Pergamon

Tetrahedron Letters, Vol. 37, No. 5, pp. 719-722, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02251-1

Synthesis of GA_{32}, the Major Bioactive Gibberellin from Immature Seeds of *Prunus persica*

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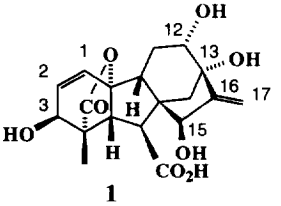
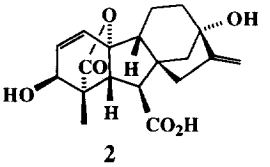
Abstract: More reliable methods have been developed for the preparation of 12- and 15β-hydroxy gibberellins and applied to the synthetic conversion of GA_3 (gibberellic acid) (**2**) into GA_{32} (**1**), the major bioactive gibberellin from peach (*Prunus persica*) and other *Prunus* spp.

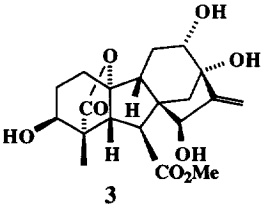
Gibberellin A_{32} ("GA_{32}"), isolated from the immature seeds of peaches, apricots and other *Prunus* species[1-5] (**1**) is one of the most biologically potent[2,6,7] of the 100 odd gibberellins obtained to date from natural sources. It is also one of the least accessible (approximately 3.8mg may be isolated from 100Kg of unripe peaches), and so we have undertaken its preparation from the readily available fungal gibberellin GA_3 (**2**) with a view to facilitating a comprehensive examination of its potential for regulating plant growth and development. We had made the methyl ester of GA_{86} (**3**) in order to confirm a tentative assignment of structure,[8] and that preparation serves as a useful model for the synthesis of GA_{32} (**1**). With the more labile A-ring functionality in **1**, plus the objective of making the parent acid rather than the methyl ester, however, the need for several changes to the previously used procedures became necessary, including the use of a more labile protecting group for the 7-carboxyl. Most importantly, an improved method was required for the introduction of the 15β-hydroxyl, a step that had been very low yielding in the preparation of **3**.



1



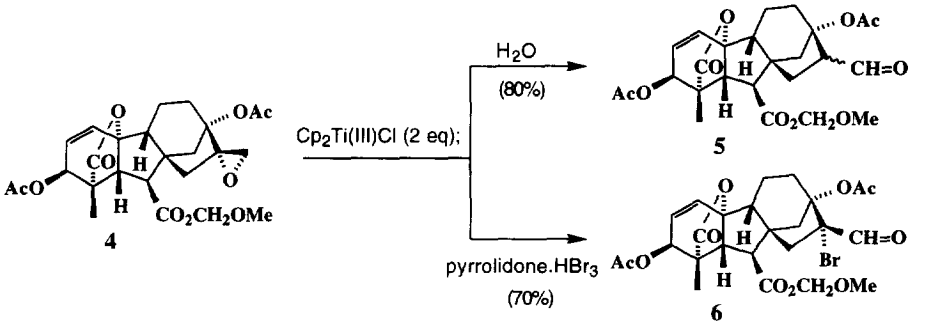
2



3

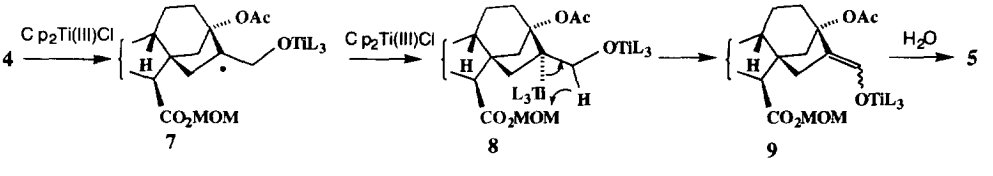
One of the entry points for the synthesis of **3** had been the pyridinium chlorochromate oxidation of the 15α-hydroxy derivative of the diacetate of GA_3 methyl ester,[8] but this procedure failed on the corresponding methoxymethyl ester. Fortunately, an alternative approach based on the treatment of epoxide **4**[9] with two equivalents of bis(cyclopentadienyl) titanium(III) chloride (Cp_2TiCl) proved to be an effective and more general

method for the preparation of 17-aldehydes (Scheme 1). The titanium reagent has been used by Nugent and Rajanbabu to generate α-oxy-carbon radicals, which undergo cyclisation with suitably located olefinic bonds.[10] It had been reported that if two equivalents of reagent were used, the cyclised radical was reduced to a titanium alkyl intermediate which could then be trapped by I_2. Within the present context, however, we discovered that treatment of epoxide **4** with one equivalent of Cp_2TiCl afforded equal amounts of starting material and aldehyde **5** as a 4:1 mixture of endo (16β) and exo isomers (16α), while if two equivalents of the titanium (III) complex were used, an excellent yield of aldehyde resulted.[11] If tri-*n*-butylstannane was included as a co-reagent, a high yield of 17-carbinol was obtained.



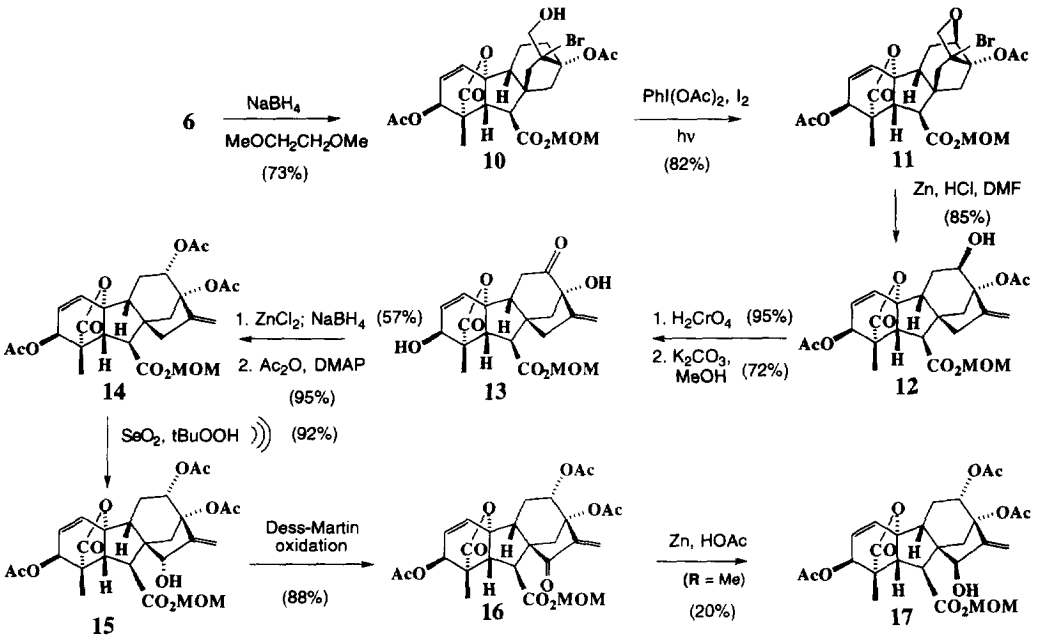
Scheme 1

It appears, therefore, that the initial free radical **7** formed from **4** (Scheme 2) is reduced more readily than the parent epoxide, affording the titanium alkyl **8**. This intermediate is unstable, however, and undergoes hydride elimination to form enolate **9**.[12] If, instead of simply quenching the reaction mixture with dilute acid, pyrrolidone hydrotribromide[13] was added in combination with triethylamine (to prevent protonation) to the presumed enolate **9**, bromo aldehyde **5** was formed in good yield as a 4:1 mixture with the 16β-bromo epimer.



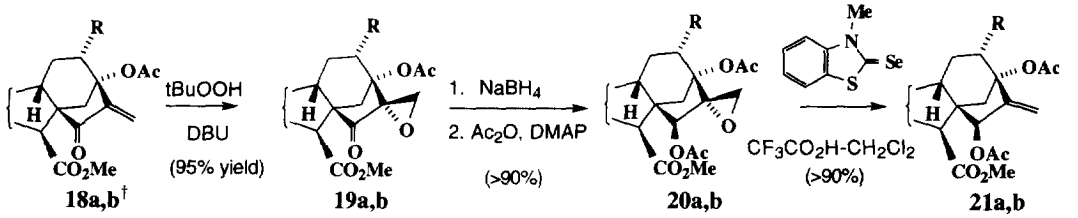
Scheme 2

With a satisfactory synthesis of bromo aldehyde **6** in hand, the synthesis was continued as outlined in Scheme 3,[14] and closely followed the preparation of the 1,2-dihydro analogue **3** (GA_{86}),[8] except for the selection of alternative reagents for the two oxidation steps. The transannular oxidation **10**→**11** was carried out with diacetoxyiodobenzene[15] in place of lead tetraacetate, affording a cleaner product in enhanced yield, while the Dess-Martin periodinane reagent[17] was substituted for the previously used Swern procedure[16] which was found to be unsatisfactory for the oxidation of 15-carbinol **15** to enone **16**. Following the MacMillan procedure for introduction of the 15β-ol function,[18] reduction of **16** by zinc-acetic acid was examined, but gave mainly the 1,4-reduction product. Only a very modest yield (20%) of the target 15β-ol **17** was obtained, as in the preparation of **3**. We therefore elected to explore the option of temporarily masking the 17-methylene group during the reduction of the C(15) carbonyl function. The initial studies were carried out on the GA_3 enone **18a**[19] and then applied to the 12α-acetoxy analogue **18b** as indicated in Scheme 4.



Scheme 3

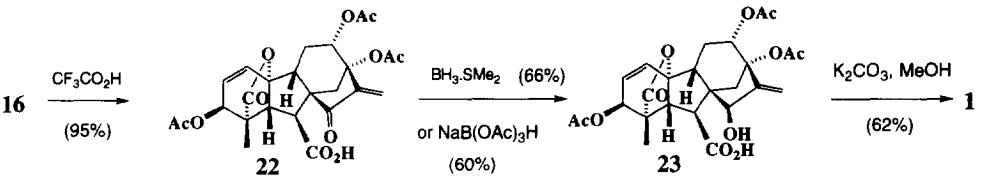
Conjugate addition of various nucleophiles to **18** was effected without difficulty, but the epoxide **19** proved to be the most useful intermediate;[20] hydride reduction followed by acetylation to give **20**, then deoxygenation[21] gave excellent results for both the GA_3 and the 12-substituted series. While the conditions necessary for hydrolysis of the sterically hindered 15β-acetate function (K_2CO_3-MeOH) were satisfactory for the GA_3-derived substrate **21a**, the formation of significant quantities of the isomeric 19,2-lactone[22] occurred in the case of **21b**.



†(**a**: R = H; **b**: R = OAc)

Scheme 4

We then decided to test the possibility that the free 7-carboxyl group might be enlisted to assist in the reduction of the 15-oxo function.[23] In the event, hydrolysis of the ester **16** to acid **22**, followed by reduction with either borane dimethyl sulfide complex or with sodium triacetoxyborohydride[24] afforded triacetate **23** (Scheme 5). This product could then be hydrolysed under sufficiently mild conditions so as to afford a reasonable yield of GA_{32} (**1**), even though some isomerisation of the allylic lactone function still occurred. Comparison of 500MHz ^1H NMR spectra confirmed the identity of the synthetic material with the natural gibberellin, thereby providing a final proof of structure for GA_{32} (**1**).[25] The assisted reduction[26] by a carboxyl group is unusual and it is of interest that with the borane complex, reduction of the ketone carbonyl group occurs in preference to reduction of the carboxy function.[27]



Scheme 5

Acknowledgements. We thank Bruce Twitchin for technical assistance, Professor Murofushi, University of Tokyo, for reference NMR spectra of GA_{32}, and Abbott Laboratories for a generous gift of gibberellic acid.

REFERENCES AND NOTES

1. Yamaguchi, I., Yokota, T., Murofushi, N.; Takahashi, N. *Agric. Biol. Chem.* **1970**, 34, 1439-1441.
2. Coombe, B. G. *Science*, **1971**, *172*, 856-857.
3. Yamaguchi, I., Yokota, T., Murofushi, N.; Takahashi, N. *Agric. Biol. Chem.* **1975**, 39, 2405-2410.
4. Bukovac, M. J.; Yuda, E.; Murofushi, N.; Takahashi, N. *Plant Physiol.* **1979**, 63, 129-132.
5. Blake, P. S.; Browning, G.; Chu, A. W.-L.; Mander, L. N. *Phytochemistry*, **1993**, 32, 781-784.
6. Crozier, A.; Durley, R. P. in Crozier, A. *The Biochemistry and Physiology of Gibberellins*, Vol. I, Praeger, New York, **1983**, pp 485-560.
7. Evans, L. T.; King, R. W.; Chu, A.; Mander, L. N.; Pharis, R. P. *Planta*, **1990**, 182, 97-106.
8. Bhaskar, V. K., Chu, W.-L. A., Mander, L. N., Murofushi, N., Pearce, D. R., Pharis, R. P.; Takahashi, N., Yamaguchi, I, *Tetrahedron Lett.* **1991**, 32, 6203-6207.
9. Epoxide **20** was best prepared using *p*-nitroperoxybenzoic acid, which afforded a >95% yield of the 16α,17-epoxide (exo attack). The 16β,17-isomer (endo attack), which is formed in ca 25% yield with the more commonly used *m*-chloroperoxybenzoic acid (Avent, A. G.; Baynham, M. K.; Hanson, J. R.; Hitchcock, P. B.; de Oliveira, B. H. *J. Chem. Soc. Perkin Trans. 1*, **1989**, 627-632), is recovered unchanged from the reaction with $Cp_2Ti(III)Cl$.
10. Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, 110, 8561-8562.
11. *Cf.* Scobert, R.; Höhlein U. *Synlett*, **1990**, 465-466.
12. Epoxide **20** failed to react with $Cp_2Ti(IV)Cl_2$, confirming that the formation of the aldehyde is not due to a simple Lewis acid-catalysed rearrangement.
13. Awang, D. V. C.; Wolfe, S. *Can. J. Chem.* **1969**, 47, 706-709.
14. All compounds were characterised by ^1H and ^{13}C NMR spectra, mass spectra, and HRMS
15. de Armas, P.; Concepción, J. I.; Francisco, C. J.; Salazar, J. A.; Suárez, E. J. *J. Chem. Soc. Perkin Trans. 1*, **1989**, 405-411.
16. Mancuso, A. J.; Swern, D. *Synthesis*, **1981**, 165-184.
17. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155-4156.
18. Dolan, S. C.; Holdup, D. W.; Hutchison, M; MacMillan, J. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 651-654.
19. Dolan, S. C.; MacMillan, J. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 2741-2746.
20. *Cf.* Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, 107, 1777-1778.
21. Calo, V.; Lopez, L.; Mincuzzi, A.; Pesce, G. *Synthesis*, **1976**, 200-201. Of fourteen procedures tested for deoxygenation of the epoxide, only this reagents gave satisfactory results.
22. *Cf.* Kirkwood, P. S., MacMillan, J.; Sinnott, M. L. *J. Chem. Soc. Perkin Trans. 1*, **1980**, 2117-2121.
23. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307-1370.
24. *Cf.* Evans, D. A., Chapman, V. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, 110, 3560-3584. Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, 58, 4555-4563.
25. ^1H NMR (500 MHz, CD_3OD); δ1.06 (3H, s, H-18), 1.48 (dd, *J* = 11.3, 1.5Hz, H-14β), 1.6 (ddd, *J* = 13.5, 13.5, 8.0Hz, 11α-H), 1.88 (d, *J* = 11.3Hz, H-14α), 2.04 (ddd, *J* = 13.5, 7.5, 6.0 Hz, H-11β), 2.29 (dd, *J* = 13.5, 6.0Hz, H-9), 2.66 (d, *J* = 11.2Hz, H-6), 3.15 (d, *J* = 11.2Hz, H-5), 3.46 (ddd, *J* = 8.0, 8.0, 1.5, H-12), 3.87 (d, *J* = 3.6Hz, H-3), 4.07 (t, *J* = 2.6Hz, H-15), 5.15 (d, *J* = 2.6Hz, H-17), 5.24 (d, *J* = 2.8Hz, H'-17), 5.77 (dd, *J* = 9.2, 3.6 Hz, H-2), 6.28 (dd, *J* = 9.2, 1.0 Hz, H-1).
26. Treatment of the methyl ester of **23** with $BH_3.Me_2S$ gave a mixture of polar, intractable products.
27. *Cf.* Fadel, A.; Canet, J.-L.; Salaun, J. *Tetrahedron Lett.* **1989**, 30, 6687-6690.

(*Received in UK* 8 *November* 1995; *accepted* 24 *November* 1995)