-H), and 4.81 and 4.88 (each 1 H, m, 17-H).

Reduction of the Ketone (**26**).—*ent*-3-Oxogibberell-16-ene-7,19-dioic acid 7,19-dimethyl ester (**26**) was prepared as described previously.[12] It had ^{1}H n.m.r. signals at δ 1.0 (3 H, s, 20-H), 1.21 (3 H, s, 18-H), 2.15 (1 H, d, *J* 12.5 Hz, 5-H), 3.42 (1 H, d, *J* 12.5 Hz, 6-H), 3.69 (6 H, s, OMe), and 4.82 (2 H, m, 17-H). The ketone (**26**) (680 mg) in methanol (150 ml) was treated with sodium borohydride (100 mg) in an ice-bath for 1 h. The solution was acidified, the methanol was evaporated under reduced pressure, and the residue extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water and then dried. The solvent was evaporated to give ent-3β-*hydroxygibberell*-16-*ene*-7,19-*dioic acid* 7,19-*dimethyl ester* (**27**) (620 mg) which crystallized as prisms, m.p. 93—94 °C (Found: C, 70.2; H, 8.8. $C_{22}H_{32}O_5$ requires C, 70.3; H, 8.5%), δ 0.78 (3 H, s, 20-H), 1.30 (3 H, s, 18-H), 1.84 (1 H, d, *J* 12.5 Hz, 5-H), 3.21 (1 H, d, *J* 12.5 Hz, 6-H), 3.70 (6 H, s, OMe), 3.75 (1 H, m, 3-H), and 4.87 (2 H, m, 17-H).

Elimination of the Alcohol (**27**).—The alcohol (**27**) and triphenylphosphine (1.2 g) in carbon tetrachloride (30 ml) were heated under reflux for 3.5 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave *ent*-gibberella-2,16-diene-7,19-dioic acid 7,19-dimethyl ester (**24**) (450 mg) as a gum; M^+, *m/z* 358 ($C_{22}H_{30}O_4$ requires *M*, 358), $\nu_{max.}$ 1 740, 1 660, and 880 cm^{-1}; δ 0.70 (3 H, s, 20-H), 1.24 (3 H, s, 18-H), 2.1 (1 H, d, *J* 13 Hz, 5-H), 3.35 (1 H, d, *J* 13 Hz, 6-H), 3.65 and 3.75 (each 3 H, s, OMe), 4.90 (2 H, m, 17-H), and 5.62 (2 H, m, 2- and 3-H).

Preparation of the Thiocarboxyimidazole Derivatives.—(a) Gibberellin A_{13} trimethyl ester (2 g) and *N,N*-thiocarbonyldiimidazole (2.5 g) in dry 1,2-dichloroethane (26 ml) were heated under reflux for 20 h. The solvent was evaporated and the residue was suspended in water and the product recovered in ethyl acetate. The extract was washed with water, the solvent evaporated, and the residue chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave ent-3α-*imidazolylthiocarboxygibberell*-16-*ene*-7,19,20-*trioic acid* 7,19,20-*trimethyl*

ester (**19**) (2.0 g) as a gum (Found: *M*, *m/z* 530.6350. $C_{27}H_{34}N_2O_7S$ requires *M*, 530.6343), $\nu_{max.}$ 1 720, 1 660, 885, and 760 cm^{-1}; δ 1.23 (3 H, s, 18-H), 2.65 (1 H, d, *J* 12 Hz, 5-H), 3.65 (3 H, s, OMe), 3.74 (6 H, s, OMe), 4.90 (2 H, m, 17-H), 5.85 (1 H, m, 3-H), 7.1, 7.64, and 8.40 (each 1 H, m, imidazole-H).

(b) Gibberellin A_{14} dimethyl ester (**25**) (200 mg) and *N,N*-thiocarbonyldi-imidazole (250 mg) in 1,2-dichloroethane (10 ml) were heated under reflux for 16 h. The solvent was evaporated and the residue was taken up in water and extracted with ethyl acetate. The extract was washed with water, dried, and the solvent evaporated to give a residue which was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave ent-3α-*imidazolylthiocarboxygibberell*-16-*ene*-7,19-*dioic acid* 7,19-*dimethyl ester* (**28**) (190 mg) as a gum (Found: *M*, *m/z* 486.6252. $C_{26}H_{34}N_2O_5S$ requires *M*, 486.6250), $\nu_{max.}$ 1 725br, 1 660, 890, and 760 cm^{-1}; δ 0.80 (3 H, s, 20-H), 1.20 (3 H, s, 18-H), 2.42 (1 H, d, *J* 12.5 Hz, 5-H), 3.37 (1 H, d, *J* 12.5 Hz, 6-H), 3.68 and 3.70 (each 3 H, s, OMe), 4.85 (2 H, m, 17-H), 6.02 (1 H, m, 3-H), and 7.05, 7.65, and 8.40 (each 1 H, m, imidazole-H).

Reduction of the Thiocarboxyimidazolyl Derivatives.—(*a*) The derivative (**19**) (1.5 g) in benzene (40 ml) was added dropwise to a refluxing solution of tri-n-butyltin hydride (1.5 ml) and azobisisobutyronitrile (100 mg) in benzene (20 ml). The mixture was allowed to reflux for a further 4 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum afforded gibberellin A_{25} trimethyl ester (**15**) (1 g) as a gum which was identified by its ^1H n.m.r. spectrum.[10]

(*b*) The derivative (**28**) (140 mg) in refluxing benzene (10 ml) was treated with tri-n-butyltin hydride (0.3 ml) and azobisisobutyronitrile (5 mg) for 4 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave gibberellin A_{12} dimethyl ester (**29**) (90 mg) as a gum (lit.,[14] gum), $\nu_{max.}$ 1 735, 1 660, and 875 cm^{-1}; δ 0.65 (3 H, s, 20-H), 1.10 (3 H, s, 18-H), 1.85 (1 H, d, *J* 12 Hz, 5-H), 3.36 (1 H, d, *J* 12 Hz, 6-H), 3.64 (6 H, s, OMe), and 4.80 (2 H, m, 17-H).

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