

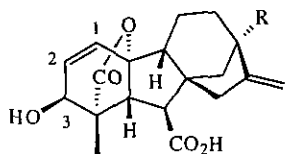
IMPROVED PROCEDURES FOR DIRECT CONVERSIONS OF NATURAL 3 β -HYDROXY-GIBBERELLINS TO 3 α -HYDROXY- AND 3-OXO-GIBBERELLINS

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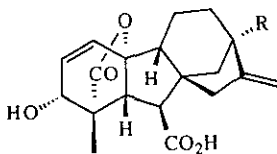
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Abstract—Natural 3 β -hydroxy-gibberellins, GA₃ (gibberellic acid) (1), GA₁ (2), and GA₄ (3), were directly converted to 3 α -hydroxy-gibberellins, 3-*epi*-GA₃ (4), -GA₁ (5) and -GA₄ (6), by highly α -biased equilibration through retro- and re-aldol mechanism with potassium *tert*-butoxide in *tert*-butyl alcohol, and to 3-oxo-gibberellins, 3-oxo-GA₉₅ (7), -GA₂₀ (8) and -GA₉ (9), by catalytic oxidation with tetrapropylammonium perruthenate.

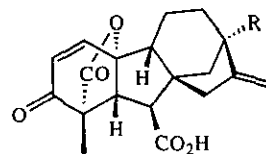
In recent study, we found that not only GA₄ (3) with 3 β -hydroxyl group (3 β -OH) but also 3-*epi*-GA₄ (6) with 3 α -OH and 3-oxo-GA₉ (9) showed the activities both in promoting hypocotyl elongation and in reduction of *GA4* gene transcript levels of *Arabidopsis thaliana*.¹ This contradicts with a hypothesis proposed by Reeve and Crozier that the 3 β -OH is the key to gibberellin (GA) activity in some plants.² The similar results are scattered in earlier papers,³ but it is still unclear what kind of functionalities at the C-3 are eligible for a variety of GA activities. In connection with the works on the structure identification of natural GAs and their syntheses, 3 α -OH- and 3-oxo-GA₅ have been prepared on occasions⁴ but the yields were unsatisfactory. With a view to supplying sufficient materials for systematic investigations on GA activities of C-3 functional variants of GAs, we report here improved procedures for direct conversions of typical natural GAs, GA₃ (gibberellic acid) (1), GA₁ (2) and 3, to the corresponding 3 α -OH-GAs, 3-*epi*-GA₃ (4), 3-*epi*-GA₁ (5) and 6, and to 3-oxo-GAs, 3-oxo-GA₉₅ (7), 3-oxo-GA₂₀ (8) and 9.



- 1 R=OH
2 1,2-dihydro, R=OH
3 1,2-dihydro, R=H



- 4 R=OH
5 1,2-dihydro, R=OH
6 1,2-dihydro, R=H

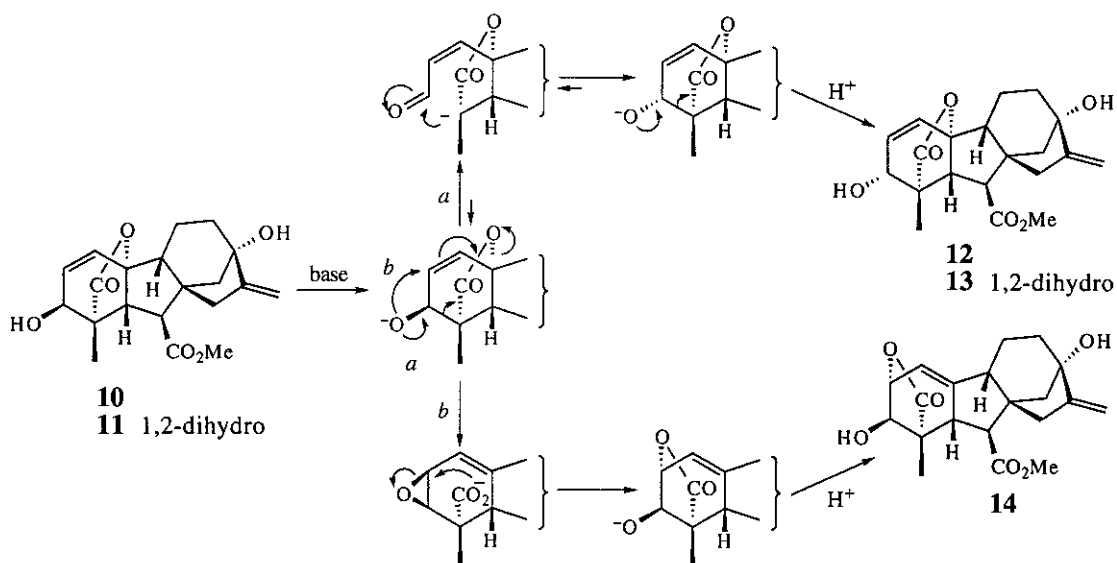


- 7 R=OH
8 1,2-dihydro, R=OH
9 1,2-dihydro, R=H

RESULTS AND DISCUSSION

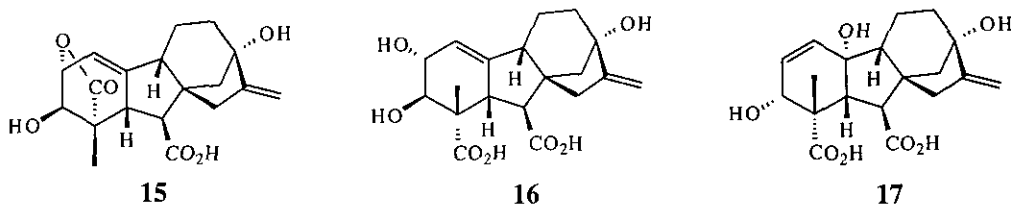
Preparations of 3 α -hydroxy-gibberellins

In previous paper,⁵ we described that treatment of GA₃ methyl ester (**10**) or GA₁ methyl ester (**11**) with sodium hydride in an aprotic medium led to a highly α -biased equilibration of the 3-hydroxyl function through retro- and re-aldol mechanism (path *a* in Scheme), giving 3-*epi*-GA₃ methyl ester (**12**) or 3-*epi*-GA₁ methyl ester (**13**) in high yields without considerable side reactions, *e.g.*, rearrangement of a 1,2-unsaturated compound (**10**) to *iso*-lactone (**14**) via an epoxide (path *b*), which is the typical reaction under basic conditions using protic solvent. However, these conditions did not work on free acids (**1**, **2** and **3**), because their low solubilities hampered the reaction. Although the competing lactone rearrangement of GA₃ (**1**) affording *iso*-GA₃ (**15**) could not be avoided, these epimerizations were consequently achieved under Kirkwood's conditions using potassium *tert*-butoxide (*t*-BuOK) in *tert*-butyl alcohol (*t*-BuOH) with some modifications:⁶ long time treatment for full equilibration and in the case of **1** the subsequent aqueous alkali hydrolysis to get isolation of 3-*epi*-GA₃ (**4**) from the by-products much easier.



When GA₃ (**1**) was treated with a large excess of *t*-BuOK in *t*-BuOH at room temperature for 7 days, the reaction reached to the stationary state, monitored by TLC. After an acidic work-up followed by refluxing in acetone for 3 h, ¹H NMR analysis showed that the product mixture consisted of **1**, 3-*epi*-GA₃ (**4**), *iso*-GA₃ (**15**) and the open lactone (**16**) in a ratio of 2:70:22:6. Since monocarboxylic acids (**1**, **4** and **15**) had similar *R_f* values on TLC each other, the purification of **4** by column chromatography was a tedious work at this stage. It is well documented that under aqueous alkali conditions, **1** is irreversibly converted to open lactone (**16**) through lactone rearrangement to **15** followed by alkali hydrolysis.^{7,8} In addition, we found here that open lactone (**17**) completely re-lactonize to **4** in refluxing acetone, but **16** did not at all. Thus, to make the purification easier and practical, the obtained mixture was treated with 1 N sodium hydroxide solution at room temperature for 20 h. As expected, after an acidic work-up followed by refluxing in

acetone for 3 h, a mixture of monocarboxylic acid (**4**) and dicarboxylic acid (**16**) was obtained. Due to the large difference of their R_f values, the obtained mixture was easily separated by column chromatography to give 3-*epi*-GA₃ (**4**) and **16** in 51 and 12% isolated yields, respectively.



As well, the treatment of 1,2-saturated compounds, GA₁ (**2**) and GA₄ (**3**), with *t*-BuOK in *t*-BuOH at room temperature for 7 days led to the formation of a 2:98 mixture of **2** and 3-*epi*-GA₁ (**5**) (86%), and a 5:95 mixture of **3** and 3-*epi*-GA₄ (**6**) (84%). The highly α -biased equilibration through retro- and re-aldol mechanism observed here was in contrast to the equilibration with low selectivities under conventional conditions:^{9,10} *e.g.*, a *ca.* 4:6 mixture of **2** and **5** was obtained both from **2** and **5** by the treatment with sodium methoxide in methanol at room temperature for 20 h.

Preparations of 3-oxo-gibberellins

Oxidation of the 3 β -hydroxyl GAs to the corresponding 3-oxo-GAs has been attained so far by using the Jones reagent,¹¹ pyridinium dichromate¹² and manganese dioxide,⁷ the latter of which is specific for an allylic alcohol, GA₃ (**1**), but their yields were not satisfactory. Among them pyridinium dichromate gave the high yields in oxidation of methyl esters of GAs, but the application to the free acids (**1**, **2** and **3**) resulted in low yields: our re-investigation suggested that this was due to the low recovery of the products by extraction procedure. Among oxidation conditions tested, catalytic oxidation with tetrapropylammonium perruthenate (TPAP)¹³ was eventually found to afford a successful result. On treatment of **1** with 3 equiv. of *N*-methylmorpholine *N*-oxide in the presence of 10 mol% TPAP and powdered 4Å molecular sieve (*ca.* 600 mg/mmol of **1**) in acetonitrile at temperatures from 0°C to room temperature for 1 h, 3-oxo-GA₉₅ (**7**) was obtained in 71% isolated yield after an usual aqueous work-up followed by column chromatography. As well, according to the same reaction procedure, **2** and **3** respectively yielded 3-oxo-GA₂₀ (**8**) (89%) and 3-oxo-GA₉ (**9**) (81%).

The simple methods described above provided a sufficient amount of 3 α -OH- and 3-oxo-GAs completely free from the parent 3 β -OH-GAs possessing high GA activities, contamination with which has been often a stumbling block to the precise assessment on GA activities of their derivatives. It is particularly noteworthy that the easy purification of 3-*epi*-GA₃ (**4**) and 3-oxo-GA₉₅ (**7**) by column chromatography allows their large-scale preparations for field trials. The starting material GA₃ (**1**) is now produced commercially in ton quantities by the fermentation of the fungus *Gibberella fujikuroi* and used in agriculture. However, the diverse activities of **1** limit its practical applications, thus calling for the commercially convenient alternative possessing a more specified activity. As well as large-scale field trials of **4** and **7**, systematic investigations on a variety of GA activities of C-3 functional variants of GAs prepared here are being undertaken.

EXPERIMENTAL

General.—Melting points were determined on Yanagimoto micromelting point apparatus and are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 Plus spectrometer in an acetone- d_6 solution. Chemical shifts were recorded as δ ppm relative to the solvent peaks: at 2.04 ppm for ^1H or at 29.80 ppm for ^{13}C . All J values are given in Hz. MS spectra, FAB-MS, were obtained with a JEOL-HX-110 mass spectrometer. Analytical TLC was conducted on micro-slides coated with Merck Kieselgel KG60F-254; the developed plates were stained with 10% (w/v) vanillin in concentrated sulfuric acid at 180°C. All reactions were carried out under a nitrogen atmosphere. Column chromatography was conducted using Wakogel C-300 [Wako Pure Chemical Industries] as the adsorbent. The ratios of mixed solvents were v/v.

Preparation of 3-epi-Gibberellins.—(a) *3-epi-GA*₃ (**4**). A solution of *GA*₃ (**1**) (1.0 g, 0.55 mmol) and *t*-BuOK (1.6 g, 14.3 mmol) in anhydrous *t*-BuOH (100 mL) was stirred at rt for 7 days. After addition of acetic acid (10 mL) to neutralize the alkali and removal of solvent, the residue was dissolved in water. The solution was acidified with 2N HCl to pH 3-4, and extracted with AcOEt. The extracts were successively washed with water and brine, dried over Na₂SO₄, and evaporated. The residue was then dissolved in acetone (50 mL) and the solution was refluxed for 3 h and evaporated to give a gum (860 mg), which was shown to consist of **1**, *3-epi-GA*₃ (**4**), *iso-GA*₃ (**15**) and the open lactone (**16**) in a ratio of 2:70:22:6 by the ^1H NMR spectrum. This gum was then dissolved in 1N NaOH (50 mL) and the solution was stirred at rt for 20 h, and acidified with 2N HCl to pH 3-4. After the same extraction procedure and the subsequent treatment in refluxing acetone as described above, the obtained foam was subjected to column chromatography. Elution with ethyl acetate gave *3-epi-GA*₃ (**4**) as a colorless amorphous powder (510 mg, 51%) [lit.,¹⁴ 173-176°C]; δ_{H} 1.23 (3H, s, 18-H₃), 2.19 (1H, dm, $J=15.6$, 15-H), 2.33 (1H, dt, $J=15.6$ and 2.8, 15-H), 2.65 and 2.85 (each 1H, ABq, $J=10.5$, 5-H and 6-H), 4.31 (1H, dd, $J=2.6$ and 1.8, 3-H), 4.86 and 5.19 (each 1H, each m, 17-H₂), 5.83 (1H, dd, $J=9.3$ and 2.6, 2-H), 6.29 (1H, dd, $J=9.3$ and 1.8 Hz, 1-H); δ_{C} 14.89 (C-18), 17.73, 39.76, 43.77, 45.64 (C-11, -12, -14 and -15), 50.39 and 55.62 (C-4 and 8), 51.82, 52.07, 58.66 (C-5, -6 and -9), 74.21 (C-3), 78.09 (C-13), 89.56 (C-10), 106.73 (C-17), 131.07 and 134.53 (C-1 and -2), 158.80 (C-16), 173.45 and 175.99 (C-7 and -19); FAB-MS m/z 347 (M+H)⁺. Elution with AcOEt-AcOH (50:1) gave dicarboxylic acid (**16**) (116 mg, 12%) as a colorless amorphous powder [lit.,⁷ an amorphous powder]; δ_{H} 1.37 (3H, s, 18-H₃), 2.24 (1H, dm, $J=16.3$, 15-H), 2.53 (1H, m, 9-H), 2.68 (1H, dt, $J=16.3$ and 2.9, 15-H), 2.98 (1H, d, $J=5.3$, 6-H), 3.14 (1H, m, 5-H), 3.92 (1H, br s, 2- or 3-H), 4.05 (1H, m, 2- or 3-H), 4.90 (1H, br s, 17-H), 5.07 (1H, m, 17-H), 5.37 (1H, dm, $J=2.6$, 1-H); δ_{C} 21.71 (C-18), 19.29, 38.68, 40.05 and 49.32 (C-11, -12, -14 and -15), 47.06, 47.18 and 50.51 (C-5, -6 and -9), 47.85 and 50.16 (C-4 and -8), 71.79 and 75.67 (C-2 and -3), 79.26 (C-13), 105.94 (C-17), 143.72 (C-1), 156.20 (C-16), 176.82 and 177.72 (C-7 and 19). The authentic samples of **15** and **16** were prepared by following the methods previously reported.^{9,7} **15**: a colorless amorphous powder [lit.,⁹ amorphous powder]; δ_{H} 1.14 (3H, s, 18-H₃), 1.32 (1H, dd, $J=10.9$ and 2.2), 1.50 (1H, dd, $J=10.9$ and 2.9), 2.28 (1H, dm, $J=16.3$, 15-H), 2.42 (1H, d, $J=6.1$, 6-H), 2.57 (1H, br d, $J=6.0$, 9-H), 2.66 (1H, dt, $J=16.3$ and 2.9), 3.32 (1H, dd, $J=6.0$ and 2.5, 5-H), 4.27 (1H, d,

$J=5.3$, 3-H), 4.68 (1H, t, $J=5.3$, 2-H), 4.91 and 5.07 (each 1H, each br s), 5.79 (1H, dt, $J=5.3$ and 2.5, 1-H); δ_C 17.35 (C-18), 19.32, 38.48, 39.90 and 49.56 (C-11, -12, -14 and -15), 46.23, 46.63 and 49.99 (C-5, -6 and -9), 49.05 and 49.70 (C-4 and -8), 74.84 and 75.74 (C-2 and -3), 78.96 (C-13), 106.22 (C-17), 114.52 (C-1), 151.86 and 155.64 (C-10 and -16), 176.15 and 177.58 (C-7 and -19).

(b) *3-epi-GA*₁ (**5**). *GA*₁ (**2**) (50 mg, 0.14 mmol) was treated with *t*-BuOK (90 mg, 0.80 mmol) in anhydrous *t*-BuOH (5 mL) at rt for 7 days. After addition of AcOH (0.5 mL) and removal of volatile materials under reduced pressure, the residue was dissolved into water, acidified to pH 3-4 with 2N HCl, and then extracted with AcOEt. The combined extracts were successively washed with water and brine, and dried over Na₂SO₄. After evaporation of the solvents, a yellow solid was dissolved into acetone (20 mL), and the solution was refluxed for 1 h and evaporated to give the residue, which was shown to consist of **2** and *3-epi-GA*₁ (**5**) in a ratio of 2:98 by the ¹H NMR spectrum. Column chromatography using AcOEt as the eluent afforded a mixture of **2** and **5** (5.2 mg, 10%), and *3-epi-GA*₁ (**5**) (38 mg, 76%) as a colorless amorphous powder [lit.,¹⁴ mp 221-224°C]: δ_H 1.12 (3H, s, 18-H₃), 2.33 (1H, dm, $J=15.6$), 2.53 and 2.63 (each 1H, ABq, J 9.8, 5-H and 6-H), 3.70 (1H, dd, J 10.8 and 5.9, 3-H), 4.85 and 5.17 (each 1H, each br s, 17-H₂); δ_C 13.52 (C-18), 18.05, 29.98, 30.38, 39.74, 43.71 and 46.12 (C-1, -2, -11, -12, -14 and -15), 52.14, 53.29 and 57.92 (C-5, -6 and -9), 50.82 and 54.96 (C-4 and -8), 73.44 (C-3), 78.16 (C-13), 92.37 (C-10), 106.60 (C-17), 158.62 (C-16), 173.95 and 177.09 (C-7 and C-19); FAB-MS m/z 349 (M+H)⁺.

(c) *3-epi-GA*₄ (**6**). The same procedure as for **2** was applied to *GA*₄ (**3**) (50 mg, 0.15 mmol). The crude mixture was shown to consist of **3** and *3-epi-GA*₄ (**6**) in a ratio of 5:95 by the ¹H NMR spectrum. Column chromatography using AcOEt afforded a mixture of **3** and **6** (11 mg, 22%), and *3-epi-GA*₄ (**6**) (31 mg, 62%) as a colorless amorphous powder [lit.,¹¹ 215-220°C]: δ_H 1.12 (3H, s, 18-H₃), 2.52 and 2.64 (each 1H, ABq, $J=10.6$, 5-H and 6-H), 2.60 (1H, br t, $J=6.1$ Hz, 13-H), 3.70 (1H, dd, $J=10.9$ and 5.9, 3-H), 4.82 and 4.95 (each 1H, each br s, 17-H₂); δ_C 13.57 (C-18), 16.75, 30.02, 30.57, 32.21, 37.62 and 44.97 (C-1, -2, -11, -12, -14 and -15), 39.67, 52.39, 54.02 and 57.37 (C-5, -6, -9 and -13), 52.73 and 54.96 (C-4 and -8), 73.25 (C-3), 92.64 (C-10), 107.41 (C-17), 158.12 (C-16), 173.90 and 177.11 (C-7 and C-19); FAB-MS m/z 333 (M+H)⁺.

Preparation of 3-Oxo-Gibberellins.—(a) *3-oxo-GA*₉₅ (**7**). To a homogeneous solution of *GA*₃ (**1**) (110 mg, 0.32 mmol), *N*-methylmorpholine *N*-oxide (113 mg, 0.96 mmol) and powdered molecular sieve 4Å (200 mg) in anhydrous acetonitrile (2 mL) was added tetrapropylammonium perruthenate (11 mg, 0.031 mmol) in one portion at 0°C and the mixture was stirred at 0°C for 30 min and then at rt for 30 min. After removal of solvent, the residue was suspended into a mixture of water and AcOEt, and acidified with 1N HCl. AcOEt layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were successively washed with water and brine, then dried over Na₂SO₄. Removal of the solvent and column chromatography using hexane-AcOEt-AcOH (1:2:0.03) as the eluent afforded *3-oxo-GA*₉₅ (**7**) (78 mg, 71%) as a colorless needles: mp 200-202°C (AcOEt-hexane) [lit.,¹² mp 202-205°C]: δ_H 1.21 (3H, s, 18-H₃), 2.23 (1H, dd, $J=11.0$ and 6.3), 2.28 (1H, ddm, $J=15.6$ and 1.9, 15-H), 2.37 (1H, dt, $J=15.6$ and 2.8, 15-H), 2.86 (1H, d, $J=10.6$, 6-H), 3.55 (1H, d, $J=10.6$, 5-H), 4.89 and 5.23 (each 1H, each br s, 17-H₂), 6.04 (1H, d, $J=9.4$, 2-H), 7.59 (1H, d, $J=9.4$, 1-H); δ_C 11.85 (C-18), 17.59, 39.60, 43.49

and 45.38 (C-11, -12, -14 and -15), 51.78, 52.40 and 62.70 (C-5, -6 and -9), 50.10 and 65.63 (C-4 and -8), 77.95 (C-13), 90.62 (C-10), 107.09 (C-17), 129.04 (C-2), 149.66 (C-1), 158.50 (C-16), 172.60 and 173.93 (C-7 and C-19), 192.98 (C-3); FAB-MS m/z 345 (M+H)⁺.

(b) 3-oxo-GA₂₀ (**8**). The same procedure as for **1** was applied to GA₁ (**2**) (60 mg, 0.17 mmol). After column chromatography using hexane-AcOEt-AcOH (1:2:0.03), 3-oxo-GA₂₀ (**8**) (53 mg, 89%) was obtained as a colorless amorphous powder [lit.,¹⁵ 125-128° from acetone-hexane]: δ_H 1.11 (3H, s, 18-H₃), 2.75 (1H, d, $J=9.6$, 6-H), 3.17 (1H, d, $J=9.6$, 5-H), 4.88 and 5.19 (each 1H, each br s, 17-H₂); δ_C 10.82 (C-18), 18.20, 31.03, 35.14, 39.61, 43.45 and 46.12 (C-1, -2, -11, -12, -14 and -15), 52.20, 53.01 and 57.57 (C-5, -6 and -9), 51.39 and 63.72 (C-4 and -8), 78.07 (C-13), 93.53 (C-10), 106.89 (C-17), 158.12 (C-16), 173.23 and 174.49 (C-7 and C-19), 201.30 (C-3); FAB-MS m/z 347 (M+H)⁺.

(c) 3-oxo-GA₉ (**9**). The same procedure as for **1** was applied to GA₄ (**3**) (51 mg, 0.15 mmol). After column chromatography using hexane-AcOEt-AcOH (2:1:0.015) as the eluent, 3-oxo-GA₉ (**9**) (41 mg, 81%) was obtained as colorless granules: mp 220-225°C (decomp) (AcOEt-hexane) [lit.,¹¹ 258-260°C (decomp.)]; δ_H 1.10 (3H, s, 18-H₃), 1.40 (1H, ddd, $J=12.7$, 10.9 and 7.6), 2.64 (1H, br t, $J=6.0$, 13-H), 2.76 (1H, d, $J=10.3$, 6-H), 3.16 (1H, d, $J=10.3$, 5-H), 4.85 (1H, br s, 17-H), 4.98 (1H, br d, J 1.1 Hz, 17-H); δ_C 10.88 (C-18), 16.86, 31.25, 32.12, 35.22, 37.64 and 44.73 (C-1, -2, -11, -12, -14 and -15), 39.54, 52.52, 53.81 and 57.13 (C-5, -6, -9 and -13), 53.25 and 63.76 (C-4 and -8), 93.77 (C-10), 107.71 (C-17), 157.68 (C-16), 173.01 and 174.53 (C-7 and C-19), 201.39 (C-3); FAB-MS m/z 331 (M+H)⁺.

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gave a 70:30 mixture of 3-*epi*-GA₃ (**4**) and dicarboxylic acid (**16**) in 75% yield, which is nearly similar result to that obtained by our modified procedure. However, our reinvestigation showed that the presence of water largely increased the formation of **16**.

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