EXPANSION OF RING B IN THE GIBBERELLINS: ENTRY TO THE RABDOSIA FAMILY OF KAURENOIDS

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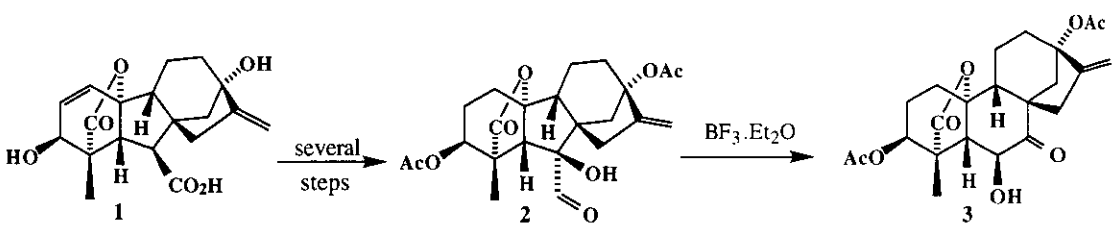
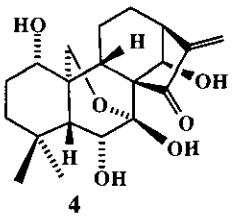
Abstract — The Lewis acid or base-catalysed rearrangement of an α-hydroxy-aldehyde derived from the gibberellin GA_{15} results in ring-expansion of the 5-membered B-ring of the gibberellin molecule and transformation into an *ent*-kaurene derivative. Further manipulation affords 19,7-acetals and access to the highly functionalised kaurenoid secondary metabolites that have been isolated from the genus *Rabdosia.*

Considerable effort has been invested in transforming kaurene derivatives into gibberellins (GAs) either by incubation with the fungus, *Gibberella fujikuroi*,[1] or by chemical means.[2-7] Most kaurenoids, however, are not as easily obtained as the more common GAs, especially gibberellic acid (GA_3) (**1**), which is available in abundance at modest cost. We have therefore been exploring the prospect of utilising (**1**) as a source of semi-synthetic kaurenoids and have recently prepared the 20-norkaurene derivative (**3**) from a sequence in which the key step was the rearrangement of hydroxy aldehyde (**2**) (Scheme 1).[8] A particularly attractive aspect of such a conversion is the opportunity to draw on the wealth of experience gained from the transformation of GA_3 (**1**) into an extensive range of other GAs.[2] The densely functionalised nature of these substrates was also expected to facilitate the preparation of the more complex kaurenoids that show interesting therapeutic potential.[9] Of special interest is the *Rabdosia* family of *seco*-B-ring diterpenes, many of which have antibacterial and antineoplastic properties, *e.g.* oridonin (**4**),[10] enmein (**5**)[11] and shikodonin (**6**).[12]



Scheme 1



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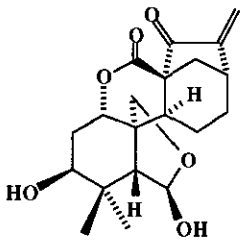

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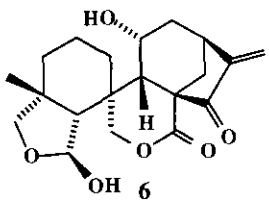

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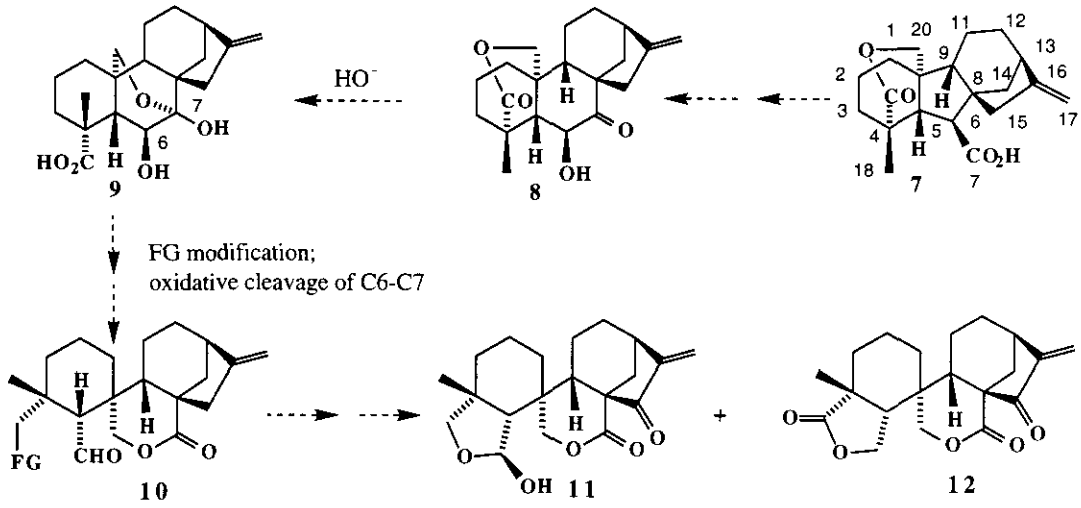
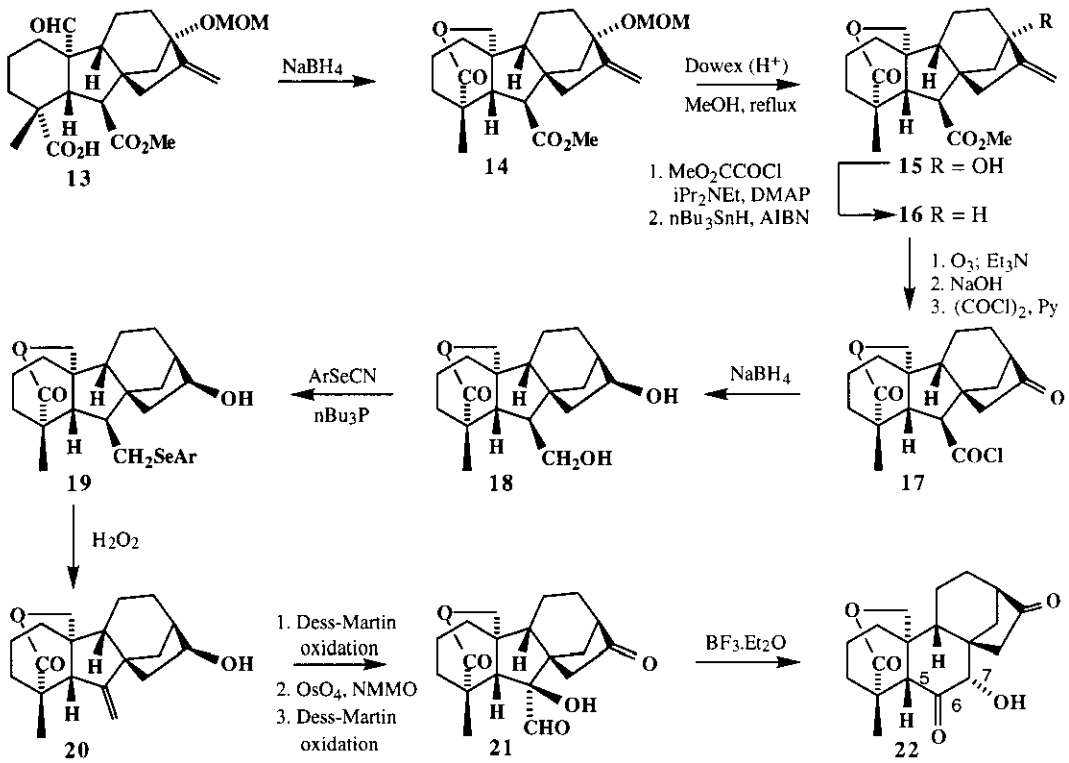
In this paper we describe our attempts to the transform the gibberellin, GA_{15} (**7**), into the hemiacetal (**9**) *via* ketol (**8**) as outlined in Scheme 2 with a view to preparing the *seco*-derivatives (**10**). This sequence was expected to give access to the kaurenoids macrocalyxoformin (**11**)[13] and longirabdolactone (**12**),[14] while serving as a model for the preparation, *inter alia*, of the more complex derivatives (**5**) and (**6**).



Scheme 2

The starting point for the present study was aldehyde (**13**) [available in 7 steps from **1**][15] which was converted into GA_{44} methyl ester (**15**)[16] and thence the methyl ester (**16**) of GA_{15} (**7**) by deoxygenation[17] at C-13 (Scheme 3). After ozonolysis of the 16-methylene group, the ester function was hydrolysed and the resulting keto acid reduced to diol (**18**) *via* the derived acyl chloride (**17**). Application of the Grieco procedure[18] resulted in selective reaction of the sterically less hindered primary 7-carbinol function to afford selenide (**19**) which underwent oxidative elimination to the 6-methylene derivative (**20**). Attempts to prepare the 6,7-diol from **20** by reaction with OsO_4 (*N*-methylmorpholine *N*-oxide as co-oxidant)[19] were unsatisfactory because of difficulties in isolating the resulting very polar triol, so **20** was oxidised[20] to the 16-ketone first, converted into the 6,7-diol and thence the hydroxy aldehyde (**21**). Ring expansion[21] by treatment with boron trifluoride etherate, as for **2** → **3** , proceeded smoothly, but instead of the expected 6-hydroxy-7-one being obtained, the isomeric 7α-hydroxy-6-one (**22**) was formed, as was

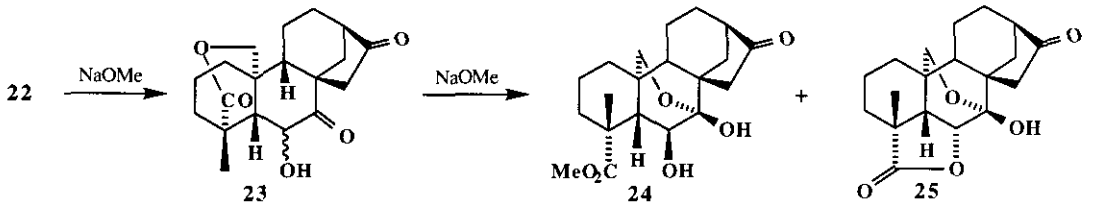
evident from the observation of singlets at δ 3.86, 3.49 and 2.25 for H-7, the 7-OH (hydrogen bonded) and H-5, respectively, in the ^{1}H-NMR spectrum of the product. Assuming a chair conformation for the B-ring, hydrogen bonding between the 6-carbonyl function and the 7-hydroxyl is consistent with an equatorial conformation and therefore 7α-stereochemistry for the latter group. No attempt was made to confirm this assignment, however, in view of the planned ketol isomerisation descibed below.



Scheme 3

The formation of ketol (**3**) from **2** has been rationalised earlier in terms of the 1,2-shift of the C5-C6 bond affording a chair-like transition state in preference to the alternative migration of the C8-C6 bond (which would have led to a boat conformation for the B-ring).[22] In the case of the C_{20} substrate, there is a strong steric repulsion between C20 and C11 which appears to be relieved more effectively by migration of the C8-C6 bond, whereas in **2**, the 10α-oxygen substituent has a smaller steric demand and is angled away from C11 because of the 19,10-γ-lactone bridge. Although ketol (**22**) does not allow direct formation of a 7,20-hemiacetal [*cf.* **8** → **9**], base catalysed isomerisation of **22** [23] and hydrolysis of the lactone function could be expected to afford access to acetal (**24**) *via* ketol (**23**). In the event, treatment of **22** with NaOMe (Scheme 4) afforded a 2:1 mixture of the acetals (**24**) and (**25**). Structure (**24**) was evident from NMR spectra, which indicated the presence of a methoxycarbonyl group (3H singlet at δ_H 3.70), a 6β-hydroxy substituent (doublet at δ_H 4.65, $J_{5,6}$ = 4.6 Hz) and the 7,20-hemiacetal structure (2H singlet at δ_H 3.87 and a quaternary carbon at δ_C 97.0; C-7 carbonyl group absent). The 7,20-hemiacetal structure in

25 was also evident from a resonance at δ_C 97.0 for C-7, although in this case the ^{1}H-NMR spectrum displayed an AB pattern for the H-20 protons [doublets at δ 3.75 and 3.94 (J = 10. 2 Hz)]. A doublet was again observed for H-6 (δ 4.63, J = 6.3 Hz), consistent with the 19,6α-lactone moiety.



Scheme 4

Lactone (**25**) appears to be the thermodynamically preferred product, since it was recovered unchanged from re-treatment with NaOMe. Moreover, if a large excess of NaOMe was used, **25** became the major product. A more direct and efficient route to **25** was available by treating aldehyde (**21**) with potassium hydride, however. Under these conditions, **25** was the only observed product.

It can be readily envisaged that further manipulation of acetals (**24**) and (**25**) should lead to the kaurenoids macrocalyxoformin (**11**) and longirabdolactone (**12**), while the basic strategy and methodology that has been established so far may be applied to the preparation of more complex derivatives such as shikodonin (**6**). Further studies towards these objectives are continuing.

EXPERIMENTAL SECTION

General methods: IR spectra (ν_{max}) were recorded on a Perkin-Elmer 683 spectrophotometer and NMR spectra on a Varian Gemini 300 spectrometer. For ^{1}H NMR spectra recorded in $CDCl_3$, the residual peak of $CHCl_3$ was used as the internal reference (7.25 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for ^{13}C NMR spectra. MS (70 eV) were recorded on a VG Autospec spectrometer. All reactions were conducted under an atmosphere of nitrogen. Flash chromatography was conducted using Merck Kieselgel 60. Note on nomenclature: Structures are named as derivatives of *ent*-gibberellane.[24] The α,β stereochemical descriptors in the body of the text describe structures as depicted; when preceded by *ent*, the descriptors are inverted.

***ent*-20-Hydroxy-13-methoxymethoxy-gibberell-16-ene-7,19-dioic acid 7-methyl ester 19,20-lactone (14).** To **13** (250 mg, 0.595 mmol) in dry, distilled dimethoxyethane (25 mL) at 0° C, was added $NaBH_4$ (68 mg, 1.78 mmol). The mixture was stirred at 0° C and allowed to warm slowly to rt over 4 h. AcOH (5 mL) was added and the mixture was stirred for a further 20 min, then diluted with AcOEt (35 mL). The mixture was washed with sat. $NaHCO_3$ (4x30 mL), sat. brine (1x30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude lactone. Purification was carried out by silica gel chromatography using AcOEt:hexane (1:3) as eluting solvent to give pure lactone (**14**) as a white crystalline compound (211 mg, 88%): Rf 0.39 (AcOEt:hexane, 1:2); mp 153-154 °C (ethyl acetate-hexane). IR (KBr disc) 1039, 1149, 1731 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, s, 4-

Me), 2.77 (1H, d, J = 12.6 Hz, H6), 3.37 (3H, s, 13-OCH_2OMe), 3.70 (3H, s, 7-CO_2Me), 4.09 (1H, d, J_{gem} = 12.3 Hz, 20-pro-*S*-H), 4.40 (1H, d, J_{gem} = 12.3 Hz, 20-pro-*R*-H), 4.54, 4.73 (2x1H, ABd, J = 7.1 Hz, 13-OCH_2OMe), 4.97 (1H, d, J = 3.0 Hz, H-17), 5.10 (1H, d, J = 3.0 Hz, H'-17). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.3 (C-11), 20.4 (C-2), 22.9 (C-18), 37.7 (C-1), 38.0 (C-3), 39.5 (C-14), 40.3 (C-12), 41.2 (C-10), 42.3 (C-4), 45.1 (C-15), 47.1 (C-8), 51.6 (C-6), 51.7 (7-CO_2Me), 52.8 (C-5), 55.0 (C-9), 55.1 (13-OCH_2OMe), 74.0 (C-20), 93.4 (C-13), 91.7 (13-OCH_2OMe), 107.2 (C-17), 153.1 (C-16), 173.0, 174.9 (C-7, C-19). MS (EI) *m/z* 404 (M^+, 100%), 389 (80), 373 (34), 359 (22), 344 (54), 331 (80), 313 (34), 299 (62), 285 (80), 271 (72), 255 (42), 243 (44), 225 (50), 211 (72), 179 (76). HRMS (EI) *m/z* calc'd for M^+ $C_{23}H_{32}O_6$: 404.2199; found: 404.2211. *Anal.* Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.31; H, 8.25.

***ent*-20-Hydroxy-13-methyloxalyl-gibberell-16-ene-7,19-dioic acid 7-methyl ester 19,20-lactone.** A solution of lactone (**14**) (180 mg, 0.427 mmol) in MeOH-H_2O (50 mL, 9:1) was treated with Dowex-50W resin (H^+) (200 mg) and heated under reflux for 3 h. The filtered solution was reduced to dryness and the residual 13-carbinol (**15**) dissolved in dry CH_2Cl_2 (15 mL). Diisopropylethylamine (447 µL, 2.56 mmol), dimethylaminopyridine (cat), and methyloxalyl chloride (236 µL, 2.56 mmol) were added and the mixture stirred at rt overnight. The mixture was diluted with AcOEt (30 mL), and washed with sat. $NaHCO_3$ (25 mL) and sat. brine (25 mL). The aq. washes were then extracted with AcOEt (15 mL), the combined organic phases dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was chromatographed on silica gel using AcOEt:hexane (1:2), to give the 13-oxalate as a white crystalline solid (171 mg, 90%): Rf 0.27 (AcOEt:hexane, 1:2); mp 195-197 °C (ethyl acetate-hexane). IR (KBr disc) 1162, 1206, 1724, 1747, 2938 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, s, 4-Me), 2.78 (1H, d, J = 12.6 Hz, H-6), 3.69 (3H, s, 7-CO_2Me), 3.87 (3H, s, 13-$O(CO)_2OMe$), 4.10 (1H, d, J_{gem} = 12.5 Hz, 20-pro-*S*-H), 4.39 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*R*-H), 5.02 (1H, br s, H-17), 5.23 (1H, br s, H'-17). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.6 (C-11), 20.5 (C-2), 23.1 (C-18), 35.8 (C-1), 38.2 (C-3), 39.4 (C-14), 39.6 (C-12), 41.4 (C-10), 42.5 (C-4), 43.8 (C-15), 48.3 (C-8), 51.4 (C-6), 51.9 (7-CO_2Me), 52.8 (C-5), 53.4 (13-$O(CO)_2OMe$), 54.9 (C-9), 73.9 (C-20), 87.4 (C-13), 108.6 (C-17), 151.5 (C-16), 156.2, 158.1 (2x-$O(CO)_2OMe$), 172.8, (C-7), 174.8 (C-19). MS (EI) *m/z* 446 (M^+, 100%), 415 (17), 400 (10), 386 (36), 341 (50), 310 (31), 282 (74), 237 (81). HRMS (EI) *m/z* calcd for M^+ $C_{24}H_{30}O_8$: 446.1941; found: 446.1944. *Anal.* Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.67; H, 7.05.

***ent*-20-Hydroxy-gibberell-16-ene-7,19-dioic acid 7-methyl ester 19,20-lactone (16).** A solution of the oxalate prepared above (170 mg, 0.381 mmol) in dry, degassed toluene (20 mL) was brought to reflux and tri-*n*-butyltin hydride (154 µL, 0.571 mmol) added, followed by AIBN (cat), and the mixture stirred at reflux for 3 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using hexane, then AcOEt:hexane (1:4), to give the 13-deoxy product (**16**) as a white solid (115 mg, 88%) and then starting oxalate (21 mg, 12%): Rf 0.74 (AcOEt:hexane, 1:1); mp 198 °C (ethyl acetate-hexane) (lit.[25] 198-200 °C). IR (KBr disc) 1727, 2935 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, s, 4-Me), 2.15 (1H, d, J = 12.9 Hz, H-5), 2.62 (1H, m, H-13), 2.75 (1H, d, J = 12.6 Hz, H-6), 3.67 (3H, s, 7-CO_2Me), 4.07 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*S*-H), 4.39 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*R*-H), 4.79 (1H, br s, H-17), 4.92 (1H, br s, H'-17). ^{13}C-NMR (75 MHz, $CDCl_3$): δ

15.8 (C-11), 20.6 (C-2), 23.2 (C-18), 31.3 (C-12), 36.3 (C-1), 38.2 (C-3), 39.2 (C-13), 39.8 (C-14), 41.7 (C-10), 42.5 (C-4), 46.0 (C-15), 49.6 (C-8), 51.7 (7-CO_2Me), 51.9 (C-6), 52.4 (C-5), 55.6 (C-9), 74.3 (C-20), 106.5 (C-17), 156.6 (C-16), 173.5, (C-7), 175.2 (C-19). MS (EI) *m/z* 344 (M^+, 4%), 312 (28), 298 (20), 284 (71), 239 (100), 195 (29), 155 (15), 129 (15). HRMS (EI) *m/z* calcd for M^+ $C_{21}H_{28}O_4$: 344.1988; found: 344.1986. *Anal.* Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.91; H, 8.50.

***ent*-20-Hydroxy-16-oxo-17-norgibberellane-7,19-dioic acid 7-methyl ester 19,20-lactone.** Ozone was bubbled through a solution of lactone (**16**), (70 mg, 0.203 mmol) in CH_2Cl_2-MeOH (12 mL, 3:1) at -78 °C for 40 sec. The solvent was removed by bubbling nitrogen through the solution, the residue taken up in CH_2Cl_2 (12 mL) and triethylamine (113 µL, 0.813 mmol) added. The mixture was stirred for 20 h at rt then the solvent removed under reduced pressure and the residue chromatographed on silica gel using AcOEt:hexane (1:2, 1:1), to give the norketone as a white solid (55 mg, 78%): Rf 0.35 (AcOEt:hexane, 1:1); mp 175-176 °C (ethyl acetate-hexane). IR (KBr disc) 1727, 2933 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, s, 4-Me), 2.14 (1H, d, J = 12.7 Hz, H-5), 2.42 (1H, m, H-13), 2.79 (1H, d, J = 12.8 Hz, H-6), 3.69 (3H, s, 7-CO_2Me), 4.12 (1H, d, J_{gem} = 11.9 Hz, 20-pro-*S*-H), 4.43 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.6 (C-11), 20.4 (C-2), 23.0 (C-18), 24.3 (C-12), 34.0 (C-1), 38.1 (C-3), 39.6 (C-14), 41.8 (C-10), 42.4 (C-4), 44.6 (C-13), 48.2 (C-8), 51.9 (C-15, 7-CO_2Me overlapped), 52.5 (C-5), 52.8 (C-6), 55.9 (C-9), 73.8 (C-20), 172.9, (C-7), 174.7 (C-19), 219.6 (C-16). MS (EI) *m/z* 346 (M^+, 100%), 318 (78), 300 (13), 286 (58), 273 (37), 258 (41), 241 (52), 227 (33), 213 (43), 201 (52), 187 (54), 145 (49). HRMS (EI) *m/z* calcd for M^+ $C_{20}H_{26}O_5$: 346.1780; found: 346.1787. *Anal.* Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 68.90; H, 7.50.

***ent*-20-Hydroxy-16-oxo-17-norgibberellane-7,19-dioic acid 19,20-lactone.** The methyl ester prepared above (102 mg, 0.294 mmol) in MeOH (450 µL) and 2M NaOH (5.6 mL), was heated at reflux for 7 h. The solvent was removed under reduced pressure and the residue taken up in MeOH (80 mL). The mixture was then acidified with Dowex 50W (H^+) resin to pH 3-4, with cooling. The resin was filtered off and the solvent removed under reduced pressure to give the title acid as a white solid, (92 mg, 94 %): Rf 0.13 (AcOEt:hexane:MeOH:AcOH, 100:100:1:1); mp 264 °C (ethyl acetate-hexane). IR (KBr disc) 1158, 1704, 1739 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, s, 4-Me), 2.12 (1H, d, J = 12.8 Hz, H-5), 2.48 (1H, m, H-13), 2.83 (1H, d, J = 12.8 Hz, H-6), 4.15 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*S*-H), 4.45 (1H, d, J_{gem} = 12.2 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.6 (C-11), 20.4 (C-2), 23.0 (C-18), 24.3 (C-12), 34.0 (C-1), 38.1 (C-3), 39.7 (C-14), 41.9 (C-10), 42.5 (C-4), 44.7 (C-13), 48.2 (C-8), 51.9 (C-15), 52.4 (C-5), 52.6 (C-6), 55.9 (C-9), 73.9 (C-20), 175.1 (C-19), 176.5 (C-7), 220.4 (C-16). MS (EI) *m/z* 332 (M^+, 100%), 314 (6), 304 (43), 286 (87), 273 (26), 258 (43), 245 (38), 229 (17), 215 (18), 201 (35), 187 (25), 159 (22), 145 (29). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{24}O_5$: 332.1624; found: 332.1628.

***ent*-20-Hydroxy-16-oxo-17-norgibberellane-7,19-dioic acid 19,20-lactone 7-acyl chloride (17).** A solution of the acid prepared above (100 mg, 0.301 mmol) in dry THF (2 mL) containing pyridine (365 µL, 4.51 mmol) was added *via* cannular to oxalyl chloride (262 µL, 3.01 mmol) in dry THF (5 mL) at -40 °C. The solution was allowed to warm to rt, and stirred for 5 h. The reaction mixture was filtered

through a sintered funnel and washed into a dry flask with dry benzene. Residual oxalyl chloride was removed by azeotroping with benzene (4x10 mL) and the residue was filtered through a plug of celite into a dry flask. The solvent was removed under reduced pressure to give the acid chloride (**17**) (118 mg, ~100%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, s, 4-Me), 2.04 (1H, d, J = 12.1 Hz, H-5), 2.51 (1H, m, H-13), 3.32 (1H, d, J = 12.1 Hz, H-6), 4.16 (1H, d, J_{gem} = 11.8 Hz, 20-pro-*S*-H), 4.42 (1H, d, J_{gem} = 12.1 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7 (C-11), 20.3 (C-2), 24.0 (C-18), 24.3 (C-12), 33.9 (C-1), 38.0 (C-3), 39.5 (C-14), 41.6 (C-10), 42.5 (C-4), 44.6 (C-13), 48.9 (C-8), 51.1 (C-15), 53.6 (C-5), 56.4 (C-9), 64.4 (C-6), 73.4 (C-20), 174.0 (C-7), 174.2 (C-19), 217.9 (C-16). MS (EI) *m/z* 350 (M^+, 100%), 332 (3), 315 (69), 286 (79), 273 (48), 259 (53), 243 (53), 229 (47), 213 (23), 199 (38), 187 (40), 159 (27). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{23}O_4Cl$: 350.1285; found: 350.1287.

***ent*-7,16α,20-Trihydroxy-17-norgibberellan-19-oic acid 19,20-lactone (18).** To the above acid chloride **17** (0.301 mmol) in dry, distilled dimethoxyethane (6 mL) at 0 °C, was added $NaBH_4$ (57 mg, 1.51 mmol). The mixture was stirred at 0 °C and allowed to warm slowly to rt overnight. AcOH (20 drops) was added and the mixture was stirred for a further 20 min, then diluted with AcOEt (15 mL). The mixture was washed with sat. $NaHCO_3$ (4x8 mL), sat. brine (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude alcohol, then silica gel chromatography using AcOEt:hexane, 1:1 as the eluting solvent gave pure diol (**18**) as a white crystalline compound (80 mg, 82%): Rf 0.21 (AcOEt:hexane:MeOH:AcOH, 66:33:1:1); mp 249 °C (ethyl acetate-hexane). IR (KBr disc) 1159, 1724, 1738, 2937, 3412, 3521 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, s, 4-Me), 1.94 (1H, d, J = 11.6 Hz, H-5), 2.18 (1H, m, H-13), 2.37 (1H, dd, J_1 = 11.6 Hz, J_2 = 12.3 Hz, H-6), 3.16 (1H, br s, 7-OH), 3.69 (1H, m, H-7), 3.84 (1H, m, H'-7), 3.98 (1H, d, J_{gem} = 12.0 Hz, 20-pro-*S*-H), 4.17 (1H, m, H-16), 4.40 (1H, d, J_{gem} = 12.0 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.9 (C-11), 17.4 (C-2), 20.4 (C-12), 23.8 (C-18), 35.7 (C-1), 36.6 (C-13), 38.4 (C-3), 40.9 (C-14), 41.4 (C-10), 42.6 (C-4), 44.5 (C-15), 48.7 (C-8), 49.1 (C-5), 50.9 (C-6), 58.9 (C-9), 61.0 (C-7), 72.0 (C-16), 74.9 (C-20), 177.1 (C-19). MS (EI) *m/z* 320 (M^+, 4%), 32 (16), 284 (100), 272 (8), 257 (19), 244 (36), 225 (37), 213 (37), 199 (24), 185 (16), 143 (22). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{28}O_4$: 320.1988; found: 320.1986. *Anal.* Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.84; H, 8.66.

***ent*-16α,20-Dihydroxy-7-(2'-nitrophenylselenenyl)-17-norgibberellan-19-oic acid 19,20-lactone (19).** To diol (**18**) (150 mg, 0.462 mmol) in THF (20 mL), was added *o*-nitrophenyl selenocyanate (1.05 g, 4.62 mmol), followed by the dropwise addition of *n*-tributylphosphine (1.15 mL, 4.62 mmol) at rt. The resulting mixture was stirred for 1 h, after which time, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (AcOEt:hexane:MeOH:AcOH, 100:100:1:1) to give the *o*-nitrophenylselenide (**19**) (210 mg, 90%) as dark orange crystals: Rf 0.43 (AcOEt:hexane:MeOH:HOAc, 66:33:1:1); mp 197-199 °C (ethyl acetate-hexane). IR (KBr disc) 1019, 1037, 1090, 1717, 2872, 2914, 2928, 2961 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.42 (3H, s, 4-Me), 2.23 (2x1H, m, H-5, H-6 overlapped), 2.47 (1H, dd, J_{gem} = 13.5 Hz, $J_{15,16}$ = 7.7 Hz, H-15β), 2.83 (1H, m, H-7), 3.50 (1H, m, H'-7), 4.02 (1H, d, J_{gem} = 12.1 Hz, 20-pro-S-H), 4.30 (1H, m, H-16), 4.42 (1H, d, J_{gem} = 12.1 Hz, 20-pro-*R*-H), 7.31 (1H, dd, J_1 = 7.0 Hz, J_2 = 8.3 Hz, H-4'), 7.42 (1H, d, J =

7.0 Hz, H-6'), 7.54 (1H, dd J_1 = 6.8 Hz, J_2 = 8.3 Hz, H-5'), 8.26 (1H, d, J = 6.9 Hz, H-3'). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.1 (C-11), 17.3 (C-2), 20.4 (C-12), 25.3 (C-18), 28.8 (C-7), 36.8 (C-1), 37.1 (C-13), 38.8 (C-3), 41.5 (C-14), 41.9 (C-10), 43.0 (C-4), 44.4 (C-15), 46.3 (C-5), 49.5 (C-8), 56.4 (C-9), 59.5 (C-6), 72.0 (C-16), 74.4 (C-20), 125.5 (4'), 126.3 (C-3'), 128.9 (C-6'), 133.1 (C-1'), 133.8 (C-5'), 146.7 (C-2'), 175.6 (C-19). MS (EI) *m/z* 505 (M^+, ^{80}Se, 91%), 503 (M^+, ^{78}Se, 54%), 488 (43), 486 (22), 429 (8), 382 (2), 303 (13), 285 (28), 257 (51), 227 (37). HRMS (EI) *m/z* calcd for M^+ $C_{25}H_{31}NO_5{}^{80}Se$: 505.1367; found: 505.1386. *Anal.* Calcd for $C_{25}H_{31}NO_5Se$: C, 59.52; H, 6.19; N, 2.78. Found: C, 59.32; H, 6.11; N, 2.70.

***ent*-16α,20-Dihydroxy-17-norgibberell-6-en-19-oic acid 19,20-lactone (20).** A solution of (**19**) (210 mg, 0.417 mmol) in THF (40 mL) containing 30% hydrogen peroxide (473 μL, 4.17 mmol), was stirred at 0 °C for 1.5 h, and then allowed to warm to rt over 10.5 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using AcOEt:hexane (1:2) to give the alkene (**20**) as a clear oil (98 mg, 78%). Crystallisation from CH_2Cl_2/hexane gave a white solid: Rf 0.31 (AcOEt:hexane, 1:1); mp 161 °C (ethyl acetate-hexane). IR (KBr disc) 1158, 1166, 1702, 2920, 2939, 3480 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, s, 4-Me), 2.18 (1H, s, H-5), 2.37 (1H, m, H-13), 3.92 (1H, d, J_{gem} = 11.7 Hz, 20-pro-*S*-H), 4.19 (1H, d, J_{gem} = 11.5 Hz, 20-pro-*R*-H), 4.35 (1H, m, H-16), 4.91 (1H, d, J = 2.3 Hz, H-7), 5.03 (1H, d, J = 2.3 Hz, H'-7). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.2 (C-11), 17.8 (C-2), 20.3 (C-12), 23.0 (C-18), 33.5 (C-1), 37.2 (C-3), 37.4 (C-13), 40.5 (C-14), 53.3 (C-15), 41.5, 41.8 (C-4, C-10) 49.3 (C-8), 55.2 (C-9), 57.0 (C-5), 72.3 (C-16), 74.6 (C-20), 104.4 (C-7), 156.0 (C-6), 175.9 (C-19). MS (EI) *m/z* 302 (M^+, 55%), 284 (36), 260 (16), 244 (100), 226 (30), 212 (23), 199 (34), 186 (35), 152 (34). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{26}O_3$: 302.1882; found: 302.1883.

***ent*-20-Hydroxy-16-oxo-17-norgibberell-6-en-19-oic acid 19,20-lactone.** A solution of (**20**) (68 mg, 0.225 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin reagent[20] (143 mg, 0.338 mmol), and stirred for 3 h. The solution was diluted with AcOEt (20 mL), and $Na_2S_2O_3$ (1 g) dissolved in sat. $NaHCO_3$ (5 mL) was added to the mixture, which was stirred for further 30 min. The organic phase was separated and washed with sat. $NaHCO_3$ (15 mL), water (15 mL), sat. brine (15 mL), then dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was chromatographed on silica gel using AcOEt:hexane (1:1), to give the 16-one as a white crystalline solid (60 mg, 89%): Rf 0.27 (AcOEt:hexane, 1:1); mp 165° C (polymorphic change), then 192-194 °C (ethyl acetate-hexane). IR (KBr disc) 1148, 1725, 1737, 2939 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.44 (3H, s, 4-Me), 2.10 (1H, d, J = 17.5 Hz, H-15), 2.20 (1H, s, H-5), 2.27 (1H, dd, J = 17.5, 3.4 Hz, H'-15), 2.48 (1H, dd, J = 10.0, 5.0 Hz, H-13), 3.98 (1H, d, J_{gem} = 11.5 Hz, 20-pro-*S*-H), 4.25 (1H, d, J_{gem} = 11.6 Hz, 20-pro-*R*-H), 5.05 (1H, s, H-7), 5.15 (1H, s, H'-7). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.6 (C-11), 20.2 (C-2), 22.9 (C-18), 24.9 (C-12), 31.9 (C-1), 37.0 (C-3), 40.4 (C-14), 41.4, 41.9 (C-4, C-10), 44.7 (C-13), 47.6 (C-8), 54.6, 54.9 (C-5, C-9), 56.1 (C-15), 74.3 (C-20), 105.8 (C-7), 154.0 (C-6), 175.2 (C-19), 220.7 (C-16). MS (EI) *m/z* 300 (M^+, 100%), 282 (6), 272 (21), 258 (28), 242 (84), 227 (25), 213 (22), 199 (43), 185 (27), 151 (55). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{24}O_3$: 300.1725; found: 300.1725.

***ent*-6α,7,20-Trihydroxy-16-oxo-17-norgibberellan-19-oic acid 19,20-lactone.** To a solution of the olefin prepared above (60 mg, 0.20 mmol) in acetone/water (6 mL, 5:1), was added *N*-methyl morpholine-*N*-oxide (117 mg, 1.00 mmol), and OsO_4 (cat) dissolved in *t*-BuOH (100 μL), and the mixture stirred at 40 °C for 4 weeks. $NaHSO_3$ (10 mg) was added to the mixture, which was diluted with water (4 mL) and stirred for 30 min. The mixture was extracted with AcOEt (2x10 mL), and the combined organic phases were washed with water (12 mL), sat. brine (12 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was chromatographed on silica gel using AcOEt:hexane (2:1), to give the 6β,7-diol (51 mg, 76%) as a white solid, plus some starting alkene (5 mg, 8%): Rf 0.36 (AcOEt:hexane, 2:1); mp 197-198 °C (ethyl acetate-hexane). IR (KBr disc) 1144, 1708, 1727, 1743, 2948 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, s, 4-Me), 1.92 (1H, s, H-5), 2.45 (1H, m, H-13), 2.48 (1H, d, J = 16.8 Hz, H-15), 3.65 (2H, br s, 6-OH, 7-OH), 3.76, 3.85 (2x1H, ABd, J = 10.1 Hz, H-7, H'-7), 4.11 (1H, d, J_{gem} = 11.9 Hz, 20-pro-*S*-H), 4.43 (1H, d, J_{gem} = 12.5 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7 (C-11), 20.3 (C-2), 22.5 (C-18), 24.7 (C-12), 29.7 (C-1), 38.1 (C-3), 40.9, 41.46 (C-4, C10), 41.0 (C-14), 45.1 (C-13), 52.5 (C-8), 53.1 (C-15), 56.0 (C-9), 58.6 (C-5), 63.7 (C-7), 75.6 (C-20), 80.9 (C-6), 176.9 (C-19), 222.4 (C-16). MS (EI) *m/z* 334 (M^+, 1%), 316 (1), 303 (100), 286 (8), 257 (47), 239 (24). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{26}O_5$: 334.1780; found: 334.1781. *Anal.* Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.83; H, 8.03.

***ent*-6α,20-Dihydroxy-7,16-dioxo-17-norgibberellan-19-oic acid 19,20-lactone (21).** A solution of the diol prepared above (40 mg, 0.120 mmol) in CH_2Cl_2 (8 mL) was treated with Dess-Martin reagent[20] (76 mg, 0.180 mmol), and stirred overnight. The solution was diluted with AcOEt (15 mL), and $Na_2S_2O_3$ (1 g) dissolved in sat. $NaHCO_3$ (5 mL) was added to the mixture, which was then stirred for 30 min. The organic phase was separated and washed with sat. $NaHCO_3$ (8 mL), water (8 mL), sat. brine (8 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was chromatographed on silica gel using AcOEt:hexane (1:1), to give the hydroxy aldehyde (**21**) as a white crystalline solid (35 mg, 89%), Rf 0.36 (AcOEt:hexane, 1:2); mp 160-163 °C (ethyl acetate-hexane). IR (film) 1038, 1155, 1705, 1727, 3403 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ1.15 (3H, s, 4-Me), 2.07 (1H, s, H-5), 2.46 (1H, m, H-13), 2.53 (1H, d, J = 18.1 Hz, H-15), 4.20 (1H, br s, 6-OH), 4.33 (1H, d, J_{gem} = 12.9 Hz, 20-pro-*S*-H), 4.66 (1H, d, J_{gem} = 12.9 Hz, 20-pro-*R*-H), 9.83 (1H, s, H-7). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7 (C-11), 20.4 (C-2), 21.7 (C-18), 24.0 (C-12), 29.6 (C-1), 39.1, 40.8 (C-4, C-10), 40.4 (C-3), 41.2 (C-14), 44.7 (C-13), 51.3 (C-15), 53.0 (C-8), 55.5 (C-9), 60.4 (C-5), 74.9 (C-20), 87.2 (C-6), 174.1 (C-19), 201.9 (C-7), 219.1 (C-16). MS (EI) *m/z* 332 (M^+, 19%), 314 (17), 303 (100), 286 (10), 275 (40), 257 (65), 245 (48), 229 (22). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{24}O_5$: 332.1624; found: 332.1639.

***ent*-7α,20-Dihydroxy-6,16-dioxo-17-norkauran-19-oic acid 19,20-lactone (22).** To the hydroxy aldehyde (**21**) (5 mg, 0.0151 mmol) in dry CH_2Cl_2 (1 mL), was added boron trifluoride etherate (2.5 μL, 0.020 mmol), and the mixture was stirred at rt for 30 min. The mixture was diluted with AcOEt (5 mL), washed with water (2 mL), sat. brine (2 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure to give the ketol (**22**) as a white solid (5 mg, 100%): Rf 0.23 (AcOEt:hexane, 1:2); mp 186-187 °C (ethyl acetate-hexane). IR ($CHCl_3$) 3400 - 3100, 1730 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$):

δ1.27 (3H, s, H18), 2.26 (1H, s, H-5), 3.49 (1H, s, 7-OH), 3.86 (1H, s, H-7), 4.14 (1H, d, J_{gem} = 12.1 Hz, 20-pro-*S*-H), 4.83 (1H, d, J_{gem} = 12.1 Hz, 20-pro-*R*-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.6 (C-11), 20.4 (C-2), 22.4 (C-18), 28.4 (C-12), 29.6 (C-3), 35.1 (C-3), 39.0 (C-14), 40.0 (C-10), 43.6 (C-13), 45.0 (C-4), 46.1 (C-9), 51.4 (C-15), 51.6 (C-8), 55.3 (C-5), 73.4 (C-20), 82.5 (C-6), 174.7 (C-19), 210.5 (C-7), 218.5 (C-16). MS (EI) *m/z* 332 (M^+, 36%), 314 (16), 304 (25), 286 (22), 275 (100), 258 (29), 243 (24), 231 (22), 149 (56). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{24}O_5$: 332.1624; found: 332.1636.

Base-catalysed rearrangement of ketol 22. Ketol (**22**) (30 mg, 0.09 mmol) was treated with a degassed solution of NaOMe (prepared from 0.05g cleaned sodium metal, 20 mmol) in methanol (3 mL). The resulting solution was stirred for 20 h and the solvent removed under reduced pressure. The residue was partitioned between 1M HCl and AcOEt. The aq. layer was extracted further with AcOEt and the combined organic layers were washed with water (to pH 5; back extracted with AcOEt), brine, dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in CH_2Cl_2 and added to an excess of ethereal diazomethane at 0 °C. After 30 min, the residual diazomethane was removed with a stream of nitrogen and the solvent evaporated. The residue was purified by chromatography on silica gel with AcOEt:hexane (4.5:5.5) to elute **25** as a colourless gum (5.4 mg, 18%), increasing to AcOEt:hexane (3:2) to elute **24** as a colourless gum (13.6 mg, 42%). Treatment of **22** (25 mg, 0.07 mmol) as above with *ca.* 5x the amount of NaOMe yielded **25** (14.6 mg, 53%) and **24** (8.7 mg, 32%).

Methyl *ent*-6α,7α-dihydroxy-7β,20-epoxy-16-oxo-17-norkauran-19-oate (24): IR ($CHCl_3$) 3500 - 3150, 1730 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, s, 4-Me), 1.88 (1 H, dd, *J* = 12.1 Hz, *J* = 4 Hz, H-14), 3.70 (3H, s, OMe), 3.87 (2 H, s, H-20), 4.65 (1H, d, *J* = 4.6 Hz, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.5 (C-11), 19.7 (C-2), 24.0 (C-12), 27.2 (C-14), 28.0 (C-18), 29.5 (C-1), 36.1 (C-10), 37.3 (C-3), 42.1 (C-13), 44.9 (C-4), 45.9 (C-8), 50.9 (C-15), 51.9 (OMe), 52.2 (C-5), 58.7 (C-9), 65.2 (C-20), 73.0 (C-6), 97.0 (C-7), 177.5 (C-19), 223.0 (C-16), MS (EI) *m/z* 364 (M^+, 47%), 332 (100), 314 (31), 286 (29), 273 (56), 258 (37), 239 (47), 149 (54), 119 (37), 105 (60), 91 (97), 79 (78), 67 (55), 3650 - 3100, 1725. HRMS (EI) *m/z* calcd for M^+ $C_{20}H_{28}O_6$: 364.188589; found: 364.188246.

***ent*-6β,7α,-Dihydroxy-7β,20-epoxy-16-oxo-17-norkauran-19-oic acid 6,19-lactone (25)**: IR ($CHCl_3$) 3500 - 3200, 1750, 1720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, s, 4-Me), 3.75 (1H, dd, *J* = 10.2, 1.7 Hz, H-20), 3.94 (1H, d, *J* = 10.2 Hz, H-20), 4.63 (1H, d, *J* = 6.3 Hz, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.5 (C-11), 17.7 (C-2), 25.7 (C-12), 27.3 (C-14), 27.9 (C-18), 29.55 (C-3), 29.6 (C-1), 33.6 (C-10), 40.4 (C-4), 42.6 (C-13), 46.2 (C-8), 49.7 (C-5), 50.1 (C-15), 52.9 (C-9), 65.2 (C-20), 78.2 (C-6), 94.5 (C-7), 1180.3 (C-19), 221.3 (C-16). MS (EI) *m/z* 332 (M^+, 42%), 288 (29), 2261 (100), 243 (17), 107 (17), 93 (34), 79 (29). HRMS (EI) *m/z* calcd for M^+ $C_{19}H_{24}O_5$: 332.162374; found: 332.162138.

Base-catalysed rearrangement of hydroxy aldehyde (21). Hydroxy aldehyde (**21**) (4 mg, 0.012 mmol) was dissolved in dry THF (0.25 mL) and added to a suspension of washed KH (from 1.5 mg of 35% dispersion in mineral oil) in THF (0.1 µL) at 0 °C. The mixture was stirred at rt for 30 min, then poured into a two phase mixture of AcOEt and sat. NH_4Cl. The organic layer was separated, the aq. layer extracted with further AcOEt and the combined organic layers washed with brine, dried (Na_2SO_4) and evaporated to dryness. The ^{1}H-NMR spectrum of the product showed that only **25** had been formed.

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