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Stereoselective Functionalization at C-2 and C-3 of the Gibberellin *via* an Intramolecular Free Radical Cyclization Approach

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Abstract: Stereoselective functionalization at C-2 and C-3 of the gibberellin skeleton was achieved *via* an intramolecular free radical cyclization approach using a tethered C-19 halomethyl ester as the radical precursor.

Keywords: Gibberellin, lactonization, free radical cyclization.

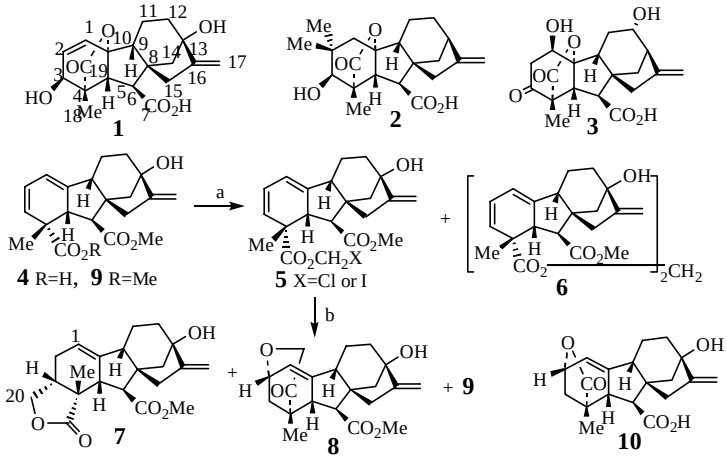
The gibberellins (GAs) are a group of naturally-occurring tetracyclic diterpenoid plant growth hormones which are widely present in higher plants and some fungal species. To date over one hundred GAs have been identified and found to be involved in almost every aspect and stage of the growth and development of plants[1].

Among the GAs identified to date, gibberellic acid (GA_3) **1** is the most active and widely used naturally occurring gibberellin. However structure-activity relationship studies by modification of some of the GAs have led to the discovery of unnatural GA analogous with much higher activity then GA_3. For example, 2,2-dimethyl GA_4 **2** is 100 times more active then GA_3 and 50 times more active then GA_{33} **3**[2]. In all those methods reported for the modification of the GA skeleton so far, functionalization at C-2 and C-3 on the α-face is more difficult to achieve due to the fact that α-face of the GA molecule is sterically more hindered then β-face. Herein we wish to report a novel method for the stereoselective functionalization at C-2 and C-3 on the α-face of the GA molecule *via* an intramolecular free radical cyclization using a tethered C-19 halomethyl ester **5** as the radical precursor.

The halomethyl ester **5** was prepared from the known diene acid[3] **4** derived from **1**. Treatment of **4** with potassium hydrogen carbonate and chloromethyl iodide and a catalytic amount of 18-crown-6 ether afforded **5** in 35% yield as an inseparable mixture of chloride and iodide in a ratio of ~ 3:1 as identified by NMR spectroscopy. The remaining product being the methylene dicarboxylate **6** (60%) which can be saponified and recycled. Reaction of **5** with tri-n-butyltin hydride and a catalytic amount of AIBN in toluene under reflux gave the C-2 and C-3 cyclized compound **7** and **8** in 18% and 45% yields respectively together with 17% of the dimethyl ester **9**, a dehalogenated product (**Scheme**). The structure of the two isomeric lactones **7** and **8** were elucidated by spectroscopic methods. The IR spectra of **7** and **8** showed a lactone carbonyl band

at 1770 cm^{-1} and 1765 cm^{-1} respectively which can be assigned to a five- and six-membered lactone. The ^{1}HNMR spectra of the two compounds displayed much difference, especially in ring A olefinic signals. The H-1 of the five membered lactone **7** displays a broad singlet at 5.31 ppm whereas that of six membered lactone **8** shows a multiplet at 5.50 ppm which is very similar to the H-1 signal of the isolactone **10** in multiplicity.

Scheme



In conclusion we have developed a stereoselective functionalization at C-2 and C-3 of the gibberellin utilising a free radical lactonisation approach *via* a tethered C-19 halomethyl ester. The lactone **7** and **8** can be converted to various GA analogues with substituents at either 2- or 3- position of the α-face of the gibberellin skeleton.

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References and notes

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4. Selected data for : (**7**) Found M^+ 358.1798, $C_{21}H_{26}O_5$ calcd. 358.1780; IR ν (cm^{-1}) 1770 (lactone C=O); ^{1}HNMR (270MHz, $CDCl_3$ δppm): 1.37 (s, 3H, H-18), 2.93 (br. s, 1H, H-5), 3.69 (d, 1H, *J* 4.6Hz, H-6), 3.74 (s, 3H, CO_2CH_3), 3.87 (dd, 1H, *J* 9.0 and 3.0Hz, H-20), 4.38 (dd, *J* 9.0 and 6.0Hz, 1H, H-20), 4.99 and 5.13 (each br. s, each 1H, H-17), 5.31(br. s, 1H, H-1). (**8**) Found M-H_2O 340.1680, $C_{21}H_{24}O_4$ calcd. 340.1674; IR ν (cm^{-1}) 1765 (lactone C=O); ^{1}HNMR (270MHz, $CDCl_3$ δppm): 1.33 (s, 3H, H-18), 2.55 (br. s, 1H, H-5), 3.43 (d, 1H, *J* 4.0Hz, H-6), 3.72 (s, 3H, CO_2CH_3), 3.78 (dd, 1H, *J* 9.0 and 7.5Hz, H-20), 4.33 (t, 1H, *J* 9.0Hz, H-20), 4.97 and 5.12 (each br. s, each 1H, H-17), 5.50 (ddd, 1H, *J* 6.0, 3.0 and 3.0Hz, H-1).

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