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DITERPENOID TOTAL SYNTHESIS, AN A→B→C APPROACH

V. TOTAL SYNTHESIS OF dl-CARNOSOL DIMETHYL ETHER AND dl-CARNOSIC ACID DIMETHYL ETHER

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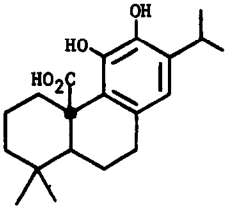
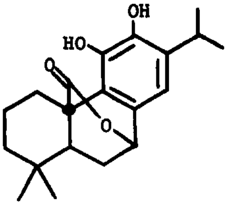
We recently reported total synthesis of the ethyl ester dimethyl ether of carnosic acid (I) (1), which is unusual among tricyclic diterpenoids in containing an angular carboxyl function. We now report a new method for construction of the 11,12-dihydroxylated C-ring in this system. The new approach is advantageous in that a lengthy sequence for introduction of the 11-oxygen is avoided and the 7-oxygen may be easily retained for synthesis of systems such as carnosol (II) (2).



I



II

Addition of the sodium enolate of 1-methylsulfonoxy-4-methyl-2-pentanone [prepared by condensation of dimethyl sulfoxide with ethyl isovalerate (3)] to the unsaturated keto aldehyde III (1) affords the adduct IV as a pair of crystalline diastereomeric racemates, m.p. 167-168°* and 137-140°.** Exposure of either adduct to 50% aqueous acetic acid (4)

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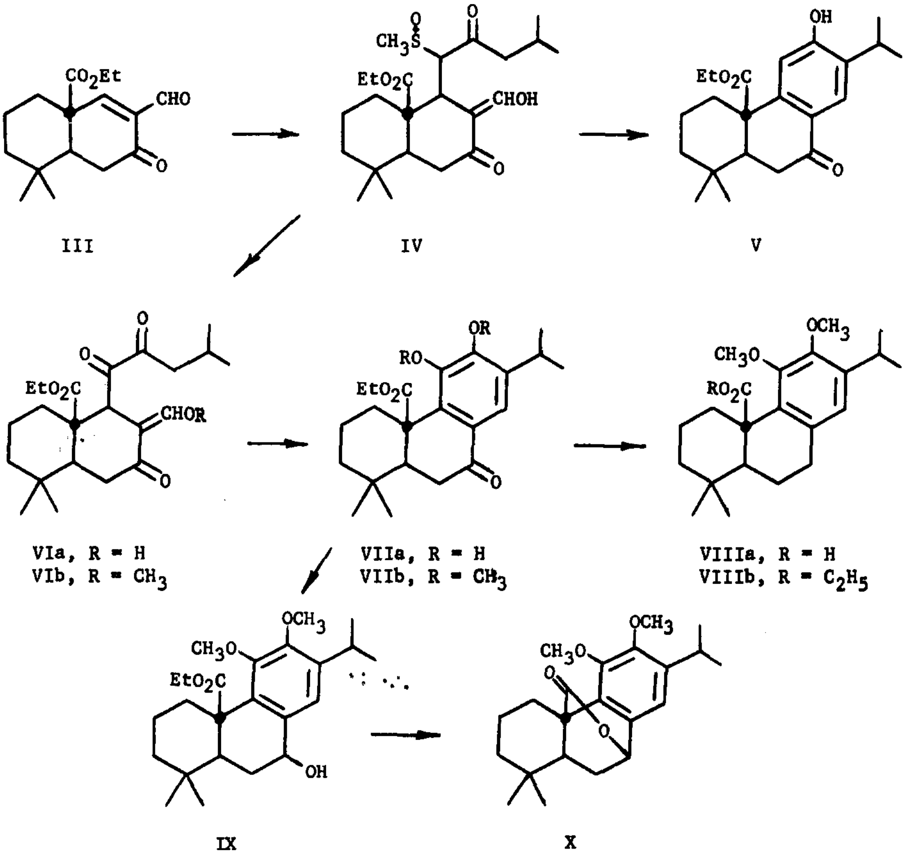
*Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds for which m.p. data are reported. All compounds were handled only in racemic form, although only a single enantiomer is depicted in structural formulations.

**This sample of the low-melting racemate was contaminated with 5% of the higher-melting isomer.

converts it to the α-diketone VIa, an oil, the methyl enol ether of which (VIb, m.p. 87.5-88°) undergoes cyclization in methanolic sodium methoxide to produce the keto catechol VIIa, m.p. 123-124°. Hydrogenolysis of the corresponding dimethyl ether (VIIb, m.p. 91-92°) affords ethyl *dl*-carnosate dimethyl ether (VIIIb, m.p. 89-90°) identical with a sample synthesized by the route reported earlier (1). Ester cleavage by potassium *t*-butoxide in dimethyl sulfoxide (1) produces *dl*-carnosic acid dimethyl ether, VIIIa (m.p. 230.5-231.5°). Reduction of the keto dimethyl ether VIIb with sodium borohydride followed by lactonization of the hydroxy ester IX, m.p. 116-117°, with potassium *t*-butoxide in benzene (cf. 2b) affords *dl*-carnosol dimethyl ether, X (m.p. 155-156°).



β-Keto sulfoxides such as IV are useful in this sequence for synthesis not only of 11,12-dioxygenated diterpenoids, but also for the more common 11-deoxy-12-phenolic derivatives such as ferruginol (5). Exposure of the keto sulfoxide IV to dimethyl sulfoxide containing concentrated hydrochloric acid brings about cyclization with elimination of the methylsulfonoxy group, producing the keto phenol V, identical with that which had been synthesized earlier by a slightly longer route (1).

Further synthetic transformations utilizing such β-keto sulfoxides will be reported later.

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