Pergamon

Tetrahedron 54 (1998) 11637–11650

TETRAHEDRON

A general protocol for the hydroxylation of C-14 in gibberellins: synthesis of 14β-hydroxy-GA_1 methyl ester

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Received 3 June 1998; revised 13 July 1998; accepted 16 July 1998

Abstract

A general protocol for the 14-hydroxylation of the gibberellin molecule has been developed and is illustrated by the conversion of gibberellic acid (GA_3) into the methyl ester of 14β-hydroxy GA_1. The key steps involved oxidative cleavage of the methylene group, hydrogenation and acyloin rearrangement of the resulting 13-hydroxy-17-nor-16-one to afford the 8α,13α diastereomer. A hydroxy group was introduced adjacent to the 16-one function and then a further acyloin rearrangement effected, thereby restoring the normal gibberellin configuration with the extra hydroxyl located at C-14. Wittig methylenation under forcing conditions, followed by deprotection then afforded the target gibberellin. The sterically hindered methoxycarbonyl function group in this compound was unexpectedly partially transformed into an isopropenyl group.

Keywords: Terpenoids; Rearrangements; Hydroxylation; Wittig reactions.

The identification of new plant gibberellins ("GAs"), available in only trace amounts, has depended heavily on GCMS to provide a tentative structure, and then on partial synthesis from one of the more readily available fungal gibberellins, *e.g.* gibberellic acid (GA_3) (**1**), to confirm the provisional assignment [1,2]. Although most positions in GA_3 and its derivatives are accessible, functionalisation of the C-ring presents a significant synthetic challenge, especially if the labile functionality in the A-ring of GA_3 is to be preserved. Functionalisation of C-11 [3] and of C-12 [4] has been effected through transannular processes, while hydroxylation of C-14 has been achieved by means of an ingenious route involving a double rearrangement of the C/D-ring system, as outlined in Scheme 1 [5]. Although a 14-hydroxylated GA has yet to be identified from natural sources, the mass spectra of a number of recently isolated GAs appeared to be consistent with a 13,14-dihydroxylation pattern. We have, accordingly, sought to establish a general protocol for the preparation of such GAs with a view to providing a set of reference structures.

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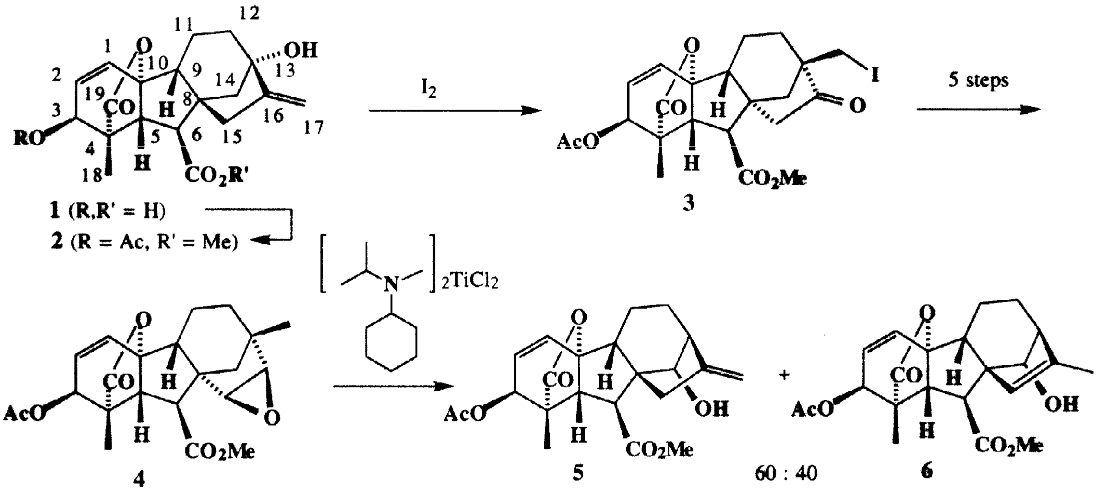
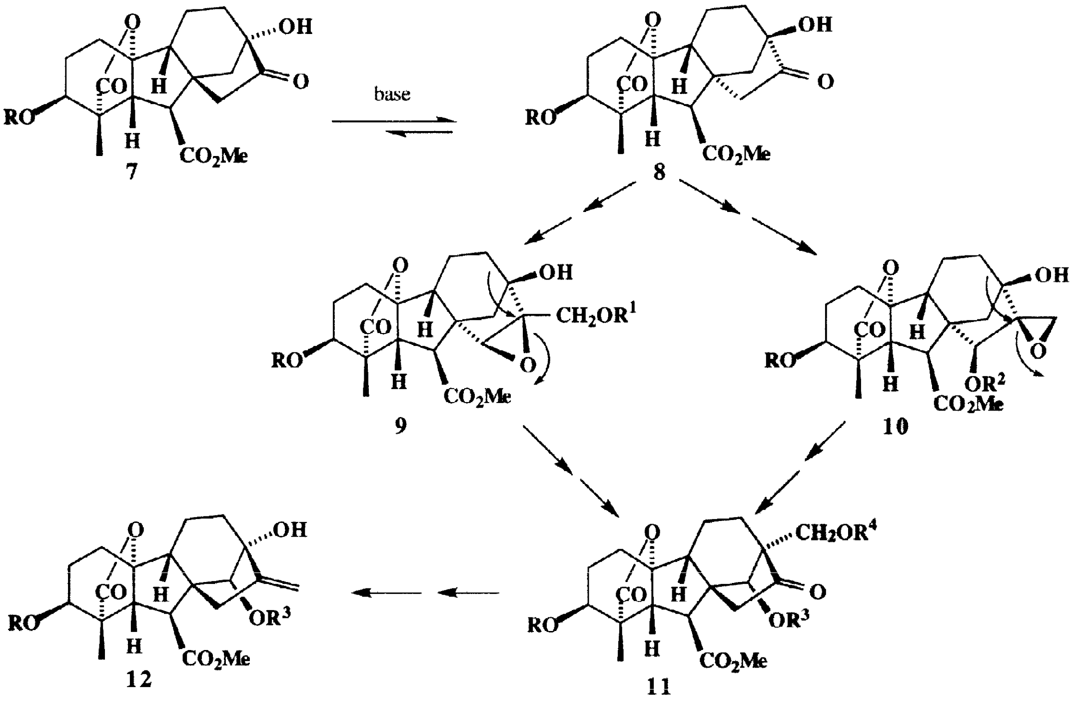
PII: S0040-4020(98)00690-5



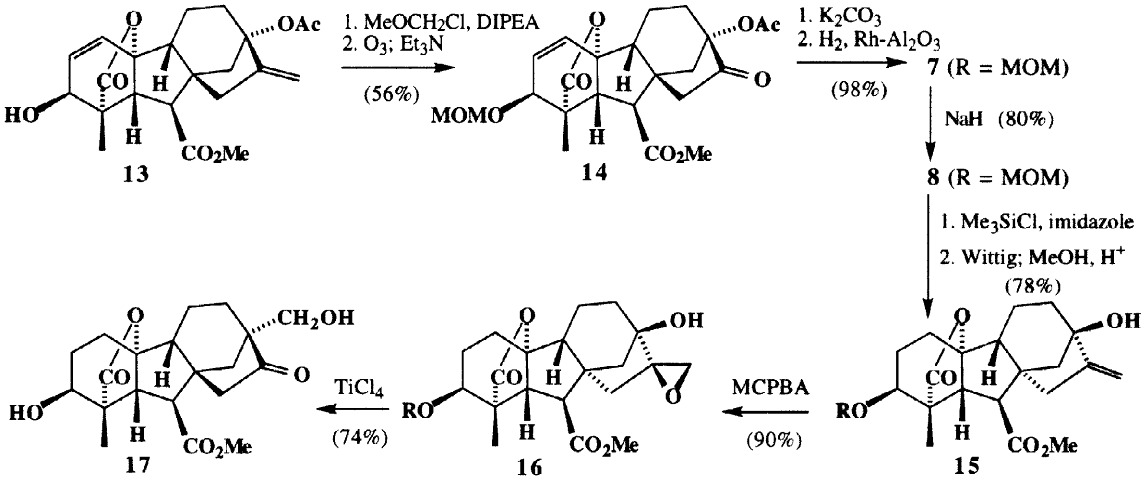
Scheme 1

Our first synthetic plan broadly followed the strategy encompassed by Scheme 1, but was predicated on an acyloin rearrangement to achieve the initial "stereochemical inversion" of the D-ring. We sought to "preserve" the 13-hydroxyl in this way with the expectation that it would be of greater assistance in driving the subsequent rearrangement to re-establish the normal GA skeleton and would also allow us to avoid the problem of generating alkene isomers as occurred in the formation of **5** and **6**. *A priori*, it appeared that treatment of either epoxide **9** or **10** should lead to **11** in which the 13-substituent could be oxidatively cleaved back to a hydroxyl. An outline of the plan, in this case leading to a derivative of 14β-hydroxy-GA$_1$ (**12**), is provided in Scheme 2.



Scheme 2

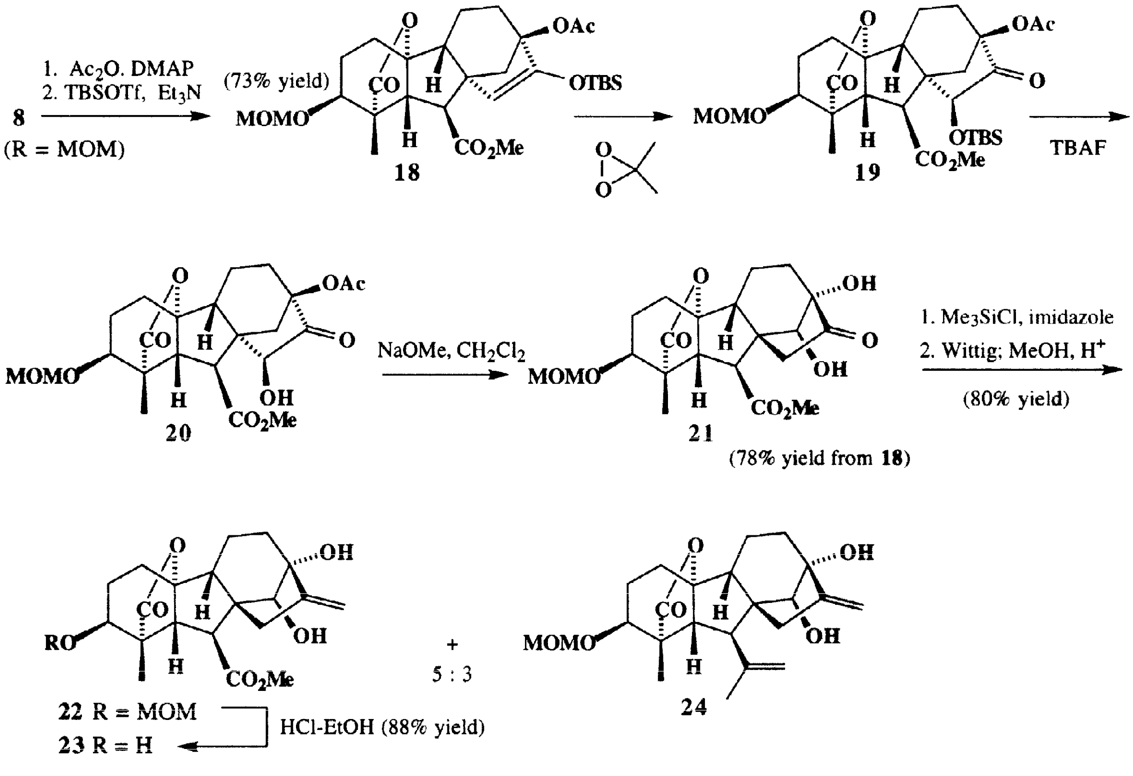
The C-ring in GAs normally adopts a boat-like conformation [6]. Migration of C-12 to C-16 as in **1**→**3**, however, allows the C-ring to take up the energetically favoured chair conformation [7]. Thus, it was expected that treatment of ketol **7** with a strong base should result in rearrangement [8,9] to the isomeric ketol **8**. In order to test our proposed strategy, we carried out the sequence summarised in Scheme 3. Thus, the 13-acetate (**13**) derived from GA3 methyl ester [10] was masked as the 3-methoxymethyl ether (to provide stability towards strong base at a subsequent stage) and the 17-methylene group cleaved by careful ozonolysis to give ketone **14**. Removal of the 13-acetate function and hydrogenation of the A-ring double bond then afforded the desired substrate **7**. Following treatment of a solution of this compound in dichloromethane with NaH, an 82% yield of the isomeric ketol **8** was obtained, along with starting material. A highly characteristic feature of C_{19}-GA ^1H NMR spectra is an isolated AB spin system derived from H-5 and H-6 in the range 2.5-3.5 ppm, with a coupling constant of J = ~10 Hz (*e.g.* for **7**, J = 10.6 Hz) [1,11]. Because of a smaller torsion angle between H-C-5 and H-C-6 in 8α,13α-GAs, however, J is reduced to ~7 Hz, so any rearrangement to this structural type is readily evident. Thus, the rearrangement to **8** was confirmed by the observation of an AB system at δ 3.24 and 2.65, (J = 6.7 Hz) for H-5 and H-6, respectively. Re-equilibration of ketol **8** with base afforded a 1:4 mixture of **7** and **8**, indicating that this ratio represents a thermodynamic preference for the latter isomer.



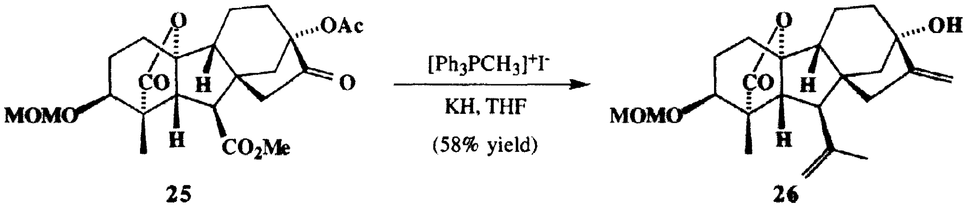
Scheme 3

Wittig methylenation of the 13-trimethylsilyl ether of **8**, followed by TMS removal, led to **15**, the epoxide **16** from which, rearranged smoothly to ketone **17**, thereby providing strong encouragement for the expectation that **11** could be prepared in an analogous manner. Accordingly, 15β-hydroxylation of **15** was effected with SeO_2 - *t*-BuOOH and then reaction with *m*-chloroperoxybenzoic acid gave epoxide **10** (R = $MeOCH_2$, R^2 = H); acetate **10** (R = $MeOCH_2$, R^2 = Ac) was also prepared. Neither of these compounds could be rearranged with any of the titanium based Lewis acids employed by Fraga *et al.* with epoxide **4** [5], however, while the use of more acidic reagents (*e.g.* $TiCl_4$, $BF_3.Et_2O$) afforded complex mixtures. It appears that the electronegative 15-substituent must inhibit the formation of the incipient 16-cationic centre required to initiate rearrangement.

Given these results, we were discouraged from investigating the preparation and rearrangement of epoxide **9** (R = $MeOCH_2$, R^1 = H), deciding instead to explore the alternative strategy of a second acyloin rearrangement to re-establish the normal GA skeleton. In the event, this approach was successful and is outlined in Scheme 4. Thus, hydroxylation at C-15 was effected by treatment of the enol TBDMS ether **18** [12] with dimethyl dioxirane [13,14], thereby affording a mixture of **19** and **20**. The former product could be readily desilylated with TBAF and it was apparent from the deshielding of H-6 in **20** (δ 3.28 compared with δ 2.65 in **8**) that hydroxylation had occurred on the more exposed *exo*-face of the D-ring. Treatment of **20** with sodium methoxide resulted in hydrolysis of the 13-acetate function and rearrangement to dihydroxy ketone **21**, as indicated by the signals in the ^1H NMR spectrum from H-5 and H-6 at δ 3.27 and 3.15, respectively, the coupling (J = 9.4 Hz) between these protons showing that the regular GA stereochemistry had been re-established; the isomerisation was equally effective with silyl ether **19**. Since the equilibrium between ketols **7** and **8** had strongly favoured **8**, the high yield of **21** came as an agreeable surprise. Presumably, the alignment of the dipoles associated with the hydroxy and carbonyl groups in ring-D of **20** destabilises this isomer, relative to **21**. *Ab initio* molecular orbital calculations indicate that the cisoid conformer of glycolaldehyde, for example, is of significantly higher energy (ΔE = 24kJ) than the transoid form [15]. Since a similar outcome was also obtained with ether **19**, any hydrogen bonding between the 16-carbonyl and the 15-hydroxyl in **20** presumably had little or no bearing on the position of equilibrium.



Scheme 4



Scheme 5

The full GA skeleton was then reconstituted by Wittig methylenation of the 13,14-bis(TMS) ether of **21**. Because of the additional steric hindrance from the 14-OTMS group, relatively vigorous conditions were required for this last step, which did not proceed at room temperature. When heated at reflux for 16 hours, the desired product **22** was obtained (after removal of theTMS protecting groups), but as a 5:3 mixture with the isopropenyl derivative **24**. Application of the same reaction conditions to the simpler GA_1 derivative **25** (Scheme 5) showed that this unusual Wittig process was not peculiar to 14-substituted gibberellins when **26** was produced similarly in 30% yield; moreover this outcome could be improved to 60% by extending the reaction time to 3 days (with repeated additions of ylide). These results may be broadly rationalised in terms of ylide attack on the methoxycarbonyl group, then addition of a nucleophile (adventitious hydroxide ion?) at phosphorus, followed by formation of triphenylphosphine oxide and the 7-methyl ketone [16]. Further reaction with the ylide would then afford the isopropenyl derivative. By conducting the Wittig reaction at 50°C, however, only **22** was obtained.

Finally, exposure of **22** to acid resulted in hydrolysis of the 3-MOM group to give 14-hydroxy-GA_1 methyl ester (**23**), the overall structure and stereochemistry of which was confirmed by single crystal X-ray crystallography (Figure 1). Application of the methodology to the preparation of further 13,14-dihydroxy GAs has been equally successful and comparisons with unknown endogenous GAs are being undertaken.

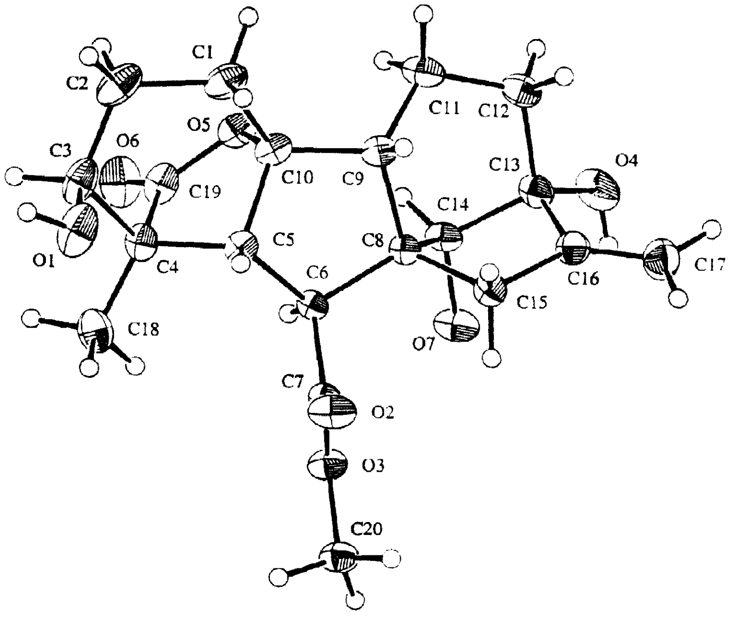


Figure 1: Ortep diagram of 14-hydroxy gibberellin A_1 methyl ester

EXPERIMENTAL

General directions: Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 683 spectrophotometer in 0.25 mm NaCl solution cells using $CHCl_3$ as solvent. NMR spectra were recorded on a Varian Gemini 300 spectrometer (ppm). For ^1H spectra recorded in $CDCl_3$, the residual peak of $CHCl_3$ was used as the internal reference (7.25 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for ^{13}C spectra. Mass spectra (70 eV) were recorded on a VG Autospec spectrometer. Flash chromatography was conducted using Merck Kieselgel 60. Note on nomenclature: Structures are named as derivatives of *ent*-gibberellane [17]. The α,β stereochemical descriptors in the body of the text describe structures as depicted; when preceded by *ent*, the descriptors are inverted.

***ent*-13-Acetoxy-10β-hydroxy-3α-methoxymethoxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** A soln of GA_3 methyl ester 13-acetate (**13**) [10] (6 g, 15 mmol), *i*-Pr_2NEt (4 ml, 22.5 mmol), 4-*N,N*-dimethylaminopyridine (DMAP) (90 mg, 0.75 mmol) and 75 ml of CH_2Cl_2 at 0°C under N_2, was treated dropwise with $MeOCH_2Cl$ (1.4 ml), warmed to 25°C slowly and then kept overnight. The reaction mixture was quenched with sat. $NaHCO_3$ at 0°C, then the organic layer washed with brine (100 ml x 2) and dried over Na_2SO_4. Chromatography on silica gel (EtOAc/hexane, 1:3) afforded a white solid (6.1g, 91% yield), m.p. 135-137°C. IR 3040, 1770, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 300MHz) δ 1.19 (3H, s, 4-Me), 2.00 (3H, s, OAc), 2.75 (1H, d, *J* = 11.0 Hz, H6), 3.29 (1H, d, *J* = 11.0 Hz, H5), 3.36 (3H, s, OMe), 3.71 (3H, s, CO_2Me), 3.79 (1H, d, *J* = 3.7 Hz, H3), 4.66 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.72 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.97 (1H, br s, H17), 5.14 (1H, br s, H'17), 5.92 (1H, dd, *J* = 9.3, 3.7 Hz, H2), 6.2 (1H, d, *J* = 9.3 Hz, H1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 16.6 (C11), 21.8 (MeCO), 36.1 (C12), 39.7 (C14), 42.5 (C15), 50.3, 50.7 (C5, C6), 50.9 (C8), 51.9 (CO_2Me), 53.1 (C4), 53.1 (C9), 55.6 (OMe), 74.8 (C3), 84.0 (C13), 90.1 (C10), 96.7 (OCH_2O), 107.9 (C17), 131.2, 132.2 (C1, C2), 153.4 (C16), 169.7 (Ac), 172.1 (C7), 178.0 (C19). MS (EI) *m/z* 446 (M^+, 29 %), 415 (57), 386 (31), 354 (100), 339 (15), 322 (35), 297 (38), 280 (56), 255 (14), 237 (37), 222 (65), 209 (27), 195 (21), 179 (16), 162 (22), 155 (21), 142 (16), 129 (17), 115 (16), 105 (14), 91 (23), 77 (14). HRMS found 446.1944, $C_{24}H_{30}O_8$ requires 446.1941.

***ent*-13-Acetoxy-10β-hydroxy-3α-methoxymethoxy-16-oxo-17,20-dinorgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (14).** A soln of the methoxymethyl ether prepared above (4.48 g, 10 mmol) in CH_2Cl_2 (500 ml) was cooled to -70°C in an acetone-dry ice bath, then treated with a stream of ozonised oxygen (1%, 25 l/h). Et_3N (18ml) was added to the soln at the same temp when TLC indicated that ca 80% of the substrate had been consumed. The mixture was kept overnight and allowed to warm to 25°C. The soln was washed with brine, dried and after chromatography on silica gel (EtOAc/hexane, 1:3~1:1), the desired product was obtained (2.5 g, 56% yield) as a white solid, m.p. 175-177°C. Calcd for $C_{23}H_{28}O_9$ C, 61.60; H, 6.29; found C, 61.52; H, 6.52. IR 3030, 1775, 1765, 1735 cm^{-1}. ^1H NMR ($CDCl_3$, 300MHz) δ 1.23 (3H, s, 4-Me), 2.04 (3H, s, OAc), 2.72 (1H, d, *J* = 14.4 Hz, H14), 2.79 (1H, d, *J* = 10.8 Hz, H6), 3.32 (1H, d, *J* = 10.8 Hz, H5), 3.37 (3H, s, OMe), 3.75 (3H, s, CO_2Me), 3.99 (1H, d, *J* = 3.7 Hz, H3), 4.67 (1H, d, *J* = 6.8 Hz, OCH_2O), 4.73 (1H, d, *J* = 6.8 Hz, OCH_2O), 5.96 (1H, dd, *J* = 9.4, 3.7 Hz, H2), 6.27 (1H, d, *J* = 9.4 Hz, H1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 16.3 (C11), 20.7 (OAc), 30.3 (C12), 36.8 (C14), 36.8 C15), 47.9 (C8), 48.2 (C4), 51.0, 51.5 (C5, C6), 52.3 (OMe), 53.3 (C9), 55.7 (OMe), 74.7 (C3), 82.5 (C13), 89.9 (C10), 96.8 (OCH_2O), 131.6, 131.7 (C1, C2), 169.9 (Ac), 171.5 (C7), 177.7 (C19), 211.9 (C16). MS (EI) *m/z* 448 (M^+, 51%), 417 (15), 403 (27), 388 (27), 356 (17), 343 (16), 328 (22), 316 (48), 299 (67), 284 (43), 271 (100), 256 (91), 242 (78), 229 (40), 211 (98), 197 (67), 169 (55), 155 (83), 143 (55), 128 (32), 115 (28), 105 (19), 91 (33), 77 (20). HRMS found 448.1735, $C_{23}H_{28}O_9$ requires 448.1733.

***ent*-10β,13-Dihydroxy-3α-methoxymethoxy-16-oxo-17,20-dinorgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (7, R = $MeOCH_2$).** A soln of K_2CO_3 (0.25 M, 100ml) was added to a soln of norketone **14** (2.24 g, 5 mmol) in MeOH (200 ml). The mixture was stirred at 25°C for 30 min and then the MeOH was removed under reduced pressure. After chromatography on silica gel (EtOAc/hexane, 1:2), the 13-hydroxy ketone (1.83 g, 90% yield) was obtained and dissolved in EtOAc and THF (1:1, 150 ml) containing Rh-Al_2O_3 (5%, 180 mg). After stirring this mixture under a H_2 atmosphere (balloon) at 25°C overnight, the catalyst was removed by filtration and the solvent evaporated under reduced pressure to afford **7** (R = $MeOCH_2$) as a white solid (1.8g, 100% yield), m.p. 181-183°C. Calcd for $C_{21}H_{28}O_8$ C, 61.75; H, 6.91; found C, 61.14; H, 7.16. IR 3520, 1775, 1750, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, 4-Me), 2.23 (1H, dd, *J* = 18.3, 3.4 Hz, H15β), 2.42 (1H, dd, *J* = 11.6, 3.4 Hz, H14α), 2.72 (1H, d, *J* = 10.6 Hz, H6), 3.23 (1H, d, *J* = 10.6 Hz, H5), 3.38 (3H, s, OMe), 3.66 (1H, br s, H3), 3.71 (3H, s, CO_2Me), 4.62 (1H, d, *J* = 7.0 Hz), 4.73 (1H, d, *J* = 7.0 Hz, OCH_2O). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5 (C18), 17.0 (C11), 24.7 (C1), 27.3 (C2), 32.9 (C12), 40.9 (C14), 46.6 (C15), 48.0 (C8), 52.1 (C6), 52.2, 52.5, 52.5 (CO_2**Me**, C9, C5), 54.3 (C4), 55.8 (OMe), 75.1 (C3), 78.7 (C13), 92.8 (C10), 95.8 (OCH_2O), 172.2 (C7), 177.5 (C19), 218.0 (C16). MS (EI) *m/z* 408 (M^+, 19%), 376 (45), 348 (50), 316 (100), 304 (42), 286 (34), 272 (27), 258 (39), 243 (30), 213 (26), 201 (13), 187 (15), 171 (11), 157 (22), 143 (15), 129 (11), 117 (10), 105 (14), 91 (18), 79 (11). HRMS found 408.1780, $C_{21}H_{28}O_8$ requires 408.1784.

***ent*-10β,13-Dihydroxy-3α-methoxymethoxy-16-oxo-17,20-dinor-8β,13β-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (8).** NaH (68mg, 60% in mineral oil; washed with hexane) was added to a soln of ketone **7** (R = $MeOCH_2$) (340 mg) in CH_2Cl_2 (10 ml) at 25°C under N_2. The mixture was kept overnight and quenched with KH_2PO_4 soln (10 ml, 20%) at 0°C. After washing with brine, drying (Na_2SO_4) and chromatography on silica gel (EtOAc/hexane, 1:2~1:1), the ketol **8** was obtained as a white solid (280 mg, 82% yield), m.p. 159 - 160 °C. Calcd for $C_{21}H_{28}O_8$, C, 61.75; H, 6.91; found C, 61.47; H, 6.89. IR 3520, 1770, 1750, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s, 4-Me), 2.17 (1H, d, *J* = 19.5 Hz, H15β), 2.60 (1H, d, *J* = 6.7 *Hz*, H6), 3.06 (1H, dd, *J* = 19.5, 3.8 Hz, H15α), 3.24 (1H, d, *J* = 6.7 *Hz*, H5), 3.88 (3H, s, OMe), 3.68 (1H, br s, H3), 3.73 (3H, s, CO_2Me), 4.63 (1H, d, *J* = 6.9 Hz, OCH_2O), 4.74 (1H, d, *J* = 6.9 Hz, OCH_2O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (C18), 17.9 (C11), 24.5 (C1), 26.1 (C2), 34.9 (C12), 46.3 (C14), 47.4 (C15), 47.8 (C8), 51.0 (C6), 52.2 (CO_2**Me**), 52.5, 54.0 (C5, C9), 53.3 (C4), 55.9 (OMe), 75.8 (C3), 81.3 (C13), 91.7 (C10), 95.8 (OCH_2O), 173.1 (C7), 177.6 (C19), 216.1 (C16). MS (EI) *m/z* 408 (M^+, 77%), 376 (95), 365 (24), 348 (100), 330 (34), 316 (80), 304 (66), 286 (65), 274 (56), 258 (67), 243 (69), 215 (56), 199 (41), 187 (47), 173

(37), 157 (60), 145 (47), 129 (42), 117 (34), 105 (46), 91 (54), 77 (43). HRMS found 408.1787, $C_{21}H_{28}O_8$ requires 408.1784.

***ent*-10β,13-Dihydroxy-3α-methoxymethoxy-20-nor-8β,13β-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (15).** Trimethylsilyl chloride (25 μl) was added dropwise to a mixture of **8** (R = $MeOCH_2$) (16 mg, 0.04 mmol) and *i*-Pr_2NEt (36 μl) in CH_2Cl_2 (1 ml) under N_2 at 0°C and the mixture allowed to warm to 25°C over 30 min. After stirring for 12 h the reaction was quenched with sat. $NaHCO_3$ at 0°C, diluted with CH_2Cl_2 (10 ml), washed with cold brine and dried over Na_2SO_4. After removal of solvent, THF (0.5 ml) was added to the residue and Wittig reagent in THF (1.0 ml), [prepared from the reaction of Ph_3PCH_3I (80mg) with KOtBu (23mg) at 25°C for 2h] added at 25°C. The reaction mixture was kept at 25°C overnight, quenched by sat. NH_4Cl and 10 ml of EtOAc added. The organic layer was washed with brine and dried, then the solvent was removed under reduced pressure. Pyridinium toluenesulfonate (40 mg) in MeOH (2 ml) was added to the residue and the mixture stirred at 25°C for 3 h. Removal of solvent and chromatography on silica gel (EtOAc/hexane, 1:3~1:1) afforded **15** (14.8 mg, 92% yield) as a white solid, m.p. 157-158 °C. ^1H NMR ($CDCl_3$, 300MHz) δ 1.20 (3H, s, 4-Me), 2.32 (1H, ddd, *J* = 17.4, 2.2, 2.2 Hz, H15β), 2.50 (1H, d, *J* = 6.9 Hz, H6), 3.11 (1H, dd, *J* = 17.4, 2.3 Hz, H15α), 3.17 (1H, d, *J* = 6.9 Hz, H5), 3.38 (3H, s, OMe), 3.67 (1H, d, *J* = 2.7 Hz, H3), 3.71 (3H, s, CO_2Me), 4.62 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.73 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.79 (1H, br s, H17), 4.95 (1H, t, *J* = 2.2 Hz, H'17). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5 (C18), 18.6 (C11), 24.5 (C1), 26.2 (C2), 38.8 (C12), 42.7 (C15), 49.8 (C14), 50.2 (C8), 50.8 (C6), 51.9 (CO_2**Me**), 53.3 (C4), 53.4, 53.8 (C5, C9), 55.8 (OMe), 76.0 (C3), 80.9 (C13), 92.1 (C10), 95.8 (OCH_2O), 102.6 (C17), 154.1 (C16), 173.8 (C7), 178.2 (C19). MS (EI) *m/z* 406 (M^+, 24 %), 388 (3), 374 (35), 361 (16), 342 (100), 328 (13), 312 (34), 301 (29), 284 (28), 268 (12), 256 (25), 241 (30), 221 (11), 213 (15), 197 (11), 185 (12), 171 (11), 157 (17), 135 (29), 105 (22), 91 (29), 79 (18). HRMS found 406.1992, $C_{22}H_{30}O_7$ requires 406.1992.

***ent*-16α,17-Epoxy-10β,13-dihydroxy-3α-methoxymethoxy-20-nor-8β,13β-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (16).** A mixture of **15** (10 mg) and MCPBA (45 mg, pre-dried with Na_2SO_4 in CH_2Cl_2) and $NaHCO_3$ (30 mg) in CH_2Cl_2 (6 ml) was stirred at room temp for 20h. EtOAc (10 ml) was added, the mixture washed with brine, then dried (Na_2SO_4). After chromatography on silica gel (EtOAc/Hexane, 1:2), epoxide **16** was obtained as a colourless gum (9.3 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s, 4-Me), 2.51 (1H, d, *J* = 6.9 Hz, H6), 2.77, 2.93 (2x1H, d, *J* = 4.3 Hz, 2xH17), 3.19 (1H, d, *J* = 6.9 Hz, H5), 3.37 (3H, s, OMe), 3.65 (1H, br s, H3), 3.71 (3H, s, CO_2Me), 4.61, 4.72 (2x1H, d, *J* = 7.0 Hz, OCH_2O). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 17.8 (C11), 24.5 (C1), 26.2 (C2), 34.2 (C12), 41.5, 41.8 (C14, C15), 48.6 (C8), 50.2 (C17), 51.0 (C6), 52.0 (CO_2Me), 53.1 (C5), 53.3 (C4), 53.9 (C9), 55.8 (OMe), 64.6 (C16), 75.4 (C13), 75.9 (C3), 92.1 (C10), 95.8 (OCH_2O), 173.5 (C7), 178.0 (C19). MS (EI) *m/z* 422 (M^+, 7%), 405 (4), 390 (27), 362 (37), 332 (16), 318 (25), 300 (33), 290 (31), 272 (26), 256 (33), 243 (13), 227 (14), 213 (15), 195 (20), 167 (16), 156 (100), 139 (95), 129 (16), 111 (68), 91 (29), 75 (43). HRMS found 422.1939, $C_{22}H_{30}O_8$ requires 422.1940.

***ent*-3α,10β-Dihydroxy-13-hydroxymethyl-16-oxo-17,20-dinorgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (17).** Titanium tetrachloride (23 μl) was added to a soln of **16** in CH_2Cl_2 (0.5 ml) at 0°C and the reaction mixture was quenched at the same temp by sat. $NaHCO_3$ after 20 min. EtOAc (5 ml) was added, the organic layer was washed with brine and dried over Na_2SO_4. After chromatography on silica gel (EtOAc/ hexane, 1:1), **17** was obtained (3.7 mg, 74% yield). IR 3600, 3500, 1765, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s, 4-Me), 2.74 (1H, d, *J* = 10.6 Hz, H6), 3.24 (1H, d, *J* = 10.6 Hz, H5), 3.49, 3.72 (2x1H, ABd, *J* = 11.3 Hz, CH_2OH), 3.73 (3H, s, CO_2Me), 3.86 (1H, br s, H3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6 (C18), 17.0 (C11), 27.1, 27.9, 27.9 (C1, C2, C12), 36.6 (C14), 48.2 (C15), 51.3 (C8), 51.3 (C6), 52.3 (MeO), 52.5 (C5), 53.8 (CH_2OH), 54.0 (C9), 54.6 (C4), 64.8 (C13), 70.0 (C3), 93.5 (C10), 172.6 (C7), 177.9 (C19), 221.2 (C16). MS (EI) *m/z* 378 (M+, 61%), 360 (38), 346 (63), 332 (28), 318 (100), 304 (66), 286 (75), 273 (54), 256 (85), 240 (51), 227 (30), 213 (43), 197 (55), 181 (30), 169 (32), 155 (38), 143 (45), 129 (42), 117 (31), 105 (53), 91 (70), 79 (45). HRMS found 378.1674, $C_{20}H_{26}O_7$ requires 378.1678.

***ent*-10β,13,15α-Trihydroxy-3α-methoxymethoxy-20-nor-8β,13β-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** Selenium dioxide (70 mg, 60 %) and *t*-butylhydroperoxide (0.4 ml, 70 % aq.) were added to a soln of **15** (81 mg) prepared above in CH_2Cl_2 (20 ml) at room temp. The mixture was sonicated until TLC showed no starting material was left (2-2.5 h). The solid was removed by filtration through Celite and the organic layer was washed with 1 N HCl, brine and dried over Na_2SO_4. After chromatography on silica gel (EtOAc/hexane, 1:1), the title compound was obtained as a white solid (72mg, 85% yield), m.p. 203 -204 °C. Calcd for $C_{22}H_{30}O_8$ C, 62.55; H, 7.16, found C, 62.03; H, 7.27 %. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s, 4-Me), 3.20, 3.27 (2x1H, ABd, *J* = 6.8 Hz, H5, H6), 3.36 (3H, s, OMe), 3.84 (1H, br s, H3), 3.85 (3H, s, CO_2Me), 4.38 (1H, s, H15), 4.61 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.72 (1H, d, *J* = 7.0 Hz, OCH_2O), 5.23 (2H, br s, H17). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 18.2 (C11), 24.5 (C1), 26.0 (C2), 38.1 (C12), 44.1 (C6), 46.5 (C14), 51.9 (CO_2Me), 53.3 (C8), 53.7 (C5), 53.7 (C9), 54.8 (C4), 55.8 (OMe), 73.0 (C15), 76.0 (C3), 79.2 (C13), 92.0 (C10), 95.7 (OCH_2O), 108.6 (C17), 158.5 (C16), 174.5 (C7), 178.5 (C19). MS (EI) *m/z* 422 (M^+, 9%), 390 (15), 373 (28), 358 (100), 340 (40), 327 (26), 313 (25), 299 (42), 281 (52), 256 (27), 239 (32), 211 (30), 183 (24), 171 (14), 157 (22), 143 (20), 129 (21), 117 (15), 105 (24), 91 (29). HRMS found 422.1939, $C_{22}H_{30}O_8$ requires 422.1941.

***ent*-15α-Acetoxy-10β,13-dihydroxy-3α-methoxymethoxy-20-nor-8β,13β-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** Ac_2O (0.06 ml) was added to a soln of the 15-carbinol prepared above in CH_2Cl_2 (2ml) and Et_3N (0.1 ml) under N_2 at 0°C. The reaction mixture was warmed to room temp and kept for 40 h. EtOAc (10 ml) was added and the organic layer was washed with sat. $NaHCO_3$, brine and dried (Na_2SO_4). After chromatography on silica gel (EtOAc/Hexane, 1:2~1:1), the title compound was obtained as a colourless gum (32mg, 68% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s, 4-Me), 2.10 (3H, s, OAc), 2.66 (1H, d, *J* = 6.7 Hz, H6), 3.18 (1H, d, *J* = 6.7 Hz, H5), 3.37 (3H, s, OMe), 3.69 (1H, br s, H3), 3.72 (3H, s, CO_2Me), 4.61 (1H, d, *J* = 6.9 Hz, OCH_2O), 4.72 (1H, d, *J* = 6.9 Hz, OCH_2O), 5.28, 5.29 (2x1H, 2xbr s, H17), 5.80 (1H, d, *J* = 1.3 Hz, H15). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 18.5 (C11), 21.1 (OAc), 24.6 (C1), 26.3 (C2), 38.5 (C12), 45.1 (C6), 47.4 (C14), 52.2 (CO_2Me), 53.4 (C8), 53.8, 54.2 (C5, C9), 54.2 (C4), 55.9 (OMe), 75.8, 76.3 (C3, C15), 79.6 (C13), 91.1 (C10), 95.9 (OCH_2O), 111.0 (C17), 154.7 (C16), 170.1 (OAc), 173.9 (C7), 177.5 (C19). MS (EI) *m/z* 464 (M^+, 22 %), 436 (27), 422 (20), 404 (100), 389 (22), 373 (23), 342 (20), 314 (22), 298 (40), 282 (22), 256 (25), 239 (35), 211 (18), 183 (15), 155 (14), 133 (15), 105 (19), 91 (23). HRMS found 464.2056, $C_{24}H_{32}O_9$ requires 464.2046.

***ent*-15α-Acetoxy, 10β,13-dihydroxy-16β,17-epoxy-3α-methoxymethoxy-20-nor-8β,13β-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (10, R = $MeOCH_2$, R^2 = Ac).** A mixture of the acetate prepared above (18 mg) and MCPBA (80 mg, pre-dried with Na_2SO_4 in CH_2Cl_2) and $NaHCO_3$ (50 mg) in CH_2Cl_2 (10 ml) was stirred at room temp for 40h. EtOAc (20 ml) was added, the mixture washed with brine, then dried (Na_2SO_4). After chromatography on silica gel (EtOAc/Hexane, 1:2~1:1), epoxide (**10**, R = $MeOCH_2$, R^2 = Ac) was obtained as a colourless gum (15mg, 80 % yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, s, 4-Me), 2.10 (3H, s, OAc), 2.76 (1H, d, J = 5.3 Hz, H17), 2.89 (1H, d, J = 6.7 Hz, H6), 3.21 (1H, d, J = 5.3 Hz, H'17), 3.22 (1H, d, J = 6.7 Hz, H5), 3.39 (3H, s, OMe), 3.68 (1H, br s, H3), 3.75 (3H, s, CO_2Me), 4.62 (1H, d, J = 7.0 Hz, OCH_2O), 4.74 (1H, d, J = 7.0 Hz, OCH_2O), 5.37 (1H, d, J = 1.6 Hz, H15). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.4 (C18), 17.4 (C11), 20.1 (Ac), 24.3 (C1), 25.9 (C2), 34.2 (C12), 44.7 (C6), 46.4 (C14), 47.7 (C8), 52.0 (CO_2Me), 53.1 (C4), 53.4, 53.6 (C5, C9), 53.5 (C17), 55.7 (OMe), 65.2 (C16), 73.7 (C15), 74.2 (C13), 75.8 (C3), 91.9 (C10), 95.7 (OCH_2O), 169.8 (Ac), 173.6 (C7), 177.1 (C19). MS (EI) *m/z* 480 (M^+, 38 %), 451 (70), 421 (96), 405 (10), 388 (22), 374 (42), 359 (70), 348 (32), 330 (100), 315 (72), 298 (50), 284 (38), 255 (68), 243 (44), 231 (40), 225 (52), 213 (40), 205 (50), 183 (50), 173 (56), 157 (60), 145 (44), 129 (46), 115 (32), 105 (60), 91 (64), 79 (48), 71 (64), 55 (60). HRMS found 480.1987 $C_{24}H_{32}O_{10}$ requires 480.1995.

***ent*-10β,13,15β-Trihydroxy-16β,17-epoxy-3α-methoxymethoxy-20-nor-8β,13β-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (10, R = $MeOCH_2$, R^2 = H).** This compound was prepared from the parent 15-carbinol in 82% yield as described for **10** (R = $MeOCH_2$, R^2 = Ac). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (3H, s, 4-Me), 3.05 (1H, d, J = 4.4 Hz, H17), 3.14 (1H, d, J = 4.4 Hz, H'17), 3.27, 3.37 (2x1H, ABd, J = 6.8 Hz, H5, H6), 3.41 (3H, s, OMe), 3.70 (1H, br s, H3), 3.74 (3H, s, OMe), 4.23 (1H, s, H15), 4.65 (1H, d, J = 7.0 Hz, OCH_2O), 4.76 (1H, d, J = 7.0 Hz, OCH_2O). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5 (C18), 17.1 (C11), 24.6 (C1), 26.2 (C2), 33.9 (C12), 43.7 (C6), 46.0 (C14), 48.8 (C8), 52.1 (CO_2Me), 53.3 (C4), 53.3, 53.9 (C5, C9), 55.2 (C17), 55.9 (OMe), 67.4 (C16), 70.6 (C15), 74.5 (C13), 76.1 (C3), 91.7 (C10), 95.9 (OCH_2O), 174.4 (C7), 178.0 (C19). MS (EI) *m/z* 438 (M^+, 7%), 420 (5), 402 (7), 388 (10), 374 (30), 358 (20), 330 (19), 314 (21), 298 (25), 277 (100), 271 (22), 253 (23), 227 (21), 199 (44), 183 (36), 167 (24), 149 (64), 129 (25), 105 (29), 91 (36), 77 (44). HRMS found 438.1889 $C_{22}H_{30}O_9$ requires 438.1889.

***ent*-13-Acetoxy-16-t-butyldimethylsilyloxy-10β-hydroxy-3α-methoxymethoxy-17,20-dinor-8β,13β-gibberell-15-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (18).** Ac_2O (0.15 ml) was added to a soln of **8** (245 mg, 0.6 mmol), Et_3N (0.3 ml) and DMAP (8 mg) in CH_2Cl_2 (20 ml). The reaction mixture was quenched with sat.

$NaHCO_3$ when TLC showed that no starting material was left. EtOAc (20 ml) was added, the mixture washed with brine, then dried (Na_2SO_4). After chromatography on silica gel (EtOAc/Hexane, 1:3~1:1), the 13-acetate of **8** was obtained as a colourless gum (260 mg, 96% yield). *t*-Butyldimethylsilyl trifluoromethanesulfonate (0.12 ml) was added to a soln of a portion of this product (113 mg, 0.25 mmol) in CH_2Cl_2 (15 ml) containing Et_3N (0.15 ml) at room temp under N_2. The mixture was kept overnight and quenched by cold sat. $NaHCO_3$ (15 ml). The organic layer was dried over Na_2SO_4, then chromatography on alumina (neutral activity III), and elution with Et_2O/ hexane (1:9) containing 0.5% Et_3N afforded **13** (100mg, 70% yield), m.p. 103-106 °C. Calcd for $C_{29}H_{44}O_9Si$ C, 61.68; H, 7.85, found C, 61.42; H, 8.18. IR 3010, 1765, 1730, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.21 (6H, s, Me_2Si), 0.91 (9H, s, Me_3CSi), 1.22 (3H, s, 4-Me), 1.99 (3H, s, OAc), 2.58 (1H, dd, J = 8.6, 2.1 Hz, H14), 2.65 (1H, d, J = 6.0 Hz, H6), 3.12 (1H, d, J = 6.0 *Hz*, H5), 3.38 (3H, s, OMe), 3.69 (3H, s, CO_2Me), 4.35 (1H, s, H15), 4.61 (1H, d, J = 7.1 Hz), 4.73 (1H, d, J = 7.1 Hz,OCH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.1 (MeSi), -4.9 (MeSi), 14.6 (C18), 17.8 (C11), 18.8 (Me_3CSi), 21.6 (OAc), 24.5 (C1), 25.1 (C2), 25.3 (Me_3CSi), 25.7 (C12), 49.8 (C6), 50.0 (C14), 50.1 (C9), 51.8 (CO_2**Me**), 53.1 (C8), 53.6 (C4), 54.7 (C5), 55.7 (OMe), 76.0 (C3), 85.8 (C13), 91.5 (C10), 95.7 (OCH_2O), 104.9 (C15), 152.1 (C16), 169.4 (OAc), 173.7 (C7), 177.9 (C19). MS (EI) *m/z* 564 (M^+, 5%), 533 (8), 507 (99), 475 (14), 447 (41), 413 (39), 385 (69), 343 (11), 325 (18), 283 (30), 251 (20), 223 (29), 195 (11), 128 (10), 117 (100), 75 (76). HRMS found 564.2755, $C_{29}H_{44}O_9Si$ requires 564.2755.

***ent*-13-Acetoxy-10β,15α-dihydroxy-3α-methoxymethoxy-16-oxo-17,20-dinor-8β,13β-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (20).** A soln of dimethyl dioxirane in acetone (5ml, 0.07 M) was added to a soln of TBS vinyl ether (**18**) (28 mg, 0.05 mmol) in CH_2Cl_2 at -40°C. The reaction mixture was kept overnight and allowed to warm to 25°C. The solvent was removed under reduced pressure at 25°C, then 2 ml of THF, followed by TBAF (0.5ml, 1M in THF) was added and the mixture stirred for 1 h. Ketol **20** (17 mg, 80% yield) was obtained after chromatography on silica gel (EtOAc/hexane, 1:1), m.p. 118-120 °C. IR 3525, 1775, 1755, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, s, 4-Me), 2.08 (3H, s, OAc), 2.94 (1H, dd, J = 11.0, 1.8 Hz, H14), 3.26, 3.32 (2x1H, ABd, J = 6.7 Hz, H5, H6), 3.39 (3H, s, OMe), 3.70 (1H, d, J = 3.2 Hz, H3), 3.73 (3H, s, CO_2Me), 4.07 (1H, d, J = 1.8 Hz, H15), 4.64 (1H, d, J = 7.1 Hz, OCH_2O), 4.75 (1H, d, J = 7.1 Hz, OCH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.5 (C18), 17.6 (C11), 21.1 (OAc), 24.5 (C1), 26.1 (C2), 32.7 (C12), 40.1 (C14), 43.6 (C6), 52.2 (CO_2**Me**), 52.6 (C8), 53.3 (C4), 54.0, 54.4 (C9, C5), 55.9 (OMe), 73.2 (C15), 76.0 (C3), 84.4 (C13), 91.2 (C10), 95.9 (OCH_2O), 169.3 (OAc), 174.0 (C7), 177.5 (C19), 210.2 (C16). MS (EI) *m/z* 466 (M^+, 100%), 450 (6), 434 (30), 424 (14), 402 (50), 374 (66), 346 (64), 332 (32), 316 (96), 301 (64), 288 (66), 272 (72), 256 (55), 245 (50), 229 (50), 213 (50), 199 (42), 183 (40), 173 (34), 157 (43), 143 (40), 129 (37), 117 (25), 105 (41), 91 (50), 79 (30). HRMS found 466.1829, $C_{23}H_{30}O_{10}$ requires 466.1839.

***ent*-10β,13,14α-Trihydroxy-3α-methoxymethoxy-16-oxo-17,20-dinorgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (21).** 5 mg of NaH (60% in mineral oil) was added to a soln of ketol **20** (10 mg) in CH_2Cl_2 (1 ml) under a N_2 atmosphere at 25°C followed by one drop of MeOH. The reaction was quenched with sat. KH_2PO_4 and the organic layer washed with brine, dried, reduced to dryness and chromatographed on silica gel (EtOAc/hexane, 1:1) to afford **16** as a white solid (8.4 mg, 84% yield), m.p. 235 -236. °C. Calcd for $C_{21}H_{28}O_9$ C, 59.43; H, 6.65; found C, 59.14; H, 6.36%. IR 3525, 1775, 1760, 1730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s, 4-Me), 2.23 (1H, d, *J* = 18.7 Hz, H15), 2.41 (1H, d, *J* = 18.7 Hz, H15), 3.15 (1H, d, *J* = 9.4 Hz, H6), 3.27 (1H, d, *J* = 9.4 Hz, H5), 3.38 (3H, s, OMe), 3.68 (1H, br s, H3), 3.73 (3H, s, CO_2Me), 4.28 (1H, s, H14), 4.63 (1H, d, *J* = 7.1 Hz, OCH_2O), 4.74 (1H, d, *J* = 7.1 Hz, OCH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.4 (C18), 15.8 (C11), 24.6 (C1), 26.8 (C2), 32.5 (C12), 44.3 (C15), 49.8 (C6), 51.2 (C8), 52.4 (CO_2Me), 54.0, 55.6 (C9, C5), 54.3 (C4), 55.8 (OMe), 75.4, 76.7 (C14, C3), 81.5 (C13), 93.0 (C10), 95.8 (OCH_2O), 173.4 (C7), 177.4 (C19), 216.8 (C16). MS (EI) *m/z* 424 (M$^+$, 14%), 406 (6), 293 (35), 365 (97), 332 (100), 316 (30), 301 (63), 287 (32), 274 (41), 258 (51), 243 (31), 229 (28), 213 (26), 119 (30), 185 (22), 171 (20), 157 (40), 143 (27), 129 (26), 117 (18), 105 (30), 91 (34), 79 (21). HRMS found 424.1734, $C_{21}H_{28}O_9$ requires 424.1733.

***ent*-10β,13,14α-Trihydroxy-3α-methoxymethoxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (22).** Trimethylsilyl chloride (24 μl) was added dropwise to a mixture of **16** (17 mg, 0.04 mmol), *i*-Pr_2NEt (36 μl) and DMAP (4 mg) in CH_2Cl_2 (2 ml) at 0°C, the mixture allowed to warm to 25°C, then quenched by sat. $NaHCO_3$ at 0°C, washed with cold brine and dried over Na_2SO_4. After removal of solvent THF (1 ml) was added to the residue and Wittig reagent in THF [4 ml, prepared by the reaction of $[Ph_3PCH_3]^+I^-$ (80mg) and KO*t*Bu (23mg) at 25°C for 2h] added at 25°C. The reaction mixture was kept at 65°C overnight, quenched by sat. NH_4Cl and 10 ml of EtOAc added. The organic layer was washed by brine, dried and solvent was removed under reduced pressure. Pyridinium toluenesulfonate (40 mg) in MeOH (2 ml) was added to the residue and the mixture stirred at 25°C for 3 h. Removal of solvent and chromatography on silica gel (EtOAc/hexane, 1:3~1:1) afforded **24** (5 mg, 30% yield) followed by **22** 8.5 mg (50% yield), m.p. 202-203 °C. When the Wittig reacton was conducted at 50°C for 16 hr, only **22** was obtained. Calcd for $C_{22}H_{30}O_8$ C, 62.55; H, 7.16, found C, 62.33; H, 7.38%. IR 3530, 3010, 1775, 1730, 1660 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s, 4-Me), 2.60 (1H, ddd, *J* = 15.9, 2.8, 2.7 Hz, H15), 3.03 (1H, d, *J* = 9.1 Hz, H6), 3.22 (1H, d, *J* = 9.1 Hz, H5), 3.39 (3H, s, OMe), 3.67 (1H, d, *J* = 2.4 Hz, H3), 3.75 (3H, s, CO_2Me), 3.88 (1H, s, H14), 4.63 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.74 (1H, d, *J* = 7.0 Hz, OCH_2O), 5.07 (1H, s, H17), 5.30 (1H, br s, H'17). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.5 (C18), 15.9 (C11), 24.8 (C1), 27.0 (C2), 37.1 (C12), 39.4 (C15), 48.3 (C6), 52.3 (OMe), 53.5, 55.2 (C9, C5), 53.9 (C8), 54.1 (C4), 55.8 (OMe), 75.6, 79.7 (C3, C14), 80.2 (C13), 93.4 (C10), 95.9 (OCH_2O), 109.0 (C17), 154.5 (C16), 173.8 (C7), 177.8 (C19). MS (EI) *m/z* 422 (M$^+$, 36%), 404 (6), 390 (23), 362 (23), 372 (15), 343 (29), 330 (100), 314 (27), 298 (54), 283 (24), 271 (33), 253 (24), 239 (38), 227 (28), 209 (19), 197 (18), 183 (19), 171 (20), 157 (23), 143 (24), 129 (24), 117 (17), 105 (29), 91 (35), 79 (22). HRMS Found 422.1939, $C_{22}H_{30}O_8$ requires 422.1940.

7-Isopropenyl lactone (24): IR 3560, 3020, 1765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, s, 4-Me), 1.75 (3H, s, **Me**-C=CH_2), 2.80 (2H, br s, H5, H6), 3.38 (3H, s, OMe), 3.63 (1H, br s, H3), 3.84 (1H, s, H14), 4.62 (1H, d, *J* = 6.9 Hz, OCH_2O), 4.72 (1H, d, *J* = 6.9 Hz, OCH_2O), 4.86, 4.95 (2x1H, 2xs, Me-C=$\mathbf{CH_2}$), 5.03 (1H, s, H17), 5.24 (1H, br s, H'17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (C18), 16.1 (C11), 22.6 (**Me**-C=CH_2), 24.9 (C1), 27.2

(C2), 37.3 (C12), 39.5 (C15), 49.8 (C6), 53.2, 55.7 (C5, C9), 53.6 (C8), 54.8 (C4), 55.8 (OMe), 76.0 (C3), 80.3 (C13), 80.9 (C14), 93.1 (C10), 95.9 (OCH_2O), 108.0 (C17), 114.4 ($Me\text{-}C{=}CH_2$), 145.1 (C7), 155.6 (C16), 178.9 (C19). MS (EI) *m/z* 404 (M^+, 100%), 386 (35), 372 (40), 357 (38), 342 (58), 324 (38), 314 (60), 295 (34), 285 (20), 277 (40), 269 (22), 243 (38), 225 (38), 219 (72), 201 (50), 185 (28), 173 (34), 159 (32), 145 (34), 129 (38), 119 (32), 105 (50), 91 (56), 77 (50). HRMS Found 404.2197, $C_{23}H_{32}O_6$ requires 404.2199.

***ent*-3α,10β,13,14α-Tetrahydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (23).** A soln of **22** (8.4 mg) in 3% HCl-EtOH (0.5 ml) at 25°C was kept for 40 h. The reaction mixture was quenched with Et_3N and the EtOH removed under reduced pressure. EtOAc (5 ml) was added and thew mixture washed with brine. After separation on silica gel (EtOAc/hexane 1:3~1:2) **23** was obtained as a white solid (6.7 mg, 88% yield), m.p. 249-250 °C. IR 3560, 3040, 1765, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s, 4-Me), 2.60 (1H, ddd, J = 16.0, 2.8, 2.8 Hz, H15), 3.03 (1H, d, J = 9.1 Hz, H6), 3.24 (1H, d, J = 9.1 Hz, H5), 3.75 (3H, s, OMe), 3.87 (1H, br s, H3), 3.90 (1H, s, H14), 5.08 (1H, s, H17), 5.31 (1H, dd, J = 2.8, 2.2 Hz, H'17). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.5 (C18), 15.9 (C11), 26.7 (C1), 28.0 (C2), 37.1 (C12), 39.4 (C15), 48.4 (C6), 52.3 (OMe), 53.7 (C8), 54.3 (C4), 52.8, 55.4 (C9, C5), 70.3, 79.7 (C3, C14), 80.2 (C13), 93.6 (C10), 109.1 (C17), 153.5 (C16), 174.5 (C7), 179.1 (C19). MS (EI) *m/z* 378 (M^+, 44), 360 (26), 347 (18), 332 (34), 318 (100), 300 (43), 272 (42), 255 (25), 243 (26), 239 (28), 227 (27), 215 (56), 201 (50), 183 (24), 171 (21), 157 (24), 143 (26), 129 (28), 105 (32), 91 (50), 77 (40). HRMS found 378.1677, $C_{20}H_{26}O_7$ requires 378.1678.

X-ray crystal data for 14-hydroxy-GA_1 methyl ester (23): $C_{20}H_{26}O_7$, monoclinic space group $P2_1$, a = 8.800(2), b = 7.155(2), c = 14.329(3) Å, β = 100.63(2)°, V = 886.8(3) $Å^3$, Z = 2. Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.54178 Å) yielding 1520 unique reflections with $2\theta \leq 120$ °. The structure was solved by direct methods [18]. Non-hydrogen atoms were refined with anisotropic displacement factors. Coordinates of H atoms attached to O atoms were refined; other H atoms were included at calculated positions. Refinement was by full-matrix least-squares analysis on F using the teXsan Structure Analysis Software of Molecular Structure Corporation [19]. Final R = 0.038 on 1358 reflections with $I > \sigma(I)$. Further details have been deposited at the Cambridge Crystallographic Data Centre by the Editor.

7-Isopropenyl lactone (26). A soln of 3-methoxymethyl ether **25** (20 mg) in THF (2 ml) was treated with an excess of ylide from $[Ph_3PCH_3]^+I^-$ (80 mg) and KO*t*Bu (22 mg) and heated under reflux for an extended period (3 days) with similar amounts of ylide being added at the end of days 1 and 2. The product was worked up as for **22** and **24**, with diene **26** being obtained as a colourless gum (11.5 mg, 58% yield). IR 3590, 3070, 1765 cm^{-1}. ^1H NMR 1.15 (3H, s, 4-Me), 1.71 (3H, br s, $Me\text{-}C{=}CH_2$), 2.40 (1H, d, J = 11.4 Hz, H6), 2.79 (1H, d, J = 11.4 Hz, H5), 3.39 (3H, s, OMe), 3.60 (1H, br s, H3), 4.63 (1H, d, J = 6.9 Hz, OCH_2O), 4.73 (1H, d, J = 6.9 Hz, OCH_2O), 4.74, 4.90, (2x1H, 2xbr s, $Me\text{-}C{=}CH_2$), 4.91, 5.21 (2x1H, 2xbr s, H17). ^{13}C NMR 14.4 (C18), 17.4 (C11), 22.7 ($Me\text{-}C{=}CH_2$), 24.9 (C1), 28.1 (C2), 38.4 (C12), 42.6 (C14), 44.8 (C15), 44.9 (C8), 51.4 (6), 52.8, 53.1 (C5, C9), 54.9 (C4), 55.8 (OMe), 75.9 (C3), 78.2 (C13), 92.8 (C10), 96.0 (OCH_2O), 106.5 (C17), 113.8 (Me-C=CH_2), 143.3 (C7), 158.7 (C16), 178.7 (C19). MS (EI) *m/z* 388 (M^+, 100%), 370 (6), 356 (58), 326 (56), 343 (42), 308 (38), 283 (46), 254 (35), 239 (26), 227 (35), 214 (25), 199 (25), 185 (26), 173 (40), 145 (37), 135 (42), 121 (41), 105 (50), 91 (57). HRMS found 388.2242, $C_{23}H_{32}O_5$ requires 388.2249.

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