

## Partial Synthesis of [1 $\beta$ ,2 $\alpha$ ,17,17-D<sub>4</sub>] Gibberellin A<sub>1</sub>

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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<sub>1</sub> from gibberellin A<sub>3</sub> is described. Based on iodolactonisation the method provides access to gibberellin A<sub>1</sub> labeled by deuterium with both high incorporation of the isotope

and high stereoselectivity at the positions 1 $\beta$  and 2 $\alpha$ . The additional deuterium labeling at C-17 was introduced *via* the corresponding 16-norketone resulting in [1 $\beta$ ,2 $\alpha$ ,17,17-D<sub>4</sub>] gibberellin A<sub>1</sub>.

In order to follow the metabolism of [17-D<sub>2</sub>] GA<sub>20</sub> and to quantify the resulting pool of [17-D<sub>2</sub>] GA<sub>1</sub> in *Hordeum vulgare* L. multilabeled GA<sub>1</sub> 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<sub>1</sub>. In the literature syntheses of GA<sub>1</sub> 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<sub>81</sub> (epi-GA<sub>29</sub>) starting from GA<sub>3</sub> [2]. Key reaction was the known conversion of GA<sub>3</sub> **1** into iodotriol **2**, which could be selectively acylated to the corresponding 2 $\alpha$ ,13-diacetate **3**. We found that this initial approach is also suitable to transform the functionality of GA<sub>3</sub> into that of GA<sub>1</sub> 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<sub>3</sub> (**1**)) with tri-*n*-butyltin deuteride gave the [1 $\beta$ -D] GA<sub>56</sub> derivative **4** containing 0.94 atoms deuterium in 87% yield.

The deacetylation of the 2 $\alpha$ -hydroxy group of **4** after protection of the 3 $\beta$ -hydroxy group as tetrahydropyranyl ether gave **6** in 75% yield.

In order to remove the 2 $\alpha$ -hydroxy group, compound **6** was treated with phenoxythiocarbonyl chloride in the

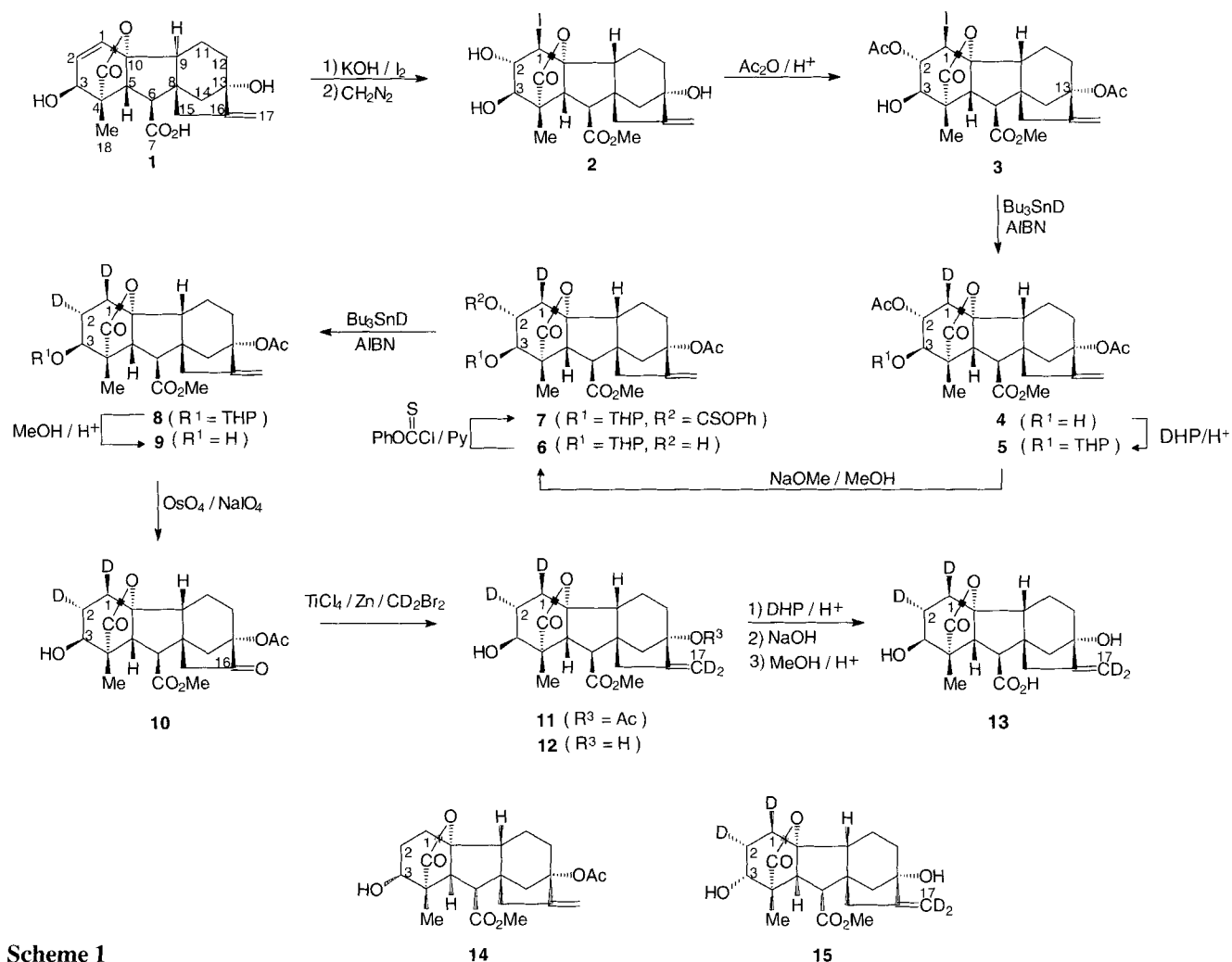
presence of pyridine to yield 90% of the corresponding phenyl thionocarbonate **7**. Radical mediated deoxygenation of **7** using tri-*n*-butyltin deuteride afforded **8** (95%), which after hydrolysis resulted in [1 $\beta$ ,2 $\alpha$ -D<sub>2</sub>] GA<sub>1</sub> 13-acetate methyl ester **9** in 92% yield from **8** (26% overall yield from GA<sub>3</sub> (**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 <sup>1</sup>H-<sup>1</sup>H-COSY and HMQC experiments of the unlabeled GA<sub>1</sub> 13-acetate methyl ester **14** the four cross peaks at  $\delta$  1.93, 1.81 ( $\delta$  <sup>13</sup>C 27.9) and 1.805, 1.68 ( $\delta$  <sup>13</sup>C 29.0) were assigned to the protons at C-1 and C-2, respectively. In the NOE difference spectrum of **14** irradiation at  $\delta$  4.48 (3 $\beta$ -OH) and 3.25 (5 $\beta$ -H) gave positive enhancement of the multiplet at 1.81 ppm, which therefore was assigned to 1 $\beta$ -H.

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

The <sup>2</sup>H NMR spectrum displayed two broad signals with nearly the same intensity at  $\delta$  1.79 and 1.65.

In the <sup>1</sup>H NMR spectrum of **9** the signal at  $\delta$  1.79 appears as broad singlet, whereas the signal at  $\delta$  1.91 is superimposed with H-9 and H-11 $\alpha$ . On the basis of the proton chemical shifts obtained for H-1 $\alpha$  ( $\delta$  1.93)



Scheme 1

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

Consequently, both reduction steps with tri-*n*-butyl

deuteride have taken place under retention of configuration.

For further confirmation of the 1 $\beta$ ,2 $\alpha$ -stereochemistry of the deuterium atoms, the 3 $\beta$  alcohol **11** was epimerized to [1 $\beta$ ,2 $\alpha$ ,17,17-D<sub>4</sub>] epi-GA<sub>1</sub> methyl ester **15** in methanol with a catalytical amount of potassium carbonate [3]. This 3 $\alpha$ -alcohol **15** also contained 3.78 atoms deuterium, indicating that the label at C-2 remained. The <sup>1</sup>H NMR spectrum of **15** displayed a double doublet at  $\delta$  3.70,  $J = 5.8/5.8$  Hz assigned to 3 $\beta$ -H. The vicinal coupling constant of H-3 $\beta_{ax}$  with H-2 of 5.8 Hz proves H-2 to be equatorial orientated and hence the presence of a H-2 $\beta$  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<sub>4</sub>-CD<sub>2</sub>Br<sub>2</sub> [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 3 $\beta$ -hydroxy group as the tetrahydropyranyl ether (to avoid epimerisation at C-3), gave the required [ $1\beta,2\alpha,17,17\text{-D}_4$ ] GA<sub>1</sub> **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 2 $\alpha$  position the labeled GA<sub>1</sub> synthesized by this method represents not only an ideal internal standard for quantitative analysis but also a potent precursor for studying the stereochemistry of 2 $\beta$ -hydroxylations and 1,2- and 2,3-dehydrogenations.

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## Experimental

<sup>1</sup>H NMR spectra were recorded at 300 MHz, unless otherwise stated, using a VARIAN GEMINI 2000-300BB. <sup>1</sup>H-<sup>1</sup>H COSY, HMQC and NOE difference spectra (500 MHz, Aceton-d<sub>6</sub>) and the <sup>2</sup>H NMR spectrum (76.7 MHz, Aceton) were recorded on a VARIAN UNITY 500. All chemical shifts  $\delta$  (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 (MERCCK) using N<sub>2</sub> positive pressure. Bu<sub>3</sub>SnD was obtained from FLUKA.

Nomenclature and numbering of the *ent*-gibberellane skeleton see [5] and [6], respectively.

### *ent*-2 $\beta,3\alpha,10\beta,13$ -Tetrahydroxy-1 $\alpha$ -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<sub>3</sub> (1g. 2.89 mmol) yield 690 mg (65%).

Found: M<sup>+</sup> 504.0618. C<sub>20</sub>H<sub>25</sub>IO<sub>7</sub> req. M<sup>+</sup> 504.0645. – <sup>1</sup>H NMR (Me<sub>2</sub>CO-d<sub>6</sub>):  $\delta$  1.13 (s, 18-H<sub>3</sub>), 2.63 (d,  $J=9.6$  Hz, 6-H), 3.73 (s, CO<sub>2</sub>Me), 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<sub>2</sub>). – EIMS,  $m/z$  (rel. int.): 504 (M<sup>+</sup>, 34), 472 (16), 454 (25), 445 (100), 359 (17), 345 (20), 327 (45), 317 (29), 299 (57), 281 (34), 271 (29), 255 (36).

### *ent*-2 $\beta,13$ -Diacetoxy-3 $\alpha,10\beta$ -dihydroxy-1 $\alpha$ -iodo-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**3**)

A mixture of 1 $\beta$ -iodo-GA<sub>56</sub> 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 1 $\beta$ -iodo-GA<sub>56</sub> 2,13-diacetate methyl ester **3** as a gum (860 mg, 78%).

Found: M<sup>+</sup> 588.1022. C<sub>24</sub>H<sub>29</sub>IO<sub>9</sub> req. M<sup>+</sup> 588.0856.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.20 (s, 18-H<sub>3</sub>), 2.02 and 2.06 (2s, 2 Ac), 2.71 (d,  $J=10.0$  Hz, 6-H), 3.75 (s, CO<sub>2</sub>Me), 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<sub>2</sub>), 5.45 (br, 2-H). – <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>, derived from HMQC):  $\delta$  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<sup>+</sup>, 34), 546 (100), 528 (10), 487 (17), 401 (9), 383 (18), 359 (21), 297 (24), 237 (24).

### *ent*-1 $\alpha$ -Deuterio-2 $\beta,13$ -diacetoxy-3 $\alpha,10\beta$ -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 [ $1\beta\text{-D}$ ] GA<sub>56</sub> 2,13-diacetate methyl ester **4** as a gum (590 mg, 87%) containing 0.94 deuterium atoms per molecule.

Found: M<sup>+</sup> 463.1979. C<sub>24</sub>H<sub>29</sub>O<sub>9</sub>D req. M<sup>+</sup> 463.1953.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.17 (s, 18-H<sub>3</sub>), 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<sub>2</sub>Me), 4.99 (br, 17-H and 2-H), 5.15 (br, 17-H). – EIMS,  $m/z$  (rel. int.): 463 (M<sup>+</sup>, 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*-1 $\alpha$ -deuterio-13-acetoxy-2 $\beta,3\alpha,10\beta$ -trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-methyl ester-19,10-lactone (**6**)

[ $1\beta\text{-D}$ ] GA<sub>56</sub> 2,3-diacetate methyl ester **4** (590 mg, 1.27 mmol) in dichloromethane (8.5 ml) was stirred with 2,3-dihydropyrane (DHP, 400  $\mu$ l) 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. – <sup>1</sup>H NMR (Me<sub>2</sub>CO-d<sub>6</sub>):  $\delta$  1.05 and 1.12 (2s, 18-H<sub>3</sub>), 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<sub>A</sub>), 3.54 and 3.66 (each br, 3-H), 3.71 and 3.72 (2s, CO<sub>2</sub>Me), 3.89 (m, 6'-H<sub>B</sub>), 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<sub>2</sub>). – EIMS,  $m/z$  (rel. int.): 505 (M<sup>+</sup>, 0.3), 421 (10), 389 (6), 361 (9), 329 (8), 298 (8), 85 (100).

### 3-*O*-Tetrahydropyranyl derivative of *ent*-1 $\alpha$ -deuterio-13-acetoxy-3 $\alpha,10\beta$ -dihydroxy-2 $\beta$ -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  $\mu$ l) and phenoxythiocarbonyl chloride (195  $\mu$ l) were added. After 4 hr the solvents were evaporated and the residue was partitioned 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. –  $^1\text{H NMR}$  ( $\text{Me}_2\text{CO-d}_6$ ):  $\delta$  1.14 and 1.18 (2s, 18-H<sub>3</sub>), 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<sub>2</sub>Me), 3.51 (m, 6'-H<sub>A</sub>), ca 3.90 (m, 6'-H<sub>B</sub>), 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<sub>2</sub>), 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-1 $\alpha,2\beta$ -Dideuterio-13-acetoxy-3 $\alpha,10\beta$ -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  $\mu\text{l}$ ) 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 [ $1\alpha,2\beta\text{-D}_2$ ] GA<sub>1</sub> 13-acetate methyl ester **8** (400 mg, 95%) could be obtained as a diastereomeric mixture.

Found:  $M^+$  490.2500.  $\text{C}_{27}\text{H}_{34}\text{O}_8\text{D}_2$  requires  $M^+$  490.2536.

$^1\text{H NMR}$  ( $\text{Me}_2\text{CO-d}_6$ ):  $\delta$  1.05 and 1.12 (2s, 18-H<sub>3</sub>), 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<sub>A</sub>), 3.62 (br, 3-H), 3.71 and 3.72 (2s, CO<sub>2</sub>Me, masking other 3-H), 3.80–3.95 (m, 6'-H<sub>B</sub>), 4.68–4.77 (2m, 2'-H), 4.95 and 5.14 (each broad, 17-H<sub>2</sub>). – 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 [ $1\beta,2\alpha\text{-D}_2$ ] GA<sub>1</sub> 13-acetate methyl ester **9** (305 mg, 92%) containing 1.88 atoms deuterium.

Found:  $M^+$  406.1943.  $\text{C}_{22}\text{H}_{26}\text{O}_7\text{D}_2$  req.  $M^+$  406.1916.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.14 (s, 18-H<sub>3</sub>), 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<sub>2</sub>Me), 3.84 (d,  $J=2.4$  Hz, 3-H), 4.99 and 5.14 (each br, 17-H<sub>2</sub>).

$^1\text{H NMR}$  ( $\text{Me}_2\text{CO-d}_6$ , 500 MHz):  $\delta$  1.06 (s, 18-H<sub>3</sub>), 1.79 (2 $\beta$ -H), 1.91 (1 $\alpha$ -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<sub>2</sub>Me), 3.71 (3-H), 4.48 (d,  $J=4.3$  Hz, 3 $\beta$ -OH), 4.94 and 5.12 (each br, 17-H<sub>2</sub>). –  $^{13}\text{C NMR}$  (500 MHz,  $\text{Me}_2\text{CO}$ , derived from HMQC):  $\delta$  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-1 $\alpha,2\beta$ -Dideuterio-13-acetoxy-3 $\alpha,10\beta$ -dihydroxy-16-oxo-17,20-bisnorgibberell-7,19-dioic acid 7-methyl ester-19,10-lactone (10)*

To [ $1\beta,2\alpha\text{-D}_2$ ] GA<sub>1</sub> 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 [ $1\beta,2\alpha\text{-D}_2$ ] GA<sub>1</sub> 13-acetate-16-norketone methyl ester **10** (215 mg, 70%).

Found:  $M^+$  408.1730.  $\text{C}_{21}\text{H}_{24}\text{O}_8\text{D}_2$  req.  $M^+$  408.1753.

$^1\text{H NMR}$  ( $\text{Me}_2\text{CO-d}_6$ ):  $\delta$  1.09 (s, 18-H<sub>3</sub>), 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<sub>2</sub>Me), 4.54 (d,  $J=4.1$  Hz, 3 $\beta$ -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<sub>4</sub> and CD<sub>2</sub>Br<sub>2</sub> 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-1 $\alpha,2\beta,17,17$ -tetra-deuterio-3 $\alpha,10\beta$ -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.  $\text{C}_{22}\text{H}_{24}\text{O}_7\text{D}_4$  req.  $M^+$  408.2086.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.14 (s, 18-H<sub>3</sub>), 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<sub>2</sub>Me), 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-1 $\alpha,2\beta,17,17$ -tetra-deuterio-3 $\alpha,10\beta,13$ -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.  $\text{C}_{20}\text{H}_{22}\text{O}_8\text{D}_4$  req.  $M^+$  366.1980.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.15 (s, 18-H<sub>3</sub>), 2.70 (d,  $J=10.4$  Hz, 6-H), 3.21 (d,  $J=10.2$  Hz, 5-H), 3.72 (s, CO<sub>2</sub>Me), 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-1 $\alpha,2\beta,17,17$ -Tetra-deuterio-3 $\alpha,10\beta,13$ -trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone (13)*

( $1\beta,2\alpha,17,17\text{-D}_4$ ) GA<sub>1</sub> 13-acetate methyl ester **11** (65 mg, 0.16 mmol) in dichloromethane (1.5 ml) was stirred with 2,3-dihydropyran (45  $\mu\text{l}$ ) 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 [ $1\beta,2\alpha,$

17,17-D<sub>4</sub>] GA<sub>1</sub> **13** (37 mg, 66%) containing 3.78 atoms deuterium per molecule.

Found: M<sup>+</sup> 352.1847. C<sub>19</sub>H<sub>20</sub>O<sub>6</sub>D<sub>4</sub> req. M<sup>+</sup> 352.1824.

<sup>1</sup>H NMR (Me<sub>2</sub>CO-d<sub>6</sub>): δ 1.12 (s, 18-H<sub>3</sub>), 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<sup>+</sup>, 37), 334 (100), 316 (7), 306 (22), 292 (38), 288 (24), 263 (13), 245 (15).

Demethylation of [1β,2α,17,17-D<sub>4</sub>] GA<sub>1</sub> methyl ester **12** (31 mg) by the above described procedure should provide additional **13**.

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