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CONVERSION OF (+)-ISOALANTOLACTONE AND (+)-ALANTOLACTONE INTO (-)-ARTEMISIN

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In our total synthesis of (±)-artemisin (1)[1], (±)-3-oxo-8β(H),11α(H)-eudesm-4-en-8,13-olide (17) was a key compound, and this contribution is concerned with a successful synthesis of the optically active modification of this compound from (+)-isoalantolactone (2) and (+)-alantolactone (3)[2] as well as its conversion into natural (-)-artemisin (1).

Inspection of the structural fomulae of the starting materials and the requisite compound indicates that the main synthesis routes would involve (a) conversion of the cis lactones into the trans forms and (b) modification of the A rings to the enone structure.

Conversion of (+)-Isoalantolactone (2) into the Intermediate (10).

Sodium borohydride reduction of (+)-isoalantolactone (2) afforded (+)-dihydroisoalantolactone (4)[3], whose cis lactone ring was transformed into the trans form by the following series of conversions. Alkaline hydrolysis opened the lactone ring yielding the hydroxy acid which was immediately esterified with diazomethane to give the hydroxy ester (5), m.p.105-106.5°, $[\alpha]_D^{26}$+68.8°[4].

Chromic anhydride oxidation in acetone afforded the keto ester (6) whose alkaline hydrolysis furnished the keto carboxylic acid (7), b.p.190-195°/0.1mm, $[\alpha]_D^{20}$+28.2°.

New compound in this work have been characterised satisfactory by elemental analysis and infrared spectroscopy. Optical rotations reported refer to ethanolic solution with c≒0.7.

Thermodynamically controlled reduction (sodium in isopropyl alcohol[5]) of (7) gave the unsaturated acid (8) with 8α-hydroxyl group (equatorial), m.p.160°, $[\alpha]_D^{20}$+100°.

In sharp contrast to the facile lactonization observed in the cis series, the lactonization of this hydroxy acid could only be achieved by heating to its melting point in vacuo.

Thus having secured the desired trans lactone linkage, our next concern was the modification of the A ring.

Refluxing in acetic acid with p-toluenesulfonic acid converted the trans lactone (9), b.p.138-141°/0.1mm, $[\alpha]_D^{18}$+16.3°, into the new unsaturated trans lactone (10), b.p.130-155°/0.1mm, $[\alpha]_D^{20}$-1.40°, with an endo-cyclic double bond, and the same compound was also obtained directly from (8) by the same treatment.

Conversion of (+)-Alantolactone (3) into the Intermediate (10)

An ethanolic solution of (-)-dihydroalantolactone (11) provided through sodium borohydride reduction of (+)-alantolactone (3) was saturated with hydrogen bromide to yield a mixture of unstable adducts which was boiled with collidine without further purification to effect dehydrobromination. There was separated by chromatography an unsaturated cis lactone (12), m.p.59-62°, $[\alpha]_D^{20}$+29.7°, which was found identical with (+)-8,11α(H)-eudesm-4-en-8,13-olide[6]. This same cis lactone possessing 4:5-double bond could also be obtained from (+)-dihydroisoalantolactone (4) by following the procedure described above.

To convert the cis lactone (12) into the requisite trans lactone (10) via the same sequence of steps leading from the cis lactone (4) to the trans lactone (9) was followed the hydroxy ester (13), b.p.125-130°/0.1mm, $[\alpha]_D^{17}$+47.2°, the keto ester (14), b.p.116-122°/0.1mm, $[\alpha]_D^{18}$+41.4°, the keto carboxylic acid (15), b.p.145-150°/0.1mm, $[\alpha]_D^{18}$+32.7° and 8α-hydroxy acid (16).

Conversion of the trans Unsaturated Lactone (10) into (-)-Artemisin (1)

In order to complete the synthesis there remained the requirement of introducing the dienone structure in the A ring and α-hydroxyl group on C-6.

The trans lactone (10) was oxidized with selenium dioxide in boiling ethanol and the product was further treated with chromic anhydride in acetone. Chromatography of the product afforded needles, m.p.140-141°, $[\alpha]_D^{20}$+15.5°, which was

proved identical with (+)-3-oxo-8β(H),11α(H)-eudesm-4-en-8,13-olide (17) (m.p.142°, $[\alpha]_D^{18}$+19.4°[7]) derived from (-)-artemisin. The identity was further confirmed by the conparison with our synthetic racemic compound. By the series of transformations which we had explored in the synthesis of (±)-artemisin[1], this optically active α,β-unsaturated ketone (17) was converted into natural (-)-artemisin (1), m.p.202-204°, $[\alpha]_{405}^{20}$ -300° (c=0.1, ethanol), whose identity was established by the mixed melting point determination as well as by the comparison its infrared absorption spectrum, thin-layer chromatogram and optical rotatory dispersion curve with that of an authentic specimen.

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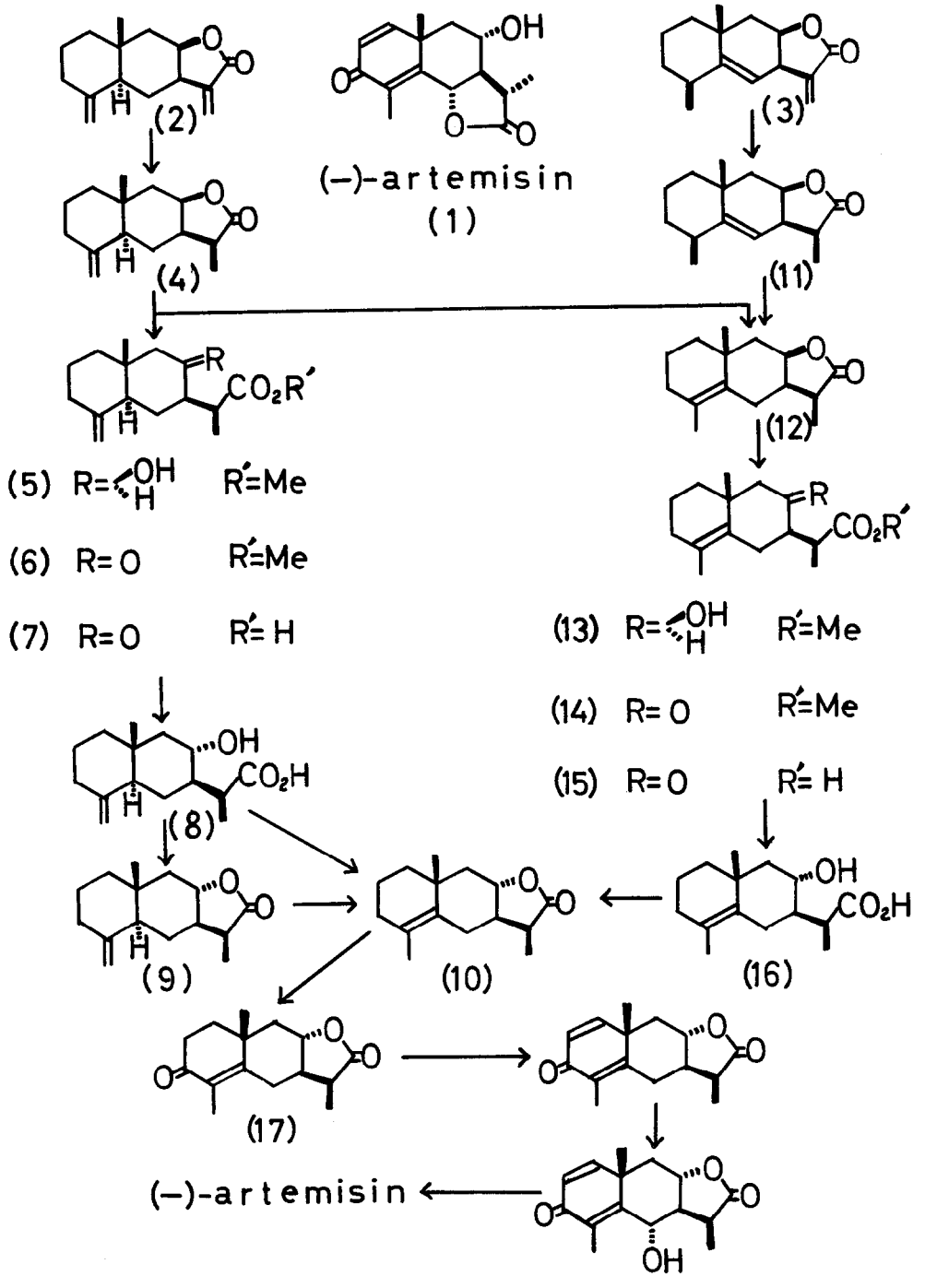
(2)
(4)
(–)-artemisin
(1)
(3)
(11)
(12)
(5) R=OH H R'=Me
(6) R=O R'=Me
(7) R=O R'=H
(13) R=OH H R'=Me
(14) R=O R'=Me
(15) R=O R'=H
(8)
(9)
(10)
(16)
(17)
(–)-artemisin