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THE TOTAL SYNTHESES OF (+)-TETRAHYDROALANTOLACTONE AND (±)-ARTEMISIN

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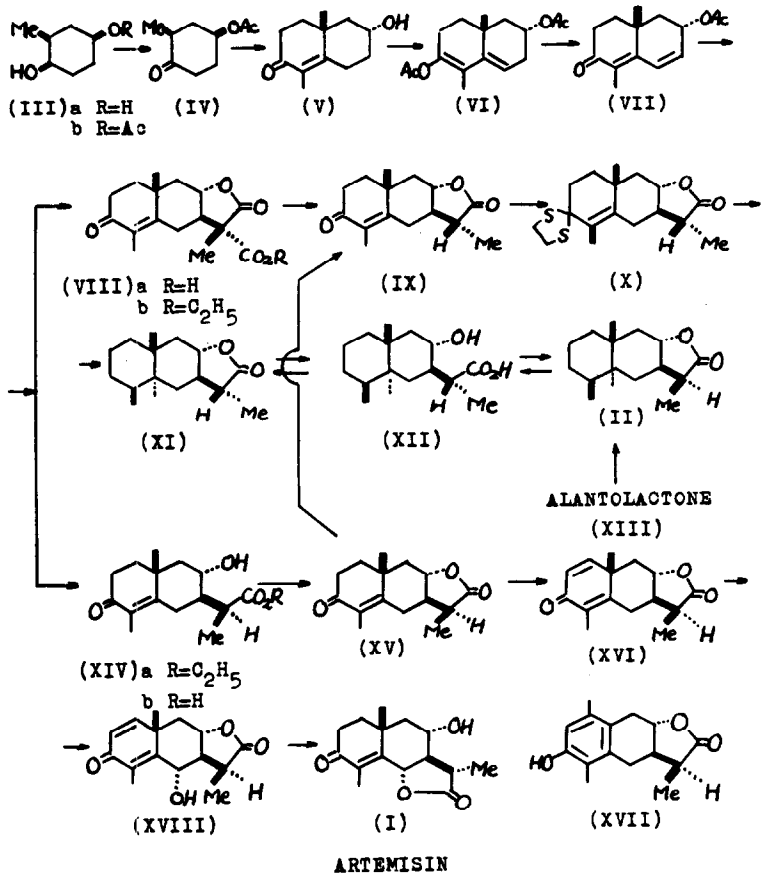
(-)-Artemisin (I) has been a key substance to establish the configurational relationship within various eudesmane sesquiterpenes[1], and its ready photoisomerization provides a means to correlate the configurations of eudesmane sesquiterpenes with thats of guiananolides[2].

In this communication, we report the total syntheses of (±)-artemisin and (+)-tetrahydroalantolactone (II) from the same intermediate (VII).

The cis-glycol (IIIa), b.p.153-157°/26 mm, prepared by the catalytic hydrogenation of toluquinone was converted into the monoacetate (IIIb), b.p.140-142°/30 mm, which was then oxidized to the ketone (IV), m.p.58-59°. The Robinson's annelation of (IV) with 1-diethylaminopentan-3-one methoiodide in the presence of sodium ethoxide afforded the bicyclic keto-alcohol (V), m.p.104°, λ_{max} 248 mμ(log ε 4.19).

Following Abe's procedure[3], (V) was converted into the enol-acetate (VI), b.p.134-135°/0.2 mm, which afforded the dienone acetate (VII), m.p.65-66°, λ_{max} 282 mμ(log ε 4.43) (Found: C,71.54; H, 7.77%) upon bromination followed by


(III)a R=H
b R=Ac
(IV)
(V)
(VI)
(VII)
(VIII)a R=H
b R=C2H5
(IX)
(X)
(XI)
(XII)
(II)
ALANTOLACTONE
(XIII)
(XIV)a R=C2H5
b R=H
(XV)
(XVI)
(XVIII)
(I)
(XVII)
ARTEMISIN

dehydrobromination with α-picoline. From the reaction mixture of the Michael condensation of the dienone acetate (VII) with diethyl methylmalonate, there were isolated the lactone carboxylic acid (VIIIa), m.p.232-234°, and its ester (VIIIb), m.p. 127-128°, λ_{max} 246 mμ(log ε 4.15) together with the hydroxy-acid ester (an oil)(XIVa).

Hydrolysis of (VIIIb) gave (VIIIa), from which the (+)-enantiomer, m.p.212-214°, $[\alpha]_D^{20}$ +34.4°(c 0.26 in ethanol) was obtained by optical resolution via the brucin salt.

Boiling with γ-collidine decarboxylated (+)-(VIIIa) to yield the (+)-keto-lactone (IX), m.p.150-151°, $[\alpha]_D^{20}$ +50.1° (c 0.59 in ethanol)(Found: C,72.50; H,8.16%)(racemic (IX), m.p.144°). Although the absolute configuration of (+)-(IX) could be deduced from its optical rotatory dispersion curve, the more confirmative evidence was obtained from its conversion into (-)-4,5α(H),11,8β(H)-eudesman-8,13-olide (XI) as follows. When (+)-(IX) was treated with ethanedithiol and boron trifluoride, the dithioketal (X), m.p.162-165°, $[\alpha]_D^{18}$ +33.9°(c 0.77 in chloroform) was obtained (racemic (X), m.p.153°). Desulfurization with Raney nickel followed by hydrogenation led to formation of (XI), m.p.89-90°, $[\alpha]_D^{20}$ -16.7°(c 0.52 in ethanol)(Found: C,76.22; H,10.21%)(racemic (XI), an oil) which was found identical with (-)-4,5α(H)-11,8β(H)-eudesman-8,13-olide derived from alantolactone (XIII) by the procedure of Cocker and co-workers.[4] The identity was further confirmed by the comparison of the hydroxylic acid (XII), m.p.154-155°, $[\alpha]_D^{18}$ +22°(c 0.54 in ethanol)(racemic (XII), m.p.145-145.5°) with an authentic sample.

Since Cocker and co-workers[4] succeeded to convert (XII) into (+)-tetrahydroalantolactone (II), the total synthesis of this compound was thus accomplished.

The hydroxy-ester (XIVa) was hydrolyzed to the hydroxy-acid (XIVb), m.p.197-199°, which was then treated with acetic anhydride and sodium acetate to give the lactone (XV), m.p. 122-123°, the ready epimerization of which to (IX) by refluxing with potassium carbonate in tetralin established its configuration. Boiling with dichlorodicyanobenzoquinone in dioxane dehydrogenated (XV) to yield the dienone (XVI), m.p. 151-154°, λ_{max} 238 mμ(log ε 4.06), whose constitution was supported by its dienone-phenol rearrangement to the phenol (XVII), m.p.267-268°(decomp), λ_{max} 286 mμ(log ε 3.28).

The dienone (XVI) was oxidized with selenium dioxide in acetic acid to yield the oily product (XVIII) which was then treated with aqueous potassium carbonate to afford (±)-artemisin (I), m.p.190-192°(Found: C,69.36; H, 6.94%).

The identity was established by the comparison of its infrared absorption spectrum and thin-layor chromatogram with thats of an authentic (-)-artemisin.

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REFERENCES

1) W. Cocker and T. B. H. McMurry, Tetrahedron, 8, 181 (1960). T. G. Hasall and D. W. Theobald, Quart. Rev., 16, 101 (1962).

2) D. H. R. Barton, J. E. D. Levisalles and J. T. Pinhey, J. Chem. Soc., 3472 (1962); D. H. R. Barton, J. T. Pinhey and R. J. Wells, ibid., 2518 (1964).

3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, J. Am. Chem. Soc., 75, 2567(1953).

4) W. Cocker, L. O. Hopkins, T. B. H. McMurry and M. A. Nisbet, J. Chem. Soc., 4721 (1961); W. Cocker and M.A. Nisbet, ibid.,534 (1963).