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A SIMPLE SYNTHETIC ROUTE TO dl-SIRENIN

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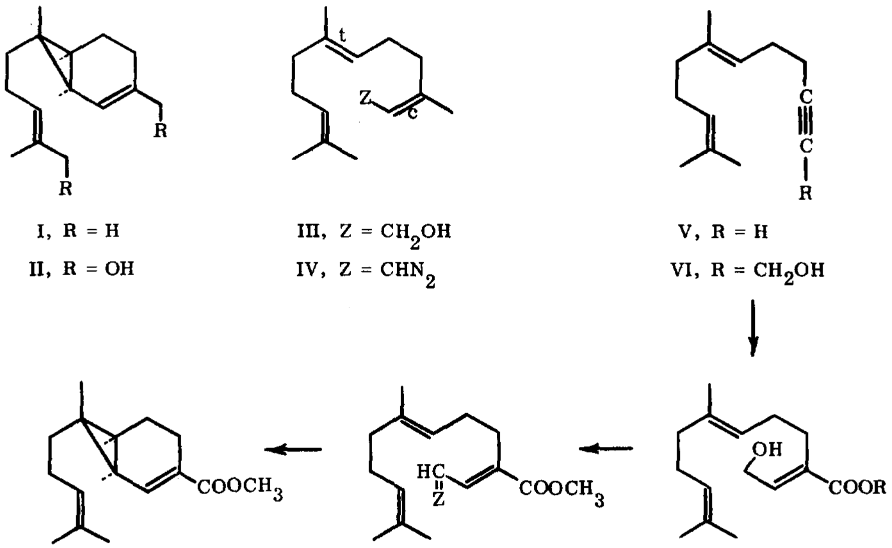
We have recently described a synthesis of sesquicarene (I), the naturally occurring parent hydrocarbon of sirenin (II), from cis,trans-farnesol (III) via the diazo compound (IV) (1,2). The cyclization of the diazoalkene of IV to form sesquicarene was effected in ca. 50% yield using cuprous iodide as catalyst. In this note we describe a synthesis of dl-sirenin which utilizes the cuprous iodide procedure and an unsaturated diazo compound analogous to IV as substrate. The sequence involved in this approach is considerably shorter than those of the previously recorded syntheses of sirenin (3-6).

Treatment of the readily available (7) acetylenic hydrocarbon V with 1.2 equivalents of n-butyllithium at -78° in tetrahydrofuran to form the lithium acetylide and then with 3 equivalents of paraformaldehyde (dried over P_2O_5) at -78 to 25° for 30 min. and 25° for 2 hr. afforded in 82% yield the acetylenic carbinol VI (8, 9). Reaction of VI with nickel carbonyl (1.5 equivalents) (10) in acetic acid--ethanol--water (1 : 15 : 2.5) at 70° for 1.5 hr. produced a mixture of products from which the hydroxy acid VII (9b) could be isolated by chromatography on silica gel (eluent hexane--CH_2Cl_2--THF, 6 : 2 : 1). Esterification of VII with ethereal diazomethane followed by chromatography on silica gel yielded the pure hydroxy methyl ester VIII (30% overall from VI) (9). Oxidation of VIII using excess activated manganese dioxide in hexane at 0° for 1 hr. gave the aldehydo ester IX (9b) which was directly converted to the hydrazone X by reaction with 3 equivalents each of hydrazine and triethylamine in ethanol at 25° for 2 hr., and thence to the diazo ester XI (9b) by oxidation with activated manganese dioxide in methylene chloride at 0° for 30 min. Slow addition of the diazo compound XI to a stirred suspension of an equivalent amount of cuprous iodide in tetrahydrofuran at 35° produced the bicyclic ester XII (11). The cyclization of XI to XII occurred in ca. 50% yield. Since the conversion of XII to dl-sirenin in two steps has already been described (4), a sequence from the acyclic hydrocarbon V to dl-sirenin consisting of nine steps has been established.

Finally we record an improvement in the reported (1) synthesis of sesquicarene from farnesol. This depends on the observation that mercuric iodide is an excellent catalyst not only for the conversion of the cis,trans-diazo compound IV to sesquicarene (I) but also for the generation of I from the trans,trans-isomer of IV. Thus it has become possible to effect the synthesis of sesquicarene starting from a commercially available farnesol consisting of the trans,trans- and cis,trans-isomers (ratio 1.5 : 1) without separation by the sequence described earlier (1) in 35% overall yield. The cyclization of the diazo compound IV admixed with the trans, trans-isomer was performed by gradual addition of the diazo substrate in tetrahydrofuran to a solution of 2 equivalents of mercuric iodide in tetrahydrofuran over ca. 30 min. at 28° followed by an additional reaction time of 20 min. ; the yield for the cyclization step is estimated at ca. 60% (12).



I, R = H
II, R = OH

III, Z = CH_2OH
IV, Z = CHN_2

V, R = H
VI, R = CH_2OH

XII

IX, Z = O
X, Z = NNH_2
XI, Z = N_2

VII, R = H
VIII, R = CH_3

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12. We are grateful to the National Science Foundation for financial assistance.