Unusual reactions of methylsulfonyl esters: syntheses of 3α-methyl and 3β-methyl gibberellin A_{20}

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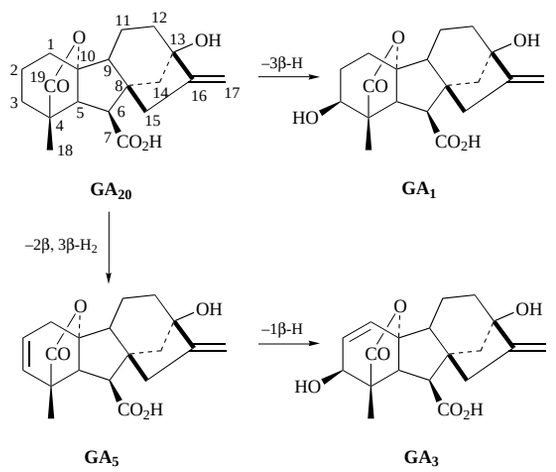
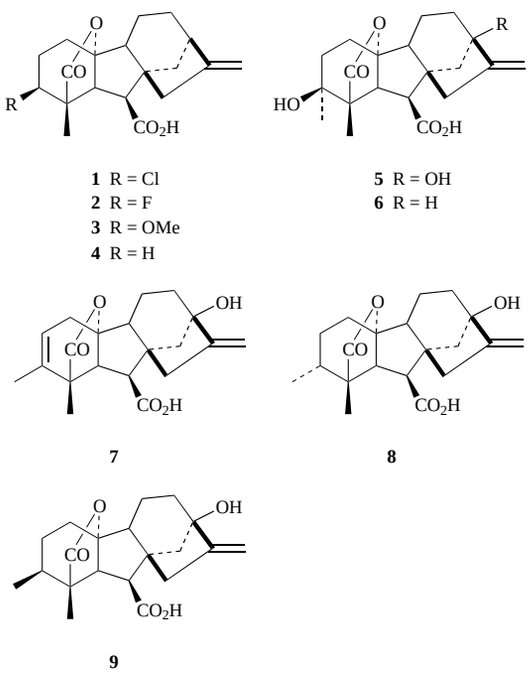
Gibberellin A_3 has been converted to 3α-methylGA_{20} 8 in 33% yield *via* catalytic hydrogenation of the 3-exo-methylene derivative 14. In an attempt to prepare 3β-methylGA_{20} 9, the 3α-methanesulfonate 25 has been treated with lithium dimethylcuprate; only the β-keto sultones 26 and 27 have been isolated (84% yield). In contrast, under similar conditions the 3α-methanesulfonate 35 gave the 2-oxopropylsulfonyloxy derivatives 36 and 37. Synthesis of 3β-methylGA_{20} has been achieved *via* reaction of the 3α-trifluoromethanesulfonate 38 with lithium dimethylcuprate. 3α-MethylGA_{20} and 3β-methylGA_{20} show similar activity to GA_{20} (and significantly less activity than GA_3) in the stimulation of stem elongation of dwarf rice seedlings.

Gibberellin 3β-hydroxylase is one of the key enzymes in gibberellin (GA) biosynthesis and is responsible for the production of bioactive gibberellins.[1] Indeed GA_1, which is formed *via* 3β-hydroxylation of GA_{20} has been proposed to be the only GA required for the control of stem elongation in pea and maize (Scheme 1).[2] More recently GA_3, which displays similar bioactivity to GA_1, has been detected in the stem tissue of maize where it is formed indirectly from GA_5.[3] 3β-Hydroxylation of GA_{20} proceeds with retention of configuration and GA_3 is formed with the loss of 1β-H, 2β-H and 3β-H.[4] Therefore GAs substituted at the 3β-position would be expected to be blocked for 3-hydroxylation and show little or no bioactivity.



Scheme 1

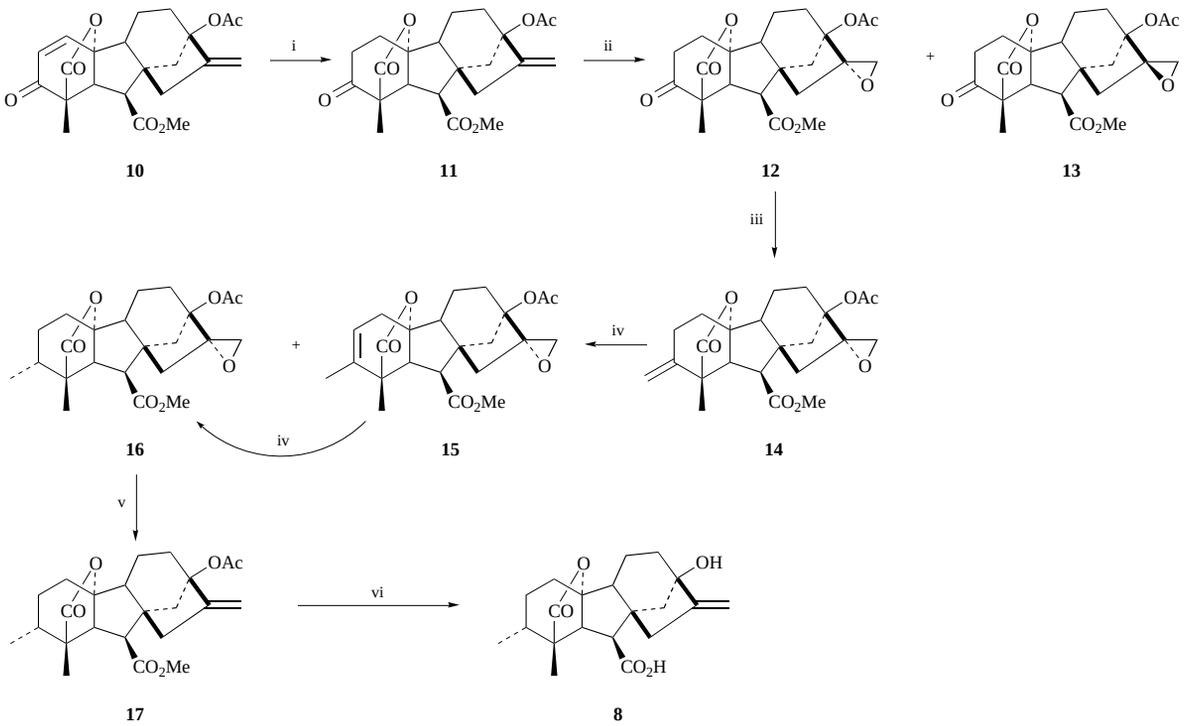
In an early investigation of the inhibition of the 3β-hydroxylation process, Beale and MacMillan prepared a series of derivatives with 3β-chloro **1**, -fluoro **2** and -methoxy **3** substituents.[5] Each compound showed similar activity to the parent compound GA_9 **4** but significantly less activity than GA_3. It was suggested that polar substituents at C-3 may mimic 3β-hydroxylated GAs in the active site. More recently Saito *et al.*[6] reported the first accounts of the syntheses and biological assessments of some 3-methylgibberellin derivatives, most notably 3α-methylGA_1 **5**, 3α-methylGA_4 **6** and 3-methylGA_5 **7**. The bioactivities of these derivatives were assessed. Each showed little inhibition of the 3β-hydroxylases isolated from *Cucurbita maxima* (giant cucumber) and *Phaseolus vulgaris* (French bean) and displayed moderate activity in stem elongation assays with *Oryza sativa* (rice) and *Cucumis sativus* (cucumber). Since both **5** and **6** have a 3β-hydroxy group (believed to be necessary for bioactivity) and there is no evidence that the 3-methyl group in the GA_5 derivative **7** would interfere with its metabolism to a bioactive GA_3 analogue, these results are not too surprising. The biological assessment of 3β-methyl gibberellin analogues would be expected to be more informative. We now describe the synthesis of 3α-methyl- and 3β-methyl-GA_{20} **8** and **9** which led to the discovery of some unexpected reactions of gibberellin 3-methanesulfonates.



Results and discussion

3α-Methylgibberellin A_{20} 8

It has been shown previously that catalytic deuteriogenation of



Scheme 2 *Reagents:* i, Bu_3SnH, $Pd(Ph_3P)_4$; ii, MCPBA, $CHCl_3$; iii, Ph_3PCH_3Br, NaH; iv, H_2, 10% Pd on $CaCO_3$; v, NaOAc, NaI, Zn, AcOH; vi, NaOH (2 M)

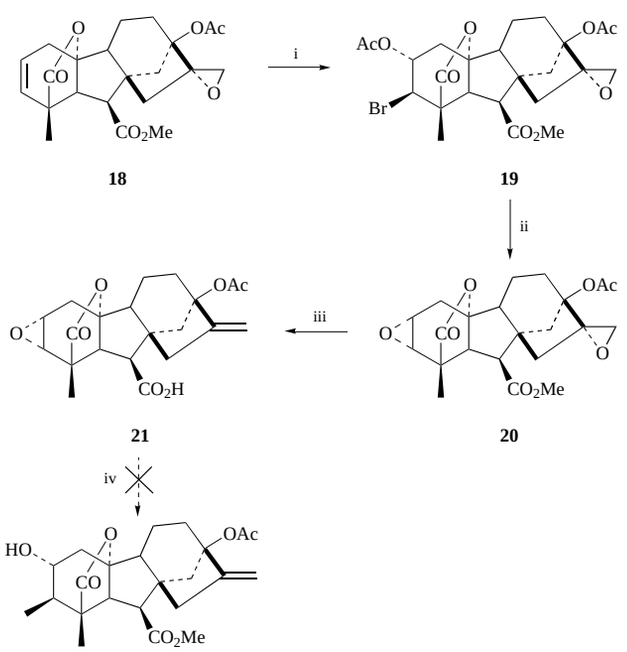
Table 1 ^{1}H NMR Assignments of the ring A protons in GA_{20} and 3α-methylGA_{20} **8**

	δ_H	
Assignment	3α-MethylGA_{20} **8**	GA_{20}
1β-H	1.52	1.39
1α-H	2.05	2.05
2β-H	1.80	1.73
2α-H	1.27	1.57
3β-H	1.73	1.51
3α-H	—	1.68
3α-CH_3	0.93	—

a 2,3-olefin in C_{19}-gibberellins occurs exclusively from the β-face with isomerisation of the double bond leading to the introduction of deuterium at the 1β, 2β and 3β positions.[7] Therefore, by analogy, the proposed route for the synthesis of 3α-methylGA_{20} was *via* catalytic hydrogenation of the exo-methylene **14** or of the 3-methyl-2-olefin **15**. Olefin **14** was prepared as shown in Scheme 2. Selective reduction of the 1,2-double bond in the known enone **10**[8] was achieved in excellent yield using Bu_3SnH in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0).[9] Protection of the exocyclic olefin as the epoxide followed by a Wittig methylenation at C-3 gave **14** in 48% yield over the two steps. Catalytic hydrogenation of **14** gave an inseparable mixture of the unsaturated ester **15** and a fully reduced product. Exhaustive hydrogenation of the mixture gave solely the 3α-methyl derivative **16**. The 16,17-olefin was regenerated using the method of Cornforth[10] and the 13-acetate and 7-methyl ester hydrolysed with sodium hydroxide giving 3α-methylGA_{20} **8** in 33% overall yield from GA_3. The stereochemical assignment of the 3-methyl substituent was confirmed by the ^{1}H NMR and ^{1}H–^{1}H phase sensitive COSY spectra. The assignments of the ring A protons in **8** are shown in Table 1 and, as expected, they bear a close similarity to the reported assignments of the parent compound GA_{20}.[7] Although the 3-proton was partially masked, 2α-H was clearly visible as a doublet of triplets of doublets (J_{gem} 14 Hz, 2 × $J_{ax,ax}$ each 12 Hz and $J_{ax,eq}$ 6 Hz) confirming that ring A was in a chair conformation with an equatorial methyl group at C-3. The chair conformation of ring A was substantiated by the signal assigned to 1β-H which resonated at δ 1.52 as a doublet of doublets of doublets (J_{gem} 13 Hz, $J_{ax,ax}$ 12 Hz and $J_{ax,eq}$ 6 Hz).

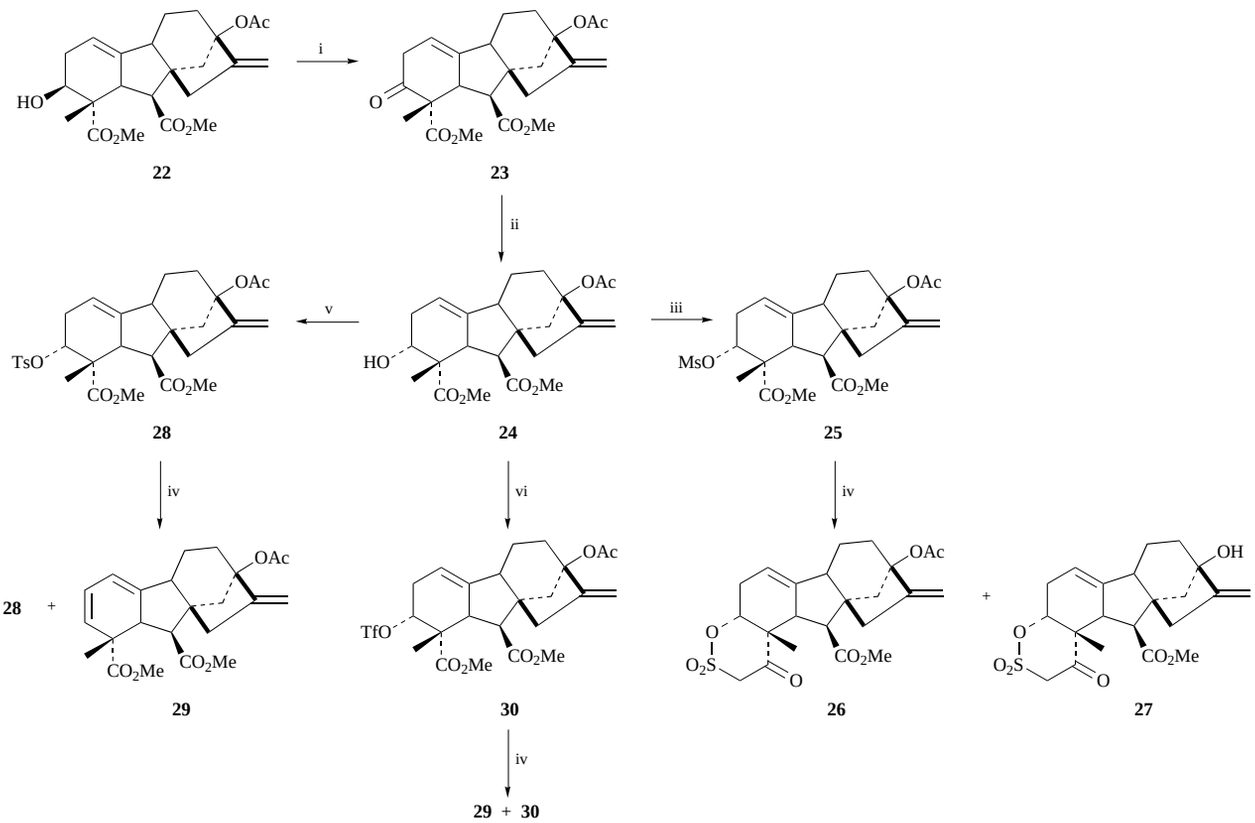
3β-Methylgibberellin A_{20} 9

Three approaches were examined for the synthesis of 3β-methylGA_{20} each based upon the use of an organometallic reagent to displace a leaving group at the 3α-position. First the 2α,3α-epoxide **21** was prepared in a three-stage procedure from



Scheme 3 *Reagents:* i, $CH_3CONHBr$, NaOAc, AcOH; ii, K_2CO_3, MeOH; iii, NaOAc, NaI, Zn, AcOH; iv, organometallic reagents

the known olefin **18** (Scheme 3).[7] Reaction of **18** with *N*-bromoacetamide and lithium acetate in acetic acid gave the



Scheme 4 *Reagents:* i, CrO_3, H_2SO_4, H_2O, Me_2CO; ii, $NaBH_4$, MeOH; iii, MsCl, pyridine; iv, Me_2CuLi; v, TsCl, pyridine; vi, Tf_2O, pyridine

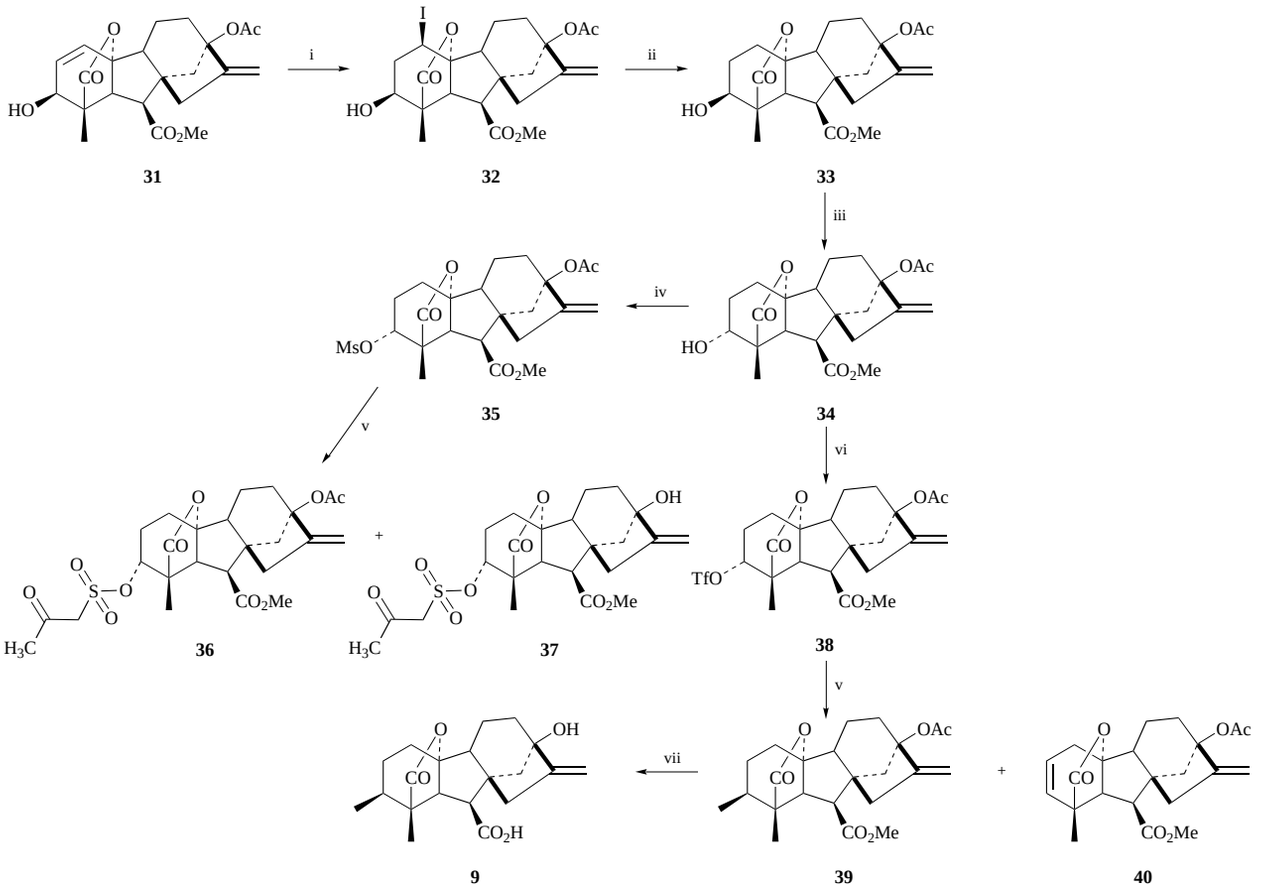
bromo acetate **19** as the sole product in 91% yield. Treatment of **19** with anhydrous potassium carbonate in methanol gave the diepoxide **20** which under Cornforth conditions[10] led to selective regeneration of the exocyclic olefin. Treatment of **21** with lithium dimethylcuprate in the presence or absence of boron trifluoride–diethyl ether[11] returned starting material. Higher order dimethylcyanocuprates have been reported to be more effective towards the opening of di- and tri-substituted epoxides[12] but treatment of **21** with lithium dimethylcyanocuprate in the presence or absence of boron trifluoride again returned starting material. Similar results were obtained with a copper catalysed Grignard reagent[13] and with trimethylaluminium.[14] The inert nature of the 2α,3α-epoxide was surprising and it was apparent that a different leaving group at C-3 was required.

It has been reported that sulfonate esters may be displaced with organocuprate reagents[15] and indeed we have shown in the gibberellin field that reaction of a bridgehead methanesulfonate with a range of lithium dialkylcuprate reagents gives 13-alkylated derivatives.[16] 3α-Methanesulfonate **25**, toluene-*p*-sulfonate **28** and trifluoromethanesulfonate **30** were prepared from hydroxy ester **22** (Scheme 4). The 3β-alcohol was inverted *via* a two-stage oxidation-reduction procedure giving the 3α-alcohol **24** in 68% yield which was then converted to the sulfonate esters **25**, **28** and **30** under standard conditions. The methanesulfonate **25** was treated with lithium dimethylcuprate at −10 °C for 4 h giving a mixture of two products which were purified by flash chromatography. The ^{1}H NMR spectrum of the major product displayed a singlet at δ 3.71 assigned to a methyl ester and a pair of doublets (each J 16.5 Hz) at δ 4.12 and 4.32. In addition there was a signal present at δ 4.84 (t, J 5 Hz) of similar chemical shift (δ 4.83) to 3β-H in the starting material **25**. Hence the compound was tentatively assigned as keto sultone **27** and this was confirmed by the ^{13}C NMR [δ 198 (C-19), 175 (C-7) and 61 (19-CO*C*H$_2$)] and mass spectrum (M^+, 422.1391). The less polar compound was the corresponding 13-acetate **26**. The reaction can be envisaged as proceeding *via* abstraction of the acidic proton on the sulfonyl ester followed by nucleophilic attack of the resultant anion on C-19. The formation of the sultone was unexpected and although the reaction is unusual, the formation of sultones has been reported in carbohydrate chemistry[17] and more recently in a study of the citreamicin antibiotics.[18]

Reaction of the 3α-toluene-*p*-sulfonate **28** with lithium dimethylcuprate returned starting material and the eliminated product **29**. Similar results were obtained with the trifluoromethanesulfonate. Hence none of these reactions had led to the formation of the required 3β-methyl gibberellin. The final approach to the target compound also involved the displacement of a good leaving group at C-3 but this time on a substrate with the 19,10γ-lactone intact. It was anticipated that in this case, if deprotonation of the methanesulfonate **35** occurred, then there would be insufficient orbital overlap of the resultant anion with the lactone carbonyl to form a sultone-type product. In addition it was hoped the competing elimination reaction to form the 2,3-olefin may be less of a problem.

The 3α-methanesulfonate **35** was prepared from **31** as shown in Scheme 5. Hydrogenolysis of the allylic lactone moiety followed by iodolactonisation gave the iodide **32** as previously described.[19] Barton and co-workers have recently reported that dialkyl phosphites can be used in place of the more commonly used tributylstannane in the radical reduction of halides.[20] Treatment of iodide **32** with dimethyl phosphite in the presence of benzoyl peroxide gave GA_1 methyl ester **33** in 87% yield. The high yield of **33** and the low toxicity and cost of the reagent combine to make dehalogenation with dimethyl phosphite an attractive alternative in GA chemistry. Inversion of the 3β-alcohol proceeded smoothly and the resultant 3α-alcohol **34** converted to 3α-methanesulfonate **35** in excellent yield.

Treatment of **35** with 5 equiv. of lithium dimethylcuprate at −10 °C for 4 h gave a mixture of products which was separated into two components by flash chromatography (Scheme 5). The



Scheme 5 *Reagents:* i, H_2, 10% Pd on $CaCO_3$, MeOH, pyridine then I_2, CH_2Cl_2, $NaHCO_3$; ii, DMP, $(PhCO_2)_2$, toluene, heat; iii, CrO_3, H_2SO_4, H_2O, Me_2CO then $NaBH_4$, MeOH; iv, MsCl, pyridine; v, Me_2CuLi; vi, Tf_2O, pyridine; vii, NaOH (2 M)

less polar fraction was a 1:1 mixture of starting material and a new product; the more polar fraction gave a very similar ^{1}H NMR spectrum showing two compounds in which it was evident that the 13-hydroxy rather than 13-acetoxy group was present. In an attempt to obtain pure products, the reaction was repeated with 10 equiv. of lithium dimethylcuprate. The ^{1}H NMR spectrum of the less polar product displayed a doublet of doublets (*J* 11 and 6 Hz) at δ 4.79 which was very similar to the signal assigned to 3-H in the starting methanesulfonate δ 4.73 (dd, *J* 11 and 6 Hz); however no singlet was apparent at *ca.* δ 3.0 which could be assigned to the CH_3 of the methanesulfonate. There were new signals apparent in the spectrum of the product which were not present in that of the starting material: at δ 2.41 (3 H, s), 4.15 (1 H, d, *J* 14.5 Hz) and 4.19 (1 H, d, *J* 14.5 Hz). Interestingly the ^{13}C NMR spectrum had a signal at δ 194 characteristic of a ketonic carbonyl as well as signals at δ 172 and 175 assigned to C-19 and C-17 respectively. A structure in accord with these data is the 2-oxopropylsulfonyloxy gibberellin **36** and the more polar product was the corresponding 13-alcohol **37**. The reaction may be envisaged as proceeding *via* deprotonation of the methanesulfonate methyl to generate the anion which then undergoes intermolecular attack on the bridgehead acetate of a further GA molecule. To confirm this proposal, both the corresponding 13-deoxy- and 13-hydroxygibberellin 3α-methanesulfonates **41** and **42** were treated with lithium dimethylcuprate but both simply returned starting material. In contrast reaction of GA_1 3β-methanesulfonate 13-acetate **43** with lithium dimethylcuprate gave the 3β-(2-oxopropylsulfonyloxy) derivatives **44** and **45**. Interestingly in all of these cases no elimination or displacement of the 3-methanesulfonate had occurred.

Reaction of the trifluoromethanesulfonate **38** with lithium dimethylcuprate gave the protected 3β-methylGA_{20} derivative **39** and substantial amounts of elimination product **40** (49%) (Scheme 5). In the ^{1}H NMR spectrum of **38**, the protons assigned to the 3-methyl group resonated at δ 1.07 (d, *J* 7 Hz) whereas in the corresponding 3α-methyl derivative **17** the 3-methyl group resonated at δ 0.93 (d, *J* 7 Hz). Treatment of **39** with aqueous sodium hydroxide gave the required 3β-methylGA_{20} **9**.

Table 2 Rice seedling bioassay

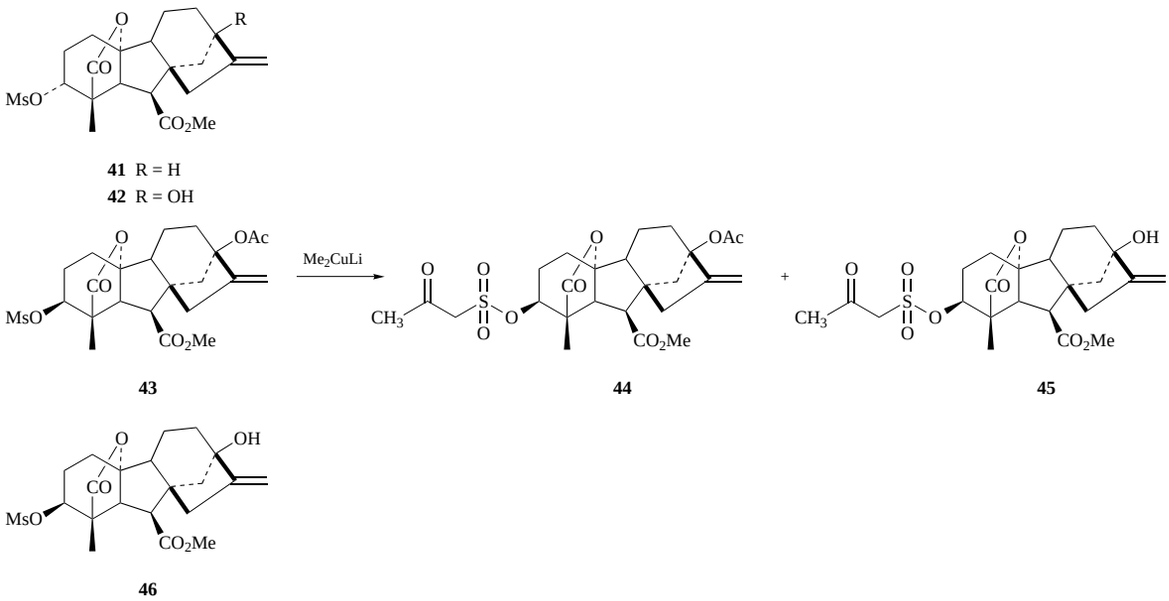
	Length (mm)	
	Second leaf sheath	Total
Control	16	22
GA_3	57	73
GA_{20}	26	42
3α-MeGA_{20} **8**	24	35
3β-MeGA_{20} **9**	28	38

Bioassay of 8 and 9 with Tanginbozu dwarf rice

The biological activities of 3α-methylGA_{20} **8** and 3β-methyl GA_{20} **9** were assessed in a bioassay with Tanginbozu dwarf rice against GA_{20}, GA_3 and a control. After 7 days the total lengths of the plants were measured and the results are given in Table 2. It is apparent that both **8** and **9** exhibit significantly less activity than GA_3 but interestingly show approximately the same activity as each other, albeit very low. The alkylated gibberellins will be tested in further bioassays.

Experimental

General experimental details have been described previously.[21] Enone **10** was prepared as described by Beale and MacMillan.[8] Only selected ^{1}H NMR data are reported. For the numbering system used throughout this paper see structure GA_{20}, Scheme 1.



***ent*-13-Acetoxy-10β-hydroxy-3-oxo-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 11**

Enone **10** (1.75 g, 4.38 mmol) in THF (75 ml) was added to tetrakis(triphenylphosphine)palladium(0) (150 mg, 3 mol%) in THF (20 ml) at room temperature under a nitrogen atmosphere. Tributylstannane (2.30 ml, 8.75 mmol) was added slowly over a period of 1.5 h. The reaction mixture was stirred for 0.5 h at room temperature and then worked-up as usual to give an orange oil which was purified by flash column chromatography. Elution with 5% ethyl acetate in light petroleum removed the tin residues. Further elution with 40% ethyl acetate in light petroleum returned the title compound **11** as a white powder, which was recrystallised from acetone–light petroleum (1.76 g), mp 158–160 °C (lit.,[8] reports this as a gum); δ_H 1.17 (s, 18-H_3), 2.03 (s, $OCOCH_3$), 2.87 (d, *J* 10, 6-H), 3.10 (d, *J* 10, 5-H), 3.73 (s, OCH_3), 5.00 and 5.16 (2 br s, 17-H_2); *m/z* 402 (M^+, 30%), 371 (9), 360 (97), 342 (24), 83 (27), 55 (27) and 43 (100).

Treatment of 3-oxoGA_1 methyl ester 13-acetate 11 with 3-chloroperoxybenzoic acid

Ketone **11** (700 mg, 1.74 mmol) and 3-chloroperoxybenzoic acid (720 mg of a 50–60% commercial supply) were stirred in chloroform (150 ml) for 18 h. The reaction mixture was diluted with chloroform (50 ml) and washed sequentially with aq. sodium sulfite (2 × 10 ml), saturated aq. sodium hydrogen carbonate (3 × 40 ml) and water (2 × 20 ml). The chloroform was dried (Na_2SO_4) and was removed under reduced pressure to give a gum, which was purified by flash column chromatography. Elution with 30% ethyl acetate in light petroleum returned unchanged starting material (157 mg). Further elution with 45% ethyl acetate in light petroleum returned the 16β,17-*epoxide* **13**, which crystallised from acetone–light petroleum as needles (155 mg), mp 152–155 °C (Found: C, 63.4; H, 5.9. $C_{22}H_{26}O_8$ requires C, 63.16; H, 6.22%); δ_H 1.16 (s, 18-H_3), 2.00 (s, $OCOCH_3$), 2.81 (d, *J* 5.5, 17-H) partially masking 2.82 (d, *J* 10, 6-H), 3.05 (d, *J* 5.5, 17-H), 3.11 (d, *J* 10, 5-H) and 3.74 (s, OCH_3); *m/z* 418 (M^+, 13%), 390 (11), 387 (12), 376 (52), 358 (45), 319 (64), 287 (100), 273 (56), 213 (33), 91 (69), 71 (41) and 55 (88). Further elution with 45% ethyl acetate in light petroleum gave the 16α,17-*epoxide* **12**, which crystallised from acetone–light petroleum (316 mg), mp 161–165 °C (Found: C, 63.2; H, 6.1. $C_{22}H_{26}O_8$ requires C, 63.16; H, 6.22%); δ_H 1.18 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.76 (d, *J* 5.5, 17-H), 2.86 (d, *J* 10, 6-H), 3.10 (d, *J* 5.5, 17-H) partially masking 3.11 (d, *J* 10, 5-H) and 3.73 (s, OCH_3); *m/z* 418 (M^+, 8%), 390 (9), 387 (13), 376 (100), 375 (32), 358 (39), 319 (38), 287 (60), 273 (42), 243 (30), 111 (26), 91 (56), 77 (26) and 55 (60). Finally elution with 45 and 50% ethyl acetate in light petroleum gave *ent*-13-acetoxy-10β,16β,17-trihydroxy-3-oxo-20-norgibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone which crystallised from ethyl acetate–light petroleum (106 mg), mp 179–180 °C (Found: C, 60.2; H, 6.6. $C_{22}H_{28}O_9$ requires C, 60.55; H, 6.42%); δ_H 1.16 (s, 18-H_3), 2.08 (s, $OCOCH_3$), 2.82 (d, *J* 10, 6-H), 3.08 (d, *J* 10, 5-H), 3.71 (d, *J* 12, C*H*OH), 3.75 (s, OCH_3) and 3.84 (d, *J* 12, C*H*OH); *m/z* 436 (M^+, 11%), 401 (89), 394 (34), 376 (71), 362 (24), 359 (39), 358 (33), 316 (35), 298 (29), 287 (54), 274 (31), 141 (20), 91 (65) and 55 (100).

***ent*-13-Acetoxy-16β,17-epoxy-10β-hydroxy-3-methylene-20-norgibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone 14**

Methyltriphenylphosphonium bromide (2 g) in THF (25 ml) was gently warmed with sodium hydride (480 mg of a 60% dispersion in mineral oil, pre-washed with hexane), under nitrogen, with stirring, until a pale green colour appeared. The mixture was stirred at room temperature for 16 h and then allowed to settle. An aliquot (12 ml) of the yellow supernatant (10 ml) was added to the 3-oxo-16α,17-epoxide **12** (450 mg, 1.08 mmol) and stirred for 4 h at room temperature under a nitrogen atmosphere. Acetone (5 ml) was added and the solvents were removed under a stream of nitrogen gas. The crude mixture was purified by flash column chromatography. Elution with 40% ethyl acetate in light petroleum gave the required 3-*methylene derivative* **14**, which crystallised from ethyl acetate–light petroleum as needles (385 mg), mp 141–143 °C (Found: M^+, 416.1842. $C_{23}H_{28}O_7$ requires *M*, 416.1835); δ_H 1.23 (s, 18-H_3), 2.01 (s, $OCOCH_3$), 2.72 (d, *J* 10.5, 5-H), partially masking 2.73 (d, *J* 5, 17-H), 2.82 (d, *J* 10.5, 6-H), 3.11 (d, *J* 5, 17-H), 3.73 (s, OCH_3), 4.93 and 4.97 (2 br s, 3-CH_2); *m/z* 416 (M^+, 5%), 385 (3), 372 (6), 357 (2), 343 (3), 330 (5), 312 (41), 294 (31), 271 (24), 253 (26), 225 (22) and 43 (100).

***ent*-13-Acetoxy-16β,17-epoxy-10β-hydroxy-3β-methyl-20-norgibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone 16**

Alkene **14** (100 mg, 0.24 mmol) in THF (8 ml) was stirred under a hydrogen atmosphere in the presence of 10% palladium on calcium carbonate (15 mg) for 1 h at room temperature. The catalyst was filtered off and washed with ethyl acetate (50 ml) and the solvents removed under reduced pressure, to give solely the 3α-*methyl derivative* **16**, which crystallised from ethyl acetate–light petroleum (102 mg), mp 149–152 °C (Found: M^+, 418.1990. $C_{23}H_{30}O_7$ requires *M*, 418.1992); δ_H 0.89 (d, *J* 6.5, 3α-CH_3), 1.01 (s, 18-H_3), 1.97 (s, $OCOCH_3$), 2.55 (d, *J* 10.5, 5-H),

2.69 (d, *J* 5.5, 17-H), 2.73 (d, *J* 10.5, 6-H), 3.06 (d, *J* 5.5, 17-H) and 3.68 (s, OCH_3); *m/z* 418 (M^+, 3%), 387 (4), 376 (32), 358 (10), 319 (11), 314 (14), 287 (13), 273 (26), 241 (17), 213 (13), 105 (10), 91 (20), 55 (34) and 43 (100).

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

16α,17-Epoxide **16** (350 mg, 0.84 mmol) in acetone (4 ml) was added to a stirred mixture of sodium acetate (824 mg, 10.0 mmol), sodium iodide (1.26 g, 8.37 mmol) and freshly activated zinc powder (655 mg, 10.0 mmol) in acetic acid (7.5 ml) and water (1.5 ml). The green–grey mixture was stirred at room temperature for 2 h and then worked-up. The zinc was filtered off and washed with water (50 ml) and ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organic fractions were washed with aq. sodium thiosulfate (2 × 10 ml) and water (2 × 25 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The crude mixture was purified by flash column chromatography. Elution with 12.5 and 15% ethyl acetate in light petroleum returned the required *olefin* **17**, which crystallised from ethyl acetate–light petroleum (315 mg), mp 161–165 °C (Found: M^+, 402.2053. $C_{23}H_{30}O_6$ requires *M*, 402.2042); δ_H 0.93 (d, *J* 7, 3α-CH_3), 1.04 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.59 (d, *J* 10.5, 5-H), 2.73 (d, *J* 10.5, 6-H), 3.72 (s, OCH_3), 4.98 and 5.12 (2 br s, 17-H_2); *m/z* 402 (M^+, 10%), 371 (6), 370 (4), 360 (58), 342 (24), 328 (15), 314 (30), 300 (26), 272 (24), 258 (25), 155 (10), 105 (12), 55 (18) and 43 (100).

***ent*-10β,13-Dihydroxy-3β-methyl-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone (3α-methylGA$_{20}$) 8**

3α-MethylGA_{20} methyl ester 13-acetate **17** (180 mg, 0.45 mmol) in methanol (5 ml) and 6 M sodium hydroxide (10 ml) was heated to reflux for 48 h. The usual work-up gave a gum, which was purified by flash column chromatography. Elution with 50% ethyl acetate in light petroleum (containing 2% acetic acid) gave the required 3α-*methylGA*$_{20}$ **8** which crystallised from ethyl acetate–light petroleum as needles (128 mg), mp 187–188 °C (Found: C, 68.9; H, 7.6. $C_{20}H_{26}O_5$ requires C, 69.36; H, 7.51%); δ_H 0.94 (d, *J* 6.5, 3α-CH_3), 1.08 (s, 18-H_3), 1.27 (dtd, *J* 6, 12 and 14, 2α-H), 1.52 (ddd, *J* 6, 12 and 13, 1β-H), 2.54 (d, *J* 10, 5-H), 2.74 (d, *J* 10, 6-H), 4.96 and 5.27 (2 br s, 17-H_2); δ_C 14.5 (3-CH_3), 15.8 (C-18), 17.1 (C-11), 28.8 and 31.1 (C-1 and C-2), 38.1 (C-12), 38.3 (C-3), 42.8 and 44.4 (C-14 and C-15), 49.6 (C-8), 51.4 (C-9), 52.2 (C-4), 53.0 (C-6), 58.8 (C-5), 78.3 (C-13), 93.1 (C-10), 107.7 (C-17), 155.8 (C-16), 175.3 (C-7) and 178.4 (C-19); *m/z* 346 (M^+, 68%), 328 (91), 302 (50), 300 (58), 289 (82), 272 (24), 259 (97), 213 (43), 173 (53), 105 (63), 91 (94), 79 (60), 69 (45) and 55 (100). The methyl ester trimethylsilyl ether derivative gave KRI 1057; *m/z* 432 (M^+, 100%), 417 (14), 403 (5), 375 (53), 359 (5), 315 (13), 235 (9), 207 (44), 180 (13), 167 (9), 73 (67) and 55 (6).

***ent*-2β,13-Diacetoxy-3α-bromo-16β,17-epoxy-10β-hydroxy-20-norgibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone 19**

Gibberellin A_5 methyl ester 13-acetate 16α,17-epoxide **18**[7] (1.10 g, 2.74 mmol), *N*-bromoacetamide (945 mg, 6.84 mmol) and lithium acetate dihydrate (630 mg, 6.16 mmol), were stirred in acetic acid (10 ml) for 18 h at room temperature. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (2 × 30 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* (residual acetic acid was removed by azeotropic distillation with toluene). The crude reaction mixture was purified by flash column chromatography. Elution with 55% ethyl acetate in light petroleum returned the *bromo acetate* **19** as a foam (1.35 g) (Found: M^+, 540.1032, $C_{24}H_{29}O_9{}^{79}Br$ requires *M*, 540.0994); δ_H 1.21 (s, 18-H_3), 2.01 and 2.05 (2 s, 2 and 13 $OCOCH_3$), 2.76 (d, *J* 5.5, 17-H), 2.80 (d, *J* 10.5, 6-H), 3.09 (d, *J* 5.5, 17-H), 3.35 (d, *J* 10.5, 5-H), 3.74 (s, OCH_3), 4.11 (br s, 3-H) and 5.34 (br s, 2-H); *m/z* 542 (M^+, 4%) and 540 (M^+, 4%), 500 (14), 498 (14), 359 (6), 351 (7), 349 (7), 341 (8), 296 (21), 197 (17), 155 (11), 55 (11) and 43 (100).

***ent*-13-Acetoxy-2β,3β : 16β,17-diepoxy-10β-hydroxy-20-norgibberellane-7,19-dioic acid 7-methyl ester 19,10-lactone 20**

Bromo acetate **19** (1.30 g, 2.41 mmol) in methanol (40 ml) was stirred with potassium carbonate (665 mg, 4.82 mmol) for 10 min at room temperature. The usual work-up gave a yellow solid, which was crystallised from acetone–light petroleum to give the *diepoxide* **20** (994 mg), mp 146–149 °C (Found: M^+, 418.1619. $C_{22}H_{26}O_8$ requires *M*, 418.1627); δ_H 1.34 (s, 18-H_3), 1.99 (s, $OCOCH_3$), 2.42 (dd, *J* 1.8 and 12, 14α-H), 2.58 (d, *J* 16, 15α-H), 2.64 (d, *J* 10, 6-H), 2.73 (d, *J* 5.5, 17-H), 2.98 (d, *J* 10, 5-H), 3.09 (d, *J* 5.5, 17-H), 3.20 (d, *J* 4, 3-H), 3.32 (t, *J* 4, 2-H) and 3.74 (s, OCH_3); *m/z* 418 (M^+, 3%), 396 (6), 387 (9), 376 (59), 314 (19), 287 (25), 273 (13), 241 (13), 197 (18), 155 (16), 91 (19), 55 (27) and 43 (100).

***ent*-13-Acetoxy-2β,3β-epoxy-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 21**

Diepoxide **20** (950 mg, 2.27 mmol) in acetone (10 ml), was added dropwise to a stirred mixture of sodium iodide (1.02 g, 6.82 mmol), sodium acetate (2.37 g, 27.2 mmol) and freshly activated zinc powder (1.50 g, 22.7 mmol) in acetic acid (10 ml) and water (1 ml). The reaction mixture was stirred at room temperature for 2 h and then worked-up. The zinc was filtered off and washed with water (50 ml) and ethyl acetate (75 ml). The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organic fractions were washed with aq. sodium thiosulfate (2 × 20 ml) and water (2 × 30 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The crude mixture was purified by flash column chromatography. Elution with 35% ethyl acetate in light petroleum gave the 2α,3α-*epoxide* **21**, which was crystallised from ethyl acetate–light petroleum (596 mg), mp 164–165 °C (Found: C, 65.7; H, 7.0. $C_{22}H_{26}O_7$ requires C, 65.67; H, 6.47%); δ_H 1.34 (s, 18-H_3), 2.01 (s, $OCOCH_3$), 2.60 (d, *J* 10, 6-H), 2.97 (d, *J* 10, 5-H), 3.19 (d, *J* 3.5, 3-H), 3.30 (t, *J* 4, 2-H), 3.74 (s, OCH_3), 4.98 and 5.11 (2 br s, 17-H_2); *m/z* 402 (M^+, 23%), 376 (14), 360 (19), 328 (36), 298 (43), 282 (17), 239 (17), 195 (17), 155 (19), 91 (33), 55 (26) and 43 (100).

***ent*-13-Acetoxy-3-oxo-20-norgibberella-1(10),16-diene-7,19-dioic acid 7,19-dimethyl ester 23**

3β-Hydroxy-1,10-olefin **22**[7] (1.00 g, 2.48 mmol) in acetone (60 ml) was treated with Jones reagent at 0 °C, until the orange colour persisted. The reaction was stirred for a further 0.5 h at 0 °C and then quenched by dropwise addition of methanol (10 ml). Half of the solvent was removed *in vacuo*, and the reaction mixture was worked-up as usual and purified by flash column chromatography. Elution with 25 and 30% ethyl acetate in light petroleum gave the required β-*keto ester* **23** as a gum (715 mg) (Found: M^+, 416.1850. $C_{23}H_{28}O_7$ requires *M*, 416.1835); δ_H 1.33 (s, 18-H_3), 2.01 (s, $OCOCH_3$), 3.18 (br s, 5-H and 6-H), 3.69 and 3.72 (2 s, 7 and 19 OCH_3), 5.04 (br s, 17-H_2) and 5.54 (m, 1-H); *m/z* 416 (M^+, 17%), 401 (19), 385 (8), 369 (9), 357 (66), 356 (63), 324 (39), 297 (100), 237 (55) and 43 (42).

***ent*-13-Acetoxy-3β-hydroxy-20-norgibberella-1(10),16-diene-7,19-dioic acid 7,19-dimethyl ester 24**

Sodium borohydride (680 mg, 18.0 mmol) was slowly added to ketone **23** (1.50 g, 3.61 mmol) in methanol (70 ml) at room temperature. The reaction was stirred for 1.5 h and then worked-up as normal. Purification of the product by flash chromatography, eluting with 40% ethyl acetate in light petroleum returned the 3β-alcohol **22** (63 mg); spectroscopic data as previously described.[7] Further elution with 45% ethyl acetate in light petroleum gave the required 3α-*alcohol* **24** as a gum

(1.43 g) [Found: $(M - 18)^+$, 400.1884. $C_{23}H_{28}O_6$ requires *M*, 400.1886]; δ_H 1.33 (s, 18-H_3), 1.98 (s, $OCOCH_3$), 2.77 (d, *J* 5, 6-H), 2.92 (m, 5-H), 3.65 (s, OCH_3), 3.71 (br s, OCH_3 and 3-H), 4.98 (br s, 17-H_2) and 5.37 (br s, 1-H); *m/z* 418 (M^+, 1%), 400 (9), 385 (27), 368 (27), 340 (77), 325 (58), 281 (94), 221 (89), 91 (40) and 43 (100).

***ent*-13-Acetoxy-3β-methylsulfonyloxy-20-norgibberella-1(10),16-diene-7,19-dioic acid 7,19-dimethyl ester 25**

3α-Alcohol **24** (325 mg, 0.78 mmol) in pyridine (5 ml) and methanesulfonyl chloride (180 μl, 2.33 mmol) were stirred for 2 h at room temperature. 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 3α-methanesulfonate **25** as a foam (352 mg) [Found: $(M - 31)^+$, 465.1569. $C_{23}H_{29}O_8S$ requires *M*, 465.1583]; δ_H 1.34 (s, 18-H_3), 1.99 (s, $OCOCH_3$), 2.65 (d, *J* 5, 6-H), 2.70 (m, 5-H), 3.05 (s, OSO_2CH_3), 3.69 and 3.72 (2 s, 7 and 19 OCH_3), 4.83 (dd, *J* 7 and 9, 3-H), 4.98 (br s, 17-H_2) and 5.38 (m, 1-H); *m/z* 465 [$(M - 31)^+$, 4%], 436 (2), 414 (1), 368 (53), 340 (81), 325 (57) and 281 (100).

Reaction of the 1,10-olefin 3α-methanesulfonate 25 with lithium dimethylcuprate

Lithium dimethylcuprate [prepared from copper(I) iodide (230 mg, 1.07 mmol) and methyllithium (1.40 ml, 2.02 mmol) in diethyl ether (5 ml)] was added to the 3α-methanesulfonate **25** (100 mg, 0.20 mmol) in diethyl ether (3 ml) at −10 °C under a nitrogen atmosphere. The reaction mixture was stirred at −10 °C for 3 h and then allowed to warm to room temperature over 1 h. The usual work-up gave a blue–grey gum which was purified by flash column chromatography. Elution with 25% ethyl acetate in light petroleum gave the β-*keto sultone* 13-*acetate* **26** as a gum (11 mg) (Found: M^+, 464.1508. $C_{23}H_{28}O_8S$ requires *M*, 464.1504); δ_H 1.37 (s, 18-H_3), 2.01 (s, $OCOCH_3$), 3.70 (s, OCH_3), 4.09 and 4.30 (2 d, each *J* 16, OSO_2CH_2CO), 4.82 (t, *J* 5, 3-H), 4.99 (br s, 17-H_2) and 5.37 (m, 1-H); *m/z* 464 (M^+, 8%), 433 (4), 422 (35), 404 (31), 362 (31), 344 (32), 281 (46), 239 (70), 221 (48) and 43 (100). Further elution with 30% ethyl acetate in light petroleum gave the β-*keto sultone* **27** as a gum (61 mg) (Found: M^+, 422.1391. $C_{21}H_{26}O_7S$ requires *M*, 422.1399); δ_H 1.37 (s, 18-H_3), 3.71 (s, OCH_3), 4.12 and 4.32 (2 d, each *J* 16.5, OSO_2CH_2CO), 4.84 (t, *J* 5, 3-H), 4.98 and 5.15 (2 br s, 17-H_2) and 5.37 (m, 1-H); δ_C 19.0 (C-11), 22.8 (C-18), 26.7, 37.8 and 39.5 (C-12, C-14 and C-15), 45.9 and 48.0 (C-5 and C-6), 49.2 (C-2), 49.5 and 49.8 (C-4 and C-8), 51.2 and 52.2 (C-9 and OCH_3), 61.4 (OSO_2–CH_2–CO), 79.0 (C-3), 81.6 (C-13), 107.0 (C-1), 109.5 (C-17), 141.7 (C-10), 154.2 (C-16), 174.8 (C-7) and 197.7 (C-19); *m/z* 422 (M^+, 5%), 391 (2), 390 (3), 388 (5), 362 (32), 299 (7), 239 (100), 211 (31) and 84 (13).

***ent*-13-Acetoxy-3β-(4-methylphenylsulfonyloxy)-20-norgibberella-1(10),16-diene-7,19-dioic acid 7,19-dimethyl ester 28**

3α-Alcohol **24** (500 mg, 1.20 mmol), DMAP (75 mg, 0.60 mmol) and 4-methylbenzenesulfonyl chloride (2.29 g, 12.0 mmol) were stirred in pyridine (20 ml) at room temperature for 96 h, with monitoring by TLC. The usual work-up gave a brown oil, which was purified by flash column chromatography. Elution with 20% ethyl acetate in light petroleum gave the required 3α-*toluene*-p-*sulfonate* **28** as a foam (464 mg) [Found: $(M - 31)^+$, 541.1889. $C_{29}H_{33}O_8S$ requires *M*, 541.1896]; δ_H 1.09 (s, 18-H_3), 1.98 (s, $OCOCH_3$), 2.45 (s, $OSO_2C_6H_4CH_3$), 2.63 (d, *J* 4.5, 6-H), 2.70 (m, 5-H), 3.65 and 3.69 (2 s, 7 and 19 OCH_3), 4.60 (dd, *J* 7 and 9.5, 3-H), 4.96 (br s, 17-H_2), 5.28 (m, 1-H), 7.33 and 7.79 (2 d, each *J* 8.5, $OSO_2C_6H_4CH_3$); *m/z* 541 [$(M - 31)^+$, 2%], 512 (1), 480 (4), 414 (2), 385 (35), 340 (86), 281 (100), 221 (70), 173 (26), 155 (72) and 91 (97).

Treatment of the 3α-toluene-*p*-sulfonate 28 with lithium dimethylcuprate

Lithium dimethylcuprate [prepared from copper(I) iodide (170 mg, 0.89 mmol) and methyllithium (1.25 ml, 1.75 mmol) in diethyl ether (5 ml)] was added to the 3α-toluene-*p*-sulfonate **28** (100 mg, 0.17 mmol) in diethyl ether (2.5 ml) and THF (1 ml), at −10 °C under nitrogen. The yellow solution was stirred at −10 °C for 6 h with monitoring by TLC and then allowed to warm to room temperature over 3 h. The usual work-up gave a gum which was purified by flash column chromatography. Elution with 20% ethyl acetate in light petroleum returned unchanged starting material **28** (76 mg); spectroscopic data as previously described.

The above reaction was repeated with 10 equiv. of lithium dimethylcuprate [from copper(I) iodide (340 mg, 1.78 mmol) and methyllithium (2.65 ml, 3.50 mmol) in diethyl ether (7.5 ml)]. The reaction was stirred at −10 °C for 1 h and then warmed to room temperature over 28 h, with monitoring by TLC. The usual work-up gave a gum which was purified by flash column chromatography. Elution with 10% ethyl acetate in light petroleum gave the triene **29** as a gum (11 mg) (Found: M^+, 400.1885. $C_{23}H_{28}O_6$ requires *M*, 400.1886); δ_H 1.33 (s, 18-H_3), 1.99 (s, $OCOCH_3$), 2.94 (d, *J* 4.5, 6-H), 3.31 (m, 5-H), 3.65 and 3.71 (2 s, 7 and 19 OCH_3), 5.00 (br s, 17-H_2), 5.38 (d, *J* 9.5, 3-H), 5.63 (ddd, *J* 2.5, 2.5 and 6, 1-H) and 6.08 (dd, *J* 6 and 9.5, 2-H); *m/z* 400 (M^+, 5%), 340 (22), 325 (22), 308 (15), 296 (12), 281 (39), 221 (43) and 43 (100). Further elution with 20% ethyl acetate in light petroleum returned unchanged starting material **28** (59 mg); spectroscopic data as previously described.

***ent*-13-Acetoxy-3β-trifluoromethylsulfonyloxy-20-norgibberella-1(10),16-diene-7,19-dioic acid 7,19-dimethyl ester 30**

Trifluoromethanesulfonic anhydride (120 μl, 0.72 mmol) was added dropwise to a stirred solution of the 3α-alcohol **24** (100 mg, 0.24 mmol) in dichloromethane (4 ml) and pyridine (60 μl, 0.72 mmol) at −10 °C under a nitrogen atmosphere. A yellow–white precipitate formed immediately and the pale orange solution was stirred at −10 °C for 20 min and then allowed to warm to room temperature over 1 h, with monitoring by TLC. The reaction mixture was poured into dichloromethane (20 ml), washed with 10% copper sulfate solution (2 × 5 ml), saturated aqueous sodium hydrogen carbonate (2 × 10 ml) and brine (10 ml). The dichloromethane layer was dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The resulting trifluoromethanesulfonate, a clear gum, was used immediately in the following cuprate reaction.

Lithium dimethylcuprate [prepared from copper(I) iodide (227 mg, 1.19 mmol) and methyllithium (2.10 ml, 2.39 mmol) in diethyl ether (5 ml)], was added to the 3α-trifluoromethanesulfonate **30** (as prepared above) in diethyl ether (2 ml) at −78 °C under nitrogen. The yellow solution was stirred at −78 °C for 3 h with monitoring by TLC and then warmed up to −10 °C over 2 h and then worked-up as usual. The crude mixture was purified by flash column chromatography. Elution with 5% ethyl acetate in light petroleum returned the 3α-trifluoromethanesulfonate **30** as a gum (64 mg) [Found: $(M - 60)^+$, 490.1258. $C_{22}H_{25}O_7SF_3$ requires *M*, 490.1273]; δ_H 1.37 (s, 18-H_3), 1.99 (s, $OCOCH_3$), 2.75 (br s, 5-H and 6-H), 3.71 and 3.73 (2 s, 7-OCH_3 and 19-OCH_3), 5.02 (br s, 17-H_2 and 3-H) and 5.37 (m, 1-H); δ_F(84 MHz, external $CFCl_3$) −75.5; δ_C 18.5 (C-11), 22.4 (C-18), 22.9 ($OCOCH_3$), 30.9, 35.3 and 38.6 (C-12, C-14 and C-15), 43.8 (C-2), 46.0 (C-5 or C-6), 48.2 (C-8), 49.9 (C-5 or C-6), 51.2 (C-4), 51.3 (C-9), 52.3 and 52.5 (7-OCH_3 and 19-OCH_3), 86.0 (C-13), 92.0 (C-3), 106.8 (C-17), 112.8 (C-1), 119.0 (q, *J* 320, CF_3), 140.0 (C-10), 149.9 (C-16), 169.9 and 171.1 (C-7 and C-19) and 175.4 ($OCOCH_3$); *m/z* 519 [$(M - 31)^+$, 1%], 490 [$(M - 60)^+$, 3%], 490 (3), 458 (4), 430 (3), 429 (3), 415 (2), 400 (19), 340 (47), 326 (27), 298 (51), 239 (66), 221 (53), 155 (37), 69 (30) and 43 (100). Further elution with 15% ethyl acetate in light petroleum returned the triene **29** (7 mg); spectroscopic data as described previously. Finally elution with 50% ethyl acetate in light petroleum returned the 3α-alcohol **24** (36

mg); spectroscopic data consistent with previously obtained values.

The reaction was repeated using lithium dimethylcuprate [prepared from copper(I) iodide (227 mg, 1.19 mmol) and methyllithium (2.10 ml, 2.39 mmol) in diethyl ether (5 ml)], which was added to the 3α-trifluoromethanesulfonate **30** in diethyl ether (2 ml) at −25 °C under nitrogen. The reaction was stirred at −25 °C for 4 h and then warmed to −5 °C over 6 h. The usual work-up returned the crude product which was purified by flash column chromatography. Elution with 15% ethyl acetate in light petroleum returned the triene **29** (78 mg); spectroscopic data as previously described. Further elution with 45% ethyl acetate in light petroleum returned the 3α-alcohol **24** (9 mg); spectroscopic data consistent with previously obtained values.

Dehalogenation using dimethylphosphite

1β-Iodide **32**[7] (500 mg, 0.94 mmol) in toluene (25 ml) was heated to reflux. Benzoyl peroxide (15 mg) and dimethyl phosphite (605 μl, 6.60 mmol) were added slowly and the mixture was heated under reflux for 24 h with monitoring by TLC. The solvent was removed *in vacuo* and the residue purified by flash column chromatography. Elution with 40% ethyl acetate in light petroleum returned unchanged starting material **32** (46 mg). Further elution with 50% ethyl acetate in light petroleum gave GA_1 methyl ester 13-acetate **33** (330 mg), mp 131–132 °C (lit.,[7] mp 137–140 °C); spectroscopic data as described previously.

ent-13-Acetoxy-10β-hydroxy-3β-methylsulfonyloxy-20-nor-gibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 35

3-*epi*-Gibberellin A_1 methyl ester 13-acetate **34**[7] (300 mg, 0.74 mmol) in pyridine (5 ml) and methanesulfonyl chloride (170 μl, 2.23 mmol) were stirred for 2 h at room temperature. The usual work-up gave a gum which was purified by flash column chromatography. Elution with 45 and 50% ethyl acetate in light petroleum gave the required 3α-*methanesulfonate* **35** as a gum (310 mg) (Found: M^+, 482.1607. $C_{23}H_{30}O_9S$ requires *M*, 482.1611); δ_H 1.19 (s, 18-H_3), 2.09 (s, $OCOCH_3$), 2.69 (d, *J* 10, 5-H), 2.77 (d, *J* 10, 6-H), 3.07 (s, OSO_2CH_3), 3.74 (s, OCH_3), 4.73 (dd, *J* 6 and 11, 3-H), 5.00 and 5.15 (2 br s, 17-H_2); *m/z* 482 (M^+, 7%), 451 (4), 440 (75), 422 (13), 344 (30), 298 (47), 282 (100), 223 (60), 155 (65), 105 (69), 91 (79) and 79 (85).

Treatment of 3α-methanesulfonate 35 with lithium dimethylcuprate

Lithium dimethylcuprate in diethyl ether (5 ml) [prepared from copper(I) iodide (200 mg, 1.06 mmol) and methyllithium (1.48 ml, 2.07 mmol)] was added dropwise to the 3α-methanesulfonate **35** (100 mg, 0.21 mmol) in diethyl ether (3 ml) and THF (1 ml) at −10 °C, under a nitrogen atmosphere. The mixture was stirred at −10 °C for 4 h and then allowed to warm to room temperature over 4 h. The crude product was recovered by the usual work-up and purified by flash column chromatography. Elution with 30% ethyl acetate in light petroleum gave a complex mixture of unidentifiable compounds. Further elution with 40% ethyl acetate in light petroleum gave a 1:1 mixture of starting material **35** and the 3α-(2-oxopropylsulfonyloxy) 13-acetoxy derivative **36** (27 mg); δ_H 1.18 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.41 (s, $OSO_2CH_2COCH_3$), 2.67 (d, *J* 10, 5-H), 2.77 (d, *J* 10, 6-H), 3.74 (s, OCH_3), 4.15 and 4.19 (2 d, each *J* 14.5, $OSO_2CH_2COCH_3$), 4.79 (dd, *J* 6.5 and 11, 3-H), 4.99 and 5.14 (2 br s, 17-H_2); δ_H **35**; as previously described; *m/z* 524 (M^+, **36**, 12%) and 482 (M^+, **35**, 6%). (Repeated flash chromatography failed to separate the two compounds.) Finally, further elution with 50 and 55% ethyl acetate in light petroleum returned a 1.2:1 mixture of the 2-oxopropylsulfonyloxy derivative **37** and the 13-hydroxy-3α-methanesulfonate **42** (31 mg); δ_H 1.19 (s, 18-H_3), 2.67 (d, *J* 10, 5-H), 2.77 (d, *J* 10, 6-H), 3.06 (s, OSO_2CH_3), 3.73 (s, OCH_3), 4.72 (dd, *J* 6.5 and 11, 3-H), 4.96 and 5.26 (2 br s, 17-H_2); δ_H 1.20 (s, 18-H_3), 2.41 (s, $OSO_2CH_2COCH_3$), 2.67 (d, *J* 10, 5-H), 2.77 (d, *J* 10, 6-H), 3.74 (s, OCH_3), 4.16 and 4.20 (2 d, each *J* 14.5, $OSO_2CH_2COCH_3$), 4.79 (dd, *J* 6.5 and 11, 3-H), 4.96 and 5.26 (2 br s, 17-H_2); *m/z* 482 (M^+, **37**, 16%) and 440 (M^+, **42**, 8%).

The reaction was repeated using 10 equiv. of lithium dimethylcuprate [prepared from copper(I) iodide (402 mg, 2.12 mmol) and methyllithium (2.95 ml, 4.14 mmol) in diethyl ether (5 ml)]. The mixture was stirred at −10 °C for 2.5 h and then allowed to warm to room temperature for 6 h. The crude product was recovered by the usual work-up and purified by flash column chromatography. Elution with 30% ethyl acetate in light petroleum gave a complex mixture of at least two components (17 mg) unidentifiable by ^1H NMR spectroscopy. Further elution with 40 and 45% ethyl acetate in light petroleum returned a 1:6 mixture of **35** and **36** (37 mg); spectroscopic values consistent with those obtained previously. Finally elution with 60% ethyl acetate in light petroleum gave a 1:4 mixture of **42** and **37** (36 mg). Repeated flash chromatography of this mixture gave on elution with 57.5% ethyl acetate in light petroleum a clean sample of the 3α-(2-*oxopropylsulfonyloxy*) *derivative* **37** as a gum (22 mg) (Found: M^+, 482.1604. $C_{23}H_{30}O_9S$ requires *M*, 482.1611); δ_H as described previously; δ_C 13.2 (C-18), 17.3 (C-11), 27.0 and 29.5 (C-1 and C-2), 30.7 ($OSO_2CH_2COCH_3$), 38.0 (C-12), 42.9 and 45.4 (C-14 and C-15), 50.5 (C-8), 50.9, 52.2, 52.3 and 56.9 (C-5, C-6, C-9 and 7-OCH_3), 52.6 (C-4), 62.4 ($OSO_2CH_2COCH_3$), 78.1 (C-13), 81.1 (C-3), 91.6 (C-10), 107.6 (C-17), 156.3 (C-16), 172.3 (C-19), 174.9 (C-7) and 194.4 ($OSO_2CH_2COCH_3$); *m/z* 482 (M^+, 68%), 464 (6), 450 (82), 438 (7), 423 (37), 362 (7), 344 (38), 312 (58), 303 (100), 300 (95), 284 (56), 241 (90), 157 (52), 135 (69), 106 (67), 91 (68) and 55 (62).

ent-13-Acetoxy-10β-hydroxy-3α-methylsulfonyloxy-20-nor-gibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 43

Gibberellin A_1 methyl ester 13-acetate **33** (120 mg, 0.30 mmol) in pyridine (3 ml) and methanesulfonyl chloride (69 μl, 0.89 mmol) were stirred for 2 h at room temperature. The usual work-up gave the crude product which was purified by flash chromatography. Elution with 50% ethyl acetate in light petroleum returned the required 3β-*methanesulfonate* **43** as a gum (143 mg) (Found: M^+, 482.1601. $C_{23}H_{30}O_9S$ requires *M*, 482.1611); δ_H 1.18 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.69 (d, *J* 10.5, 6-H), 3.10 (s, OSO_2CH_3), 3.12 (d, *J* 10.5, 5-H), 3.73 (s, OCH_3), 4.74 (br s, 3-H), 5.00 and 5.17 (2 br s, 17-H_2); *m/z* 482 (M^+, 1%), 451 (2), 440 (6), 422 (1), 386 (8), 355 (4), 344 (25), 242 (25), 282 (100), 223 (27), 105 (25), 91 (25) and 79 (26).

Treatment of the 3β-methanesulfonate 43 with lithium dimethylcuprate

Lithium dimethylcuprate [prepared from copper(I) iodide (101 mg, 0.53 mmol) and methyllithium (740 μl, 1.04 mmol) in diethyl ether (5 ml)] was added dropwise to the 3β-methanesulfonate **43** (50 mg, 0.10 mmol) in diethyl ether (2.5 ml) at −10 °C under a nitrogen atmosphere. The mixture was stirred at −10 °C for 6 h with monitoring by TLC and then allowed to warm to room temperature over 18 h. The crude product was recovered by the usual work-up and purified by flash column chromatography. Elution with 55% ethyl acetate in light petroleum gave a 2:7 mixture of the starting material **43** and the 3β-(2-oxopropylsulfonyloxy) 13-acetate **44** (12 mg); δ_H(major component) 1.18 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.46 (s, $OSO_2CH_2COCH_3$), 2.68 (d, *J* 10.5, 6-H), 3.08 (d, *J* 10.5, 5-H), 3.73 (s, OCH_3), 4.16 and 4.23 (2 d, each *J* 14, $OSO_2CH_2COCH_3$), 4.83 (br s, 3-H), 5.00 and 5.16 (2 br s, 17-H_2); δ_H(minor component); as previously described; *m/z* 524 (M^+, **44**, 14%) and 482 (M^+, **43**, 1%) both apparent. (Repeated flash chromatography failed to separate the two compounds.) Further elution with 60 and 62.5% ethyl acetate in light petroleum returned a 1:4 mixture of the 13-hydroxy-3β-methanesulfonate **46** and the 13-hydroxy-3β-(2-oxopropylsulfonyloxy) compound **45** (30 mg); δ_H(major com-

ponent) 1.18 (s, 18-H_3), 2.46 (s, $OSO_2CH_2COCH_3$), 2.68 (d, *J* 10.5, 6-H), 3.07 (d, *J* 10.5, 5-H), 3.74 (s, OCH_3), 4.18 and 4.24 (2 d, each *J* 14, $OSO_2CH_2COCH_3$), 4.83 (br s, 3-H), 4.97 and 5.27 (2 br s, 17-H_2); δ_H(minor component) 1.18 (s, 18-H_3), 2.69 (d, *J* 10, 6-H), 3.11 (d, *J* 10, 5-H), 3.12 (s, OSO_2CH_3), 3.73 (s, OCH_3), 4.74 (br s, 3-H), 4.97 and 5.27 (2 br s, 17-H_2); *m/z* 482 (M^+, **45**, 11%) and 440 (M^+, **46**, 7%). (Repeated flash column chromatography failed to separate the two compounds.)

ent-13-Acetoxy-10β-hydroxy-3β-trifluoromethylsulfonyloxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone 38

Trifluoromethanesulfonic anhydride (250 μl, 1.49 mmol) was added dropwise to a stirred solution of the 3α-alcohol **34** (200 mg, 0.50 mmol) in dichloromethane (6 ml) and pyridine (200 μl, 2.48 mmol) at −10 °C under nitrogen. An off-white precipitate was formed immediately and the orange–yellow solution was stirred for 1 h at −10 °C and then warmed to room temperature for 1 h. The reaction mixture was poured into dichloromethane (20 ml) and washed sequentially with 10% aq. copper sulfate (2 × 5 ml), saturated aq. sodium hydrogen carbonate (2 × 10 ml) and brine (10 ml). The dichloromethane was dried over anhydrous sodium sulfate and the solvent removed under vacuum. The resulting trifluoromethanesulfonate **38**, a pale yellow gum, was used immediately in the cuprate reaction. A sample of the trifluoromethanesulfonate was purified by flash chromatography eluting with 20% ethyl acetate in light petroleum to give **38** as a white foam (Found: M^+, 536.1313. $C_{23}H_{27}O_9F_3S$ requires *M*, 536.1328); δ_H 1.22 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.71 (d, *J* 10, 6-H), 2.78 (d, *J* 10, 5-H), 3.75 (s, CO_2CH_3), 4.88 (dd, *J* 11 and 6.3, 3-H), 4.99 and 5.16 (each br s, 17-H_2); *m/z* 536 (M^+, 19%), 505 (9), 494 (81), 476 (17), 462 (10), 435 (14), 344 (50) and 282 (100).

Treatment of the 3α-trifluoromethanesulfonate 38 with lithium dimethylcuprate

Lithium dimethylcuprate [prepared from copper(I) iodide (480 mg, 2.52 mmol) and methyllithium (3.54 ml, 4.95 mmol) in diethyl ether (10 ml)] was added dropwise to the 3α-trifluoromethanesulfonate **38** (as prepared above) in diethyl ether (4 ml) at −10 °C under a nitrogen atmosphere. The mixture was stirred at −10 °C for 2 h and then worked-up as normal. The crude product was purified by flash column chromatography. Elution with 20% ethyl acetate in light petroleum, returned the required ent-13-*acetoxy*-10β-*hydroxy*-3α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* **39** as a gum (7 mg) (Found: M^+, 402.2043. $C_{23}H_{30}O_6$ requires *M*, 402.2042); δ_H 1.04 (s, 18-H_3), 1.07 (d, *J* 7, 3β-CH_3), 2.02 (s, $OCOCH_3$), 2.70 (d, *J* 10.5, 6-H), 2.80 (d, *J* 10.5, 5-H), 3.72 (s, OCH_3), 4.98 and 5.14 (2 br s, 17-H_2); *m/z* 402 (M^+, 39%), 371 (16), 360 (100), 342 (58), 328 (31), 314 (72), 298 (85), 283 (62), 282 (62), 258 (54), 157 (38), 129 (44), 105 (53), 91 (71) and 55 (69). Further elution with 30 and 40% ethyl acetate in light petroleum returned GA_5 methyl ester 13-acetate **40** (94 mg); spectroscopic data consistent with previously obtained values.[7] Finally, elution with 50% ethyl acetate in light petroleum returned the original 3α-alcohol **34** (38 mg); spectroscopic data as previously described.

The reaction was repeated using lithium dimethylcuprate (5 equiv., prepared as previously described), which was added dropwise to the 3α-trifluoromethanesulfonate **38** in diethyl ether (4 ml) at −78 °C under a nitrogen atmosphere. The reaction was stirred at −78 °C for 1.5 h. No reaction was apparent by TLC and so the reaction was warmed to −42 °C and was stirred at this temperature for 1.5 h. The usual work-up gave a pink gum which was purified by flash column chromatography. Elution with 20% ethyl acetate in light petroleum, returned the required 3β-methyl compound **39** (27 mg); spectroscopic data as previously described. Further elution with 25% ethyl acetate in light petroleum returned a 2:1 mixture of the 3β-methyl derivative **39** and GA_5 methyl ester 13-acetate **40** (14 mg). Further elution with 30% ethyl acetate in light petroleum returned GA_5 methyl ester 13-acetate **40** (34 mg); spectroscopic data as previously described.[7] Finally elution with 50 and 60% ethyl acetate in light petroleum returned *epi*-GA_1 methyl ester 13-acetate **34** (57 mg); spectroscopic data consistent with previously obtained values.

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

3β-MethylGA_{20} 13-acetate 7-methyl ester **39** in methanol (5 ml) and sodium hydroxide (6 M, 10 ml) was heated to reflux for 16 h. After cooling, the usual work-up gave required acid **9** as a gum (18 mg, 100%) (Found: M^+, 346.1783. $C_{20}H_{26}O_5$ requires *M*, 346.1780); δ_H 1.07 (d, *J* 7, 3-CH_3), 1.09 (s, 18-H_3), 2.71 (d, *J* 10.5, 5-H), 2.75 (d, *J* 10.5, 6-H), 4.96 and 5.28 (each br s, 17-H_2); *m/z* 346 (M^+, 40%), 328 (100), 300 (26), 289 (75), 282 (22), 258 (16) and 83 (72).

Tanginbozu dwarf rice immersion assay

Tanginbozu dwarf rice seedlings[22] were soaked in water for 2 days at 28 °C under constant light (the water was changed at 12 h intervals) by which time the coleoptiles had emerged. The germinated seeds were selected for uniformity and were placed in groups of six in cylindrical vials (18 mm diameter and 50 mm depth), which contained sterile water (1 ml) and a methanolic solution of the substrate (10 μg in 10 μl). Two vials containing sterile water (1 ml) and methanol (10 μl) were used as controls. After 7 days the total length of the plants was measured (see Table 2).

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References

1 T. J. Ingram, J. B. Reid and J. MacMillan, *Planta*, 1986, **168**, 414; S. Fujioka, H. Yamane, C. R. Spray, P. Gaskin, J. MacMillan, B. O. Phinney and N. Takahashi, *Plant Physiol.*, 1988, **88**, 1367; M. Kobayashi, A. Sakurai, H. Saka and N. Takahashi, *Plant Cell Physiol.*, 1989, **30**, 963; M. Nakayama, H. Yamane, N. Murofushi, N. Takahasi, L. N. Mander and H. Seto, *J. Plant Growth Regul.*, 1991, **10**, 115.

2 T. J. Ingram, J. B. Reid, I. C. Murfet, P. Gaskin, C. L. Willis and J. MacMillan, *Planta*, 1984, **160**, 455; C. R. Spray, B. O. Phinney, P. Gaskin, S. J. Gilmour and J. MacMillan, *Planta*, 1984, **160**, 464.

3 S. Fujioka, H. Yamane, C. R. Spray, B. O. Phinney, P. Gaskin, J. MacMillan and N. Takahashi, *Plant Physiol.*, 1990, **94**, 127; N. Murofushi, I. Honda, R. Hirasawa, I. Yamaguchi, N. Takahashi and B. O. Phinney, *Agric. Biol. Chem.*, 1991, **55**, 435.

4 K. S. Albone, P. Gaskin, J. MacMillan, V. A. Smith and J. Weir, *Planta*, 1989, **177**, 108; K. S. Albone, P. Gaskin, J. MacMillan and C. L. Willis, *Plant Physiol.*, 1990, **94**, 132.

5 M. H. Beale and J. MacMillan, *Phytochemistry*, 1981, **20**, 693; G. V. Hoad, B. O. Phinney, V. M. Sponsel and J. MacMillan, *Phytochemistry*, 1981, **20**, 703.

6 T. Saito, Y. Kamiya, H. Yamane, A. Sakurai, N. Murofushi and N. Takahashi, *Biosci. Biotechnol. Biochem.*, 1992, **56**, 1046.

7 K. S. Albone, J. MacMillan, A. R. Pitt and C. L. Willis, *Tetrahedron*, 1986, **42**, 3203.

8 M. H. Beale and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1980, 877.

9 E. Keinan and P. A. Gleize, *Tetrahedron Lett.*, 1982, **23**, 477.

10 J. W. Cornforth, R. H. Cornforth and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.

11 C. R. Johnson, R. W. Herr and D. M. Wieland, *J. Org. Chem.*, 1973, **38**, 4263 and references cited therein; Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 947; A. Alexakis, D. Jachiet and J. F. Normant, *Tetrahedron*, 1986, **42**, 5607.

12 B. H. Lipshutz and S. Sengupta, *Org. React. (N. Y.)*, 1992, **41**, 135; B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski and D. A. Parker, *J. Org. Chem.*, 1984, **49**, 3928.

13 G. H. Posner, *Org. React. (N. Y.)*, 1975, **22**, 253; C. Huynh, G. Linstrumelle and F. Derguini-Bouchmechal, *Tetrahedron Lett.*, 1979, 1503.
14 M. Fukumasa, K. Furuhashi, J. Umezawa, O. Takahashi and T. Hirai, *Tetrahedron Lett.*, 1991, **32**, 1059.
15 C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, 1973, **95**, 7777 and 7783.
16 M. Penny and C. L. Willis, *J. Chem. Soc., Chem. Commun.*, 1993, 1111.
17 A. Calvo-Mateo, M. J. Camarasa, A. Diaz-Ortiz and F. G. de las Heras, *J. Chem. Soc., Chem. Commun.*, 1988, 114.
18 M. F. Reich, V. J. Lee, J. Ashcroft and G. O. Morton, *J. Org. Chem.*, 1993, **58**, 5288.
19 E. J. Corey, T. M. Brennam and R. L. Carney, *J. Am. Chem. Soc.*, 1971, **93**, 7318.
20 D. H. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1992, **33**, 2311.
21 K. Hanson, J. A. O'Neill, T. J. Simpson and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2493.
22 Y. Murakami, *Bot. Mag.*, 1968, **81**, 33.

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