

A-RING SUBSTITUTION OF HYDROFLUORENE COMPOUND DERIVED
FROM 1-ABIETIC ACID.*¹

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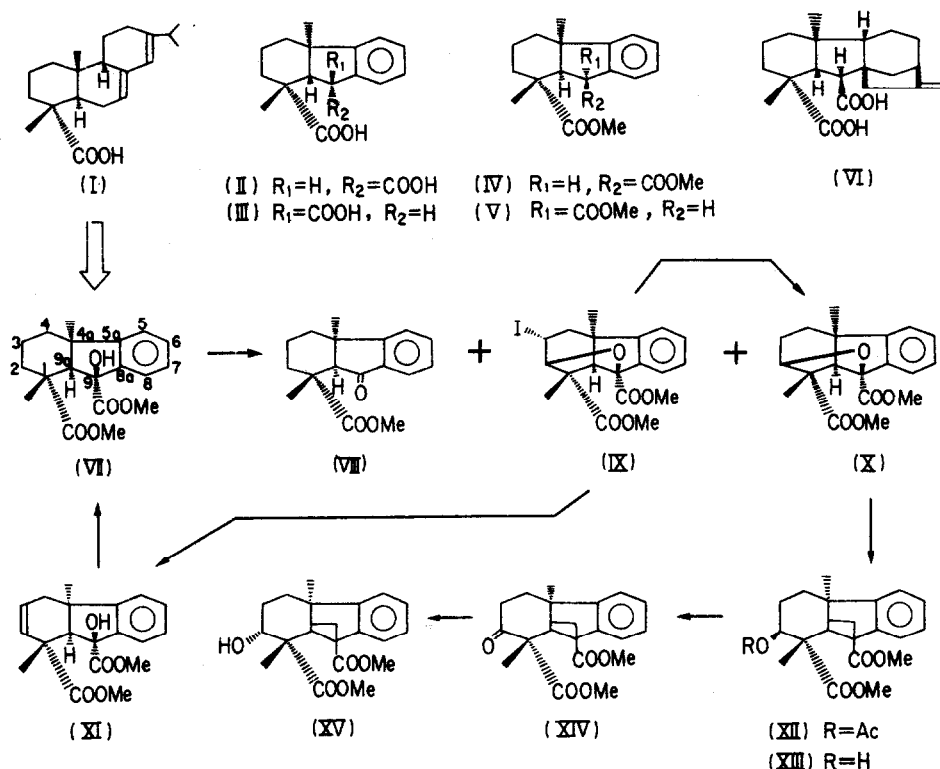
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It is attractive that a strong sweetener¹ (II) and a compound² (III) having the gibberellin skeleton (cf. gibberellin A₁₂ (VI)) were found among the hydrofluorenes derived from 1-abietic acid (I). However, the derivatives do not have any A-ring substituent and the substitution method has not yet been found. It is expected that the A-ring modification will open a wider possibility for their utilization. The present investigation was undertaken to develop a new method for the A-ring substitution.

Hydrofluorene³ (VII) is regarded as a potential intermediate in the conversion of 1-abietic acid (I) to hydrofluorene derivatives and was used as the starting material in this study. Since the conformation of the A/B-ring fusion in (VII) can be assumed to be non-steroid type in the same way as in (IV) and (V),² the molecular model shows that 9-hydroxy group is located near the C-2 site in A-ring. Accordingly, intramolecular radical reaction (Pb(OAc)₄, I₂, benzene) of 9-hydroxy group of (VII) to C-2 position was undertaken. The resulting product was chromatographed to be separated into the known keto ester⁴ (VIII) (15.8% yield) and two kinds of unknown esters; (IX), C₁₉H₂₁O₅I, bp 155-160° (bath temp.)/0.07mmHg, (7.8% yield), NMR τ: 8.77, 8.38(s, 3H; 1- and 4a-Me), 6.18, 6.16(s, 3H; 1- and 9-COOMe), 6.60(d, 1H, J=1Hz*²; 9a-αH), 5.30(d, 1H, J=1Hz*²; 2-αH), 8.20

*1 New compounds indicated by mp and bp gave satisfactory analytical values. NMR spectra were measured at 100 MHz in CDCl₃ vs. Me₄Si as internal reference.

*2 The coupling can be understood as the long-range coupling between 9a-αH and 2-αH by the W-rule.⁵



(dd, 1H, $J=12.4, 14.8\text{Hz}$; 4- αH), 7.92(dd, 1H, $J=7, 14.8\text{Hz}$; 4- βH), 6.31(dd, 1H, $J=7, 12.4\text{Hz}$; 3- βH), and (X), $C_{19}H_{22}O_5$, mp 102–104°, (59.8% yield), NMR τ : 8.61, 8.46(s, 3H; 1- and 4a-Me), 6.23, 6.17(s, 3H; 1- and 9-COOMe), 6.66(d, 1H, $J=1\text{Hz}^{*2}$; 9a- αH), 5.67(dd, 1H, $J=1^{*2}, 6.5\text{Hz}$; 2- αH).

The oily iodide (IX) was reduced (H_2 , 10% Pd-C, EtOH-Et₃N, room temp.) to the main product (X). The iodide (IX) was also correlated to the starting hydrofluorene (VII) via unsaturated diester (XI), mp 124.5–126°, NMR(60 MHz) τ : 6.55 (br. s, 1H; 9a- αH), 4.20(s, 2H; 2- and 3-olefinic H), by reductive cleavage (Zn, AcOH, reflux) and successive hydrogenation (H_2 , Pt, EtOH). Considering the above chemical relation in addition to the molecular formula and the NMR spectrum, both products (IX and X) can be assumed to have a same skeleton as (VII) and to

have 2,9-epoxy bridge. Iodine atom in (IX) would reasonably be located at C-3 position.

Detailed analyses of NMR patterns and coupling constants due to 2- α H in (X) and to 2- α H, 3- β H and 4-H₂ in (IX) suggest the following A-ring structure. Since only the doublet splitting ($J=6.5\text{Hz}$) at 5.67 τ due to 2- α H in (X) was observed, the conformation of A-ring having 2,9-epoxy bridge should be in boat form (the flagpoles are at C-1 and C-4) ($\phi_{2\alpha3\alpha}=20^\circ$, $J_{\text{calc.}}=8.8$; $\phi_{2\alpha3\beta}=100^\circ$, $J_{\text{calc.}}=0.5^{*3}$). Furthermore, no coupling of 2- α H (5.30 τ) in (IX) to 3- β H shows that iodine has α -configuration in the boat A-ring ($\phi_{2\alpha3\beta}=100^\circ$, $J_{\text{calc.}}=0.5^{*3}$). This elucidation was also ascertained by ABX type coupling ($J_{3\beta4\alpha}=12.4\text{Hz}$, $J_{3\beta4\beta}=7\text{Hz}$, $J_{4\alpha4\beta}=14.8\text{Hz}$) between 3- β H and 4-H₂ ($\phi_{3\beta4\alpha}=170^\circ$, $J_{\text{calc.}}=15.5$; $\phi_{3\beta4\beta}=50^\circ$, $J_{\text{calc.}}=4.1^{*3}$). Thus, the structures of two epoxy esters (IX and X) were clearly determined.

Next, hydrofluorenes having A-ring substituent were synthesized from (X). Cleavage of the epoxy bridge ($\text{BF}_3\text{-Et}_2\text{O}$, Ac_2O , room temp.) gave the acetate (XII), mp 106-107°, NMR τ : 4.39(t, 1H, $J=3\text{Hz}$; 2- α H). Acid hydrolysis (HCl , EtOH , reflux) of (XII) afforded hydroxy diester (XIII), mp 157-160°, NMR τ : 5.66(br. s ($W_{\frac{1}{2}}\text{H}=8\text{Hz}$), 1H; 2- α H) and acetylation (Ac_2O , pyridine, room temp.) of (XIII) reverted it to the original acetate (XII). The 2 β -hydroxy diester (XIII) was oxidized (Jones reagent, acetone) to the ketone (XIV), mp 153-155°, NMR τ : 7.28-7.10 (m, 2H; 3-H₂), and (XIV) was reduced (NaBH_4 , MeOH , room temp.) to the 2 α -hydroxy diester (XV), mp 180-184°, NMR τ : 6.93-6.57(m ($W_{\frac{1}{2}}\text{H}=30\text{Hz}$), 1H; 2- β H). The configurational assignments of 2-hydroxy group in (XIII) and (XV) were determined by comparison of NMR patterns due to 2- α H and 2- β H.

Thus, the first attempt on the substitution of hydrofluorene A-ring was accomplished. The resulting epoxy diesters (IX and X) are regarded as an important intermediate for the syntheses of 2-, 3-, and 4-substituted hydrofluoro-

*3 The coupling constants ($J_{\text{calc.}}$) were calculated from the dihedral angle (ϕ) of the conformational model by using the equation of Williamson and Johnson.⁶

renes. The reaction opens the possibility for synthesizing more interesting compounds such as a sweetener and gibberellin skeleton. This study is in progress.

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