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GIBBERELLINS—LXXXIX[1]

SYNTHESIS OF GIBBERELLIN A_{55} AND A_{57} AS WELL AS 1-OXYGENATED GIBBERELLIN A_5 AND A_{20} ANALOGUES—A NEW PRINCIPLE FOR THE REGIOSELECTIVE TRANSPOSITION OF AN ALLYLIC ALCOHOL FUNCTION[2]

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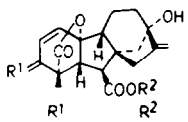
Abstract—The synthesis of a series of 1-oxygenated gibberellins starting from GA_3 (**1**) is described. Nucleophilic addition of hydrazoic acid to 3-dehydro GA_3 (**2**) was followed by $NaBH_4$ reduction of the resulting 1-azido-3-ketones **4** and **5** to the corresponding azido alcohols **8–10**, and photolysis of the latter compounds to instable 1-imines which were smoothly hydrolysed to the 1-oxo-3-hydroxy gibberellins **13** and **14**. Subsequent $NaBH_4$ reduction led to GA_{57} (**19**) and GA_{55} (**20**) and their 3-epimers, **17** and **18** respectively. In further steps 1-oxo-GA_5 (**21**), 1α- and 1β-hydroxy-GA_5 (**23** and **24**), 1-oxo-GA_{20} (**25**) as well as 1α- and 1β-hydroxy-GA_{20} (**26** and **27**) were available. The structures of the synthesized gibberellins were determined by physical data, in regard to the stereochemistry at C-1 and C-3 especially on the basis of ^{1}H NMR and ORD measurements.

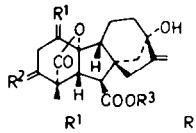
Up till now 59 native gibberellins are known[3,4]† which have yielded (together with many chemically modified analogues) important informations concerning structure-activity relationships of this class of diterpenoid phytohormones.[5] Continuing earlier systematic studies in this field,[6,7] we now report reaction sequences starting from the easily accessible GA_3 (**1**) and leading to a series of 1-oxygenated[8] gibberellins among them the scarce hormones GA_{55} (**20**) and GA_{57} (**19**) as well as 1-oxo and 1-hydroxy GA_5 and GA_{20} analogues.

First in our reaction pathway for the introduction of an oxygen function at position 1 was the smooth nucleophilic addition of hydrazoic acid to the Δ^1-enone bond of 3-dehydro GA_3 (**2**), readily available upon oxidation of GA_3 (**1**) with Attenburrow-MnO_2,[9] giving a 1:2.8 mixture of both 1-epimeric 1-azido ketones **4** and **5** with azide IR absorption at λ_{max} 2103 and 2132 cm^{-1} and a typical positive carbonyl cotton effect at 286 nm were obtained which could not be separated because of a strong tendency to re-elimination, giving back **2**. The configurational assignment at the newly created asymmetric centre C-1 in the mixture followed from ^{1}H-NMR data. Thus, in the 1α-azido compound **4** the double doublet of the axial C-1 methine proton at (δ) ppm 4.45 (X part of the ABX-system) shows $J_{AX} + J_{BX} = 11$ Hz whereas the corresponding 1β main epimer **5** with an equatorial C-1 methine proton exhibits the expected smaller value ($J_{AX} + J_{BX} = 8$ Hz)[10] for the corresponding signal at

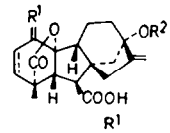
†Note added in proof. In the meantime the gibberellins A_{60}, A_{61} and A_{62} were described, whereas GA_{60} is identical with compound **27** synthesized in this paper. See P. S. Kirkwood and J. MacMillan, *J. Chem. Soc.* Perkin I 689 (1982).



	R^1	R^2
1	H, β-OH	H
2	O	H
3	O	CH_3



	R^1	R^2	R^3
4	H, α $-N_3$	O	H
5	H, β $-N_3$	O	H
6	H, α $-N_3$	O	CH_3
7	H, β $-N_3$	O	CH_3
8	H, α $-N_3$	H, α $-$OH	H
9	H, β $-N_3$	H, α $-$OH	H
10	H, β $-N_3$	H, β $-$OH	H
11	H, β $-N_3$	H, α $-$OH	CH_3
12	H, β $-N_3$	H, β $-$OH	CH_3
13	O	H, α $-$OH	H
14	O	H, β $-$OH	H
15	O	H, β $-$OH	CH_3
16	NOH	H, β $-$OH	H
17	H, α-OH	H, α $-$OH	H
18	H, β-OH	H, α $-$OH	H
19	H, α-OH	H, β $-$OH	H
20	H, β-OH	H, β $-$OH	H



	R^1	R^2
21	Δ^2 O	H
22	Δ^2 O	Ac
23	Δ^2 H, α-OH	H
24	Δ^2 H, β-OH	H
25	O	H
26	H, α-OH	H
27	H, β-OH	H

(δ) ppm 4.71. Similar the methyl ester **3** reacted to the epimeric azido keto esters **6** and **7** in a 1:1.8 ratio. The crude mixture of **4** and **5** was reduced directly with $NaBH_4$ leading to the crystalline epimeric azido alcohols **8–10**, obtained after chromatographic separation in 24, 23 and 40% yield, respectively. Their configurations at C-1 and 3 were deduced from the chemical shifts and coupling pattern of the 1-, 3- and 5-proton signals in the ^{1}H-NMR spectra. Thus, in both azido-alcohols **9** and **10** the C-1 methine protons appear as double doublets at (δ) ppm 4.17 and 4.08 with $J_{AX}+J_{BX}$ values of 8 and 7 Hz, respectively, due to equatorial–equatorial and equatorial–axial interactions[11] with both protons at C-2. Therefore, **9** and **10** could be regarded as 1β-epimers. On the other hand the 3-methine protons are present as double doublets with the striking different $J_{AX}+J_{BX}$ values of 18 and 7 Hz at (δ) ppm 3.79 and 3.76, respectively, indicating 3α- and 3β-stereochemistry of **9** and **10**. Similar typical coupling patterns were found earlier for the 3-epimers GA_1 and epi-GA_1.[12] The different stereochemistry at C-3 effects furthermore dramatically the chemical shift of the C-5 proton.[13] Thus, in **9** the 5-proton doublet appears at 2.69 (J = 10 Hz) whereas the corresponding signal of the 3β-hydroxy epimer **10** is found downfield, shifted to 3.52 by virtue of diaxial deshielding. In agreement with a 1α,3α-configuration of the third epimeric azido alcohol **8** for the 1- and 3-methine proton signals $J_{AX}+J_{BX}$ = 15 and 22 Hz, respectively, are observed and the 5-proton doublet appears high field shifted at (δ) ppm 2.70. The fourth theoretically possible epimer with 1α,3β-stereochemistry could be detected in the $NaBH_4$ reduction product of **4** + **5** only in traces.

In the next step of our reaction sequence the azido group in **8–10** was transformed to an oxo function via azide photolysis. Thus, UV-irradiation (λ = 254 nm) of the 1β,3β-azido alcohol **10** in THF or CH_2Cl_2 gave under loss of nitrogen the corresponding instable 1-imino compound[14] which underwent smoothly hydrolysis to 1-oxo GA_1 **14**. Under similar conditions both 1-stereoisomeric 3α-hydroxy azides **8** and **9** as well as the methyl ester **12** were transformed to 1-oxo-3-epi-GA_1 (**13**) and its methyl ester **15**, respectively. In agreement with the above mentioned NMR assignment for the starting azido alcohols **8–10** at C-3 the 3α-hydroxy ketone **13** exhibits a smaller carbonyl Cotton effect (a = −36) than its 3β-epimer **14** (a = −52) as expected from the octant rule (Fig. 1). Ketone **14** was furthermore characterized by its oxime **16**.

$NaBH_4$ reduction of the 3β-hydroxy ketone **14** afforded in 62% yield a 7:1 ratio of 1α- and 1β-hydroxy-GA_1 (**19** and **20**), isolated from Murofushi *et al.*[15] as the metabolites GA_{57} and GA_{55} from the culture broth of *Gibberella fujikuroi*. In a similar manner from the 3α-hydroxy ketone **13** a 1:1.6 ratio of 3-epi GA_{57} and 3-epi GA_{55} (**17** and **18**) was obtained in 88% yield. In this way all four stereoisomeric 1,3-dihydroxylated gibberellins **17–20** were available as suitable models for structure activity studies. Other synthetic routes to special isomers of this structural type have been published earlier by Adam[13] as well as Murofushi *et al.*[15]

Dehydration of both 3-epimeric hydroxy ketones **13** and **14** with acetic anhydride/pyridine afforded in 68% yield 1-oxo-GA_5 (**21**) besides small amounts of its 13-acetoxy derivative **22**. The presence of an enone system was proved by typical UV absorption at λmax (ϵ) 254 and 350 nm (2540 and 40) as well as 2 doublets (J = 10 Hz) in the NMR spectrum of **21** at 6.04 and 7.14 (δ) ppm for the vinylic protons at C-2 and C-3. Both enones exhibit an extremely large negative Cotton effect (a = −1600) in the $\pi \rightarrow \pi^*$ region of the enone chromophore.

$NaBH_4$ reduction of the enone **21** afforded 1α- and 1β-hydroxy GA_5 (**23** and **24**). The chromatographic behavior of both epimers was very similar. Thus, the separation was monitored by NMR (5-H doublets at 2.96 and 3.44, respectively) yielding 33 and 10% of pure **23** and **24**. Compound **24** may be regarded as a structural isomer of the highly active phytohormone GA_3 (**1**) in which the allylic Δ^1-3β-hydroxy function is shifted to the Δ^2-1β-hydroxy position. Thus, the herewith described synthesis of **24** from **1** may be from general interest as a

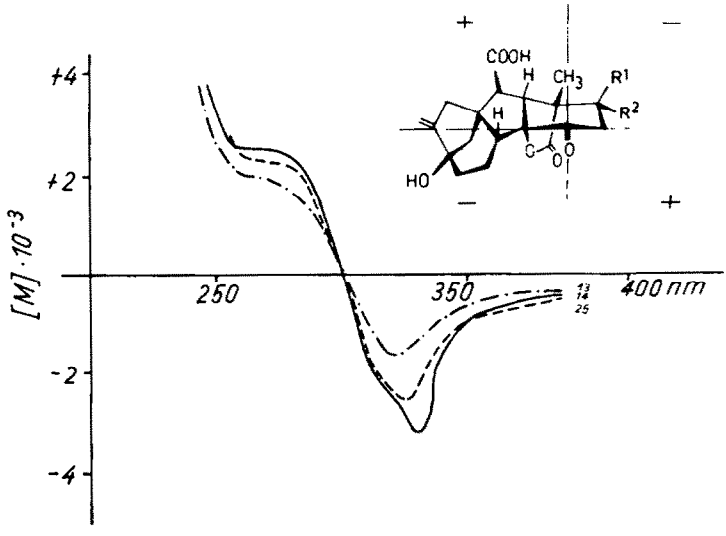


Fig. 1. Optical rotatory dispersion and octant projection of 1-oxo-3-epi-GA_1 (**13**, R^1=H, R^2=OH), 1-oxo-GA_1 (**14**, R^1=OH, R^2=H) and 1-oxo-GA_{20} (**25**, R^1=R^2=H).

new method for such a regioselective allylic transposition.

Selective catalytic hydrogenation of the enone **21** with 10% $Pd/CaCO_3$ in pyridine[16] led to 1-oxo GA_{20} (**25**) with a negative carbonyl Cotton effect at 300 nm (a = −47). In agreement with the octant rule (Fig. 1) the measured molecular amplitude of this parent 1-oxo gibberellin was found intermediate between the 3α- and 3β-hydroxylated ketones **13** and **14**. $NaBH_4$ reduction of **25** gave 1α- and 1β-hydroxy GA_{20} (**26** and **27**) obtained upon SiO_2 chromatography (NMR monitoring) in 48 and 28% yield, respectively.

In preliminary studies GA_{57} (**19**) and GA_{55} (**20**) as well as 1-oxo GA_1 (**14**) showed about 50% of the parent GA_1 activity in the dwarf rice test. In the dwarf pea test the found values for compounds **19** and **20** are 15% and for **14** 35%. From special interest is the high value of 100% GA_1 activity observed for 1β-azido GA_1 (**10**) in both test systems.[17] With 2β-methyl GA_4 and 2,2-dimethyl GA_4 other highly bioactive phytohormone analogues have been published very recently.[18,19] Shift of the allylic alcohol function to the 3β-hydroxy-Δ^2-position (**1** → **24**) effects a dramatically drop to 2 and 4% of the GA_3 bioactivity in the dwarf pea and dwarf maize test, respectively.

EXPERIMENTAL

Mps are corrected. IR: UR-10 instrument (Zeiss, Jena) in nujol. UV and $[\alpha]_D$ in MeOH. ORD: JASCO ORD/UV-5 spectrometer in MeOH. MS: Electron-attachment mass spectrograph of the Research Institute Manfred von Ardenne, Dresden. ^{1}H-NMR: 60 MHz Zeiss instrument ZKR 60, 100 MHz Varian instrument HA 100 or 200 MHz Bruker instrument WP 200 in acetone-d_6 soln (if not otherwise noted) with HMDS as an internal standard, chromatography: Silica gel Woelm for partition chromatography. Photochemical reactions were carried out in a quartz flask under argon at 25–30° using two external Hanovia Reading lamps (each 50 W, λ = 254 nm).

1α-Azido-3-dehydro-GA$_1$ (**4**) *and 1β-azido-3-dehydro-GA$_1$* (**5**)

To a soln of 280 mg **2** in 30 ml abs THF was added a soln (5 ml) of HN_3 (from 1 g NaN_3) in 5 ml ether and the mixture was left at room temp for 2 days. After evaporation of the solvent 315 mg of an amorphous 1:2.8 mixture of **4** + **5** was obtained. IR: ν_{max} 908 (>C=CH$_2$), 1703 and 1719 (CO), 1782 (γ-lactone), 2103 and 2132 (azide) and 3408 cm^{-1} (OH). UV (c = 0.937): λ_{max} (ε) 286 nm (259). ORD (c = 0.937): $[M]_{320}$ + 4117°, $[M]_{268}$ − 5764°, a = +99. MS: *m/z* 344 (M^+–HN_3), 326 (344–H_2O), 316 (344–CO), 300 (344–CO_2). NMR (60 MHz): 4.45 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1β–H), 4.71 (δ) ppm (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz, 1α–H).

1α-Azido-3-dehydro-GA$_1$ methyl ester (**6**) *and 1β-azido-3-dehydro-GA$_1$ methyl ester* (**7**)

To a soln of 1.074 g **3** in 250 ml CH_2Cl_2 was added a soln (25 ml) of HN_3 (from 3 g NaN_3) in ether and the mixture was left at room temp for 2 days. After evaporation 1.200 g amorphous mixture of **6** + **7** in 1:1.8 ratio was obtained. IR: ν_{max} 907 (>C=CH$_2$), 1176 (methyl ester C–O), 1723 (CO), 1779 (γ-lactone), 2102 (azide) 3078 (>C=CH$_2$) and 3400 cm^{-1} (OH). UV (c = 0.910): λ_{max} (ε) 290 nm (267). ORD (c = 0.910): $[M]_{322}$ + 4835°, $[M]_{258}$ − 5714°, a = +105.5. MS: *m/z* 358 (M^+–HN_3), 340 (358–H_2O), 314 (358–CO_2). NMR (60 MHz): 4.30 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 1β–H), 4.72 (δ) ppm (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1α–H).

1α-Azido-3-epi-GA$_1$ (**8**), *1β-azido-3-epi-GA$_1$* (**9**) *and 1β-azido-GA$_1$* (**10**)

A mixture of 1.133 g **4** + **5** in 200 ml MeOH was reduced with 550 mg $NaBH_4$ during 0.5 h under stirring at room temp. After acidification with 10 ml diluted AcOH (10%) the solvent was removed, the residue solved in 50 ml H_2O and the soln extracted with EtOAc. The collected extracts were washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to give 1.270 g of crude product which was chromatographed on 62 g SiO_2 (30 ml fractions). Elution with benzene/ether 4:6 v/v yielded in the fractions 36–49 509 mg (40%) of **10** with m.p. 239–41°C (dec, acetone/n-hexane) and $[\alpha]_D^{25}$ − 62.5° (c = 0.160). IR: ν_{max} 906 (>C=CH$_2$), 1704 (CO), 1762 (γ-lactone), 2113 (azide) and 3453 cm^{-1} (OH). MS: m/z 389 (M^+), 371 (M^+–H_2O), 361 (M^+–N_2), 343 (361–H_2O). NMR (100 MHz): 1.07 (s, 18–H_3), 2.56 (d, J = 10 Hz, 6-H), 3.52 (d, J = 10 Hz, 5-H), 3.76 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 3α–H), 4.08 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1α–H), 4.86 and 5.16 (δ) ppm (17–H_2). (Found: C, 58.55; H, 5.93; N, 10.59. $C_{19}H_{23}O_6N_3$ requires: C, 58.61; H, 5.92; N, 10.80%.)

Elution with benzene/ether 2:8 v/v yielded in the fractions 50–83: 296 mg (23%) amorphous **9** with $[\alpha]_D^{26}$ − 11.9° (c = 0.311). IR: ν_{max} 908 (>C=CH$_2$), 1707 (CO), 1763 (γ-lactone), 2102 (azide), 3078 (>C=CH$_2$) and 3420 cm^{-1} (OH). MS: *m/z* 389 (M^+), 371 (M^+–H_2O), 361 (M^+–N_2), 344 (M^+–2–HN_3). NMR (100 MHz): 1.11 (s, 18–H_3), 2.55 (d, J = 10 Hz, 6–H), 2.69 (d, J = 10 Hz, 5–H), 3.79 (dd, J_1 = 12 Hz, J_2 = 6 Hz, 3β–H), 4.17 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1α–H), 4.85 and 5.18 (δ) ppm (17–H_2). (Found: C, 58.47; H, 5.99; N, 10.53. $C_{19}H_{23}O_6N_3$ requires: C, 58.61; H, 5.92; N, 10.80%.)

Further elution with ether/AcOH 98:2 v/v yielded in the fractions 95–115: 306 mg (24%) amorphous **8** with $[\alpha]_D^{22}$ + 45.3° (c = 0.256). IR ν_{max} 907 (>C=CH$_2$), 1706 (CO), 1762 (γ-lactone), 2101 (azide and 3400 cm^{-1} (OH). MS: *m/z* 389 (M^+), 371 (M^+–H_2O), 361 (M^+–N_2), 348, 343. NMR (100 MHz): 1.09 (s, 18–H_3), 2.44 (d, J = 10 Hz, 6–H), 2.69 (d, J = 10 Hz, 5–H), 3.74 (dd, J_1 = 16 Hz, J_2 = 6 Hz, 3β–H), 3.74 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1β–H), 4.80 and 5.18 (δ) ppm (17–H_2). (Found: C, 58.27; H, 6.06; N, 10.90. $C_{19}H_{23}O_6N_3$ requires : C, 58.61; H, 5.92; N, 10.80%.)

1β-Azido-3-epi-GA$_1$-methyl ester (**11**) *and 1β-azido-GA$_1$-methyl ester* (**12**)

A mixture of 2.41 g **6** + **7** in 250 ml MeOH was reduced with 1.20 g $NaBH_4$ during 0.5 h under stirring at room temp. Usual work-up gave 2.42 g of crude product which was chromatographed on 120 g SiO_2 (60 ml fractions). Elution with CH_2Cl_2/EtOAc 95:5 v/v yielded in the fractions 82–102: 944 mg (39%) **12** as needles (acetone/n-hexane) with m.p. 193–95° (dec) and $[\alpha]_D^{23}$ − 66.9° (c = 0.329). IR: ν_{max} 907 (>C=CH$_2$), 1177 (methyl ester C–O), 1657 (>C=CH$_2$), 1733 (CO), 1758 (γ-lactone), 2118 (azide), 3080 (>C=CH$_2$), 3420 and 3460 cm^{-1} (OH). MS: m/z 402 (M^+ − 1), 370 (M^+ − 1–CH_3OH), 359 (M^+ − 1–HN_3). NMR (100 MHz): 1.06 (s, 18–H_3), 2.60 (d, J = 10 Hz, 6–H), 3.53 (d, J = 10 Hz, 5–H), 3.66 (s, $COOCH_3$), 3.78 (3α-H), 4.07 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1α–H), 4.83 and 5.14 (δ) ppm (17–H_2). (Found: C, 59.93; H, 6.28; N, 10.35. $C_{20}H_{25}O_6N_3$ requires: C, 59.55; H, 6.20; N, 10.42%.)

Further elution with CH_2Cl_2/EtOAc 8:2 v/v gave in the fractions 103–146 805 mg (25%) amorphous **11** with $[\alpha]_D^{22}$ − 10.2° (c = 0.304). IR: ν_{max} 906 (>C=CH$_2$), 1174 (methyl ester C–O), 1772 (γ-lactone), 2098 (azide), 3073 (>C=CH$_2$) and 3420 cm^{-1} (OH). MS: m/z 403 (M^+), 371 (M^+–CH_3OH). NMR (100 MHz): 1.05 (s, 18–H_3), 2.63 (d, J = 10 Hz, 6-H), 2.88 (d, J = 10 Hz, 5–H), 3.71 (s, $COOCH_3$), 3.90 (3β–H), 4.21 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1α–H), 4.91 and 5.21 (δ) ppm (17–H_2).(Found: C, 59.61; H, 6.38; N, 10.29. $C_{20}H_{25}O_6N_3$ requires: C, 59.55; H, 6.20; N, 10.42%.)

1-Oxo-3-epi-GA$_1$ (**13**)

(a) *From 1α-azido-3-epi-GA$_1$* (**8**). A soln of 80 mg **8** in 40 ml

moist THF was irradiated in a quartz flask ($\lambda = 254$ nm). After 7 h **8** was consumed (IR monitoring). The solvent was evaporated and the residue chromatographed on 4 g SiO_2 (2 ml fractions). Elution with ether/AcOH 98:2 v/v yielded in the fractions 108–125: 29 mg (40% amorphous **13** with $[\alpha]_D^{24} - 25.4°$ (c = 0.261). IR: ν_{max} 903 (>C=CH$_2$), 1706 and 1728 (CO), 1775 (γ-lactone and 3400 cm^{-1} (OH). MS: *m/z* 362 (M^+), 344 (M^+–H_2O), 334 (M^+–CO), 326 (M^+–$2H_2O$), 316 (344–CO), 302 (334–CH_3OH), 300 (M^+–H_2O-CO_2). UV (c = 0.980): λ_{max} (ε) 280 nm (115). ORD (c = 0.980): $[M]_{322} - 1660°$, $[M]_{272} + 1940°$ a = −36. NMR (100 MHz): 1.21 (s, 18–H_3), 2.68 (d, J = 10 Hz, 6–H), 2.75 (d, J = 10 Hz, 5–H), 4.00 (dd, J_1 = 9 Hz, J_2 = 7 Hz, 3β–H), 4.85 and 5.16 (δ) ppm (17–H_2). (Found: C, 63.12; H, 6.08. $C_{19}H_{22}O_7$ requires: C, 62.98; H, 6.08%.)

(b) *From* 1β-*azido*-3-*epi*-GA_1 (**9**). A soln of 90 mg **9** in 45 ml moist THF was irradiated for 2 h, worked up as usual and the residue chromatographed on 4.5 g SiO_2 (2.5 ml fractions). Elution with ether/AcOH 98:2 v/v gave in the fractions 66–121: 38 mg (44%) amorphous **13** with $[\alpha]_D^{24} - 26.1°$ (c = 0.345), identical in every respect with **13** prepared via method a).

1-*Oxo*-GA_1 (**14**)

A soln of 678 mg **10** in 500 ml moist THF was irradiated for 2 h, worked up as usual and the residue chromatographed on 35 g SiO_2 (15 ml fractions). Elution with benzene/ether 1:1 v/v yielded in the fractions 26–46: 142 mg (21%) starting material **10**. The fractions 47–140 gave 275 mg (56%) **14** as needles with m.p. 224–227° (acetone/n-hexane) and $[\alpha]_D^{25} - 49.5°$ (c = 0.323). IR: ν_{max} 894 (>C=CH$_2$), 1703 and 1732 (CO), 1758 (γ-lactone), 3069 (>C=CH$_2$) and 3490 cm^{-1} (OH). UV (c = 1.28): λ_{max} (ε) 280 nm (115). ORD (c = 1.28): $[M]_{323} - 2680°$, $[M]_{272} + 2500°$, a = −52. MS: *m/z* 362 (M^+), 344 (M^+–H_2O), 334 (M^+–CO), 326 (M^+–$2H_2O$) and 362 (M^-), 343, 316 (334–H_2O) and 300 (344–CO_2). NMR (100 MHz): 1.21 (s, 18–H_3), 2.78 (d, J = 10 Hz, 6–H), 2.97 (dd, J_1 = 16 Hz, J_2 = 5.5 Hz, 2–H_2), 3.49 (d, J = 10 Hz, 5–H), 4.08 (dd, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 3α–H), 4.86 and 5.16 (δ) ppm (17–H_2.)

1-*Oxo*-GA_1 *methyl ester* (**15**)

A soln of 102 mg **12** in 50 ml moist THF was irradiated for 2 h, worked up as usual and the residue chromatographed on 5 g SiO_2 (2.5 ml fractions). Elution with CH_2Cl_2/EtOAc 9:1 v/v gave in the fractions 72–90: 43 mg (45%) amorphous **15** with $[\alpha]_D^{22} - 48.4°$ (c = 0.239). IR: ν_{max} 904 (>C=CH$_2$), 1708 and 1735 (CO), 1782 (γ-lactone), 3078 (>C=CH$_2$) and 3490 cm^{-1} (OH). UV (c = 1.11): λ_{max} (ε) 280 nm (88). ORD (c = 1.11): $[M]_{325} - 2780°$, $[M]_{274} + 1930°$, a = −47. MS: *m/z* 376 (M^+), 358 (M^+–H_2O), 348 (M^+–CO), 330 (M^-–HCOOH), 304 (348–CO_2) and 376 (M^-), 348 (M^-–CO), 332 (M^-–CO_2), 314 (332–H_2O). NMR (60 MHz): 1.14 (s, 18–H_3), 2.67 (d, J = 10 Hz, 6–H), 2.94 (dd, J_1 = 16 Hz, J_2 = 5.5 Hz, 2–H_2), 3.59 (d, J = 10 Hz, 5–H), 3.76 (s, $COOCH_3$), 4.18 (dd, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 3α–H), 4.99 and 5.27 (δ) ppm (17–H_2). (Found: C, 63.66; H, 6.22. $C_{20}H_{24}O_7$ requires: C, 63.83; H, 6.38%.)

1-*Oximino*-GA_1 (**16**)

To a soln of 38 mg **14** in 0.8 ml abs pyridine 10 mg NH_2OH·HCl was added and left for 26 h at room temp. After evaporation of the solvent *in vacuo* the residue was solved in 10 ml diluted AcOH (10%) and the soln extracted with EtOAc. The residue (40 mg) recovered from the EtOAc was chromatographed on 1.5 g SiO_2 (1 ml fractions). Elution with benzene/ether 3:7 v/v the fractions 35–85 gave 22 mg (55%) **16** which crystallized from benzene/ether in needles with m.p. 194–97° and $[\alpha]_D^{26} - 58.8°$ (c = 0.289). IR: ν_{max} 903 (>C=CH$_2$), 1665 (C=N), 1705 (CO), 1770 (γ-lactone) and 3335 cm^{-1} (OH). UV (c = 1.45): λ_{max} (ε) 276 nm (110). MS: *m/z* 377 (M^+), 359 (M^+–H_2O), 333 (M^+–CO_2) and 315 (M^+–H_2O–CO_2). NMR (200 MHz): 1.13 (s, 18–H_3), 2.65 (d, J = 10 Hz, 6–H), 3.30 (dd, J_1 = 15 Hz, J_2 = 2.5 Hz, 2–H_2), 3.38 (d, J = 10 Hz, 5–H), 3.91 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 3α–H), 4.85 and 5.15 (δ) ppm (17–H_2).

1α-*Hydroxy*-3-*epi*-GA_1 (**17**) *and* 1β-hydroxy-3-epi-GA_1 (**18**)

A soln of 130 mg **13** in 50 ml MeOH was reduced with 100 mg $NaBH_4$. After 0.5 h the solvent was removed *in vacuo*, the residue acidified with 15 ml of diluted AcOH (10%) and the soln extracted with EtOAc. The residue recovered from the EtOAc was chromatographed on 7 g SiO_2 (4 ml fractions). With ether/AcOH 98:2 v/v in the fractions 107–143: 70 mg (54%) amorphous **18** with $[\alpha]_D^{22} + 26.2°$ (c = 0.350) was eluted. IR: ν_{max} 900 (>C=CH$_2$), 1702 and 1716 (CO), 1754 (γ-lactone) and 3430 cm^{-1} (OH). MS: *m/z* 364 (M^+), 346 (M^+–H_2O), 330, 328 (M^+–$2H_2O$), 312, 302 (M^+–H_2O–CO_2). NMR (200 MHz, pyridine-d_5): 1.72 (s, 18–H_3), 3.34 (d, J = 10 Hz, 6–H), 3.94 (d, J = 10 Hz, 5–H), 4.43 (d, J = 3.5 Hz, 1α–H), 4.44 (m, 3β–H), 4.93 and 5.54 (δ) ppm (17–H_2), lit[13]: m.p. 150–53° (dec, from acetone/n-hexane), $[\alpha]_D^{25} + 21.0°$. (Found: C, 62.44; H, 6.83. $C_{19}H_{24}O_7$ requires: C, 62.64; H, 6.59%). Further elution with ether/AcOH 95:5 v/v gave in the fractions 189–256 44 mg (34%) amorphous **17** with $[\alpha]_D^{23} + 4.9°$ (c = 0.351). IR: ν_{max} 902 (>C=CH$_2$), 1716 and 1738 (CO), 1750 (γ-lactone) and 3400 cm^{-1} (OH). MS: *m/z* 364 (M^+), 346 (M^+–H_2O), 328 (M^+–$2H_2O$), 320 (M^+–CO_2), 302 (M^+–H_2O–CO_2). NMR (200 MHz, pyridine-d_5): 1.67 (s, 18–H_3), 3.06 (d, J = 10 Hz, 6–H), 3.33 (d, J = 10 Hz, 5–H), 4.21 (m, 1β- and 3β–H), 4.84 and 5.46 (δ) ppm (17–H_2), Lit.[15] m.p. 174–77°. (Found: C, 62.61; H, 6.81. $C_{19}H_{24}O_7$ requires: C, 62.64; H, 6.59%.)

GA_{57} (1α-*hydroxy*-GA_1, **19**) *and* GA_{55} (1β-*hydroxy*-GA_1, **20**)

A soln of 270 mg **14** in 60 ml MeOH was reduced with 200 mg $NaBH_4$. After 0.5 h worked up as usual and crude product (250 mg) chromatographed on 15 mg SiO_2 (7 ml fractions). Elution with ether/AcOH 98:2 v/v yielded in the fractions 97–116 21 mg (8%) **20** with m.p. 260–263° (MeOH/ether) and $[\alpha]_D^{24} + 38.6°$ (c = 0.285). IR: ν_{max} 910 and 1665 (>C=CH$_2$), 1706 and 1740 (CO), 1770 (γ-lactone) and 3440 cm^{-1} (OH). MS: *m/z* 364 (M^+), 346 (M^+–H_2O), 328 (M^+–$2H_2O$), 320 (M^+–CO_2), 300 (328–CO), 284 (328–CO_2) and 362 (M^-–2), 344 (362–H_2O), 320 (M^-–CO_2), 318 (362–CO_2), 300 (318–H_2O). NMR (200 MHz, pyridine-d_5): 1.64 (s, 18–H_3), 2.81 (m, 2–H_2), 3.27 (d, J = 10 Hz, 6–H), 4.17 (d, J = 3.5 Hz, 3α–H), 4.37 (d, J = 3.5 Hz, 1α–H), 4.54 (d, J = 10 Hz, 5–H), 4.92 and 5.54 (δ) ppm (17–H_2), lit[15b]: m.p. 245–47° (dec, acetone/n-hexane), $[\alpha]_D^{22} + 41.0°$ (c = 0.275, lit[15b] amorphous, the NMR data given there are in agreement with our values.

Further elution with ether/AcOH 95:5 v/v gave in the fractions 121–196 140 mg (54%) **19** with m.p. 147–50° (MeOH/ether) and $[\alpha]_D^{24} + 19.2°$ (c = 0.365). IR: ν_{max} 900 (>C=CH$_2$), 1703 and 1716 (CO), 1760 (γ-lactone) and 3400 cm^{-1} (OH). MS: *m/z* 364 (M^+), 346 (M^+–H_2O), 328 (M^+–$2H_2O$), 320 (M^+–CO_2), 319, 302 (M^+–H_2O–CO_2), 300 (346–HCOOH), 290. NMR (200 MHz, pyridine-d_5): 1.58 (s, 18–H_3), 3.20 (d, J = 10 Hz, 6–H), 3.94 (d, J = 10 Hz, 5–H), 4.15 (t, J = 4 Hz, 3α–H), 4.60 (dd, J_1 = 10 Hz, J_2 = 6 Hz, 1β–H), 4.93 and 5.53 (δ) ppm (17–H_2), lit[15] amorphous; the NMR data given[15] are in agreement with our values.

1-*Oxo*-GA_5 (**21**) *and* 13-*acetoxy*-1-*oxo*-GA_5 (**22**)

To a soln of 260 mg **14** in 3 ml abs pyridine, 3 ml Ac_2O was added and kept for 1.5 h at room temp. After evaporation of the solvent *in vacuo* the residue was chromatographed on 15 g SiO_2 (7 ml fractions). Elution with benzene/ether 6:4 v/v gave in the fractions 32 and 33: 24 mg (9%) amorphous **22** with $[\alpha]_D^{21} - 66.5°$ (c = 0.316). IR: ν_{max} 902 and 1660 (>C=CH$_2$), 1703 and 1735 (CO), 1780 cm^{-1} (γ-lactone). UV (c = 0.813): λ_{max} (ε) 350 and 254 nm (31 and 2764). ORD (c = 0.813): $[M]_{270} - 35740°$, $[M]_{229} + 124{,}000°$, a = −1600. MS: *m/z* 386 (M^+), 344 (M^+–CH_2CO^-), 326 (344–H_2O), 300 (344–CO_2) and 385 (M^-–1), 342 (385–CH_3CO), 327, 298 (342–CO_2). NMR (100 MHz): 1.31 (s, 18–H_3), 2.79 (d,

J = 10 Hz, 6–H), 3.45 (d, J = 10 Hz, 5–H), 4.93 and 5.12 (17–H_2), 6.04 (d, J = 10 Hz, 2–H), and 7.14 (δ) ppm (d, J = 10 Hz, 3–H).

Further elution with benzene/ether 1:1 and 4:6 v/v yielded in the fractions 38–90 170 mg (68%) **21** which crystallized from acetone/n-hexane as needles with m.p. 206–210° (dec) and $[\alpha]_D^{22}$ – 58.7° (c = 0.375). IR: ν_{max} 903 and 1665 (>C=CH_2), 1702 and 1736 (CO), 1780 cm^{-1} (γ-lactone). UV (c = 0.690): λ_{max} (ϵ) 350 and 254 nm (40 and 2543). ORD (c = 0.690): $[M]_{268}$ – 44870°, $[M]_{229}$ + 119650°, a = – 1645. MS: *m/z* 344 (M^+), 326 (M^+–H_2O), 316 (M^+–CO), 300 (M^+–CO_2) and 343 (M^-–1), 329, 300 (M^-–CO_2), 282 (M^-–CO_2–H_2O), 256 (M^-–$2CO_2$). NMR (100 MHz): 1.30 (s, 18–H_3), 2.74 (d, J = 10 Hz, 6–H), 3.41 (d, J = 10 Hz, 5–H), 4.84 and 5.18 (17–H_2), 6.04 (d, J = 10 Hz, 2–H) and 7.12 (δ) ppm (d, J = 10 Hz, (3–H).

21 was also obtained in the same manner by dehydration of a mixture of **13** + **14**.

1α-Hydroxy-GA₅ (**23**) *and 1β-hydroxy-GA₅* (**24**)

A soln of 270 mg **21** in 50 ml MeOH was reduced with 200 mg $NaBH_4$ for 0.5 h. After usual work up gave a residue which was chromatographed on 16 g SiO_2 (8 ml fractions). Elution with benzene/ether 3:7 v/v yielded in the fractions 162–259: 28 mg (10%) **24** which crystallized from acetone/n-hexane in needles with m.p. 152–155° (dec) and $[\alpha]_D^{24}$ – 62.2° (c = 0.225). IR: ν_{max} 906 and 1654 (>C=CH_2), 1700 (CO), 1755 (γ-lactone), 3035 (–CH=CH–), 3089 (>C=CH_2) and 3390 cm^{-1} (OH). MS: *m/z* 346 (M^+), 328 (M^+–H_2O), 312, 310 (M^+–$2H_2O$), 302 (M^+–CO_2), 284 (302–H_2O) and 345 (M^-–1), 344 (M^-–2), 300 (344–CH_2). NMR (200 MHz, pyridine-d_5): 1.30 (s, 18–H_3), 2.97 (d, J = 10 Hz, 6–H), 3.44 (d, J = 10 Hz, 5–H), 4.38 (d, J = 3 Hz, 1α–H), 4.85 and 5.49 (17–H_2), 5.82 (d, J = 9 Hz, 2–H) and 6.10 (δ) ppm (dd, J_1 = 9 Hz, J_2 = 3 Hz, 3–H). (Found: C, 65.61; H, 6.15. $C_{19}H_{22}O_6$ requires: C, 65.90; H, 6.36%.)

Further elution with ether as well as ether/AcOH 98:2 v/v afforded in the fractions 276–334: 91 mg (33%) **23** which crystallized from acetone/n-hexane in needles with m.p. 141–144° (dec) and $[\alpha]_D^{25}$ – 35.6° (C = 0.278). IR: ν_{max} 906 and 1652 (>C=CH_2), 1700 and 1715 (CO), 1759 (γ-lactone), 3030 (–CH=CH–), 3088 (>C=CH_2) and 3390 cm^{-1} (OH). MS: *m/z* 346 (M^-), 328 (M^+–H_2O), 310 (M^+–$2H_2O$), 302 (M^+–CO_2), 284 (302–H_2O), respectively, 345 (M^-–1), 303 (345–CH_2CO), 290. NMR (200 MHz, pyridine-d_5): 1 28 (s, 18–H_3), 2.84 (d, J = 10 Hz, 6–H), 2.96 (d J = 10 Hz, 5–H), 4.21 (d, J = 3 Hz, 1β–H), 4.67 and 4.92 (17–H_2), 5.82 (d, J = 9 Hz, 2–H) and 5.96 (δ) ppm (dd, J_1 = 9 Hz, J_2 = 3 Hz, 3–H). (Found: C, 65.92; H, 6.30. $C_{19}H_{22}O_6$ requires: C, 65.90; H, 6.36%.)

1-Oxo-GA₂₀ (**25**)

A Pd catalyst was prepared by hydrogenation of 10 mg Pd $(OH)_2/CaCO_3$ (10%) in 3 ml abs pyridine, a soln of 60 mg **21** in 3 ml abs pyridine was added and the hydrogenation continued until one equivalent of H_2 was taken up. After filtration the solvent was evaporated and the residue chromatographed on 3 g SiO_2 (1.5 ml fractions). Elution with benzene/ether 1:1 v/v afforded in the fractions 36–87: 36 mg (59%) **25** which crystallized from acetone/n-hexane in fine needles with m.p. 122–125° and $[\alpha]_D^{25}$ – 39.3° (c = 0.280). IR: ν_{max} 900 (>C=CH_2), 1722 and 1734 (CO), 1773 (γ-lactone), 3070 (>C=CH_2) and 3350 cm^{-1} (OH). UV (c = 1.62): λ_{max} (ϵ) 290 nm (56). ORD (c = 1.62): $[M]_{324}$ – 2480°, $[M]_{276}$ + 2220°, a = – 47. MS: *m/z* 346 (M^+), 328 (M^+– H_2O), 318 (M^+–CO), 304 (M^+–CH_2CO^-), 302 (M^+–CO_2) and 346 (M^-), 302 (M^-–CO_2), 300 (M^-–HCOOH). NMR (200 MHz): 1.20 (s, 18–H_3), 2.83 (d, J = 10 Hz, 6–H), 2.98 (d, J = 10 Hz, 5–H), 4.90 and 5.22 (δ) ppm (17–H_2). Hydrogenation of **21** in THF/pyridine gave the same product in 63% yield.

1α-Hydroxy-GA₂₀ (**26**) *and 1β-hydroxy-GA₂₀* (**27**)

A soln of 150 mg **25** in 30 ml MeOH was reduced with 150 mg $NaBH_4$ for 1 h. After usual work up the residue was chromatographed on 7.5 g SiO_2 (4 ml fractions). Elution with benzene/ether 1:1 v/v yielded in the fractions 112–151 21 mg (14%) **27** which crystallized from acetone/n-hexane in fine needles with m.p. 253–255° (dec) and $[\alpha]_D^{26}$ + 6.3° (c = 0.270). IR ν_{max} 904 and 1655 (>C=CH_2), 1722 and 1734 (CO), 1760 (γ-lactone), 3072 (>C=CH_2) and 3280 cm^{-1} (OH). MS: *m/z* 348 (M^+), 330 (M^+–H_2O), 303, 289 and 347 (M^-–1), 330 (M^-–H_2O), 302 (M^-–HCOOH), 284 (302–H_2O). NMR (200 MHz): 1.04 (s, 18–H_3), 2.61 (d, J = 10 Hz, 6–H), 3.11 (d, J = 10 Hz, 5–H), 3.96 (t, J = 3 Hz, 1α–H), 4.87 and 5.19 (δ) ppm (17–H_2).

Further elution with benzene/ether H 1:9 v/v afforded in the fractions 152–173: 36 mg (24%) **26** which crystallized from acetone/n-hexane in fine needles with m.p. 228–232° (dec) and $[\alpha]_D^{26}$ + 4.8° (c = 0.415). IR: ν_{max} 906 (>C=CH_2), 1704 and 1718 (CO), 1773 (γ-lactone) and 3365 cm^{-1} (OH). MS: *m/z* 348 (M^+), 330 (M^-–H_2O), 312 (M^-–$2H_2O$), 289 and 347 (M^-–1), 330 (M^-–H_2O), 302 (M^-–HCOOH). 284 (302–H_2O). NMR (200 MHz): 1.02 (s, 18–H_3), 2.54 (d, J = 10 Hz, 6–H), 2.63 (d, J = 10 Hz, 5–H), 3.87 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1β–H), 4.85 and 5.20 (δ) ppm (17–H_2).

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