Entry into the Podocarpane Series Through a Biogenetic-like Stereoselective Olefin Cyclization

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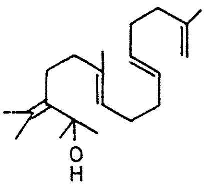
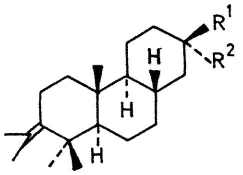
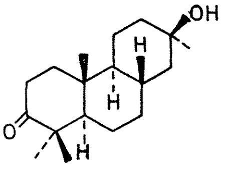
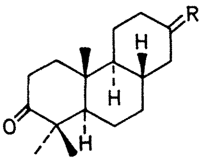
In connection with a study of the acid-catalysed cyclization of polyolefinic allylic alcohols,[1] we examined the behaviour of the tetraenol(I) in the hope that its cyclization would lead to tricyclic compounds such as (IIb), oxidative cleavage of which would afford products like (III) having a substitution pattern found in many natural polycyclic terpenoids. This has now been achieved and the salient results are set forth below.

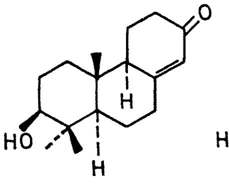

(I)

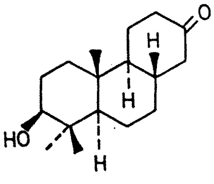

(II) a; R^1=Me, R^2=OH
b; R^1=OH, R^2=Me


(III)


(IV) R=O
(V) R=CH_2

The tetraenol (I) was synthesized by the addition of methyl-lithium to the tetraenone (XV) which was produced by the alkylation[2] of the sodium enolate of mesityl oxide with the bromo-triene (XIV) in liquid ammonia and tetrahydrofuran. Chromatography (Florisil) of the product effected separation of the trienone (XV) and its $\beta\gamma$-tautomer in 22 and 25% yield, respectively. These two isomers were isolated in 69 and 28% yield, respectively, when the $\beta\gamma$-tautomer was treated with potassium hydroxide in t-butyl alcohol at room temperature to effect equilibration; thus the desired isomer (XV) was readily accessible. The bromo-triene (XIV) was prepared by a method developed by W. Stern and V. A. Fung in our laboratory. The enyne (VIII), from the coupling of prop-2-ynyl bromide with methallylmagnesium chloride, was treated with ethylmagnesium bromide, then with paraformaldehyde, giving the enynol (IX) in 73% yield. This compound, on treatment with phosphorus tribromide, lithium bromide, and collidine in ether at −30°, was converted (87% yield) into the bromide (X) which was allowed to condense with the sodium enolate of 1-(ethoxycarbonylacetyl)-1-methylcyclopropane in tetrahydrofuran.[3] The crude alkylation product (XI) was then treated with barium hydroxide and aqueous ethanol. Acidification gave the enynone (XII) in 43% overall yield from (X). Treatment of this product with lithium aluminium hydride in ether, followed by an excess of sodium in liquid ammonia,[4] afforded the *trans*-dienol (XIII) which was converted into the bromotriene (XIV) (76% yield) by a modification (developed by B. Staskun) of a general method for effecting this type of transformation.[3] This modification involved treatment of (XIII) with *o*-phenylene phosphochloridite and pyridine in ether[5] (to give the phosphite ester) followed by zinc bromide in ether,[3] for 5 hr. at room temperature.


(VI)


(VII)

Treatment of a methylene chloride solution of the tetraenol (I) at −78° with trifluoroacetic acid for 5 min., followed by lithium aluminium hydride to effect cleavage of the resulting trifluoroacetates, afforded a mixture which was submitted to short-path distillation, then t.l.c. on silica gel. In addition to a hydrocarbon fraction (see below), two crystalline tricyclic alcohols (IIa) and (IIb) were isolated in 23 and 29% yields, respectively. The epimer (IIb) (m.p. 101—102°) with the axial hydroxy-group had lower retention times on t.l.c. and g.l.c. than the isomer (IIa) (m.p. 115—116°) with the equatorial hydroxy-group. Dehydration of (IIa) with phosphorus oxychloride in pyridine gave a mixture of dienes which were shown by n.m.r. analysis to have a large preponderance of that isomer with the exocyclic methylene group; while similar treatment of (IIb) gave mainly isomers with endocyclic double bonds in ring c. These results are consistent with the known behaviour[6] of equatorial and axial hydroxy-groups, respectively, in such an environment. The configuration of the ring fusion was proved as follows. The known racemic 3β-hydroxypodocarp-8(14)-en-13-one (VI)[7] was reduced with lithium and ammonia in dioxan to give the saturated hydroxy-ketone, m.p. 180—183°, which undoubtedly has the B/C *trans*-(8β)-configuration (VII).[8] This hydroxy-ketone (VII) was treated with methyl-lithium and the product oxidized with Jones' reagent[9] to give a single hydroxy-ketone, m.p. 117—119°, which most certainly is the substance (III) resulting from equatorial attack by the methyl-lithium.[10] Ozonolysis[11] of the cyclization product (IIb) gave material which proved, by mixed m.p., t.l.c., i.r., and n.m.r. comparison, to be identical with the authentic hydroxy-ketone (III). Ozonolysis of the cyclization product (IIa) followed by dehydration with phosphorus oxychloride and pyridine, afforded a mixture, rich in the enone (V). Ozonolysis of this product readily afforded the dione (IV), m.p. 128—130°, which proved to be identical, by mixed m.p., t.l.c., and g.l.c., with authentic material, m.p. 130—132°, prepared by oxidation of the hydroxy-ketone (VII) with Jones' reagent.†

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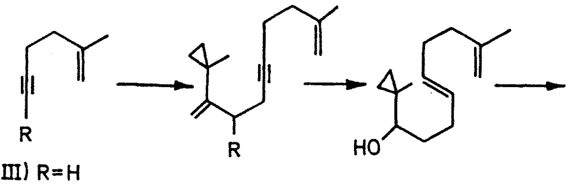
† All of the new substances described herein have been fully characterized by combustion analysis and i.r. and n.m.r. spectroscopy.

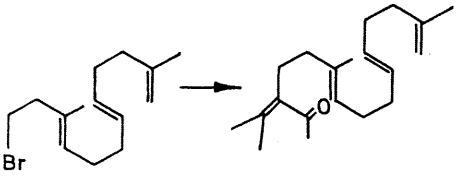
The cyclization of the tetraenol (I) is highly stereoselective. The tricyclic material, produced in over 50% yield, appears to belong exclusively to the *trans, anti, trans*-stereochemical series. The hydrocarbon fraction obtained from the cyclization reaction product was a complex mixture, the principal component of which was the pentaene resulting from dehydration of (I). Treatment of this pentaene under conditions known to effect cyclization of the alcohol (I) gave only trace amounts of tricyclic products. This behaviour is in striking contrast to that observed in another series.[1b] When the cyclization of (I) was carried out as described above but with deuteriotrifluoroacetic acid, ***there was no deuterium incorporation in the tricyclic products*** as shown by mass spectrometry. This result proves that the cyclization proceeds without the intermediacy of any incompletely cyclized olefinic compounds, a behaviour which is analogous to that established for the enzymic cyclization of squalene.[12]



(VIII) R=H
(IX) R=CH$_2$OH
(X) R=CH$_2$Br

(XI) R = CO$_2$Et
(XII) R = H

(XIII)



(XIV)

(XV)

We thank Professor Gilbert Stork for a specimen of synthetic racemic 3β-hydroxypodocarp-8(14)-en-13-one (VI). We also thank the U.S. Public Health Service, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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