

TOTAL SYNTHESIS OF (\pm)-STEVIOL*

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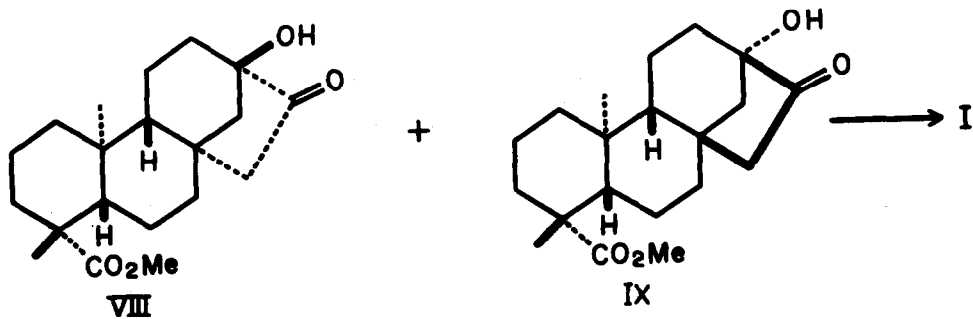
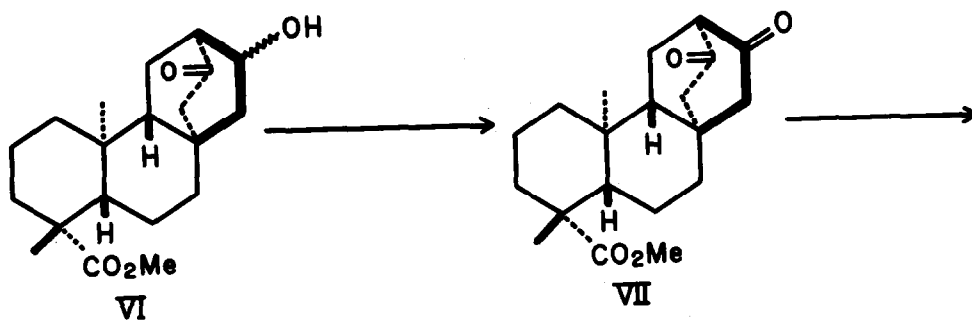
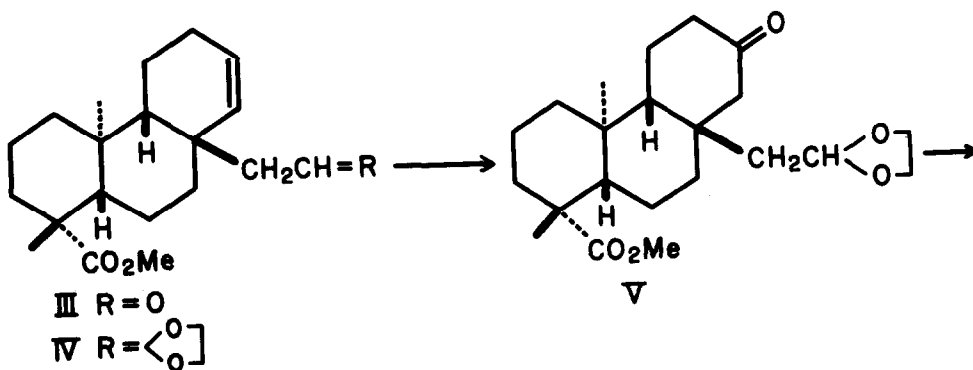
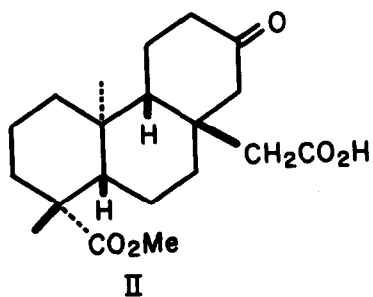
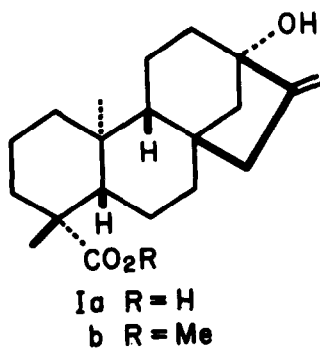
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Steviol (Ia) is the aglucon of stevioside, the remarkably sweet glucoside abundant in Stevia rebaudiana Bertoni (1-4). Recent discovery of its gibberellin-like activity (5) prompted us to search a route to the total synthesis of (\pm)-steviol. A simple solution of this problem has now been provided by the application of our novel method (6) for the construction of a bicyclo[3.2.1]octane ring system with a bridgehead tertiary hydroxyl group.

The starting aldehyde (III)(7) was the key intermediate employed in our synthesis of the (\pm)-seco acid (II), a degradation product of steviol methyl ester (Ib)(8). This was converted into the corresponding oily acetal (IV, 99% yield)(9) by treatment with ethylene glycol and p-TsOH in benzene. Hydroboration-oxidation ($B_2H_6-H_2O_2$) followed by the Jones oxidation of the olefin (IV) afforded a mixture of two isomeric ketones. This was separated by fractional crystallization and chromatography on alumina to give the desired ketone (V, 62% yield), m.p. 114-115°, and the isomer with a carbonyl group at C-14, m.p. 157-158° (13% yield).

Acetal cleavage with aqueous acid-acetone solution of the keto acetal (V) yielded a tetracyclic ketol (VI, 92.5% yield), m.p. 178-179°, formed by aldol-type cyclization (cf.

* Diterpenoid Total Synthesis - XIV. This work was presented at the Annual Meeting of the Agricultural Chemical Society of Japan, Fukuoka, April 2, 1970. Part XIII, K. Mori and M. Matsui, Tetrahedron, in the press.



10). Jones chromic acid smoothly oxidised the ketol (VI) to give a bicyclo[2.2.2]octane-2,6-dione (VII, 95% yield), m.p. 230.5°, $\nu(\text{KBr})$ 1745, 1715 cm^{-1} . This key intermediate in toluene was heated with amalgamated mossy zinc and hydrochloric acid (the Clemmensen reduction) (6, cf.11) to give a mixture of two ketols (VIII and IX). Chromatographic purification of the mixture on silicic acid employing benzene-ethyl acetate (9 : 1) as the eluant afforded in earlier fractions a ketol (VIII, 19% yield), m.p. 196°, δ (60MHz, CDCl_3) 0.69 (3H, s), 1.18 (3H, s), 3.61 (3H, s) ppm. Subsequently the desired ketol (IX, 41% yield), m.p. 217°, δ (60 MHz, CDCl_3) 0.88 (3H, s), 1.18 (3H, s), 3.64 (3H, s) ppm, was eluted. The IR spectra (CHCl_3) of these racemic ketols were identical with the corresponding authentic spectra of the optically active ketols (4, 12, 13).

Condensation of the ketol (IX) with methylenetriphenylphosphorane generated (\pm)-steviol methyl ester (Ib, 67% yield), m.p. 141-143°, $\nu(\text{KBr})$ 3500, 3070, 1700, 1655, $\nu(\text{CHCl}_3)$ 3600, 1720, 1660 cm^{-1} , δ (60MHz, CDCl_3) 0.80 (3H, s), 1.15 (3H, s), 3.64 (3H, s), 4.90 (2H, m) ppm. The IR (CHCl_3) and NMR spectra of this material were superimposable on those of the optically active authentic sample. Hydrolysis of the ester (Ib) with KOBu^t in DMSO (14) gave (\pm)-steviol (Ia, 63% yield), m.p. 246°, $\nu(\text{KBr})$ 3450, 3250, 1685 cm^{-1} , δ (60MHz, $\text{DMSO}-d_6$) 0.87 (3H, s), 1.10 (3H, s), 4.79 (2H, m) ppm. The spectral properties of the racemic product coincided with those of the natural product.

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12. The ketol IX seems to be the product favoured by kinetic control. This will be discussed in our full paper.
13. The ketol IX was also prepared by the more lengthy route (Y. Nakahara, K. Mori and M. Matsui, unpublished) based on the work of Ireland [R.A. Bell, R.E. Ireland and L.N. Mander, J. Org. Chem. 31, 2536 (1966)].
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