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Partial Synthesis of [1β,2α,17,17-D_4] Gibberellin A_1

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Dedicated to Professor Dr. K. Schreiber on the Occasion of his 70th Birthday

Abstract. An efficient route for an alternative synthesis of gibberellin A_1 from gibberellin A_3 is described. Based on iodolactonisation the method provides access to gibberellin A_1 labeled by deuterium with both high incorporation of the isotope and high stereoselectivity at the positions 1β and 2α. The additional deuterium labeling at C-17 was introduced *via* the corresponding 16-norketone resulting in [1β,2α,17,17-D_4] gibberellin A_1.

In order to follow the metabolism of [17-D_2] GA_{20} and to quantify the resulting pool of [17-D_2] GA_1 in *Hordeum vulgare* L. multilabeled GA_1 of high isotope content was required to serve as internal standard. For this, in addition to the labeling at C-17, two more deuterium atoms should be introduced in ring A of GA_1. In the literature syntheses of GA_1 stereospecific labeled in ring A are described where catalytic hydrogenation with deuterium gas was used [1]. In order to substitute the hydrogenation step a new route for introducing deuterium at C-1 and C-2 has been worked out.

In 1991 Beale *et al.* reported an efficient route for the synthesis of GA_{81} (epi-GA_{29}) starting from GA_3 [2]. Key reaction was the known conversion of GA_3 **1** into iodo triol **2**, which could be selectively acylated to the corresponding 2α,13-diacetate **3**. We found that this initial approach is also suitable to transform the functionality of GA_3 into that of GA_1 by simple reactions, which allow labeling at C-1 and C-2 (see scheme 1). Reduction of the iodide **3** (obtained in 51% overall yield from GA_3 (**1**)) with tri-*n*-butyltin deuteride gave the [1β-D] GA_{56} derivative **4** containing 0.94 atoms deuterium in 87% yield.

The deacetylation of the 2α-hydroxy group of **4** after protection of the 3β-hydroxy group as tetrahydropyranyl ether gave **6** in 75% yield.

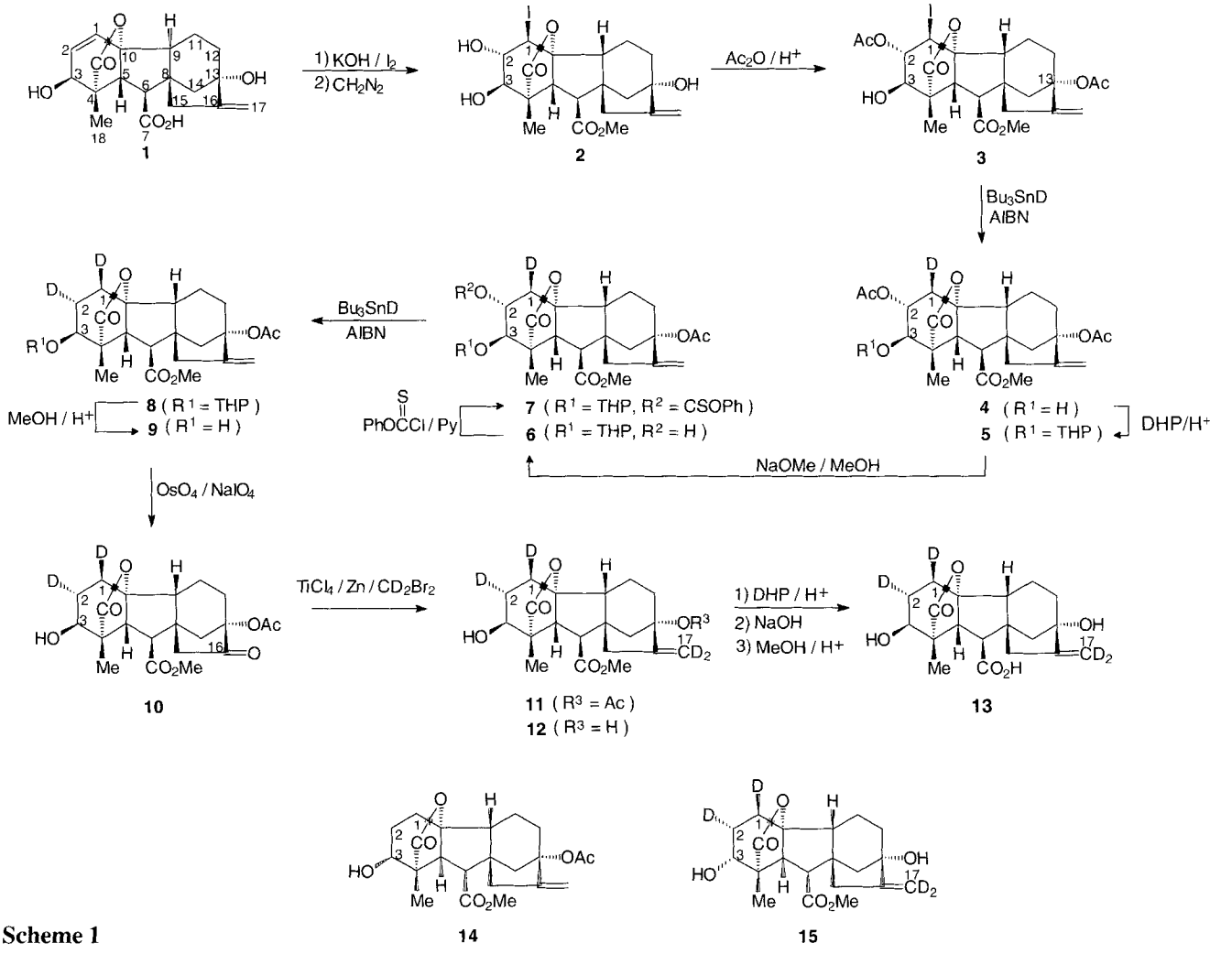
In order to remove the 2α-hydroxy group, compound **6** was treated with phenoxythiocarbonyl chloride in the presence of pyridine to yield 90% of the corresponding phenyl thionocarbonate **7**. Radical mediated deoxygenation of **7** using tri-*n*-butyltin deuteride afforded **8** (95%), which after hydrolysis resulted in [1β,2α-D_2] GA_1 13-acetate methyl ester **9** in 92% yield from **8** (26% overall yield from GA_3 (**1**)). Compound **9** contains 1.88 atoms deuterium per molecule.

The stereochemistry of the deuterium atoms introduced at C-1 and C-2 of **9** was established by extended NMR investigations including the compounds **14** and **15**. From ^{1}H-^{1}H-COSY and HMQC experiments of the unlabeled GA_1 13-acetate methyl ester **14** the four cross peaks at δ 1.93, 1.81 (δ ^{13}C 27.9) and 1.805, 1.68 (δ ^{13}C 29.0) were assigned to the protons at C-1 and C-2, respectively. In the NOE difference spectrum of **14** irradiation at δ 4.48 (3β-OH) and 3.25 (5β-H) gave positive enhancement of the multiplet at 1.81ppm, which therefore was assigned to 1β-H.

In the HMQC spectrum of the double deuterium labeled compound **9** the carbon signals of both C-1 (δ 27.5) and C-2 (δ 28.5) show only one cross peak at δ 1.91 and 1.79, respectively.

The ^{2}H NMR spectrum displayed two broad signals with nearly the same intensity at δ 1.79 and 1.65.

In the ^{1}H NMR spectrum of **9** the signal at δ 1.79 appears as broad singlet, whereas the signal at δ 1.91 is superimposed with H-9 and H-11α. On the basis of the proton chemical shifts obtained for H-1α (δ 1.93)



Scheme 1

and H-1β (δ 1.81) of the unlabeled compound **14,** the signal at δ 1.91 for **9** can be assigned to H-1α. In the NOE difference spectrum of **9**, irradiation at δ 1.79 (H-2) gives positive enhancement of both H-3α (δ 3.71) and OH-3β (δ 4.48) as well as H-1α, showing H-2 to be equatorial orientated. Therefore, the broad singlet at δ 1.79 is assigned to H-2β. Thus, the sterical arrangement of the two deuterium atoms of compound **9** are 1β and 2α, respectively. For an estimation of the stereoselectivity of the two deuteration steps the proton traces of the HMQC spectrum of **9** at C-1 (δ 27.5) and C-2 (δ 28.5) were carefully inspected. In the first case in addition to the signal of H-1α at δ 1.91 a signal with a relative low intensity (below 10%) was observed at δ 1.80, which should belong either to H-1β of a 1α-deuterated compound or to unlabeled amounts present in **9**. In the case of the C-2 trace the H-2β signal at δ 1.79 appears exclusively. From the signal-to-noise ratio it can be estimated that more than 95% of deuterium at C-2 is located in the 2α-position.

Consequently, both reduction steps with tri-*n*-butyl deuteride have taken place under retention of configuration.

For further confirmation of the 1β,2α-stereochemistry of the deuterium atoms, the 3β alcohol **11** was epimerizised to [1β,2α,17,17-D$_4$] epi-GA$_1$ methyl ester **15** in methanol with a catalytical amount of potassium carbonate [3]. This 3α–alcohol **15** also contained 3.78 atoms deuterium, indicating that the label at C-2 remained. The ^{1}H NMR spectrum of **15** displayed a double doublet at δ 3.70, *J*= 5.8/5.8 Hz assigned to 3β-H. The vicinal coupling constant of H-3β_{ax} with H-2 of 5.8 Hz proves H-2 to be equatorial orientated and hence the presence of a H-2β proton.

In order to introduce additional deuterium label at the 17-position, the 16-norketone **10** was prepared in 70% yield from **9** by oxidative cleavage of the 16,17-olefine with sodium periodate and catalytical amounts of osmium tetroxide.

Methylenation of **10** was accomplished using Lombardo's reagent Zn–TiCl$_4$–CD$_2$Br$_2$ [4]. This method resulted in both **11** (30% yield) containing 3.78 atoms

deuterium and **12** (16% yield) formed during work up with the same deuterium content. Alkaline hydrolysis of **11**, after protection of the 3β-hydroxy group as the tetrahydropyranyl ether (to avoid epimerisation at C-3), gave the required [1β,2α,17,17-D_4] GA_1 **13**, containing 3.78 atoms deuterium per molecule.

With respect to both the high deuterium content and the high stereoselectivity of the deuteration especially at the 2α position the labeled GA_1 synthesized by this method represents not only an ideal internal standard for quantitative analysis but also a potent precursor for studying the stereochemistry of 2β-hydroxylations and 1,2-and 2,3-dehydrogenations.

We are indebted to the Kultusministerium des Landes Sachsen-Anhalt (FKZ 919 A 0931) for financial support.

Experimental

^{1}H NMR spectra were recorded at 300 MHz, unless otherwise stated, using a VARIAN GEMINI 2000-300BB. ^{1}H-^{1}H COSY, HMQC and NOE difference spectra (500 MHz, Aceton-d_6) and the ^{2}H NMR spectrum (76.7 MHz, Aceton) were recorded on a VARIAN UNITY 500. All chemical shifts δ (ppm) are related to TMS. The 70 eV-EI mass spectra and high resolutions were acquired using an AMD-402 mass spectrometer. Flash chromatography was performed on Kieselgel 60, 230–400 mesh (MERCK) using N_2 positive pressure. Bu_3SnD was obtained from FLUKA.
Nomenclature and numbering of the *ent*-gibberellane skeleton see [5] and [6], respectively.

ent-2β,3α,10β,13-Tetrahydroxy-1α-iodo-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**2**)

Prepared according the procedure given in [2] starting from GA_3 (1g, 2.89 mmol) yield 690 mg (65%).
Found: M$^+$ 504.0618. $C_{20}H_{25}IO_7$ req. M$^+$ 504.0645. – ^{1}H NMR (Me_2CO-d_6): δ 1.13 (s, 18-H_3), 2.63 (d, J = 9.6 Hz, 6-H), 3.73 (s, CO_2Me), 3.76 (br, 3-H), 3.86 (d, J = 9.6 Hz, 5-H), 4.43 (br, 1-H), 4.63 (broad, 2-H), 4.92 and 5.21 (each br, 17-H_2). – EIMS, *m/z* (rel. int): 504 (M$^+$, 34), 472 (16), 454 (25), 445 (100), 359 (17), 345 (20), 327 (45), 317 (29), 299 (57), 281 (34), 271 (29), 255 (36).

ent-2β,13-Diacetoxy-3α,10β-dihydroxy-1α-iodo-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**3**)

A mixture of 1β-iodo-GA_{56} methyl ester **2** (950 mg, 1.88 mmol), acetic anhydride (15 ml) and toluene-*p*-sulfonic acid (15 mg) was stirred at room temperature for 3 days. Usual work up gave the crude product which was purified by flash chromatography. Elution with 45% ethyl acetate in hexane gave the 1β-iodo-GA_{56} 2,13-diacetate methyl ester **3** as a gum (860 mg, 78%).
Found: M$^+$ 588.1022. $C_{24}H_{29}IO_9$ req. M$^+$ 588.0856.
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 18-H_3), 2.02 and 2.06 (2s, 2 Ac), 2.71 (d, J=10.0 Hz, 6-H), 3.75 (s, CO_2Me), 3.77 (br, 3-H), 3.82 (d, J=10.0 Hz, 5-H), 4.28 (dd, J=1.5/0.8, 1-H), 5.03 and 5.16 (each br, 17-H_2), 5.45 (br, 2-H). – ^{13}C NMR (500 MHz, $CDCl_3$, derived from HMQC): δ 14.4 (C-18), 21.8 (C-1), 48.1 (C-5), 50.5 (C-6), 52.1 (OMe), 74.4 (C-3), 78.2 (C-2), 108.1 (C-17). – EIMS, *m/z* (rel. int.): 588 (M$^+$, 34), 546 (100), 528 (10), 487 (17), 401 (9), 383 (18), 359 (21), 297 (24), 237 (24).

ent-1α-Deuterio-2β,13-diacetoxy-3α,10β-dihydroxy-20-norgibberell-16-ene-7,19 dioic acid 7-methyl ester-19,10-lactone (**4**)

A solution of **3** (860 mg,1.46 mmol), tri-*n*-butyltin deuteride (1.25 ml) and a crystal of 2,2'-dimethyl-2,2'-azopropionitrile (AIBN) in toluene (100 ml) was refluxed for 2 hr. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 55% ethyl acetate in hexane gave [1β-D] GA_{56} 2,13-diacetate methyl ester **4** as a gum (590 mg, 87%) containing 0.94 deuterium atoms per molecule.
Found: M$^+$ 463.1979. $C_{24}H_{29}O_9D$ req. M$^+$ 463.1953.
^{1}H NMR ($CDCl_3$): δ 1.17 (s, 18-H_3), 2.02 and 2.04 (2s, 2 Ac), 2.74 (d, J=10.4 Hz, 6-H), 3.26 (d, J=10.4 Hz, 5-H), 3.72 (3-H), 3.73 (s, CO_2Me), 4.99 (br, 17-H and 2-H), 5.15 (br, 17-H). – EIMS, *m/z* (rel. int.): 463 (M$^+$, 16), 432 (7), 421 (100), 403 (16), 389 (9), 371 (14), 361 (31), 343 (35), 329 (32), 311 (18), 301 (26).

3-O-Tetrahydropyranyl (THP) derivative of ent-1α-deuterio-13-acetoxy-2β,3α,10β-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**6**)

[1β-D] GA_{56} 2,3-diacetate methyl ester **4** (590 mg, 1.27 mmol) in dichloromethane (8.5 ml) was stirred with 2,3-dihydropyrane (DHP, 400 µl) and pyridinium-*p*-toluenesulfonate (35 mg) for 4 hr at room temperature. The reaction mixture was worked up to give the tetrahydropyranyl ether **5**, which was dissolved in methanol (8.5 ml) and deacetylated by adding 0.5N sodium methoxide solution (1.7 ml). After 15 minutes at room temperature the reaction was stopped by adding of acetic acid. Flash chromatography with 65% ethyl acetate in hexane gave **6** (480 mg, 75%) as a mixture of diastereoisomers as shown by its NMR spectrum. – ^{1}H NMR (Me_2CO-d_6): δ 1.05 and 1.12 (2s, 18-H_3), 1.97 (s, Ac), 2.62 and 2.63 (2d, each J=10.7 Hz, 6-H), 3.21 and 3.23 (2d, each J=10.7 Hz, 5-H), ca 3.50 (m, 6'-H_A), 3.54 and 3.66 (each br, 3-H), 3.71 and 3.72 (2s, CO_2Me), 3.89 (m, 6'-H_B), 4.09 and 4.28 (each br, 2-H), 4.68–4.77 (2m, 2'-H), 4.94 and 5.13 (each br, 17-H_2). – EIMS, *m/z* (rel. int.): 505 (M$^+$, 0.3), 421 (10), 389 (6), 361 (9), 329 (8), 298 (8), 85 (100).

3-O-Tetrahydropyranyl derivative of ent-1α-deuterio-13-acetoxy-3α,10β-dihydroxy-2β-phenoxythiocarbonyl-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**7**)

To a stirred solution of **6** (480 mg, 0.95 mmol) in dichloromethane (6.5 ml) dry pyridine (290 µl) and phenoxythiocarbonyl chloride (195 µl) were added. After 4 hr the solvents were evaporated and the residue was partitionated between ethyl acetate and water. The organic phase was washed with dilute hydrochloric acid and water, dried and evaporated. Flash chromatography with 35% ethyl acetate in hexane yielded **7** (550 mg, 90%) as a gummy mixture of the

two diastereoisomers. – ^{1}H NMR (Me_2CO-d_6): δ 1.14 and 1.18 (2s, 18-H_3), 1.98 (s, Ac), 2.70 and 2.71 (2d, each *J*=10.7 Hz, 6-H), 3.34 and 3.36 (2d, each *J*=10.7 Hz, 5-H), 3.74 and 3.75 (2s, CO_2Me), 3.51 (m, 6'-H_A), ca 3.90 (m, 6'-H_B), 3.85 and 3.96 (each br, 3-H), 4.91 and 5.07 (2m, 2'-H), 4.96 and 5.16 (each br, 17-H_2), 5.59 and 5.94 (each br, 2-H), 7.11–7.50 (m, ArH). – EIMS, *m/z* (rel. int.): 610 (0.3), 487 (0.7), 404 (3), 343 (3), 312 (2.5), 299 (1.5), 282 (2), 240 (1), 222 (3), 85 (100).

ent-1α,2β-Dideuterio-13-acetoxy-3α,10β-dihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone (**9**)

The thiocarbonate **7** (550 mg, 0.86 mmol) in dry toluene (16 ml) was heated to reflux with tri-*n*-butyltin deuteride (470 μl) and a crystal of AIBN for 6 hr under an argon atmosphere. After evaporation of the solvent the residue was purified by flash chromatography with 35% ethyl acetate in hexane. The 3-O-tetrahydropyranyl derivative of [1α,2β-D_2] GA_1 13-acetate methyl ester **8** (400 mg, 95%) could be obtained as a diastereomeric mixture.
Found: M^+ 490.2500. $C_{27}H_{34}O_8D_2$ requires M^+ 490.2536.
^{1}H NMR (Me_2CO-d_6): δ 1.05 and 1.12 (2s, 18-H_3), 1.97 (s, Ac), 2.61 and 2.62 (2d, each *J*=10.7 Hz, 6-H), 3.24 (d, *J*=10.7 Hz, 5-H), 3.45–3.55 (m, 6'-H_A), 3.62 (br, 3-H), 3.71 and 3.72 (2s, CO_2Me, masking other 3-H), 3.80–3.95 (m, 6'-H_B), 4.68–4.77 (2m, 2'-H), 4.95 and 5.14 (each broad, 17-H_2). – EIMS, *m/z* (rel. int): 490 (M^+, 4), 459 (6), 448 (7), 430(11), 406 (61), 388 (36), 378 (16), 360 (10), 346 (38), 328 (37), 318 (17), 303 (36), 284 (100), 85 (76).
A solution of the THP ether **8** (400 mg, 0.82 mmol) in methanol (20 ml) and toluene-*p*-sulfonic acid (20 mg) was stirred at room temperature until the hydrolysis was complete (3 hr, TLC monitoring). The methanol was removed *in vacuo* and the residue was taken up in ethyl acetate, washed with water and evaporated. Flash chromatography, eluting with 55% ethyl acetate in hexane gave [1β,2α-D_2] GA_1 13-acetate methyl ester **9** (305 mg, 92%) containing 1.88 atoms deuterium.
Found: M^+ 406.1943. $C_{22}H_{26}O_7D_2$ req. M^+ 406.1916.
^{1}H NMR ($CDCl_3$): δ 1.14 (s, 18-H_3), 2.02 (s, Ac), 2.70 (d, *J*=10.7 Hz, 6-H), 3.22 (d, *J*=10.5 Hz, 5-H), 3.72 (s, CO_2Me), 3.84 (d, *J*=2.4 Hz, 3-H), 4.99 and 5.14 (each br, 17-H_2).
^{1}H NMR (Me_2CO-d_6, 500 MHz): δ 1.06 (s, 18-H_3), 1.79 (2β-H), 1.91 (1α-H), 1.96 (s, Ac), 2.61 (d, *J*=10.4 Hz, 6-H), 3.25 (d, *J*=10.4 Hz, 5-H), 3.70 (s, CO_2Me), 3.71 (3-H), 4.48 (d, *J*=4.3 Hz, 3β-OH), 4.94 and 5.12 (each br, 17-H_2). – ^{13}C NMR (500 MHz, Me_2CO, derived from HMQC): δ 14.9 (C-18), 27.5 (C-1), 28.5 (C-2), 52.1 (OMe), 52.2 (C-6), 52.2 (C-5), 70.1 (C-3), 107.7 (C-17). – EIMS, *m/z* (rel. int.): 406 (M^+, 8), 388 (1), 374 (9), 364 (100), 346 (13), 332 (12), 304 (26), 284 (57).

ent-1α,2β-Dideuterio-13-acetoxy-3α,10β-dihydroxy-16-oxo-17,20-bisnorgibberellan-7,19-dioic acid 7-methyl ester-19,10-lactone (**10**)

To [1β,2α-D_2] GA_1 13-acetate methyl ester **9** (305 mg, 0.75 mmol) in tetrahydrofuran (6 ml) and water (6 ml) osmium tetroxide (1 crystal) and sodium metaperiodate (350 mg) were added at 0 °C. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. After drying and evaporating the residue was purified by flash chromatography. Elution with 65% ethyl acetate in hexane gave [1β,2α-D_2] GA_1 13-acetate-16-norketone methyl ester **10** (215 mg, 70%).
Found: M^+ 408.1730. $C_{21}H_{24}O_8D_2$ req. M^+ 408.1753.
^{1}H NMR (Me_2CO-d_6): δ 1.09 (s, 18-H_3), 1.99 (s, Ac), 2.70 (d, *J*=10.7 Hz, 6-H), 3.30 (d, *J*=10.7 Hz, 5-H), 3.73 (br, 3-H), 3.75 (s, CO_2Me), 4.54 (d, *J*= 4.1 Hz, 3β-OH). – EIMS, *m/z* (rel. int.): 408 (M^+, 11), 377 (8), 366 (21), 348 (7), 338 (15), 320 (100), 306 (73), 274 (95), 260 (74).

Methylenation of the 16-norketone **10**

To a stirred solution of **10** (215 mg, 0.53 mmol) in dichloromethane (20 ml) the methylenation reagent (10 ml), prepared from Zn, $TiCl_4$ and CD_2Br_2 in tetrahydrofuran, was added at room temperature under an argon atmosphere [4]. After stirring for 3 hr at room temperature the mixture was dropped into a slurry of sodium hydrogencarbonate (8 g) and water (4 ml) under vigorous stirring. The clear organic solution was separated and the aqueous residue extracted with ethyl acetate. The combined organic solutions were dried and evaporated. Flash chromatography with 55% ethyl acetate in hexane gave

(i) ent-13-Acetoxy-1α,2β,17,17-tetradeuterio-3α,10β-dihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester 19,10-lactone (**11**)

(65 mg, 30%) containing 3.78 atoms deuterium per molecule
Found: M^+ 408.2073. $C_{22}H_{24}O_7D_4$ req. M^+ 408.2086.
^{1}H NMR ($CDCl_3$): δ 1.14 (s, 18-H_3), 2.02 (s, Ac), 2.70 (d, *J*=10.4 Hz, 6-H), 3.22 (d, *J*=10.4 Hz, 5-H), 3.72 (s, CO_2Me), 3.84 (d, *J*=1.4 Hz, 3-H). – EIMS *m/z* (rel. int.): 408 (M^+, 22), 366 (100), 348 (30), 334 (25), 306 (31), 286 (54), 260 (26), 245 (16), 227 (18) and

(ii) ent-1α,2β,17,17-tetradeuterio-3α,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**12**)

(31 mg, 16%), containing 3.78 atoms deuterium per molecule.
Found: M^+ 366.1966. $C_{20}H_{22}O_6D_4$ req. M^+ 366.1980.
^{1}H NMR ($CDCl_3$): δ 1.15 (s, 18-H_3), 2.70 (d, *J*=10.4 Hz, 6-H), 3.21 (d, *J*=10.2 Hz, 5-H), 3.72 (s, CO_2Me), 3.84 (br, 3-H). – EIMS, *m/z* (rel. int.): 366 (M^+, 37), 348 (11), 334 (100), 320 (13), 307 (43), 288 (26), 277 (19), 261 (14), 245 (16).

ent-1α,2β,17,17-Tetradeuterio-3α,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone (**13**)

(1β,2α,17,17-D_4) GA_1 13-acetate methyl ester **11** (65 mg, 0.16 mmol) in dichloromethane (1.5 ml) was stirred with 2,3-dihydropyrane (45 μl) and pyridinium-*p*-toluenesulfonate (4.5 mg) for 3 hr at room temperature. Work up yielded a gum which was dissolved in methanol (2ml) and refluxed with 2M aqueous sodium hydroxide (14ml) for 8 hr. Work up gave a single product by TLC which was stirred in methanol (5 ml) with toluene-*p*-sulfonic acid (5mg) for 3 hr at room temperature. The mixture was diluted with ethyl acetate, washed with water, dried and evaporated. Purification by flash chromatography with ethyl acetate-hexane-acetic acid (90:10:2) gave [1β,2α,

17,17-D_4] GA_1 **13** (37 mg, 66%) containing 3.78 atoms deuterium per molecule.
Found: M^+ 352.1847. $C_{19}H_{20}O_6D_4$ req. M^+ 352.1824.
^1H NMR (Me_2CO-d_6): δ1.12 (s, 18-H_3), 2.58 (d, J=10.4 Hz, 6-H), 3.23 (d, J=10.2 Hz, 5-H), 3.72 (br, 3-H). – EIMS, *m/z* (rel. int.): 352 (M^+, 37), 334 (100), 316 (7), 306 (22), 292 (38), 288 (24), 263 (13), 245 (15).
Demethylation of [1β,2α,17,17-D_4] GA_1 methyl ester **12** (31 mg) by the above described procedure should provide additional **13**.

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