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

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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 plants\textsuperscript{1}. 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 skeleton, the known gibberellins can be classified into two major groups, \textit{i.e.}, C\textsubscript{20}-gibberellins (C\textsubscript{20}-GAs, \textit{e.g.} GA\textsubscript{12}, GA\textsubscript{53}) which contain the full twenty diterpenoid carbon atoms and C\textsubscript{19}-gibberellins (C\textsubscript{19}-GAs, \textit{e.g.} GA\textsubscript{9}, GA\textsubscript{20}) in which carbon-20 is oxidatively lost and a 19,10-\(\gamma\)-lactone is formed (Scheme 1).

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme1.png}
\end{center}
\end{scheme}

The biosynthetic pathway concerning the oxidation and subsequent removal of carbon-20 in C\textsubscript{20}-GAs to form C\textsubscript{19}-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 years\textsuperscript{2}. During the course of our investigation into this process, we needed to have access to C\textsubscript{20}-GAs such as \textsuperscript{2} from a more abundant C\textsubscript{19}-GA such as GA\textsubscript{3} \textsuperscript{5}. A successful route for such transformation could then be applied for the synthesis of isotope-labeled C\textsubscript{20}-GAs for biological studies.

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 \(\alpha\)-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 GA\(_{12}\) 1 or GA\(_{13}\) 2.

Scheme 2

This planned transformation started with epoxide 6 which was prepared from readily available GA\(_{3}\) 5 as shown in Scheme 3. GA\(_{3}\) methyl ester bisacetate 10, prepared from GA\(_{3}\) 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 (mCPBA) gave the desired epoxide 6 as the major product in 56% yield after separation of the minor terminal epoxide.

Scheme 3

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 compound\(^{7} 12\) 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 \(^1\)H-NMR spectrum of 12 displayed two singlet methyl signals at \(\delta\) 1.08 and \(\delta\) 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 double doublet at \(\delta\) 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
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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% 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

Figure 2
(e.g. in 6) to form a complex 15 in which the 1α-H undergoes a superfacial 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 1810.

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References and notes

7. Selected data for 12: HRMS (EI) Found M+ - H2O, 474.2231; C26H34O8 calcd. 474.2253; 1H NMR (270 MHz, CDCl3, δ ppm): 1.08 (s, 3H, 1-CH3), 1.21 (s, 3H, 18-CH3), 2.03 and 2.14 (each s and 3H, 3- and 13-OAc), 2.62 (dd, 1H, J 10.3 and 13.0Hz, H-10), 3.26 (d, 1H, J 10.3Hz, H-6), 3.70 and 3.72 (each s and 3H, 2 x CO2CH3), 4.97 and 5.07 (each br. s and 1H, 17-H2), 5.48 (t, 1H, J 3.0Hz, H-3). MS m/z (%): 492 (0.5, M+), 474 (2, M+ - H2O), 442 (20), 414 (32), 382 (49), 354 (66), 295 (22), 258 (91) (17), 91 (12), 43 (100).

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