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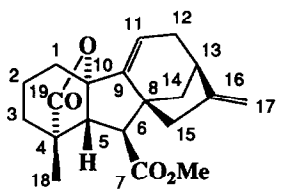
SYNTHESIS OF GA_{73} METHYL ESTER, A POTENT GIBBERELLIN-DERIVED ANTHERIDIOGEN FROM GAMETOPHYTES OF THE FERN LYGODIUM JAPONICUM

Petra Kraft-Klaunzer, Mark Furber, Lewis N. Mander,* Bruce Twitchin

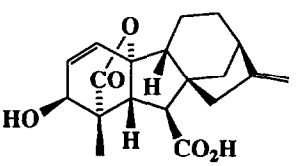
Research School of Chemistry, Australian National University, GPO Box 4, Canberra, A.C.T. 2601, Australia

Summary: Iodolactonisation of gibberellin Δ^9-ene-19-oic acids followed by DBU induced dehydrohalogenation provides good access to gibberellin $\Delta^{9(11)}$-enes, including the potent antheridiogen, $\Delta^{9(11)}$-didehydro-GA_9 methyl ester (**1**), isolated from gametophytes of the fern *Lygodium japonicum.*

Gibberellin A_9 (GA_9) methyl ester was isolated by the Takahashi group from gametophytes of the fern *Lygodium japonicum* and shown to induce antheridia formation at 10^{-10} molar concentrations.[1] However, the amount of compound present in the culture medium was too low to account for the total activity of the extract and the presence of a second, more potent, substance was suspected. Careful fractionation of 12 litres of culture filtrate yielded 40 nanograms of a second antheridiogen which appeared from mass spectra as though it was probably a didehydro-derivative of GA_9 methyl ester. From comparison with a series of synthetic candidates, the structure was shown to be **1**,[2] and in this Letter we disclose the details of its preparation from GA_7 (**2**) using procedures which should prove to be of general utility for the structural manipulations of this type of molecule which are often required to establish the identity of new metabolites.



1



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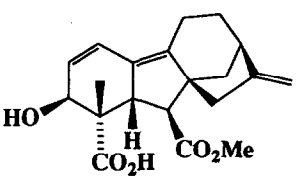
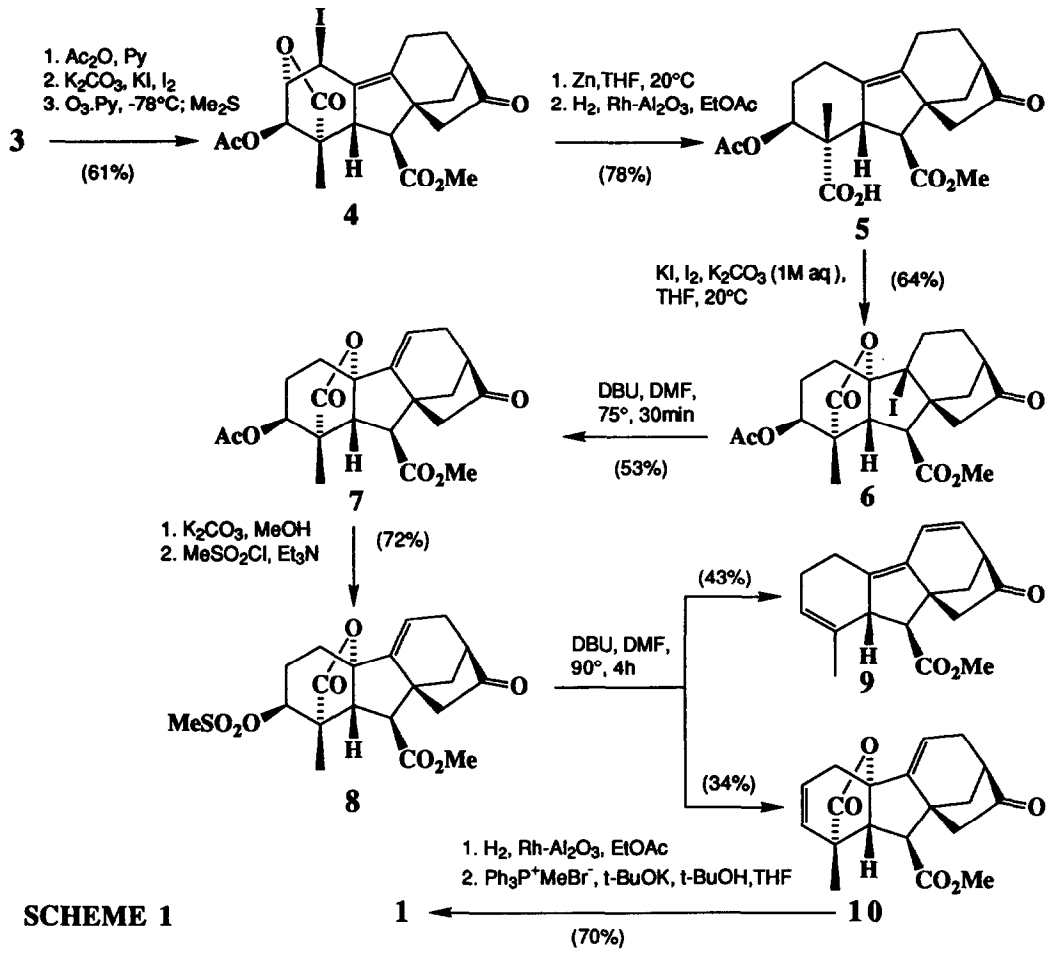


3

The central part of our strategy for introducing the $\Delta^{9(11)}$-alkene bond was based on the premise of effecting iodolactonisation of a suitable Δ^9-ene-19-oic acid, followed by elimination of HI from the product, as indicated by the sequence **5**→**6**→**7** (Scheme 1). In order to test this hypothesis, **5** was prepared from the methyl ester of **2** by first heating this substrate in hydrazine hydrate[3] to produce the triene acid **3**.[4,5] Temporary masking of the Δ^1-alkene bond by formation of the 1-iodo-2,19-lactone function allowed the 16-methylene group to be selectively ozonised, affording the 17-nor-16-one **4**. After reconstitution of the Δ^1-alkene function by means of a 1,2-reductive elimination, it was removed by catalytic hydrogenation, thereby providing access to the Δ^9-acid **5**. This readily underwent the planned iodolactonisation to form **6** and this, in turn, was converted into enone **7**, m.p. 211-12°, by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). The labile nature of the allylic lactone function in enone **7** hindered our efforts to remove the oxygen function from C(3), but this was

ultimately achieved by DBU induced elimination of the corresponding mesylate **8**, m.p. 182-3°, to give diene **10**, although the major product was the double elimination product **9**. Selective hydrogenation of the less hindered Δ^2 olefinic bond in **10** followed by Wittig methylenation, then afforded the desired ester **1**.[6]

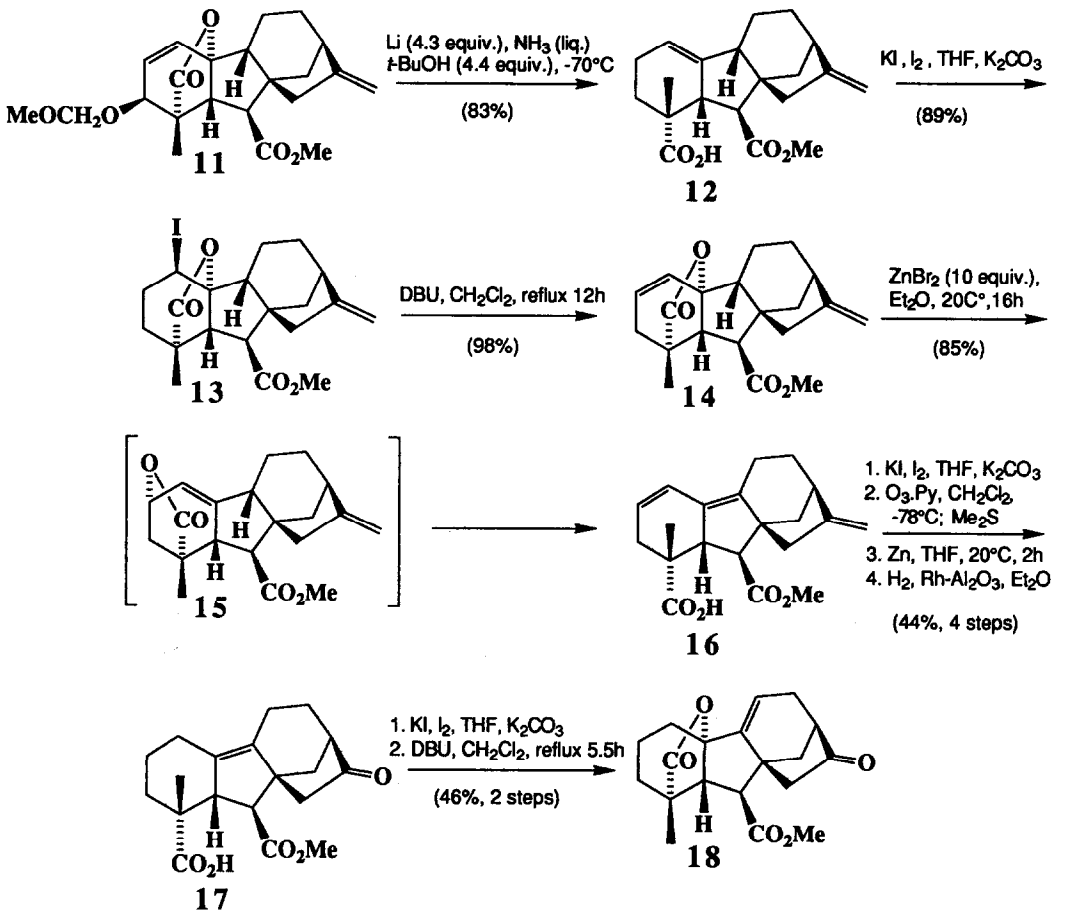


SCHEME 1

While the preparation of **1** in this way allowed confirmation of the structure of the natural antheridiogen, it did not provide a satisfactory basis for obtaining sufficient quantities of material for further studies on its biological properties.[7] An alternative sequence involving deoxygenation of the A-ring prior to the elaboration of the labile $\Delta^{9(11)}$-allylic lactone function was therefore devised. The successful realisation of the new and more efficient approach is outlined in Scheme 2.

The first stage of this preparation was aimed at removal of oxygen from C(3). This was realised by careful reduction of the GA_7 derivative **11** with lithium in liquid ammonia,[8] affording the half-ester **12**, m.p.125-7°, which underwent iodolactonisation to form **13**, m.p. 152-4°. When treated with DBU, **13** gave rise to olefinic lactone **14**, m.p. 100-101°, and this was readily isomerised by zinc bromide to the triene acid **16**, m.p.88-91°. The expected product was the allylic isomer **15**,[9] and although this was formed, it was rapidly transformed

through to **16**. To allow selective reduction of the Δ^1-double bond, a further cycle of iodolactonisation, ozonolysis and reduction as before, gave olefinic acid **17**, 158-60°,[10] which was then transformed into **18**, m.p. 151-3°, *via* the 9β-iodolactone, m.p.118-20°.



SCHEME 2

The synthesis of **1** was completed by Wittig methylenation of ketone **18** as before,and the material obtained in this manner was shown to induce antheridia in prothalli of *L. japonicum* at dilutions approaching the femto-molar level (32% at 10^{-14}M; 98% at 10^{-13}M). Inhibition of archegonia formation was observed with picomolar solutions (16% at 10^{-12}M; 70% at 10^{-11}M), while dark germination of spores was promoted by slightly higher concentrations (12% at 10^{-11}M; 70% at 10^{-10}M).[7] The zinc halide based procedure for the preparation of triene acid **16** from allylic lactone **14** provides a major advance over the classical hydrazine methodology,[3] although the outcome for any particular substrate is unexpectedly sensitive to the nature of the functionality elsewhere in the molecule. It nevertheless provides a useful adjunct to an earlier method for functionalisation of the C-ring[11] and applications to the synthesis of several new gibberellins functionalised at C(11)[12] as well as to the improved synthesis of other fern antheridiogens are in progress.[13]

Acknowledgements. We thank the Deutsche Forschungsgemeinschaft for financial support to P.K.-K., and Abbott Laboratories for the provision of gibberellins.

References and Notes

(1) Yamane, H.; Takahashi, N.; Takeno, K.; Furuya, M. *Planta*, **1979**, *147*, 251.

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

(3) Grove, J.; Mulholland, T.P.C. *J. Chem. Soc.* **1960**, 3007.
Furber, M.; Mander, L.N. *J. Am. Chem. Soc.* **1987**, *109*, 6389.

(4) Although the yield in this preparation is only 25%, the hydrazine based procedure has hitherto provided the most direct access to gibberellin Δ^9-enes. The corresponding 7,19-dicarboxylic acid was formed as well (20% yield) and may also be utilised in the preparation of **4** (although the yield is inferior).

(5) All new compounds were fully characterised by ^1H and ^{13}C NMR spectra, IR spectra, low resolution mass spectra, and microanalysis and/or HRMS. Yields refer to isolated, chromatographically homogeneous compounds.

(6) Obtained as a colourless oil; R_f 0.73 (Et_2O-hexane, 2 : 1); IR ($CHCl_3$) υ_{max} 1770 (s), 1730 (s), 1680 (w), 1660 (w) cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) 5.81 (1H, ddd, $J_{11,12\beta}$ = 3.8Hz, $J_{11,12\alpha}$ = 2.9Hz, $J_{11,13}$ = 1.0Hz, H11), 4.99 (1H, s, br, H17), 4.87 (1H, s, br, H17'), 3.72 (3H, s, CO_2Me), 2.93 (1H, m, H13), 2.73 (1H, d, $J_{6\alpha,5\beta}$ = 11.4Hz, H6α), 2.54 (1H, d, $J_{5\beta,6\alpha}$= 11.4Hz, H5), 2.49 (1H, ddd, J_{gem} = 18.0Hz, $J_{12\alpha,13}$ = 4.4Hz, $J_{12\alpha,11}$ = 2.9Hz, H12α), 2.36 (1H, dm, J_{gem} = 15.6Hz, H15α), 2.18 (1H, m), 2.12 (1H, dd, J_{gem}= 10.7Hz, $J_{14\beta,13}$ = 5.6Hz, H14β), 2.09 (1H, ddd, J_{gem} = 18.0Hz, $J_{12\beta,11}$ = 3.8Hz, $J_{12\beta,13}$ = 2.3Hz, H12β), 1.98 (1H, dt, J_{gem} = 15.6Hz, J = 2.7Hz, H15β), 1.85 (1H, m), 1.76 -1.50 (5H, m), 1.10 (3H, s, 4β-Me); ^{13}C NMR (50MHz, $CDCl_3$) 178.94 (C19), 172.47 (C7), 154.50 (C16), 146.85 (C9), 123.65 (C11), 107.87 (C17), 89.28 (C10), 57.28 (C5), 52.51 (C8), 52.02 (OMe), 49.38 (C4), 48.35 (C6), 44.10 (C15), 40.93 (C13), 39.47 (C12), 37.30 (C14), 34.97 (C3), 30.44 (C1), 19.65 (C2), 17.13 (C18); LRMS 328 (M^+, 4%), 297 (7), 284 (M^+-CO_2, 100), 269 (13), 241 (12), 225 (67), 183 (22); HRMS Found: 328.1675 (M^+), $C_{20}H_{24}O_4$ requires: 328.1674. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.75.

(7) Takeno, K.; Yamane, H.; Yamaguchi, T.; Takahashi, N.; Furber, M.; Mander, L.N. *Plant and Cell Physiol.* **1988**, *30*, 201.

(8) *Cf.* Dawe, R.D.; Mander, L.N.; Turner, J.V. *Tetrahedron Lett.* **1985**, *26*, 363.

(9) The reaction of the 3β-acetate methyl ester of **2**, for example, affords a 90% yield of the corresponding $\Delta^{1(10)}$-19,2 lactone (Furber, M.; Mander, L.N.; Patrick, G.L. *J. Org. Chem.* **1990**, in press).

(10) We also examined the obviously more direct approach to **17** from **13** by oxidising this compound to the corresponding 17-nor-16-one, eliminating HI with DBU, and then treating the resulting 16-one (corresponding to **14**) with $ZnBr_2$ / Et_2O. However, this reaction afforded a 19:33:48 mixture of the 16-oxo analogues of **14**, **15**, and **16**, respectively.

(11) Chu, A; Mander, L.N. *Tetrahedron Lett.* **1988**, *29*, 2727.

(12) Enone **7** and an analogue have been employed as intermediates in the synthesis of the 11β-hydroxy gibberellins, GA_{35} and GA_{80} (*cf.* Mander, L.N.; Patrick, G.L. *Tetrahedron Lett.* **1990**, *31*, 423).

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

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