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Confirmation of structure and synthesis of three new 11β-OH C_{20} gibberellins from loquat fruit

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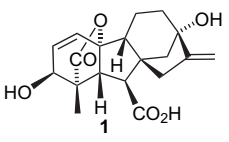
Abstract

Three new 11β-hydroxy C_{20} gibberellins have been isolated from immature loquat fruit and their structures were established as 11β-hydroxy-GA_{12}, 11β-hydroxy-GA_{15} and 11β-hydroxy-GA_{53}, respectively, by direct GC–MS comparisons with authentic samples obtained from gibberellic acid by multistep syntheses. An advanced intermediate (**30**) was prepared in 20 steps from which 6 11β-hydroxy C_{20} gibberellins were prepared by parallel routes involving up to a further 5 steps for each sequence. The key steps involved a much improved synthesis of gibberellenic acid derivatives, a Lewis acid catalysed cyclisation of a diazoketone, a domino-hydroboration of a diene and oxidative cleavage of a ketone derived enolate.

1. Introduction

The gibberellins ('GAs') form a large group of highly functionalised diterpenoid acids, which are distributed widely throughout the plant Kingdom where they play an important role in plant growth and development.[1–4] They are also produced by a number of microorganisms[5] and gibberellic acid (**1**) is obtained commercially in tonne quantities by fermentation of the fungus *Gibberella fujikuroi* (now identified[6] as *Fusarium fujikuroi*). Of the 132 hitherto known naturally occurring GAs, 107 have been found exclusively in higher plants (including angiosperms, gymnosperms and ferns), 11 in the fungus only and the rest from both sources. Rather than assigning trivial names to naturally occurring GAs, a number has been assigned to each variant and a registry coordinated, until recently, by MacMillan and Takahashi.[7] Gibberellic acid (**1**), for example, is identified as GA_3. The database is now maintained by Hedden and Kamiya: http://www.plant-hormones.info/gibberellin_nomenclature.htm. More than a third of known GAs are based on the C_{20} *ent*-gibberellane skeleton **2** with the variations of structure arising from different oxidation levels and hydroxylation patterns. The other GAs are based on the 20-nor-*ent*-gibberellane structure **3** and incorporate a 19,10-γ-lactone function as in GA_3.



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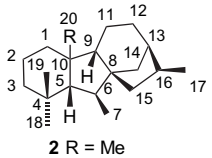

2 R = Me
3 R = H

Progress in gibberellin research in higher plants would have occurred very much more slowly without the original isolation in relatively large quantities of GAs from *F. fujikuroi*. Some of the richer plant sources afford milligram quantities, but concentrations in the order of ng kg^{-1} are more usual and with these more modest quantities, it is only with the knowledge derived from chemical[8] and metabolic[9] studies on the fungal GAs and the availability of semi-synthetic GAs[10,11] that structure determination becomes reasonably feasible. Even at the

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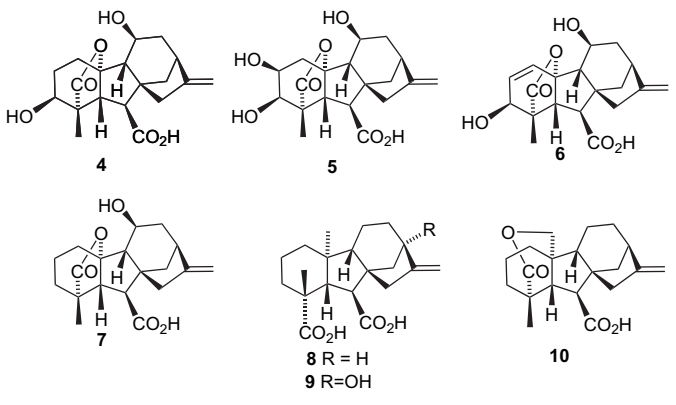
sub nanogram level, it is often possible to arrive at quite a good estimate of molecular structure from fragmentation patterns in the mass spectra of silylated methyl ester ('Me-TMS') derivatives. Then, these tentative assignments may be confirmed by synthesis from one of the fungal GAs. When the assumptions are wrong, useful information is still gained and the deduction of the correct structure facilitated. Most importantly, comparisons may be made with the extensive database of GC–MS information held at Rothamsted Reseach, Harpenden, Herts., UK (http://www.rothamsted.ac.uk) a large part of which has been published in an atlas by Gaskin and MacMillan.[12]

It is within this context that we have undertaken further investigations of GAs isolated from loquat trees (*Eribotrya japonica* Lindl.), which are cultivated in the warm regions of Japan and other Asian countries. The fruits are edible and commercially important. Twelve gibberellins ('GAs'), four of which possess an 11-hydroxy substituent, namely GA_{35} (**4**), GA_{50} (**5**), GA_{80} (**6**) and GA_{84} (**7**) have been previously identified as endogenous gibberellins in immature seeds.[13,14] Recently, we have isolated three further GAs from this source, one corresponding to a mono-hydroxy derivative of GA_{12} (**8**), another corresponding to a dihydroxy derivative of GA_{12}, and one corresponding to a mono-hydroxy derivative of GA_{15} (**10**). Given their provenance and through the elimination of known GAs, it appeared likely that they were hydroxylated at the C-11 locus.

Of special interest was a prominent peak at *m/z* 295 in the mass spectrum of the Me-TMS derivative of the putative dihydroxy GA_{12} that we believed would be consistent with a derivative of GA_{53} (**9**) bearing a hydroxyl attached to either ring C or D. As with the Me-TMS derivatives of all 13-hydroxy GAs, the mass spectrum of GA_{53} displays a characteristic ion of *m/z* 207 attributed to a ring C+D fragment; an additional Me_3SiO group would add 88 mass units.[12] Given that the 12α, 12β and 15β isomers are known GAs, and hydroxylation at C-14 has yet to be observed for a native GA, it appeared most likely, therefore, that this last GA was an 11-hydroxy GA_{53}. To establish the identity of the new GAs, we embarked upon the synthesis of a series of 11-hydroxy C_{20} GAs, and in anticipation of future discoveries, our approach encompassed a full set of both 11,13-dihydroxy and 11-hydroxy derivatives. Thus, as outlined in Scheme 1, our initial target became the advanced intermediate **15** from which we could expect to prepare all of the desired GAs.



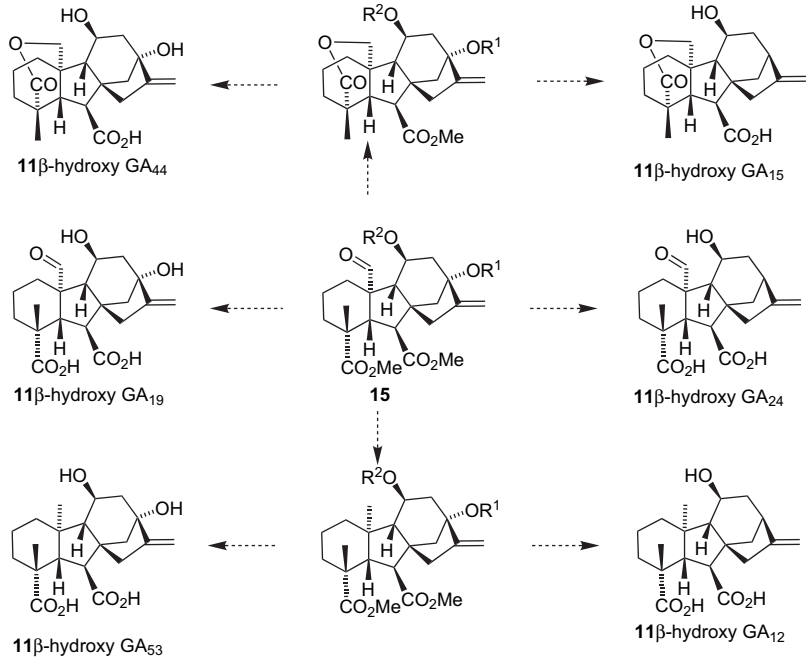
2. Results and discussion

Our synthetic plan for the preparation of **15** is outlined in Scheme 2, the critical conversion being the cyclisation of diazoketone **11** to afford **12**,[15] which, if successful, would combine the introduction of functionality into the C-ring with the incorporation of C(20). Hydroboration of the product 9(11),16-diene[16] would then be expected to provide diol **13** by means of a concerted two-stage process involving addition of diborane to the *exo* face of the 16-ene bond followed by intramolecular addition of the resulting *endo* borane function to the 9(11)-ene bond. An important aspect of this conversion would be the concomitant restoration of the correct 9β stereochemistry. Subsequent oxidative cleavage of the C(19)–C(20) bond[17] should then afford **15**.

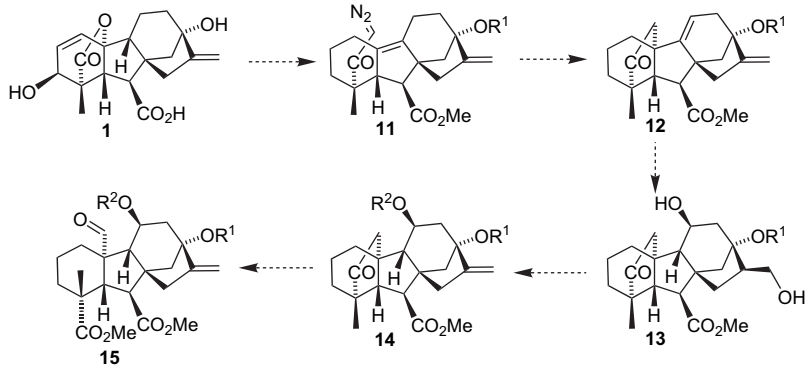
As outlined in Scheme 3, the preparation of a suitable analogue of diazoketone **11** began with the 7-methyl ester (**18**) of gibberellenic acid (**17**). Gibberellenic acid is readily prepared from GA_3 (**1**) in 37% yield by heating with hydrazine hydrate.[18] However, so that we could discriminate between the two carboxyl functions, we had previously treated GA_3 methyl ester (**16**) under equivalent conditions and had obtained the desired mono-ester **18** in only 23% yield.[19] Fortunately, through the simple expedient of using hydrazine monohydrochloride in DMF, we were able to elevate the yield to 39% (56% net, based on recovered starting material). To remove the A-ring double bond, **18** was first protected as its MOM ester and oxidized to trienone **19** as before,[19] but then treated with $NaBH_4$–CuCl,[20] which provided a superior yield (90%) of diene acid **20** as opposed to our previous routine[19] using L-Selectride followed by $Li(O^tBu)_3H$ (62% over two steps). The 3-hydroxyl was removed by using the Barton–McCombie protocol[21] and then, following protection of the 13-hydroxyl through acetylation and selective hydrolysis of the MOM ester group, diazoketone **22** was prepared by treatment of the 19-acyl chloride with diazomethane.

The next stage of the synthesis is outlined in Scheme 4. Thus, cyclisation of diazoketone **22** was effected in essentially quantitative yield with $BF_3{\cdot}Et_2O$ and the product ketone **23** was converted into the 19-MOM ether **24** in preparation for the hydroboration step, which, in due course, afforded a mixture of the desired diol **26** (65% yield) and alcohol **25** (26%). Reconstitution of the 16-ene function had previously been achieved on similar GA substrates through a rather convoluted six-step sequence,[16] but fortunately a much more direct conversion to **28** could be achieved via the selenenyl ether **27** using the Grieco procedure.[22] Finally, after conversion of the 19-MOM ether function back to the 19-one and replacement of the acetate protecting groups with MOM ethers to give **29**, oxidative cleavage (KH, DMF; O_2) followed by methylation (CH_2N_2) furnished aldehyde **30**.

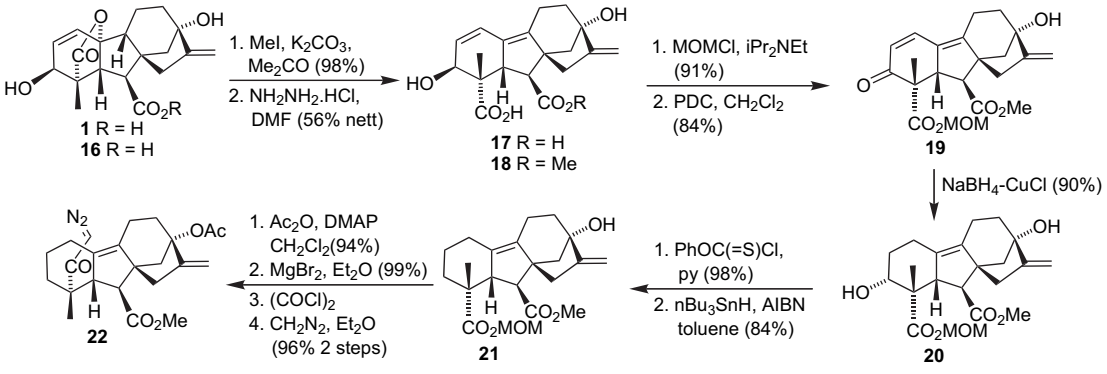
From here, we could envisage the straightforward preparation of 11-hydroxy and 11,13-dihydroxy C_{20} GAs through simple functional group manipulations. Thus, as summarized in Scheme 5, the MOM protecting groups were removed from **30** to reveal 11β-hydroxy GA_{19} (**31**). Next, reduction ($NaBH_4$) of **30** followed by deprotection afforded the GA_{44}



Scheme 1.



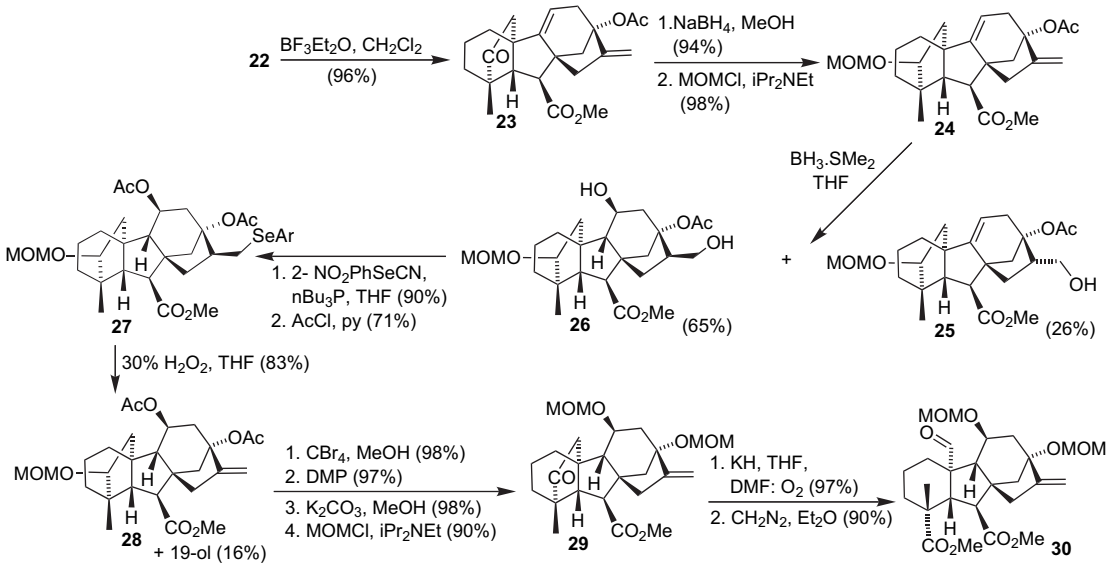
Scheme 2.



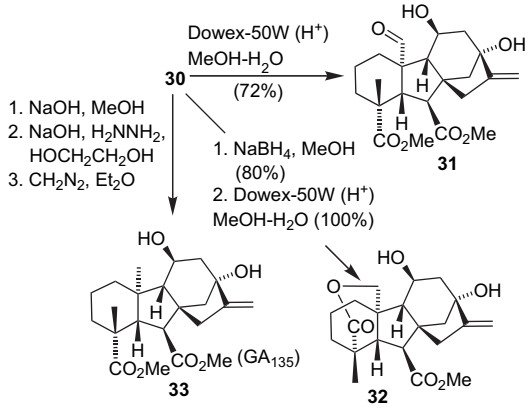
Scheme 3.

analogue **32**, while ester hydrolysis of **30** followed by Wolff–Kishner reduction, protecting group removal and re-methylation yielded the GA_{53} derivative **33**. This last product, after silylation, proved to have the same mass spectrum and GC retention time as the dimethyl ester of the dihydroxy GA_{12} gibberellin isolated from loquat and has been assigned as GA_{135}.

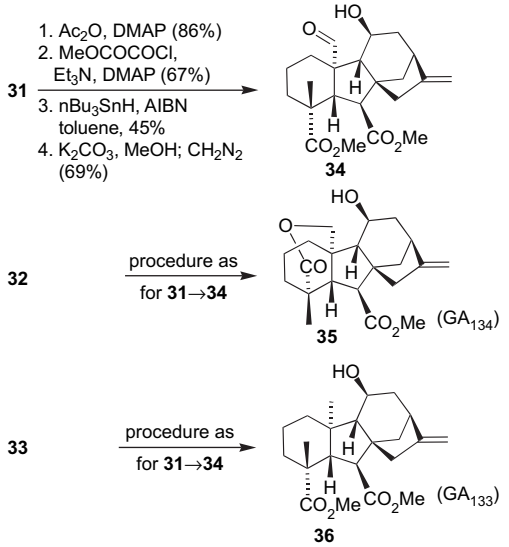
To prepare the 13-desoxy analogues (Scheme 6), the 11β-hydroxyl in each of **31**, **32** and **33** was selectively acetylated and



Scheme 4.



Scheme 5.



Scheme 6.

the 13-hydroxyl removed by treatment of the derived methyl oxalates with $^{n}Bu_3SnH$.[23] Comparisons by GC–MS as for **33** showed that lactone **35** and diester **36** were identical with their naturally occurring counterparts and accordingly, the parent GAs were assigned as GA_{134} and GA_{133}, respectively.

3. Conclusion

The methyl esters of six 11β-hydroxy C_{20} GAs have been prepared, three of which correspond to endogenous GAs from loquat fruit. Given earlier experience with the isolation of GAs, the remaining GAs are likely to be found also in this species. Flexible and reliable procedures have been developed for the preparation of these GAs and will have considerable utility for the preparation of further derivatives. Of particular note is the improved access to gibberellenate type GAs, the use of a high yielding cyclisation of a 19-diazomethyl ketone to bridge the divide between C_{19} and C_{20} derivatives, and the much improved 'recovery' of the 16-ene function from 11β,17-diol intermediates.[24]

4. Experimental

4.1. GA isolation and purification

Seeds (49 g fresh weight) were collected from immature fruits of loquat (*E. japonica* Lindl.) harvested 90 days after full bloom and then extracted with 80% aqueous MeOH (3×100 mL). After filtration, MeOH was removed in vacuo at 45 °C. The aqueous residue was adjusted to pH 3.0 with 1 M HCl and partitioned against hexane (3×100 mL) followed by EtOAc (3×100 mL). The combined EtOAc phase was then partitioned against 0.5 M K-Pi buffer, pH 8.3 (3×100 mL). The combined aqueous phase was mixed with PVP (5 g) and then filtered. The aqueous phase was adjusted to pH 3.0 with 5 N HCl and partitioned against EtOAc (3×100 mL).

The combined EtOAc phase was dried over Na_2SO_4. After filtration, the EtOAc fraction was evaporated in vacuo and then dissolved in a small amount of MeOH. The solution was prepurified through a Bondesil DEA (5 g) column (packed with MeOH). After sample loading, the column was washed with MeOH (100 mL) and then with MeOH containing 1% HOAc (100 mL). GAs were eluted with MeOH containing 1% HOAc. The eluate was then reduced to dryness in vacuo and the residue dissolved in a small amount of 30% aqueous MeOH. The solution was chromatographed by HPLC on a Senshu-Pak ODS-4253-D column (25×1 cm ID), eluting with a linear gradient of H_2O (containing 1% HOAc)−MeOH. The linear gradient elution conditions were as follows: 30% MeOH for 2 min; followed for 30 min from 30 to 100% MeOH; and finally 18 min with 100% MeOH. The total elution time was 50 min, with a flow rate of 3 mL/min^{-1}, and 36 fractions (1 fraction/1 min) were collected. The fractions were dried in vacuo and bioassayed by a dwarf rice (cv. Tanginbozu) microdrop based procedure.[25] Fraction numbers 21−22, 22−26, 27−28 and 29−32 were, respectively, combined, and then further chromatographed by HPLC on Nucleosil $N(CH_3)_2$-4151-N columns (15×1 cm ID), eluted with MeOH containing 0.1% HOAc at a flow rate of 2 mL/min^{-1}, and 2 min fractions were collected, dried and bioassayed, as already described. After purification on ODS and/or Nucleosil $N(CH_3)_2$ columns, the fractions showing GA-like activity were dissolved in MeOH (20 μL) and methylated with ethereal CH_2N_2 (100 μL) at room temperature. They were then dried and trimethylsilylated in glass tubes with *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (MSTFA, 20 μL) at 70 °C. The derivatives were analysed using a Hewlett−Packard 5989 mass spectrometer equipped with a HP 5890 GC. The samples (1 μL) were injected into a fused silica cross-linked 5% phenylmethylsilicone capillary column (30 m×0.25 mm ID, 0.25 μm film thickness, WCOT DB-1). The oven temperature program started at 60 °C and after 2 min was increased at 20 °C min^{-1} to 210 °C, then increased at 2 °C min^{-1} to 280 °C and finally kept at 280 °C for 20 min. The electron energy was 70 eV and the source temperature was 250 °C.

5. Preparation of synthetic gibberellins

5.1. General directions

Melting points (mp) were recorded on a Reichert hot-stage and are uncorrected. Microanalysis were conducted by the Australian National University Analytical Services Unit, Canberra. Low resolution EI mass (LRMS) spectra (70 eV) and high resolution accurate mass measurements (HRMS) were recorded on a Ficons VG autospec double focussing mass spectrometer. The molecular ion (M^+), if present, significant high mass ions and the more intense low mass ions are reported. Data are presented in the following order: *m*/*z* value; relative intensity as a percentage of the base peak. Infrared (IR) spectra (ν_{max}) were recorded on a Perkin−Elmer 1800 Fourier Transform Infrared spectrophotometer as a thin film deposited from a chloroform solution on NaCl disks, unless otherwise stated. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz; ^{13}C NMR spectra were recorded at 75.5 MHz. For proton spectra recorded in deuterated chloroform, the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. Data are recorded as follows: chemical shift, numbers of protons, multiplicity and coupling constants (Hz) Assignments were based on chemical shift and homodecoupling experiments. Distortionless enhancement by polarisation transfer (DEPT) and the attached proton test (APT) were used in the assignment of carbon spectra. Two dimensional NMR experiments were recorded on the following instruments: Varian Gemini 300 and Varian Inova 500 spectrometers. The pulse sequences used were homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY), heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HETCOR) and ^{1}H−^{13}C correlation via long-range couplings (HMQC and HMBC). Flash chromatography was conducted with Merck Kieselgel 60 silica gel as the adsorbent unless indicated otherwise. Ethanol-free ethereal diazomethane was prepared from Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide).

5.1.1. ent-3α,13-Dihydroxy-20-norgibberella-1,9,16-triene-7,19-dioic acid 7-methyl ester (**18**)

To a solution of **16** (30 g, 83.24 mmol) in DMF (250 mL) was added hydrazine monohydrochloride (70 g, 1.02 mmol). The suspension was then heated at 135 °C under a nitrogen atmosphere until it became homogeneous. The temperature was quickly reduced to 120 °C and the solution was stirred at this temperature for an additional 2 h, allowed to cool to room temperature and then cooled in an ice-bath. The mixture was poured into ice-water (600 mL), acidified to pH 3 with 6 M HCl and extracted with EtOAc (3×400 mL). The combined organic extracts were washed with 1 M HCl (2×400 mL) then concentrated to dryness in vacuo. The crude product was dissolved in EtOAc (200 mL) and partitioned in a solution of saturated $NaHCO_3$ and Na_2CO_3 (1:1, 2×150 mL). The combined aq phase was washed with EtOAc (3×200 mL), then acidified with concentrated HCl to pH 3 and extracted with EtOAc (3×300 mL). The combined organic phases were concentrated to give the desired triene acid **18** (11.83 g, 32.84 mmol, 39%) as an oil. The combined organic layers containing starting material and aromatic products were concentrated in vacuo and subjected to the above same reaction conditions to give an additional amount of **18** (5.074 g, 14.08 mmol, 17%). Spectroscopic data of **18** were fully consistent with those previously reported.[19]

5.1.2. ent-3β,13-Dihydroxy-20-norgibberella-9,16-diene-7,19-dioic acid 19-methoxymethyl ester 7-methyl ester (**20**)

A suspension of trienone **19** (250 mg, 0.62 mmol) and CuCl (316 mg, 3.19 mmol) in MeOH (15 mL) at 0 °C was stirred for 2 h at which time sodium borohydride (254.2 mg, 6.2 mmol) was added portionwise. The mixture was stirred for 15 min at this temperature then warmed to room temperature and stirred for an additional 30 min. A black precipitate was removed by filtration, the filtrate was then acidified using 20%

NaH_2PO_4 solution (30 mL), concentrated to remove MeOH and the aqueous phase extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (2×50 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 2:1) yielded the desired diol **20** (225.5 mg, 0.56 mmol, 90%) as a yellowish oil and its 3β-epimer (14 mg, 0.034 mmol, 6%). Spectroscopic data for **20** were consistent with those previously reported.[19]

5.1.3. *ent-13-Hydroxy-3β-phenoxythionocarbonyloxy-20-norgibberella-9,16-diene-7,19-dioic acid 19-methoxymethyl ester 7-methyl ester*

A stirred solution of diol **20** (4.6 g, 11.317 mmol) in CH_2Cl_2 (230 mL) and pyridine (2.3 mL, 9.24 mmol), at 0 °C under nitrogen was treated dropwise with phenyl chlorothionocarbonate (5 g, 28.67 mmol), and the mixture stirred at this temperature for 1 h then allowed to warm to room temperature, with stirring overnight. The reaction mixture was worked-up by addition of CH_2Cl_2 (500 mL). The mixture was washed successively with water (500 mL), 0.1 M HCl (500 mL), water (500 mL), saturated aq $NaHCO_3$ solution (500 mL), water (500 mL) and brine (500 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:1.5) afforded the desired thionocarbonate (6.02 g, 11.09 mmol, 98%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3498, 3075, 2938, 2849, 1733, 1661, 1590. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s, H18), 1.36–2.61 (12H, m), 2.76 (1H, d, J=7.0 Hz, H6), 3.20 (1H, t, J=5.5 Hz, H5), 3.48 (3H, s, $-OCH_2OCH_3$), 3.72 (3H, s, $-CO_2CH_3$), 4.95 (1H, s, H17), 5.13 (1H, t, J=2.6 Hz, H′17), 5.21, 5.28 (2×1H, ABd, J=6.1 Hz, $-OCH_2OCH_3$), 5.37 (1H, q, J_1=10.3 Hz, J_2=5.8 Hz, H3), 7.06–7.43 (5H, m, C_6H_5). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6 (C11), 21.5 (C18), 22.0 (C2), 25.1 (C1), 39.1 (C14 and C12), 50.7 (C6), 51.9 (C15 and $-CO_2CH_3$), 52.6 (C4), 55.5 (C8), 56.6 (C5), 57.7 ($-OCH_2OCH_3$), 79.2 (C13), 88.4 (C3), 90.8 ($-OCH_2OCH_3$), 105.7 (C17), 121.8 (2×C_{ortho}), 126.5 (C_{para}), 126.9 (C10), 129.5 (2×C_{meta}), 135.5 (C9), 153.2 (C_{ipso}), 154.3 (C16), 171.2 (C7 and *C*S), 174.3 (C19). MS (EI) *m/z* 540 ([M^+−2H], 10%), 509 (8), 496 (32), 481 (35), 465 (10), 449 (54), 417 (26), 388 (82), 357 (100), 339 (32), 311 (78), 297 (68), 283 (58), 267 (86), 251 (38), 239 (84), 221 (46), 211 (36), 195 (36), 179 (34), 169 (34), 157 (50), 142 (38), 129 (34), 115 (26), 94 (48), 77 (42), 65 (34). HRMS (EI) *m/z* calcd for [M^+−2H], $C_{29}H_{32}O_8S$: 540.1818; found: 540.1827.

5.1.4. *ent-13-Hydroxy-20-norgibberella-9,16-diene-7,19-dioic acid 19-methoxymethyl ester 7-methyl ester (**21**)*

To a solution of thionocarbonate prepared above (3.2 g, 5.9 mmol) in toluene (340 mL) at room temperature under nitrogen were added tributyltin hydride (3.64 mL, 14.24 mmol) and AIBN (1.28 g, 1.94 mmol). The mixture was degassed for 20 min under reduced pressure then filled with nitrogen and heated at 80 °C for 3 h, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure, providing a residue, which was resolved by chromatography on silica gel (EtOAc/hexanes, 1:3), yielding the desired product **21** (1.933 g, 4.95 mmol, 84%) as a white solid, which was recrystallised from EtOAc/hexanes to afford white crystals of the title compound, mp: 94–95 °C. IR (Neat) ν_{max} (cm^{-1}): 3499, 3074, 2934, 2869, 1732, 1660. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s, H18), 1.20–2.30 (14H, m), 2.94 (1H, t, J=5.2 Hz, H5), 3.24 (1H, d, J=7.02 Hz, H6), 3.43 (3H, s, $-OCH_2OCH_3$), 3.69 (3H, s, $-CO_2CH_3$), 4.93 (1H, s, H17), 5.11 (1H, d, J=2.3 Hz, H′17), 5.18, 5.20 (2×1H, ABd, J=5.2 Hz, $-OCH_2OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (C11), 21.9 (C2), 24.6 (C1), 25.0 (C18), 37.9 (C3), 39.2 (C12), 39.5 (C14), 47.4 (C15), 50.3 (C6), 51.5 ($-CO_2CH_3$), 52.1 (C4), 55.1 (C8), 57.1 (C5), 57.4 ($-OCH_2OCH_3$), 79.4 (C13), 89.9 ($-OCH_2OCH_3$), 105.2 (C17), 128.7 (C10), 133.6 (C9), 154.9 (C16), 174.5 (C7), 175.5 (C19). MS (EI) *m/z* 390 (M^+, 35%), 372 (13), 358 (16), 345 (66), 330 (51), 313 (90), 300 (70), 285 (100), 267 (66), 241 (91), 223 (44), 197 (23), 184 (28), 171 (26), 157 (44), 143 (36), 129 (42), 115 (31), 91 (38), 69 (22). HRMS (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_6$: 390.2042; found: 390.2048. Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.40; H, 7.55.

5.1.5. *ent-13-Acetoxy-20-norgibberella-9,16-diene-7,19-dioic acid 19-methoxymethyl ester 7-methyl ester*

A stirred solution of alcohol **21** (3.395 g, 8.69 mmol), triethylamine (12 mL, 86.95 mmol) and DMAP (430 mg, 3.48 mmol) in CH_2Cl_2 (100 mL) at 0 °C under nitrogen was treated dropwise with acetic anhydride (17 mL, 86.95 mmol). After being stirred for 1 h, the ice-bath was removed and the solution was left overnight to warm to room temperature, with stirring. The reaction mixture was re-cooled in an ice-bath and quenched by dropwise addition of water (50 mL). After extracting with CH_2Cl_2 (3×100 mL), the combined organic extracts were washed successively with saturated aq $NaHCO_3$ solution (500 mL), water (500 mL) and brine (500 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:6) yielded the desired acetate (3.53 g, 8.15 mmol, 94%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 2935, 1738, 1661. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 1.20–2.52 (14H, m), 2.00 (3H, s, CH_3CO_2-), 2.91 (1H, t, J=5.5 Hz, H5), 3.19 (1H, d, J=7.0 Hz, H6), 3.41 (3H, s, $-OCH_2OCH_3$), 3.66 (3H, s, $-CO_2CH_3$), 4.96 (1H, br s, H17), 5.00 (1H, br s, H′17), 5.16, 5.22 (2×1H, ABd, J=6.0 Hz, $-OCH_2OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (C11), 22.2 (C2), 22.3 (CH_3CO_2-), 24.8 (C1), 25.4 (C18), 37.1 (C3), 38.2 (C12), 39.5 (C14), 47.7 (C15), 47.9 (C4), 50.6 (C6), 51.9 ($-CO_2CH_3$), 56.2 (C8), 57.4 (C5), 57.8 ($-OCH_2OCH_3$), 86.5 (C13), 90.3 ($-OCH_2OCH_3$), 105.8 (C17), 129.5 (C10), 133.5 (C9), 151.2 (C16), 169.8 (CH_3CO_2-), 174.8 (C7), 175.7 (C19). MS (EI) *m/z* 432 (M^+, 12%), 387 (23), 372 (100), 355 (31), 340 (86), 327 (47), 296 (31), 283 (50), 267 (37), 250 (25), 223 (50), 181 (27), 169 (21), 155 (21), 143 (22), 129 (23), 115 (19), 91 (22). HRMS (EI) *m/z* calcd for M^+, $C_{24}H_{32}O_7$: 432.2148; found: 432.2149.

5.1.6. ent-13-Acetoxy-20-norgibberella-9,16-diene-7,19-dioic acid 7-methyl ester

To a solution of acetate prepared above (1.94 g, 4.48 mmol) in Et_2O (150 mL) at room temperature under a nitrogen atmosphere was added $MgBr_2$ (4.23 g, 22.5 mmol), and the suspension stirred for 15 h. The reaction mixture was quenched by addition of saturated NH_4Cl solution (250 mL) and then extracted with EtOAc (3×250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to furnish the desired 19-oic acid (1.733 g, 4.46 mmol, 99%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 2935, 2870, 1732, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s, H18), 1.23–2.56 (14H, m), 2.04 (3H, s, CH_3CO_2–), 2.93 (1H, t, J=5.6 Hz, H5), 3.23 (1H, d, J=6.9 Hz, H6), 3.70 (3H, s, –CO_2CH_3), 4.97 (1H, br s, H17), 5.01 (1H, t, J=1.8 Hz, H′17), 9.70 (1H, br s, –CO_2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3 (C11), 22.0 (C2), 22.1 (*C*H_3CO_2–), 24.6 (C1), 25.3 (C18), 36.9 (C3), 37.8 (C12), 39.2 (C14), 47.1 (C15), 47.9 (C4), 50.3 (C6), 51.7 (–CO_2CH_3), 56.0 (C8), 57.2 (C5), 86.4 (C13), 105.6 (C17), 129.4 (C10), 133.5 (C9), 150.9 (C16), 169.8 (CH_3CO_2–), 175.5 (C7), 179.1 (C19). MS (EI) *m/z* 390 ([M^++2H], 10%), 388 (M^+, 7%), 346 (42), 328 (100), 296 (64), 282 (24), 268 (29), 223 (45), 181 (22), 155 (21), 143 (24), 129 (26), 115 (22). HRMS (EI) *m/z* calcd for M^+, $C_{22}H_{28}O_6$: 388.1886; found: 388.1884.

*5.1.7. Methyl ent-19-diazomethyl-13-acetoxy-19-oxo-20-norgibberella-9,16-dien-7-oate (**22**)*

The previously prepared acid (875 mg, 2.25 mmol) in dry benzene (54 mL) and pyridine (923 μL, 13.99 mmol) were cannulated into a stirred solution of oxalyl chloride (1.68 mL, 18.66 mmol) in dry benzene (144 mL) at room temperature, under nitrogen. After stirring for 15 min, DMF was added (180 μL) and the mixture was stirred for 30 min, more oxalyl chloride (0.84 mL, 9.39 mmol) was added and then stirred overnight. The reaction mixture was filtered through Celite™ in a sintered funnel under nitrogen, the solid residue was washed thoroughly with dry benzene (5×50 mL), the combined organic layers were concentrated and the excess of oxalyl chloride and pyridine was removed by co-distillation with dry benzene (4×10 mL). The residue was then dissolved in dry benzene (50 mL) and slowly cannulated into a stirred solution of diazomethane in dry Et_2O (120 mL) (prepared from 10.7 g of Diazald™) at 0 °C, under nitrogen. The reaction mixture was stirred overnight then more CH_2N_2 in dry Et_2O (120 mL) was added to the reaction mixture, which was stirred for an additional 18 h, after which time TLC analysis show that the reaction was complete. The excess of CH_2N_2 was blown off by a stream of nitrogen and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:4) to give the desired diazoketone **22** (893 mg, 2.17 mmol, 96% from acid) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3100, 2932, 2866, 2103, 1773, 1735, 1661, 1637. ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, s, H18), 0.84–2.65 (14H, m), 2.03 (3H, s, CH_3CO_2–), 2.93 (1H, t, J=5.6 Hz, H5), 3.20 (1H, d, J=7.6 Hz, H6), 3.68 (3H, s, –CO_2CH_3), 4.96 (1H, br s, H17), 5.00 (1H, t, J=2.9 Hz, H′17), 5.40 (1H, s, –COC*H*=N_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2 (C11), 21.2 (C2), 22.0 (*C*H_3CO_2–), 24.6 (C1), 25.5 (C18), 37.0 (C3), 38.3 (C12), 39.3 (C14), 47.4 (C15), 49.8 (C4), 50.2 (C6), 51.6 (–CO_2CH_3), 55.9 (C8), 57.3 (C5), 60.1 (–CO*C*H=N_2), 86.2 (C13), 105.4 (C17), 129.7 (C10), 133.0 (C9), 150.9 (C16), 169.5 (CH_3CO_2–), 175.4 (C7), 198.4 (C19). MS (EI) *m/z* 413 ([M^++H], 5%), 384 (33), 346 (53), 324 (100), 296 (47), 268 (34), 237 (100), 223 (40), 195 (35), 181 (59), 167 (24), 141 (32), 115 (28), 95 (51), 59 (22). HRMS (EI) *m/z* calcd for [M^+–N_2], $C_{23}H_{28}O_5$: 384.1937; found: 384.1945.

*5.1.8. Methyl ent-13-acetoxy-19-oxo-19,20-cyclogibberella-9(11),16-dien-7-oate (**23**)*

A stirred solution of diazoketone **22** (1.30 g, 3.15 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C under nitrogen was treated dropwise with boron trifluoride etherate (816 μL, 6.30 mmol). The reaction mixture was stirred for 2.5 h, after which time TLC analysis indicated that the reaction was complete. The mixture was diluted with CH_2Cl_2 (250 mL), then washed successively with saturated aq $NaHCO_3$ solution (250 mL) and brine (250 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:4) gave ketone **23** (1.159 g, 0.28 mmol, 96%) as a white solid, which was recrystallised from EtOAc/hexanes to afford white crystals of the title compound, mp 144–145 °C. IR (Neat) ν_{max} (cm^{-1}): 2932, 2254, 2103, 1732, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s, H18), 1.23–2.44 (13H, m), 2.06 (3H, s, CH_3CO_2–), 2.46, 2.53 (2×1H, ABd, J=10.8 Hz, –COCH_2–), 3.02 (1H, dd, J=16.2, 2.8 Hz, H12b), 3.70 (3H, s, –CO_2CH_3), 5.00 (1H, br s, H17), 5.15 (1H, br s, H′17), 5.34 (1H, t, J=3.0 Hz, H11). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8 (C18), 19.9 (C2), 22.0 (*C*H_3CO_2–), 35.0 (C1), 38.7 (C3), 40.9 (C12), 42.3 (C14), 43.5 (C10), 46.3 (C15), 49.0 (C20), 49.4 (C6), 51.9 (–CO_2CH_3), 52.6 (C4), 53.4 (C8), 58.8 (C5), 85.3 (C13), 107.6 (C17), 115.3 (C11), 152.0 (C9), 154.3 (C16), 169.8 (CH_3CO_2–), 172.5 (C7), 219.8 (C19). MS (EI) *m/z* 384 (M^+, 22%), 353 (18), 342 (100), 324 (84), 292 (37), 281 (42), 264 (52), 237 (29), 223 (56), 181 (32), 155 (26), 129 (27), 91 (26). HRMS (EI) *m/z* calcd for M^+, $C_{23}H_{28}O_5$: 384.1937; found: 384.1937. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.55; H, 7.34.

5.1.9. Methyl ent-13-acetoxy-19-hydroxy-19,20-cyclogibberella-9(11),16-dien-7-oate

A stirred solution of ketone **23** (1.16 mg, 3.01 mmol) in MeOH (170 mL) at 0 °C was treated portionwise with $NaBH_4$ (1.173 g, 30.15 mmol). The mixture was stirred for 1 h at this temperature, warmed to room temperature and then neutralised by 1 M HCl solution (20 mL). After removal of MeOH, the aqueous phase was extracted with EtOAc (3×200 mL). The combined organic extracts were washed with water (250 mL) and brine (2×250 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:4) yielded the desired 19-ol (1.1 g, 2.85 mmol, 94%) as a yellowish oil. IR (Neat) ν_{max} (cm^{-1}): 3524, 2930, 2254, 1735, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, H18), 0.83–2.47 (15H, m), 2.06 (3H, s, CH_3CO_2–), 2.65 (1H, d, J=12.3 Hz, H6), 3.00 (1H, dd, J=16.0, 2.7 Hz, H12b), 3.70

(3H, s, $-CO_2CH_3$), 4.07 (1H, dd, J=10.7, 4.6 Hz, H19), 4.96 (1H, br s, H17), 5.13 (1H, br s, H′17), 5.20 (1H, t, J=3.2 Hz, H11). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (CH_3CO_2-), 22.1 (C18), 29.6 (C2), 35.2 (C1), 36.6 (C3), 40.9 (C12), 42.0 (C14), 43.7 (C10), 45.9 (C15), 46.7 (C20), 48.6 (C6), 50.1 (C4), 51.6 ($-CO_2CH_3$), 53.2 (C8), 60.9 (C5), 78.1 (C19), 85.6 (C13), 107.1 (C17), 113.2 (C11), 152.3 (C9), 156.2 (C16), 169.7 (CH_3CO_2-), 173.0 (C7). MS (EI) *m/z* 386 (M^+, 20%), 344 (85), 326 (88), 266 (37), 223 (34), 141 (21), 84 (100). HRMS (EI) *m/z* calcd for M^+, $C_{23}H_{30}O_5$: 386.2093; found: 386.2090.

5.1.10. Methyl ent-13-acetoxy-19-methoxymethoxy-19,20-cyclogibberella-9(11),16-dien-7-oate (**24**)

To a stirred solution of alcohol (215 mg, 0.56 mmol) prepared above, Hünig's base (0.5 mL, 2.78 mmol) and DMAP (20.4 mg, 0.167 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under nitrogen was added dropwise chloromethyl methyl ether (205 μL, 2.78 mmol). After stirring for 1 h at this temperature, the reaction vessel was raised to room temperature and stirred for an additional 12 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with 2 N HCl solution (75 mL) followed by water (50 mL) and brine (50 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (DCM/EtOAc, 2:1) yielded the desired MOM ether **24** (236 mg, 0.55 mmol, 98%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 2926, 2852, 1738, 1663. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s, H18), 0.81–2.51 (13H, m), 2.04 (3H, s, CH_3CO_2-), 2.13 (1H, d, J=12.0 Hz, H5), 2.64 (1H, d, J=12.1 Hz, H6), 2.96 (1H, dd, J=15.9, 2.6 Hz, H12b), 3.33 (3H, s, $-OCH_2OCH_3$), 3.67 (3H, s, $-CO_2CH_3$), 3.86 (1H, m, H19), 4.55, 4.61 (2×1H, ABd, J=6.6 Hz, $-OCH_2OCH_3$), 4.94 (1H, br s, H17), 5.10 (1H, br s, H′17), 5.17 (1H, t, J=3.4 Hz, H11). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1 (C2), 22.0 (CH_3CO_2- and C18), 35.7 (C1), 36.6 (C3), 41.0 (C12), 42.0 (C14), 43.6 (C10), 44.6 (C15), 45.8 (C20), 48.6 (C6), 50.3 (C4), 51.6 ($-CO_2CH_3$), 53.2 (C8), 55.3 (C5), 60.6 ($-OCH_2OCH_3$), 83.0 (C19), 85.6 (C13), 96.5 ($-OCH_2OCH_3$), 107.1 (C17), 113.2 (C11), 152.6 (C9), 156.6 (C16), 169.8 (CH_3CO_2-), 173.2 (C7). MS (EI) *m/z* 430 (M^+, 28%), 388 (93), 370 (100), 281 (22), 265 (26), 223 (22), 84 (97). HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{34}O_6$: 430.2355; found: 430.2354.

5.1.11. Methyl ent-13-acetoxy-11α,17-dihydroxy-19-methoxymethoxy-19,20-cyclogibberell-an-7-oate (**26**) and methyl ent-13-acetoxy-17-hydroxy-19-methoxymethoxy-16-epi-19,20-cyclogibberell-9(11)-en-7-oate (**25**)

To a stirred solution of diene **24** (492 mg, 1.14 mmol) in dry THF (80 mL) at 0 °C under a nitrogen atmosphere was added dropwise a 2 N solution of diborane–dimethyl sulfide complex in THF (0.8 mL, 1.6 mmol). After 1 h, the reaction mixture was left to warm to room temperature and stirring continued for an additional 8 h. Analysis of the reaction mixture by TLC showed the absence of starting material. The reaction mixture was quenched with EtOH (16 mL), stirred for 10 min, 2 N NaOAc (16 mL) added, the mixture re-cooled to 0 °C and then 30% H_2O_2 (18 mL) added dropwise. After 30 min, the reaction mixture was again warmed to room temperature and then stirred overnight. The water (160 mL) was added to the mixture, stirred for 15 min and then solid NaCl added to form a saturated solution that was extracted with a solution of 10% 2-butanol/EtOAc (3×200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 2:1) yielded the by-product **25** (132.9 mg, 0.296 mmol, 26%) as a colourless oil and the desired diol **26** (344.6 mg, 0.74 mmol, 65%) as a colourless oil.

Diol **26**: IR (Neat) ν_{max} (cm^{-1}): 3442, 2927, 1733. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s, H18), 0.82–2.51 (19H, m), 2.02 (3H, s, CH_3CO_2-), 2.55 (1H, d, J=12.3 Hz, H6), 3.36 (3H, s, $-OCH_2OCH_3$), 3.68 (4H, s, $-CO_2CH_3$ and H17), 3.86 (2H, m, H′17 and H19), 4.12 (1H, ddd, J=9.9, 9.3, 8.7 Hz, H11), 4.58, 4.60 (2×1H, ABd, J=6.6 Hz, $-OCH_2OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1 (CH_3CO_2-), 22.2 (C18), 29.7 (C2), 35.4 (C1), 36.2 (C3), 38.2 (C12), 39.2 (C14), 40.2 (C10), 43.9 (C15), 45.3 (C20), 48.3 (C6), 49.1 (C4), 51.5 ($-CO_2CH_3$), 51.6 (C16), 52.2 (C8), 55.3 (C5), 61.3 ($-OCH_2OCH_3$), 62.9 (C17), 64.3 (C9), 67.7 (C11), 83.0 (C19), 85.1 (C13), 96.5 ($-OCH_2OCH_3$), 170.9 (CH_3CO_2-), 173.9 (C7). MS (EI) *m/z* 466 (M^+, 14%), 435 (17), 404 (30), 388 (98), 361 (80), 344 (61), 326 (100), 312 (38), 238 (41), 267 (46), 241 (33), 225 (27), 211 (32), 183 (27), 159 (30), 145 (49), 131 (41), 107 (54), 91 (56). HRMS (EI) *m/z* calcd for [M^+-CH_3O], $C_{24}H_{35}O_7$: 435.2382; found: 435.2381.

17-ol **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, s, H18), 0.82–2.37 (17H, m), 2.04 (3H, s, CH_3CO_2-), 2.63 (1H, d, J=12.2 Hz, H6), 3.35 (3H, s, $-OCH_2OCH_3$), 3.58 (2H, br s, H17 and H′17), 3.70 (3H, s, $-CO_2CH_3$), 3.87 (1H, m, H19), 4.56, 4.63 (2×1H, ABd, J=6.6 Hz, $-OCH_2OCH_3$), 5.21 (1H, t, J=3.7 Hz, H11). MS (EI) *m/z* 448 (M^+, 7%), 406 (100), 388 (86), 346 (91), 287 (81), 257 (39), 199 (41), 171 (33), 157 (56), 129 (25), 91 (23). HRMS (EI) *m/z* calcd for [M^+-CH_3OH], $C_{24}H_{32}O_6$: 406.2355; found: 406.2363.

5.1.12. Methyl ent-13-acetoxy-11α-hydroxy-19-methoxymethoxy-17-(2-nitrophenyl selenenyl)-19,20-cyclogibberellan-7-oate

A solution of diol **26** (44.4 mg, 0.095 mmol) in THF (2 mL) and 2-nitrophenyl selenocyanate (58 mg, 0.28 mmol) at 0 °C under nitrogen was treated dropwise with a solution of tri-*n*-butylphosphine (50 μL, 0.25 mmol). After 40 min, the mixture was allowed to warm to room temperature and stirred overnight. Analysis by TLC showed the absence of starting material. The mixture was concentrated under reduced pressure, dissolved in EtOAc (50 mL), and then filtered to remove tri-*n*-butylphosphine oxide. The oxide residue was rinsed with EtOAc (3×20 mL), then the combined organic layers were washed successively with saturated aq $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL), and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:2) afforded the title compound (56 mg, 0.09 mmol, 90%) as a yellowish oil. IR (Neat) ν_{max} (cm^{-1}): 3474, 3091, 2947, 1732. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 0.86 (3H, s, H18), 1.21–2.52 (18H, m), 2.06 (3H, s, CH_3CO_2–), 2.61 (1H, d, J=12.3 Hz, H6), 2.84 (1H, t, J=10.5 Hz, H12b), 3.27 (1H, dd, J=10.5, 4.8 Hz, H17), 3.36 (3H, s, $-OCH_2OCH_3$), 3.69 (3H, s, $-CO_2CH_3$), 3.90 (1H, dd, J=10.2, 3.9 Hz, H19), 4.22 (1H, ddd, J=12.0, 9.9, 7.8 Hz, H11), 4.58, 4.66 (2×1H, ABd, J=6.7 Hz, $-OCH_2OCH_3$), 7.26 (1H, m, H4′), 7.53 (2H, m, H5′ and H6′), 8.30 (1H, d, J=8.2 Hz, H3′).

5.1.13. Methyl ent-11α,13-diacetoxy-19-methoxymethoxy-17-(2-nitrophenylselenenyl)-19,20-cyclogibberellan-7-oate (27)

A stirred solution of selenenyl ether prepared above (42 mg, 0.0645 mmol) and pyridine (45 μL, 0.68 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was treated dropwise with acetyl chloride (35 μL, 0.45 mmol). After 40 min, the mixture was allowed to warm to room temperature and stirred for an additional 2 h. Analysis by TLC showed the absence of starting material. The reaction mixture was quenched by dropwise addition of water (20 mL). After extracting with EtOAc (3×20 mL), the combined organic extracts were washed successively with saturated aq NH_4Cl solution (20 mL), water (20 mL) and brine (20 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:2) furnished the desired diacetate **27** (31.7 mg, 0.05 mmol, 71%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 2950, 2852, 1738. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s, H18), 1.19–2.66 (16H, m), 2.02 (3H, s, 13-CH_3CO_2–), 2.05 (3H, s, 11-CH_3CO_2–), 2.62 (1H, d, J=12.0 Hz, H6), 2.63 (1H, m, H17), 2.79 (1H, t, J=11.1 Hz, H12b), 3.35 (3H, s, $-OCH_2OCH_3$), 3.46 (1H, dd, J=10.8, 4.8 Hz, H′17), 3.69 (3H, s, $-CO_2CH_3$), 3.92 (1H, dd, J=10.0, 3.8 Hz, H19), 4.56, 4.65 (2×1H, ABd, J=6.7 Hz, $-OCH_2OCH_3$), 5.21 (1H, ddd, J=10.8, 9.0, 8.7 Hz, H11), 7.32 (1H, m, H4′), 7.48–7.57 (2H, m, H5′ and H6′), 8.30 (1H, d, J=8.5 Hz, H3′). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9 (C2), 21.3 (11-CH_3CO_2–), 21.8 (13-CH_3CO_2–), 22.1 (C18), 28.6 (C17), 34.7 (C1), 35.3 (C3), 36.4 (C12), 39.6 (C14), 43.2 (C10), 43.8 (C15), 44.8 (C6), 45.4 (C20), 49.4 (C4), 51.5 ($-CO_2CH_3$), 51.9 (C16), 52.0 (C8), 55.3 (C5), 61.3 ($-OCH_2OCH_3$), 61.5 (C9), 69.6 (C11), 83.0 (C19), 84.9 (C13), 92.6 ($-OCH_2OCH_3$), 125.4 (C3′), 126.5 (C4′ and C6′), 129.0 (C5′), 133.3 (C1′), 133.5 (C2′), 169.9 (11-CH_3CO_2–), 170.1 (13-CH_3CO_2–), 173.5 (C7). MS (EI) m/z 693 (M^+, 9%), 663 (9), 491 (100), 431 (19), 371 (71), 327 (82), 309 (38), 295 (34), 267 (60), 223 (30), 186 (22), 91 (20). HRMS (EI) m/z calcd for M^+, $C_{33}H_{43}O_{10}NSe$: 693.2052; found: 693.2064.

5.1.14. Methyl ent-11α,13-diacetoxy-19-methoxymethoxy-19,20-cyclogibberell-16-en-7-oate (28) and methyl ent-11α,13-diacetoxy-19-hydroxy-19,20-cyclogibberell-16-en-7-oate

A solution of selenenyl ether **27** (31.7 mg, 0.046 mmol) in THF (4 mL) at 0 °C under nitrogen was treated dropwise with a solution of 30% H_2O_2 (2 mL). After 30 min, the mixture was allowed to warm to room temperature and stirred overnight. Analysis by TLC showed the absence of starting material. The mixture was quenched by dropwise addition of water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed successively with saturated aq $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:3) afforded the desired product **28** (18.6 mg, 0.038 mmol, 83%) as an oil and the corresponding 19-ol (3.4 mg, 0.008 mmol, 16%) as an oil.

Diacetate **28**: IR (Neat) ν_{max} (cm^{-1}): 3078, 2949, 2851, 2822, 1738, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s, H18), 1.14–2.23 (15H, m), 1.96 (3H, s, 13-CH_3CO_2–), 1.99 (3H, s, 11-CH_3CO_2–), 2.64 (1H, d, J=12.0 Hz, H6), 2.93 (1H, dd, J=12.9, 9.0 Hz, H12b), 3.33 (3H, s, $-OCH_2OCH_3$), 3.66 (3H, s, $-CO_2CH_3$), 3.92 (1H, dd, J=10.2, 3.9 Hz, H19), 4.54, 4.63 (2×1H, ABd, J=6.7 Hz, $-OCH_2OCH_3$), 4.98 (1H, br s, H17), 5.12 (1H, ddd, J=10.8, 9.0, 8.7 Hz, H11 overlapped), 5.15 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0 (C2), 21.2 (11-CH_3CO_2–), 22.0 (13-CH_3CO_2–), 22.2 (C18), 35.4 (C1), 36.7 (C3), 39.7 (C12), 41.2 (C14), 43.9 (C10), 44.1 (C15), 45.4 (C20), 48.8 (C4), 50.3 (C6), 51.7 ($-CO_2CH_3$), 51.8 (C8), 55.3 (C5), 58.4 ($-OCH_2OCH_3$), 61.5 (C9), 69.7 (C11), 82.2 (C19), 82.9 (C13), 96.1 ($-OCH_2OCH_3$), 108.0 (C17), 153.4 (C16), 169.5 (11-CH_3CO_2–), 169.7 (13-CH_3CO_2–), 173.4 (C7). MS (EI) m/z 490 (M^+, 7%), 459 (17), 430 (95), 388 (100), 370 (88), 343 (38), 326 (74), 308 (53), 283 (47), 267 (43), 249 (34), 223 (43), 181 (24), 105 (27), 91 (31). HRMS (EI) m/z calcd for M^+, $C_{27}H_{38}O_8$: 490.2567; found: 490.2567.

19-ol: IR (Neat) ν_{max} (cm^{-1}): 3523, 2928, 2851, 2853, 1738, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.20–2.28 (16H, m), 1.98 (3H, s, 13-CH_3CO_2–), 2.01 (3H, s, 11-CH_3CO_2–), 2.66 (1H, d, J=12.1 Hz, H6), 2.95 (1H, dd, J=12.8, 9.1 Hz, H12b), 3.69 (3H, s, $-CO_2CH_3$), 4.13 (1H, dd, J=10.9, 4.1 Hz, H19), 5.01 (1H, br s, H17), 5.16 (1H, ddd, J=11.1, 8.7, 8.4 Hz, H11 overlapped), 5.18 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2 (C2), 21.3 (11-CH_3CO_2–), 22.0 (13-CH_3CO_2– and C18), 34.9 (C1), 39.2 (C3), 39.7 (C12), 41.2 (C14), 43.9 (C10), 44.1 (C15), 45.6 (C20), 48.9 (C4), 50.3 (C6), 51.7 (C8), 51.8 ($-CO_2CH_3$), 58.3 (C5), 61.9 (C9), 69.7 (C11), 78.1 (C19), 83.0 (C13), 108.2 (C17), 153.4 (C16), 169.6 (11-CH_3CO_2–), 169.8 (13-CH_3CO_2), 173.4 (C7). MS (EI) m/z 445 ([M^+–H], 4%), 386 (27), 344 (100), 326 (67), 285 (34), 267 (25), 241 (18), 223 (31), 167 (39), 105 (27), 149 (93), 71 (33). HRMS (EI) m/z calcd for [M^+–OCH_3], $C_{24}H_{31}O_6$: 415.2120; found: 415.2117.

A stirred solution of **19-ol** (257.5 mg, 0.574 mmol) and pyridine (385 μL, 5.74 mmol) in CH_2Cl_2 (15 mL) at 0 °C under nitrogen was treated dropwise with acetyl chloride (360 μL, 4.59 mmol). After 30 min, the mixture was allowed to warm to room temperature and stirred for an additional 8 h. Analysis by TLC showed the absence of starting material. The reaction mixture was quenched by dropwise addition of water (100 mL). After extracting with EtOAc (3×75 mL), the combined organic extracts were washed successively

with saturated aq $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:4) gave diacetate **28** (272 mg, 0.55 mmol, 97%) as a yellowish oil. Spectroscopic data were identical with those obtained previously.

*5.1.15. Methyl ent-11α,13-diacetoxy-19-oxo-19,20-cyclogibberell-16-en-7-oate (**29**)*

A solution of MOM ether **28** (792.2 mg, 1.4864 mmol) in propan-2-ol (40 mL), at room temperature under nitrogen, was treated with carbon tetrabromide (592 mg, 1.784 mmol), and then stirred at 80 °C for 5 h. The reaction mixture was concentrated in vacuo to remove the propan-2-ol and the residue was purified by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:9→1:6) afforded the desired 19-ol (651 mg, 1.46 mmol, 98%) as an oil. To a solution of this product (93.2 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) was added Dess–Martin periodinane (119 mg, 0.2713 mmol). The suspension was stirred for 2.5 h, at room temperature. The mixture was diluted with Et_2O (30 mL) and then poured into a solution (50 mL) of saturated aq $NaHCO_3$ containing $Na_2S_2O_3$ (5 g). The mixture was stirred for 30 min, at which point Et_2O (70 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (2×50 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution (50 mL), H_2O (50 mL), followed by brine (50 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:4) yielded the desired 19-one (90 g, 0.2025 mmol, 97%) as a white solid, which was recrystallised from EtOAc/hexanes to afford white crystals: mp 174–175 °C. IR (Neat) ν_{max} (cm^{-1}): 2933, 1731, 1663. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s, H18), 1.41–2.47 (16H, m), 1.99 (3H, s, 13-CH_3CO_2–), 2.00 (3H, s, 11-CH_3CO_2–), 2.95 (1H, dd, J=12.8, 8.9 Hz, H12b), 3.68 (3H, s, $-CO_2CH_3$), 5.03 (1H, br s, H17), 5.05 (1H, ddd, J=11.1, 8.7, 8.1 Hz, H11), 5.19 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0 (11-CH_3CO_2–), 19.8 (C2), 21.1 (13-CH_3CO_2–), 21.9 (C18), 37.7 (C1), 37.9 (C3), 40.6 (C12), 43.3 (C14), 43.7 (C10), 44.0 (C15), 48.5 (C20), 48.6 (C4), 51.4 (C6), 52.0 ($-CO_2CH_3$), 53.4 (C8), 57.6 (C5), 59.4 (C9), 65.9 (C11), 82.7 (C13), 108.5 (C17), 153.0 (C16), 169.7 (11-CH_3CO_2–), 169.8 (13-CH_3CO_2), 172.8 (C7), 219.3 (C19). MS (EI) *m/z* 444 (M^+, 3%), 384 (58), 342 (100), 324 (69), 283 (49), 255 (27), 239 (25), 211 (28), 105 (18), 91 (26). HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{32}O_7$: 444.2148; found: 444.2147. Anal. Calcd for $C_{23}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 66.96; H, 7.62.

5.1.16. Methyl ent-11α,13-dihydroxy-19-oxo-19,20-cyclogibberell-16-en-7-oate

A solution of diacetoxy ketone prepared above (73.2 mg, 0.16 mmol) in MeOH (6 mL) and 0.5 M K_2CO_3 (3 mL) at room temperature was stirred overnight. The mixture was concentrated to remove MeOH, the residue added to saturated aq NH_4Cl solution (20 mL) and H_2O (10 mL), and the mixture extracted with 20% 2-butanol/EtOAc (3×30 mL). The combined organic extracts were washed with brine (30 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:2) gave the desired diol (58.4 mg, 0.16 mmol, 98%) as a glassy white solid. IR (Neat) ν_{max} (cm^{-1}): 3436, 2932, 1732, 1661. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.44–2.42 (18H, m), 2.53 (1H, dd, J=12.9, 8.4 Hz, H12b), 3.68 (3H, s, $-CO_2CH_3$), 3.94 (1H, ddd, J=10.5, 9.3, 9.0 Hz, H11), 4.96 (1H, br s, H17), 5.28 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.2 (C18), 20.0 (C2), 38.0 (C1), 38.2 (C3), 43.1 (C12), 44.5 (C14), 44.9 (C10), 48.0 (C15), 48.7 (C20), 49.3 (C4), 51.9 (C6), 52.0 ($-CO_2CH_3$), 53.6 (C8), 59.6 (C5), 61.1 (C9), 68.1 (C11), 77.6 (C13), 107.3 (C17), 157.1 (C16), 173.0 (C7), 220.1 (C19). MS (EI) *m/z* 360 (M^+, 37%), 342 (12), 328 (100), 300 (47), 257 (17), 180 (22), 91 (15). HRMS (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found: 360.1935.

*5.1.17. Methyl ent-11α,13-bis(methoxymethoxy)-19-oxo-19,20-cyclogibberell-16-en-7-oate (**29**)*

To a stirred solution of 19-one prepared above (100 mg, 0.28 mmol) in dry CH_2Cl_2 (50 mL) under nitrogen were added Hünig's base (586 μL, 3.33 mmol) and DMAP (20 mg, 0.162 mmol) and then cooled to 0 °C. The mixture was then treated dropwise with chloromethyl methyl ether (218 μL, 2.78 mmol). After 30 min, the reaction mixture was warmed to room temperature and stirred for 24 h. Analysis by TLC revealed that only 40% of the starting material had been converted to the desired product. The mixture was cooled to 0 °C then Hünig's base (600 mL, 0.1938 mmol) and chloromethyl methyl ether (200 μL, 2.27 mmol) were added dropwise. After 30 min, the reaction mixture was warmed to room temperature and stirred for an additional 3 days. The reaction mixture was diluted with CH_2Cl_2 (400 mL), washed with 1 M HCl (250 mL), water (250 mL), saturated aq $NaHCO_3$ solution (250 mL), followed by brine (250 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:3→1:2) afforded the desired bis-MOM ether **29** (111.5 mg, 0.25 mmol, 90%) as a yellowish oil. IR (Neat) ν_{max} (cm^{-1}): 2931, 1736, 1661. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s, H18), 1.02–2.47 (16H, m), 2.72 (1H, dd, J=12.9, 8.7 Hz, H12b), 3.35 (3H, s, 13-OCH_2OCH_3), 3.36 (3H, s, 11-OCH_2OCH_3), 3.68 (3H, s, $-CO_2CH_3$), 3.81 (1H, ddd, J=10.8, 9.0, 8.7 Hz, H11), 4.50, 4.53 (2×1H, ABd, J=2.4 Hz, 13-OCH_2OCH_3), 4.65, 4.72 (2×1H, ABd, J=6.9 Hz, 11-OCH_2OCH_3), 5.03 (1H, br s, H17), 5.17 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.2 (C18), 20.1 (C2), 38.1 (C1 and C3), 41.0 (C12), 43.5 (C14), 45.2 (C10), 46.3 (C15), 47.8 (C20), 48.7 (C4), 52.0 (C6), 53.6 (C8), 55.5 ($-CO_2CH_3$), 56.1 (C5), 59.2 (11-OCH_2OCH_3 and 13-OCH_2OCH_3), 59.8 (C9), 73.1 (C11), 82.6 (C13), 91.9 (13-OCH_2OCH_3), 95.3 (11-OCH_2OCH_3), 108.4 (C17), 153.1 (C16), 173.0 (C7), 219.9 (C19). MS (EI) *m/z* 448 (M^+, 5%), 417 (26), 403 (88), 386 (100), 371 (56), 356 (27), 342 (97), 327 (30), 311 (38), 283 (56), 255 (20), 239 (28), 225 (21), 211 (24), 108 (68), 91 (36). HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_7$: 448.2461; found: 448.2464.

Anal. Calcd for $C_{21}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.00; H, 7.92.

*5.1.18. Dimethyl ent-11α,13-bis(methoxymethoxy)-20-oxo-gibberell-16-ene-7,19-dioate (**30**)*

A stirred solution of ketone **29** (120 mg, 0.27 mmol) in dry DMF (11 mL) was degassed for 20 min before adding THF (15 mL) and cooled to 0 °C under an atmosphere of nitrogen. To the reaction mixture an excess of dry (oil free) potassium hydride (washed with 3×40 mL hexanes) (approximately 120 mg, 0.3 mmol) was added and the suspension stirred at this temperature for 2 h. The reaction flask was then thoroughly flushed with nitrogen before a steady stream of dry oxygen gas was passed through the solution. After 40 min, TLC analysis indicated that the reaction was complete and the reaction flask was again thoroughly flushed with nitrogen before carefully quenching with methanol (3 mL). The mixture was diluted with a solution of 20% 2-butanol/EtOAc (120 mL), neutralised with a solution of saturated NaCl (75 mL) and saturated NaH_2PO_4 (125 mL), and then extracted with 20% 2-butanol/EtOAc (2×80 mL). The combined organic extracts were washed with brine (100 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:3→1:1) yielded the desired aldehyde acid (isolated as a cyclic tautomer) (125 mg, 0.26 mmol, 97%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 3340, 2926, 2854, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.80–2.77 (14H, m), 2.00 (1H, d, J=12.6 Hz, H5), 3.37 (6H, s, 11-OCH_2OCH_3 and 13-OCH_2OCH_3), 3.70 (3H, s, $-CO_2CH_3$), 4.00 (1H, m, H11), 4.61 (2H, d, J=6.6 Hz, 13-OCH_2OCH_3), 4.55, 4.72 (2×1H, ABd, J=7.2 Hz, 11-OCH_2OCH_3), 4.84 (1H, br s, H19), 4.99 (1H, br s, H17), 5.12 (1H, br s, H′17), 5.60 (1H, br s, −OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2 (C2), 23.3 (C18), 33.3 (C1), 40.0 (C3), 41.3 (C12), 42.6 (C14), 45.7 (C10), 46.3 (C15), 46.8 (C4), 47.4 (C8), 51.2 (C6), 52.1 ($-CO_2CH_3$), 53.9, 55.4 (11-OCH_2OCH_3 and 13-OCH_2OCH_3), 55.9 (C5), 61.2 (C9), 72.7 (C11), 82.5 (C13), 91.9 (13-OCH_2OCH_3), 96.9 (11-OCH_2OCH_3), 99.0 (C20), 107.3 (C17), 152.3 (C16), 172.9 (C7), 175.1 (C19). MS (EI) *m/z* 480 (M^+, 33%), 418 (40), 373 (28), 358 (30), 345 (22), 328 (28), 313 (28), 300 (24), 269 (28), 241 (28), 211 (28), 179 (23), 149 (44), 135 (34), 119 (26), 111 (34), 91 (100), 83 (76), 69 (94). HRMS (EI) *m/z* calcd for M^+, $C_{25}H_{36}O_9$: 480.2359; found: 480.2359.

To a stirred solution of aldehyde acid (17 mg, 0.0343 mmol) in dry Et_2O (5 mL) was added a solution of diazomethane in Et_2O (20 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 2 h, TLC analysis indicated that the reaction was complete, the Et_2O and excess diazomethane were blown off under a stream of nitrogen to give a residue, which was purified by chromatography on silica gel (EtOAc/hexanes, 1:4) to yield the desired aldehyde **30** (15.3 mg, 0.031 mmol, 90%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 2930, 1729. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, s, H18), 0.82–2.56 (12H, m), 2.03 (1H, d, J=12.6 Hz, H5), 3.31 (3H, s, 13-OCH_2OCH_3), 3.36 (3H, s, 11-OCH_2OCH_3), 3.38 (1H, m, H12b overlapped), 3.63 (3H, s, 19-CO_2CH_3), 3.73 (3H, s, 7-CO_2CH_3), 3.74 (1H, m, H11 overlapped), 3.91 (1H, d, J=12.9 Hz, H6), 4.52, 4.56 (2×1H, ABd, J=7.2 Hz, 13-OCH_2OCH_3), 4.45, 4.75 (2×1H, ABd, J=7.2 Hz, 11-OCH_2OCH_3), 4.99 (1H, br s, H17), 5.11 (1H, br s, H′17), 9.68 (1H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (C2), 28.0 (C18), 34.6 (C1), 37.5 (C3), 41.2 (C12), 45.2 (C14), 45.3 (C15), 46.0 (C4), 46.3 (C8), 50.2 (C6), 51.7, 51.9 (7- and 19-CO_2CH_3), 55.5, 56.0 (11-OCH_2OCH_3 and 13-OCH_2OCH_3), 56.5 (C5), 59.4 (C10), 62.1 (C9), 71.0 (C11), 82.4 (C13), 91.8 (13-OCH_2OCH_3), 95.3 (11-OCH_2OCH_3), 107.5 (C17), 152.2 (C16), 174.4 (C7), 176.5 (C19), 205.7 (C20). MS (EI) *m/z* 494 (M^+, 1%), 460 (25), 432 (48), 417 (23), 400 (17), 373 (39), 345 (38), 328 (86), 300 (100), 283 (36), 269 (34), 241 (45), 225 (27), 211 (41), 179 (24), 149 (20), 135 (41), 109 (27), 91 (26).

*5.1.19. Dimethyl ent-11α,13-dihydroxy-20-oxogibberell-16-ene-7,19-dioate (11β-OH GA_{19} dimethyl ester) (**31**)*

Dowex resin (300 mg of wet resin, pretreated by washing with water, 1 M NaOH, water, 1 M HCl and then water until the water filtrate was neutral) was added to a stirred solution of aldehyde **30** (7.5 mg, 0.015 mmol) in methanol (4 mL) and water (1 mL). The reaction mixture was then heated under reflux for 48 h. The reaction mixture was cooled to room temperature, diluted with methanol (10 mL), filtered through a pad of Celite™ and the solid residue was washed thoroughly with methanol (5×5 mL). The combined organic extracts were treated with saturated $NaHCO_3$ (four drops) and then concentrated in vacuo to remove MeOH and water. The residue was partitioned between a mixture of saturated NaCl (30 mL) and 20% 2-butanol/EtOAc (35 mL), and then extracted with 20% 2-butanol/EtOAc (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel (EtOAc/hexanes, 1:3→1:1) yielded the desired dihydroxy aldehyde **31** (5.2 mg, 0.013 mmol, 84%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 3468, 2950, 1725. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 1.13–2.41 (12H, m), 2.27 (1H, d, J=12.9 Hz, H5), 2.63 (1H, d, J=12.9 Hz, H15a), 3.64 (3H, s, 19-CO_2CH_3), 3.74 (5H, s, 7-CO_2CH_3, H6 and H12b overlapped), 3.88 (1H, ddd, J=10.5, 8.4, 8.1 Hz, H11), 4.97 (1H, br s, H17), 5.25 (1H, br s, H′17), 9.71 (1H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C2), 28.3 (C18), 34.8 (C1), 37.5 (C3), 44.8 (C12), 45.3 (C14), 45.5 (C15), 46.7 (C4), 48.6 (C8), 50.1 (C6), 51.8, 51.9 (7- and 19-CO_2CH_3), 56.3 (C5), 59.5 (C10), 63.9 (C9), 65.8 (C11), 77.3 (C13), 107.0 (C17), 156.1 (C16), 174.1 (C7), 176.3 (C19), 205.7 (C20). MS (EI) *m/z* 406 (M^+, 7%), 404 (9), 388 (14), 374 (49), 356 (43), 328 (70), 314 (31), 300 (100), 286 (18), 269 (46), 257 (35), 241 (55), 225 (22), 197 (30), 171 (22), 157 (25), 135 (59), 117 (21), 105 (37), 91 (49), 77 (31), 59 (31). HRMS (EI) *m/z* calcd for M^+, $C_{22}H_{30}O_7$: 406.1191; found: 406.1192; calcd for [M^+−2H], $C_{22}H_{28}O_7$: 404.1835; found: 404.1833. GC–MS (bis-TMS ether methyl ester) 550 (M^+, 5%), 519 (9), 432 (50), 405 (23), 372 (28), 313 (23), 295 (40), 269 (46), 237 (50), 208 (100), 167 (48), 117 (41).

*5.1.20. ent-11α,13,20-Trihydroxygibberell-16-ene-7,19-dioic acid 7-methyl ester 19,20-lactone (11β-OH GA_{44} methyl ester) (**32**)*

To a stirred solution of aldehyde **30** (64.5 mg, 0.134 mmol) in dry THF (20 mL) was added MeOH (10 mL) and the mixture cooled to 0 °C under an atmosphere of nitrogen. $NaBH_4$ was then added portionwise (140 mg, 3.55 mmol) and the resulting mixture was stirred for 3 h before warming to room temperature. The mixture was then concentrated to remove MeOH and THF, and the residue was partitioned between EtOAc (80 mL) and a solution (60 mL) of saturated NaCl and saturated NaH_2PO_4 (60 mL). The aqueous phase was extracted with EtOAc (2×60 mL), the combined organic extracts were washed with brine (2×100 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:3→1:1.5) yielded the desired lactone (50 mg, 0.11 mmol, 80%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 2931, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 0.85–2.36 (12H, m), 2.22 (1H, d, J=12.9 Hz, H5), 2.71 (1H, dd, J=12.9, 8.4 Hz, H12β), 2.80 (1H, d, J=12.9 Hz, H6), 3.36 (3H, s, 13-OCH_2OCH_3), 3.38 (3H, s, 11-OCH_2OCH_3), 3.70 (4H, s, $-CO_2CH_3$ and H11 overlapped), 4.24 (1H, d, J_{gem}=12.0 Hz, 20-pro-S-H), 4.40 (1H, dd, J_{gem}=12.0 Hz, $J_{20,1\beta}$=1.8 Hz, 20-pro-R-H), 4.51, 4.54 (2×1H, ABd, J=4.8 Hz, 13-OCH_2OCH_3), 4.66, 4.72 (2×1H, ABd, J=7.2 Hz, 11-OCH_2OCH_3), 5.01 (1H, br s, H17), 5.13 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C2), 23.3 (C18), 39.7 (C1), 39.9 (C3), 41.2 (C12), 41.6 (C14), 42.7 (C10), 45.7 (C15), 46.1 (C4), 46.5 (C8), 51.7 (C6), 52.1 ($-CO_2CH_3$), 53.1 (C5), 55.5 (13-OCH_2OCH_3), 56.3 (11-OCH_2OCH_3), 60.3 (C9), 70.2 (C11), 73.8 (C20), 82.5 (C13), 91.9 (13-OCH_2OCH_3), 95.2 (11-OCH_2OCH_3), 107.9 (C17), 152.3 (C16), 172.9 (C7), 174.8 (C19). MS (EI) *m/z* 464 (M^+, 29%), 433 (35), 419 (84), 405 (51), 391 (100), 372 (28), 358 (35), 343 (20), 329 (29), 301 (53), 285 (38), 269 (57), 253 (41), 225 (35), 211 (41), 179 (40), 159 (27), 145 (32), 129 (28), 105 (44), 91 (57). HRMS (EI) *m/z* calcd for $[M+1]^+$, $C_{25}H_{37}O_8$: 465.2488; found: 465.2486.

Dowex resin (500 mg of wet resin, pretreated by washing with water, 1 M NaOH, water, 1 M HCl and then water until the water filtrate was neutral) was added to a stirred solution of lactone (50 mg, 0.11 mmol) in methanol (20 mL) and water (5 mL). The reaction mixture was then heated to 70 °C and stirred for 48 h. The reaction mixture was cooled to room temperature, diluted with methanol (10 mL), filtered through a pad of Celite™ and washed with methanol (5×5 mL). The combined organic extracts were treated with saturated $NaHCO_3$ (30 drops) and then concentrated to remove MeOH and water. The residue was partitioned between a mixture of saturated NaCl (50 mL) and 20% 2-butanol/EtOAc (50 mL), and then extracted with 20% 2-butanol/EtOAc (2×40 mL). The combined organic extracts were washed with brine (3×30 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was washed with hexanes (4×15 mL) before purification by chromatography on silica gel (EtOAc/hexanes, 1:1→1:1.5) to yield the desired lactone-diol **32** (40.5 mg, 0.11 mmol, 100%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 3418, 2927, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 0.86–2.42 (14H, m), 2.24 (1H, d, J=12.9 Hz, H5), 2.53 (1H, dd, J=12.9, 5.7 Hz, H12β), 2.80 (1H, d, J=12.9 Hz, H6), 3.70 (3H, s, $-CO_2CH_3$), 3.86 (1H, ddd, J=10.5, 9.3, 8.7 Hz, H11), 4.36 (1H, d, J_{gem}=12.3 Hz, 20-pro-S-H), 4.40 (1H, dd, J_{gem}=12.3 Hz, $J_{20,1\beta}$=2.1 Hz, 20-pro-R-H), 4.94 (1H, br s, H17), 5.26 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C2), 23.4 (C18), 39.8 (C1), 39.9 (C3), 41.6 (C12), 42.7 (C14), 45.0 (C10), 45.1 (C15), 46.7 (C4), 49.2 (C8), 51.6 (C6), 52.1 ($-CO_2CH_3$), 53.0 (C5), 62.3 (C9), 65.2 (C11), 73.8 (C20), 77.5 (C13), 106.8 (C17), 156.4 (C16), 172.9 (C7), 175.0 (C19). MS (EI) *m/z* 376 (M^+, 100%), 345 (24), 316 (54), 298 (32), 271 (37), 253 (82), 227 (41), 213 (23), 197 (22), 159 (33), 145 (27), 121 (21), 105 (31), 91 (46), 77 (28). HRMS (EI) *m/z* calcd for $[M^+ + H]$, $C_{21}H_{29}O_6$: 377.1964; found: 377.1957. GC–MS (bis-TMS ether methyl ester) 520 (M^+, 21%), 489 (4), 430 (11), 386 (5), 371 (11), 313 (5), 295 (100), 281 (18), 239 (44), 207 (14), 167 (15), 117 (19).

*5.1.21. Dimethyl ent-11α,13-dihydroxygibberell-16-ene-7,19-dioate (11β-OH GA_{53} dimethyl ester) (**33**)*

To a mixture of aldehyde **30** (19.5 mg, 0.041 mmol) in MeOH (1 mL) was added 2 N NaOH (3 mL) and the resulting mixture heated at 100 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with a solution of 20% 2-butanol/EtOAc (50 mL) and acidified with a solution of saturated NaCl (30 mL), saturated NaH_2PO_4 (120 mL) and 10% H_3PO_4 (10 mL) to pH ~4, before extracting with 20% 2-butanol/EtOAc (2×30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentration in vacuo. The obtained residue was washed with hexanes (4×15 mL) to give the diacid as a white solid (18.9 mg). This compound was dissolved in ethylene glycol (2.5 mL) and anhydrous hydrazine (0.1 mL) was added. The reaction mixture was heated at 115 °C for 2 h and then two pellets of NaOH (~200 mg) were added. The mixture was heated at 115 °C for 1 h before raising the temperature to 180 °C and stirring at this temperature overnight. The reaction mixture was cooled to room temperature, diluted with a solution of 20% 2-butanol/EtOAc (60 mL) and then acidified with a solution of saturated NaCl (50 mL), saturated NaH_2PO_4 (100 mL) and 10% H_3PO_4 (2 mL) to pH ~4, before extracting with 20% 2-butanol/EtOAc (2×30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The obtained oil was washed with hexanes (4×15 mL) to give a mixture of diacid and ethylene glycol, which was co-evaporated with toluene (3×1 mL), then dissolved in MeOH (1 mL) and cooled to 0 °C in an ice-bath under an atmosphere of nitrogen. A solution of diazomethane in Et_2O (5 mL) was then added to the reaction mixture. After stirring overnight the Et_2O and excess diazomethane were blown off under a stream of nitrogen, and the residue concentrated in vacuo to remove MeOH and give the crude product. The resulting oil was washed with hexanes (4×15 mL) to dissolve the product and the combined organic extracts were concentrated to give the crude diacid free from ethylene glycol.

This material was chromatographed on silica gel (EtOAc/hexanes, 1:9) to give the desired product (11.7 mg, 0.024 mmol, three steps overall yield 60%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 2948, 2822, 1731, 1661. ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (3H, s, H20), 1.08 (3H, s, H18), 0.97–2.40 (11H, m), 1.93 (1H, d, J=12.6 Hz, H5), 2.51 (1H, dd, J=13.2, 8.4 Hz, H12β), 3.34 (3H, s, 13-OCH_2OCH_3), 3.37 (4H, s, 11-OCH_2OCH_3 and H6 overlapped), 3.67 (3H, s, 19-CO_2CH_3), 3.70 (3H, s, 7-CO_2CH_3), 3.93 (1H, ddd, J=9.6, 7.8, 7.5 Hz, H11), 4.54, 4.64 (2×1H, ABd, J=6.9 Hz, 13-OCH_2OCH_3), 4.54, 4.75 (2×1H, ABd, J=7.5 Hz, 11-OCH_2OCH_3), 4.97 (1H, br s, H17), 5.08 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 29.0 (C18), 37.6 (C1), 40.4 (C3), 42.6 (C12), 43.8 (C14), 44.5 (C10), 45.4 (C15), 45.9 (C4 and C8), 51.1 (C6), 51.5, 51.6 (7- and 19-CO_2CH_3), 55.5 (C5), 56.0 (13-OCH_2OCH_3), 56.8 (11-OCH_2OCH_3), 62.6 (C9), 70.5 (C11), 82.6 (C13), 91.8 (13-OCH_2OCH_3), 94.8 (11-OCH_2OCH_3), 106.9 (C17), 152.4 (C16), 174.9 (C7), 177.4 (C19). GC–MS (EI) m/z 448 ([M^+–CH_3OH], 49%), 418 (16), 407 (57), 358 (60), 388 (53), 343 (67), 327 (37), 314 (100), 299 (67), 283 (80), 273 (46), 255 (44), 239 (41), 227 (33), 211 (34), 197 (23), 181 (81), 171 (27), 159 (33), 149 (43), 133 (26), 121 (39), 107 (47), 91 (42), 79 (28). HRMS (EI) m/z calcd for M^+, $C_{26}H_{40}O_8$: 480.2723; found: 480.2719.

Dowex resin (500 mg of wet resin, pretreated by washing with water, 1 M NaOH, water, 1 M HCl and then water until the water filtrate was neutral) was added to a stirred solution of diester (33 mg, 0.069 mmol) in methanol (16 mL) and water (4 mL). The reaction mixture was then heated at 70 °C for 24 h, cooled to room temperature, diluted with methanol (10 mL), filtered through a pad of Celite™, which was washed with methanol (5×10 mL). The combined organic extracts were treated with saturated $NaHCO_3$ (1 mL) and then concentrated to remove MeOH and water. The residue was partitioned between a mixture of saturated NaCl (100 mL) and 20% 2-butanol/EtOAc (100 mL), and then extracted with 20% 2-butanol/EtOAc (2×80 mL). The combined organic extracts were washed with brine (3×30 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/hexanes, 1:1.5→1:1) to give **33** (25 mg, 0.0637 mmol, 93%) as a colourless oil. IR (Neat) ν_{max} (cm^{-1}): 3434, 2930, 2854, 1727. ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, s, H20), 1.09 (3H, s, H18), 0.78–2.38 (14H, m), 1.94 (1H, d, J=12.6 Hz, H5), 2.39 (1H, dd, J=13.2, 8.1 Hz, H12β), 3.38 (1H, d, J=12.6 Hz, H6), 3.67 (3H, s, 19-CO_2CH_3), 3.70 (3H, s, 7-CO_2CH_3), 4.02 (1H, ddd, J=7.8, 7.2, 6.9 Hz, H11), 4.96 (1H, br s, H17), 5.23 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8 (C20), 19.6 (C2), 28.9 (C18), 37.4 (C1), 40.5 (C3), 43.6 (C12), 44.3 (C14), 45.0 (C10), 46.3 (C15), 46.5 (C4), 49.2 (C8), 50.8 (C6), 51.5 (7- and 19-CO_2CH_3), 56.9 (C5), 65.0 (C9), 65.8 (C11), 77.4 (C13), 106.7 (C17), 156.9 (C16), 175.1 (C7), 177.5 (C19). GC–MS (EI) m/z 392 (M^+, 2%), 360 (15), 332 (18), 314 (100), 299 (49), 286 (7), 272 (10), 255 (31), 239 (11), 229 (13), 213 (15), 199 (9), 185 (8), 173 (10), 159 (12), 145 (11), 133 (8), 121 (11), 107 (14), 91 (7), 79 (12). HRMS (EI) m/z calcd for [M^++H], $C_{22}H_{33}O_6$: 393.2277; found: 393.2276. GC–MS (bis-TMS ether methyl ester), retention time 17.41 min; m/z 536 (M^+, 25%), 521 (4), 463 (5), 446 (10), 419 (35), 387 (25), 372 (9), 346 (9), 295 (100), 251 (19), 239 (41), 207 (16), 181 (49), 147 (14), 117 (33); KRI 2632. Endogenous material: identical mass spectrum, KRI 2631.

5.1.22. *Dimethyl ent-11α-hydroxy-20-oxogibberell-16-ene-7,19-dioate (11β-hydroxy-GA$_{24}$ methyl ester)*

Acetic anhydride (18 μL, 0.092 mmol) was added dropwise to a stirred solution of diol **31** (34 mg, 0.083 mmol), triethylamine (17.6 μL, 0.125 mmol) and a catalytic amount of DMAP (10 mg) in CH_2Cl_2 (10 mL) at 0 °C, under nitrogen. The resulting mixture was stirred for 30 min at this temperature and then warmed to room temperature for 30 min. The reaction mixture was cooled in an ice-bath, quenched by dropwise addition of water (1 mL), stirred for 5 min and then added 1 M HCl (40 mL) and brine (20 mL). After extraction with EtOAc (3×30 mL), the combined organic extracts were washed with saturated aq $NaHCO_3$ solution (20 mL) and brine (3×20 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:4→2:1) gave the 11-acetate (33 mg, 0.074 mmol, 88%) as a clear oil that solidified on standing. IR (Neat) ν_{max} (cm^{-1}): 3455, 2955, 2876, 1731. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 1.15–2.48 (15H, m), 1.96 (3H, s, CH_3CO_2–), 3.62 (3H, s, 19-CO_2CH_3), 3.73 (3H, s, 7-CO_2CH_3), 3.85 (1H, d, J=12.6 Hz, H6), 4.95 (1H, s, H17), 4.96 (1H, ddd, J=8.4, 8.1, 6.6 Hz, H11), 5.21 (1H, br s, H′17), 9.65 (1H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (C2), 21.1 (CH_3CO_2–), 28.1 (C18), 34.2 (C1), 37.3 (C3), 44.4 (C12), 45.0 (C14), 45.4 (C15), 45.9 (C4), 46.8 (C8), 49.9 (C6), 51.7, 51.9 (7- and 19-CO_2CH_3), 56.4 (C5), 59.0 (C10 and C13), 60.7 (C9), 67.8 (C11), 107.0 (C17), 155.2 (C16), 169.7 (CH_3CO_2–), 174.4 (C7), 176.3 (C19), 204.8 (C20). MS (EI) m/z 448 (M^+, 0.5%), 416 (7), 388 (41), 355 (12), 328 (56), 300 (100), 282 (13), 269 (21), 241 (54), 135 (28). HRMS (EI) m/z calcd for M^+, $C_{24}H_{32}O_8$: 448.2097; found: 448.2094.

To a solution of this acetate (29.5 mg, 0.071 mmol) in CH_2Cl_2 (10 mL) under nitrogen were added triethylamine (50 μL, 0.38 mmol) and a catalytic amount of DMAP (10 mg), and cooled to 0 °C. The resulting mixture was treated dropwise with methyl oxalyl chloride (27 μL, 0.29 mmol) and stirred for 45 min, after which time TLC analysis indicated that reaction was complete. The reaction mixture was quenched by dropwise addition of a solution (40 mL) of saturated NaCl and saturated NaH_2PO_4 (1:1), stirred for 15 min and then extracted with CH_2Cl_2 (60 mL and 2×40 mL). The combined organic extracts were washed successively with saturated aq $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:6→2:1) afforded the desired methyl oxalate (23.5 mg, 0.044 mmol, 67%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 2956, 2876, 1771, 1733, 1665. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s, H18), 1.14–2.42 (12H, m), 1.97 (3H, s, CH_3CO_2–), 2.24 (1H, d, J=12.9 Hz, H5), 2.88 (1H, dd, J=13.5, 8.7 Hz,

H12β), 3.61 (3H, s, 19-CO_2CH_3), 3.74 (3H, s, 7-CO_2CH_3), 3.86 (3H, s, $-O(CO)_2OCH_3$), 3.88 (1H, d, J=12.9 Hz, H6 overlapped), 4.98 (1H, ddd, J=8.7, 8.4, 6.6 Hz, H11), 5.01 (1H, br s, H17), 5.20 (1H, br s, H′17), 9.64 (1H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C2), 21.2 (CH_3CO_2-), 28.5 (C18), 34.6 (C1), 37.5 (C3), 40.5 (C12), 43.9 (C14), 44.5 (C15), 45.3 (C4), 47.7 (C8), 49.8 (C6), 52.0, 52.3 (7- and 19-CO_2CH_3), 53.7 ($-O(CO)_2OCH_3$), 56.6 (C5), 59.1 (C10), 60.4 (C9), 67.5 (C11), 86.0 (C13), 109.4 (C17), 150.2 (C16), 156.1, 158.3 ($-O(CO)_2OCH_3$), 169.7 (CH_3CO_2-), 174.3 (C7), 176.5 (C19), 204.9 (C20). MS (EI) m/z 534 (M^+, 1.2%), 502 (9), 474 (59), 431 (17), 414 (49), 386 (100), 342 (38), 327 (30), 310 (70), 282 (72), 223 (66). HRMS (EI) m/z calcd for M^+, $C_{27}H_{34}O_{11}$: 534.2101; found: 534.2102.

To a solution of this oxalate (57.8 mg, 0.11 mmol) in toluene (30 mL) at room temperature under nitrogen were added tributyltin hydride (66 μL, 0.14 mmol) and AIBN (18 mg, 0.107 mmol). The mixture was degassed for 15 min then blanketed with nitrogen and heated to 80 °C for 3 h, after which time TLC analysis indicated that reaction was complete. The reaction mixture was concentrated to remove solvent and the products were separated by chromatography on silica gel (EtOAc/hexanes, 1:15→1:10) to yield the deoxygenated gibberellin (21 mg, 0.049 mmol, 45%) as a glassy white solid. IR (Neat) ν_{max} (cm^{-1}): 2949, 2874, 1734, 1659. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s, H18), 1.14–2.57 (13H, m), 1.97 (3H, s, CH_3CO_2-), 2.24 (1H, d, J=12.9 Hz, H5), 2.66 (1H, m, H12β), 3.61 (3H, s, 19-CO_2CH_3), 3.72 (3H, s, 7-CO_2CH_3), 3.92 (1H, d, J=12.9 Hz, H6), 4.73 (1H, ddd, J=9.6, 9.0, 8.1 Hz, H11), 4.86 (1H, br s, H17), 4.96 (1H, br s, H′17), 9.63 (1H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (C2), 21.1 (CH_3CO_2-), 28.2 (C18), 34.4 (C1), 37.2 (C3), 37.4 (C12), 38.4 (C14), 38.5 (C13), 45.2 (C15), 46.2 (C4), 49.9 (C8), 50.2 (C6), 51.6, 51.8 (7- and 19-CO_2CH_3), 55.9 (C5), 59.4 (C10), 60.6 (C9), 68.2 (C11), 107.3 (C17), 154.9 (C16), 169.8 (CH_3CO_2-), 174.5 (C7), 176.4 (C19), 204.8 (C20). MS (EI) m/z 432 (M^+, 0.6%), 400 (9), 372 (36), 340 (19), 312 (46), 284 (100), 269 (17), 253 (24), 225 (54), 197 (20), 183 (23), 155 (22), 105 (22), 91 (30). HRMS (EI) m/z calcd for M^+, $C_{24}H_{32}O_7$: 432.2148; found: 432.2144.

To a stirred solution of acetate (14.5 mg, 0.033 mmol) in MeOH (4 mL) at 0 °C was added 0.5 M K_2CO_3 (2 mL). After 30 min, the reaction mixture was warmed to room temperature and stirred for 4.5 h, after which time TLC analysis showed the absence of starting material. The mixture was quenched with saturated aq NH_4Cl solution (4 mL) and then concentrated to remove MeOH and water. The residue was diluted with a solution of 20% 2-butanol/EtOAc (60 mL) and acidified with a 1:1 solution (10 mL) of brine and saturated NaH_2PO_4 to pH|4, and then extracted with 20% 2-butanol/EtOAc (3×30 mL). The combined organic extracts were washed with brine (30 mL) and dried over $MgSO_4$. After concentration, the residue was co-evaporated with toluene (3×1 mL), dissolved in Et_2O (4 mL) and then cooled in an ice-bath at 0 °C under an atmosphere of nitrogen. This solution was added to a solution of diazomethane in Et_2O (10 mL). After stirring overnight the Et_2O and excess diazomethane were blown off by a stream of nitrogen to give the crude product. The obtained residue was chromatographed on silica gel (EtOAc/hexanes, 1:15→1:5) that furnished the desired product **34** (9 mg, 0.023 mmol, 69%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3496, 3068, 2929, 2873, 2855, 2739, 1729, 1659. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 0.87–2.67 (15H, m), 2.26 (1H, d, J=12.9 Hz, H5), 3.64 (3H, s, 19-CO_2CH_3), 3.69 (1H, ddd, J=9.0, 8.4, 8.1 Hz, H11), 3.72 (3H, s, 7-CO_2CH_3), 3.90 (1H, d, J=12.9 Hz, H6), 4.87 (1H, br s, H17), 4.99 (1H, br s, H′17), 9.72 (3H, s, H20). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C2), 28.3 (C18), 34.9 (C1), 37.2 (C3), 37.5 (C12), 38.7 (C13), 41.8 (C14), 45.3 (C15), 46.3 (C4), 49.9 (C8), 50.3 (C6), 51.7 (7- and 19-CO_2CH_3), 55.8 (C5), 59.9 (C10), 64.1 (C9), 65.8 (C11), 107.4 (C17), 155.6 (C16), 174.6 (C7), 176.6 (C19), 206.3 (C20). MS (EI) m/z 390 (M^+, 3%), 372 (11), 358 (13), 340 (28), 312 (55), 298 (23), 284 (100), 269 (17), 253 (42), 241 (18), 225 (57), 209 (17), 197 (29), 183 (20), 165 (29), 145 (24), 129 (29), 105 (40), 91 (63). HRMS (EI) m/z calcd for M^+, $C_{22}H_{30}O_6$: 390.2042; found: 390.2048. GC–MS (TMS ether methyl ester), retention time 19.72 min; m/z 462 (M^+, 7%), 430 (33), 402 (45), 387 (19), 372 (35), 343 (19), 312 (49), 284 (100), 270 (22), 253 (26), 225 (58), 209 (19), 197 (22), 155 (23), 129 (21), 91 (17); KRI 2814. Endogenous material: identical mass spectrum, KRI 2814.

*5.1.23. ent-11α,20-Dihydroxygibberell-16-ene-7,19-dioic acid 7-methyl ester 19,20-lactone (11β-OH GA_{15} methyl ester) (**35**)*

A stirred solution of alcohol **32** (31.3 mg, 0.083 mmol), triethylamine (18 μL, 0.125 mmol) and a catalytic amount of DMAP (10 mg) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was treated dropwise with acetic anhydride (22 μL, 0.104 mmol). The mixture was stirred for 30 min then raised to room temperature for an additional 30 min, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was cooled in an ice-bath and quenched by dropwise addition of water (2 mL), stirred for 15 min and then acidified with 1 M HCl (10 mL). After extracting with EtOAc (3×50 mL), the combined organic extracts were washed successively with saturated aq $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/CH_2Cl_2, 1:6→1:1) yielded the desired acetate (33.1 mg, 0.079 mmol, 95%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3454, 2926, 1732. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.26–2.40 (13H, m), 2.04 (3H, s, CH_3CO_2-), 2.24 (1H, d, J=12.6 Hz, H5), 2.66 (1H, dd, J=13.2, 9.3 Hz, H12β), 2.83 (1H, d, J=12.6 Hz, H6), 3.71 (3H, s, $-CO_2CH_3$), 4.20 (1H, d, J_{gem}=12.8 Hz, 20-pro-S-H), 4.39 (1H, dd, J_{gem}=12.0 Hz, $J_{20,1\beta}$=2.1 Hz, 20-pro-R-H), 4.96 (1H, ddd, J=10.5, 9.3, 8.7 Hz, H11 overlapped), 4.97 (1H, br s, H17), 5.27 (1H, dd, J=3.0, 1.8 Hz, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C2), 21.3 (CH_3CO_2-), 23.4 (C18), 39.2 (C1), 39.6 (C3), 41.5 (C12), 42.6 (C14), 45.1 (C10), 45.4 (C15), 45.5 (C4), 46.7 (C8), 51.5 (C6),

52.2 (−CO_2CH_3), 52.9 (C5), 59.1 (C9), 66.8 (C11), 73.6 (C20), 77.2 (C13), 107.2 (C17), 155.6 (C16), 169.8 (CH_3CO_2−), 172.7 (C7), 174.6 (C19). MS (FAB) *m/z* 419 ([M^++H], 100%), 390 (6), 375 (15), 242 (23), 155 (10), 147 (29), 145 (59), 130 (71), 101 (18). HRMS (EI) *m/z* calcd for M^+, $C_{23}H_{30}O_7$: 418.1991; found: 418.1988.

A stirred solution of this acetate (33.5 mg, 0.08 mmol) in triethylamine (56 μL, 0.4 mmol) and a catalytic amount of DMAP (10 mg) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was treated dropwise with methyl oxalyl chloride (31 μL, 0.32 mmol). The mixture was stirred for 45 min, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was quenched by dropwise addition of a 1:1 solution (20 mL) of saturated NaCl and saturated NaH_2PO_4, stirred for 15 min and then extracted with CH_2Cl_2 (50 mL and 2×30 mL). The combined organic extracts were washed successively with saturated aq $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:5) afforded the desired oxalate (38.8 mg, 0.077 mmol, 96%) as a clear oil that solidified on standing. IR (Neat) ν_{max} (cm^{-1}): 2943, 1735. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.42−2.41 (12H, m), 2.04 (3H, s, CH_3CO_2−), 2.25 (1H, d, *J*=12.9 Hz, H5), 2.83 (1H, d, *J*=12.6 Hz, H6), 3.03 (1H, dd, *J*=12.9, 9.3 Hz, H12β), 3.71 (3H, s, −CO_2CH_3), 3.88 (3H, s, −$O(CO)_2OCH_3$), 4.20 (1H, d, J_{gem}=12.0 Hz, 20-pro-S-H), 4.38 (1H, dd, J_{gem}=12.3 Hz, $J_{20,1\beta}$=1.8 Hz, 20-pro-R-H), 5.00 (1H, ddd, *J*=9.9, 9.3, 9.0 Hz, H11), 5.10 (1H, br s, H17), 5.27 (1H, d, *J*=1.8 Hz, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (C2), 21.1 (CH_3CO_2−), 23.3 (C18), 39.2 (C1), 39.5 (C3), 40.3 (C12), 41.5 (C14), 42.5 (C10), 43.6 (C15), 44.5 (C4), 47.4 (C8), 51.5 (C6), 52.2 (−CO_2CH_3), 52.7 (−$O(CO)_2OCH_3$), 53.6 (C5), 58.7 (C9), 66.1 (C11), 73.4 (C20), 85.4 (C13), 109.6 (C17), 150.3 (C16), 156.0, 157.9 (−$O(CO)_2OCH_3$), 169.8 (CH_3CO_2−), 172.5 (C7), 174.5 (C19). MS (EI) *m/z* 504 (M^+, 100%), 473 (11), 399 (18), 384 (20), 339 (19), 281 (28), 235 (47), 181 (19), 131 (18), 91 (14), 69 (24). HRMS (EI) *m/z* calcd for [M^++H], $C_{26}H_{33}O_{10}$: 505.2074; found: 505.2068.

To a solution of this oxalate (38 mg, 0.075 mmol) in toluene (20 mL) at room temperature under nitrogen were added tributyltin hydride (46 μL, 0.166 mmol) and AIBN (12 mg, 0.072 mmol). The mixture was degassed for 20 min then blanketed with nitrogen and heated to 80 °C for 3 h, after which time TLC analysis indicated that the reaction was complete. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:6→1:4) to yield the desired product (10 mg, 0.025 mmol, 33%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 2941, 2873, 1735, 1658. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 0.90−2.32 (12H, m), 2.03 (3H, s, CH_3CO_2−), 2.23 (1H, d, *J*=12.6 Hz, H5), 2.66 (1H, m, H12β), 2.96 (1H, br s, H13), 2.82 (1H, d, *J*=12.9 Hz, H6), 3.70 (3H, s, −CO_2CH_3), 4.17 (1H, d, J_{gem}=12.3 Hz, 20-pro-S-H), 4.40 (1H, dd, J_{gem}=12.3 Hz, $J_{20,1\beta}$=1.8 Hz, 20-pro-R-H), 4.78 (1H, ddd, *J*=10.5, 9.0, 8.4 Hz, H11), 4.88 (1H, br s, H17), 5.00 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C2), 21.4 (CH_3CO_2−), 23.4 (C18), 37.4 (C1), 38.5 (C3), 38.6 (C13), 39.4 (C12), 39.7 (C14), 41.8 (C10), 42.7 (C15), 46.4 (C4), 50.1 (C8), 51.7 (C6), 52.0 (−CO_2CH_3), 52.6 (C5), 59.3 (C9), 67.1 (C11), 73.7 (C20), 106.7 (C17), 154.8 (C16), 170.0 (CH_3CO_2−), 173.1 (C7), 174.7 (C19). GC−MS (EI) retention time 17.11−17.37 min; *m/z* 402 (M^+, 30%), 371 (8), 310 (48), 296 (22), 237 (100), 225 (17), 209 (15), 195 (17), 181 (14), 169 (12), 155 (14), 141 (13), 129 (14), 117 (9), 105 (12), 91 (19), 79 (11).

To a solution of this acetate (10 mg, 0.025 mmol) in MeOH (5 mL) at 0 °C was added 0.5 M K_2CO_3 (2.5 mL). After 30 min, the reaction mixture was warmed to room temperature and stirred for a further 4.5 h. The mixture was concentrated to remove MeOH and water. The residue was quenched with saturated aq NH_4Cl solution (40 mL) and EtOAc (50 mL), and then extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine (30 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:5→1:3) afforded the desired product **35** (6.5 mg, 0.018 mmol, 72%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3453, 2937, 2870, 1733. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 1.19−2.71 (15H, m), 2.22 (1H, d, *J*=12.6 Hz, H5), 2.81 (1H, d, *J*=12.6 Hz, H6), 3.69 (3H, s, −CO_2CH_3), 3.67 (1H, ddd, *J*=10.5, 9.6, 8.7 Hz, H11 overlapped), 4.35 (1H, d, J_{gem}=12.3 Hz, 20-pro-S-H), 4.42 (1H, dd, J_{gem}=12.0 Hz, $J_{20,1\beta}$=2.1 Hz, 20-pro-R-H), 4.85 (1H, br s, H17), 4.99 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C2), 23.4 (C18), 37.0 (C1), 38.9 (C13), 39.9 (C3 and C12), 41.9 (C14), 42.7 (C10), 42.8 (C15), 46.5 (C4), 50.2 (C8), 51.8 (C6), 51.9 (−CO_2CH_3), 52.7 (C5), 62.8 (C9), 65.3 (C11), 73.9 (C20), 107.4 (C17), 155.5 (C16), 173.2 (C7), 175.1 (C19). MS (EI) *m/z* 360 (M^+, 50%), 328 (18), 300 (32), 282 (27), 255 (32), 237 (70), 211 (32), 183 (15), 166 (29), 149 (64), 129 (29), 119 (22), 105 (37), 91 (58), 81 (50), 69 (78). HRMS (EI) *m/z* calcd for M^+, $C_{21}H_{28}O_5$: 360.1937; found: 360.1940. GC−MS (EI) (TMS ether methyl ester) retention time 23.70 min; *m/z* 432 (M^+, 13%), 372 (89), 357 (3), 327 (6), 310 (17), 296 (22), 282 (65), 237 (100), 225 (23), 209 (23), 195 (24), 181 (19), 155 (24), 129 (18), 117 (12), 91 (17); KRI.

*5.1.24. Dimethyl ent-11α-hydroxygibberell-16-ene-7,19-dioate (11β-OH GA_{12} dimethyl ester) (**36**)*

A stirred solution of alcohol **33** (35 mg, 0.089 mmol), triethylamine (19 μL, 0.133 mmol) and a catalytic amount of DMAP (10 mg) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was treated dropwise with acetic anhydride (22 μL, 0.107 mmol). The mixture was stirred for 25 min then warmed to room temperature for a further 30 min, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was cooled in an ice-bath, quenched by dropwise addition of water (2 mL), stirred for 15 min and then added 1 M HCl (20 mL) and brine (20 mL). After extracting with EtOAc (3×50 mL), the combined organic extracts were washed with brine (2×20 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel

(EtOAc/CH_2Cl_2, 1:5→1:3) gave the desired acetate (32.5 mg, 0.075 mmol, 84%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3485, 2949, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (3H, s, H20), 1.08 (3H, s, H18), 0.87–2.38 (13H, m), 1.93 (1H, d, J=12.6 Hz, H5), 1.96 (3H, s, CH_3CO_2–), 2.51 (1H, dd, J=13.5, 8.7 Hz, H12β), 3.37 (1H, d, J=12.9 Hz, H6), 3.36 (3H, s, 19-CO_2CH_3), 3.69 (3H, s, 7-CO_2CH_3), 4.91 (1H, br s, H17), 5.11 (1H, ddd, J=8.4, 8.1, 6.9 Hz, H11), 5.18 (1H, dd, J=3.3, 1.5 Hz, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1 (C20), 19.7 (C2), 21.4 (C18), 29.1 (CH_3CO_2–), 37.4 (C1), 40.3 (C3), 43.7 (C12), 44.4 (C14), 48.9 (C10), 45.5 (C15), 46.1 (C4), 46.3 (C8), 50.8 (C6), 51.5, 51.6 (7- and 19-CO_2CH_3), 56.6 (C5), 61.1 (C9), 68.1 (C11), 77.3 (C13), 106.2 (C17), 155.9 (C16), 169.9 (CH_3CO_2–), 174.7 (C7), 177.2 (C19). MS (EI) m/z 436 ([M^++2H], 14%), 402 (86), 314 (100), 299 (29), 255 (33), 105 (27), 84 (48), 69 (27). HRMS (EI) m/z calcd for M^+, $C_{24}H_{34}O_7$: 434.2304; found: 434.2303.

A stirred solution of this acetate (33 mg, 0.076 mmol), triethylamine (53 μL, 0.38 mmol) and DMAP catalyst (10 mg) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was treated dropwise with methyl oxalyl chloride (29 μL, 0.304 mmol). The mixture was stirred for 45 min, after which time TLC analysis indicated that the reaction was complete. The reaction mixture was quenched by dropwise addition of a 1:1 solution (20 mL) of saturated NaCl and saturated NaH_2PO_4, stirred for 15 min and then extracted with CH_2Cl_2 (60 mL and 2×40 mL). The combined organic extracts were washed successively with saturated aq $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL), and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:7) yielded the desired oxalate (32 mg, 0.062 mmol, 81%) as a clear oil that solidified on standing. IR (Neat) ν_{max} (cm^{-1}): 2951, 2851, 1772, 1732, 1665. ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (3H, s, H20), 1.09 (3H, s, H18), 0.87–2.38 (12H, m), 1.93 (1H, d, J=12.9 Hz, H5), 1.97 (3H, s, CH_3CO_2–), 2.94 (1H, dd, J=12.9, 8.7 Hz, H_{12b}), 4.39 (1H, d, J=12.6 Hz, H6), 3.66 (3H, s, 19-CO_2CH_3), 3.70 (3H, s, 7-CO_2CH_3), 3.86 (3H, s, $-O(CO)_2OCH_3$), 5.04 (1H, br s, H17), 5.16 (1H, ddd, J=8.4, 8.1, 7.2 Hz, H11 overlapped), 5.19 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.2 (C20), 19.7 (C2), 21.3 (C18), 29.1 (CH_3CO_2–), 37.4 (C1), 40.4 (C3), 41.0 (C12), 43.5 (C14), 43.8 (C10), 44.4 (C15 and C4), 45.6 (C8), 50.5 (C6), 51.6, 51.8 (7- and 19-CO_2CH_3), 53.5 ($-O(CO)_2OCH_3$), 56.4 (C5), 60.6 (C9), 67.5 (C11), 86.2 (C13), 108.5 (C17), 150.4 (C16), 150.8, 158.0 ($-O(CO)_2OCH_3$), 169.7 (CH_3CO_2–), 174.4 (C7), 177.1 (C19). MS (EI) m/z 520 (M^+, 4%), 488 (6), 460 (8), 400 (100), 385 (25), 341 (17), 296 (17), 281 (9), 237 (22), 149 (11), 109 (12), 71 (22). HRMS (EI) m/z calcd for M^+, $C_{27}H_{36}O_{10}$: 520.2308; found: 520.2309.

To a solution of the oxalate (32 mg, 0.0615 mmol) in toluene (18 mL) at room temperature under nitrogen were added tributyltin hydride (35.5 μL, 0.135 mmol) and AIBN (10 mg, 0.0597 mmol). The mixture was degassed for 20 min and then heated to 80 °C for 3 h under nitrogen. The reaction mixture was concentrated to remove solvent and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:7→1:6) to afford the desired product (9.5 mg, 0.0227 mmol, 37%) as an oil, which was used directly in the next reaction.

To a solution of this product (8.5 mg, 0.020 mmol) in MeOH (5 mL) cooled at 0 °C was added 0.5 M K_2CO_3 (2.5 mL). After 30 min, the reaction mixture was warmed to room temperature and stirred for an additional 48 h, then concentrated to remove MeOH and water. The residue was quenched with saturated aq NH_4Cl solution (40 mL) and EtOAc (50 mL), and extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine (30 mL) and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (EtOAc/hexanes, 1:8) furnished the desired product **36** (3.5 mg, 0.009 mmol, 46%) as an oil. IR (Neat) ν_{max} (cm^{-1}): 3489, 3067, 2928, 2854, 1730, 1658. ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, s, H20), 1.11 (3H, s, H18), 0.68–2.42 (15H, m), 2.65 (1H, m, H5), 3.36 (1H, d, J=12.6 Hz, H6), 3.68 (3H, s, 19-CO_2CH_3), 3.69 (3H, s, 7-CO_2CH_3), 3.85 (1H, ddd, J=8.4, 8.1, 7.8 Hz, H11), 4.86 (1H, br s, H17), 4.98 (1H, br s, H′17). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.9 (C20), 19.7 (C2), 29.2 (C18), 37.5 (C1), 38.1 (C3), 39.0 (C13), 40.9 (C12), 42.6 (C14), 44.0 (C10), 44.4 (C15), 46.5 (C4), 49.2 (C8), 51.1 (C6), 51.45, 51.48 (7- and 19-CO_2CH_3), 56.4 (C5), 65.3 (C9), 65.8 (C11), 106.7 (C17), 156.5 (C16), 175.3 (C7), 177.7 (C19). MS (EI) m/z 376 (M^+, 15%), 344 (58), 316 (49), 298 (100), 283 (62), 257 (23), 239 (44), 197 (23), 159 (53), 119 (21), 105 (31), 91 (35). HRMS (EI) m/z calcd for M^+, $C_{22}H_{32}O_5$: 376.2250; found: 376.2248. GC–MS (TMS ether methyl ester) 448 (M^+, 2%), 416 (8), 388 (10), 373 (11), 345 (2), 341 (4), 326 (4), 299 (36), 298 (100), 283 (38), 267 (4), 239 (40), 223 (10), 207 (12), 197 (12), 183 (11), 167 (10), 157 (9), 143 (8), 129 (8), 105 (8), 91 (10); KRI 2549. Endogenous material: identical mass spectrum, KRI 2549.

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