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EXPERIMENTS DIRECTED TOWARD THE TOTAL SYNTHESIS OF POLYCYCLIC TERPENES. PART VII. SYNTHESIS OF METHYL 7α-GIBBANE-10β-CARBOXYLATE.

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Among many tetracyclic diterpenes gibberellins are well known for their high biological activities and also for their structural characteristics — gibbane skeleton(I).

In the previous paper(1) we reported the stereoselective conversion of tetracyclic diacetate(II) into tetracyclic triacetate(VIII) in three steps.

In this communication we wish to report the synthetic sequence for the conversion of VIII into 7α-gibbane compounds like XI.

Recently we reported the synthesis of 7α-gibbane compound having C-10 formyl group(III) starting from β-naphthol in 23 steps(2) but the stereochemistry of C-10 formyl group was remained to be determined. Now this problem was settled by the following reaction.

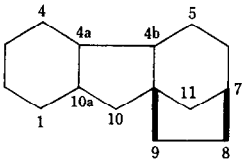
Jones oxidation of III followed by the treatment with diazomethane and subsequent chromatography over alumina gave the corresponding ester(IV) m.p. 155-158°, ν_{max} 3440, 1734, 1700, 1250 and 1020 cm^{-1}, τ 4.85(2H overlapping signals 1H singlet for C-10aβ hydroxyl proton and 1H diffused quartet for C-2β proton), 5.35(1H quartet, J=5,12 cps, for C-8 proton), 6.29(3H singlet for O-methyl proton) 7.39(1H singlet for C-10α proton), 7.95 and 7.99(two 3H singlet for acetate methyl protons), 9.03, 9.08 and 9.18(three 3H singlets for three tert. methyl protons), and also the β-lactone(V), ν_{max} 1807, 1725, 1250, 1052 and 805 cm^{-1}, τ 5.1-5.4(2H broad signals for C-2β and C-8 protons), 6.85(1H singlet for C-10α

proton), 7.93 and 7.97(two 3H singlets for two acetate methyl protons), 8.95, 9.00, and 9.03(three 3H singlets for three tert. methyl protons). The ratio of the formation of ester(IV) and β-lactone(V) is about 5:1. Some compounds having β-lactone part structure on the five membered ring have been known in the steroid field(3).

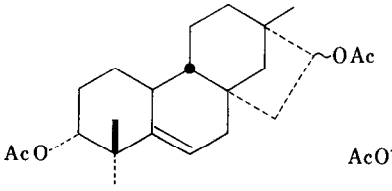
The formation of β-lactone during Jones oxidation of III was regarded as an evidence that C-10a hydroxyl and C-10 formyl group were in the cis relationship. And the reaction was reasonably expained by considering the nucleophilic participation of the hydroxyl group at C-10a during the oxidation process to produce intermediates (III→VI→VII→V)(4). The participation of water molecule in the solvent instead of the hydroxyl group at C-10a gave the ester(IV) after esterification. As the configulation of C-10a hydroxyl group had been determined as β, the formyl group at C-10 was also assigned as β configulation.

Next the transformation of VIII into 7α-gibbane compounds was studied. VIII was oxidized by ozone in dichloromethane at -60° and the resulting ozonide was reduced by zinc powder and acetic acid to give ketoaldehyde(IX), ν_{max} 1742, 1710, 1255, 1228, 1045 and 1036 cm^{-1}, τ 0.27(1H diffused singlets for aldehyde proton), 5.17-5.40(2H multiplet for C-2β and C-8 protons), 5.46 and 5.85 (AB quartet, J=11 cps for C-1α acetoxymethyl protons),7.97 and 8.00(6H and 3H singlets for three acetate methyl protons), 8.92 and 9.05(two 3H singlets for two tert. methyl protons).

The ketoaldehyde(IX) was directly transformed into 7α-gibbane-C-10-aldehyde(X), m.p. 151-154°, by the intramolecular aldol condensation on alumina column. The structure of X was established by the reaction sequence and was confirmed by the following spectral data, ν_{max} 3460, 1735, 1700, 1260, 1240 and 1025 cm^{-1}, τ 0.14(1H doublet, J=2 cps, for aldehyde proton), 4.80(1H broad signals for C-2β proton), 5.28(1H quartet, J=5, 11 cps, for C-8 proton), 5.60 and 5.87(AB quartet, J=12 cps, for C-1α acetoxymethyl protons), 5.93(1H singlet for C-10aβ hydroxyl proton), 6.97(1H doublet, J=2 cps, for C-10α proton), 7.93 and 7.98(6H and 3H singlets for three acetate methyl protons), 9.00(6H singlet for two tert. methyl protons).



I



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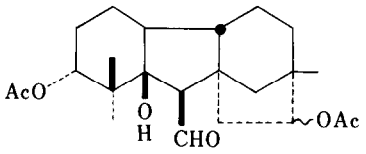

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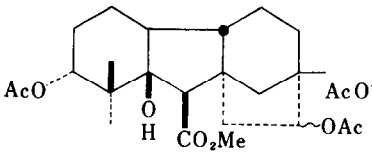

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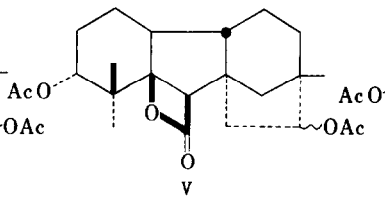

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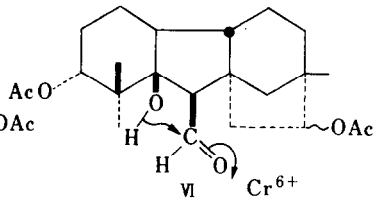
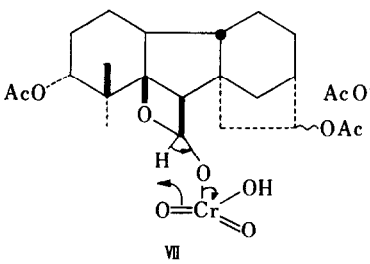


VI



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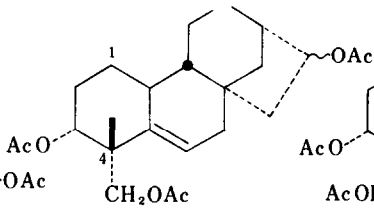
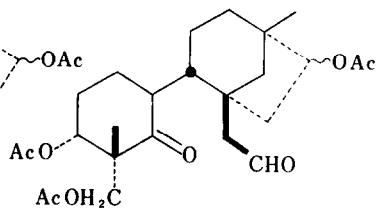


VIII



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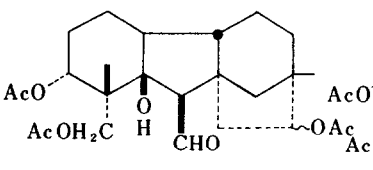
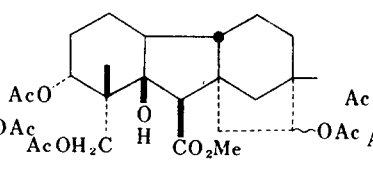
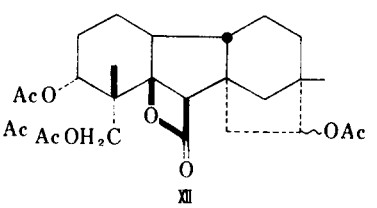


X



XI



XII

Jones oxidation of X followed by the treatment with diazomethane and subsequent chromatographic separation over alumina gave the ester(XI), m.p. 152-154° and the β-lactone(XII), m.p. 138-140°, in the ratio of about 5:1. The structures of XI and XII were confirmed by the following spectral data; the ester(XI), ν_{max} 3460, 1740, 1703, 1250 and 1035 cm^{-1}, τ 4.60(1H singlet for C-10aβ hydroxyl proton), 4.75(1H broad signals for C-2β proton), 5.35(1H diffused quartet for C-8 proton), 5.63 and 5.88(AB quartet, J=12 cps for C-1α acetoxymethyl protons), 6.28(3H singlet for O-methyl protons), 7.05(1H singlet for C-10α proton), 7.96 and 8.00(6H and 3H singlets for three acetate methyl protons), 9.05 and 9.10(two 3H singlets for two tert. methyl protons); the β-lactone(XII), ν_{max} 1825, 1743, 1240, 1050 and 1035 cm^{-1}, τ 5.05(1H broadsignals for C-2β proton), 5.35(1H broad signals for C-8 proton), 5.75(2H diffused singlet for C-1α acetoxymethyl protons), 6.57(1H singlet for C-10α proton), 7.93 and 7.96(3H and 6H singlets for three acetate methyl protons), 8.83 and 9.00(two 3H singlets for two tert. methyl protons).

The low field shifts of C-2β proton of X(τ 4.80) and XI(τ 4.75) from that of the compound VIII(τ 5.37)(1) were most probably due to the deshielding effect of C-10a hydroxyl group, so the hydroxyl group was assigned as β configuration and had the 1,3 diaxial relationship with C-2β proton(2). The formation of β-lactone XII by the oxidation of X was explained in the same way as in the case of the formation of β-lactone V and the configuration of formyl group of X and the methoxycarbonyl group of XI were assigned as β(5).

The above described 7α-gibbane compounds, the structure of which were determined unambiguously, though different in the D ring stereochemistry from naturally occurring gibberellins which have 7β-gibbane skeleton, may have some biological activities.

REFERENCES

Satisfactory analyses were obtained for all crystalline compounds. I.R. spectra were measured as Nujol mulls for solid samples and as films for liquid samples, unless otherwise stated. N.M.R. spectra were determined at

100 Mc in deuteriochloroform using TMS as an internal reference.

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5. These stereochemical assignments were further supported by the lower field shifts of C-10 proton signals of compounds X(τ 6.97) and XI(τ 7.05) when compared with those of III(τ 7.43) and IV(τ 7.39), which were reasonably explained by the deshielding effect of acetoxymethyl group at C-1α of X and XI, confirming the α configuration of C-10 protons of X and XI.