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A STEREOSELECTIVE SYNTHESIS OF (±)-JUVABIONE

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Juvabione (13,R=Me), a sesquiterpene derivative from Abies balsama (L.) Miller, shows juvenile hormone activity in the hemipteran bug Pyrrhocoris apterus (L.).[1] This compound has been obtained by several non-stereoselective syntheses,[2] and recently[3] by a stereospecific conversion of (+)-limonene into (+)-juvabione. We now describe a stereoselective synthesis of (±)-juvabione utilising the general method of Birch and Hill[4] for the synthesis of 4-substituted cyclohexenones.

Reaction of 1-methoxycyclohexa-1, 4-diene with trans-6-methylhept-2-en-4-one in an evacuated sealed glass tube at 180° for 4 days, with in situ conjugation of the diene,[5] gave a 1:1 mixture of the Diels-Alder adducts (1) and (2) in 75-80% yield. Unlike the diastereoisomeric juvabiones and related monocyclic compounds, these isomers can be separated by distillation (spinning-band column); the rigid ring system and consequent fixed and different relations of the carbonyl and double bond ensuring sufficient differences in properties. The isomers (1)b.p. 125-126°/5 mm. and (2)b.p. 135-136°/5 mm. showed the expected spectra; in particular the high CHMe resonance (τ9.24) in the p.m.r. spectrum of (1) can be assigned to the endo-Me group, which falls within the shielding envelope of the double bond.[6]

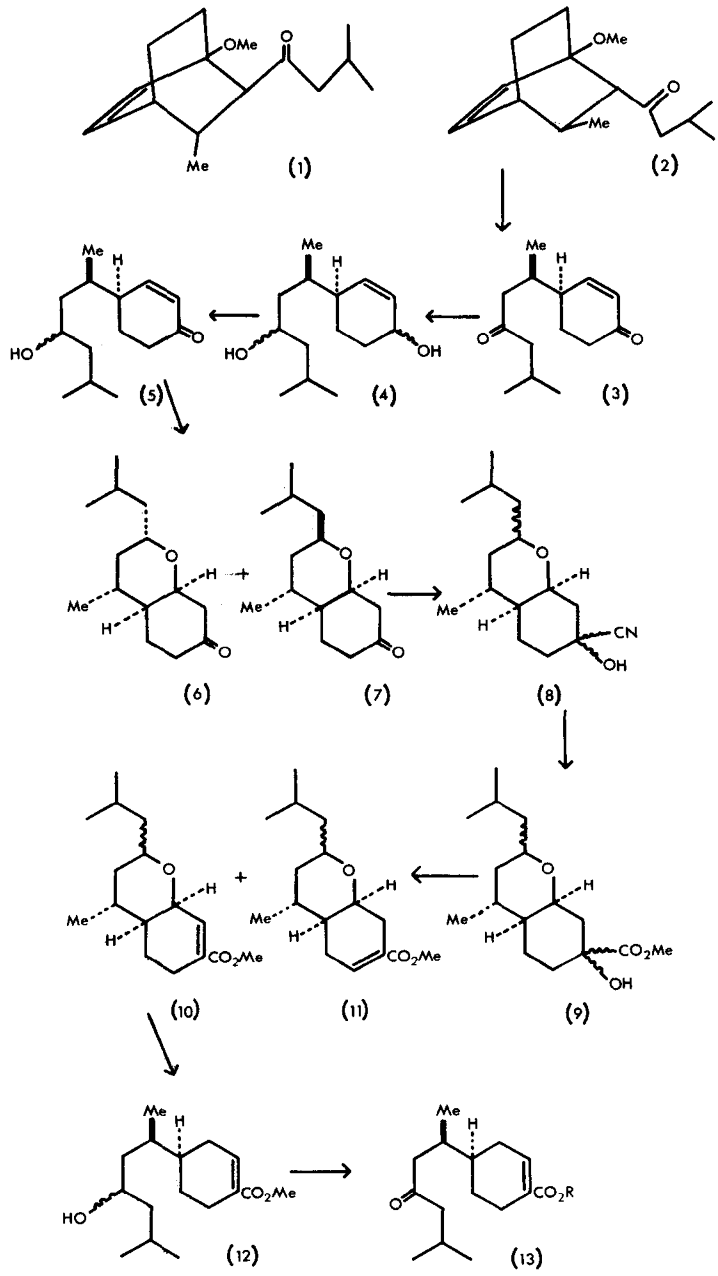
Reaction of (2) with perchloric acid in acetic acid[4] gave in high yield the expected diketone (3), which was reduced by sodium borohydride to the stereoisomeric mixture of diols (4). Manganese dioxide oxidation of (4) afforded a mixture of two keto-ethers (5:1) m.p. 59.5-60.5° and 57.5-58.0°, respectively, which were separated by chromatography on silica gel. Both had the expected spectra and the p.m.r. spectra showed cis-fusion of the two ring in both cases ($J\sim 3$ cps for the junction protons). The isomers differ therefore by the configuration of the side-chain, i.e. are (6) and (7), not necessarily respectively, and are formed from the two isomers of (5). Although both (6) and (7) could lead to (±)-juvabione only the major isomer was employed.

The cyanohydrins (8) were produced by the action of potassium cyanide and acetic acid on the major keto-ether, and were converted into the methyl esters (9) using methanolic hydrogen chloride. Dehydration of (9) with phosphorus oxychloride and pyridine gave a 2:1 mixture (g.l.c.) of the unsaturated esters (10) and (11) which could be separated by chromatography on silica gel, the structures being confirmed by spectra and analyses. In particular the p.m.r. spectrum of (10) shows the olefinic proton coupled (J 5.5 cps) to a ring-junction proton.

Reaction of (10) with calcium in liquid ammonia resulted in cleavage of the allylic ether, the product (12) on treatment with chromic acid in acetone giving (±)-juvabione (13,R=Me), identical by p.m.r., i.r. and mass spectra with natural (+)-juvabione.[1] Saponification of (13,R=Me) gave (±)-todomatuic acid (13,R=H), m.p. 66-67°, identical by m.p., i.r. and p.m.r. spectra with the published values of Mori and Matsui.[2]

A simple non-stereoselective synthesis was achieved by hydrogenation of the double bond in (3), selective reaction of the cyclohexanone carbonyl with hydrogen cyanide, conversion of the nitrile group into the methyl ester, and dehydration with phosphorus oxychloride.

The synthesis of the unnatural stereoisomer, and further reactions of the diketone and the keto-ethers will be reported in detail elsewhere.


(1)
(2)
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(12)
(13)
OMe
Me
H
HO
OH
O
CN
CO2Me
CO2R

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