Syntheses of Methyl Esters of Gibberellin A_{15} and Gibberellin A_{37}

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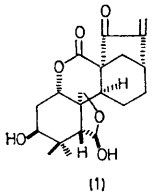
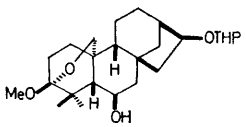
Summary The syntheses of gibberellin A_{15} methyl ester (**16**) and gibberellin A_{37} methyl ester (**21**) from enmein (**1**), and their more direct total synthesis from 5-methoxy-2-tetralone *via* the key intermediate (**2**) are described.

RECENTLY, we reported the total synthesis of enmein (**1**).[1,2] We have now attempted to convert enmein (**1**) and the key intermediate (**2**) in the synthesis of (**1**) into C_{20} gibberellins.

Enmein (**1**) was converted into the compound (**3**) as described elsewhere,[2] and methylated with MeI in the presence of NaH to give the methyl ether (**4**) in order to protect the hydroxy-group. Treatment of (**4**) with Na in liquid NH_3 gave the triol (**5**) (31%) and the diol (**6**) (45%). Treatment of (**5**) with $MeC_6H_4SO_3H$-*p* in MeOH, partial acetylation at 7-OH, oxidation to the 6-ketone, and treatment of the product with KOH gave the acyloin (**7**), which on acetylation, Meerwein–Ponndorf reduction, and further


(1)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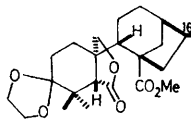
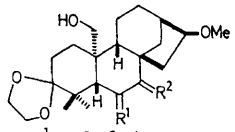
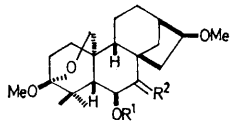
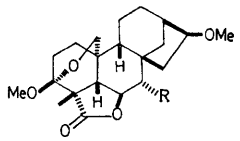
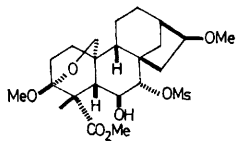

(3) R = H
(4) R = Me

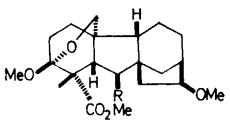

(5) R^1 = α-OH, β-H; R^2 = α-H, β-OH
(6) R^1 = α-H, β-OH; R^2 = H_2

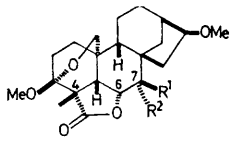

(7) R^1 = H; R^2 = O
(8) R^1 = H; R^2 = α-OAc, β-H
(24) R^1 = H; R^2 = H_2

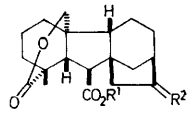

(9) R = OAc
(23) R = H

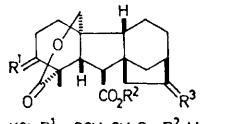

(10)

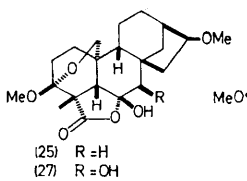
acetylation afforded (**8**). The yields in steps (**5**)—(**8**) were almost quantitative. Treatment of the alcohol (**8**) with $Pb(OAc)_4$ and iodine under irradiation gave the lactone (**9**) as the major product. This compound on alkaline hydrolysis, methylation (CH_2N_2), and partial mesylation gave compound (**10**) in high yield. Treatment of (**10**) with NaOMe in MeOH at reflux yielded the gibberellane derivative (**11**)[3] (50%), m.p. 123—124 °C, and the 4,6-*cis*-lactone (**12**) (43%), which was probably formed *via* a 6,7-β-epoxide as an intermediate. The lactone (**12**) on Jones oxidation, $NaBH_4$ reduction to the 7α-ol, followed by mesylation gave the 7α-mesylate (**13**), which on treatment with KOH in Bu^tOH and water at reflux under conditions described by Hanson *et al.*[3a] followed by methylation (CH_2N_2) gave (**11**). Almost quantitative yields were obtained in each step. The rearrangement of (**13**) to (**11**) requires stronger conditions than those required for the rearrangement of (**10**) to (**11**), but the former excludes the possibility of epoxide formation and gives the gibberellane derivative as the sole product.

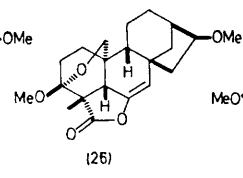

(11) R = CHO
(14) R = CO_2H

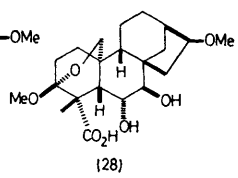

(12) R^1 = OH; R^2 = H
(13) R^1 = H, R^2 = OMs


(15) R^1 = Me, R^2 = α-H, β-OMe
(16) R^1 = Me, R^2 = CH_2
(17) R^1 = H, R^2 = CH_2


(18) R^1 = -SCH_2CH_2S-; R^2 = Me; R^3 = α-H, β-OH
(19) R^1 = -SCH_2CH_2S-; R^2 = Me; R^3 = CH_2
(20) R^1 = O; R^2 = Me, R^3 = CH_2
(21) R^1 = α-H, β-OH; R^2 = Me; R^3 = CH_2
(22) R^1 = α-H, β-OH, R^2 = H, R^3 = CH_2


(25) R = H
(27) R = OH


(26)


(28)

THP = tetrahydropyran-2-yl, Ms = methanesulphonyl

The aldehyde (**11**) on Jones oxidation gave the carboxylic acid (**14**), which on treatment with ethanedithiol in the presence of BF_3–Et_2O gave the dithioacetal. Its methyl ester, obtained (54% from **14**) by reaction with diazomethane, on desulphurisation with Raney nickel gave a 2,3-unsaturated compound which on catalytic hydrogenation afforded the lactone (**15**) (80%). The protecting group was removed by further reaction with ethanedithiol and BF_3–Et_2O to give the 16β-ol (74%) after methylation (CH_2N_2) of the partially hydrolysed product.† This product on Jones oxidation (93%), followed by Wittig reaction, gave gibberellin A_{15} methyl ester (**16**) (51%), m.p. 199—201 °C (lit.[4] 198—200 °C). The structure of (**16**) was confirmed by elemental analysis and spectroscopic data. Compound (**16**) has been hydrolysed to gibberellin A_{15} (**17**) by Nagata *et al.* in their total synthesis.[5,6]

The methyl ester of (**14**) (CH_2N_2), on prolonged treatment with ethanedithiol and BF_3–Et_2O, gave (**18**) after simultaneous demethylation, thioacetalisation, and lactonisation.

† The details of the preliminary investigation for removing this protecting group will be published elsewhere.

The alcohol (**18**) was oxidised to give the 17-nor-16-one which, after Wittig reaction, afforded the 17-methylene derivative (**19**) (62%). The ethylene dithioacetal group at C-3 was removed by reaction with *N*-chlorosuccinimide[7] to give the 3-one (**20**), m.p. 248—250 °C. This ketone, on Meerwein–Ponndorf reduction, gave two products in a ratio of *ca.* 2:1; the major product was characterized as the 3β-ol (**21**). This compound gave crystals on standing, m.p. 195—197 °C (lit.[8]: oil), which were identical with those of an authentic sample of gibberellin A_{37} methyl ester[9] (n.m.r. and mass spectra and t.l.c.). Its conversion into gibberellin A_{37} is in progress.

The more direct total synthesis was carried out as follows. The intermediate (**2**)[1] in the total synthesis of enmein (**1**) gave, after the hypoiodite reaction [$Pb(OAc)_4$–I_2, $h\nu$], acid hydrolysis, and methylation (CH_2N_2, BF_3–Et_2O) of the resulting 16β-ol, the lactone (**23**), m.p. 220—221 °C, which was also prepared in 75% yield from the diol (**6**) by treatment with H_2SO_4 in MeOH followed by the hypoiodite reaction of the resulting product (**24**). The lactone (**23**) on acid ($HClO_4$) hydrolysis followed by Jones oxidation gave the hydroxy lactone (**25**) (76%). Dehydration of (**25**) with $SOCl_2$ in pyridine afforded the Δ^6-derivative (**26**), m.p. 272—274 °C, as the sole product. On epoxidation (*m*-chloroperbenzoic acid, aq. $NaHCO_3$, CH_2Cl_2) followed by treatment with BF_3–Et_2O in wet benzene, compound (**26**) gave the 7-functionalised product (**27**), m.p. 224—227 °C (65%), which on reduction with $LiAlH_4$ at 0 °C yielded the dihydroxy-carboxylic acid (**28**) and the lactone (**12**). Lactonisation of (**28**) into (**12**) was carried out by treatment with HCl in MeOH. Compound (**12**) could be converted into gibberellins A_{15} and A_{37} methyl esters as already described.

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[3] For similar rearrangements, see (a) J. R. Hanson and J. Hawker, *Tetrahedron Letters*, 1972, 4299; (b) P. Hedden and J. MacMillan, *J.C.S. Perkin I*, 1974, 587.
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