

A NEW METHOD FOR THE CONSTRUCTION OF A BICYCLO [3.2.1] OCTANE
RING SYSTEM WITH A BRIDGEHEAD HYDROXYL GROUP -
A PARTIAL SYNTHESIS OF (-)-EPIALLOGIBBERIC ACID*

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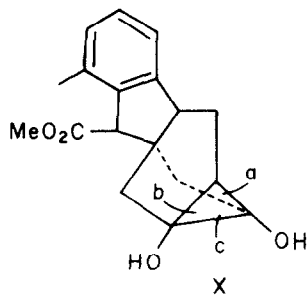
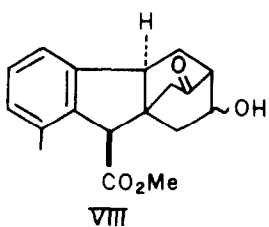
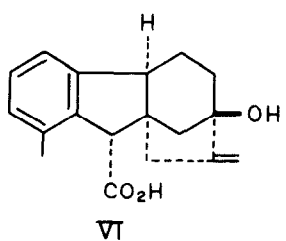
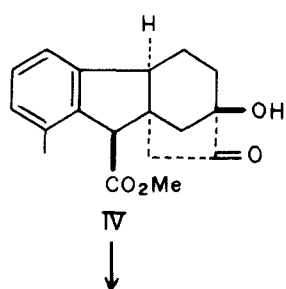
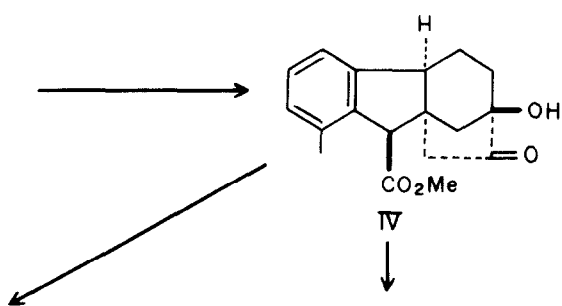
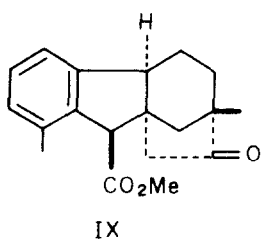
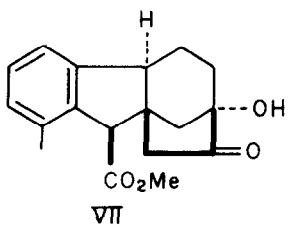
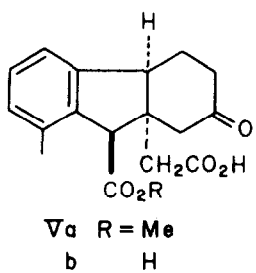
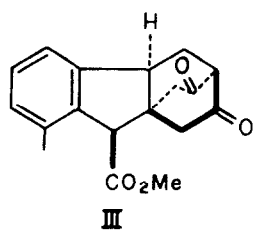
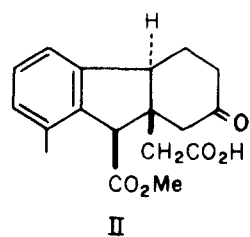
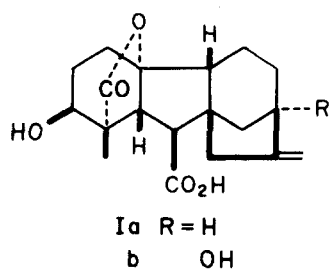
After the completion of the total synthesis of (\pm)-gibberellin A₄ (Ia)(1), we focused our attention on the synthesis of gibberellin A₁ (Ib)(2) which contains a bicyclo [3.2.1] octane ring system with an exocyclic methylene group adjacent to a bridgehead tertiary hydroxyl group. Although two different methods (3,4) have been devised for the construction of this system we felt it necessary to find a shortcut which is described below.

The key reaction is the conversion of a bicyclo [2.2.2] octane-2,6-dione into a bicyclo [3.2.1] octan-1-ol-7-one. A β -diketone (III), m.p. 192-194°, readily available from the keto acid (II) by the published method (5), was chosen as the starting material. This was treated with zinc dust in boiling acetic acid to give three reduction products: IV (48% yield), VII (6.6%) and VIII (0.15%).

The major product (IV) crystallized directly from the crude gummy reaction product and melted at 145-146°, ν_{\max} (nujol) 3520 (OH), 1740 (CO, CO₂Me), 1600 (C=C)cm⁻¹; δ (CDCl₃, ppm from TMS at 100 MHz) 2.21 (3H, s, MeAr), 2.75 (1H, s, -OH, intensity decreased after D₂O addition), 3.80 (3H, s, -CO₂Me), 4.18 (1H, s, CHCO₂Me)ppm. A chemical proof of the

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structure (IV) was provided by its periodate oxidation to give a keto acid (Va), m.p. 154-155°, ν_{\max} (nujol) \sim 3400- \sim 2600, 1715 (CO, CO₂Me), 1680 (CO₂H), 1595 (C-C)cm⁻¹; δ (CDCl₃) 2.19 (3H, s, MeAr), 3.72 (3H, s, -CO₂Me), 4.25 (1H, s, CHCO₂Me), \sim 8.1 (1H, broad, -CO₂H) ppm. This, upon alkaline hydrolysis, yielded a dicarboxylic acid (Vb), m.p. 216-218°, ν_{\max} (nujol) \sim 3200- \sim 2600, 1725 (CO), 1670 (CO₂H)cm⁻¹, identified by IR and mixed m.p. with an authentic sample prepared from the diketone (III)(5). The proposed stereochemistry (IV) was also supported by the ORD and CD comparisons of the ketol (IV) with those of the known ketol (VII)(6) and methyl gibberate (IX)(7). Negative Cotton effect curves were observed for the ketol (IV, ORD: $[\phi]_{328m\mu}$ -800°, peak; $[\phi]_{286}$ + 1260°, trough; $[\phi]_{228}$ + 3200°, second trough. CD: $[\theta]_{310m\mu}$ -830°. EtOH soln, c=0.07) and methyl gibberate (IX, ORD: $[\phi]_{324m\mu}$ -5300°, peak; $[\phi]_{280}$ + 8700°, trough; $[\phi]_{228}$ + 23400°, second trough. CD: $[\theta]_{300m\mu}$ -5700°. EtOH soln, c=0.08) while the isomeric ketol (VII) exhibited a positive Cotton effect curve (ORD: $[\phi]_{324m\mu}$ + 2400°, peak; $[\phi]_{275}$ -7000°, trough. CD: $[\theta]_{307m\mu}$ + 3500°. EtOH soln, (c=0.07).

A decisive evidence for the structure IV was afforded by the conversion of the ketol (IV) into (-)-epiallogibberic acid (VI). The ketol (IV) was successively treated with triphenylmethylene phosphorane in THF-t-BuOH and aqueous sodium hydroxide to give the tetracyclic acid (VI), m.p. 240-242°, ν_{\max} (nujol) 3450 (OH), \sim 3200- \sim 2600, 1680 (CO₂H), 1595 (C-C), 900 (-CH₂)cm⁻¹, in 9% yield. Epimerization of the carboxyl group took place during the hydrolysis (8). The IR spectrum of the synthetic acid was completely identical in every detail with that of the (+)-acid (antipode of VI), m.p. 242-244°, prepared from gibberellic acid (8a), but its ORD curve (plain negative curve with a minimum at 236m μ , $[\phi]$ -24000°; CD: $[\theta]_{230m\mu}$ -20000°. EtOH soln, c=0.02) was antipodal to that of the (+)-acid (plain positive curve with a maximum at 236m μ , $[\phi]$ + 16000°; CD: $[\theta]_{230m\mu}$ + 15000°. EtOH soln, c=0.13).

The mother liquor obtained by removing the crystalline IV was chromatographed over alumina to give two other products. The earlier eluates gave the isomeric ketol (VII), m.p. 130-132°, ν_{\max} (nujol) 3520 (OH), 1745 (CO), 1715 (CO₂Me)cm⁻¹; δ (CDCl₃) 2.19 (3H, s, MeAr), 2.9 δ (1H, s, -OH), 3.81 (3H, s, -CO₂Me), 4.05 (1H, s, CHCO₂Me)ppm, identified with an authentic sample by spectral comparisons and mixed m.p. Another product, m.p. 193-194°, ν_{\max} (nujol) 3500 (OH), 1730 (CO₂Me), 1710 (CO), 1585 (C-C)cm⁻¹; δ (CDCl₃) 2.18 (3H,

s, MeAr), 3.78 (3H, s, -COMe), 4.50 (1H, m, J=18Hz, CHOH) ppm; CD: $[\theta]_{300\text{m}\mu}^{-330^\circ}$, $[\theta]_{228}^{+2100^\circ}$ (EtOH soln, c=0.07), was shown to be VIII, since it gave the β -diketone (III) when oxidized with the Jones chromic acid reagent (9).

This skeletal rearrangement probably involves a trachylobane-type cyclopropane diol (X), generated by the intramolecular pinacol condensation, as the intermediate. Cleavage of the bonds a, b and c as depicted in the formula will afford the three ketols IV, VII and VIII, respectively (10,11).

Application of this reaction to the conversion of gibberellin A₄ (Ia) into A₁ (Ib) as well as the total synthesis of the keto acid (II) is in progress.

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9. This ketol (VIII) showed a complex negative Cotton effect ORD curve which was difficult to interpret. IR measurement (kindly carried out by Mr. G. Yabuta of this Laboratory) of a dilute soln of VIII (in CHCl₃, insoluble in CCl₄) did not give useful results. The stereochemistry, therefore, remains to be determined.
10. Very recently a similar rearrangement under the Clemmensen condition has been observed with a simpler monoterpene system. V. T.-C. Chuang and R.B. Scott, Jr. Chem. Commun. 758 (1969).
11. An attempt was made to obtain (±)-steviol methyl ester nor-ketone by the rearrangement of a β -diketone with atisane skeleton but it was unsuccessful under the condition described in this paper. Further studies on this point are expected.