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SYNTHESES OF C_{20} GIBBERELLIN A_{36} AND A_{37} METHYL ESTERS FROM GIBBERELLIC ACID

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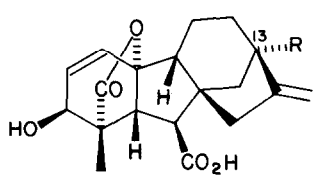
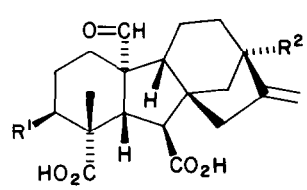
Summary: Gibberellic acid **1** has been stereospecifically transformed into the methyl esters of the C_{20} gibberellins A_{36} **4** and A_{37} **5** through a sequence which features three concurrent reductive processes and a novel oxidative cleavage of a ketone enolate.

We have recently described the efficient conversion of gibberellic acid (GA_3) **1** into the biosynthetically important C_{20} gibberellin A_{19} (GA_{19}) **3** which was hitherto available in only trace amounts.[1] In a continuation of a programme aimed at making available for biological studies the rarer C_{20} gibberellins, we sought to refine and extend this strategy to the partial synthesis of GA_{36} **4** and its congeners.[2] The most obvious substrate for the preparation of GA_{36} **4** was GA_7 **2** because this lacks a C-13 hydroxy group, but the very much higher cost of this material relative to **1** led us to examine the utilisation of the latter compound instead.[3] In this Letter we describe the conversion of GA_3 **1** into the methyl esters of GA_{36} **4** and GA_{37} **19**, as well as an improved synthesis of GA_{19} **3**.

Hydrogenolysis of **1** methyl ester (H_2/Pd-$BaCO_3$/piperidine) was used to dismantle the A-ring allylic lactone function without reduction of the C(16) methylene group. This gave the $\Delta^{1,10}$ olefinic acid **6** (mp 236-238°)[4] which was acetylated and converted into diazoketone **7** (mp 171-172°)[5] by standard procedures.[6] The future C(20) atom was then inserted stereospecifically by intramolecular cyclopropanation (copper-bronze, THF-cyclohexane) to give ketone **8** (146-147°) in 75% yield. Acetate functions at C(3) and C(13) were selected with the dual purpose of preventing interference by the 3-oxy function in the

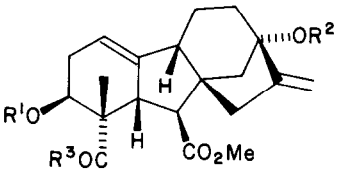


1 R = OH
2 R = H

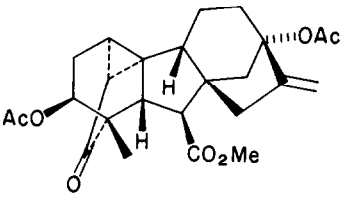


3 R^1 = H, R^2 = OH
4 R^1 = OH, R^2 = H
5 R^1, R^2 = OH

cyclopropanation process and facilitating alkyl-oxygen fission at C(13) in the subsequent reduction step.[7] Thus, when **8** was treated with lithium in liquid ammonia/t-butyl alcohol/THF[8] the 13-deoxy ketone **9** (mp 155-158°) was obtained as the major product in a 2.5:1 mixture with acetate **10** (total yield : 49%). Although the yield of **9** was only modest, it is the product of three concurrent reductive processes (regioselective hydrogenolysis of the cyclopropyl ring,[8] deoxygenation at C(13),[9] and deacylation of the 3-acetoxy group[7]) carried out in the presence of the potentially reducible 7-methoxycarbonyl and C(16) methylene groups. Moreover, liberation of the 3-hydroxyl by the reductive procedure proved to be the only way in which this could satisfactorily be achieved. Base-catalysed hydrolysis, for example, was accompanied by epimerisation at C(3) as a consequence of a retro-aldol process,[10] while hydrolysis in acidic media resulted either in concomitant isomerisation or hydration of the C(16) methylene group.



6 R^1, R^2 = H; R^3 = OH
7 R^1, R^2 = Ac; R^3 = $CH{=}N_2$



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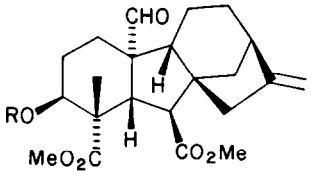
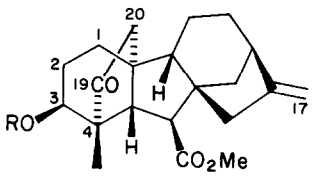
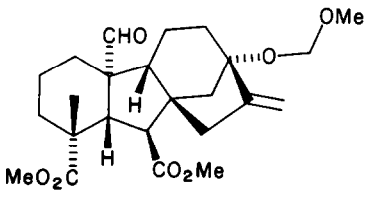


13 R = Si^tBuMe_2
14 R = H
15 R = CH_2OMe



9 R = H
10 R = Ac
11 R = Si^tBuMe_2
12 R = CH_2OMe



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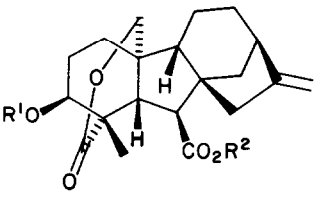

17 R^1 = CH_2OMe, R^2 = Me
18 R^1 = H, R^2 = Me
19 R^1, R^2 = H

We turned next to the oxidative cleavage of C(19)-C(20) in **9**. This process had been effected previously in the analogous GA_{19} intermediate by selective ozonolysis of the derived C(19) enol methyl ether, but had proved to be rather inefficient.[1] We therefore decided to examine the reaction of the enolate anion derived from the C(19) carbonyl function with molecular oxygen. This was found to be ideally suited to our purpose and in a typical experiment, silyloxy ketone **11** was prepared (TBDMSCl, DMAP, DMF, 80°C, 48hr, 84% yield) and treated with potassium hydride (1.2 equiv) in dimethyl formamide-tetrahydrofuran (2:3) at -30°C for 2h and then stirred under an oxygen atmosphere for 5 min at 0°C. After cooling to -20°C, methyl iodide was added and aldehyde **13** isolated in 95% yield. Similar oxidations have traditionally been conducted in t-butyl alcohol and when a methylene group is attached to the carbonyl function, have led to diosphenols.[11] The formation of a seco aldehyde is unprecedented[12], and may be a consequence of the aprotic conditions and/or the very hindered steric environment of C(20). The GA_{19} precursor **16** was also obtained in 95% yield by application of this new procedure.

Fluoride mediated removal of the protecting silyl group ($nBu_4^+F^-$, 8 equiv., 0°C, 3 days, 49% yield) from aldehyde **13** afforded GA_{36} dimethyl ester **14** with ^{1}H-NMR spectroscopic data corresponding to those reported by Bearder and MacMillan,[2] and a mass spectrum identical with that of an authentic sample. Because the t-butyldimethylsilyl group was so difficult to remove, we also investigated the possibility of utilising the methoxymethyl function to mask the C(3) hydroxyl. Keto alcohol **9** could not be derivatised by the more usual method ($MeOCH_2Cl$,iPr_2NEt)[13], but when treated with dimethoxymethane and a trace of toluene p-sulfonic acid (PhH, 80°C, 20h)[14] afforded a 98% yield of **12** (mp 152-153°C). Oxidative cleavage as before furnished aldehyde **15** (98% yield) and thence **14** by very brief (<5 minutes) treatment with dimethyl boron bromide at -78°C.[15] Alternatively, the intermediate aldehydo carboxylate was not methylated, but reduced by sodium borohydride to the GA_{37} derivative **17**, which was similarly deprotected by dimethyl boron bromide to give GA_{37} methyl ester **18**, whose identity was also confirmed by NMR and mass spectroscopic comparisons.[16]

With the methodology reported in this paper and our earlier communication[1], it is now possible to gain access to most C_{20} gibberellins by means of relatively short and efficient syntheses. Many of these gibberellins are of considerable importance to unresolved biosynthetic questions. Current efforts are concerned with the preparation of suitably labelled derivatives which should be vital to the elucidation of these problems.

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2. J.R. Bearder and J. MacMillan, J. Chem. Soc. Perkin I, 1973, 2824.

3. A 1:1 mixture of GA_7 with its 1,2-dihydro derivative, GA_4, is available to research workers at an approximate cost of $10 per gram, while GA_3 is available on the same basis for less than $1 per gram. Pure GA_7 costs approximately $150 per gram.

4. D.F. Jones and P. McCloskey, J. Appl. Chem., 1963, **13**, 324.

5. All new compounds were fully characterised by NMR, IR, and mass spectra. Satisfactory microanalyses (<0.4%) and/or high resolution mass measurements were also obtained.

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8. L.N. Mander, R.H. Prager, and J.V. Turner, Aust. J. Chem., 1974, **27**, 2645; J.V. Turner, B.F. Anderson and L.N. Mander, Aust. J. Chem., 1980, **33**, 1061.

9. GA_3 **1** has been converted into GA_7 **2** by treatment of a 13-methanesulfonate derivative with tri-n-butylstannane (M.H. Beale and J. MacMillan, J. Chem. Research(S), 1980, 289.

10. Epimerisation at C(3) in C_{19} gibberellins, e.g. GA_3, occurs very readily through a retro-aldol reaction under weakly basic conditions[3] (J. MacMillan and R.J. Pryce, J. Chem. Soc. C., 1967, 740). We have found it possible to hydrolyse 3-acyloxy derivatives of these natural gibberellins by exercising due care: L. Lombardo, L.N. Mander and J.V. Turner, Aust. J. Chem., 1981, **34**, 745. Neither **8** nor **10** could be deacetylated under equivalent conditions without extensive epimerisation, however. Clearly, the incipient C(4) carbanion would be more effectively stabilised by the cyclopentanone moiety (relative to the γ-lactone function).

11. W. Von E. Doering and R.M. Haines, J. Am. Chem. Soc., 1954, **76**, 482; B. Camerino, B. Patelli, and R. Sciaky, Tetrahedron Lett., 1961, **16**, 554; E.J. Bailey, D.H.R. Barton, J. Elks and J.F. Templeton, J. Chem. Soc., 1962, 1578.

12. Fragmentation to a keto acid has been reported (A.J. Birch, C.W. Holzapfel, and R.W. Rickards, Tetrahedron, 1966, Suppl. 8, Part II, 359), but in this case the presumed intermediate is derived from oxidation at a tertiary carbon centre; i.e. the elimination pathway to the normal diosphenol is not available.

13. G. Stork and T. Takahashi, J. Am. Chem. Soc., 1977, **99**, 1275.

14. cf. K. Fuji, S. Nakano and E. Fujita, Synthesis, 1975, 276.

15. Y. Guindon, H.E. Morton and C. Yoakim, J. Org. Chem., 1984, **49**, 3912. Partial isomerisation of the Δ(16) olefinic bond was observed after 5 minutes.

16. A formal total synthesis of GA_{37} has been completed by utilising a relay intermediate from the seco-kaurenoid enmein[37] (E. Fujita, M. Node and H. Hori, J. Chem. Soc. Perkin I, 1974, 165). In this sequence GA_{37} methyl ester **18** was demethylated to **19** by lithium n-propanethiolate (W.S. Johnson and P.A. Bartlett, Tetrahedron Lett., 1970, 4459). GA_{37} has also been synthesised from the corresponding 20-oic acid, GA_{13} (D.H. Bowen, C. Cloke, D.M. Harrison and J. Macmillan, J. Chem. Soc. Perkin Trans. I, 1979, 1918). (±)-GA_{38} **5** methyl ester has been prepared by total synthesis: L. Lombardo and L.N. Mander, J. Org. Chem., 1983, **48**, 2298.

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