Displacement of bridgehead sulfonate esters with organometallic reagents: synthesis of 13-alkylated gibberellins

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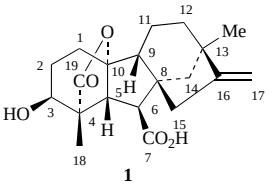
Gibberellin A_3 is converted to 13-methyl GA_4 in nine steps and 58% overall yield. A key step in the synthesis is the substitution of a bridgehead sulfonate ester by an alkyl group. A series of organometallic reagents have been investigated to effect this transformation; optimal yields are obtained from reaction of a methanesulfonate with a Gilman-type organocuprate in diethyl ether, in the presence of boron trifluoride–diethyl ether, thus enabling a variety of bridgehead substituents to be introduced in good to excellent yield.

It is currently believed that only one of the 108 known gibberellin (GA) phytohormones, GA_1, regulates stem elongation in *Pisum sativum* (pea),[1] *Zea mays* (maize)[2] and *Oryza sativa* (rice).[3] Other GAs endogenous to these plants, *e.g.* GA_{20}, only exhibit biological activity *via* their metabolism to GA_1 (Scheme 1). Recently however, GA_4 has been detected in the stem tissue of maize[4] where it is metabolised to GA_1.[5] Gibberellin A_4 promotes stem elongation in maize, but it is not known whether GA_4 is active *per se*, or by virtue of its metabolism to GA_1. No genetic mutant of maize which specifically blocks 13-hydroxylation is currently available to probe this bioactivity; therefore alternative methods of investigation were considered. One such approach was to assess the bioactivity of GA_4 analogues possessing a 'chemical block' at C-13, such that bridgehead hydroxylation may not occur. Suitable analogues could be 13-alkylated gibberellins; our initial target compound was therefore 13-methyl GA_4 **1**.



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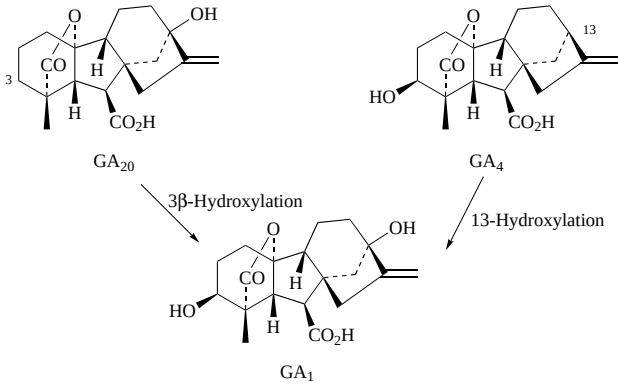
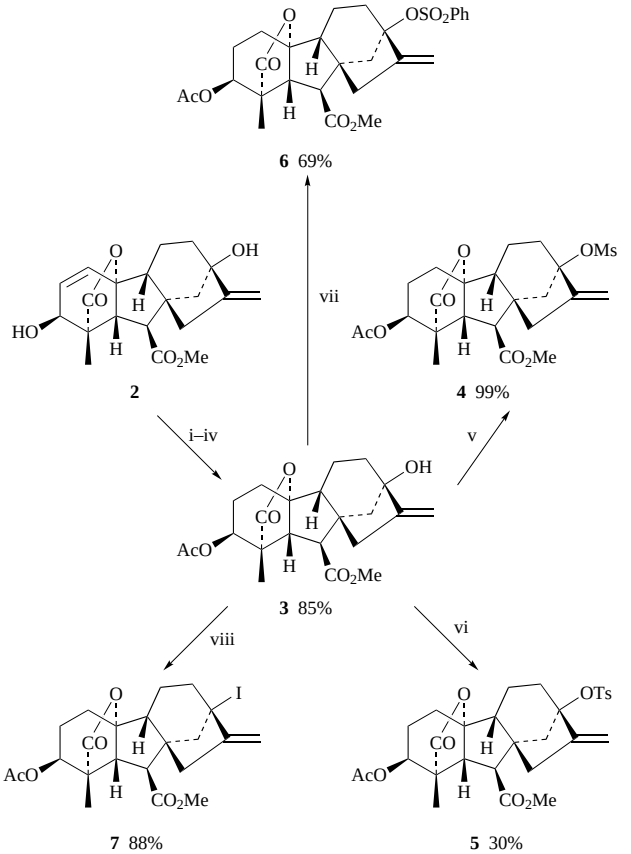


Scheme 1 Biosynthesis of gibberellin A_1 in maize

Lithium dialkylcuprates have been used extensively to introduce alkyl groups to molecules *via* nucleophilic attack on α,β-unsaturated carbonyl compounds, epoxides, halides and primary and secondary sulfonate esters.[6] In a preliminary communication,[7] we described a novel displacement of a tertiary methanesulfonate (mesylate) using a Gilman type organocuprate[8] in the presence of boron trifluoride–diethyl ether, that allowed a facile, high-yielding, direct incorporation of a 13-alkyl group into the gibberellin skeleton. We now report in full our investigations into the displacement of leaving groups (including sulfonate esters and halides) by organometallic reagents at bridgehead positions in bicyclo[3.2.1]octenes and the application of the optimised reaction conditions to the synthesis of 13-methyl GA_4 **1**.

Results and discussion

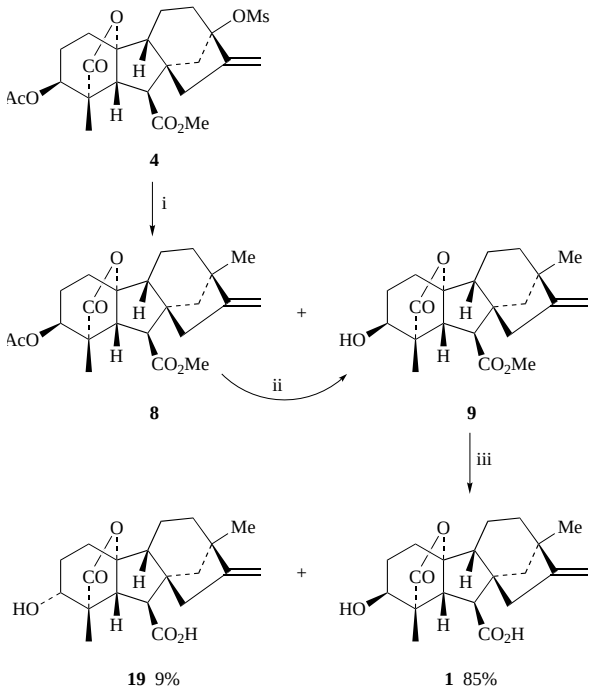
The known protected gibberellin, 3-*O*-acetyl GA_1 7-methyl ester **3**[9] was prepared in four steps and 85% overall yield from the methyl ester of the commercially available gibberellic acid (GA_3) **2** (Scheme 2) using an analogous procedure to that



Scheme 2 *Reagents and conditions:* i, Ac_2O, pyridine; ii, H_2, Pd on $CaCO_3$, MeOH, pyridine; iii, I_2, $NaHCO_3$ THF, CH_2Cl_2; iv, Bu_3SnH, azoisobutyronitrile (AIBN), toluene; v, MsCl, pyridine; vi, TsCl, pyridine; vii, $PhSO_2Cl$, pyridine; viii; I_2, Ph_3P, imidazole

previously reported for the synthesis of GA_1 13-*O*-acetyl 7-methyl ester.[10] Alcohol **3** was used as the precursor to a series of compounds with a good leaving group at C-13 including the mesylate **4**, toluene-*p*-sulfonate (tosylate) **5**, and benzenesulfonate **6** which were prepared using the appropriate sulfonyl chloride in pyridine. Treatment of 3-*O*-acetyl GA_1 7-methyl ester **3** with iodine in the presence of imidazole and triphenylphosphine in refluxing toluene[11] gave the corresponding 13-iodide **7** in 88% yield.

With a series of compounds with a good leaving group at the bridgehead position in hand, their reactions with organometallic reagents were investigated. Mesylate **4** was treated with five equivalents of lithium dimethylcuprate for 1 h at −10 °C in a diethyl ether–THF mixture. Three products were isolated from the reaction mixture. The less polar product was 3β-*O*-acetyl 13-methyl GA_4 7-methyl ester **8** (38%) (Scheme 3). The ^1H NMR spectrum of **8** was consistent with the introduction of a bridgehead methyl group, displaying two 3-proton singlets at δ 1.06 and 1.14 (assigned to 18-H_3 and 13-CH_3 respectively). In addition, the signals assigned to the olefinic protons had been shifted upfield in comparison with the starting material and their resonances were separated by only 0.04 ppm—comparable with the 17-H_2 resonances of gibberellins lacking the 13-hydroxy group. The more polar product was the hydrolysed derivative 13-methyl GA_4 7-methyl ester **9** (12%). A small amount of 3-*O*-acetyl GA_1 methyl ester **3** was also isolated. The reaction was then repeated with the addition of boron trifluoride–diethyl ether (7.5 equiv.), resulting in higher yields of the 13-methylated products **8** and **9** (39 and 40% respectively, Table 1).



Scheme 3 *Reagents and conditions:* i, Me_2CuLi, $BF_3{\cdot}Et_2O$; ii, K_2CO_3, MeOH, H_2O; iii, PrSH, NaH, HMPA

Next the displacement of other C-13 leaving groups with lower-order cuprates was investigated. Treatment of the 13-tosylate **5** or benzenesulfonate **6** with lithium dimethylcuprate in the presence of boron trifluoride–diethyl ether gave 13-methyl GA_4 derivative **8** in 70 and 29% yields respectively. In contrast, the attempted displacement of a poorer leaving group at C-13, the bridgehead acetate **10**, returned starting material and the hydrolysis product, 13-*O*-acetyl GA_1 7-methyl ester **11**.

The reaction of primary and secondary halides with lower-order organocuprates to give alkyl substituted products are well documented;[6] however, the attempted displacement of tertiary halides have generally been unsuccessful. The reported exceptions are the reaction of the tertiary bromide of 1-bromoadamantane with pentafluorocopper[12,13] and the displacement of the bridgehead bromide of a bicyclic [3.3.1] ketone which occurs with lithium dimethylcuprate in the presence of *n*-propyl bromide and is believed to proceed *via* conjugate addition to an enone.[14] Treatment of 3-*O*-acetyl 13-iodo GA_4 7-methyl ester **7** with lithium dimethylcuprate–boron trifluoride–diethyl ether gave a mixture of the 13-methyl derivatives **8** (20%) and **9** (39%). The products isolated from this reaction were each contaminated with a trace amount (~5%) of the reduced compounds **12** and **13** with hydrogen at the bridgehead position. These proved to be inseparable from the corresponding 13-methyl compounds, but were readily identifiable from their ^1H NMR spectra. The analogous reduction of cyclic secondary iodides is often a significant side reaction with organocuprates.[6]

The use of other organometallic reagents proved to be either less effective or unsuitable for the bridgehead displacement reaction. Treatment of mesylate **4** with the higher-order, Lipshutz type, organocuprate dimethylcyanocopper lithium,[15] in the presence or absence of boron trifluoride–diethyl ether gave only poor yields of 13-methyl gibberellin **8**, even after greatly extended reaction times. This result is in accord with the reaction of secondary mesylates with higher-order cuprates, which are found to proceed sluggishly and in poor yield, unless a very large excess of the organocopper reagent is used.[16] Reaction of iodide **7** with lithium dimethylcyanocuprate in the absence or presence of boron trifluoride–diethyl etherate resulted mainly in reduction to give **12**. Only a small amount (<10%) of the 13-methyl derivative **8** was isolated.

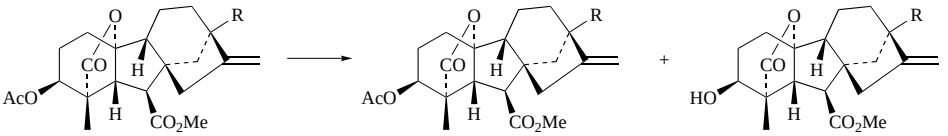
The final organometallic reagents which were investigated were based on aluminium and magnesium. Although it has been reported that trialkylaluminium reagents are able to displace tertiary iodides,[17] in the case of reaction of the gibberellin 13-iodide **7** with trimethylaluminium in dichloromethane we found that only the reduction product **12** was formed. Reaction of mesylate **4** under identical conditions simply returned unreacted starting material. In contrast, treatment of mesylate **4** with ethylmagnesium bromide–copper iodide–boron trifluoride–diethyl ether[6] gave a complex mixture of products from which the 13-ethyl derivative **14** was isolated in a 25% yield. Under identical conditions the iodide **7** gave **14** in 40% yield.

From the results of these investigations it is apparent that the optimal conditions for the bridgehead substitution reactions were treatment of mesylate **4** with a lower-order Gilman type cuprate in diethyl ether (containing a small amount of THF to aid the solubility of the GA starting material), in the presence of boron trifluoride–diethyl ether. The use of THF as the sole reaction solvent, or reaction without the addition of the Lewis acid led to poor yields of the 13-methyl analogues **8** and **9**. Similar constraints have been reported in many other reactions of organocuprates, where the selective use of a particular solvent, or the judicious choice of a Lewis acid have proved necessary to obtain maximal yield of products.[6,18]

These optimised reaction conditions were used to prepare a range of 13-substituted GA derivatives, as shown in Table 2. Gibberellin A_4 derivatives with 13-ethyl, **14** and **15**, *n*-butyl, **16**, and phenyl, **17**, substituents were successfully prepared in moderate to excellent yield. The lower yield of the aromatic derivative **17** could be due to the steric factors hindering approach of the more bulky organocopper reagent, or due to partial decomposition of the reagent, which has previously been observed during the formation of lithium diphenylcuprate using copper(I) iodide.[12]

Isotopically labelled GAs have been extensively used to investigate the metabolism, transport and accumulation of gibberellins in plants.[19] The new bridgehead displacement reaction proved valuable for the preparation of carbon-13 labelled GA

Table 1



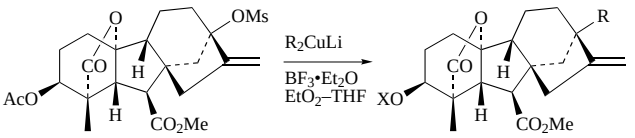
8 R = Me
12 R = H
14 R = Et

9 R = Me
11 R = OAc
13 R = H

Starting material	Yield (%)		Recovered s.m.[a] (%)
(i) With Me_2CuLi, $BF_3{\cdot}Et_2O$			
4 R = OMs	**8** (39)	**9** (40)	—
5 R = OTs	**8** (70)	—	9
6 R = OSO_2Ph	**8** (29)	—	41
10 R = OAc	—	**11** (21)	71
7 R = I	**8** (20), **12** (<5)	**9** (39), **13** <(5)	3
(ii) With Me(CN)CuLi, $BF_3{\cdot}Et_2O$			
4 R = OMs	**8** (10)	—	57
7 R = I	**8** (10), **12** (37)	—	42
(iii) With Me_3Al			
4 R = OMs	—	—	Quant.
7 R = I	**12** (26)	—	30
(iv) With EtMgBr, CuI, $BF_3{\cdot}Et_2O$			
4 R = OMs	**14** (25)	—	—
7 R = I	**14** (40)	—	—

[a] s.m. = starting material

Table 2



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R	Yield (%) X = Ac	Yield (%) X = H
Me	**8** (39)	**9** (40)
Et	**14** (24)	**15** (53)
Bu^n	**16** (76)	—
Ph	**17** (40)	—
$^{13}CH_3$	**18** (72)	—

analogues. [^{13}C]Methyllithium was readily formed by reaction of iodo[^{13}C]methane with lithium metal in diethyl ether, then used in the preparation of lithium di[^{13}C]methylcuprate. Subsequent reaction of the labelled organocopper reagent with mesylate **4** led to successful introduction of a [^{13}C]methyl bridgehead substituent to give **18** in 72% yield. The incorporation of the isotopic label was apparent from the NMR and mass spectral data. The ^{1}H NMR spectrum showed a doublet centred at δ 1.14 (J 125.5 Hz) for the bridgehead methyl group and the ^{13}C NMR spectrum displayed an intense signal at δ 27.2. The mass spectrum showed complete incorporation of the label with a molecular ion at m/z 403. This approach may be simply adapted for the synthesis of the radiolabelled isotopomer.

Having successfully introduced a methyl substituent into the 13-position of the gibberellin framework it was simply necessary to hydrolyse the 3-*O*-acetyl and 7-methyl ester protecting groups to complete the synthesis of our target molecule, 13-methyl GA_4 **1**. Careful hydrolysis of the 3β-acetate of **8** with aqueous potassium carbonate in methanol gave **9** in quantitative yield (Scheme 3). Under more vigorous hydrolysis conditions, epimerisation to the more stable 3α-alcohol occurs.[20] Finally, deprotection of the 7-methyl ester under non-aqueous conditions using sodium *n*-propanethiolate in HMPA[21] gave 13-methyl GA_4 **1** in 68% yield from mesylate **4** and in a pleasing 58% overall yield. A small amount (9%) of the corresponding 3α-alcohol **19** was also formed in the demethylation reaction but these epimers were separable by flash chromatography.

The effect of gibberellins on the enhancement of stem elongation is pronounced on dwarf plants which have a blocked gibberellin biosynthetic pathway and is the basis of many gibberellin bioassay systems.[22] Preliminary studies on the bioactivity of 13-methyl GA_4 **1** have been carried out with dwarf rice seedlings (*Oryza sativa*)[23] and it was found that **1** had significantly less activity than GA_1 and GA_{20}. The results of these bioassays will be published in full elsewhere.

In conclusion, a novel bridgehead displacement of tertiary sulfonate esters with organocopper reagents has been developed, which enables the high yielding completion of the quaternary centre. The utility of the reaction was demonstrated in a short synthesis of the biologically important gibberellin, 13-methyl GA_4 **1**. The optimal conditions were found to involve reaction of a bridgehead mesylate with a lower-order lithium dialkylcuprate in the presence of boron trifluoride–diethyl ether. Other organocopper, and organomagnesium and organolithium, reagents were found to be less effective or unsuitable.

Experimental

For the numbering scheme used throughout the paper, see Scheme 1.

All organic solvents were distilled prior to use; light petroleum refers to the fraction with the boiling range 60–80 °C. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Mass spectra were recorded using an AEI MS9 spectrometer or a Fisions Autospec® spectrometer at an

ionisation potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM GX-270 or GX-400 spectrometers as solutions in deuteriochloroform (unless stated otherwise) using tetramethylsilane as the internal standard. NMR chemical shifts are expressed as δ values relative to tetramethylsilane (J values in Hz). Flash chromatography[24] was carried out using Merck (40–63 μm) or Fluka (220–440 mesh) silica gel. TLC was performed using precoated Merck Kieselgel 60_{254} aluminium backed plates; bands were visualised by UV light, or by spraying with 5% sulfuric acid in ethanol and heating with a hot air gun.

Methyl- and butyl-lithium were obtained from commercial suppliers. Phenyllithium was prepared according to the literature procedure;[25] ethyl- and [^{13}C]methyl-lithium were prepared by analogous methods. All alkyllithium reagents were titrated against diphenylacetic acid[26] prior to use. Copper(I) iodide was purified from aqueous potassium iodide according to the method of Kauffman and Teter,[27] then dried at 125 °C and 10 mmHg for at least 72 h. Copper(I) cyanide was dried at 40 °C and 1 mmHg for 72 h before use. All reactions involving organometallic reagents were performed in flame-dried glassware under a positive pressure of nitrogen. Unless otherwise stated, all reactions were worked-up by the following procedure: the reaction mixture was poured into water and ethyl acetate, the pH was adjusted to 2 with 2 M HCl and the products extracted with ethyl acetate. The combined organic extracts were washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo*.

***ent*-3α-Acetoxy-10β-hydroxy-13-methylsulfonyloxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 4**

Methanesulfonyl chloride (1.20 ml, 15.5 mmol) was added to a solution of 3-*O*-acetyl GA_1 methyl ester **3** (2.50 g, 6.19 mmol) in pyridine (20 ml) and the mixture was stirred at room temperature for 3 h. The usual work-up returned the crude product, which was purified by flash chromatography. Elution with 45% ethyl acetate in light petroleum returned the *title methanesulfonate* **4**, which was crystallised from acetone–light petroleum (2.96 g, 99%), mp 147–148 °C (Found: C, 57.29; H, 6.40; S, 6.50%; M^+ 482.1604. $C_{23}H_{30}O_9S$ requires C, 57.26; H, 6.22; S, 6.64%; M, 482.1611); δ_H 1.06 (s, 18-H_3), 2.14 (s, OCOCH_3), 2.71 (d, J 10.5, 6-H), 3.05 (s, OSO_2CH_3), 3.19 (d, J 10.5, 5-H), 3.75 (s, OCH_3), 4.96 (br s, 3-H), 5.14 and 5.37 (2 br s, 17-H_2); *m*/*z* 482 (M^+, 1%), 451 (14), 422 (59), 398 (98), 318 (82), 282 (99), 223 (77) and 43 (65).

***ent*-3α-Acetoxy-10β-hydroxy-13-toluene-*p*-sulfonyloxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 5**

3-*O*-Acetyl gibberellin A_1 methyl ester **3** (300 mg, 0.74 mmol), toluene-*p*-sulfonyl chloride (1.42 g, 7.43 mmol) and DMAP (230 mg, 1.86 mmol) in pyridine (12.5 ml), were stirred at room temperature for 3 days, under a nitrogen atmosphere. Further toluene-*p*-sulfonyl chloride (283 mg, 1.49 mmol) and DMAP (91 mg, 0.74 mmol) were added and the reaction was stirred for a further 7 days at room temperature, with monitoring by TLC. The crude product was recovered by the usual work-up and purified by flash chromatography. Elution with 35% ethyl acetate in light petroleum returned the *title toluene*-p-*sulfonate* **5** as a foam (124 mg, 30%) (Found: M^+, 558.1924. $C_{29}H_{34}O_9S$ requires M, 558.1924); δ_H 1.05 (s, 18-H_3), 2.13 (s, OCOCH_3), 2.45 (s, $OSO_2C_6H_4CH_3$), 2.67 (d, J 10.5, 6-H), 3.17 (d, J 10.5, 5-H), 3.73 (s, OCH_3), 4.95 (br s, 3-H), 5.09 and 5.32 (2 br s, 17-H_2), 7.33 and 7.76 (2 d each J 8.5, $OSO_2C_6H_4CH_3$); *m*/*z* 558 (M^+, 3%), 527 (3), 517 (2), 498 (13), 454 (16), 386 (17), 282 (45), 155 (35) and 91 (100). Further elution with 50% ethyl acetate in light petroleum returned unchanged starting material **3** as a gum (204 mg, 68%).

***ent*-3α-Acetoxy-10β-hydroxy-13-phenylsulfonyloxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 6**

A mixture of 3-*O*-acetyl GA_1 methyl ester **3** (150 mg, 0.37 mmol), benzenesulfonyl chloride (0.47 ml, 3.68 mmol) and DMAP (113 mg, 0.93 mmol) in pyridine (10 ml) was stirred at room temperature for 27 days. The reaction mixture was diluted with ethyl acetate (30 ml) and washed with saturated aq. copper sulfate (2 × 50 ml) and brine (50 ml), then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give the crude product which was purified by flash column chromatography. Elution with 20% ethyl acetate in light petroleum gave the 13-benzenesulfonate **6** as a colourless gum (139 mg, 69%) (Found: M^+, 544.1793. $C_{28}H_{32}O_9S$ requires M, 544.1801); δ_H 1.05 (s, 18-H_3), 2.13 (s, OCOCH_3), 2.68 (d, J 10.5, 6-H), 3.16 (d, J 10.5, 5-H), 3.73 (s, OCH_3), 4.96 (br s, 3-H), 5.14 and 5.33 (2 br s, 17-H_2), 7.54 (t, J 7.5, Ar), 7.63 (t, J 7.5, Ar) and 7.89 (d, J 7.5, Ar); *m*/*z* 544 (M^+, 2%), 513 (8), 484 (28), 440 (58), 334 (43), 283 (55), 282 (100), 255 (25), 239 (23), 223 (29), 143 (31), 105 (18) and 77 (88).

***ent*-3α-Acetoxy-10β-hydroxy-13-iodo-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 7**

3-*O*-Acetyl gibberellin A_3 methyl ester **3** (500 mg, 1.24 mmol) in dry toluene (25 ml) was heated to reflux under nitrogen in the presence of triphenylphosphine (487 mg, 1.86 mmol) and imidazole (169 mg, 2.48 mmol). A solution of iodine (393 mg, 1.55 mmol) in toluene (5 ml) was added and the mixture was heated for a further 2 h. The reaction mixture was left to cool and then poured into ethyl acetate (50 ml) and saturated aq. sodium hydrogen carbonate (100 ml), and extracted with ethyl acetate (3 × 40 ml). The combined organic layers were washed with aq. sodium thiosulfate (2 × 10 ml), brine (2 × 20 ml) and water (20 ml), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude iodide was purified by flash chromatography. Elution with 25% ethyl acetate in light petroleum returned the 13-iodide **7** which crystallised from acetone–light petroleum as colourless needles (560 mg, 88%), mp 132–134 °C (Found: C, 51.7; H, 5.4. $C_{22}H_{27}IO_6$ requires C, 51.36; H, 5.25%); δ_H 1.07 (s, 18-H_3), 2.14 (s, OCOCH_3), 2.64 (d, J 10, 6-H), 3.15 (d, J 10, 5-H), 3.75 (s, OCH_3), 4.97 (d, J 2.5, 3-H), 5.22 and 5.62 (2 br s, 17-H_2); *m*/*z* 514 (M^+, 1%), 483 (1), 472 (1), 454 (1), 426 (4), 410 (2), 387 (13), 283 (100), 223 (35) and 91 (13).

Treatment of methanesulfonate 4 with lithium dimethylcuprate

Lithium dimethylcuprate (0.78 mmol) in diethyl ether (3.5 ml) was added dropwise to a solution of the 13-methanesulfonate **4** (75 mg, 0.16 mmol) in diethyl ether (2 ml) and THF (0.5 ml) at −10 °C. The pale yellow solution was stirred at −10 °C for 5 h and then worked-up as usual. Purification by flash chromatography and elution with 20% ethyl acetate in light petroleum gave ent-3α-*acetoxy*-10β-*hydroxy*-13-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **8**, which crystallised from ethyl acetate–light petroleum as needles (24 mg, 38%), mp 154–156 °C [Found $(M - 60)^+$, 342.1843. $C_{21}H_{26}O_4$ requires (M − 60), 342.1831]; δ_H 1.06 (s, 18-H_3), 1.14 (s, 13-CH_3), 2.14 (s, OCOCH_3), 2.66 (d, J 10.5, 6-H), 3.17 (d, J 10.5, 5-H), 3.72 (s, OCH_3), 4.85 and 4.89 (2 br s, 17-H_2) and 4.97 (br s, 3-H); *m*/*z* 402 (M^+, 1%), 370 (8), 342 (14), 325 (5), 310 (7), 298 (100), 238 (57), 91 (26) and 43 (38). Further elution with 30% ethyl acetate in light petroleum returned ent-3α,10β-*dihydroxy*-13-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **9** as a gum (7 mg, 12%) (Found: M^+, 360.1917. $C_{21}H_{28}O_5$ requires M, 360.1936); δ_H 1.13 (s, 18-H_3), 1.15 (s, 13-CH_3), 2.67 (d, J 10.5, 6-H), 3.20 (d, J 10.5, 5-H), 3.71 (s, OCH_3), 3.84 (br s, 3-H), 4.84 and 4.89 (2 br s, 17-H_2); *m*/*z* 360 (M^+, 7%), 342 (9), 328 (100), 300 (68), 298 (44), 238 (29), 91 (12) and 55 (10). Finally elution with 50% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_1 methyl ester **3** as a gum (8 mg, 13%)—spectroscopic data consistent with that obtained previously.

Treatment of mesylate 4 with lithium dimethylcuprate and boron trifluoride–diethyl ether

Lithium dimethylcuprate (3.60 mmol) in diethyl ether (10 ml)

was added dropwise to a stirred solution of methanesulfonate **4** (350 mg, 0.73 mmol) in diethyl ether (6 ml) and THF (1 ml) at −10 °C. Boron trifluoride–diethyl ether (670 μl, 5.45 mmol) was added dropwise to the pale yellow solution and the resulting yellow solution was stirred at −10 °C for 1 h. The usual work-up gave a clear gum, which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum gave 3-*O*-acetyl 13-methyl GA_4 methyl ester **8** (115 mg, 39%)—spectroscopic data as previously described. Further elution with 30% ethyl acetate in light petroleum returned 13-methyl GA_4 methyl ester **9** (104 mg, 40%) as a gum—spectroscopic data as previously obtained.

Reaction of toluene-*p*-sulfonate 5 with lithium dimethylcuprate and boron trifluoride–diethyl ether

A solution of lithium dimethylcuprate (0.76 mmol) in diethyl ether (5 ml) was added dropwise to a stirred solution of the 13-toluene-*p*-sulfonate **5** (85 mg, 0.15 mmol) in diethyl ether (3 ml) and THF (1 ml) at −10 °C. Boron trifluoride–diethyl ether (140 μl, 1.14 mmol) was added dropwise and the resulting yellow solution was stirred at −10 °C for 5 h. The crude product was recovered by the usual work-up and was purified by flash chromatography. Elution with 25% ethyl acetate in light petroleum returned 3-*O*-acetyl 13-methyl GA_4 7-methyl ester **8** (43 mg, 70%)—spectroscopic data as previously described. Further elution with 40% ethyl acetate in light petroleum returned unreacted starting material **5** (8 mg, 9%).

Reaction of benzenesulfonate 6 with lithium dimethylcuprate and boron trifluoride–diethyl ether

To a stirred solution of the benzenesulfonate **6** (56 mg, 0.10 mmol) in diethyl ether (2 ml) and THF (1 ml) at −10 °C was added a solution of lithium dimethylcuprate (0.53 mmol) in diethyl ether. Boron trifluoride–diethyl ether (140 μl, 1.14 mmol) was then added and the reaction stirred at −10 °C for 1 h and then room temperature for 1 h. Water (5 ml) was added and the reaction mixture worked up as normal. Elution with 20% ethyl acetate in light petroleum gave the 3-*O*-acetyl 13-methyl GA_4 **8** (12 mg, 29%)—spectroscopic data as described previously. Further elution with 30% ethyl acetate in light petroleum returned the benzenesulfonate starting material **6** (23 mg, 41%).

Treatment of di-*O*-acetyl GA_1 7-methyl ester 10 with lithium dimethylcuprate and boron trifluoride–diethyl ether

Lithium dimethylcuprate (1.12 mmol) in diethyl ether (6 ml) was added dropwise to a stirred solution of di-*O*-acetyl GA_1 methyl ester **10**[29] (100 mg, 0.22 mmol) in diethyl ether (3 ml) and THF (0.5 ml) at −10 °C. Boron trifluoride–diethyl ether (210 μl, 1.68 mmol) was added dropwise and the resulting pale yellow solution was stirred at −10 °C for 10 h, then allowed to warm to room temperature over 4 h. The usual work-up gave a gum, which was purified by flash chromatography. Elution with 35% ethyl acetate in light petroleum returned unreacted starting material **10** (71 mg, 71%). Further elution with 55% ethyl acetate in light petroleum gave 13-*O*-acetyl GA_1 methyl ester **11** which crystallised from acetone–light petroleum as needles (19 mg, 21%) mp 131–132 °C (lit. mp[9] 137–140 °C); δ_H 1.14 (s, 18-H_3), 2.02 (s, $OCOCH_3$) 2.69 (d, *J* 11, 6-H), 3.21 (d, *J* 11, 5-H), 3.72 (s, OCH_3), 3.93 (br s, 3-H), 4.99 and 5.14 (2 br s, 17-H_2); *m*/*z* 404 (M^+, 24%), 372 (10), 362 (100), 344 (32), 282 (46) and 43 (86).

Treatment of iodide 7 with lithium dimethylcuprate and boron trifluoride–diethyl ether

A solution of lithium dimethylcuprate (0.98 mmol) in diethyl ether (5 ml) was added dropwise to a stirred solution of the 13-iodide **7** (100 mg, 0.19 mmol) in diethyl ether (3 ml) and THF (1.5 ml) at −10 °C. Boron trifluoride–diethyl ether (180 μl, 1.46 mmol) was added dropwise and the resulting pale yellow solution was stirred at −10 °C for 2 h. The crude product was recovered by the usual work-up and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl 13-methyl GA_4 methyl ester **8** (16 mg, 20%)—spectroscopic data as previously obtained, containing ~5% of 3-*O*-acetyl GA_4 methyl ester **12**. Further elution with 25% ethyl acetate in light petroleum returned unchanged starting material **7** (3 mg, 3%). Further elution with 30% ethyl acetate in light petroleum gave 13-methyl GA_4 methyl ester **9** (27 mg, 39%)—spectroscopic data as previously obtained, containing ~5% of GA_4 methyl ester **13**.

Treatment of 13-methanesulfonate 4 with lithium dimethylcyanocuprate

A solution of lithium dimethylcyanocuprate (1.04 mmol) in diethyl ether (2 ml) was added dropwise to a solution of the 13-methanesulfonate **4** (100 mg, 0.21 mmol) in diethyl ether (3 ml) and THF (1 ml), at −10 °C. Boron trifluoride–diethyl ether (190 μl, 1.56 mmol) was added dropwise to the colourless solution and the resulting pale yellow solution was stirred at −10 °C for 8 h, with monitoring by TLC and then warmed to room temperature over 14 h. The usual work-up gave a gum, which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned the 13-methyl derivative **8** (11 mg, 13%)—spectroscopic data as before. Further elution with 50% ethyl acetate in light petroleum returned unchanged starting material **4** (62 mg).

The above reaction was repeated as above but without the addition of boron trifluoride–diethyl ether. The colourless solution was stirred at −10 °C for 8 h, with monitoring by TLC, and then warmed to room temperature over 15 h. The usual work-up gave a gum, which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned the 3-*O*-acetyl 13-methyl GA_4 methyl ester **8** (8 mg, 10%)—spectroscopic data as before. Further elution with 50% ethyl acetate in light petroleum returned unreacted starting material **4** (57 mg). Finally, further elution with 50% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_1 methyl ester **3** (3 mg, 4%)—spectroscopic data as previously described.

Treatment of iodide 7 with lithium dimethylcyanocuprate

A solution of lithium dimethylcyanocuprate (0.98 mmol) in diethyl ether (2 ml) was added dropwise to a solution of the 13-iodide **7** (100 mg, 0.19 mmol) in THF (1 ml) and diethyl ether (2 ml) at −10 °C. Boron trifluoride–diethyl ether (180 μl, 1.46 mmol) was added dropwise and the pale yellow solution was stirred at −10 °C for 6 h, with monitoring by TLC, and then warmed to room temperature over 16 h. The crude product was recovered by the usual work-up and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_4 methyl ester **12** as a gum[28] (39 mg, 52%); δ_H 1.06 (s, 18-H_3), 2.15 (s, $OCOCH_3$), 2.64 (m, 13-H), 2.69 (d, *J* 11, 6-H), 3.17 (d, *J* 11, 5-H), 3.72 (s, OCH_3), 4.86 (br s, 17-H) and 4.97 (2H, br s, 17-H and 3-H); *m*/*z* 388 (M^+, 12%), 358 (21), 346 (12), 328 (59), 205 (12), 179 (10), 105 (41) and 43 (100)—containing a small amount (<10%) of 3-*O*-acetyl 13-methyl GA_4 methyl ester **8**. Further elution with 25% ethyl acetate in light petroleum returned unchanged starting material **7** (35 mg).

The reaction was repeated as above but without the addition of boron trifluoride–diethyl ether. The pale yellow solution was stirred at −10 °C for 6 h, with monitoring by TLC, and then warmed to room temperature over 16 h. The crude product was recovered by the usual work-up and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_4 methyl ester **12** (27 mg, 37%), containing a small amount (<10%) of 3-*O*-acetyl 13-methyl GA_4 methyl ester **8**—spectroscopic data as previously described. Further elution with 25% ethyl acetate in light petroleum returned unchanged starting material **7** (42 mg).

Reaction of iodide 7 with trimethylaluminium

Trimethylaluminium (0.37 ml, 0.73 mmol of a 2.0 M solution in hexanes) was added dropwise to a stirred solution of the 13-iodide **7** (75 mg, 0.15 mmol) in dichloromethane (7.5 ml), at −20 °C. The reaction was stirred at −20 °C for 3 h, warmed to 0 °C for 3 h then allowed to warm to room temperature over 18 h. The usual work-up gave a clear gum, which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_4 methyl ester **12** (15 mg, 26%) which was recrystallised from acetone–light petroleum mp 135–136 °C (lit. mp[28] 138 °C)—spectroscopic data as described above. Further elution with 25% ethyl acetate in light petroleum returned unreacted starting material **7** (22 mg).

Treatment of methanesulfonate 4 with trimethylaluminium

Trimethylaliuminium (0.40 ml, 0.78 mmol of a 2.0 M solution in hexanes) was added dropwise to a stirred solution of methanesulfonate **4** (50 mg, 0.10 mmol) in dichloromethane (5 ml), at −5 °C. The reaction was stirred at −5 °C for 4 h and then allowed to warm to room temperature over 18 h. The usual work-up gave a clear gum, which by ^{1}H NMR spectroscopy was shown to contain only unreacted starting material.

Treatment of methanesulfonate 5 with a Grignard reagent under copper catalysis

Ethylmagnesium bromide (1.55 mmol) in diethyl ether (4 ml) was added to a suspension of copper(I) iodide (296 mg, 1.56 mmol) in diethyl ether (2 ml) at −10 °C. The resulting black suspension was stirred at −10 °C for 10 min. A solution of the 13-methanesulfonate **4** (75 mg, 0.16 mmol) in diethyl ether (2 ml) and THF (1 ml) was added dropwise, followed immediately by boron trifluoride–diethyl ether (144 µl, 1.17 mmol) and the resulting grey mixture was stirred at −10 °C for 2.5 h. The usual work-up gave the crude product, which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned the ent-3α-*acetoxy*-10β-*hydroxy*-13-*ethyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **14** as a clear gum (23 mg, 25%) (Found: M^+, 416.2199. $C_{24}H_{32}O_6$ requires M^+, 416.2190); δ_H 0.82 (t, J 7.5, CH_2CH_3), 1.06 (s, 18-H_3), 2.14 (s, $OCOCH_3$), 2.68 (d, J 10.5,6-H), 3.17 (d, J 10.5, 6-H), 3.73 (s, OCH_3), 4.83 and 4.89 (2 br s, 17-H_2) and 4.98 (br s, 3-H); *m*/*z* 416 (M^+, 12%), 398 (9), 384 (19), 375 (2), 356 (27), 338 (3), 312 (100), 283 (49), 223 (41), 105 (29) and 91 (32). Further elution with 50% ethyl acetate in light petroleum returned unidentifiable products of decomposition.

Reaction of iodide 7 with a Grignard reagent under copper catalysis

Ethylmagnesium bromide (1.95 mmol) in diethyl ether (5 ml) was added to a suspension of copper(I) iodide (372 mg, 1.96 mmol) in diethyl ether (2.5 ml) at −10 °C. The resulting black suspension was stirred at −10 °C for 10 min. A solution of the 13-iodide **7** (100 mg, 0.19 mmol) in diethyl ether (4 ml) and THF (1 ml) was added dropwise, followed by boron trifluoride–diethyl ether (180 µl, 1.46 mmol). The grey mixture was stirred at −10 °C for 2 h then worked-up as usual and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned the 13-ethyl compound **14** (32 mg, 40%)—spectroscopic data as previously described.

Treatment of methanesulfonate 4 with lithium dimethylcuprate and boron trifluoride–diethyl ether in THF

A solution of lithium dimethylcuprate (1.05 mmol) in THF (5 ml) was added dropwise to a stirred solution of the 13-methanesulfonate **4** (100 mg, 0.21 mmol) in THF (4 ml) at −10 °C. Boron trifluoride–diethyl ether (190 µl, 1.56 mmol) was added dropwise to the pale yellow solution and the resulting yellow solution was stirred at −10 °C for 8 h. The usual work-up gave a gum which was purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl 13-methyl GA_4 methyl ester **8** (11 mg, 13%). Further elution with 30 and 35% ethyl acetate in light petroleum returned 13-methyl GA_4 methyl ester **9** (19 mg, 25%). Finally, elution with 50% ethyl acetate in light petroleum gave 3-*O*-acetyl GA_1 methyl ester **3** (18 mg, 21%).

Treatment of methanesulfonate 5 with lithium diethylcuprate and boron trifluoride–diethyl ether

A solution of lithium diethylcuprate (1.03 mmol) in diethyl ether (7.5 ml) was added dropwise to a solution of methanesulfonate **5** (100 mg, 0.21 mmol) in diethyl ether (4 ml) and THF (1 ml), at −10 °C. Boron trifluoride–diethyl ether (190 µl, 1.56 mmol) was slowly added to the blue–purple solution and the resulting purple solution was stirred at −10 °C for 3 h. The crude product was recovered by the usual work-up and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned 3-*O*-acetyl 13-ethyl GA_4 **14** as a clear gum (21 mg, 24%). Further elution with 30% ethyl acetate in light petroleum returned ent-3α,10β-*dihydroxy*-13-*ethyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **15** as a gum (41 mg, 53%) (Found: M^+, 374.2086. $C_{22}H_{30}O_5$ requires M, 374.2093); δ_H 0.82 (t, J 7.5, CH_2CH_3), 1.15 (s, 18-H_3), 2.68 (d, J 10.5, 6-H), 3.20 (d, J 10.5, 5-H), 3,.72 (s, OCH_3), 3.85 (br s, 3-H), 4.82 and 4.88 (2 br s, 17-H_2); *m*/*z* 374 (M^+, 9%), 356 (11), 342 (71), 328 (17), 314 (100), 296 (25), 284 (53), 253 (42), 224 (85) and 91 (69).

***ent*-3α-Acetoxy-13-*n*-butyl-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 16**

A solution of lithium di(*n*-butyl)cuprate (1.82 mmol) in diethyl ether (5 ml) was added dropwise to methanesulfonate **4** (175 mg, 0.36 mmol) in diethyl ether (6.5 ml) and THF (1.5 ml) at −10 °C. Boron trifluoride–diethyl ether (0.36 ml, 2.90 mmol) was added immediately to the dark purple solution and the resulting blue–grey solution was stirred at −10 °C for 2 h. The usual work-up returned a brown gum, which was purified by flash chromatography. Elution with 17.5% ethyl acetate in light petroleum gave the 13-n-*butyl derivative* **16** as a clear gum (123 mg, 76%) (Found: M^+, 444.2502. $C_{26}H_{36}O_6$ requires M, 444.2512); δ_H 0.89 (br m, $CH_2CH_2CH_2CH_3$), 1.06 (s, 18-H_3), 2.14 (s, $OCOCH_3$), 2.66 (d, J 10.5, 6-H), 3.17 (d, J 10.5, 5-H), 3.73 (s, OCH_3), 4.84 and 4.88 (2 br s, 17-H_2) and 4.97 (br s, 3-H); δ_C 14.0 and 14.4 [C-18 and $(CH_2)CH_3$], 17.4 (C-11), 21.1 ($OCOCH_3$), 23.5 (CH_2), 25.4 (CH_2), 27.0, 27.5 and 37.3 (CH_2 C-1 and C-2), 38.0 and 41.2 (C-12 and C-15), 45.8 (C-14), 45.9 (C-13), 50.3 (C-8), 51.2, 52.2 and 52.8 (C-5, C-6 and OCH3), 53.0 (C-4), 71.4 (C-3), 93.5 (C-10), 105.7 (C-17), 159.5 (C-16), 170.2 (C-7), 173.1 (C-19) and 177.0 ($OCOCH_3$); *m*/*z* 444 (M^+, 3%), 426 (3), 412 (12), 384 (15), 352 (5), 340 (82), 71 (47), 57 (68), 43 (100), 41 (42) and 29 (23). Further elution with 60% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_1 7-methyl ester **3** (8 mg, 5%)—spectroscopic data as previously described.

***ent*-3α-Acetoxy-10β-hydroxy-13-phenyl-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 17**

A solution of lithium diphenylcuprate (0.83 mmol) in diethyl ether (7.5 ml) was added dropwise to a solution of methanesulfonate **4** (80 mg, 0.17 mmol) in diethyl ether (3 ml) and THF (0.5 ml), at −10 °C. Boron trifluoride–diethyl ether (150 µl, 1.24 mmol) was added dropwise to the dark green solution and the resulting yellow–green solution was stirred at −10 °C for 2 h. The crude product was recovered by the usual work-up, and purified by flash chromatography. Elution with 20% ethyl acetate in light petroleum returned the 13-*phenyl* GA_4 *derivative* **17**, which crystallised from dichloromethane (31 mg, 40%) mp 152–153 °C (Found: C, 72.0; H, 7.0. $C_{28}H_{32}O_6$ requires C, 72.41; H, 6.90%); δ_H 1.09 (s, 18-H_3), 2.15 (s, $OCOCH_3$), 2.73 (d, J 10, 6-H), 3.22 (d, J 10, 5-H), 3.76 (s, OCH_3), 4.77 and 4.99 (2 br s, 17-H_2), 5.01 (br s, 3-H) and 7.29–7.38 (m, C_6H_5); δ_C 14.5 (C-18),

17.4 (C-11), 21.2 ($OCOCH_3$), 25.5 and 27.2 (C-1 and C-2), 37.9 (C-15), 45.3 and 45.9 (C-12 and C-14), 50.1 and 50.9 (C-8 and C-4), 51.0, 52.1, 52.3 and 52.5 (C-5, C-6, C-9 and OCH_3), 53.0 (C-13), 71.6 (C-3), 93.5 (C-10), 109.6 (C-17), 125.9, 126.4, 128.1 and 146.9 (C_6H_5), 158.5 (C-16), 170.2 (C-7), 173.2 (C-19) and 176.9 ($OCOCH_3$); *m*/*z* (M^+, 54%), 446 (3), 432 (8), 404 (24), 372 (6), 360 (100), 301 (47), 272 (24), 129 (30) and 91 (50). Further elution with 60% ethyl acetate in light petroleum returned 3-*O*-acetyl GA_1 7-methyl ester **3** (11 mg, 16%)—spectroscopic data as previously described.

***ent*-3α-Acetoxy-10β-hydroxy-13-[^{13}C]-methyl-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 18**

A solution of lithium di[^{13}C]methylcuprate (0.78 mmol) in diethyl ether (5 ml) was added dropwise to a solution of methanesulfonate **4** (75 mg, 0.16 mmol) in diethyl ether (3 ml) and THF (0.5 ml) at 0 °C. Boron trifluoride–diethyl ether (140 μl, 1.17 mmol) was added dropwise to the pale yellow solution and the resulting yellow solution was stirred at 0 °C for 2 h. The crude product was recovered by the usual work-up, and purified by flash chromatography. Elution with 25% ethyl acetate in light petroleum returned the title compound **18** as a gum (45 mg, 72%); δ_H 1.06 (s, 18-H_3), 1.14 (d, *J* 125.5, $^{13}CH_3$), 2.14 (s, $OCOCH_3$), 2.66 (d, *J* 10.5, 6-H), 3.17 (d, *J* 10.5, 5-H), 3.72 (s, OCH_3), 4.85 and 4.90 (2 br s, 17-H_2) and 4.97 (br s, 3-H); *m*/*z* 403 (M^+, 2%), 385 (3), 371 (6), 343 (10), 313 (9), 299 (100), 283 (17), 239 (57) and 105 (9).

***ent*-3α,10β-Dihydroxy-13-methyl-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 9**

Aq. potassium carbonate (1 ml; 20%) was added to a solution of 3-*O*-acetyl 13-methyl GA_4 methyl ester **8** (105 mg, 0.26 mmol) in methanol (6 ml). The reaction mixture was stirred at room temperature for 5 min. The usual work-up gave the title compound **9** as a gum (94 mg, 100%)—spectroscopic data as described above.

***ent*-3α-10β-Dihydroxy-13-methyl-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone (13-methyl GA_4) 1**

n-Propanethiol (320 μl, 3.51 mmol) was added dropwise over 10 min to a stirred suspension of sodium hydride (250 mg, 5.21 mmol of a 50% suspension in mineral oil, prewashed with dry hexane) in freshly distilled hexamethylphosphoramide (HMPA) (2.5 ml) at room temperature under nitrogen. The reaction was stirred for 1 h and then allowed to settle. An aliquot of the green supernatant (1.50 ml) was transferred under nitrogen to 13-methyl GA_4 methyl ester **9** (90 mg, 0.25 mmol) and stirred at room temperature for 16 h. The usual work-up returned the crude product, which was purified by flash chromatography. Elution with ethyl acetate–light petroleum (50 : 50) returned 13-*methyl GA*$_4$ **1**, which crystallised from acetone–light petroleum as colourless needles (74 mg, 85%) mp 192–193 °C (Found: C, 69.5; H, 7.5. $C_{20}H_{26}O_5$ requires C, 69.36; H, 7.51%); δ_H 1.13 (s, 18-H_3), 1.19 (s, 13-CH_3), 2.68 (d, *J* 10, 6-H), 3.13 (d, *J* 10, 5-H), 3.86 (br s, 3-H), 4.85 and 4.90 (2 br s, 17-H_2); δ_C 14.6 (C-18), 17.2 (C-11), 26.1 (13-CH_3), 27.2 and 27.9 (C-1 and C-2), 39.0 (C-12), 42.4 (C-14), 42.6 (C-13), 45.0 (C-15), 50.3 (C-8), 51.1 (C-5), 51.4 (C-6), 52.7 (C-9), 54.4 (C-4), 70.3 (C-3), 94.2 (C-10), 105.7 (C-17), 159.5 (C-16), 177.6 (C-7) and 178.6 (C-19); *m*/*z* 346 (M^+, 14%), 328 (32), 310 (9), 300 (36), 284 (100), 105 (20) and 77 (15). The Me TMSi derivative showed KRI 2516; *m*/*z* 432 (M^+, 14%), 328 (32), 310 (9), 300 (36), 284 (100), 257 (21), 243 (34), 239 (91), 238 (87), 197 (25), 129 (66), 105 (27), 75 (63) and 73 (100). Further elution with 60% ethyl acetate in light petroleum gave ent-3β,10β-*dihydroxy*-13-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **19** as a gum (8 mg, 9%) (Found: M^+, 346.1788. $C_{20}H_{26}O_5$ requires *M*, 346.1780; δ_H 1.13 (s, 18-H_3), 1.24 (s, 13-CH_3), 2.49 (d, *J* 10, 5-H), 2.77 (d, *J* 10, 6-H), 3.70 (br s, 3-H), 4.85 and 4.89 (2 s, 17-H_2); *m*/*z* 346 (M^+, 24%), 328 (90), 310 (27), 300 (100), 282 (32), 272 (18), 256 (17), and 91 (32).

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