

Unexpected Stereospecific Rearrangement-Addition Reaction of Trisubstituted Gibberellin Epoxides with Trimethylaluminium

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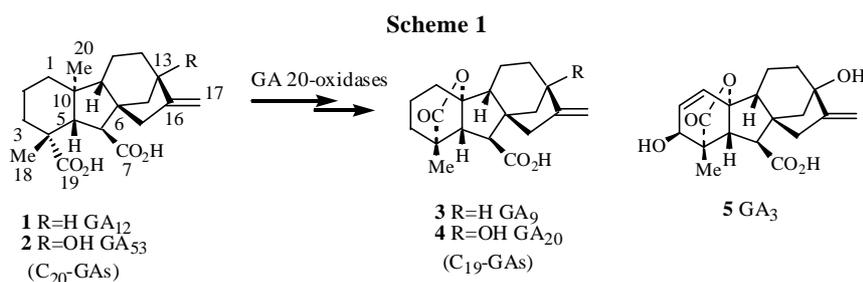
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Abstract: A novel rearrangement-addition reaction of trisubstituted gibberellin epoxides with trimethylaluminium is reported. The reaction proceeds stereospecifically to give tertiary methyl alcohols. The possible mechanism for the reaction is also discussed.

Keywords: Gibberellin, epoxide, trimethylaluminium, rearrangement-addition reaction.

The gibberellins (GAs) are diterpenoid plant growth hormones which are essential to the normal growth and development of plants¹. Over one hundred GAs have been identified to date and most of these compounds are present in nature only in minute quantities. Based on their carbon skeleta, the known gibberellins can be classified into two major groups, *i.e.*, C₂₀-gibberellins (C₂₀-GAs, *e.g.* GA₁₂, GA₅₃) which contain the full twenty diterpenoid carbon atoms and C₁₉-gibberellins (C₁₉-GAs, *e.g.* GA₉, GA₂₀) in which carbon-20 is oxidatively lost and a 19,10- γ -lactone is formed (**Scheme 1**).

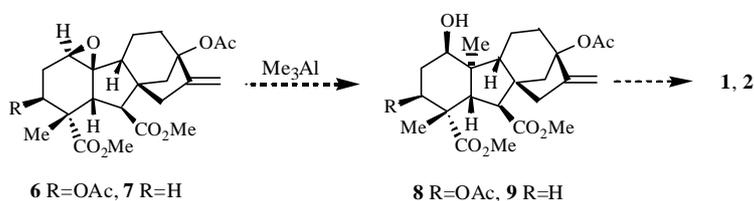


The biosynthetic pathway concerning the oxidation and subsequent removal of carbon-20 in C₂₀-GAs to form C₁₉-GAs (**Scheme 1**) is one of the most important processes in which GA 20-oxidases are involved. Considerable progress has been made in this area in recent years². During the course of our investigation into this process, we needed to have access to C₂₀-GAs such as **2** from a more abundant C₁₉-GA such as GA_{3 **5**. A successful route for such transformation could then be applied for the synthesis of isotope-labeled C₂₀-GAs for biological studies.}

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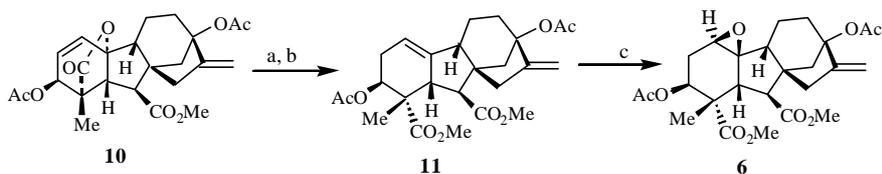
A plausible route for the introduction of the 20-methyl group seemed to be *via* a nucleophilic opening of a trisubstituted gibberellin epoxide such as **6** or **7** with trimethylaluminium (**Scheme 2**) since it has been shown that the reaction of substituted epoxides with alkylaluminium reagents generally occurs at the more substituted position and in an *anti* sense to the epoxy moiety^{3,4}. If such a reaction works with **6** or **7**, the methyl anion would attack the epoxide from the α -face to give the required C-20 methyl compounds **8** or **9** with defined stereochemistry. Further functional group manipulation would give access to the required GA₁₂ **1** or GA₅₃ **2**.

Scheme 2



This planned transformation started with epoxide **6** which was prepared from readily available GA₃ **5** as shown in **Scheme 3**. GA₃ methyl ester bisacetate **10**, prepared from GA₃ by methylation with ethereal diazomethane and bisacylation of the two hydroxy groups, was hydrogenated^{5,6} with deactivated palladium catalyst followed by methylation of the carboxylic acid with diazomethane gave the dimethyl ester **11** in 89% yield over two steps. Selective epoxidation of **11** with *m*-chloroperbenzoic acid (*m* CPBA) gave the desired epoxide **6** as the major product in 56% yield after separation of the minor terminal epoxide.

Scheme 3



Reagents: a. 10% Pd/CaCO₃, pyridine., H₂; b. CH₂N₂; c. *m*CPBA

Reaction of the epoxide **6** with excess trimethylaluminium afforded a new compound but the structure of this product turned out unexpectedly to be the 1-methylated compound⁷ **12** rather than the required 10-methyl compound **8**. The structure of **12** was elucidated by extensive NMR studies and its stereochemistry confirmed by NOE experiments. The ¹H-NMR spectrum of **12** displayed two singlet methyl signals at δ 1.08 and δ 1.21 ppm which indicated that addition of methyl anion to the epoxy moiety had indeed occurred. However the signal of 5-H appeared as a doublet at δ 2.62 ppm indicating that 5-H was coupled to a second proton apart from

6-H. This result suggested that the methyl group introduced in the reaction was not at 10 position otherwise the signal of 5-H should appear as a doublet.

Proton decoupling experiments revealed that the coupling constants of 5-H and 10-H was 13.0 Hz which is the typical coupling pattern of a *trans*-fused A/B ring gibberellin structure since in a *cis*-fused pattern 5-H and 10-H has a much smaller coupling constant of *ca* 5.4 Hz. Therefore 10-H should be at the α -face as shown in **12**. NOE experiments carried out on deacylated **14** (the two acetyl groups were removed to avoid possible overlap of signals) further confirmed the stereochemistry of the 1-methyl group and 10-H. Thus irradiation at 1-methyl signal at δ 1.08 ppm enhanced the signals of 3-H (δ 5.48 ppm), 6-H (δ 3.26 ppm) and 10-H (δ 2.62 ppm) by 7.5%, 6% and 10% respectively with 10-H having the highest magnitude of enhancement (**Figure 1**) These NOE results indicated that 1-methyl was indeed on the α -face and sterically close to 3-H, 6-H and 10-H. Therefore the reaction of epoxide **6** with trimethylaluminium had occurred stereospecifically. The reaction also proceeded well on the analogous epoxide **7** giving the 1-methyl alcohol **13** in 70%

Scheme 4

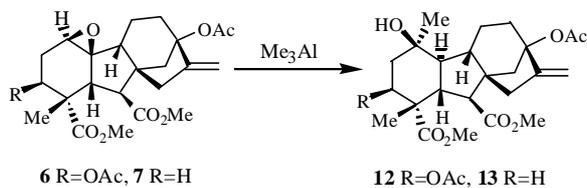
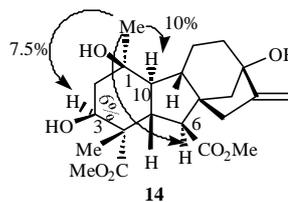
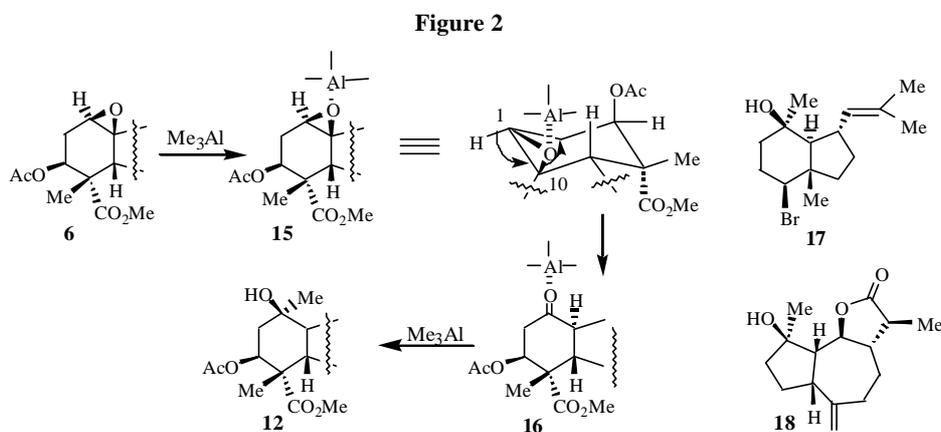


Figure 1



yield.

Mechanistically this unexpected reaction of trisubstituted gibberellin epoxides with trimethylaluminium can be explained as shown in **Figure 2**. Apart from nucleophilic attack to the epoxy functionality, it has been known that organoaluminium reagents can promote the rearrangement of substituted epoxides to form ketones⁸. It is therefore plausible to assumed that the aluminum reagent first coordinates with the epoxide moiety



(e.g. in **6**) to form a complex **15** in which the 1 α -H undergoes a superficial hydrogen migration to give the 1-ketone intermediate **16**. The methyl anion can then attack the ketone **16** from the less hindered α -face to give the methyl alcohol **12**.

In conclusion, the reaction of trimethylaluminium with trisubstituted gibberellin epoxides **6** and **7** have been found to give 1-methyl alcohols. The reaction is likely to proceed *via* an organoaluminium promoted stereospecific rearrangement-addition reaction. This novel reaction can have potential application in the synthesis of natural products containing a tertiary methyl alcohol unit such as oppsitol⁹ **17** and compressanolide **18**¹⁰.

Acknowledgment

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