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TOTAL SYNTHESIS OF DOLABRADIENE[1]

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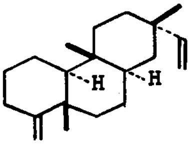
The structure (1) for dolabradiene, a diterpene isolated from the leaf oil of Thujopsis dolabrata Sieb. et Zucc., has been reported[2] already. In this paper we report the total synthesis of dolabradiene.

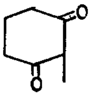


(1)

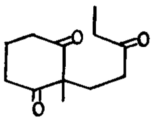
Addition of ethylvinyl ketone to 2-methylcyclohexane-1,3-dione[3] (2) in the presence of potassium fluoride[4] in dry xylene afforded an oily triketone[4] (3), b.p. 129-131°/1mm, ν_{max}^{liquid}: 1715, 1694 cm^{-1}, which on dehydrative cyclization with benzoic acid - triethylamine[6] gave the enedione (4) m.p. 39-40°, ν_{max}^{KBr}: 1710, 1673, 1610 cm^{-1}, and $\tau(CCl_4)$: 8.60, 8.23, (3 protons each, sharp) in 71% yield from (2).

The reaction between ethylvinyl ketone and (2) when carried out in dimethylsulfoxide did not stop at the formation of (3), but instead gave (4) in 33% yield together with a 45% yield of the acid (6), m.p. 59-61°, ν_{max}^{KBr}: 1697, 1658, 1623 cm^{-1},$\tau(CCl_4)$: 8.95 (triplet, J = 4 cps, 3 protons), 8.80 (doublet, J = 6 cps, 3 protons). Reaction of compound (4) with the methiodide of 1-N,N-diethylaminobutan-3-one in the presence of sodium methoxide gave only a low yield (less than 10%) of the tricyclic dienedione (12), m.p. 163-164°, λ_{max}^{MeOH}: 239 mμ (logε 4.13); ν_{max}^{KBr}: 1708, 1662, 1645 (shoulder), 1615 cm^{-1}; $\tau(CDCl_3)$: 8.55, 8.50 (3 protons each, sharp), 4.22 (singlet, 1 proton) 4.05 (triplet, J = 3.5 cps, 1 proton). The fact that the vinylic proton at C_1 in (12) appears as a triplet indicates that ring A is in a deformed chair-like conformation and that this deformation is probably due to the non-bonding interaction between the C_5- and C_9-methyl groun which therefore are in a cis-relationship.

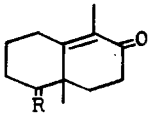
Since the yield of (12) from the above reaction sequence was so low, the following roundabout route was adopted. When the enedione (4) was treated with ethylene glycol-tosic acid, selective ketalization of the saturated carbonyl group resulted and gave a 90% yield of the ketal ketone (5), m.p. 55-56°, ν_{max}^{KBr}: 1663, 1612 cm^{-1}; $\tau(CCl_4)$: 8.72, 8.28 (3 protons each, sharp), 6.10 (4 protons, sharp). Reaction of compound (5) with ethyl formate and sodium methoxide yielded the oily hydroxymethylene ketone (7), ν_{max}^{liquid}: 1643 cm^{-1}, which was treated, without purification, with N-methylaniline to afford the methylanilino compound (8), m.p. 148-149°, ν_{max}^{KBr}: 1640 cm^{-1}, in 76% yield from (5). When (8) was allowed to react with acrylonitrile in the presence of Triton-B catalyst, it gave the cyanoketone (9), m.p. 128.5-129.5°, ν_{max}^{KBr}: 2246 cm^{-1}.



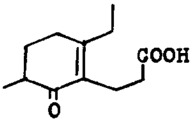
(2)



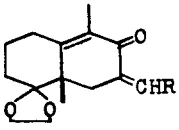
(3)



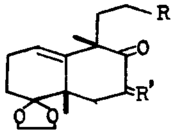
(4) R=O
(5) R=



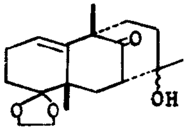
(6)



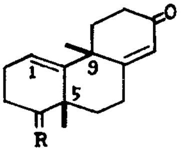
(7) R=OH
(8) R=N<$^{Me}_{Ph}$



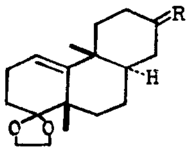
(9) R=CN, R'=CHN<$^{Me}_{Ph}$
(10) R=COOH, R'=H_2



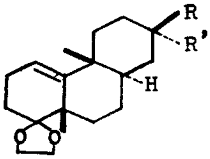
(11)



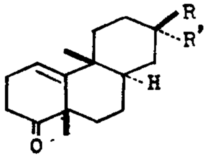
(12) R=O
(13) R=



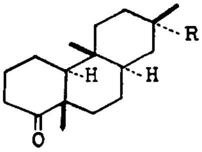
(14) R=O
(15) R=CHCOOBu(t)
(16) R=C$(CN)_2$



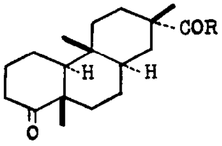
(17a) R=Me, R'=CH$(CN)_2$
(17b) R=CH$(CN)_2$, R'=Me



(18a) R=Me, R'=CH_2COOH
(18b) R=CH_2COOH, R'=Me



(19) R=CH_2COOH
(20) R=CH:CPh_2



(21) R=OH
(22) R=Cl
(23) R=SEt
(24) R=H

No epimer of (9) was separated. Hydrolysis of pure compound (9), or of the crude cyanoethylated product, in refluxing aqueous ethylene glycol monoethyl ether with potassium hydroxide afforded the keto acid (10), m.p. 167-169°, ν_{max}^{KBr}: 3125, 1735, 1695 cm^{-1},τ(methyl ester in CCl_4): 8.80, 8.83 (3 protons each, sharp), 4.52 (triplet, J = 4 cps, 1 proton): the yield was 67% from (8) when the crude cyanoethylated compound was hydrolyzed.

The reaction between (10) and methyl lithium gave a 55% yield of the hydroxyketone (11), m.p. 176-177°, ν_{max}^{KBr}: 3360, 1705 cm^{-1}, τ($CDCl_3$): 8.90, 8.82, 8.69 (3 protons each, sharp), 4.40 (quartet, 1 proton), and treatment of this product with sodium methoxide afforded the dienone (13), m.p. 126-127°, ν_{max}^{KBr}: 1659, 1641 (shoulder), 1617 cm^{-1}; τ($CDCl_3$): 8.53 (3 protons, sharp) 4.38 (triplet, J = 4 cps, 1 proton), 4.20 (singlet, 1 proton), in 66% yield from (11). Removal of the ketal group in compound (13) with dilute mineral acid afforded the dienedione (12). Compound (13) was subjected to a Birch reduction[7], using tertiary butanol as the proton donor, and the product was oxidized with chromic anhydride-pyridine to give the saturated ketone (14), m.p. 130.5-131°, ν_{max}^{KBr}: 1709 cm^{-1}, τ($CDCl_3$): 8.71, 8.60 (3 protons, each), 4.45 (triplet, J = 3.5 cps, 1 proton). When the ketone (14) was allowed to react with diethyl-t-butyl phosphonoacetate[8], it formed the cyclohexylidene acetate (15), m.p. 130-153° (probably a mixture of the cis- and trans-isomers), ν_{max}^{KBr}: 1706, 1645 cm^{-1}; which when treated with methyl magnesium iodide showed no signs of reaction. An attempt was made therefore to introduce a group which was a more powerful electron attractor than the ester group, in order to achieve the expected addition of Grignard reagent. Condensation of the saturated ketone (14) with malononitrile in the presence of acetic acid - ammonium acetate gave the cyclohexylidene malononitrile (16), in 91% yield from (14), m.p. 140-141°, ν_{max}^{KBr}: 2230, 1643, 1603 cm^{-1}, τ(CCl_4): 8.80, 8.68 (3 protons, each), 4.67 (triplet, J = 3 cps, 1 proton). When (16) was treated with methyl magnesium iodide, the expected addition reaction occurred; separation of the crude product by alumina chromatography afforded two epimers, the crystalline dinitrile (17a) in 55% yield from (16), m.p. 183-185°, ν_{max}^{KBr}: 2250, 1645 cm^{-1}, and the gummy dinitrile (17b) in 37% yield from (16), ν_{max}^{liquid}: 2250, 1642 cm^{-1}. The cyano groups in both these dinitriles were quite resistant to hydrolysis, but hydrolysis and decarboxylation occurred when they were refluxed in ethylene glycol containing 20% potassium hydroxide, and thus afforded a crystalline ketal acid, ν_{max}^{KBr}: 3175, 1725 cm^{-1}, from (17a), and an gummy acid, ν_{max}^{liquid}: 2600, 1740 cm^{-1}, from (17b). Both the above products, without purification, were treated with dilute mineral acid to remove the ketal group; (17a) gave a 79% yield of the ketoacetic acid (18a), m.p. 159-161,5°, ν_{max}^{KBr}: 3100, 1728 (carboxyl), 1689 (carbonyl), 1643 cm^{-1}, τ(methyl ester in CCl_4): 9.01, 8.95, 8.67 (3 protons, each) 7.77 (2 protons, sharp), 4.39 (triplet, J = 4 cps, 1 proton); (17b) afforded a 47% yield of the ketoacetic acid (18b), m.p. 188-190°, ν_{max}^{KBr}: 2600, 1706, 1696, 1644 cm^{-1}, τ(methyl ester in CCl_4): 9.02, 8.95, 8.67 (3 protons, each), 7.87 (2 protons, sharp), 4.39 (triplet, J = 4 cps, 1 proton).

The carboxyl group and the carbonyl group of the keto-acetic acid (18a) in the solid state showed abnormal infrared absorption, but in chloroform solution they showed normal values (2600, 1702 cm^{-1}). From this it seemed to us that intermolecular interactions between the carbonyl and carboxyl groups occur when the acid (18a) is in the solid state and that this may be attributed to the fact that (18a) is a racemate. Such abnormality was not observed with the compound (18b), and it was therefore assumed that the acetic acid residue has the axial configuration in the ketoacetic acid (18a).

Although the unsaturated bond in (18a) resisted catalytic reduction, its methyl ester could be hydrogenated at 100° under pressure in the presence of palladium on carbon catalyst. The product was oxidized with chromic anhydride and then hydrolyzed to the saturated (±)-keto acid (19), m.p. 172-174°, ν_{max}^{KBr}: 3050, 1724, 1679 cm^{-1}; the infrared spectrum of (19) in chloroform solution was identical with that of the (-)-ketoacetic acid (mentioned later) derived from dolabradiene. The quinidine methohydroxide salt[9] of (19) after recrystallization from tetrahydrofuran had m.p. 201-202° (decomp.), and on decomposition with dilute mineral acid it formed the (-)-ketoacetic acid, (19) m.p. 162-163°, ν_{max}^{KBr}: 1710, 1698 (shoulder), RD:$[\alpha]_{700}-43°$, $[\alpha]_{600}-52°$, $[\alpha]_{310}+155°$, $[\alpha]_{280}-900°$ (c = 0.39 in MeOH), and this was identical in every respect with the compound which had been derived from the natural product. The remaining steps of the synthesis were therefore completed by using the (-)-ketoacetic acid derived from dolabradiene. The keto acid (21)[1], obtained from the oxidation of dolabradiene, was converted into the (-)-ketoacetic acid (19) in 28% yield by a modified Arndt-Eistert reaction[10]. The ketoacetic acid, after being converted into the ketal and then methylated with diazomethane, was allowed to react with phenyl lithium; the product when treated with tosic acid in acetic acid formed the diphenylethylene (20) in 64% yield from (19), m.p. 157-158°, λ_{max}^{MeOH} 247 mμ (log ε 4.15). An unsuccessful attempt was made to prepare the keto aldehyde[1] (24) by ozonolysis of (20) and reduction of the product. The ozonide was therefore treated with chromic anhydride which afforded the keto acid (21); treatment of this with thionyl chloride gave the acid chloride (22), m.p. 139-142°, ν_{max}^{KBr}: 1806, 1704 cm^{-1}. Because (22) resisted Rosenmund reduction, it was converted with lead ethylmercaptide into the thiol ester (23), m.p. 113-114°, ν_{max}^{KBr}: 1700, 1668 cm^{-1}, and then desulfurized with deactivated Raney nickel[11] to give the keto aldehyde (24). Both (21) and (24) were identical with the respective compound obtained from oxidation of dolabradiene. Reaction of (24) with triphenylmethylene phosphorane in dimethylsulfoxide[12] gave dolabradiene (1) which was identified by infrared, and retention time on gas chromatography.

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