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SYNTHESIS OF THE SKELETON OF BIOLOGICALLY ACTIVE NATURAL COMPOUND. c-HOMOPERHYDROFLUORENE.*

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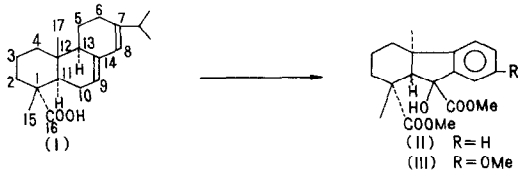
Attention of many chemists has been focussed on the biogenetically and physiologically attractive gibberellin group and numerous studies concerned have been carried out in many laboratories.

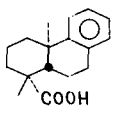
Since a few years ago, synthesis of the basic skeleton of gibberellin has also attracted us. It has been previously reported that abietic acid (I), available from Japanese pine trees and having a perhydrophenanthrene skeleton, is transformed into hexahydrofluorene derivatives (II and III) by the applica-



(I)

(II) R=H
(III) R=OMe

* This work will be published in detail elsewhere. New compounds indicated by m.p. gave satisfactory analytical values and had gas-liquid chromatographic purity. All NMR spectra were measured at 60 MC in CCl_4 vs Me_4Si as internal reference.



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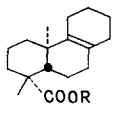
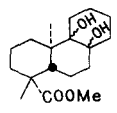


(V) R=H
(VI) R=Me



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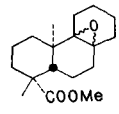

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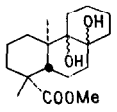

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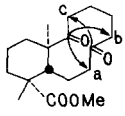
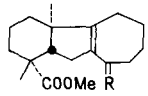
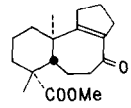


(X)



(XI) R=O
(XII) R=S,S
(XIII) R=H₂



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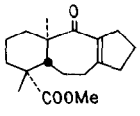

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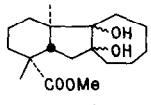

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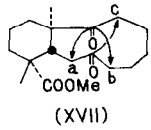

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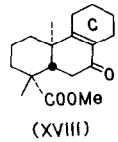

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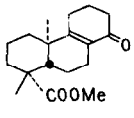
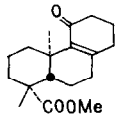
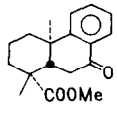


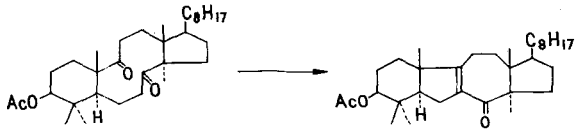
(XIX)



(XX)



(XXI)



(XXII) (XXIII)

tion of benzilic acid rearrangement[1].

In the present paper, synthesis of c-homoperhydrofluorene(XI) regarded as a potential intermediate for the preparation of gibberellin group will be discussed.

Deoxy-enantio-podocarpic acid (IV), prepared from l-abietic acid (I) via several steps[2], was reduced with lithium metal in ethylamine in the presence of tert.-amyl alcohol[3] to $\Delta^{13,14}$-acid (V), m.p. 142-144° (85% yield), ν_{max}^{KBr} 1700 cm^{-1}, τ 9.15(17-Me), 8.75(15-Me).

From the corresponding $\Delta^{13,14}$-methyl ester (VI), m.p. 84-87°, ν_{max}^{KBr} 1720 cm^{-1}, τ 9.26(17-Me), 8.84(15-Me), 6.41(COOMe), 13,14-diketo ester (X), m.p. 101-103°, ν_{max}^{KBr} 1720, 1695 cm^{-1}, was synthesized by the following two routes.

In the first method, cis-13,14-diol ester (VII)**, m.p. 157-160°, ν_{max}^{KBr} 3480, 1725 cm^{-1}, τ 9.12(17-Me), 8.84(15-Me), 6.42 (COOMe), obtained by hydroxylation of (VI) with osmium tetroxide in benzene containing pyridine, was oxidatively cleaved with lead tetraacetate in acetic acid to give the diketo ester (X) (65% yield from (VI)). In the second way, (VI) was treated with perphthalic acid and the resultant mixture was chromatographed on alumina to give two stereoisomers of 13,14-epoxy ester(VIII),** m.p. 108-110° (71% yield), ν_{max}^{KBr} 1725, 1145 cm^{-1}, τ 9.23(17-Me), 8.89(15-Me), 6.44(COOMe) and m.p. 147-151° (7.5% yield), ν_{max}^{KBr} 1720, 1140 cm^{-1}, τ 9.26(17-Me), 8.92(15-Me), 6.44(COOMe). Both epoxides (VIII) were left to stand in 50% acetone aq containing

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** Stereochemistry of cis- and trans-13,14-diol ester (VII and IX), and two kinds of isomeric epoxy ester (VIII) will be discussed on basis of reaction mechanism of their formation and chemical shift of their methyl groups at a later date.

a small amount of sulfuric acid at room temperature to yield identical trans-13,14-diol ester (IX)**, m.p. 114-116°(50% yield from the respective epoxy isomer), ν_{max}^{KBr} 3580, 3510, 1705 cm^{-1}, τ 9.08(17-Me), 8.85(15-Me), 6.40(COOMe). Oxidation of the trans-diol (IX) with lead tetraacetate gave the same 13,14-diketo ester (50% yield) as in the case of the cis-diol (VII).

Aldol condensation of the diketo ester (X) by heating with 10% potassium hydroxide aq-methanol gave a product (XI), m.p.92-94° (65% yield), ν_{max}^{KBr} 1725, 1639(7-membered ring α,β-unsaturated ketone), 1608 cm^{-1}, τ 9.28(17-Me), 8.80(15-Me), 6.40(COOMe), together with a small amount of undeterminated isomer, $C_{18}H_{26}O_3$, m.p. 112-114°. In the ring closure reaction of the diketo ester (X), three possible ways of closure (a, b and c pathways as shown in formula (X)) and the corresponding three products (XI, XIV and XV) can be considered. Accordingly, the problem of the structure of the major product (XI) was settled by the following examination.

Thioketal formation of the α,β-unsaturated keto ester (XI) in question with ethylene dithiol in the presence of p-toluenesulfonic acid or boron trifluoride-etherate in acetic acid quantitatively afforded (XII), m.p. 92-94°, ν_{max}^{KBr} 1725 cm^{-1}, τ 9.38(17-Me), 8.79(15-Me), 6.70(), 6.37(COOMe), which was treated with Raney nickel(W-7) to give an oily compound (XIII), the NMR spectrum of which lacked the resonance due to protons of the thioketal group. Osmium tetroxide treatment of (XIII) followed by oxidative cleavage with lead tetraacetate gave an oily 13,9-diketo ester (XVII), $\nu_{max}^{CCl_4}$ 1735, 1700 cm^{-1}, through cis-13,9-diol ester (XVI), m.p. 151-153°, ν_{max}^{KBr} 3450, 1730, 1700 cm^{-1}, τ 9.38(17-Me), 8.85(15-Me), 6.39(COOMe). The condensation

product of the oily 13,9-diketo ester(XVII) obtained by boiling with 10% potassium hydroxide aq-methanol as in the case of (X), was chromatographed to afford two isomers, $C_{18}H_{26}O_3$, m.p. 144-146° (55% yield), ν_{max}^{KBr} 1723, 1658, 1640 cm^{-1}, τ 9.25(17-Me), 8.82(15-Me), 6.36(COOMe) and m.p. 102-104° (31% yield), ν_{max}^{KBr} 1720, 1660(6-membered ring α,β-unsaturated ketone), 1618 cm^{-1}, τ 9.10(17-Me), 8.81(15-Me), 6.36(COOMe).

Structure of the former compound(m.p. 144-146°) still remains ambiguous. However, the structure of the latter(m.p. 102-104°) was shown to be (XVIII) by i) elimination of ketone group and ii) aromatization of the C-ring of (XVIII). Thus, the ketone group of (XVIII) was removed by thioketalization and subsequent reduction with Raney nickel to give a compound, whose infrared spectrum (CCl_4) and retention time of gas-liquid chromatography (4.55 min., 2% QF-1 on Anakrom) were completely identical with those of $\Delta^{13,14}$-ester (VI). Furthermore, bromination of (XVIII) with N-bromosuccimide in the presence of benzoyl peroxide followed by dehydrobromination with boiling γ-collidine yielded prisms, m.p. 142-146°, whose m.p., mixed m.p., infrared spectrum (CCl_4) and retention time of gas-liquid chromatography (10.8 min.,1.5% SE-30 on Anakrom) were identical with those of methyl 9-oxo-enantio-podocarpate (XXI)[2]. These experimental facts clearly show that one (m.p. 102-104°) of the condensed compounds derived from the diketo ester(XVII)(b pathway in (XVII)) has a structure of 9-keto-$\Delta^{13,14}$-ester (XVIII).

Formation of the condensation product with structure (XVIII) can only be accounted for by cyclization (a pathway) in the diketone (X) to give (XI), followed by condensation (b pathway)

in the diketone (XVII); all other cyclization would give α,β-unsaturated ketone having perhydrophenanthrene skeleton (XIX and XX) and having other skeleton. This establishes structure (XI) for this condensation product. Analogous cyclization mode ((XXII)⟶(XXIII)) in steroid field[4] is also consistent with our present observation.

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