Tetrahedron Letters, Vol.31, No.3, pp423-426, 1990 0040-4039/90 $3.00 + .00
Printed in Great Britain Pergamon Press plc

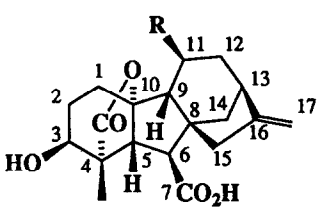
A GENERAL PROCEDURE FOR THE PREPARATION OF 11β–HYDROXY GIBBERELLINS: SYNTHESIS OF THE METHYL ESTERS OF GA_{35} AND 11β-HYDROXY-GA_7

Lewis N. Mander* and Graham L. Patrick

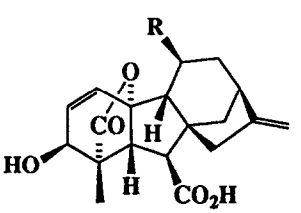
Research School of Chemistry, Australian National University, GPO Box 4, Canberra, A.C.T. 2601, Australia

Summary: Hydroboration of gibberellin 9(11),16-dienes provides good access to 11β,17-diols from which 11β-hydroxy gibberellins may be prepared, *eg.* gibberellin A_{35} (**2**) and 11β-hydroxy gibberellin A_7 (**4**), a new gibberellin from *Lolium temulentum*.

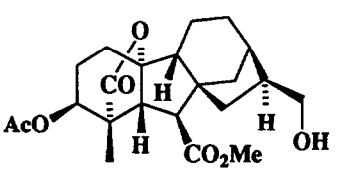
Hydroxylation at C(11) in gibberellins occurs in only 3 of the 80 known gibberellins ("GAs") discovered to date,[1] but a new compound isolated from rye grass (*Lolium temulentum*) and seeds of loquat fruit (*Eriobotrya japonica*) is thought to be 11β-hydroxy-GA_7 (**4**).[2] Moreover, further 11β-hydroxylated GAs have also been tentatively identified in the latter species.[3] We have accordingly undertaken the synthesis of gibberellins of this general type with a view to confirming the constitution of the natural metabolites, the details of which are disclosed in this Letter.



1 R = H
2 R = OH



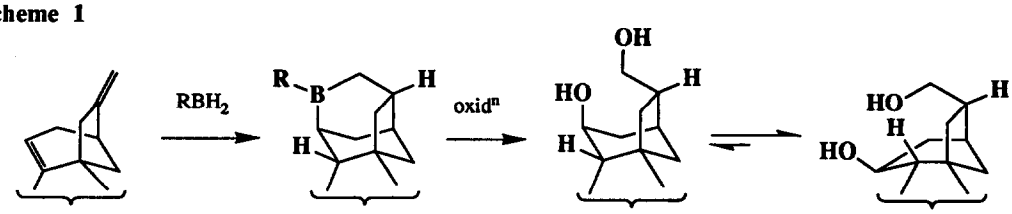
3 R = H
4 R = OH



5
6 1,2-didehydro

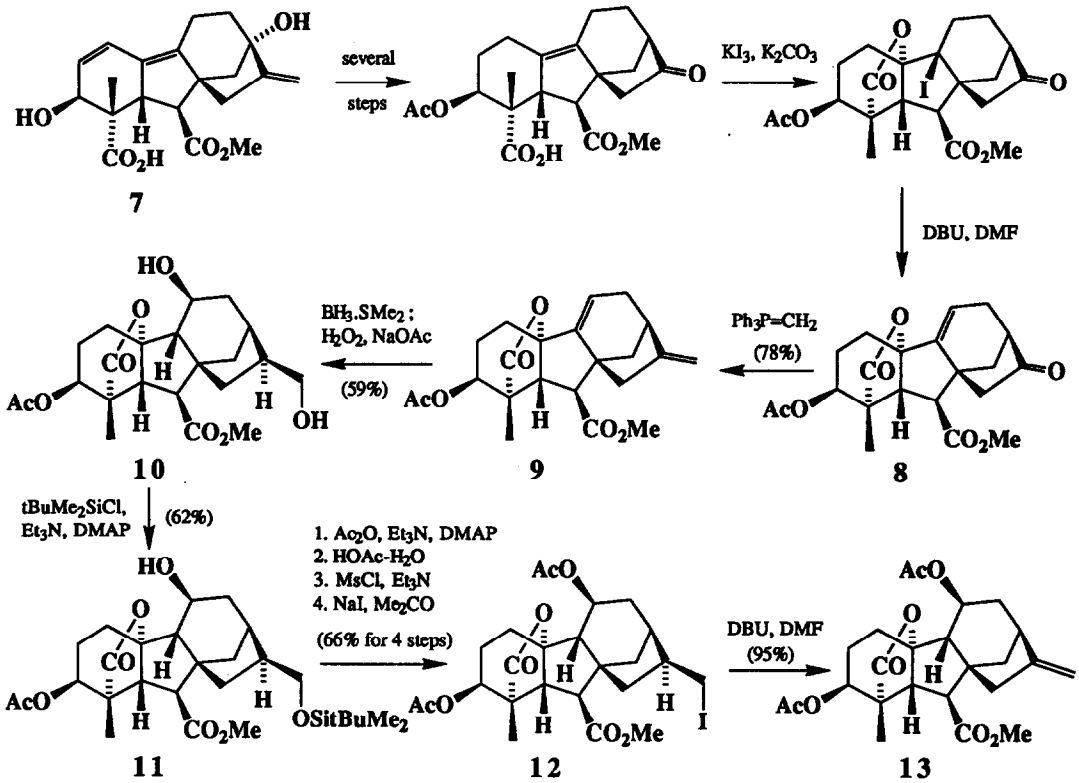
We envisaged that a feasible approach (Scheme 1) might be based on the hydroboration of a suitable 9(11),16-diene,[4] involving the initial addition of the borane to the *exo*-face of the more accessible Δ^{16}-ene function, followed by intramolecular addition to the upper face of the $\Delta^{9(11)}$ double bond; oxidation in the usual way could then be expected to afford an 11β,17-diol from which it appeared that the target compounds could be obtained.[5] The initial hydroboration step was first tested on a number of simple gibberellins and we were pleased to find that, *inter alia*, the 3-acetate methyl ester of GA_4 (**1**) could be converted into the 17-hydroxy derivative **5** in 81% yield, and that the GA_7 analogue could also be transformed efficiently into **6** (70% yield+18% recovered starting material).

Scheme 1



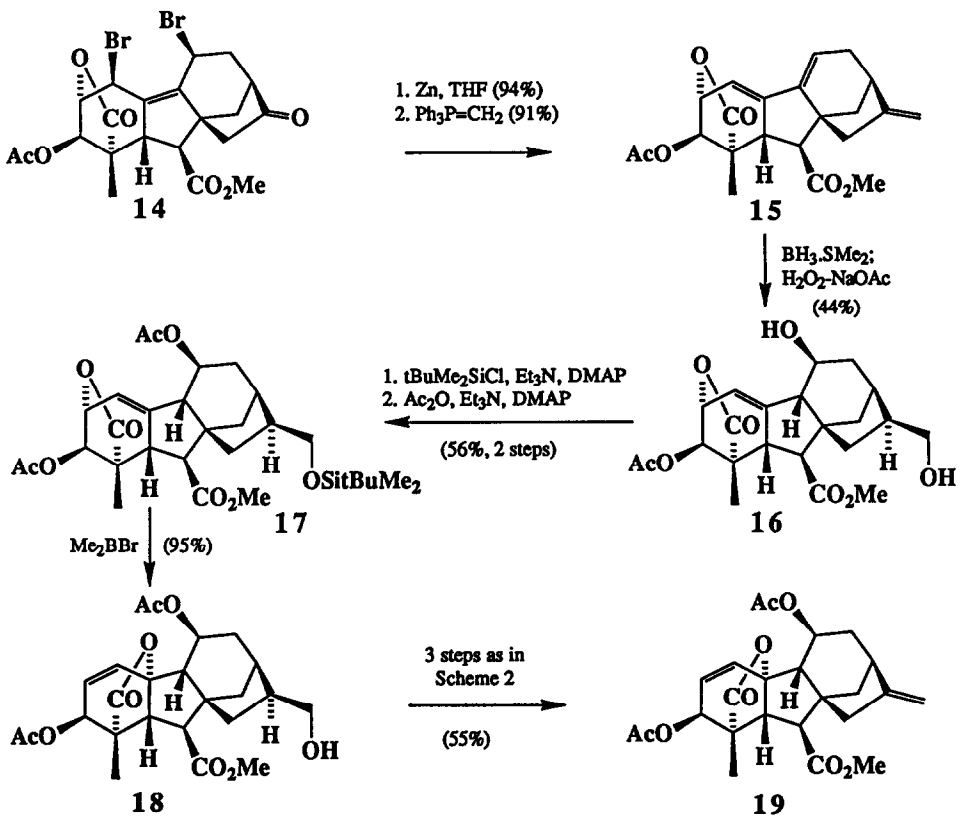
We then proceeded to test the plan by undertaking the synthesis of the methyl ester of the known gibberellin, GA_{35} (**2**) (Scheme 2). The sequence began with enone **8**, which had been prepared from the monomethyl ester of gibberellenic acid **7**,[6] an intermediate in the synthesis of GA_{73} methyl ester,[7] (a potent antheridiogen isolated from prothallia of the fern *Lygodium japonicum*).[8] Hydroboration of the diene **9**, which could be readily prepared from **8** by Wittig methylenation, afforded the expected diol **10**. This was protected as the 17-*t*-butyldimethylsilyl ether **11** so as to allow selective acetylation of the 11β-hydroxyl, a necessary prelude to restoring the 16-methylene function.[9] This was achieved by DBU induced elimination of HI from iodide **12** which was formed from **11** as indicated. Removal of the two acetate functions (K_2CO_3-MeOH) from the resulting diene **13** gave the methyl ester of GA_{35} (**2**)[10] which was shown to be identical with an authentic sample by direct comparison (^{1}H-NMR spectrum and g.c.m.s.).[11]

Scheme 2



Having demonstrated the practicality of making 11β-hydroxy gibberellins in this way, we addressed the more difficult task of making **4**. Although this compound could, in principle, be prepared from **2**, we sought a more direct route and this was found in the sequence outlined in Scheme 3. Dibromide **14** is readily prepared from GA_7 (**3**) in only 4 steps and has been utilised in a recent synthesis of the principal antheridiogen from *Anemia phyllitidis*.[12] We envisaged that reduction of **14** under appropriate conditions followed by Wittig methylenation would lead to triene **15**, which appeared to be a suitable candidate for the double hydroboration process. In the event, triene **15** was formed in high overall yield and is much more readily prepared than the simpler diene **9**, although the hydroboration reaction to give **16** was less efficient. Apart from the need to effect a 1,3-transposition of the allylic lactone function in the A-ring (**17**→**18**),[13] the remainder of the synthesis leading to diacetate **19** was then essentially a duplicate of the earlier preparation of **13**. Methanolysis finally afforded the methyl ester of **4** which was shown to be the same as the methyl ester derived from the *Lolium* metabolite by g.c.m.s. of the 3,11-bistrimethylsilyl ethers.[14]

Scheme 3



This current study augments the earlier methodology which we have developed for the introduction of a hydroxy group at C(12) in a range of gibberellins (by means of a hypoiodite mediated transannular oxidation of 16a-bromo-17-carbinols).[15] The combined invesigations have allowed us to establish useful sets of reference

compounds and spectroscopic data which should facilitate structure determinations of further new gibberellins functionalised in the C-ring.

Acknowledgements

We gratefully acknowledge the provision of an authentic sample of GA_{35} methyl ester by Dr H. Yamane and a generous gift of gibberellins from Abbott laboratories. We also thank Mr Nakayama, University of Tokyo, and Dr D.Pearce, University of Calgary, for carrying out the g.c.m.s. comparisons.

References

1 N. Takahashi, I. Yamaguchi, and H. Yamane, in Chemistry of Plant Hormones, N. Takahashi (Ed.), CRC Press, Boca Raton, Florida, 1986, pp. 57-151.

2 D. Pearce and R.P. Pharis, unpublished results.

3 E. Yuda, T. Yokota, M. Nonaka, Y. Fukushima, S. Nakagawa, N. Katsura, Y. Ota, N. Murofushi and N. Takahashi, *Chemistry Express*,1987, **2**, 499. M. Koshioka, D. Pearce, R.P. Pharis and Y. Murakami, *Agric. Biol. Chem.*, 1988, **52**, 1353.

4 This type of reaction has been successfully carried out on an equivalent kaurenoid substrate, methyl grandiflorenate (N.J. Lewis and J. MacMillan, *J. Chem. Soc. Perkin Trans. I*, 1980, 1270).

5 N. Fukazawa, M. Funamizu, Y. Kitahara and T. Kato, *Chem. Lett.*, 1976, 1253.

6 J.F. Grove and T.P.C. Mulholland, *J. Chem. Soc.*, 1960, 3007.

7 M. Furber, unpublished results. *Cf.* L.N. Mander, *Pure and Appl. Chem.*, 1989, **61**, 397.

8 H. Yamane, Y. Satoh, K. Nohara, M. Nakayama, N. Murofushi, N. Takahashi, K. Takeno, M. Furuya, M. Furber and L.N. Mander, *Tetrahedron Lett.*, **29**, 1988, 3959.

9 In the absence of acylation, cyclic ether formation is likely to take place (*cf.* refs. 5 and 6).

10 H. Yamane, I. Yamaguchi, N. Murofushi and N. Takahashi, *Agric. Biol. Chem.*, 1974, **38**, 649.

11 All compounds were fully characterised by ^{1}H and ^{13}C-NMR spectra, IR and mass spectra, and HRMS or elemental analysis.

12 M. Furber and L.N. Mander, *Tetrahedron Lett.*, **29**, 1988, 3339.

13 M. Furber and L.N. Mander, *J. Am. Chem. Soc.*, **110**, 1988, 4084.

14 Selected spectroscopic data for **4** (methyl ester): ^{1}H-NMR (500MHz) δ($CDCl_3$) 1.25 (s, 3H, 4-Me), 1.34 (dd, 1H, J_{gem}=12.9Hz, $J_{12\beta,11\alpha}$=9.4Hz, H-12β), 1.64 (broad s, 2H, H-14,14'), 1.89 (d, 1H, J_{gem}= 15.4Hz, H-15α), 1.95 (d, 1H, $J_{9\beta,11\alpha}$=10.8Hz, H-9β), 2.23 (d, 1H, J_{gem}=15.4Hz, H-15β), 2.51 (dt, 1H, J_{gem}= 13.2Hz, $J_{12\alpha,11\alpha}$=8.4Hz, $J_{12\alpha,13}$=8.4Hz, H-12α), 2.71 (broad d, 1H, $J_{13,12\alpha}$=8.4Hz, H-13), 2.82 (d, 1H, $J_{6\alpha,5\beta}$=11.2Hz, H-6α), 3.25 (d, 1H, $J_{5\beta,6\alpha}$=11.2Hz, H-5β), 3.73 (s, 3H, OMe), 4.16 (e, 1H, $W_{1/2}$=12Hz, H-3α), 4.25 (ddd, 1H, $J_{11\alpha,9\beta}$=10.8Hz, $J_{11\alpha,12\beta}$=9.4Hz, $J_{11\alpha,12\alpha}$=8.4Hz, H-11α) 4.92 (broad s, 1H, H-17), 5.06 (broad s, 1H, H-17'), 5.87 (dd, 1H; $J_{2,1}$=9.35Hz, $J_{2,3}$=3.64Hz H-2) 6.65 (d, 1H, $J_{1,2}$=9.35Hz, H-1).
^{13}C-NMR (125.7 MHz) δ ($CDCl_3$) 14.4 (C-18) 36.6 (C-12) 38.3 (C-13) 41.4 (C-14) 44.6 (C-15) 50.6 (C-6) 52.1 (OMe) 52.2 (C-5) 52.5 (C-8) 53.3 (C-4) 57.7 (C-9) 64.7 (C-11) 69.5 (C-3) 90.5 (C-10) 108.5 (C-17) 131.5 (C-1) 135.0 (C-2) 155.5 (C-16) 172.4 (C-7) 178.6 (C-19).
Mass spectrum (bisTMS ether methyl ester): 504 (M^+, 7%) 414 (2) 370 (3) 355 (11) 295 (13) 280 (60) 267 (5) 221 (63) 193 (23) 179 (19) 165 (13) 129 (11) 75 (36) 73 (100). KRI 2667.

15 A. Chu and L.N. Mander, *Tetrahedron Lett.*, **29**, 1988, 2727.

(Received in UK 27 November 1989)