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# STEREOCONTROLLED SYNTHESIS OF GIBBERELLIN $A_{19}$ FROM GIBBERELLIC ACID

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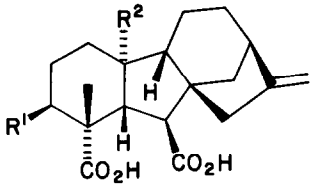
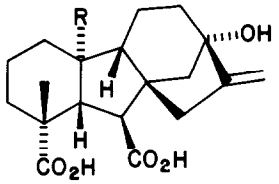
Summary: The biosynthetically important C-20 gibberellin, gibberellin $A_{19}$ **5**, has been prepared from the readily obtained C-19 gibberellin, gibberellic acid **8**, by means of an efficient stereocontrolled ten step sequence.

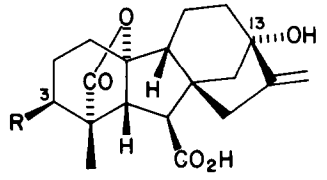
Gibberellin $A_{19}$ **5** ($GA_{19}$)[1] has been strongly implicated as a key intermediate in the postulated "early 13-hydroxylation" biosynthetic pathway between the C-20 gibberellin, $GA_{12}$ **1**, and the C-19 gibberellin, $GA_1$ **7**, in several higher plants,[2] i.e **1** → **3** → **4** → **5** → **6** → → **7**. Whilst $GA_{36}$ **2**, the equivalent gibberellin in the alternative "early 3-hydroxylation" sequence leading to **7**,[2] is available as a minor metabolite from the fermentation of Gibberella fujikuroi,[3] $GA_{19}$ **5** has only ever been isolated once in significant quantities (by Tamura *et al.*[1], who obtained 14mg from 44 tons (!) of bamboo shoots). Further amounts of $GA_{19}$ are presently much in demand for biosynthetic and related studies, so we have investigated the practicality of preparing **5** from gibberellic acid **8**, the only 13-hydroxylated gibberellin which is available in useful amounts. The successful outcome of this investigation not only provides the first example of the conversion of a C-19 gibberellin into a C-20 gibberellin, but also serves as a model for the preparation of other C-20 derivatives.[4]



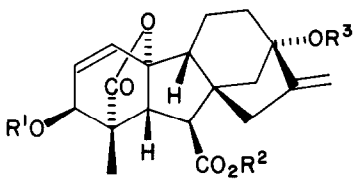

**1** $R^1$ = H, $R^2$ = Me
**2** $R^1$ = OH, $R^2$ = CH=O



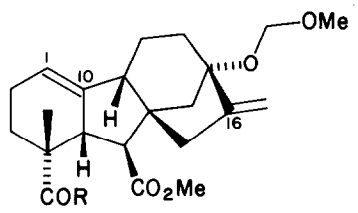

**3** R = Me
**4** R = $CH_2OH$
**5** R = CH=O



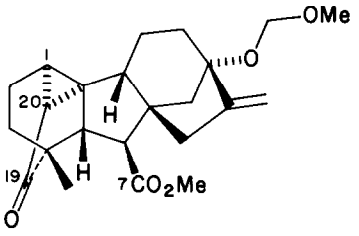

**6** R = H
**7** R = OH



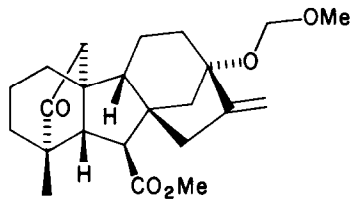
**8** $R^1, R^2, R^3 = H$
**9** $R^1, R^3 = H$; $R^2 = Me$
**10** $R^1, R^3 = CH_2OMe$; $R^2 = Me$



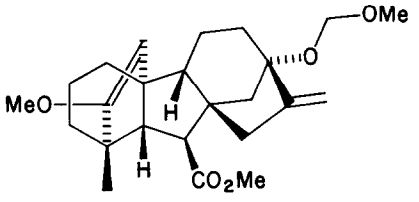
**11** R = OH
**12** R = Cl
**13** $R = CH{=}N_2$



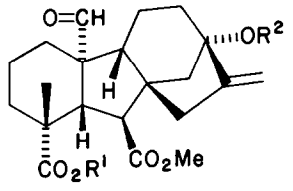
**14**



**15**



**16**



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

A successful synthesis of $GA_{19}$ **5** from gibberellic acid **8** must contend with several major difficulties: the introduction of C(20) into the very hindered C(10) site on the concave α-face of the gibberellin molecule,[5] the elaboration of an aldehyde function in a 1,3-syn-diaxial relationship to the C(19) carboxy function, and the multifunctional nature of the substrate. We were especially concerned that the labile methylene cyclopentanol moiety could be preserved, thereby avoiding a wasteful degradation/reconstitution cycle. We chose, therefore, to introduce the C(20) formyl group by means of an intramolecular cyclopropanation reaction based on diazoketone **13**, followed by reductive cleavage of the C(1)-C(20) bond in the product **14**, and then oxidative cleavage of the C(19)-C(20) bond. Excellent precedents for the sequence **13** → **14** → **15** had been established by one of us (J.V.T.) during earlier syntheses of other bicyclo[3,2,1]octanone derivatives, and the theoretical basis for the expected outcome is provided in reports of that work.[6]

Clearly, the execution of this plan was contingent upon an efficient synthesis of a suitable olefinic acid precursor, and in the event, **11** was readily prepared in 93% yield by lithium liquid ammonia t-butyl alcohol[7] reduction at -65°C of the 3,13-bismethoxymethyl ether **10** derived ($ClCH_2OMe$, $iPr_2NEt$, DMAP, 20°C, 48h) from methyl gibberellate **9**.[8] Acid **1** was converted into acid chloride **12** by oxalyl chloride – pyridine – DMF at 0°C (conditions designed to preserve the Δ1(10) and Δ(16) olefinic bonds)[6] and thence diazoketone **13** by treatment with an excess of diazomethane at 0°C (overall yield 83%). Cyclopropanation was best effected with copper-bronze (0.6g/mmole, THF-cyclohexane (1:2.5), reflux 1h; 87% yield) and the structure of the expected cyclopropyl ketone, m.p. 127-127.5°C, $[\alpha]_D^{25}$ + 47.8°, confirmed, inter alia, by examination of $^{13}C$- NMR spectra, which showed methine resonances for C(1) and C(20) at unusually high field, i.e. at δ 30.43 and 31.80, respectively, thereby furnishing evidence of the cyclopropyl ring.

Hydrogenolysis of the C(1)-C(20) bond in **14** was effected with lithium liquid ammonia t-butyl alcohol at -65°C to give **15**, m.p. 182-183.5°C, $[\alpha]_D^{25}$ + 44.8°, accompanied by a mixture of the corresponding C(19) carbinols.[6] The latter compounds were readily converted into **15** by pyridine dichromate oxidation,[9] however (total yield of **15** : 87%). Again, $^{13}C$-NMR spectra were consistent with structure **15**, in that they contained two extra methylene resonances (δ 36.59, 40.32) and two fewer methine resonances relative to **14**.

Functionalization of the extremely hindered C(20) position in **15** as a prelude to oxidative fission proved to be very difficult. Hydroxylation with $MoO_5$.Py.HMPA/lithium diisopropylamide[10], for example, was ineffective, although some success was obtained by substituting potassium hydride as the base. Enol silylation was no more satisfactory, but methyl enol ether **16** was obtained in 65% yield by sequential treatment of **15** with potassium hydride, dimethyl formamide and methyl iodide. Some C-methylation was obtained under these conditions, but no useful results could be achieved with "harder" electrophiles, e.g. methyl methanesulfonate, trimethyloxonium fluoroborate, or methoxymethyl chloride.[11] Selective oxidative cleavage of the more electron-rich C(19)-C(20) olefinic bond in **16** was then effected by ozone – pyridine in $CHCl_3$ – MeOH at -78°C[12] followed by treatment with dimethyl sulfide to afford the $GA_{19}$ derivative **17** in high yield. Removal of the 13-methoxymethyl group ($CHCl_3$-MeOH, trace $Me_3SiCl$, 20°C, 2h) readily afforded $GA_{19}$ dimethyl ester **18**, the $^1H$-NMR and IR spectroscopic constants of which were the same as those reported for naturally derived material.[1] Moreover, the identity of **18** was confirmed by direct comparison of its mass spectrum with that of an authentic sample.

No chemistry has previously been reported for $GA_{19}$ **5** or the dimethyl ester **18**. We found, however, that hydrolysis of the dimethyl ester **17** to the half ester **19** was very rapid, as could be expected with assistance from the C(20) formyl group. Further hydrolysis to the dicarboxylic acid required forcing conditions (20% KOH, MeOH-$H_2O$, 1:1; reflux, 18h), but was achieved in high yield, and after removal of the methoxymethyl group (MeOH-$CHCl_3$-3MHCl, 10:2:1; 22°C, 4 days), $GA_{19}$ **5** was obtained. This material had m.p. 244-247°C following shrinkage and a polymorphic change at 121-126°C (lit.[1] dimorphic forms: 236-237°C; or shrinkage at 124-126°C). $^1$H-NMR spectra were poorly resolved, as a consequence of equilibrium with the lactol tautomer,[3] but treatment with diazomethane furnished the dimethyl ester **18**, which was identical with material obtained earlier.

Current studies are focussed on improvements to the oxidative cleavage of the C(19)-C(20) bond in **15**, and on extensions of the synthetic strategy to the preparation of further C-20 gibberellins, including $GA_{36}$ **2**. The results of these investigations should be reported shortly.

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References and Footnotes.

1. S. Tamura, N. Takahashi, N. Murofushi, J. Kato, Y. Wada, E. Watanabe, and T. Aoyama, Tetrahedron Lett., 1966, 2465; N. Murofushi, S. Iriuchijima, N. Takahashi, S. Tamura, J. Kato, Y. Wada, E. Watanabe, and T. Aoyama, Agr. Biol. Chem., 1966, **30**, 917.
2. V. M. Sponsel in "The Biochemistry and Physiology of Gibberellins", Vol. 1, ed. A. Crozier, Praeger, New York, 1983, p.151.
3. J.R. Bearder and J. MacMillan, Agr. Biol. Chem., 1972, **36**, 342; J. Chem. Soc. Perkin Trans 1, 1973, 2824.
4. P. Hedden, ACS Symp. Ser., 1979, **111**, 19.
5. Dimethyl lithium cuprate has been added successfully to Δ1(10)-en-2-ones, but affords 10β-derivatives. J. MacMillan, personal communication.
6. J.V. Turner, B.F. Anderson, and L.N. Mander, Aust. J. Chem., 1980, **33**, 1061. L.N. Mander, J.V. Turner, and B.G. Coombe, Aust. J. Chem., 1974, **27**, 1985.
7. Lithium metal was added progressively until thin layer chromatography indicated complete consumption of starting material. Reduction of the C(7) methoxycarbonyl group was minimal under these conditions. Reduction of methyl gibberellate **9** itself afforded a mixture of 3-hydroxy and 3-desoxy products.
8. All new compounds gave correct HRMS and/or microanalytical data and were fully characterised by IR, $^1$H- and $^{13}$C-NMR, and mass spectra which were consistent with structural assignments.
9. E. J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.
10. E. Vedejs, D.A. Engler, and J.E. Telschow, J. Org. Chem., 1978, **43**, 188.
11. C.L. Edwards, Ph.D. Dissertation, University of Texas, Austin, 1974. Cited (ref. 121) in V.V. Kane, V. Singh, A. Martin, and D.L. Doyle, Tetrahedron, 1983, **39**, 345.
12. G. Slomp and J.L. Johnson, J. Am. Chem. Soc., 1958, **80**, 915.

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