Pergamon

Tetrahedron Letters 39 (1998) 1991–1994

TETRAHEDRON LETTERS

Synthesis of 12-Hydroxy 9,15-Cyclogibberellins

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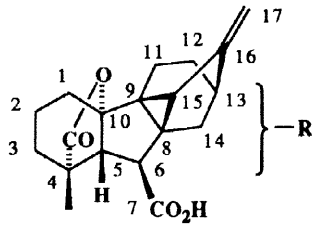
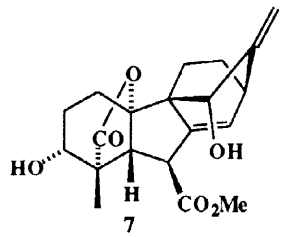
Received 28 November 1997; revised 5 January 1998; accepted 9 January 1998

Abstract: The methyl esters of 9β,15-cyclogibberellins, 12α- and 12β-hydroxy-GA_{103} have been synthesised and shown by GC-MS to correspond to two metabolites of GA_{103} formed by exposure to prothallia of the ferns *Anemia phyllitidis*, *Lygodium japonicum* and *Lygodium circinnatum*.

The unusual family of gibberellins ("GAs") (**1**)-(**6**) has been discovered recently in developing apple seeds.[1] GA_{104} (**2**) had been identified previously as the major antheridiogen in gametophytes of the fern *Anemia mexicana*,[2] while GA_{103} (**1**) and GA_{107} (**5**) have been shown to be the probable biosynthetic precursors of the fern antheridiogen, antheridic acid (**7**) by feeding deuterium labelled derivatives to prothallia of *Anemia phyllitidis*.[3] In order to probe the biosynthetic origins of **7** and related antheridiogens more thoroughly, the fate of [17,17-$^2H_2$]-GA_{103} in metabolic studies conducted with the related ferns, *Lygodium japonicum* and *L. circinnatum* was also explored, resulting in the formation of [17,17-$^2H_2$]-GA_{108} (**6**), 2-*epi*-GA_{105}, 11-*epi*-GA_{108} and two further products that were tentatively identified by GC-MS as 12β- and 12α-hydroxy-GA_{103}.[4] This last GA was also formed during the biosynthetic studies with *Anemia phyllitidis*.[3]



1 R = H (GA_{103})
2 R = 1β-OH (GA_{104})
3 R = 2β-OH (GA_{105})
4 R = 3β-OH (GA_{106})
5 R = 3α-OH (GA_{107})
6 R = 11β-OH (GA_{108})



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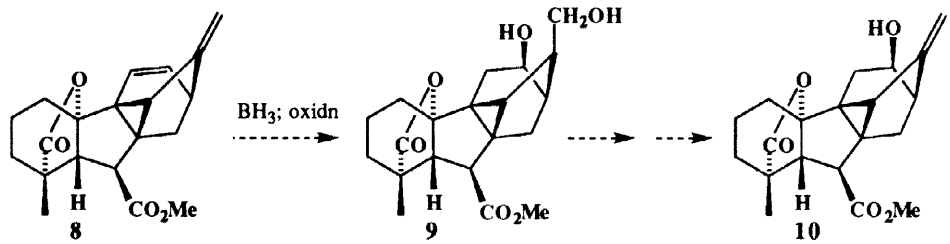
We have recently reported on the preparation of the methyl esters of all 1-, 2-, 3- and 11-hydroxy derivatives of 9,15-cycloGA$_9$.[5] In this Letter we describe the synthesis of the 12-hydroxy analogues and show that they correspond to the remaining metabolites formed from [17,17-$^2H_2$]-**1** by the fern prothallia.

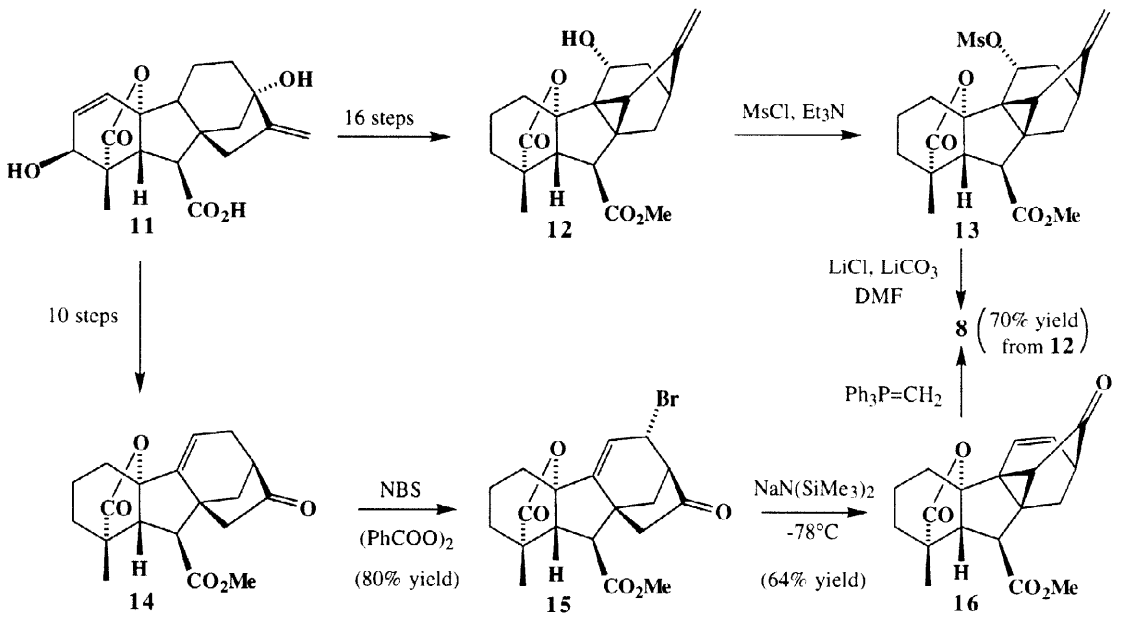


8 **9** **10**

Scheme 1

PII: S0040-4039(98)00113-0

The synthetic plan (Scheme 1) for the preparation of 12β-hydroxy-GA_{103} (**10**) was based on the expectation that the addition of borane to the exocyclic double bond in **8** would occur predominantly on the *exo* face followed by the intramolecular addition of the alkylborane thus formed to the Δ^{11}-alkene bond, thereby affording a 12,17-cycloborane. Oxidation to diol **9**, followed by functional group manipulation, could then be expected to lead to the target structure **10**.[6]



Scheme 2

As outlined in Scheme 2, diene **8** was first prepared from the cyclogibberellin **12** by conversion into the mesylate **13** followed by elimination with DBU.[7] The preparation of **12** from gibberellic acid (**11**)[5] required 16 steps, however, and so we explored the alternative route based on the intramolecular alkylation **15** → **16**. This conversion was highly successful,[8] and given the more direct accessibility of enone **14** (10 steps from **11**),[9] this became our preferred approach. Hydroboration of diene **8** with $Me_2S.BH_3$ furnished a 66% yield of diol **9**, the structure of which was confirmed by single crystal X-ray analysis of the derived monoacetate **17** (Fig. 1).[10] The syntheses of **10** and its 12-epimer were then completed as outlined in Scheme 3.

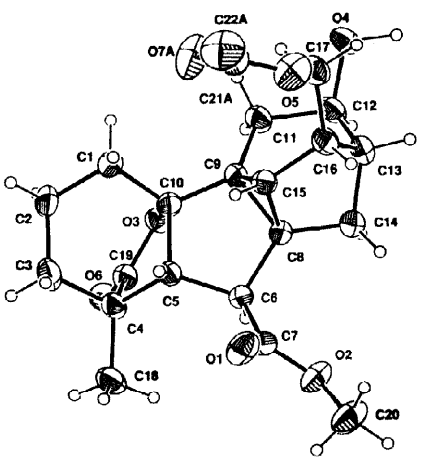
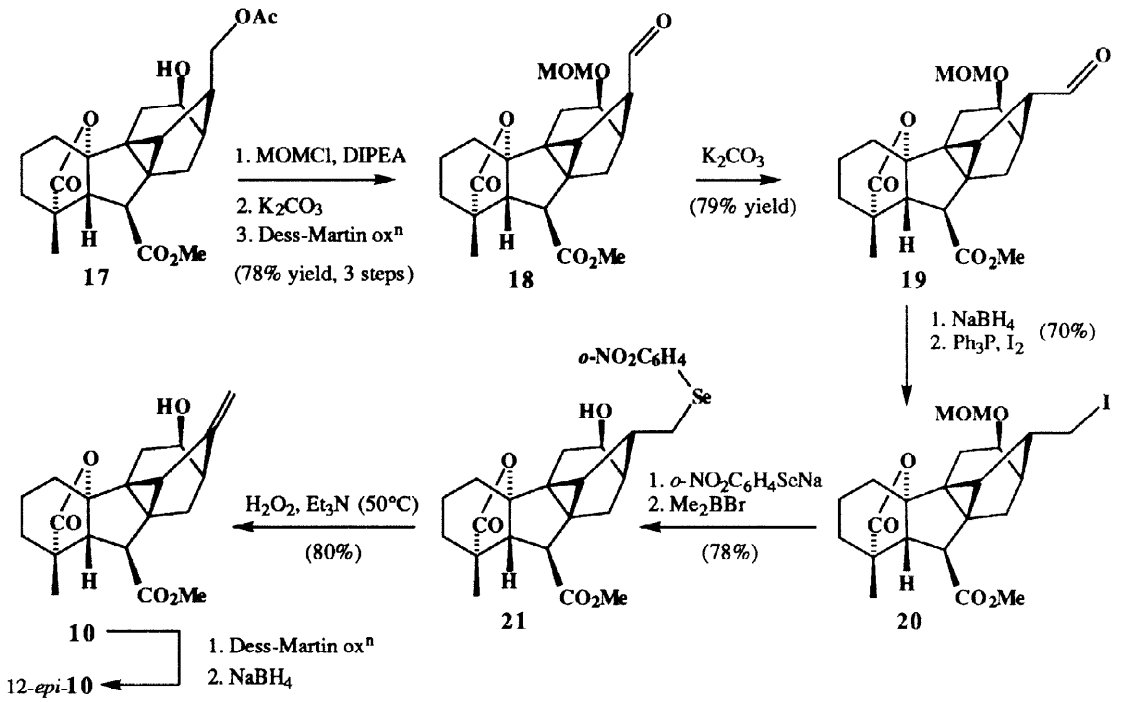


Figure 1: Ortep diagram of cyclogibberellin **17**. Ellipsoids show 30% probability levels and hydrogen atoms are drawn as circles with small radii. Only the major orientation of the disordered acetate group is shown.



Scheme 3

In order to avoid interference from the 12β-hydroxyl during the restoration of the 17-methylene group, it was essential to effect spatial separation between the 12β- and 17-substituents. This was achieved by masking the 12-hydroxyl (MOM ether), removing the 17-acetate function, oxidising[14] the 17-carbinol, and isomerising the resulting 17-aldehyde **18** with base to the thermodynamically favoured *exo*-aldehyde **19**. Reduction, formation of the 17-iodide **20**, displacement with *o*-nitrophenyl selenide[15] and removal of the MOM protecting group[16] then gave **21**, the selenoxide from which smoothly underwent elimination[17] at 50°C to afford the target alkene **10**.[18,19] A sample of **10** was oxidised to the 12-oxo derivative and this product reduced with $NaBH_4$. This treatment returned mainly **10**, accompanied by only a trace of the 12α-epimer, but sufficient to carry out GC-MS comparisons[20] of the trimethylsilyl derivatives.[21] These comparisons showed that both **10** and its 12-epimer corresponded to two of the metabolites of [17,17-$^2H_2$]-GA_{103} (**1**) isolated from *L. japonicum* and *L. circinnatum*,[4] while 12-*epi*-**10** corresponded to the unidentified metabolite (M^+ 418, KRI 2457) formed from [17,17-$^2H_2$]-**1** during the biosynthetic studies conducted with *A. phyllitidis*.[3,22] These new gibberellins usefully extend the library of reference compounds, while the new methods for assembling the 9,15-cyclogibberellin structure and for hydroxylating the C(12) position are proving to be of general utility for the assembly of related structures.

Acknowledgement. The authors are indebted to Drs Yamane and Yamauchi for comparing the synthetic cyclogibberellins with the methyl esters of the GA_{103} metabolites from *A. phyllitidis*, *L. japonicum* and *L. circinnatum*, and for the provision of the GC-MS data.

References and Notes

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7. All new compounds were characterised by ^{1}H and ^{13}C NMR spectra, LRMS and HRMS. Satisfactory microanalyses were obtained for compounds **8**, **9**, **17**, **18**, **19** and **20**.
8. The C(8)-C(15) bond in cyclogibberellin **16** undergoes base-catalysed cleavage with extreme ease. It is therefore important to conduct this reaction at low temperature and neutralise any excess of base before allowing the mixture to warm up. *Cf.* Furber, M.; Mander, L. N.; Patrick, G. L. *J. Org. Chem.* **1990**, *55*, 4860-4870.
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10. $C_{22}H_{28}O_7$, orthorhombic space group $P2_12_12_1$, a = 10.125(1), b = 10.631(2), c = 19.551(1) Å, V = 2104.4(3) Å^3, Z = 4. Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.54178 Å) yielding 1808 unique reflections with $2\theta \leq 120$ °. The structure was solved by direct methods.[11] Disorder was observed for the acetate group attached at O(5). Non-hydrogen atoms (with the exception of those comprising the minor component of the disorder) were refined with anisotropic displacement factors. H atoms were included at calculated positions (the H atom on O(4) from a difference electron-density map). Refinement was by full-matrix least-squares analysis on F using teXsan[12] and Xtal[13] software. Final R = 0.051 on 1578 reflections with $I > 3\sigma(I)$. Further details have been deposited by the editor at the Cambridge Crystallographic Data Centre.
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17. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.
18. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.01 (1H, s, H17), 4.90 (1H, s, H'17), 3.87 (1H, m, H12α), 3.72 (3H, s, OMe), 2.89 (1H, d, $J_{6,5}$ = 8.9 Hz, H6), 2.65 (1H, dd, $J_{11\alpha,11\beta}$ = 14.8 Hz, $J_{11\alpha,12\alpha}$ = 9.2 Hz, H11α), 2.41 (1H, m, H13), 2.12 (1H, d, $J_{5,6}$ = 8.9 Hz, H5), 2.04 (1H, dd overlapped, $J_{14\beta,14\alpha}$ = 11.9 Hz, $J_{14\beta,13}$ = 6.2 Hz, H14β), 2.02 (1H, s, H15), 1.65 (1H, dd overlapped, $J_{11\beta,11\alpha}$ = 14.8 Hz, $J_{11\beta,12\alpha}$ = 3.8 Hz, H11β), 1.63 (1H, d overlapped, $J_{14\alpha,14\beta}$ = 11.9 Hz, H14α), 1.09 (3H, s, H18); ^{13}C NMR (75.5 MHz, $CDCl_3$) 178.6 (C19), 172.7 (C7), 146.2 (C16), 106.9 (C17), 92.9 (C10), 68.5 (C12), 56.4 (C5), 52.2 ($-CO_2CH_3$), 48.0 (C4), 47.4 (C6), 45.7 (C13), 41.4 (C8), 37.4 (C9), 35.0 (C14), 30.8 (C11), 30.2 (C15), 28.4, 27.2 (C1, C3), 19.1 (C2), 16.7 (C18); LRMS 344 ($M^{\cdot+}$, 14%), 326 ($M^{\cdot+}-H_2O$, 4), 312 (22), 300 (20), 285 (24), 266 (16), 256 (39), 254 (98), 240 (100), 223 (16), 211 (15), 197 (62), 181 (22); HRMS found 344.1622 ($M^{\cdot+}$), $C_{20}H_{24}O_5$ requires 344.1624.
19. Given the propensity of the cyclopropyl ring in these systems to fragment, we chose to restore the 17-methylene group by means of the mild selenoxide based methodology. It was found subsequently, however, that **10** could be obtained more directly, simply by effecting the elimination of HI with DBU (DMF, 50°C, 48 h, 59% yield).
20. Yamauchi, T.; Yamane, H., unpublished results.
21. GC-MS (12β-OTMS) 416 ($M^{\cdot+}$, 100), 401 (15), 357 (23), 326 (33), 313 (38), 254 (26), 240 (30), 223 (47), 196 (26); KRI 2487. Metabolite from [17,17-$^2H_2$]-GA_{103}: 418 ($M^{\cdot+}$, 100%), 359 (33), 328 (29), 315 (40), 256 (34), 242 (39), 225 (66), 198 (29); KRI 2486.[4] (12α-OTMS) 416 ($M^{\cdot+}$, 100), 326 (29), 313 (39), 298 (7), 281 (11), 267 (12), 254 (26), 240 (28), 223 (43), 196 (24); KRI 2458. Metabolite from [17,17-$^2H_2$]-GA_{103}: 418 ($M^{\cdot+}$, 100%), 328 (32), 315 (45), 269 (18), 256 (28), 242 (48), 225 (58), 198 (25); KRI 2457;[3] 2456.[4]
22. The metabolites from *L. japonicum* and *L. circinnatum* were obtained directly as their methyl esters while the metabolite from *A. phyllitidis* was first isolated as the free acid.