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Synthetic and structural studies on novel gibberellins

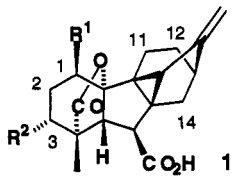
Milan Pour, Geoffrey R. King, Nathaniel J.T. Monck, Jonathan C. Morris, Hongbin Zhang and Lewis N. Mander,

Research School of Chemistry, Institute of Advanced Studies, Australian National University, Canberra, A.C.T. 0200, Australia.

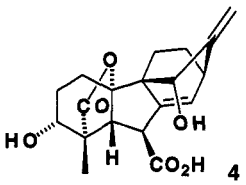
Abstract : The structure elucidation of a number of metabolites isolated during biosynthetic studies on gibberellin-like fern antheridiogens from the *Anemia* genus has been undertaken by synthesising a series of reference samples from gibberellin A_7. Two of the metabolites were shown to be the 12β- and 12α-hydroxy derivatives of 9β,15-cyclogibberellin A_9 (**1**) while the 11β-hydroxy isomer was identical with a new gibberellin (GA_{108}) from developing apple seeds. In a cognate study, an efficient total synthesis of this type of gibberellin has been developed, the key step being the intramolecular cyclopropanation reactions of the aromatic ring in tetralin 2-diazomethyl ketones to give stable norcaradiene products. The [4+2] cycloaddition of selected dienophiles to some of these products allows the rapid stereo-controlled assembly of (**1**) and related gibberellins.

INTRODUCTION

The 1β-hydroxy-9,15-cyclogibberellin (**2**) was isolated from gametophytes of the fern *Anemia mexicana* in which it promotes antheridia formation (ref. 1, 2), and was the first gibberellin to be isolated with the unusual 9β,15β-cyclo skeleton. Incorporation studies (ref. 3) have shown that (**1**) (GA_{103}) and the 3α-hydroxy derivative (**3**) (GA_{107}) are the probable biosynthetic precursors to the major antheridiogen, antheridic acid (**4**), from *A. phyllitidis* (ref. 4, 5), while a new family of cyclogibberellins comprised of the parent (**1**) and several hydroxy derivatives has recently been isolated from apple seeds (ref. 6).



1 R^1=H, R^2=H
2 R^1=OH, R^2=H
3 R^1=H, R^2=OH



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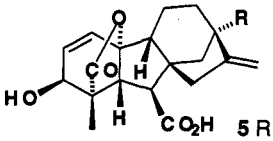

5 R = H
6 R = OH

Because of the low natural abundance of all of these gibberellins ("GAs"), identification has entailed chemical synthesis of putative structures and comparison of the mass spectra and Kovats retention indices (KRIs) of synthetic and natural compounds following GC-MS (ref. 7). Within this context, the fungal GA (**5**) had been converted (ref. 8) into the key intermediates (**7**) and (**8**) (Fig. 1), from which it was a reasonably straightforward task to prepare and confirm the structures of (**1**) and derivatives hydroxylated at C-1, C-2 and C-3 (ref. 6). In a continuation of our investigations into, *inter alia*, the biosynthetic pathway leading to (**4**), we have undertaken the structure elucidation of a number of metabolites that were isolated during the incorporation studies (ref. 9), again by synthesis of likely candidates. We also hoped that progress in this area would shed light on the constitution of further, as yet, unidentified endogenous GA-like antheridiogens from these fern species.

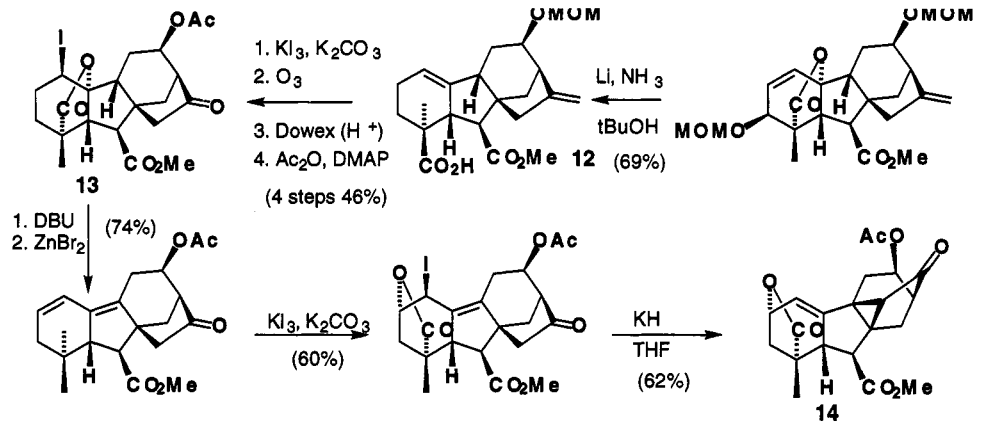

Fig. 4 Synthesis of an advanced intermediate leading to 12β-hydroxy-9,15-cyclogibberellin A_9

As the key step in the transposition, we envisaged that hydroboration of an 11,16-diene, would proceed *via* addition of the reagent to the more exposed methylene function followed by intramolecular delivery of boron to C(12) as outlined in Fig. 5 (ref. 11). The realisation of the complete synthesis, incorporating this step, is outlined in Fig. 6.

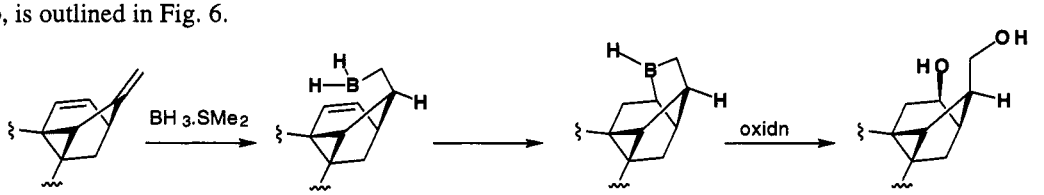

Fig. 5 Strategy for the 12-hydroxylation of a cyclogibberellin.

The requisite diene (**15**), prepared by elimination of the 11β-mesylate derived from (**9**), was converted into the 12β, 17-diol as planned, the outcome of the reaction being confirmed by determining the X-ray crystal structure of the derived monoacetate (**16**). Reconstitution of the 16-methylene group was rendered difficult by the tendency for the 12β- and 17-substituents to interact, but after several false starts, the difficulty was resolved by protecting the 12-hydroxyl in (**16**), preparing aldehyde (**17**), and then effecting isomerisation with base to afford the more stable *exo*-isomer (**18**). Reduction and conversion to iodide (**19**), liberation of the 12-hydroxyl and elimination with DBU then afforded the target 12β-carbinol (**20**), the trimethylsilyl (TMS) ether of which had the same KRI and mass spectrum as one of the *Anemia* metabolites. Parallel metabolic studies with *Lygodium japonicum* (ref. 9) had afforded an isomer of (**20**) that gave an identical

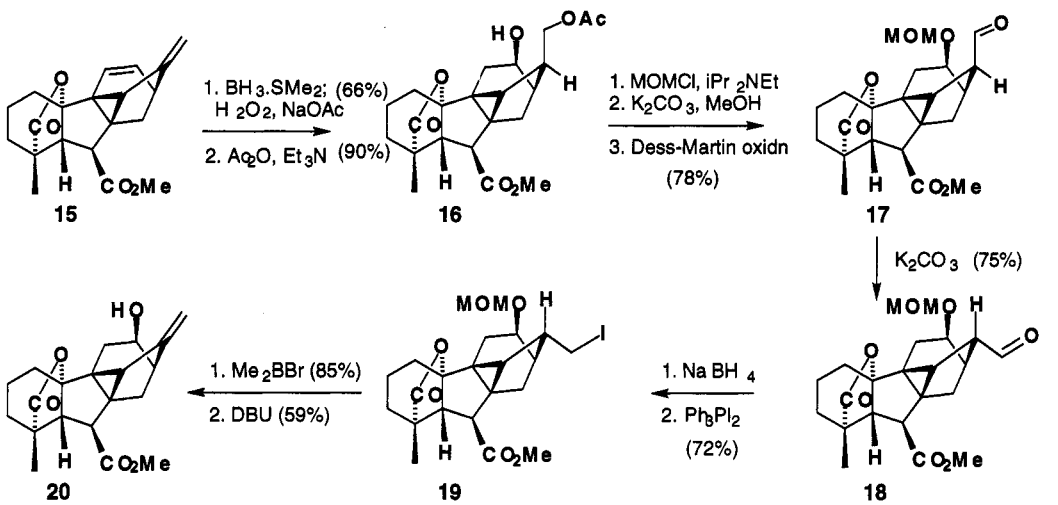

Fig. 6 Synthesis of 12β-hydroxy-9,15-cyclogibberellin A_9

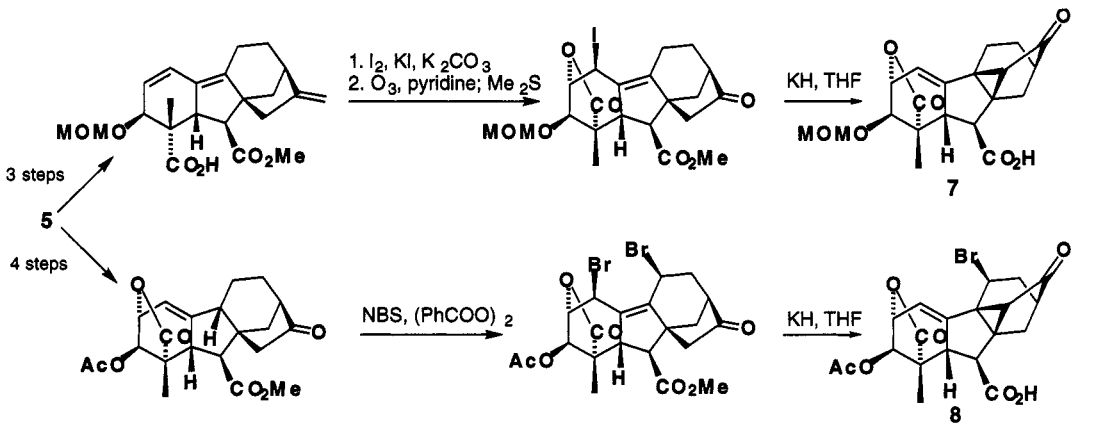

Fig. 1 Approaches to the synthesis of 9,15-cyclogibberellins.

SYNTHESIS OF NEW CYCLOGIBBERELLINS

Evidence that one of the metabolites was a derivative of (**1**) hydroxylated in the C-ring was obtained when treatment of *A. phyllitidis* prothallia with 11β,12β,17,17-d_4-GA_{103} (prepared from **8**) afforded a d_3-metabolite (ref. 9). Our initial synthetic efforts were therefore directed towards the preparation of 11- and 12-hydroxy derivatives of (**1**). Bromo ketone (**8**) was converted readily into the 11α- and 11β-carbinols (**9**) and (**10**) (Fig. 2), respectively, but neither corresponded to the d_3-metabolite obtained above. The 11β-epimer, however, proved to be identical with the methyl ester of one of the new apple gibberellins (later assigned as GA_{108}) (ref. 6). We turned our attention, therefore, to the preparation of the 12-hydroxy isomers of (**1**), a task that proved to be much less straightforward.

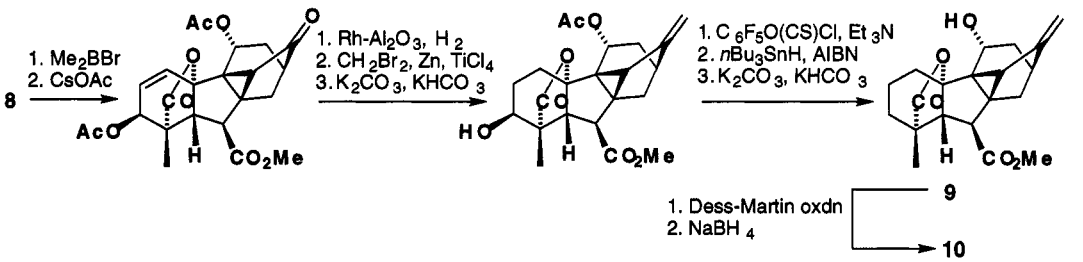

Fig. 2 Synthesis of 11β-hydroxy-9,15-cyclogibberellin A_9 (GA_{108})

Having established effective methods (ref. 10) for the introduction of a 12-hydroxy function into gibberellic acid (**6**), (Fig. 3), we set out on the preparation of the analogue (**14**) (Fig. 4) by adapting the sequence that had furnished (**7**). Thus, modification of the functionality in the 12-hydroxy intermediate (**11**) followed by Birch reduction afforded the diene acid (**12**), from which it was a simple task to make the 12β-acetoxy iodide (**13**) and thence (**14**). Unfortunately, this synthesis had become unduly protracted (22 steps) and so we turned our attention to the alternative approach of achieving a 1,2-transposition (11→12) of the hydroxy group in (**9**).

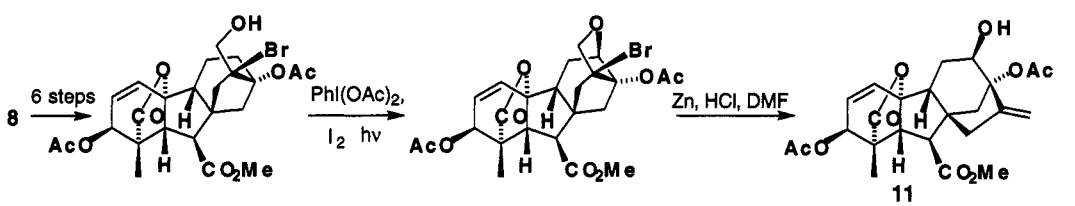

Fig. 3 Introduction of hydroxyl into the C-12 position of the gibberellin molecule

mass spectrum (TMS ether) but different KRI. This GA was therefore assumed to be the 12α-epimer, a conclusion that was verified when a small sample was obtained from (**20**) by means of an oxidation/ reduction cycle.

TOTAL SYNTHESIS OF GIBBERELLINS: A NEW STRATEGY

By this stage, all of the more readily accessible hydroxylated derivatives of (**1**) had been assembled, but there still remained a number of unidentified metabolites and natural GAs from these fern species. Given the protracted nature of some of these partial syntheses, we turned to the option of making further derivatives by total synthesis. Recent work (ref. 12) on the intramolecular cyclopropanation reactions of the aromatic ring in tetralin diazomethyl ketones had offered the prospect of a general approach that would be competitive in efficiency and brevity with the partial syntheses beginning with fungal gibberellins, while providing the additional flexibility that we believed would be required. The advanced intermediate (**21**) may be made in only 7 steps from 1,6-dimethoxynaphthalene and thus far it has been possible to complete the syntheses of GA_{103} (**1**) in 18 steps, and the exceptionally potent antheridiogen isolated from several *Lygodium* species (ref. 13), GA_{73} methyl ester (**22**), in only 15 steps (Fig. 7). The sequences were completed with essentially complete stereo-control and are significantly shorter than the partial syntheses beginning with fungal gibberellins (ref. 14); they are also significantly more direct than most earlier total syntheses of gibberellins (ref. 15). Although the present study has been conducted with racemates, good methodology for the synthesis of enantiopure starting materials is available (ref. 16).

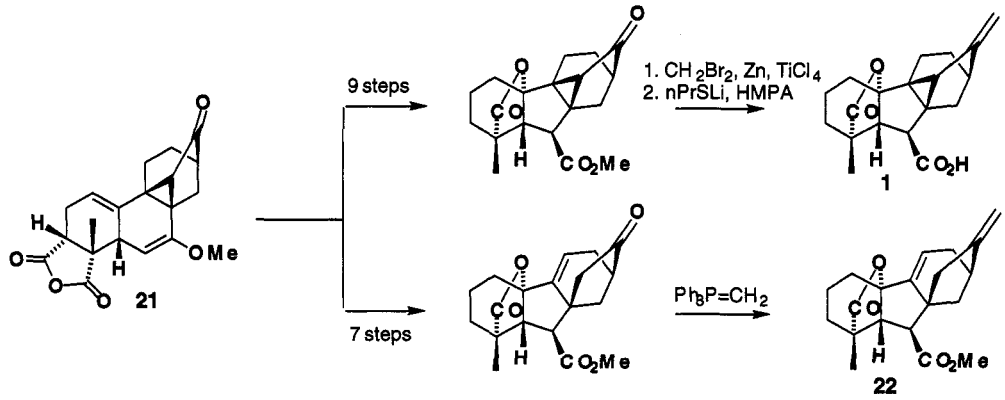

Fig. 7 Total syntheses of (±)-GA_{103} and (±)-GA_{73} methyl ester.

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