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Synthesis of 12-Hydroxy C_{20}-Gibberellins

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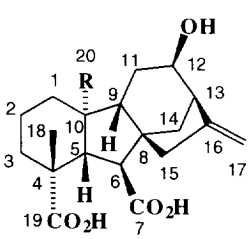
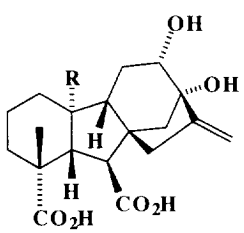
Abstract: Gibberellic acid (GA_3) (**6**) has been converted into 12-hydroxylated derivatives of gibberellins GA_{19} and GA_{24} with a view to confirming tentative assignments of structure to 12-hydroxy C_{20}-gibberellins isolated from several plant species. The conversions were initiated by reducing 12-substituted analogues of **6** with Li-NH_3 to afford either diene carboxylic acid **8** or its 12α-epimer, then introducing C20 substituents by means of the copper catalysed intramolecular cyclopropanations of the derived diazoketones **9** and **19**. Li-NH_3 reductions of the resulting cyclopropyl ketones **11** and **22** furnished ketones **12**, **22** and **23**, which could be oxidatively cleaved by treatment of their enolate anions with molecular oxygen, thereby providing the key intermediate aldehydes **13**, **24** and **25** from which the target GAs could be prepared.

The 12β-hydroxy C_{20}-gibberellins **1**,[1] **2**[2] and **3**[3,4] are believed to occur in a number of cruciferous plants, while the 12α,13-hydroxy C_{20}-gibberellins **4**[5] and **5**[6] have been tentatively identified as endogenous gibberellins ("GAs") in *Brassica campestris*. The latter isolations are of particular interest from a biosynthetic perspective, given the occurrence of several 12α,13-dihydroxy C_{19}-GAs in the same plant.[7-9] We have therefore undertaken the synthesis of this new class of GAs with a view to confirming the provisional structure assignments and to establishing a set of reference 12-hydroxy C_{20}-GAs for future identifications.[10] This objective has been achieved by combining together methodology previously established for the preparation of 12-hydroxy C_{19}-GAs[7,11,12] and of C_{20}-GAs,[13-15] respectively, from gibberellic acid (GA_3) (**6**).

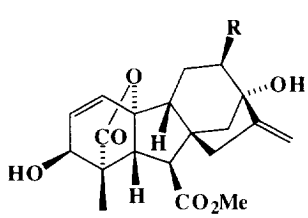
It appeared that the 12β-hydroxy GA **7**, available in 9 steps from **6**, could serve as a precursor to both the 12β-hydroxy and 12α,13-dihydroxy sets of compounds, given that efficient methods[7,11] for both stereochemical inversion at C12 and 13-deoxygenation had been establised in 12,13-dihydroxy C_{19}-GAs.



1 R = Me
2 R = CH_2OH (19,20-lactone)
3 R = CH=O

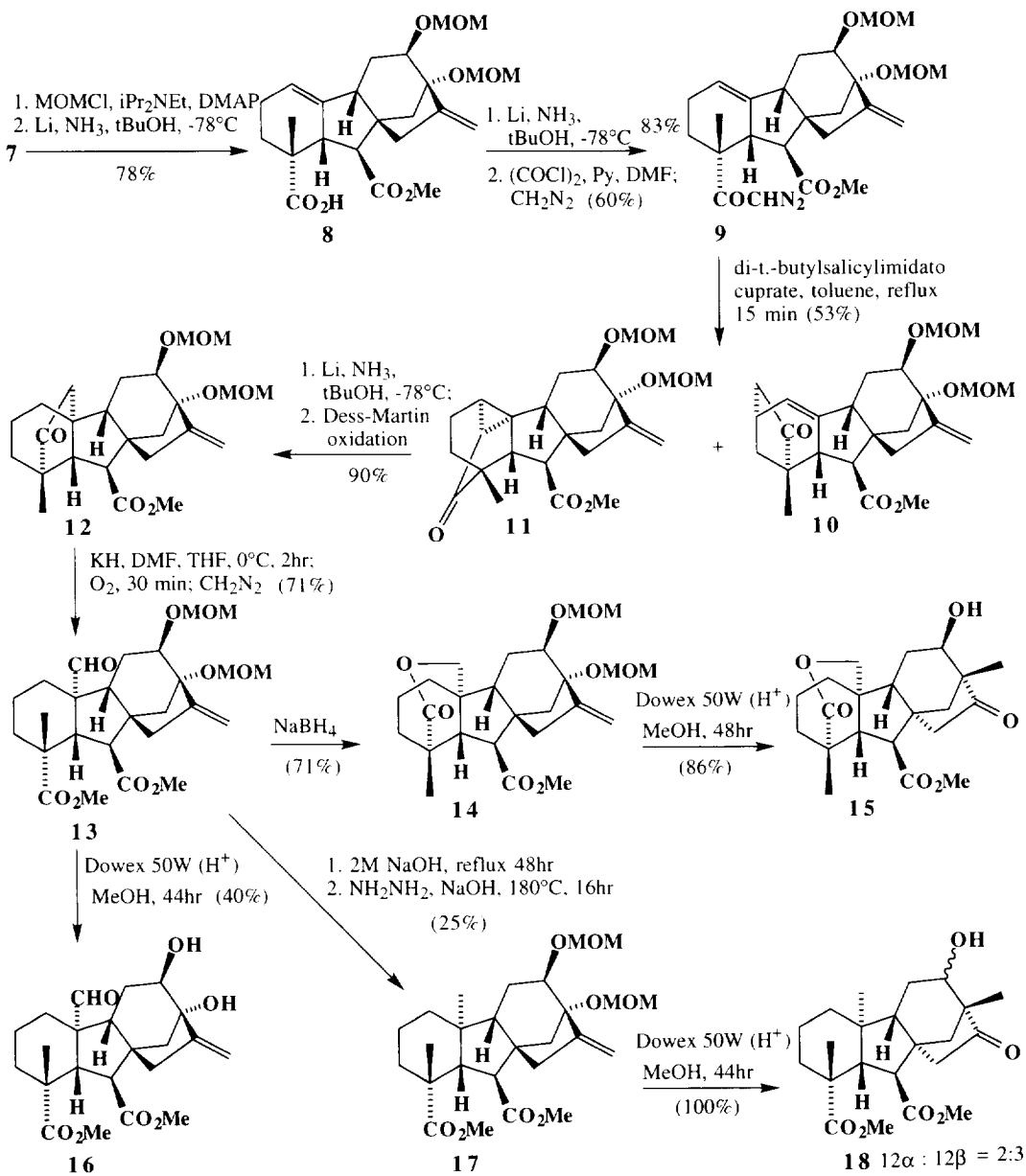


4 R = Me
5 R = CH=O



6 R = H
7 R = OH

Accordingly, **7** was converted into aldehyde **13** as outlined in Scheme 1. Thus, the tri(methoxymethyl) ether of **7**, was prepared and then reduced by Li-NH_3 to afford acid **8**. The derived diazoketone **9**, however, failed to react under conditions (copper-bronze, reflux in cyclohexane-THF) that had induced highly efficient intramolecular cyclopropanation in the related system lacking the 12-MOM ether function,[13] while reaction with $Cu(acac)_2$, the preferred catalyst for the 2β,13-di-MOM analogue,[15] afforded only a low yield of the desired

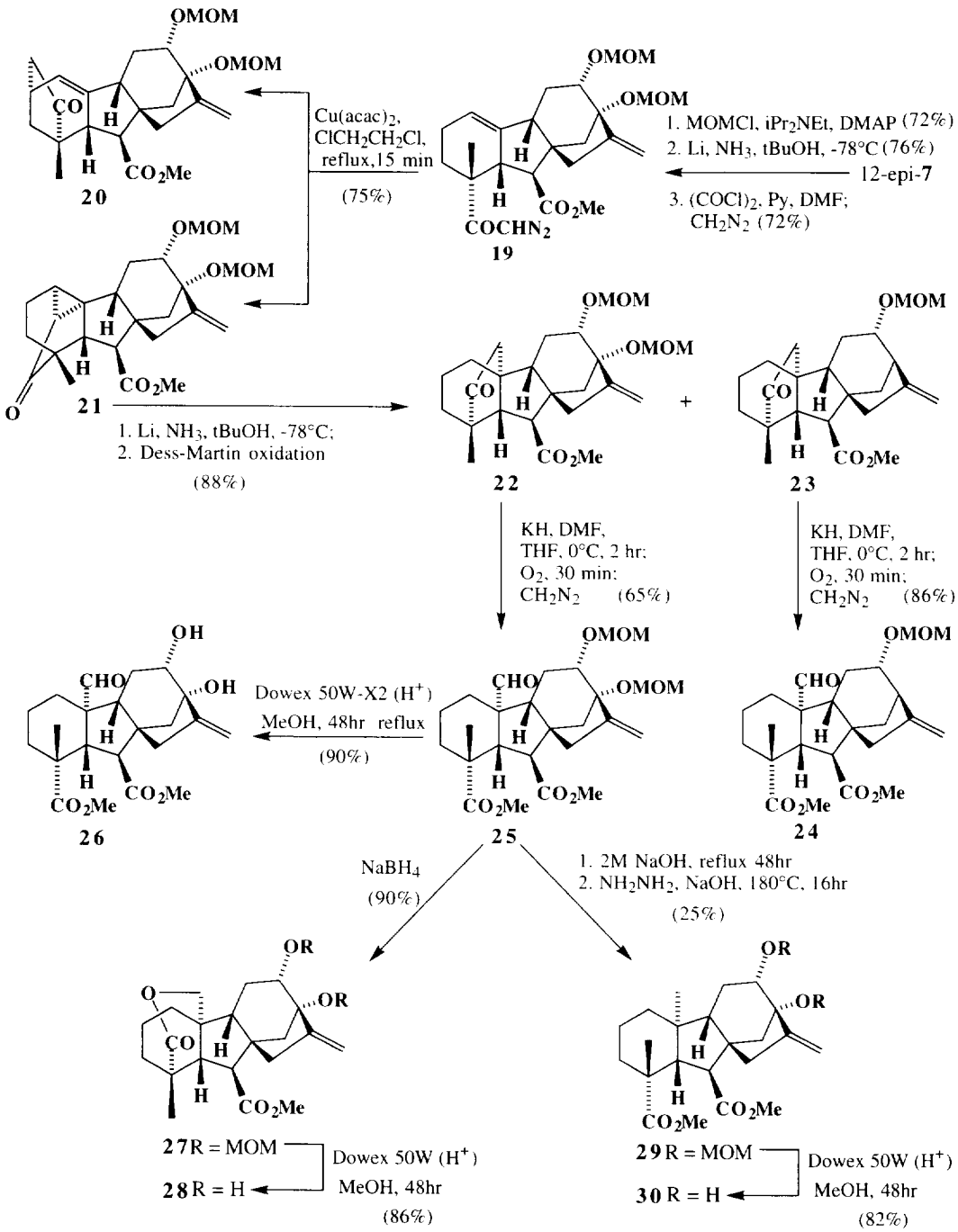


Scheme 1. Synthesis of 12β,13-Dihydroxy C_{20}-Gibberellins.

cyclopropyl ketone **11**, the main product **10** arising from insertion into the 2α-CH bond. Fortunately, use of bis(*N*-*t*.-butylsalicylaldiminato) copper (II)[16] gave a reasonable yield of **11**, Li-NH_3 reduction of which, followed by Dess-Martin oxidation,[17] afforded **12**. Oxidative cleavage of the potassium enolate of **12** by molecular oxygen gave access to the key aldehyde **13**, from which the protected 12β-hydroxy analogues of GA_{44} **14** and GA_{53} **17** could readily be made. The Wolf-Kishner reduction of the 7,19-dicarboxylic acid derived from **13** afforded only a low yield of **17**, but thus far, it has proven to be the only effective procedure[18] for aldehydes of this type, as a consequence of steric hindrance and the potential for interference from the 19-carboxy substituent. Poor as the yields are, they are normally better if the reduction is carried out on the dicarboxylic acid, rather than on the parent ester. Deprotection of **13** to 12β-hydroxy-GA_{19} (**16**) could be effected under the standard conditions of reflux in methanol over Dowex resin (developed earlier[19] for such a purpose), albeit in modest yield, but under these conditions, both **14** and **17** underwent rearrangement to ketones **15** and **18**, respectively. The epimeric mixture **18** presumably arises from a subsequent retroaldol/aldol process. It has been our experience that for the Wagner-Meerwein rearrangement to occur with simpler 13-hydroxy GAs, more strongly acidic conditions are required,[20] and we conclude, therefore, that the 12β-hydroxyl assists in protonation of the 16-methylene function.

Clearly, these difficulties could be solved by choosing an alternative masking group for the hydroxy functions in **7**, but given that one of our objectives was the 12α,13-dihydroxy set of GAs, we chose to prepare the 12-epimer of **7** (GA_{87} methyl ester)[21] and commit this material to an analogous sequence (Scheme 2). In the event, generally higher yields and more reliable outcomes were obtained. A further (unanticipated) advantage of the 12α-epimeric series was the option of inducing hydrogenolysis of the 13-substituent during the second Li-NH_3 reduction. 12α-Hydroxy GA_3 (GA_{87}) methyl ester was converted into its tri(methoxymethyl) ether as for the 12β-epimer, and thence into the derived diazomethyl ketone **19**. Unlike the 12β-analogue, the new diazoketone reacted with Cu-bronze to give cyclopropyl ketone **21**, although the yield was only 25%, the major product **20** (44% yield) arising from CH bond insertion. A similar outcome was obtained with the bis(*N*-*t*.-butylsalicylaldiminato) copper (II) complex, but with $Cu(acac)_2$, **21** was the major product (3:1 ratio).[21] Li-NH_3 reduction of this compound following the standard protocol (*cf.* the reduction of cyclopropyl ketone **11**) afforded not only the expected ketone **22** (50% yield), but the 13-desoxy product **23** (38% yield) as well. The structure of the latter compound was evident from mass and NMR spectra: only one methoxymethoxy group was evident while a new doublet at 2.71 ppm in the ^1H NMR spectrum could be assigned to H-13. ^{13}C NMR also indicated the loss of a methoxymethoxy group and the appearance of a new methine signal for C-13 at 46.5 ppm. It was found that the ratio of **23** : **22** could be controlled by the amount of lithium metal being added to the reaction. A high yield (78%) of the di(methoxymethyl) ether **22** could be obtained if the reaction was stopped after the addition of 2 equivalents of lithium. Reaction with an excess of lithium (followed by oxidation with Dess-Martin), however, afforded mainly **23**, mixed with compounds resulting from reduction of the ester functionality. These results indicate that the cyclopropyl ring is reduced before the reductive removal of the 13-methoxymethoxy group, but that the 13-deoxygenation proceeds at a similar rate to the reductions of the cyclopentanone and ester functions. It was also found that **22** could be converted into the **23** by Birch reduction (followed by oxidation of the C(19) carbinol function), provided that a lithium salt was added first.

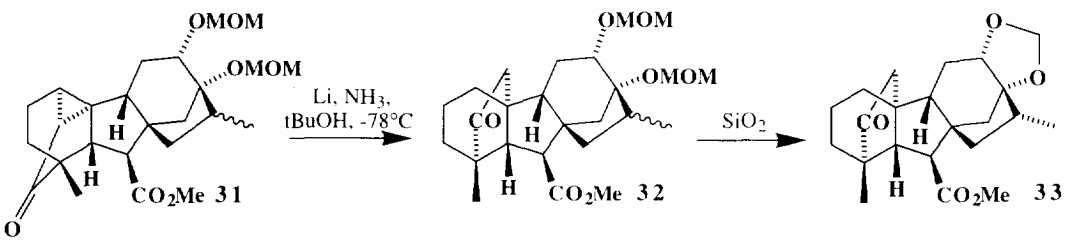
It has been established that acetoxy groups in the C(13) position can be removed during Birch reductions of cyclopropyl ketones[14] and the mechanism for this process can be understood by transfer of an electron from the lithium metal into the π^* molecular orbital of the carbonyl group followed by fragmentation to a tertiary radical that undergoes further reduction, then protonation.[22] For the deoxygenation of **22**, however, a different deoxygenation mechanism must apply, since the 13-methoxymethoxy group does not possess a sufficiently low-lying unoccupied molecular orbital to accommodate an electron in the initial step. It is proposed, therefore, that a solvated electron adds to the terminal olefin function, resulting in ejection of the methoxymethoxide anion, this loss being assisted by chelation of the (almost) coplanar 12α and 13-methoxymethyloxy substituents to lithium cations formed during the reduction. This process forms an allylic



Scheme 2. Synthesis of 12α,13-Dihydroxy C_{20}-Gibberellins.

radical delocalised over C13, C16 and C17 thereby violating Bredt's rule,[23] but examination of models shows a dihedral angle of 65° between the singly occupied orbital at C-13 and the 16,17-π orbital, allowing overlap to occur to a limited extent; clearly, the electron density will be greatest at C-13. Analogous anti-Bredt structures have been invoked as possible intermediates in the formation of 13-selenides in work reported by Willis *et al.*[24]

Experimental evidence to show that the alkene function was essential for the deoxygenation process could be obtained by subjecting the 16,17-dihydrocyclopropyl ketone mixture **31** to the conditions of the Li-NH_3 reduction (Scheme 3). This mixture of compounds was formed in a 3:1 ratio of exo/endo (16α:16β) epimers by hydrogenation of the cyclopropyl ketone **22** over Rh-Al_2O_3. It was found that the addition of a large excess of lithium metal (followed by oxidation with Dess-Martin reagent[17] to reconstitute the bridged ketone) did not result in any deoxygenation, the only products isolated from the reaction being the expected mixture of di(methoxymethyloxy)cyclopentanones **32**. One surprising side reaction was observed during chromatography of **32**, however. It was found that the *exo*-methyl isomer decomposed cleanly on silica gel to form the dioxolane compound **33**, presumably as a consequence of steric compression from the 16α-methyl group.



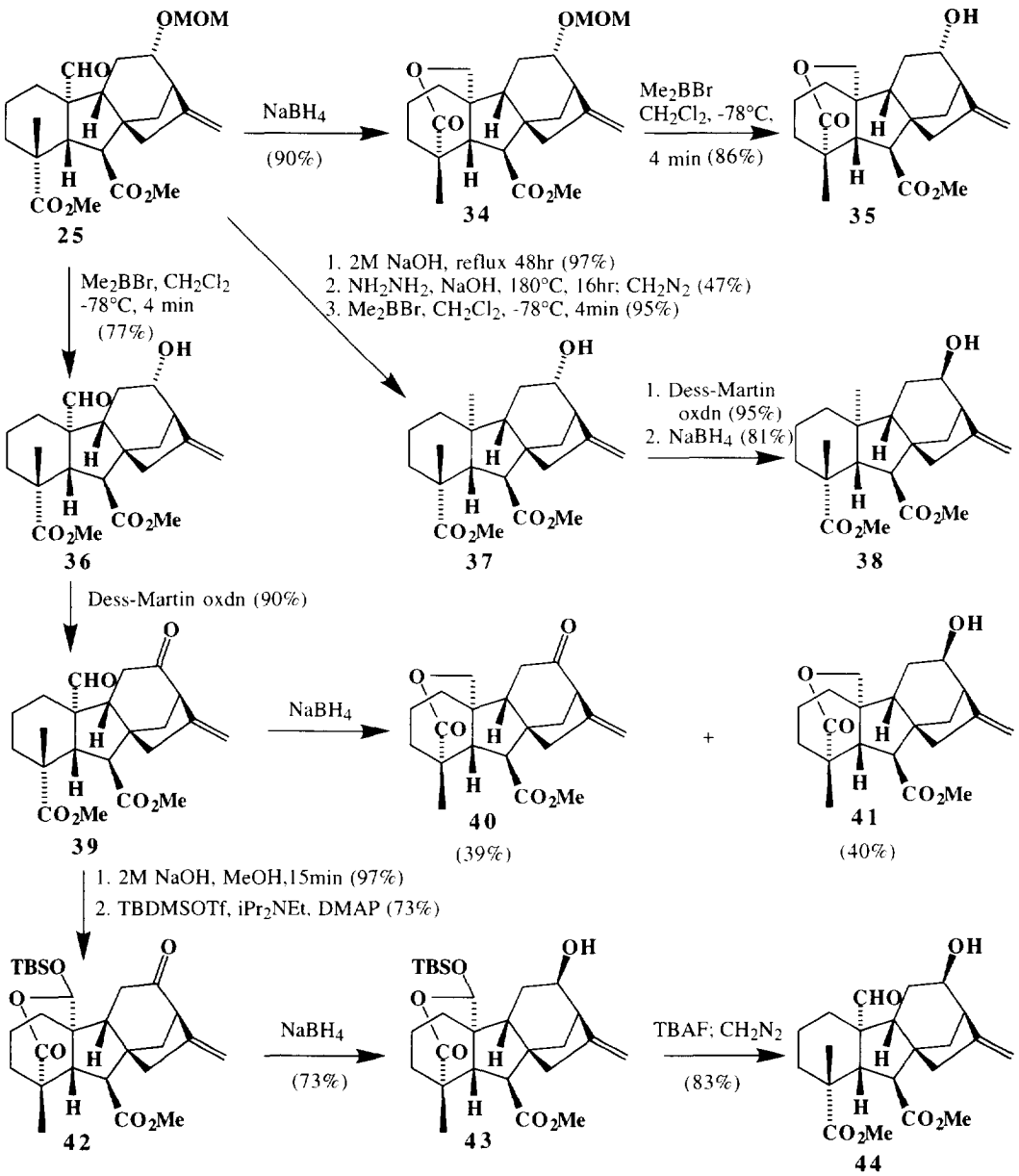
Scheme 3. Li-NH_3 Reduction of 16,17-Dihydrogibberellins.

Nevertheless, the factors controlling the loss of the 13-substituent are clearly finely balanced. A re-examination of the Li-NH_3 reduction of the 12β-epimer with an excess of reagent did not reveal any loss of the bridgehead substituent. Similarly, there was no indication that the equivalent loss occurred during the Li-NH_3 reductions of either of the tri(methoxymethyloxy) Δ^1-lactones. To effect removal of the 13-substituent from substrates of this kind, it has been necessary to carry out the reduction on 13-sulfonates.[25]

Both bridged ketones **22** and **23** underwent oxidative cleavage smoothly as for **12**. Aldehyde **22** obtained thus could then be transformed into the 12α-hydroxylated methyl esters of GA_{19}, GA_{44} and GA_{53}, **26**, **28** and **30** by simple refunctionalisation and deprotection steps, the latter proceeding smoothly without any indication of the rearrangements that had been a problem in the 12β series. Aldehyde **24** could be similarly converted into the 12α-hydroxylated methyl esters of GA_{15}, GA_{24} and GA_{12}, **35**, **36** and **37**, respectively (Scheme 4), although to avoid isomerisation of the Δ^{16}-enes to the Δ^{15}-isomers, the final deprotection step with dimethylboron bromide[26] in each of these cases required great care. The 12β-epimers, **38**, **41** and **44**, could then be obtained by simple oxidation/reduction cycles of the 12α-derivatives. As established earlier for C_{19}-GAs,[11] the 12-oxo-derivatives are reduced stereoselectively by borohydride to the 12β-carbinols. To avoid reduction of the reactive aldehyde functionality in the preparation of 12β-hydroxy-GA_{24} **44**, however, it was necessary to mask the 19-oxo group temporarily, a process that was readily achieved by selective hydrolysis (assistance from the 20-formyl substituent) of the 19-ester group, followed by silylation to form **42**. An attempt at direct reduction of the 12-oxo-aldehyde **39** yielded equal amounts of 12-oxo-GA_{15} methyl ester (**40**) and 12β-hydroxy-GA_{15} methyl ester (**41**), but no trace of 12β-hydroxy-GA_{24} derivative **44**.

With authentic samples of these GA methyl esters in hand, it has been possible to establish that 12β-hydroxy-GA_{12} (**1**) is present in shoots and flowering buds of stock (*Matthiola incana*),[1] and that 12β-hydroxy GA_{15} **2** and 12β-hydroxy GA_{24} **3** are almost certainly native to japanese radish (*Raphanus sativa*). The isolation of **2** and **3** is being repeated so that direct comparisons can be made; details will be published

elsewhere. The tentative identification of the 12α-hydroxy derivatives of GA_{53} and GA_{19} requires further study, however. The range of hitherto available synthetic C_{20}-GAs, namely 3β hydroxy,[14] 13-hydroxy,[13] 2β,13-dihydroxy,[15,27] 3β,13-dihydroxy,[28] and 13,15β-dihydroxy[29] derivatives, has been usefully augmented by the new analogues. Their availability has not only facilitated the identification of the new GAs, but a knowledge of their mass spectral fragmentation patterns will also assist in locating the position of hydroxy groups in further naturally occurring C_{20}-GAs.



Scheme 4. Synthesis of 12α- and 12β-Hydroxy C_{20}-Gibberellins.

EXPERIMENTAL

General directions: Infrared spectra (υ_{max}) were recorded on a Perkin-Elmer 683 spectrophotometer in 0.25 mm NaCl solution cells using deuterochloroform. NMR spectra were recorded on the following instruments: Varian Gemini 300, VXR300 and VXR500. For proton spectra recorded in chloroform, the residual peak of $C\underline{H}Cl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. Where indicated by † or *, assignments may be interchanged. Mass spectra (70 eV) were recorded on a VG Micromass 7070F double focussing mass spectrometer. Flash chromatography was conducted according to the method of Still and coworkers[120] using Merck Kieselgel 60; medium pressure liquid chromatography (MPLC) was conducted using a Duramat® pump, a Water Associate Differential Refractometer R40 diffractometer and Merck Lobar® Fertigsäule Größe LiChroprep® Si60 (40-63μm) columns.

Methoxymethylation of *ent*-10β-Hydroxy-3α,12α,13-trihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone. Diisopropylethylamine (DIPEA) (1.60 ml, 9.2 mmol, 12.6 eq), a catalytic amount of DMAP, then methoxymethyl chloride (MOMCl) (0.70 ml, 9.1 mmol, 12.5 eq) was added to a solution of triol **7** (270 mg, 0.73 mmol) in dry CH_2Cl_2 (30 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left to warm to room temperature. After 4 days, sat. $NaHCO_3$ solution (20 ml) was added and the reaction was left stirring for 20 min. The layers were separated and the aqueous phase was back extracted with CH_2Cl_2 (2x20 ml). The combined organic phases were washed with HCl (1M, 2x20 ml), brine (2x20ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc 2:1 - 1:1) afforded in order of elution:

***ent*-10β-Hydroxy-3α,12α,13-tri(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone** (230 mg, 62%, as a colourless oil). **IR** ν_{max} 1775, 1735 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23 (3H, s, H18), 1.50 - 2.40 (7H, m), 2.74 (1H, d, J = 10.3 Hz, H6), 3.31 (1H, d, J = 10.3 Hz, H5), 3.36, 3.38, 3.39 (3x3H, s, $-OCH_2OC\underline{H}_3$), 3.74 (3H, s, $-CO_2CH_3$), 4.01 (1H, d, J = 3.6 Hz, H3), 4.22 (1H, m, H12), 4.54, 4.80 (2x1H , ABd, J = 7.2 Hz, $12\text{-}OC\underline{H}_2OCH_3$†), 4.67, 4.86 (2x1H, ABd, J = 6.6 Hz, $13\text{-}OC\underline{H}_2OCH_3$†), 4.68, 4.73 (2x1H, ABd, J = 6.9 Hz, $3\text{-}OC\underline{H}_2OCH_3$†), 5.16 (1H, br s, H17), 5.27 (1H, br s, H'17), 5.94 (1H, dd, J_1 = 8.8 Hz, J_2 = 3.6 Hz, H2), 6.31 (1H, d, J = 8.8 Hz, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (C18), 25.9 (C11), 42.2 (C14), 43.4 (C15), 48.7 (C9), 50.1 (C8), 50.4 (C6), 52.1 ($-CO_2\underline{C}H_3$), 53.2 (C4), 53.8 (C5), 55.3, 55.4, 55.7 ($3xOCH_2O\underline{C}H_3$), 75.0 (C3), 78.2 (C12), 86.8 (C13), 90.4 ($13\text{-}O\underline{C}H_2OCH_3$), 91.5 (C10), 96.1, 96.8 ($12\text{-}O\underline{C}H_2OCH_3$, $3\text{-}O\underline{C}H_2OCH_3$), 112.8 (C17), 131.3 (C1), 132.1 (C2), 144.5 (C16), 172.4, (C7), 178.1 (C19). LRMS (EI) *m/z* 508 (M^+, 4%), 477 (26), 463 (30), 446 (28), 420 (22), 401 (30), 375 (32), 357 (52), 325 (78), 313 (38), 295 (46), 267 (90), 253 (54), 235 (52), 223 (62), 209 (100). HRMS found 508.2308, $C_{26}H_{36}O_{10}$ requires 508.2308.

***ent*-3α,10β-Dihydroxy-12α,13-di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone** (60 mg, 16%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.20 - 2.30 (8H, m), 2.76 (1H, d, J = 10.3 Hz, H6), 3.21 (1H, d, J = 10.3 Hz, H5), 3.35, 3.38, (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.73 (3H, s, $-CO_2CH_3$), 4.15 (1H, d, J = 3.6 Hz, H3), 4.21 (1H, dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, H12), 4.54, 4.80 (2x1H, ABd, J = 7.1 Hz, $12\text{-}OC\underline{H}_2OCH_3$†), 4.66, 4.85 (2x1H, ABd, J = 6.5 Hz, $13\text{-}OC\underline{H}_2OCH_3$†), 5.16 (1H, br s, H17), 5.27 (1H, br s, H'17), 5.90 (1H, dd, J_1 = 9.2 Hz, J_2 = 3.6 Hz, H2), 6.32 (1H, d, J = 9.2 Hz, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C18), 25.9 (C11), 42.3 (C14), 43.4 (C15), 48.8 (C9), 50.2 (C6), 50.4 (C8), 52.2 ($-CO_2\underline{C}H_3$), 53.3 (C5), 53.4 (C4), 55.4, 55.4 ($12\text{-}OCH_2O\underline{C}H_3$, $13\text{-}OCH_2O\underline{C}H_3$), 69.8 (C3), 78.3 (C12), 86.8 (C13), 90.5 ($13\text{-}O\underline{C}H_2OCH_3$), 91.6 (C10), 96.1 ($12\text{-}O\underline{C}H_2OCH_3$), 113.0 (C17), 132.5 (C1), 132.5 (C2), 144.4 (C16), 172.6 (C7), 178.3 (C19).

***ent*-12α,13-Di(methoxymethoxy)-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester (8).** The tri(methoxymethyl) ether prepared above (310 mg, 0.61 mmol) was dissolved in dry THF (5 ml) containing *t*-butyl alcohol (500 μl, 5.3 mmol, 8.7 eq). After cooling to -78°C, liquid NH_3 (approximately 120 ml) was distilled into the flask from a $NaNH_2$ solution. Lithium metal (approximately 20 mg, 3.0 mg

atom) was added in small pieces with vigorous stirring. Upon the appearance of a deep blue colour, the reaction was quenched with saturated NH_4Cl solution (5 ml). The NH_3 was allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in EtAc (50 ml) and acidified with phosphoric acid (10%, 20 ml). The layers were separated and the aqueous layer was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (3x15 ml) to pH 4, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a yellow oil. Chromatography (hexane/EtAc/acetic acid, 2:1:0.1) afforded the acid **8** (228 mg, 83%) as a colourless oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, s, H18), 0.85 - 2.65 (12H, m), 2.83 (1H, br s, H5), 3.09 (1H, d, J = 5.2 Hz, H6), 3.33, 3.40 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO2CH3), 3.79 (1H, dd, J_1 = 10.0 Hz, J_2 = 7.0 Hz, H12), 4.57, 4.78 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.67, 4.90 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.13 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.44 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (C2), 26.1 (C18), 26.5 (C11), 34.5 (C3), 39.1 (C14), 43.3 (C8), 43.7 (C15), 46.9 (C9), 49.2 (C4), 49.5 (C6), 51.1 (C5), 51.6 (-$CO_2\underline{C}H_3$), 54.9, 55.2 (12-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 77.5 (C12), 86.5 (C13), 91.2 (13-$O\underline{C}H_2OCH_3$), 96.8 (12-$O\underline{C}H_2OCH_3$), 110.1 (C17), 114.0 (C1), 140.5 (C10), 145.6 (C16), 176.4 (C7), 181.0 (C19). LRMS (EI) *m/z* 450 (M^+, 19%), 405 (50), 388 (15), 373 (41), 343 (35), 328 (53), 314 (46), 297 (51), 283 (100), 269 (44), 255 (47), 239 (43), 211 (56), 129 (36), 105 (47). HRMS found 450.2252, $C_{24}H_{34}O_8$ requires 450.2254.

Methyl *ent*-19-Chloro-12α,13-di(methoxymethoxy)-19-oxo-20-norgibberella-1(10),16-dien-7-oate (9). A vigorously stirred solution of oxalyl chloride (0.54 ml, 6.1 mmol, 12 eq) in dry ether (10 ml) containing 1 drop of DMF under an atmosphere of nitrogen was cooled to -30°C. The acid **8** (230 mg, 0.51 mmol) dissolved in dry ether (4.0 ml) and pyridine (1.5 ml) was slowly added to the oxalyl chloride solution. The solution was then left overnight to warm to room temperature. The reaction was worked up by filtering through a sintered funnel and washing the solid residue thoroughly with dry ether (5x20 ml). The solvent was removed *in vacuo* and the excess oxalyl chloride and pyridine were removed by azeotroping with dry benzene (4x30 ml). Finally, filtration through a small plug of celite followed by removal of the solvent *in vacuo* furnished the desired acid chloride (197 mg, 82%) as a yellow oil. IR 1815, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, H18), 1.20 - 2.70 (11H, m), 2.87 (1H, d, J = 6.2 Hz, H6), 2.98 (1H, br s, H5), 3.35, 3.39 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.71 (3H, s, -CO_2CH_3), 3.79 (1H, dd, J_1 = 10.4 Hz, J_2 = 6.7 Hz, H12), 4.59, 4.81 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.14 (1H, br s, H17), 5.18 (1H, br s, H'17), 5.43 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (C2), 25.4 (C18), 26.5 (C11), 35.6 (C3), 39.5 (C14), 44.2 (C15), 47.0 (C9), 49.5 (C8 and C6 overlapped), 51.4 (C5), 51.8 (-$CO_2\underline{C}H_3$), 54.1 (C4), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 77.8 (C12), 86.4 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 97.0 (12-$O\underline{C}H_2OCH_3$), 110.4 (C17), 113.3 (C1), 140.7 (C10), 145.3 (C16), 176.0 (C7 and C19 overlapped). LRMS (EI) *m/z* 468 (M^+, 6%), 423 (16), 373 (7), 344 (16), 328 (40), 297 (21), 283 (100), 269 (34), 239 (30), 211 (34). HRMS found 468.1914, $C_{24}H_{33}O_7{}^{35}Cl$ requires 468.1915.

Methyl *ent*-19-Diazomethyl-12α,13-di(methoxymethoxy)-19-oxo-20-norgibberella-1(10),16-dien-7-oate (9). The acid chloride prepared above (197 mg, 0.42 mmol) in ether (10 ml) was slowly cannulated into a dried solution of diazomethane in ether (100 ml) at -30°C under an atmosphere of nitrogen. After 14 h the solvent was removed *in vacuo* and the residue was purified on silica gel (hexane/EtAc, 2:1) to afford, in order of elution, the acid chloride (20 mg, 10%), followed by the desired diazoketone **9** (146 mg, 73%) as a yellow oil. IR 2108, 1730, 1635 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.50 - 2.60 (11H, m), 2.77 (1H, br s, H5), 2.94 (1H, d, J = 5.8 Hz, H6), 3.34, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 3.82 (1H, dd, J_1 = 10.4 Hz, J_2 = 6.7 Hz, H12), 4.57, 4.79 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.90 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.39 (1H, s, -COCH=N_2), 5.42 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (C2), 26.1 (C18), 26.6 (C11), 34.5 (C3), 39.4 (C14), 43.7 (C15), 46.3 (C8), 47.0 (C9), 49.1 (C4), 49.6

(C6), 51.6 (-$CO_2\underline{C}H_3$), 51.6 (C5), 53.6 (19-$CO\underline{C}H{=}N_2$), 55.2 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 77.7 (C12), 86.5 (C13), 91.4 (13-$O\underline{C}H_2OCH_3$), 96.9 (12-$O\underline{C}H_2OCH_3$), 110.1 (C17), 113.4 (C1), 141.1 (C10), 145.6 (C16), 176.4 (C7), 197.2 (C19). LRMS (EI) *m/z* 446 (M^+-N_2, 5%), 401 (39), 369 (31), 339 (27), 311 (22), 281 (23), 267 (24), 239 (37), 225 (26), 211 (36), 195 (23), 179 (26) 143 (32), 129 (36), 105 (47), 91 (100), 69 (43). HRMS found 474.2365, $C_{25}H_{34}O_7N_2$ requires 474.2366.

Di-*t*-butylsalicylimidato Cuprate Treatment of Methyl*ent*-12α,13-Di(methoxymethoxy)-19-diazomethyl-19-oxo-20-norgibberella-1(10),16-dien-7-oate (19). The diazoketone prepared above (0.1 mmol) in toluene (2.8 ml) was added dropwise to a solution of di-*t*-butylsalicylimidato cuprate (4.2 mg, 10 mol%) dissolved in toluene (5.6 ml) at reflux, under an atmosphere of nitrogen. After 15 min, TLC analysis indicated that the reaction was complete. The solution was diluted with EtAc (20 ml), washed with NH_3 solution (2M, 2x4 ml) and brine (5 ml). The combined aqueous phases were back-extracted with EtAc (2x4 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc 2:1 - 1:1) afforded in order of elution:

Methyl *ent*-12α,13-Di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclogibberell-16-en-7-oate (10): IR 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s, H18), 1.20 - 2.60 (11H, m), 2.52 (1H, d, *J* = 6.0 Hz, H6), 2.70 (1H, br s, H5), 3.10 (1H, dd, J_1 = 6 Hz, J_2 = 2.6 Hz, H2), 3.32, 3.39 (2x3H, s, -$OCH_2O\underline{C}H_3$), 3.70 (3H, s, -$CO_2\underline{C}H_3$), 3.73 (1H, m, H12), 4.50, 4.73 (2x1H, ABd, *J* = 6.8 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.65, 4.91 (2x1H, ABd, *J* = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.16 (1H, br s, H'17), 5.74 (1H, m, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C18), 26.8 (C11), 30.9 (C2), 39.4 (C20), 43.7 (C3), 44.3 (C15), 46.2 (C9), 48.7 (C6), 49.1 (C14 and C8 overlapped), 50.9 (C4), 51.7 (-$CO_2\underline{C}H_3$), 54.8 (C5), 55.3 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 77.5 (C12), 86.2 (C13), 91.4 (13-$O\underline{C}H_2OCH_3$), 97.0 (12-$O\underline{C}H_2OCH_3$), 110.7 (C17), 121.6 (C1), 141.6 (C10), 144.8 (C16), 175.7 (C7), 219.3 (C19). LRMS (EI) *m/z* 446 (M^+, 14%), 415 (15), 401 (100), 369 (80), 339 (62), 310 (42), 267 (35), 237 (47), 211 (48), 178 (33), 145 (46), 119 (54), 105 (64), 90 (49), 56 (71). HRMS found 446.2306, $C_{25}H_{34}O_7$ requires 446.2305.

Methyl *ent*-12α,13-di(methoxymethoxy)-19-oxo-2,19-methanogibberella-1(10),16-dien-7-oate (11): IR 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, s, H18), 1.20 - 2.50 (13H, m), 2.40 (1H, d, *J* = 8.9 Hz, H5), 2.69 (1H, d, *J* = 8.9 Hz, H6), 3.34 (2x3H, s, 12-$OCH_2OC\underline{H}_3$, and 13-$OCH_2OC\underline{H}_3$ overlapped), 3.70 (3H, s, -$CO_2\underline{C}H_3$), 3.90 (1H, dd, *J* = 6.5 Hz, H12), 4.53, 4.79 (2x1H, ABd, *J* = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.62, 4.83 (2x1H, ABd, *J* = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.15 (1H, br s, H17) 5.25 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2 (C18), 17.3 (C2), 27.6 (C11), 30.0 (C1), 32.1 (C20), 38.1 (C3), 42.3 (C14), 43.1 (C10), 44.2 (C9), 45.4 (C15), 47.8 (C4), 50.5 (C8), 50.8 (C6 and -CO_2CH_3 overlapped), 51.7 (C5), 55.2, 55.4 (12-$OCH_2O\underline{C}H_3$, 13-$OCH_2O\underline{C}H_3$), 78.6 (C12), 86.4 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.4 (12-$O\underline{C}H_2OCH_3$), 112.2 (C17), 144.8 (C16), 173.9 (C7), 213.8 (C19). LRMS (EI) *m/z* 446 (M^+, 13%), 415 (15), 401 (100), 369 (46), 339 (25), 311 (23), 281 (19), 225 (19), 205 (28), 175 (39), 135 (26), 105 (29), 90 (36) 69 (31), 54 (27). HRMS found 446.2306, $C_{25}H_{34}O_7$ requires 446.2305.

Methyl *ent*-12α,13-Di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (12). Ketone **11** (26 mg, 0.058 mmol) was dissolved in dry THF (1.7 ml) containing *t*-butyl alcohol (17 µl, 0.18 mmol). After cooling to -78°C, liquid NH_3 (approximately 15 ml) was distilled into the flask from a $NaNH_2$ solution. Lithium metal (approximately 1.6 mg, 0.23 mg atom) was added in small pieces with vigorous stirring . The reaction was quenched with sat. NH_4Cl solution (5 ml) upon the appearance of a deep blue colour that persisted for 5 sec. The NH_3 was then allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in water (10 ml) and EtAc (50 ml), the layers were separated and the aqueous layer was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in CH_2Cl_2 (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After 15 min TLC

analysis indicated that the reaction was complete. Sat. $NaHCO_3$ solution containing 7% sodium thiosulfate (20 ml) was added, and reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with EtAc (60 ml), the layers were separated and the organic phase was washed with sat. $NaHCO_3$ solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1) afforded the desired cyclopentanone **12** (23.5 mg, 90%) as a colourless oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.20 - 2.40 (15H, m), 2.40 (2H, s, H5 and H6 overlapped), 3.35, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.69 (3H, s, -CO_2CH_3), 4.29 (1H, m, H12), 4.53, 4.78 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.64, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.13 (1H, br s, H17), 5.29 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 19.6 (C2), 28.9 (C11), 36.4 (C20), 37.9 (C1), 41.3 (C3), 43.3 (C14), 44.6 (C15), 48.5, 48.8 (C10, C4), 51.7 (C6), 51.8 (-$CO_2\underline{C}H_3$), 52.0 (C9), 53.6 (C8), 55.3 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 59.7 (C5), 78.5 (C12), 87.6 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 95.7 (12-$O\underline{C}H_2OCH_3$), 112.8 (C17), 144.8 (C16), 173.2 (C7), 219.8 (C19). LRMS (EI) *m/z* 448 (M^+, 1%), 417 (12), 403 (100), 388 (13), 371 (54), 341 (29), 311 (16), 283 (11), 269 (17), 239 (11), 149 (11), 121 (10), 105 (17), 91 (254), 55 (21). HRMS found 448.2460, $C_{25}H_{36}O_7$ requires 448.2461.

Dimethyl *ent*-12α,13-Di(methoxymethoxy)-20-oxo-gibberell-16-ene-7,19-dioate (13). Dry (oil free) potassium hydride (approximately 35 mg, 0 9 mmol) was added to a stirred solution of the cyclopentanone **12** (70 mg, 0.156 mmol) in dry THF (4 ml) and dry DMF (4 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was complete. The reaction was throughly flushed with nitrogen, then carefully quenched with methanol (5 ml), and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and EtAc (50 ml), the layers were separated and the aqueous phase was extracted with EtAc (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired aldehyde **13** (55 mg, 71%) as an oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.20 (1H, d, J = 12.2 Hz, H5), 3.30 (6H, s, 12-$OCH_2OC\underline{H}_3$ and 13-$OCH_2OC\underline{H}_3$ overlapped), 3.64, 3.70 (2x3H, s, -CO_2CH_3), 3.73 (1H, d, J = 12.2 Hz, H6), 3.81 (1H, m, J = 7.2 Hz, H12), 4.52, 4.81 (1H, d, J = 7.2 Hz, 13-$OC\underline{H}_2OCH_3$†), 4.62, 4.78 (1H, d, J = 6.6 Hz, 12-$OC\underline{H}_2OCH_3$†), 5.10 (1H, br s, H17), 5.16 (1H, br s, H'17), 9.67 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 26.9 (C11), 27.7 (C18), 32.9 (C1), 37.4 (C3), 44.2, 44.3 (C14, C15), 44.7 (C4), 47.9 (C8), 49.5 (C6), 51.6, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 55.6 (C9), 57.0 (C5), 59.9 (C10), 78.6 (C12), 86.0 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.5 (12-$O\underline{C}H_2OCH_3$), 111.5 (C17), 144.5 (C16), 174.9, 176.2 (C19, C7), 205.1 (C20). LRMS (EI) *m/z* 494 (M^+, 7%), 463 (9), 449 (49), 417 (100), 387 (95), 373 (89), 358 (74), 329 (70), 299 (70), 269 (46), 239 (55), 211 (39), 179 (35), 135 (29) 91 (27) 69 (28). HRMS found 494.2514, $C_{26}H_{38}O_9$ requires 494.2516.

***ent*-20-Hydroxy-12α,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (14).** $NaBH_4$ (3.7 mg, 0.09 mmol) was added to a solution of the aldehyde **13** (12.0 mg, 0.024 mmol) in methanol (4 ml) at 0°C. After 1 h, TLC analysis indicated that the reaction was complete. The solution was diluted with EtAc (50 ml) and acidified with NaH_2PO_4 solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 1:1) afforded the lactone **14** (7.0 mg, 71%) as an oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.80 - 2.40 (13H, m), 2.24 (1H, d, J = 12.6 Hz,

H5), 2.75 (1H, d, J = 12.6 Hz, H6), 3.36, 3.37 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.70 (3H, s, -CO_2CH_3), 4.07 (1H, d, J_{gem} = 12.3 Hz, 20-pro-S-H), 4.22 (1H, m, H12), 4.33 (1H, dd, J_{gem} = 12.3 Hz, $J_{20,1\beta}$ = 2.1 Hz, 20-pro-R-H), 4.52, 4.78 (2x1H, ABd, J = 7.3 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.62, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.17 (2H, br s, H17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.1 (C18), 25.9 (C11), 38.3 (C1), 39.7 (C3), 41.4 (C10), 41.7 (C14), 42.6 (C4), 45.4 (C15), 47.3 (C8), 51.7 (C6), 52.0 (-$CO_2\underline{C}H_3$), 53.0, 53 (C5, C9), 55.3, 55.4 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 74.0 (C20), 78.1 (C12), 87.7 (C13), 91.7 (13-$O\underline{C}H_2OCH_3$), 96.0 (12-$O\underline{C}H_2OCH_3$), 112.8 (C17), 144.1 (C16), 173.2, 175.0 (C19, C7). LRMS (EI) *m/z* 433 (M^+-OCH_3, 10%), 419 (100), 387 (32), 359 (20), 269 (18), 225 (16). LRMS (CI) *m/z* 465 (M^++1, 100%), 449 (20), 433 (55), 389 (30), 347 (26), 270 (15).

***ent*-12α,20-Dihydroxy-13-oxo-12(13→16)*abeo*-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (15)**. Dowex resin (100 mg of wet resin, H^+ form) was added to a solution of the lactone **14** (7 mg, 0.015 mmol) in methanol (6 ml) and water (1.0 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1 - 1:2) afforded the rearranged product **16** (4.2 mg 86%) as a slightly off white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 1.14 (3H, s, H17), 0.80 - 2.40 (12H, m), 2.29 (1H, d, J = 11.5 Hz, H5), 2.52 (1H, d, J = 18.9 Hz, H14β), 2.69 (1H, d, J = 11.5 Hz, H6), 2.73 (1H, dd, J_1 = 18.9 Hz, J_2 = 4.0 Hz, H14α), 3.55 (1H, m, H12), 3.74 (3H, s, -CO_2CH_3), 4.10 (1H, d, J_{gem} = 12.7 Hz, 20-pro-S-H), 4.50 (1H, dd, J_{gem} = 12.7 Hz, $J_{20,1\beta}$ = 2.1 Hz, 20-pro-R-H).

Dimethyl *ent*-12α,13-Dihydroxy-20-oxo-gibberell-16-ene-7,19-dioate (16). Dowex resin (150 mg of wet resin, H^+ form) was added to a solution of the aldehyde **13** (12 mg, 0.024 mmol) in methanol (8.3 ml) and water (1.7 ml). The reaction mixture was then heated under reflux for 48 h. TLC analysis indicated that two major compounds were present. The reaction mixture was diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 1:1) afforded only the desired deprotected aldehyde **13** (4 mg, 40%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.50 (15H, m), 2.23 (1H, d, J = 11.7 Hz, H5), 3.69 (4H, s, H6 and 7-CO_2CH_3# overlapped), 3.74 (4H, s, H12 and 19-CO_2CH_3# overlapped), 5.13 (2H, br s, H17), 9.74 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.7 (C18), 28.1 (C11), 33.1 (C1), 37.5 (C3), 43.3 (C14), 44.6 (C4), 48.2 (C15), 48.7 (C8), 49.1 (C6), 51.8, 51.9 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.9 (C9), 57.4 (C5), 59.9 (C10), 74.2 (C12), 79.8 (C13), 109.8 (C17), 149.0 (C16), 175.2, 176.3 (C19, C7), 205.0 (C20). LRMS (CI) *m/z* 406 (M^++1, 100%), 375 (72), 282 (78), 136 (15).

Dimethyl *ent*-12α,13-Di(methoxymethoxy)gibberell-16-ene-7,19-dioate (17). Aldehyde **13** (27 mg, 0.055 mmol) was dissolved in methanol (2.0 ml), NaOH solution (2M, 6 ml) added, and the mixture heated at reflux for 24 h. The mixture was diluted with EtAc/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc/ acetic acid, 2:1:0.1) provided the dicarboxylic acid (24.7 mg, 97%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 0.80 - 2.50 (18H, m), 2.22 (1H, d, J = 13.2 Hz, H5), 3.36 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.38 (4H, s, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 4.13 (1H, m, H12), 4.55, 4.80 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.65, 4.85 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.12 (1H, br s, H17), 5.24 (1H, br s, H'17).

Anhydrous hydrazine (0.25 ml) was added to a solution of the the dicarboxylic acid (24.0 mg, 0.051 mmol) in ethanediol (2.0 ml) and the reaction mixture was heated at 100°C for 30 min. Half a pellet of NaOH

(approximately 200 mg) was added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction was left overnight. The mixture was diluted with EtAc/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. The solvent was removed under a gentle stream of nitrogen, and finally chromatography on silica gel (hexane/EtAc, 3:1) afforded the 20-desoxy derivative **17** (6. mg, 25%) as a colourless oil. IR 1725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, s, H20), 1.04 (3H, s, H18), 0.80 - 2.30 (13H, m), 2.15 (1H, d, J = 11.4 Hz, H5), 3.35 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.36 (4H, s, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 3.90 (1H, m, H12), 4.55, 4.79 (2x1H, ABd, J = 7.1 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.66, 4.89 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.14 (1H, br s, H17), 5.18 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 19.4 (C2), 27.1 (C11), 27.9 (C18), 37.6, (C1), 38.9 (C3), 43.8, 44.2 (C4, C10), 45.1, 45.2 (C14, C15), 48.0 (C8), 50.1 (C6), 51.4, 51.6 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.3, 55.4 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 56.5 (C9), 58.5 (C5), 79.7 (C12), 86.1 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.7 (12-$O\underline{C}H_2OCH_3$), 111.0 (C17), 145.6 (C16), 175.8, 177.3 (C19, C7). LRMS (EI) *m/z* 480 (M^+, 4%), 435 (100), 403 (33), 375 (57), 344 (39), 315 (32), 299 (50), 271 (31), 241 (32), 181 (57), 143 (63), 57 (50). HRMS found 480.2723, $C_{26}H_{40}O_8$ requires 480.2723.

Dimethyl *ent*-12ζ,20-Dihydroxy-13-oxo-12(13->16)*abeo*-gibberellane-7,19-dioate (18). Dowex resin (80 mg of wet resin) was added to a solution of the ether **15** (6.0 mg, 0.012 mmol) in methanol (9 ml) and water (1.6 ml). The reaction was then heated under reflux for 44 h. The reaction mixture was cooled, diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 1:1) afforded in order of elution, the 12β-epimer of **18** (3.0 mg, 61%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (3H, s, H20), 1.07 (6H, s, H18 and H17 overlapped), 0.80 - 2.30 (12H, m), 2.08 (1H, d, J = 11.6 Hz, H5), 2.30 (1H, d, J = 18.7 Hz, H14β), 2.73 (1H, dd, J_1 = 18.7 Hz, J_2 = 4.0 Hz, H14α), 3.49 (1H, d, J = 11.6 Hz, H6), 3.56 (1H, br s, H12), 3.66, 3.73 (2x3H, s, -CO_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2 (C17), 17.1 (C20), 19.4 (C2), 27.8 (C18), 28.3 (C11), 37.7, (C1), 38.1 (C3), 42.3 (C4), 43.5 (C13), 44.0 (C10), 47.2 (C14), 49.8 (C6), 49.9 (C15), 51.4, 51.6 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.8 (C9), 57.0 (C8), 59.5 (C5), 175.4, 177.2 (C19, C7), 217.5 (C16), followed by the 12α-epimer of **18** (2.0 mg, 39%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.65 (3H, s, H20), 1.05 (3H, s, H18), 1.12 (3H, s, H17), 0.80 - 2.30 (12H, m), 2.30 (1H, d, J = 11.6 Hz, H5), 2.35 (1H, d, J = 18.9 Hz, H14β), 2.70 (1H, dd, J_1 = 18.9 Hz, J_2 = 3.8 Hz, H14α), 3.48 (1H, d, J = 11.6 Hz, H6), 3.54 (1H, br s, H12), 3.67, 3.72 (2x3H, s, -CO_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (C17), 16.2 (C20), 19.4 (C2), 27.8 (C18), 28.3 (C11), 37.7, (C1), 38.1 (C3), 42.3 (C4), 43.5 (C13), 44.0 (C10), 47.2 (C14), 49.8 (C6), 49.9 (C15), 51.4, 51.6 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.8 (C9), 57.0 (C8), 59.5 (C5), 175.4, 177.2 (C19, C7), 217.5 (C16).

Methoxymethylation of *ent*-10β-Hydroxy-3α,12β,13-trihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone. DIPEA (2.60 ml, 15.0 mmol, 13 eq), a catalytic amount of DMAP, followed by chloromethyl methyl ether (1.00 ml 13.1 mmol, 12 eq) were added to a solution of triol (410 mg, 1.10 mmol) in dry CH_2Cl_2 (30 ml) at 0°C under an atmosphere of nitrogen, and the reaction left to warm to room temperature. After 4 days, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x20 ml). The combined organic phases were washed with HCl (1M, 2x20 ml), then with brine (2x20ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1 - 1:1) afforded the desired tri(methoxymethoxy) ether (387 mg, 70%) as a colourless oil followed by the 12,13-di(methoxymethoxy) derivative (113 mg, 20%) which could be recycled.

***ent*-10β-Hydroxy-3α,12β,13-tri(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s, H18), 1.70 - 2.20 (7H, m), 2.77 (1H, d, J = 10.5 Hz, H6), 3.26 (1H, d, J = 10.5 Hz, H5), 3.33, 3.36, (3x3H, s, $-OCH_2OC\underline{H}_3$), 3.67 (1H, t, J = 7.9 Hz, H12), 3.73 (3H, s, $-CO_2CH_3$), 3.99 (1H, d, J = 3.5 Hz, H3), 4.59, 4.72 (2x1H, ABd, J = 7.0 Hz, $3\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 4.65, 4.90 (2x1H, ABd, J = 6.8 Hz, $13\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 4.66, 4.72 (2x1H, d, J = 6.9 Hz, $12\ OC\underline{H}_2OCH_3^{\dagger}$), 5.17 (1H, br s, H17), 5.21 (1H, br s, H'17), 5.93 (1H, dd, J_1 = 9.4 Hz, J_2 = 3.5 Hz, H2), 6.27 (1H, d, J = 9.4, Hz, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C18), 25.9 (C11), 37.1 (C14), 43.8 (C15), 47.2 (C9), 50.1 (C6), 50.6 (C8), 51.9 ($-CO_2\underline{C}H_3$), 53.1 (C5), 53.3 (C4), 55.0, 55.1 and 55.5 ($12\text{-}OCH_2O\underline{C}H_3$, $3\text{-}OCH_2O\underline{C}H_3$, $13\text{-}OCH_2O\underline{C}H_3$), 74.8 (C3), 79.6 (C12), 84.7 (C13), 89.9 ($13\text{-}O\underline{C}H_2OCH_3$), 91.8 (C10), 96.6, 96.9 ($12\text{-}O\underline{C}H_2OCH_3$, $3\ O\underline{C}H_2OCH_3$), 111.3 (C17), 131.2 (C1), 132.0 (C2), 150.8 (C16), 172.2 (C7), 177.8 (C19). LRMS (EI) *m/z* 508 (M^+, 4%), 477 (10), 463 (13), 446 (18), 420 (20), 401 (20), 385 (31), 371 (20), 357 (34), 341 (60), 325 (60), 309 (76), 281 (100), 267 (74), 249 (38), 235 (32), 223 (34), 209 (48). HRMS found 508.2308, $C_{26}H_{36}O_{10}$ requires 508.2308.

***ent*-3α,10β-Dihydroxy-12β,13-di(methoxymethoxy)-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.70 - 2.30 (8H, m), 2.80 (1H, d, J = 11.0 Hz, H6), 3.17 (1H, d, J = 11.0 Hz, H5), 3.34, 3.37 (2x3H, s, $13\text{-}OCH_2OC\underline{H}_3$, $12\text{-}OCH_2OC\underline{H}_3$), 3.68 (1H, t, J = 6.6 Hz, H12), 3.74 (3H, s, $-CO_2CH_3$), 4.16 (1H, d, J = 3.7 Hz, H3), 4.60, 4.73 (2x1H, ABd, J = 7.0 Hz, $12\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 4.66, 4.91 (2x1H, ABd, J = 6.8 Hz, $13\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 5.18 (1H, br s, H17), 5.23 (1H, br s, H'17), 5.90 (1H, dd, J_1 = 9.3 Hz, J_2 = 3.7 Hz, H2), 6.31 (1H, d, J = 9.3 Hz, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (C18), 26.0 (C11), 37.2 (C14), 43.9 (C15), 47.3 (C9), 50.1 (C6), 50.8 (C8), 52.2 ($-CO_2\underline{C}H_3$), 52.8 (C5), 53.4 (C4), 55.2 ($12\text{-}OCH_2O\underline{C}H_3$ and $13\text{-}OCH_2O\underline{C}H_3$ overlapped), 69.5 (C3), 79.7 (C12), 84.8 (C13), 90.1 ($13\text{-}O\underline{C}H_2OCH_3$), 91.9 (C10), 97.0 ($12\text{-}O\underline{C}H_2OCH_3$), 111.6 (C17), 132.2 (C1), 132.6 (C2), 150.8 (C16), 172.6 (C7), 178.4 (C19). LRMS (EI) *m/z* 464 (M^+, 2%), 433 (4), 419 (40), 387 (20), 357 (26), 325 (37), 281 (46), 267 (71), 253 (50), 237 (43), 223 (60), 209 (100), 181 (40), 91 (62). HRMS found 464.2048, $C_{24}H_{32}O_9$ requires 4664.2046.

***ent*-12β,13-Di(methoxymethoxy)-20-norgibberella-1(10),16-diene-7,19-dioic Acid 7-Methyl Ester**. The tri(methoxymethoxy) ether prepared above (215 mg, 0.42 mmol) was dissolved in dry THF (2 ml) containing *t*-butyl alcohol (300 µl, 3.2 mmol, 7.5 eq). After cooling to -78°C, liquid NH_3 (approximately 20 ml) was distilled into the flask from a $NaNH_2$ solution. Lithium metal (approximately 14 mg, 2.0 mg atom) was added in small pieces with vigorous stirring. Upon appearance of a persistent deep blue colour, the reaction was quenched with saturated NH_4Cl solution (5 ml) and the ammonia was allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in phosphoric acid (10%, 20 ml) and EtAc (50 ml), the layers were separated and the aqueous layer was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (3x15 ml) to pH 4, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a yellow oil. Chromatography (hexane/EtAc/acetic acid, 2:1:0.1) afforded the $\Delta^{1(10)}$-ene acid (145 mg, 76%) as a colourless oil. IR 1720 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 1.28 - 2.60 (12H, m), 2.84 (1H, br s, H5), 3.15 (1H, d, J = 5.8 Hz, H6), 3.31, 3.41 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.54 (1H, d, J = 5.3 Hz, H12), 3.70 (3H, s, $-CO_2CH_3$), 4.54, 4.72 (2x1H, ABd, J = 6.9 Hz, $12\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 4.69, 4.81 (2x1H, ABd, J = 6.5 Hz, $13\text{-}OC\underline{H}_2OCH_3^{\dagger}$), 5.04 (1H, br s, H17), 5.06 (1H, br s, H'17), 5.48 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (C2), 24.7 (C11), 26.1 (C18), 34.4 (C3), 37.4 (C14), 38.8 (C15), 43.3 (C8), 45.9 (C9), 49.7 (C4), 50.0, 50.8 (C6, C5), 51.5 ($-CO_2\underline{C}H_3$), 54.7, 55.2 ($12\text{-}OCH_2O\underline{C}H_3$, $13\text{-}OCH_2O\underline{C}H_3$), 79.2 (C12), 87.2 (C13), 91.3 ($13\text{-}O\underline{C}H_2OCH_3$), 96.3 ($12\text{-}O\underline{C}H_2OCH_3$), 108.0 (C17), 114.6 (C1), 140.9 (C10), 150.0 (C16), 176.6 (C7), 181.0 (C19). LRMS *m/z* 450 (M^+, 20%), 405 (43), 388 (20), 373 (33), 343 (38), 328 (53), 314 (47), 297 (51), 283 (100), 255 (39), 239 (42), 211 (49), 101 (66), 58 (100). HRMS found 450.2253, $C_{24}H_{34}O_8$ requires 450.2254.

Methyl*ent*-19-Chloro-12β,13-di(methoxymethoxy)-19-oxo-20-norgibberella-1(10),16-dien-7-oate (19). A vigorously stirred solution of oxalyl chloride (0.28 ml, 3.2 mmol, 10eq) in dry ether (10 ml) containing DMF (1 µl) under an atmosphere of nitrogen was cooled to -30°C. To this solution was slowly added the acid prepared above (145 mg, 0.32 mmol) dissolved in dry ether (2.5 ml) and pyridine (0.8 ml). The solution was then left overnight to warm up to room temperature. The reaction was worked up by filtering through a sintered funnel and washing the solid residue throughly with dry ether (5x20 ml). The solvent was removed *in vacuo* and excessive oxalyl chloride and pyridine were removed by azeotroping with dry benzene (4x30 ml). Finally, filtration through a small plug of Celite followed by removal of the solvent *in vacuo* furnished the desired acid chloride (134 mg, 89%) as a yellow oil. IR 1814, 1725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, s, H18), 1.70 - 2.60 (11H, m), 2.93 (1H, d, J = 6.4 Hz, H6), 2.96 (1H, br s, H5), 3.34, 3.40 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.56 (1H, d, J = 5.2 Hz, H12), 3.70 (3H, s, -CO_2CH_3), 4.57, 4.74 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3^+$), 4.69, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-$OC\underline{H}_2OCH_3^+$), 5.05 (1H, br s, H17), 5.08 (1H, br s, H'17), 5.45 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (C2), 24.7 (C11), 25.3 (C18), 35.8 (C14), 37.7 (C3), 39.2 (C15), 45.9 (C9), 50.0 (C6), 50.1 (C8), 51.1 (C5), 51.7 (-$CO_2\underline{C}H_3$), 54.1 (C4), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 79.1 (C12), 87.2 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 96.3 (12-$O\underline{C}H_2OCH_3$), 108.2 (C17), 113.8 (C1), 140.9 (C10), 149.8 (C16), 175.7, 176.2 (C7, C19). LRMS (EI) *m/z* 468 (M^+, 6%), 423 (17), 344 (16), 328 (47), 299 (29), 283 (100), 269 (24), 255 (35), 239 (53), 211 (36), 197 (17). HRMS found 468.1914, $C_{24}H_{33}O_7{}^{35}Cl$ requires 468.1915.

Methyl*ent*-12β,13-Di(methoxymethoxy)-19-diazomethyl-19-oxo-20-norgibberella-1(10),16-dien-7-oate (19). The acid chloride (140 mg, 0.30 mmol) in ether (10 ml) was slowly cannulated into a dried solution of diazomethane in ether (100 ml) at -30°C under an atmosphere of nitrogen. The solution was left to warm up overnight, whereupon the reaction was judged to be complete by TLC analysis. The solvent was removed *in vacuo* and the residue was purified on silica gel (hexane/EtAc, 2:1) to yield the diazoketone 19 (130 mg, 91%) as a yellow oil. IR 2107, 1727, 1639 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 1.60 - 2.60 (11H, m), 2.80 (1H, br s, H5), 2.90 (1H, d, J = 6.4 Hz, H6), 3.32, 3.41 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.56 (1H, d, J = 5.3 Hz, H12), 3.68 (3H, s, -CO_2CH_3), 4.55, 4.72 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3^+$), 4.70, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-$OC\underline{H}_2OCH_3^+$), 5.04 (1H, br s, H17), 5.07 (1H, br s, H'17), 5.43 (1H, s, -$COCH{=}N_2$), 5.47 (1H, br s, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (C2), 24.8 (C11), 26.1 (C18), 33.9 (C3), 37.6 (C14), 39.2 (C15), 42.0 (C9), 46.5 (C8), 49.7 (C4), 50.2, 51.1 (C6, C5), 51.5 (-$CO_2\underline{C}H_3$), 53.7 (19-$CO\underline{C}H{=}N_2$), 55.1, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 79.1 (C12), 87.1 (C13), 91.5 (13-$O\underline{C}H_2OCH_3$), 96.3 (12-$O\underline{C}H_2OCH_3$), 108.1 (C17), 114.2 (C1), 141.6 (C10), 150.1 (C16), 176.5 (C7), 197.2 (C19). LRMS (EI) *m/z* 446 (M^+-N_2, 13%), 430 (8), 415 (19), 401 (100), 369 (82), 339 (60), 311 (48), 281 (51), 251 (56), 237 (68), 211 (52), 195 (39), 179 (34) 143 (34), 121 (38), 105 (49), 91 (51). HRMS found 446.2305, $C_{25}H_{34}O_7$ (M^+-N_2) requires 446.2305.

Copper(II)acetylacetonate Treatment of Methyl*ent*-12β,13-Di(methoxymethoxy)-19-diazo methyl-19-oxo-20-norgibberella-1(10),16-dien-7-oate (19). The diazoketone **19** (47.4 mg, 0.1 mmol) in dry dichloroethane (1.1 ml) was added dropwise to a solution of copper(II)acetylacetonate (2.7 mg, 15 mol%) dissolved in dry dichloroethane (1.75 ml) at reflux, under an atmosphere of nitrogen. After 15 min, TLC analysis indicated that the reaction was complete. The solution was diluted with EtAc (25 ml), washed with NH_3 solution (2M, 2x2 ml), and brine (4 ml). The combined aqueous phases were back-extracted with EtAc (2x5 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Chromatography on silica gel (hexane/EtAc 2:1 - 1:1) afforded in order of elution:

Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-2,19-methanogibberella-1(10),16-dien-7-oate (20). (33 mg, 75%): IR 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s, H18), 1.20 - 2.40 (11H, m), 2.56 (1H, d, J = 6.6 Hz, H6), 2.81 (1H, br s, H5), 3.10 (1H, m, H2), 3.30, 3.40 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.52 (1H, m, H12), 3.69 (3H, s, -CO_2CH_3), 4.52, 4.65 (2x1H, ABd, J = 6.7 Hz, 12-$OC\underline{H}_2OCH_3^+$), 4.65, 4.82 (2x1H, ABd, J = 6.5 Hz, 13-$OC\underline{H}_2OCH_3^+$), 5.00 (2H, apparent br t, J = 2.7 Hz,

H17), 5.84 (1H, m, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C18), 25.9 (C11), 31.0 (C2), 37.3 (19-CO<u>C</u>H$_2$-), 39.0 (C15$^+$), 44.2 (C14$^+$), 45.1 (C9), 49.2 (C6), 49.3 (C3), 49.8, 50.4 (C8, C4), 51.6 (-CO$_2$<u>C</u>H$_3$), 54.5 (C5), 55.3 (13-OCH$_2$O<u>C</u>H$_3$ and 12-OCH$_2$O<u>C</u>H$_3$ overlapped), 78.9 (C12), 86.9 (C13), 91.4 (13-O<u>C</u>H$_2$OCH$_3$), 96.5 (12-O<u>C</u>H$_2$OCH$_3$), 108.4 (C17), 122.5 (C1), 141.0 (C10), 149.4 (C16), 175.8 (C7), 219.7 (C19). LRMS (EI) *m/z* 446 (M$^+$, 14%), 415 (9), 401 (100), 369 (62), 339 (51), 310 (35), 283 (28), 267 (32), 251 (37), 237 (39), 211 (33), 195 (29), 181 (23), 143 (28), 119 (42), 105 (47), 69 (32). HRMS found 446.2305, $C_{25}H_{34}O_7$ requires 446.2305.

Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclo gibberell-16-en-7-oate (21). (11 mg, 25%): mp 150 - 153°C. IR 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.19 - 2.40 (13H, m), 2.45 (1H, d, *J* = 7.5 Hz, H5), 2.61 (1H, d, *J* = 7.5 Hz, H6), 3.31 (2x3H, s, 13-OCH$_2$OC<u>H</u>$_3$ and 12-OCH$_2$OC<u>H</u>$_3$ overlapped), 3.52 (1H, d, *J* = 5.8 Hz, H12), 3.70 (3H, s, -CO$_2$CH$_3$), 4.50, 4.72 (2x1H, ABd, *J* = 7.2 Hz, 12-OC<u>H</u>$_2$OCH$_3$$^+$), 4.60, 4.83 (2x1H, ABd, *J* = 6.6 Hz, 13-OC<u>H</u>$_2$OCH$_3$$^+$), 5.15 (2H, br s, H17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (C18), 17.3 (C2), 25.9 (C11), 29.2 (C1), 32.4 (-CO<u>C</u>H-), 38.6, 38.7 (C3, C14), 41.2 (C10), 43.4 (C9), 44.8 (C15), 47.9 (C4), 51.1, 51.3 (C6, C5), 51.6 (C8), 51.7 (-CO$_2$<u>C</u>H$_3$), 55.2, 55.3 (12-OCH$_2$O<u>C</u>H$_3$, 13-OCH$_2$O<u>C</u>H$_3$), 78.6 (C12), 86.2 (C13), 91.5 (13-O<u>C</u>H$_2$OCH$_3$), 96.7 (12-O<u>C</u>H$_2$OCH$_3$), 109.2 (C17), 149.6 (C16), 174.7 (C7), 214.7 (C19). LRMS (EI) *m/z* 446 (M$^+$, 16%), 415 (14), 401 (100), 385 (10), 370 (40), 353 (14), 338 (30), 281 (26), 175 (38), 143 (26), 129 (26), 105 (38), 91 (40). HRMS found $C_{25}H_{34}O_7$, 446.2305 requires 446.2305.

Lithium-Ammonia Reduction of Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclo gibberell-16-en-7-oate (21). Ketone **21** (52 mg, 0.12 mmol) was dissolved in dry THF (3.0 ml) together with *t*-butyl alcohol (35 µl, 0.37 mmol). After cooling to -78°C, liquid NH_3 (approximately 15 ml) was distilled into the flask from a $NaNH_2$ solution. Lithium metal (approximately 3.5 mg, 0.72 mg atom) was added in small pieces with vigorous stirring. Upon the appearance of a deep blue colour that persisted for 5 sec, the reaction was quenched with saturated NH_4Cl solution (5 ml). . The NH_3 was then allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in water (10 ml) and EtAc (50 ml), the layers were separated and the aqueous layer was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in CH_2Cl_2 (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After 15 min, when TLC analysis indicated that the reaction was complete, sat. $NaHCO_3$ solution containing 7% sodium thiosulfate (20 ml) was added and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with EtAc (60 ml), the layers were separated and the organic phase was washed with sat. $NaHCO_3$ solution (10 ml), brine (10 ml) and the combined aqueous phases were back-extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1) afforded in order of elution:

Methyl *ent*-12β-Methoxymethoxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (23): 22.6 mg, 50%, slightly coloured oil). IR 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s, H18), 1.10 - 2.20 (15H, m), 2.35 (1H, d, *J* = 11.9 Hz, H5), 2.45 (1H, d, *J* = 11.9 Hz, H6), 2.71 (1H, d, *J* = 4.5 Hz, H13), 3.37 (3H, s, -OCH$_2$OC<u>H</u>$_3$), 3.65 (1H, m, H12), 3.68 (3H, s, -CO$_2$CH$_3$), 4.64, 4.74 (2x1H, ABd, *J* = 6.7 Hz, -OC<u>H</u>$_2$OCH$_3$), 5.00 (1H, br s, H17), 5.05 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (C18), 19.8 (C2), 27.9 (C11), 34.1 (-CO<u>C</u>H$_2$-), 36.5 (C14), 38.1 (C3), 43.6 (C1), 45.6, 46.5 (C15, C13), 49.1 (C10), 50.7 (C9), 51.1 (C4), 51.7 (-CO$_2$<u>C</u>H$_3$), 52.0 (C6), 53.6 (C8), 55.3 (-OCH$_2$O<u>C</u>H$_3$), 59.4 (C5), 80.3 (C12), 94.8 (-O<u>C</u>H$_2$OCH$_3$), 109.5 (C17), 151.8 (C16), 173.6 (C7), 220.3 (C19). LRMS (EI) *m/z* 388 (M$^+$, 3%), 356 (35), 328 (42), 312 (23), 296 (100), 268 (32), 253 (20), 225 (27), 197 (21), 149 (27), 105 (29), 91 (33). HRMS found 388.2250, $C_{23}H_{32}O_5$ requires 388.2249.

Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (22): 20 mg (38%) IR 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.20 - 2.20 (15H, m), 2.32 (1H, d, *J* = 11.9 Hz, H5), 2.44 (1H, d, *J* = 11.9 Hz, H6), 3.34, 3.36 (2x3H, s, -OCH$_2$OC<u>H</u>$_3$), 3.89 (1H, t,

J = 7.4 Hz, H12), 3.89 (3H, s, -CO_2CH_3), 4.58, 4.72 (2x1H, ABd, J = 6.9 Hz, 12-OC$\underline{H}_2$OCH_3†), 4.68, 4.93 (2x1H, ABd, J = 6.7 Hz, 13-OC$\underline{H}_2$OCH_3†), 5.18 (1H, br s, H17), 5.20 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (C18), 19.7 (C2), 29.6 (C11), 36.5 (-CO$\underline{C}H_2$-), 37.2 (C14), 38.0 (C3), 43.4 (C1), 45.2 (C15), 49.2, 49.3 (C10, C4), 50.4, 51.7 (C9, C6), 51.8 (-$CO_2\underline{C}H_3$), 53.7 (C8), 55.2, 55.3 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 59.6 (C5), 80.3 (C12), 85.2 (C13), 91.8 (13-O$\underline{C}H_2OCH_3$), 97.3 (12-O$\underline{C}H_2OCH_3$), 111.2 (C17), 151.4 (C16), 173.3 (C7), 219.9 (C19). LRMS (EI) *m/z* 448 (M^+, 2%), 417 (14), 403 (100), 387 (34), 371 (65), 355 (39), 341 (36), 327 (40), 311 (22), 269 (18), 149 (40), 118 (36), 105 (53). HRMS found 448.2460, $C_{25}H_{36}O_7$ requires 448.2461.

Further Lithium-Ammonia Reductions of Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclo gibberell-16-en-7-oate (21). When the reaction above was repeated with ketone **21** (60 mg, 0.133 mmol) and was quenched just as the blue/grey colour began to appear, the following product ratio was obtained, ketone **22** (47 mg, 78%) and ketone **23** (7 mg, 11%). If **21** (205 mg, 0.23 mmol) was reduced so that the blue colour persisted for at least 30 sec (ca 6eq of lithium: 16.5 mg, 2.4 mg atom), a product ratio of 2:1 of **23** (89 mg, 50%) and **22** (50 mg, 25%) was obtained, plus other reduction products resulting from reduction of the methyl ester function. When the reaction was repeated using **22** (70 mg, 0.156 mmol) as substrate, only a small amount of lithium (approximately 2 mg, 0.3 mg atom) was required for the blue colour to appear. However, after the addition of an excess of lithium acetate the reaction began again and appeared to proceed at a normal rate. This experiment provided the 13-deoxy compound **23** (24 mg, 40%), plus other products resulting, *inter alia*, from the reduction of the 7-methyl ester function.

Dimethyl *ent*-12β-Methoxymethoxy-20-oxo-gibberell-16-ene-7,19-dioate (24). An excess of dry (oil free) potassium hydride (approximately 16.1 mg, 0.40 mmol) was added to a stirred solution of the cyclopentanone **23** (28 mg, 0.072 mmol) in dry THF (3 ml) and dry DMF (3 ml) at 0°C under an atmosphere of nitrogen. After 2 h the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min, TLC analysis indicated that the reaction was complete and the reaction flask was again thoroughly flushed with nitrogen before quenching with methanol (5 ml). The DMF and other solvents were removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and EtAc (50 ml), the layers separated and the aqueous phase extracted with EtAc (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min, the solvent was removed under a gentle stream of nitrogen. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired aldehyde **24** (27 mg, 86%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.86 - 2.40 (13H, m), 2.21 (1H, d, J = 12.7 Hz, H5), 2.70 (1H, d, J = 4.5 Hz, H13), 3.31 (3H, s, -$OCH_2OC\underline{H}_3$), 3.56 (1H, dd, J = 7.1 Hz, H12), 3.62, 3.72 (2x3H, s, -CO_2CH_3), 3.92 (1H, d, J = 12.7 Hz, H6), 4.56, 4.65 (2x1H, ABd, J = 6.9 Hz, -OC$\underline{H}_2$OCH_3), 4.97 (1H, br s, H17), 5.00 (1H, br s, H'17), 9.64 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 26.2 (C11), 28.1 (C18), 32.8 (C1), 34.2 (C3), 37.7 (C14), 45.2 (C4), 46.3 (C15), 46.5 (C13), 49.7 (C8), 49.9 (C6), 51.6, 51.7 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.8 (C9), 55.3 (-$OCH_2O\underline{C}H_3$), 56.0 (C5), 59.8 (C10), 79.2 (C12), 94.6 (-O$\underline{C}H_2OCH_3$), 109.2 (C17), 150.9 (C16), 174.8, 176.4 (C19, C7), 205.0 (C20). LRMS (EI) *m/z* 434 (M^+-CH_3OH, 3%), 402 (25), 358 (17), 342 (28), 312 (92), 284 (100), 253 (21), 225 (55), 197 (32), 119 (30), 105 (32). HRMS found 402.2044 (M^+-CH_3OH), $C_{23}H_{30}O_6$ requires 402.2042.

Dimethyl *ent*-12β,13-Di(methoxymethoxy)-20-oxo-gibberell-16-ene-7,19-dioate (25). An excess of dry (oil free) potassium hydride (approximately 16.1 mg, 0.40 mmol) was added to a solution of the cyclopentanone **22** (30 mg, 0.067 mmol) in dry THF (2 ml) and dry DMF (2 ml) at 0°C with stirring under an atmosphere of nitrogen. The reaction mixture was left stirring for 2 h, after which time the reaction flask was thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 20 min TLC analysis indicated that the reaction was complete. The reaction was throughly flushed with

nitrogen then carefully quenched with methanol (5 ml), and the solvent removed *in vacuo*. The DMF was removed under high vacuum with gentle heating. The solid residue was dissolved in water (20 ml) and EtAc (50 ml), the layers separated, and the aqueous phase extracted with EtAc (2x20 ml). The combined organic phases were washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. After stirring for 10 min the solvent was removed under a gentle stream of nitrogen. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired aldehyde **25** (21.5 mg, 65%) as a colourless oil. IR 1725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 - 1.10 (2H, m,), 1.09 (3H, s, H18), 1.20 - 1.75 (5H, m, H9, 2xH2, 2xH11), 1.90 - 2.10 (2H, m, 2xH14), 2.14 - 2.22 (4H, m, [H5, J = 11.8 Hz] 1xH1 2xH15), 2.30 - 2.45 (1H, m, 1xH3), 3.32, 3.35 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.71, 3.73 (2x3H, s, -CO_2CH_3), 3.72 (1H, d, J = 11.8 Hz, H6), 4.51, 4.73 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.59, 4.78 (2x1H, ABd, J = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.09 (2H, br s, H17), 9.72 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 25.3 (C11), 27.8 (C18), 32.4 (C1), 37.6 (C3), 39.2 (C14), 44.6 (C15 and C4 overlapped), 48.8 (C8), 49.3 (C6), 51.6, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.8 (C9), 55.4, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 57.3 (C5), 59.7 (C10), 78.2 (C12), 85.9 (C13), 91.6 (13-$O\underline{C}H_2OCH_3$), 96.2 (12-$O\underline{C}H_2OCH_3$), 109.4 (C17), 149.4 (C16), 175.5, 176.2 (C19, C7), 204.6 (C20). LRMS (EI) *m/z* 494 (M^+, 4%), 462 (5), 432 (10), 417 (86), 389 (89), 373 (95), 358 (70), 329 (100), 299 (81), 269 (52), 239 (63), 211 (39), 185 (33), 155 (31) 121 (27) 91 (78). HRMS found 494.2514, $C_{26}H_{38}O_9$ requires 494.2516.

Dimethyl *ent*-12β,13-Dihydroxy-20-oxo-gibberell-16-ene-7,19-dioate (26). Dowex resin (95 mg of wet resin) was added to a solution of the aldehyde **25** (10 mg, 0.020 mmol) in methanol (4.3 ml) and water (0.7 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was cooled, diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 1:1) afforded the desired *12α-hydroxy GA19 methyl ester*(**26**) (7.4 mg 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.40 (15H, m), 2.18 (1H, d, J = 12.5 Hz, H5), 3.62 (1H, m, H12), 3.66, 3.73 (2x3H, s, -CO_2CH_3), 3.81 (1H, d, J = 12.5 Hz, H6), 5.08 (1H, br s, H17), 5.20 (1H, br s, H'17), 9.68 (1H, s, H20). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.7 (C11), 28.1 (C18), 32.8 (C1), 37.6 (C3), 41.5 (C14), 44.3 (C4), 44.9 (C15), 48.6 (C8), 49.6 (C6), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.3 (C9), 55.3 (C5), 59.5 (C10), 74.5 (C12), 79.6 (C13), 109.2 (C17), 152.4 (C16), 174.9, 176.4 (C19, C7), 205.7 (C20). LRMS (EI) *m/z* 406 (M^+, 5%), 388 (15), 374 (75), 360 (46), 328 (72), 300 (74), 273 (42), 241 (66), 213 (47), 167 (47), 135 (65), 121 (95), 105 (67), 91 (100), 77 (75), 55 (100). HRMS found 406.1991, $C_{22}H_{30}O_7$ requires 406.1992.

***ent*-20-Hydroxy-12β,13-di(methoxymethoxy)gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (27).** $NaBH_4$ (3.7 mg, 0.09 mmol) was added to a solution of aldehyde **25** (7.7 mg, 0.015 mmol) in methanol (3 ml) at 0°C. After 1 h TLC showed that reaction was complete. The solution was diluted with EtAc (50 ml) and acidified with NaH_2PO_4 solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel afforded the lactone **27** (6.0 mg, 90%) as a colourless oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s, H18), 0.80 - 2.20 (13H, m), 2.14 (1H, d, J = 12.4 Hz, H5), 2.76 (1H, d, J = 12.4 Hz, H6), 3.34, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.67 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.10 (1H, d, J = 13.7 Hz, H20), 4.56 (1H, d, J = 13.7 Hz, H'20), 4.56, 4.72 (2x1H, ABd, J = 7.1 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.67, 4.91 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.17 (2H, br s,H17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.0 (C18), 26.6 (C11), 37.9 (C1), 38.4 (C3), 39.7 (C14), 41.6, 42.6 (C10, C4), 46.1 (C15), 48.4 (C8), 51.3, 51.5 (C6, C5), 52.0 (-$CO_2\underline{C}H_3$), 53.7 (C9), 55.3, 55.5 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 74.0 (C20), 79.7 (C12), 85.5 (C13), 91.8 (13-$O\underline{C}H_2OCH_3$), 97.3 (12-$O\underline{C}H_2OCH_3$), 111.2 (C17), 150.3 (C16), 173.4, 175.2 (C19, C7). LRMS (EI) *m/z* 433 (M^+-OCH_3, 9%), 419 (100), 403 (8), 387 (30), 359 (12), 329

(11), 297 (11), 269 (18), 253 (13), 225 (18), 211 (12), 135 (11), 105 (15), 91 (18), 71 (19), 57 (25). HRMS found 433.2226 (M^+-OCH_3), $C_{24}H_{33}O_7$ requires 433.2226.

***ent*-12β,13,20-Trihydroxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (28).** Dowex resin (H^+) (100 mg of wet resin) was added to a solution of the lactone **27** (6 mg, 0.013 mmol) in methanol (6 ml) and water (1.0 ml). The reaction mixture was then heated under reflux for 48 h, after which time TLC analysis indicated that reaction was complete. The reaction mixture was cooled, diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1-1:2) afforded the desired *12α-hydroxy GA44 methyl ester* (**28**) (4.2 mg 86%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.20 (15H, m), 2.17 (1H, d, J = 12.6 Hz, H5), 2.79 (1H, d, J = 12.6 Hz, H6), 3.69 (1H, dd, J = 7.6 Hz, H12), 3.71 (3H, s, -CO_2CH_3), 4.11 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.43 (1H, dd, J_{gem} = 12.1 Hz, $J_{20.1\beta}$ = 2.3 Hz, 20-pro-R-H), 5.11 (1H, br s, H17), 5.27 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.2 (C18), 27.4 (C11), 38.3 (C1), 39.7 (C3), 41.0 (C14), 41.5 (C10), 42.6 (C4), 45.2 (C15), 48.4 (C8), 51.3 (C6), 52.0 (-$CO_2\underline{C}H_3$), 52.1, 52.8 (C5, C9), 74.1 (C20), 74.6 (C12), 79.1 (C13), 110.2 (C17), 153.2 (C16), 173.1, 175.1 (C19, C7). LRMS (EI) *m/z* 376 (M^+, 11%), 344 (13), 316 (13), 286 (9), 269 (64), 226 (100), 198 (22), 149 (9), 134 (13), 121 (17), 95 (15), 81 (20), 60 (18). HRMS found 376.1887, $C_{21}H_{28}O_6$ requires 376.1886.

Dimethyl *ent*-12β,13-Di(methoxymethoxy)gibberell-16-ene-7,19-dioate (29). Aldehyde **25** (29 mg, 0.059 mmol) was dissolved in methanol (2.0 ml) and NaOH solution (2M, 6.0 ml). The reaction mixture was heated at reflux for 24 h. The mixture was diluted with EtAc containing 2-butanol (20%, 50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4. The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc/acetic acid, 2:1:0.1) provided the dicarboxylic acid (26.6 mg, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, H18), 0.80 - 2.50 (18H, m), 2.17 (1H, d, J = 12.5 Hz, H5), 3.34 (3H, s, 13-$OCH_2OC\underline{H}_3$#), 3.37 (4H, s/d, 12-$OCH_2OC\underline{H}_3$# and H6 overlapped), 3.66 (1H, m, H12), 4.55, 4.74 (2x1H, ABd, J = 7.2 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.15 (2H, br s, H17), (H20 not observed). LRMS (EI) *m/z* 465 (M^+-H, 10%), 448 (6), 432 (10), 421 (12), 403 (52), 375 (18), 359 (100), 344 (28), 331 (32), 313 (44), 285 (58), 269 (28), 257 (22) 239 (30).

Anhydrous hydrazine (0.25 ml) was added to a solution of the above product (26.6 mg, 0.057 mmol) in ethanediol (1.5 ml) and the reaction was heated at 100°C for 30 min. Half a pellet of NaOH (approximately 200 mg) was added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction continued overnight. The mixture was cooled, diluted with EtAc/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4. The organic phase was dried over Na_2SO_4, filtered and the solvent removed *in-vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min the solvent was removed under a gentle stream of nitrogen. Chromatography on silica gel (hexane/EtAc, 3:1) afforded **29** (7.1 mg, 25%) as a colourless oil. IR 1725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, s, H20), 1.04 (3H, s, H18), 0.80 - 2.40 (13H, m), 1.89 (1H, d, J = 12.0 Hz, H5), 3.34, 3.38 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.42 (1H, d, J = 12.0 Hz, H6), 3.64 (1H, m, H12), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 4.53, 4.73 (2x1H, ABd, J = 7.0 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.68, 4.86 (2x1H, ABd, J = 6.6 Hz, 13-$OC\underline{H}_2OCH_3$†), 5.09 (2H, br s, H17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (C20), 19.4 (C2), 26.0 (C11), 28.0 (C18), 37.7 (C1), 38.9 (C3 and C14 overlapped), 43.6, 44.2 (C4, C10), 45.7 (C15), 48.5 (C8), 50.2 (C6), 51.4, 51.5 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 55.0 (C9), 55.4 (13-$OCH_2O\underline{C}H_3$ and 12-$OCH_2O\underline{C}H_3$ overlapped), 58.3 (C5), 79.6 (C12), 87.0 (C13), 91.7 (13-$O\underline{C}H_2OCH_3$), 96.8 (12-$O\underline{C}H_2OCH_3$), 109.2 (C17), 150.4 (C16), 175.9, 177.4

(C19, C7). LRMS (EI) *m/z* 480 (M^+, 6%), 448 (6), 435 (100), 403 (28), 388 (22), 375 (60), 359 (30), 315 (32), 299 (50), 271 (28), 181 (46), 149 (34), 121 (30), 95 (32) 85 (34) 71 (48), 57 (76). HRMS found 480.2723, $C_{26}H_{40}O_8$ requires 480.2723.

Dimethyl *ent*-12β,13-Dihydroxygibberell-16-ene-7,19-dioate (30). Dowex resin (H^+) (80 mg of wet resin) was added to a solution of **29** (7 mg, 0.014 mmol) in methanol (9 ml) and water (1.6 ml). The reaction mixture was then heated under reflux for 44 h. The reaction mixture was diluted with EtAc (50 ml) and filtered through a pad of celite. The filtrate was then washed with brine (10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 1:1) afforded *12α-hydroxy GA53 methyl ester* (**30**) (4.7 mg 82%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, s, H20), 1.08 (3H, s, H18), 0.80 - 2.30 (15H, m), 1.87 (1H, d, *J* = 12.5 Hz, H5), 3.36 (1H, d, *J* = 12.5 Hz, H6), 3.67 (4H, s, H12 and 7-CO_2CH_3#), 3.70 (3H, s, 19-CO_2CH_3#), 5.04 (1H, br s, H17), 5.19 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (C20), 19.6 (C2), 22.7 (C11), 28.9 (C18), 37.6 (C1), 39.5 (C3), 41.4 (C14), 43.8, 44.4 (C4, C10), 45.1 (C15), 48.0 (C8), 50.7 (C6), 51.5 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 54.2 (C9), 56.9 (C5), 75.0 (C12), 77.4 (C13), 108.7 (C17), 153.8 (C16), 175.3, 177.5 (C19, C7). LRMS (EI) *m/z* 392 (M^+, 9%), 360 (51), 332 (68), 318 (28), 300 (22), 272 (25), 255 (16), 213 (23), 181 (32), 149 (26), 121 (42), 97 (36), 83 (41), 71 (59) 57 (100). HRMS found 392.2198, $C_{22}H_{32}O_6$ requires 392.2199.

Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-1β,20-cyclo-19,20-cyclo-16ζ-gibberellan-7-oate (31). Ketone **22** (30 mg, 0.07 mmol) was dissolved in EtAc (10 ml), rhodium on alumina (5%, 15 mg) was added and the reaction was placed under an atmosphere of hydrogen and left stirring overnight. The reaction mixture was then diluted with EtAc (20 ml) and filtered through a pad of celite. The solvent was removed *in vacuo* to yield the mixture **32** in quantitative yield. A 3:1 mixture of the exo : endo isomers were formed.

16α- (exo) isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s, H18), 0.98 (3H, d, *J* = 6.7 Hz, H17), 0.80 - 2.50 (14H, m), 2.43 (1H, d, *J* = 8.2 Hz, H5), 2.61 (1H, d, *J* = 8.2 Hz, H6), 3.30, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.39 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.54, 4.84 (2x1H, ABd, *J* = 7.3 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.56, 4.67 (2x1H, ABd, *J* = 6.7 Hz, 13-$OC\underline{H}_2OCH_3$†). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (C18), 17.4 (C2), 18.4 (C17), 26.2 (C11), 29.6 (C1), 32.2 (-CO$\underline{C}$H-), 36.0 (C14), 38.4 (C16), 38.5 (C3), 43.2 (C10 and C9 overlapped), 45.1 (C15), 48.0 (C4), 51.2 (C6), 51.7 (-$CO_2\underline{C}H_3$), 51.8 (C5), 52.5 (C8), 55.5, 55.7 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 80.7 (C12), 84.7 (C13), 94.3 (13-$O\underline{C}H_2OCH_3$), 96.8 (12-$O\underline{C}H_2OCH_3$), 174.6 (C7), 214.6 (C19). LRMS (EI) *m/z* 448 (M^+, 51%), 417 (36), 372 (98), 340 (72), 312 (62), 283 (47), 205 (60), 175 (67), 148 (100), 110 (82), 91 (65), 69 (84). HRMS found 448.2460, $C_{25}H_{36}O_7$ requires 448.2461.

16β- (endo) isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.02 (3H, d, *J* = 7.4 Hz, H17), 0.80 - 2.50 (14H, m), 2.43 (1H, d, *J* = 8.0 Hz, H5), 2.53 (1H, d, *J* = 8.0 Hz, H6), 3.32, 3.36 (2x3H, s, -$OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.70 (3H, s, -CO_2CH_3), 4.54, 4.67 (2x1H, ABd, *J* = 6.8 Hz, 12-$OC\underline{H}_2OCH_3$†), 4.58, 4.76 (2x1H, ABd, *J* = 6.0 Hz, 13-$OC\underline{H}_2OCH_3$†). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (C17), 15.3 (C18), 17.4 (C2), 25.5 (C11), 29.3 (C1), 32.6 (-CO$\underline{C}$H-), 36.0 (C14), 38.8 (C16), 38.8 (C3), 39.0 (C10), 44.8 (C15), 45.2 (C9), 48.0 (C4), 51.6 (C6), 51.7 (-$CO_2\underline{C}H_3$), 52.2 (C5), 53.1 (C8), 55.0, 55.4 (13-$OCH_2O\underline{C}H_3$, 12-$OCH_2O\underline{C}H_3$), 75.0 (C12), 85.7 (C13), 92.5 (13-$O\underline{C}H_2OCH_3$), 96.8 (12-$O\underline{C}H_2OCH_3$), 174.6 (C7), 214.6 (C19).

Methyl *ent*-12β,13-Di(methoxymethoxy)-19-oxo-19,20-cyclo-16ζ-gibberellan-7-oate (32). Ketone mixture **31** (30 mg, 0.07 mmol) was dissolved in dry THF (2.0 ml) together with *t*-butyl alcohol (30 µl, 0.31 mmol). After cooling to -78°C, liquid NH_3 (approximately 15 ml) was distilled into the flask from a $NaNH_2$ solution. Lithium metal (approximately 1 - 2 mg, 0.20 - 0.4 mg atom, approximately 2 eq) was added in small pieces with vigorous stirring. The reaction was quenched with saturated NH_4Cl solution (5 ml), upon

the appearance of a deep blue colour that persisted for 30 sec. The NH_3 was then allowed to evaporate under a gentle flow of nitrogen. The white solid residue was dissolved in water (10 ml) and EtAc (50 ml), the layers were separated and the aqueous layer was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (15 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a yellow oil. The residue was dissolved in CH_2Cl_2 (10 ml) and treated with Dess-Martin periodinane (100 mg, 0.24 mmol, 2 eq). After 15 min, when TLC analysis indicated that the reaction was complete, sat. $NaHCO_3$ solution containing 7% sodium thiosulfate (20 ml) was added and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with EtAc (60 ml), the layers were separated and the organic phase was washed with sat. $NaHCO_3$ solution (10 ml), then brine (10 ml) and the combined aqueous phases were back-extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. ^1H NMR spectroscopy revealed a 3:1 mixture of the di(methoxymethyl) compounds **32**.

16α- (exo) isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 0.97 (3H, d, J = 6.6 Hz, H17), 0.80 - 2.40 (16H, m), 2.08 (1H, d, J = 11.8 Hz, H5), 2.42 (1H, d, J = 11.8 Hz, H6), 3.35, 3.37 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.51 (1H, t, J = 7.9 Hz, H12), 3.69 (3H, s, $-CO_2CH_3$), 4.58, 4.81 (2x1H, ABd, J = 6.7 Hz, 12-$OC\underline{H}_2OCH_3^+$), 4.59, 4.85 (2x1H, ABd, J = 7.2 Hz, 13-$OC\underline{H}_2OCH_3^+$). LRMS (EI) *m/z* 450 (M^+, 18%), 419 (16), 374 (60), 342 (66), 332 (100), 243 (36), 129 (48), 95 (44), 83 (46), 69 (62), 57 (82). HRMS found 450.2616, $C_{25}H_{38}O_7$ requires 450.2618.

16β- (endo) isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s, H18), 1.03 (3H, d, J = 7.3 Hz, H17), 0.80 - 2.40 (18H, m), 3.35, 3.37 (2x3H, s, $-OCH_2OC\underline{H}_3$), 3.69 (3H, s, $-CO_2CH_3$), 3.93 (1H, m, H12), 4.61, 4.76 (2x1H, ABd, J = 6.9 Hz, 12-$OC\underline{H}_2OCH_3^+$), 4.64, 4.83 (2x1H, ABd, J = 8.4 Hz, 13-$OC\underline{H}_2OCH_3^+$).

On chromatography on silica gel (hexane/EtAc, 2:1) the major exo epimer decomposed to **methyl *ent*-12β-13-ethylenedioxy-19-oxo-19,20-cyclo-16-*epi*-gibberellan-7-oate (33)** (15 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.02 (3H, d, J = 6.6 Hz, H17), 0.80 - 2.20 (16H, m), 2.36 (1H, d, J = 12.0 Hz, H5), 2.42 (1H, d, J = 12.0 Hz, H6), 3.61 (1H, dd, J_1 = 8.9 Hz, J_2 = 7.1 Hz, H12), 3.70 (3H, s, $-OCH_2OC\underline{H}_3$), 4.87 (1H, s, $-OCH_2O-$), 5.07 (1H, s, $-OCH_2O-$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (C18), 18.4 (C17), 19.8 (C2), 25.9 (C11), 36.1 ($-CO\underline{C}H_2-$), 36.3 (C16), 36.6 (C14), 38.0 (C3), 43.4 (C1), 45.7 (C15), 48.5, 48.6 (C10, C4), 51.8 ($-CO_2\underline{C}H_3$), 52.5 (C6), 53.0 (C9), 53.8 (C8), 59.5 (C5), 83.9 (C12), 86.0 (C13), 94.4 ($-OCH_2O-$), 173.4 (C7), 220.0 (C19). LRMS (EI) *m/z* 374 (M^+, 28%), 345 (8), 331 (100), 273 (10), 241 (9), 213 (10), 173 (7), 131 (7), 105 (9), 91 (12), 79 (10), 55 (16). HRMS found 374.2093, $C_{22}H_{30}O_5$ requires 374.2093.

***ent*-20-Hydroxy-12β-methoxymethoxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (34)**. $NaBH_4$ (3.7 mg, 0.09 mmol) was added to a solution of aldehyde **25** (8.0 mg, 0.018 mmol) in methanol (3 ml) at 0°C. After 1 h, the solution was diluted with EtAc (50 ml) and acidified with NaH_2PO_4 solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded lactone **34** (2.9mg, 90%) as an oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.10 (13H, m), 2.17 (1H, d, J = 12.6 Hz, H5), 2.73 (1H, d, J = 4.4 Hz, H13), 2.79 (1H, d, J = 12.6 Hz, H6), 3.36 (3H, s, $-OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.69 (3H, s, $-CO_2CH_3$), 4.10 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.44 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.3 Hz, 20-pro-R-H), 4.62, 4.72 (2x1H, ABd, J = 6.8 Hz, $-OC\underline{H}_2OCH_3$), 4.99 (1H, br s, H17), 5.17 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 23.3 (C18), 26.1 (C11), 34.3 (C1), 38.3 (C3), 39.9 (C14), 41.6 (C10), 42.7 (C4), 46.4 (C15), 46.8 (C13), 49.9 (C8), 51.6, 51.9 (C5, C6), 51.8 ($-CO_2\underline{C}H_3$), 53.0 (C9), 55.4 ($-OCH_2O\underline{C}H_3$), 74.2 (C20), 79.9 (C12), 94.9 ($-O\underline{C}H_2OCH_3$), 109.7 (C17), 150.8 (C16), 173.4, 175.1 (C19, C7). LRMS (EI) *m/z* 404 (M^+, 20%), 372

(53), 344 (34), 326 (25), 312 (32), 299 (23), 284 (38), 269 (24), 237 (25), 225 (29), 197 (29), 155 (36), 131 (32), 119 (43), 105 (47), 91 (52), 57 (100). HRMS found 404.2199, $C_{23}H_{32}O_6$ requires 404.2199.

***ent*-12β,20-Dihydroxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (35)** Lactone **34** (5.9 mg, 0.015 mmol) was dissolved in dry CH_2Cl_2 (1 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C and treated with dimethylboron bromide (approximately 50 µl, 0.51 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of CH_2Cl_2 (5 ml) and sat. $NaHCO_3$ solution (5 ml). After 5 min, the solution was diluted with EtAc (25 ml) and acidified with phosphoric acid (10%, 25 ml). The layers were separated and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1) afford the desired *12α-hydroxy GA_{15} methyl ester* **35** (4.6 mg, 86%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.10 (14H, m), 2.18 (1H, d, J = 12.6 Hz, H5), 2.60 (1H, d, J = 4.9 Hz, H13), 2.80 (1H, d, J = 12.6 Hz, H6), 3.69 (3H, s, $-CO_2CH_3$), 3.76 (1H, dd, J = 8.0 Hz, H12), 4.10 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.44 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.2 Hz, 20-pro-R-H), 4.98 (1H, br s, H17), 5.06 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 23.3 (C18), 27.1 (C11), 34.0 (C1), 38.3 (C3), 39.8 (C14), 41.5 (C10), 42.7 (C4), 46.5 (C15), 49.8 (C8), 50.4 (C13), 51.5 ($-CO_2\underline{C}H_3$), 51.9 (C5 and C6 overlapped), 53.0 (C9), 74.2 (C20), 75.1 (C12), 109.6 (C17), 150.6 (C16), 173.4, 175.2 (C19, C7). LRMS (EI) *m/z* 360 (M^+, 31%), 328 (22), 314 (15), 300 (47, 282 (37), 255 (43), 237 (100), 211 (18), 183 (17), 155 (19), 129 (18), 105 (25), 91 (33), 79 (23), 55 (23). HRMS found 360.1936, $C_{21}H_{28}O_5$ requires 360.1937.

Dimethyl *ent*-12β-Hydroxy-20-oxo-gibberell-16-ene-7,19-dioate (36). Aldehyde **25** (4.3 mg, 0.010 mmol) was dissolved in dry CH_2Cl_2 (1 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C with an acetone/dry ice bath and treated with dimethylboron bromide (approximately 50 µl, 0.51 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of CH_2Cl_2 (5 ml) and sat. $NaHCO_3$ solution (5 ml). After 5 min, the solution was diluted with EtAc (25 ml), and acidified with phosphoric acid (10%, 25 ml). The layers were separated, and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1) afforded the desired *12α-hydroxy GA_{24} methyl ester* **36** (3.0 mg, 77%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80 - 2.40 (14H, m), 2.23 (1H, d, J = 12.7 Hz, H5), 2.60 (1H, d, J = 4.5 Hz, H13), 3.64 (3H, s, 7-CO_2CH_3#), 3.73 (4H, m, 19-CO_2CH_3# and H12 overlapped), 3.95 (1H, d, J = 12.7 Hz, H6), 4.97 (1H, br s, H17), 5.03 (1H, br s, H'17), 9.68 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C2), 28.1 (C18), 28.5 (C11), 33.0 (C1), 34.0 (C3), 37.7 (C14), 45.2 (C4), 46.3 (C15), 49.5 (C13), 49.8 (C8), 50.0 (C6), 51.7, 51.8 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 53.2 (C9), 56.1 (C5), 59.9 (C10), 74.5 (C12), 109.1 (C17), 150.7 (C16), 174.8, 176.5 (C19, C7), 205.4 (C20). LRMS (EI) *m/z* 372 (M^+-H_2O, 7%), 358 (25), 326 (25), 312 (66), 284 (100), 253 (20), 225 (63), 199 (24), 183 (24), 155 (28), 129 (26), 105 (31), 91 (40), 79 (28), 57 (52). HRMS found 390.2043, $C_{22}H_{30}O_6$ requires 390.2042.

Dimethyl *ent*-12β-Hydroxygibberell-16-ene-7,19-dioate (37). Aldehyde **25** (46 mg, 0.105 mmol) was dissolved in methanol (2.0 ml) and NaOH solution (2M, 5.5 ml). The reaction mixture was heated at reflux for 12 h, cooled, diluted with EtAc containing 2-butanol (20%, 50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine to pH 4, and the organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc/acetic acid, 2:1:0.1) provided the dicarboxylic acid (41.7 mg, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s, H18), 0.80 - 2.50 (15H, m), 1.90 (1H, d, J = 13.1 Hz, H5), 2.74

(1H, m, H13), 3.37 (4H, s, -$OCH_2OC\underline{H}_3$ and H6 overlapped), 3.62 (1H, m, H12), 4.65, 4.74 (2x1H, ABd, J = 6.8 Hz, -$OC\underline{H}_2OCH_3$), 5.00 (1H, br s, H17), 5.04 (1H, br s, H'17), 6.00 (1H , br s, H20, hydroxy lactone tautomer). LRMS (EI) *m/z* 406 (M^+-H, 4%), 344 (79), 298 (71), 270 (100), 225 (47), 183 (37), 143 (42), 119 (55), 105 (76), 91 (90), 71 (71). HRMS found 406.1992, $C_{22}H_{30}O_7$ requires 406.1991.

Anhydrous hydrazine (0.50 ml) was added to a solution of the acid prepared above (41.7 mg, 0.102 mmol) in ethanediol (3.0 ml) and the reaction was heated at 100°C for 30 min. Two small pellets of NaOH (approximately 400 mg) were added and the temperature was raised to 116°C for 1 h. Finally, the temperature was raised to 180°C and the reaction continued overnight. The mixture was cooled, diluted with EtAc/20% 2-butanol (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc/2-butanol mixture (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane, after 10 min the solvent was removed under a gentle stream of nitrogen. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the 20-methyl product as a colourless oil (21.0 mg, 47%). IR 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.10 (3H, s, H18), 0.80 - 2.40 (13H, m), 1.88 (1H, d, J = 12.7 Hz, H5), 2.69 (1H, d, J = 4.9 Hz, H13), 3.32 (1H, d, J = 12.7 Hz, H6), 3.36 (3H, s, -$OCH_2OC\underline{H}_3$), 3.60 (1H, m, H12), 3.66, 3.68 (2x3H, s, -CO_2CH_3), 4.64, 4.72 (2x1H, ABd, J = 6.8 Hz, -$OC\underline{H}_2OCH_3$), 4.94 (1H, br s, H17), 4.98 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 25.9 (C11), 29.4 (C18), 33.9 (C1), 37.6 (C3), 39.9 (C14), 43.8, 44.5 (C4, C10), 46.5 (C15), 46.9 (C13), 49.1 (C8), 51.1 (C6), 51.4 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 53.4 (C9), 55.3 (12-$OCH_2O\underline{C}H_3$), 56.5 (C5), 80.2 (C12), 94.7 (12-$O\underline{C}H_2OCH_3$), 108.4 (C17), 152.1 (C16), 175.3, 177.7 (C19, C7). LRMS (EI) *m/z* 388 (M^+ - CH_3OH, 80%), 360 (33), 328 (63), 300 (78), 239 (53), 209 (46), 181 (100), 149 (38), 121 (50), 107 (61), 91 (40), 79 (29). HRMS found (M^+-CH_3OH) 388.2251, $C_{23}H_{32}O_5$ requires 388.2250.

The MOM ether obtained above (10.0 mg, 0.023 mmol) was dissolved in dry CH_2Cl_2 (1.5 ml) under at atmosphere of nitrogen. The solution was cooled to -78°C and treated with dimethylboron bromide (approximately 100 µl, 1.0 mmol). After 4 min at -78°C the solution was quickly transferred to a vigorously stirred mixture of CH_2Cl_2 (5 ml) and sat. $NaHCO_3$ solution (5 ml). After 5 min, the solution was diluted with EtAc (25 ml) and acidified with phosphoric acid (10%, 25 ml). The layers were separated and the organic phase was washed with brine (2x10 ml). The combined aqueous phases were extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 2:1) afford the desired *12α-hydroxy GA_{12} methyl ester* 37 (8.5 mg, 95%) as an off white solid. IR 1715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.10 (3H, s, H18), 0.80 - 2.30 (14H, m), 1.88 (1H, d, J = 12.7 Hz, H5), 2.56 (1H, d, J = 4.9 Hz, H13), 3.32 (1H, d, J = 12.7 Hz, H6), 3.67, 3.69 (2x3H, s, -CO_2CH_3), 3.45 (1H, m, H12), 4.93 (1H, br s, H17), 5.01 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 28.3 (C11), 29.4 (C18), 33.7 (C1), 37.3 (C3), 39.9 (C14), 43.8, 44.5 (C4, C10), 46.6 (C15), 49.1 (C8), 50.3 (C13), 51.1 (C6), 51.4 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 53.5 (C9), 56.6 (C5), 75.3 (C12), 108.3 (C17), 151.9 (C16), 175.3, 177.7 (C19, C7). LRMS (EI) *m/z* 344 (M^+ - CH_3OH, 3%), 316 (100), 298 (23), 284 (12), 257 (18), 239 (20), 197 (14), 181 (22), 121 (15), 107 (24), 91 (21), 79 (15). HRMS found 344.1986 (M^+-CH_3OH), $C_{21}H_{28}O_4$ requires 344.1988.

Dimethyl *ent*-12α-Hydroxygibberell-16-ene-7,19-dioate (38). Carbinol **37** (13.7 mg, 0.036 mmol) was dissolved in CH_2Cl_2 (5 ml) and treated with Dess-Martin periodinane (30 mg, 0.074 mmol, 2 eq). After 15 min TLC analysis indicated that the reaction was complete. Sat. $NaHCO_3$ solution containing 7% sodium thiosulfate (20 ml) was added, and reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with EtAc (40 ml), the layers were separated and the organic phase was washed with sat. $NaHCO_3$ solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the

solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired ketone (12.8 mg, 95%) as a colourless oil. IR 1720, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, s, H20), 1.11 (3H, s, H18), 0.80 - 2.40 (13H, m), 2.03 (1H, d, J = 12.7 Hz, H5), 3.11 (1H, d, J = 4.4 Hz, H13), 3.46 (1H, d, J = 12.7 Hz, H6), 3.68, 3.72 (2x3H, s, $-CO_2CH_3$), 5.03 (1H, br s, H17), 5.14 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (C20), 19.5 (C2), 29.1 (C18), 35.5 (C11), 37.4, 37.5 (C1,C3), 39.4 (C14), 44.1, 44.5 (C4, C10), 46.4 (C15), 48.6 (C8), 50.6 (C13), 51.6 (7-$CO_2\underline{C}H_3$ and 19-$CO_2\underline{C}H_3$ overlapped), 53.2 (C6), 56.6 (C9), 57.3 (C5), 111.7 (C17), 144.4 (C16), 175.0, 177.4 (C19, C7), 208.8 (C12). LRMS (EI) *m/z* 374 (M^+, 9%), 342 (24), 314 (100), 299 (32), 286 (19), 255 (35), 239 (20), 211 (25), 157 (15), 107 (26), 91 (26), 79 (18), 55 (56). HRMS found 374.2093, $C_{22}H_{30}O_5$ requires 374.2093.

$NaBH_4$ (5.0 mg, excess) was added to a solution of the ketone prepared above (11.0 mg, 0.029 mmol) in methanol (5 ml) at 0°C. After 10 min, the solution was diluted with EtAc (50 ml) and acidified with NaH_2PO_4 solution (20%, 20 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x20 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded *12β-hydroxy-GA_{12} methyl ester* **38** (9.0 mg, 81%) as an off white solid. IR 1725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H, s, H20), 1.05 (3H, s, H18), 0.80 - 2.30 (14H, m), 1.94 (1H, d, J = 12.0 Hz, H5), 2.67 (1H, t, J = 5.0 Hz, H13), 3.37 (1H, d, J = 12.0 Hz, H6), 3.67, 3.69 (2x3H, s, $-CO_2CH_3$), 3.81 (1H, br m, H12), 5.01 (1H, s, H17), 5.04 (1H, s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7 (C20), 19.5 (C2), 28.1 (C18), 28.6 (C11), 37.7 (C1), 39.1 (C3), 41.3 (C14), 43.7, 44.2 (C4, C10), 45.8 (C15), 47.5 (C13), 49.9 (C6), 50.2 (C8), 51.4, 51.5 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 56.9 (C9), 58.5 (C5), 70.9 (C12), 109.0 (C17), 149.1 (C16), 176.0, 177.4 (C19, C7). LRMS (EI) *m/z* 376 (M^+, 2%), 344 (55), 316 (100), 301 (24), 272 (20), 257 (23), 239 (13), 213 (27), 197 (16), 181 (32), 121 (24), 107 (39), 91 (36), 79 (27), 55 (30). HRMS found 376.2251, $C_{22}H_{32}O_5$ requires 376.2250.

Dimethyl *ent*-12,20-Dioxo-gibberell-16-ene-7,19-dioate (39). Hydroxy aldehyde **36** (8 mg, 0.018 mmol) was dissolved in CH_2Cl_2 (5 ml) and treated with Dess-Martin periodinane (15 mg, 0.037 mmol, 2 eq). After 15 min TLC analysis indicated that the reaction was complete. Sat. $NaHCO_3$ solution containing 7% sodium thiosulfate (20 ml) was added, and the reaction mixture was left stirring until the cloudiness had dissipated. The reaction mixture was diluted with EtAc (40 ml), the layers were separated and the organic phase was washed with sat. $NaHCO_3$ solution (10 ml) and brine (1x10 ml). The combined aqueous phases were back-extracted with EtAc (2x20 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired keto aldehyde **39** (6.5 mg, 90%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.36 (1H, d, J = 12.9 Hz, H5), 3.23 (1H, d, J = 5.0 Hz, H13), 3.63, 3.76 (2x3H, s, $-CO_2CH_3$), 4.02 (1H, d, J = 12.9 Hz, H6), 5.07 (1H, br s, H17), 5.17 (1H, br s, H'17), 9.72 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 27.8 (C18), 32.8 (C1), 35.6, 36.8, 37.5 (CH_2, CH_2, CH_2), 45.3 (C4), 46.3 (C15), 49.2 (C8), 49.6 (C13), 51.7, 51.9 (7-$CO_2\underline{C}H_3$, 19-$CO_2\underline{C}H_3$), 52.4 (C6), 55.9 (C9), 57.0 (C5), 60.1 (C10), 112.4 (C17), 143.3 (C16), 174.3, 176.4 (C19, C7), 205.0 (C20), 206.3 (C12). LRMS (EI) *m/z* 386 ($M^+ - H_2$, 5%), 356 (16), 328 (56), 300 (100), 269 (25), 256 (15), 239 (39), 225 (15), 209 (21), 197 (48), 181 (19), 149 (26), 119 (38), 91 (37), 79 (26). HRMS found 386.17230 (M^+-H_2), $C_{22}H_{26}O_6$ requires 386.1729.

$NaBH_4$ Reduction of Dimethyl *ent*-12,20-Dioxo-gibberell-16-ene-7,19-dioate (39). $NaBH_4$ (1.8 mg, 0.046 mmol, 2.2 eq) was added to a solution of keto aldehyde **39** (6.0 mg, 15.4 μmol) in methanol (2 ml) at 0°C. After 30 min TLC analysis showed the presence of two new compounds and no starting material remaining. The solution was diluted with EtAc (30 ml) and acidified with NaH_2PO_4 solution (20%, 10 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded in order of elution:

***ent*-20-Hydroxy-12-oxo-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (40)**: (2.3 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, s, H18), 0.50 - 2.50 (13H, m), 2.09 (1H, d, J = 12.6 Hz, H5), 2.63 (1H, d, J = 12.6 Hz, H6), 3.11 (1H, d, J = 4.8 Hz, H13), 3.30 (3H, s, -CO_2CH_3), 3.43 (1H, d, J = 12.0 Hz, H20), 3.83 (1H, d, J = 12.0 Hz, H'20), 5.00 (1H, s, H17), 5.36 (1H, s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (C2), 24.1 (C18), 34.9 (C11), 37.5 (C1), 38.2 (C3), 40.0 (C14), 41.6 (C10), 43.0 (C4), 47.1 (C15), 49.7 (C8), 51.6 (C13), 51.7 (-$CO_2\underline{C}H_3$), 51.8 (C6), 54.4 (C5), 56.6 (C9), 73.4 (C20), 112.5 (C17), 144.6 (C16), 173.3 (C19 and C7 overlapped), 204.8 (C12). LRMS (EI) *m/z* 358 (M^+, 70%), 328 (43), 312 (33), 298 (63), 253 (100), 225 (35), 211 (40), 197 (62), 129 (50), 105 (70), 91 (77), 79 (57), 55 (70). HRMS found 358.1780, $C_{21}H_{26}O_5$ requires 358.1780.

***ent*-12α,20-Dihydroxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (41)**: (2.4 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 1.20 - 2.30 (14H, m), 2.30 (1H, d, J = 12.7 Hz, H5), 2.77 (1H, d, J = 12.7 Hz, H6), 2.92 (1H, m, H13), 3.70 (3H, s, -CO_2CH_3), 4.07 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.19 (1H, m, H12), 4.34 (1H, dd, J_{gem} = 12.1 Hz, $J_{20,1\beta}$ = 2.4 Hz, 20-pro-R-H), 5.11 (1H, s, H17), 5.21 (1H, s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C2), 23.3 (C18), 27.8 (C11), 37.6 (C1), 38.3 (C3), 39.8 (C14), 41.6 (C10), 42.6 (C4), 45.9 (C13), 46.3 (C15), 49.9 (C8), 51.7 (C6), 52.0 (-$CO_2\underline{C}H_3$), 52.8 (C5), 53.1 (C9), 66.3 (C12), 74.2 (C20), 112.5 (C17), 147.3 (C16), 173.4, 175.1 (C19, C7), 204.8 (C12). LRMS (EI) *m/z* 360 (M^+, 40%), 328 (50), 314 (30), 300 (85), 282 (45), 255 (90), 237 (100), 211 (73), 155 (46), 129 (55), 105 (81), 91 (95), 79 (69), 55 (82). HRMS found 360.1936, $C_{21}H_{28}O_5$ requires 360.1937.

***ent*-20-Hydroxy-20-*t*-butyldimethylsilyloxy-12-oxogibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (42)**. Keto aldehyde **39** (25 mg, 0.064 mmol) was dissolved in methanol (2.5 ml), THF (3 ml), and NaOH solution (2M, 7.5 ml) and reaction left stirring for 15 min. The mixture was diluted with EtAc (50 ml) and was acidified with phosphoric acid (10%, 10 ml). The layers were separated and the aqueous phase was extracted with the EtAc (2x20 ml). The combined organic phases were washed with brine (3x10 ml) to pH 4, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to provide the monoester (23.9 mg, 97%) as a white solid. The material was used immediately without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 0.80 - 2.60 (14H, m), 2.36 (1H, d, J = 13.2 Hz, H5), 3.02 (1H, d, J = 13.2 Hz, H6), 3.25 (1H, br s, H13), 3.72 (3H, s, -CO_2CH_3), 5.08 (1H, br s, H17), 5.19 (1H, br s, H'17), 6.0 (1H, broad unresolved singlet, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C2), 23.3 (C18), 29.6 (C1), 36.5 (C1 and C3 overlapped), 39.8 (C14), 42.9 (C4), 46.6 (C15), 49.4 (C8 and C10 overlapped), 50.5 (C13), 51.4 (7-$CO_2\underline{C}H_3$), 52.1 (C6), 54.8 (C9), 55.9 (C5), (C20 not observed), 112.8 (C17), 143.0 (C16), 173.3, 175.8 (C19, C7), 208.1 (C12). LRMS (EI) *m/z* 374 (M^+, 13%), 356 (30), 342 (97), 314 (83), 300 (58), 269 (57), 257 (35), 239 (78), 223 (37), 211 (45), 197 (87), 157 (47), 131 (75), 119 (78), 105 (93), 91 (100), 79 (60). HRMS found 356.1624 (M^+-H_2O), $C_{21}H_{24}O_5$ requires 356.1624.

DIPEA (0.145 ml, 0.83 mmol, 12 eq), DMAP (catalytic amount), followed by TBDMSOTf (96 µl, 0.42 mmol, 6 eq) were added to a solution of the monoester prepared above (24 mg, 0.064 mmol) in dry CH_2Cl_2 (5 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was left to warm to room temperature. After 2 hr TLC analysis indicated the reaction was complete. Sat. $NaHCO_3$ solution (2 ml) was added and the reaction was left stirring for 5 min. The solution was diluted with EtAc (30 ml), layers were separated and the aqueous phase was back extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (1x10ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc 5:1 - 1:1) afforded the desired silyl ether **42** (23 mg, 73%) as a colourless oil. IR 1730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17, 0.24 (2x3H, s, -Si(CH_3)$_2$-), 0.90 (9H, s, -SiC(CH_3)$_3$), 1.13 (3H, s, H18), 0.90 - 2.50 (13H, m), 2.34 (1H, d, J = 13.1 Hz, H5), 2.86 (1H, d, J = 13.1 Hz, H6), 3.25 (1H, d, J = 4.5 Hz, H13), 3.71 (3H, s, -CO_2CH_3), 5.07 (1H, br s, H17), 5.20 (1H, br s, H'17), 5.63 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.60, -3.40 (-Si(CH_3)$_2$-), 17.7 (-Si$\underline{C}$(CH_3)$_3$), 20.7 (C2), 23.2 (C18), 25.6 (-SiC($\underline{C}H_3$)$_3$), 32.5 (C1), 36.6, 37.2 (C3, C11), 39.9 (C14), 42.5 (C4), 46.5 (C15), 47.5 (C8), 49.4 (C10), 50.6, 51.3 (C13, C6), 52.1 (7-$CO_2\underline{C}H_3$), 54.6 (C9), 56.0 (C5), 98.8 (C20), 112.8 (C17), 142.9 (C16),

173.0, 173.7 (C19, C7), 206.7 (C12). LRMS (EI) *m/z* 431 (M^+ - $C(CH_3)_3$, 100%), 403 (22), 387 (60), 343 (16), 300 (16), 251 (40), 240 (22), 129 (28), 97 (22), 83 (26), 71 (32), 57 (42). HRMS found 431.1888 (M^+-$C(CH_3)_3$), $C_{23}H_{31}O_6Si$ requires 431.1890.

***ent*-12α,20-Dihydroxy-20-*t*-butyldimethylsilyloxygibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (43).** $NaBH_4$ (1.1 mg, 29 μmol, 2 eq) was added to a solution of ketone **42** (7 mg, 14.3 μmol) in methanol (3 ml) at 0°C. After 15 min, the solution was diluted with EtAc (30 ml) and acidified with NaH_2PO_4 solution (20%, 10 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x10 ml). The combined organic phases were washed with brine (2x10 ml), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Chromatography on silica gel (hexane/EtAc, 3:1) afforded the desired 12β-carbinol **43** (5 mg, 73%) as a colourless oil. IR 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.18, 0.23 (2x3H, s, -$Si(CH_3)_2$-), 0.91 (9H, s, -$SiC(CH_3)_3$), 1.11 (3H, s, H18), 0.80 - 2.50 (14H, m), 2.20 (1H, d, *J* = 13.1 Hz, H5), 2.76 (1H, d, *J* = 13.1 Hz, H6), 2.91 (1H, m, H13), 3.69 (3H, s, -CO_2CH_3), 4.11 (1H, m, H12), 5.11 (1H, br s, H17), 5.20 (1H, br s, H'17), 5.49 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.60, -3.40 (-$Si(CH_3)_2$-), 17.8 (-$SiC(CH_3)_3$), 20.8 (C2), 23.4 (C18), 25.9 (-$SiC(CH_3)_3$), 30.0 (C11), 32.7 (C1), 37.3 (C3), 40.2 (C14), 42.4 (C4), 45.9 (C13), 46.5 (C15), 47.3 (C8), 50.0 (C10), 51.0 (C6), 51.9 (7-CO_2CH_3), 52.8 (C9), 54.1 (C5), 66.3 (C12), 99.4 (C20), 112.3 (C17), 147.4 (C16), 173.4, 174.2 (C19, C7). LRMS (EI) *m/z* 490 (M^+, 8%), 459 (6), 433 (23), 401 (63), 345 (11), 313 (31), 283 (36), 253 (44), 225 (20), 198 (34), 180 (47), 143 (32), 105 (34), 91 (100), 73 (92). HRMS found 490.2751, $C_{27}H_{42}O_6Si$ requires 490.2751.

Dimethyl *ent*-12α-Hydroxy-20-oxo-gibberell-16-ene-7,19-dioate (44). To a solution of the carbinol **43** (6 mg, 12 μmol) in THF and water (3.7 ml, 0.122 mmol, 10 eq) was added TBAF (1M, 42 ml, 24 umol, 2eq). After 15 min TLC indicated that the reaction was complete. The mixture was diluted with EtAc (50 ml) and was acidified with NaH_2PO_4 (20%, 10 ml). The layers were separated and the aqueous phase was extracted with EtAc (2x20 ml). The combined organic phases were washed with brine (2x10 ml) to pH 4. The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol (10 ml) and treated with an excess of diazomethane. After 10 min, the solvent was removed under a gentle stream of nitrogen, then chromatography on silica gel (hexane/EtAc, 1:1) afforded *12β-hydroxy-GA_{24} methyl ester* **44** (4.0 mg, 83%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 0.80 - 2.50 (14H, m), 2.24 (1H, d, *J* = 12.1 Hz, H5), 2.70 (1H, m, H13), 3.67 (3H, s, 7-CO_2CH_3#), 3.73 (4H, m, 19-CO_2CH_3# and H12 overlapped), 3.74 (1H, d, *J* = 12.1 Hz, H6), 5.04 (1H, br s, H17), 5.08 (1H, br s, H'17), 9.70 (1H, s, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C2), 27.9 (C18), 28.4 (C11), 33.0 (C1), 37.6 (C3), 40.7 (C14), 44.8 (C4), 45.0 (C15), 47.1 (C13), 49.3 (C6), 50.3 (C8), 51.7, 51.8 (7-CO_2CH_3, 19-CO_2CH_3), 56.0 (C9), 57.1 (C5), 59.9 (C10), 69.3 (C12), 110.0 (C17), 147.9 (C16), 175.3, 176.4 (C19, C7), 205.3 (C20). LRMS (EI) *m/z* 358 (M^+ - CH_3OH, 6%), 346 (6), 327 (77), 312 (9), 301 (10), 284 (9), 243 (11), 223 (12), 199 (85), 169 (33), 155 (57), 126 (78), 105 (35), 91 (96), 73 (52), 55 (100). HRMS found 358.1780 (M^+-CH_3OH), $C_{21}H_{26}O_5$ requires 358.1780.

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