

**THE FIRST PARTIAL SYNTHESIS OF 14-HYDROXY-GIBBERELLIN ESTERS.  
A TITANIUM (IV)-AMIDE CATALYSED REARRANGEMENT OF EPOXIDES**

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**Summary:** Methyl gibberellate has been efficiently transformed into the 14 $\beta$ -hydroxygibberellin A<sub>7</sub> methyl ester. The key step in the conversion was the rearrangement of the 3 $\beta$ -acetoxy-15 $\beta$ ,16 $\beta$ -epoxy-beyergibberellin A<sub>7</sub> methyl ester to the target gibberellin ester by means of a titanium-amide pair, which is compatible with the highly reactive ring A of the gibberellin system.

The gibberellins are a group of widely distributed plant hormones.<sup>1</sup> An extensive range of gibberellins with different hydroxylation patterns in the A-, C- and D- rings have been prepared.<sup>2,3</sup> Hitherto, no C-14 hydroxylated analogues have been isolated or chemically prepared from other gibberellins. In this communication we report on the first results of our studies to transform GA<sub>3</sub> methyl ester (1) and its fungal congeners into a range of C-14 oxygenated derivatives.

The double rearrangement of rings C and D in gibberellin chemistry has been used in the synthesis of some of these plant hormones,<sup>4</sup> and we have now used a similar strategy in the preparation of the 14 $\beta$ -hydroxygibberellin A<sub>7</sub> methyl ester. Since C-8 is fully substituted and C-13 is at a bridgehead, C-14 is a position relatively inaccessible by direct chemical means. The essential step in this synthesis was the rearrangement of a 15 $\beta$ ,16 $\beta$ -epoxybeyergibberellin derivative to the target 14 $\beta$ -hydroxygibberellin

(scheme 1). The known susceptibility of the A-ring of GA<sub>3</sub>, to both acidic and basic conditions,<sup>3</sup> was a serious obstacle which was overcome by using a titanium-amide reagent in the preparation of 14β-hydroxygibberellin A<sub>7</sub> methyl ester (9).

The transformation of methyl gibberellate (1) to the target derivative is outlined in scheme 2. The ketone (2) was prepared from methyl gibberellate as described previously<sup>5</sup> (80%). It was reduced (NaBH<sub>4</sub>, MeOH, 0°C) to give the 16-endo alcohol (3) (>98%), which was converted (MsCl, Py, 0°C) to the corresponding mesylate (4) (93%). Treatment of (4) with refluxing collidine gave the β-elimination product (5) (34%), which was converted into the 15β,16β-epoxide (6) by regioselective epoxidation (MCPBA, CHCl<sub>3</sub>, 0°C) (>98%).

Attempts to rearrange the epoxide (6) to the 14β-hydroxygibberellin A<sub>7</sub> methyl ester (7) using BF<sub>3</sub>.Et<sub>2</sub>O were unsuccessful. Instead the endocyclic isomer (8) was obtained as the main reaction product, contaminated with variable amounts of the 2,19-lactone isomer (10). We noted that the relative conformation of the oxirane ring and the methyl group in the epoxide (6) seemed suitable for a regioselective base-controlled Lewis acid rearrangement such as those used in the synthesis of allylic alcohols from epoxides.<sup>6,7</sup> In the hope that such control was possible, we treated the epoxide (6) with magnesium bromide N-isopropylcyclohexylamide (BrMgICA).<sup>6</sup> Unfortunately, the epoxide proved unreactive towards this reagent even at room temperature. We assumed that the low reactivity shown by the epoxide might be related to the acid strength of the reagent rather than to the geometric features. Consequently, we changed the Lewis acid to titanium (IV), and prepared the mono-, di- and tri-chloride titanium amide complexes.<sup>8</sup> The best result was achieved with Cl<sub>2</sub>Ti(ICA)<sub>2</sub> [3 eq., 0°C → r.t. (2h) and r.t. (7h)], giving a mixture of both isomers (7) and (8) in a 1.4:1 ratio in an 85% yield (13% of recovered starting epoxide). The Cl<sub>3</sub>TiICA [6 eq., 0°C (4h), r.t. (3h)] yielded an equimolecular mixture of both isomers (80%). However, the ClTi(ICA)<sub>3</sub> did not react after several hours at room temperature.

The total stability of the A-ring system toward these reagents is noteworthy and is in sharp contrast with the BF<sub>3</sub>.Et<sub>2</sub>O reagent. This feature is interesting and suggests that these reagents may have considerable value as Lewis acid rearrangement promoters in gibberellin chemistry.

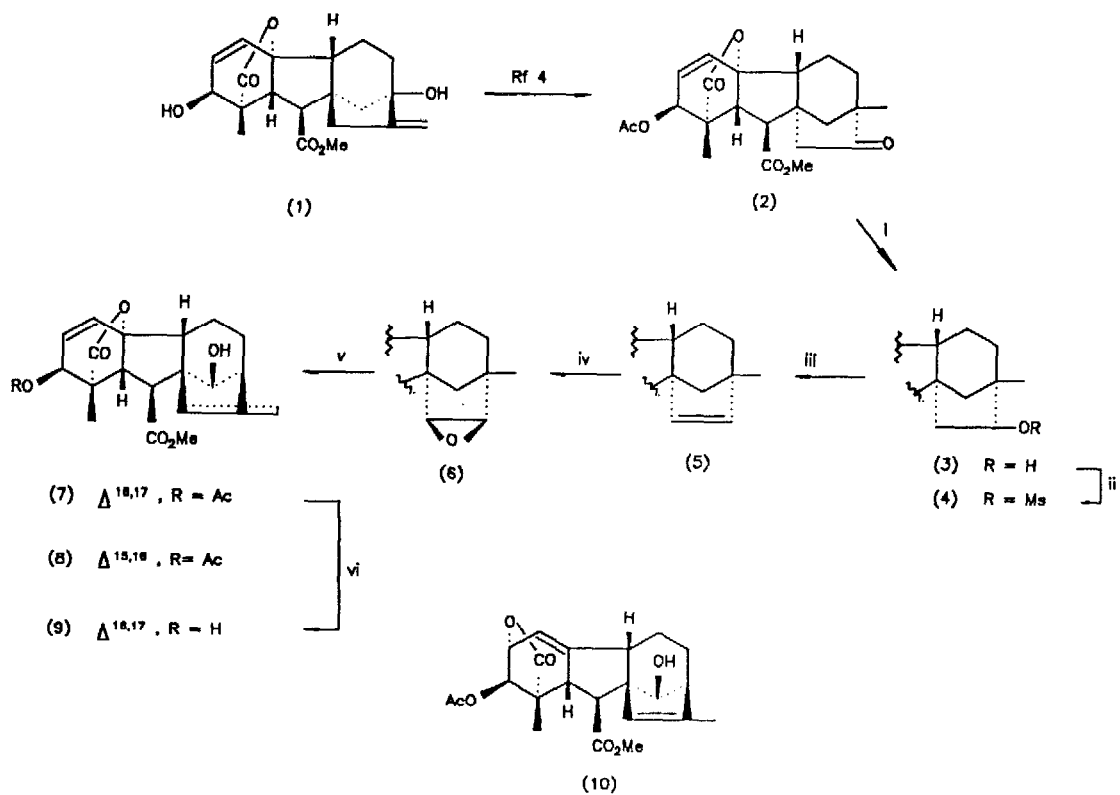
The isomeric compounds (7) and (8) were separated by flash chromatography, and (7) was carefully hydrolysed to afford the target 14β-hydroxygibberellin A<sub>7</sub> methyl ester (9). Their spectral data are in accordance with the structure (9) assigned to this compound.<sup>9,10</sup>

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Scheme 1



Scheme 2



Reagents: i)  $\text{NaBH}_4$ , MeOH,  $0^\circ\text{C}$ , 1h; ii) MsCl, Py,  $0^\circ\text{C}$ , 45 min; iii) collidine, reflux, 9h 30 min; iv) MCPBA,  $0^\circ\text{C}$ , 65 h; v)  $\text{Cl}_2\text{Ti}(\text{ICA})_2$  (3 eq.), toluene,  $0^\circ\text{C} \rightarrow \text{r.t.}$  (2h), r.t. (7h); vi)  $\text{Na}_2\text{CO}_3$ , r.t., 1h.

## References and footnotes

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8. The reagents were prepared by reaction of  $\text{TiCl}_4$  (1 eq.) with LICA (lithium N-isopropylcyclohexylamide) (3, 2 and 1 eq.) in toluene ( $0^\circ\text{C}$ , 30 min and then 1h at room temperature for the last reagent, and 1h under reflux for the first two). The reagents were prepared "in situ" and used immediately with the epoxide, running the reactions from  $0^\circ\text{C}$  to room temperature.
9.  $\text{M}^+$  at 360.1593,  $\text{C}_{20}\text{H}_{24}\text{O}_6$  requires 360.1573.  $^1\text{H}$  nmr (200 MHz,  $\text{Cl}_3\text{CD}$ )  $\delta$ : 1.28 (3H, s, H-18), 3.04 (1H, d,  $J=10.4$  Hz, H-6), 3.25 (1H, d,  $J=10.4$  Hz, H-5), 3.76 (3H, s, Me), 4.09 (1, br.s, H-14), 4.17 1H, d,  $J=3.7$  Hz, H-3), 5.01 and 5.09 (each 1H, br s, H-17), 5.90 (1H, dd,  $J=9.3$  and 3.7 Hz H-2) and 6.31 (1H, d,  $J=9.3$  Hz, H-1); MS,  $m/z$  (int. rel.), 360 ( $\text{M}^+$ , 1), 342 (8), 328 (3), 300 (2), 297 (6), 280 (5), 265 (4), 237 (9), 221 (14), 220 (5), 209 (16), 192 (10).
10. All the new compounds gave satisfactory analytical and  $^1\text{H}$  nmr, ir and mass spectral data.

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