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Cyclization of Polyenes.[1] VI. Biogenetic-Type Synthesis of Levantenolides Isolated from Turkish Tobacco

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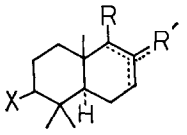
Keto acid (VII) was assumed to be a precursor in the biogenesis of levantenolides (IV and V). The syntheses of the analogous compounds (IX and X) and their cyclization to IV and V were carried out as follows. Reaction of farnesyl bromide (XV and XX) with 2,2′-di-3-methylfurylmercury afforded the corresponding furano derivatives (XVI and XXI), which were photo-oxidized to butenolide derivatives (IX and X). Biogenetic-type cyclization of IX and X with stannic chloride afforded IV, V, and XIX in moderate yields.

As it has been recognized that execution of biogenetic-type reactions in the laboratory can provide exceedingly simple and stereospecific synthetic routes to natural products (*1*), many organic chemists have achieved total syntheses of natural products based on biogenetic considerations, especially in the fields of terpenoids and alkaloids. Terpenoids having a *trans* decalin skeleton (I) as a partial structure are of special interest since such compounds, encountered in almost all di- and triterpenoids, and also in several



I

X = H or OH, R′ = CH_2 or CH_3

driman-type sesquiterpenoids, are constructed *in vivo* by the cyclization of acyclic precursors (II, III). Chemical transformations of the acyclic precursors (II), including its 2,3-oxido-derivatives (III) (*1c*) have been carried out in the laboratory by many organic chemists, demonstrating that polycyclic compounds of type I having several asymmetric centers can be constructed simply and stereospecifically from the acyclic precursors under suitable acidic conditions.

In the diterpene field only a few reports (*1c*) have been published, however, concerning biogenetic-type synthesis from an acyclic precursor; although biogenetic-type transformations (*1d*) have been achieved from the labdane type to tricyclic, and from tricyclic to tetracyclic diterpenoids, in addition to interconversion of tetracyclic compounds. We have been very interested in the cyclization of polyenes to natural products[1]

[1] Part V of this series TA. KATO, S. KANNO, and Y. KITAHARA, *Tetrahedron* **26**, 4287 (1970).
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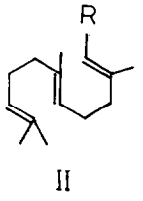
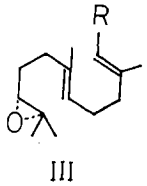


II



III

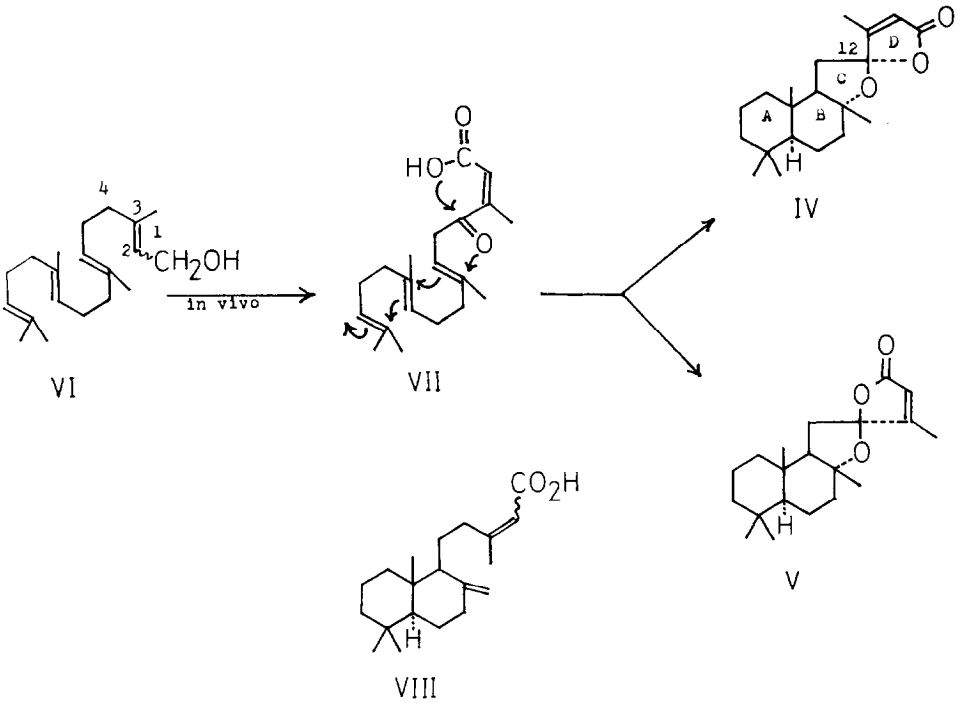
$R = CH_2OH$ (Sesquiterpene)

$= (CH_2)_2CMe{=}CHCH_2OH$ (Diterpene)

$= ((CH_2)_2CH{=}CMe)_3Me$ (Triterpene)

(*2*), and herein is reported the biogenetic-type synthesis (*3*) of labdane type diterpenes, levantenolides.

Levantenolide was isolated from Turkish tobacco by Giles and Schumacher, who demonstrated (*4*) that α- and β-levantenolides (IV and V) differ in being epimeric at

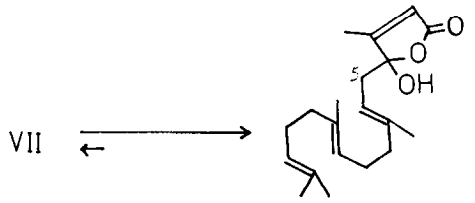


VI VII VIII

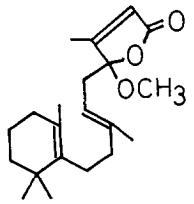
C-12 and are closely related to labdanolic acid having the unique combination of butenolide and five-membered oxide groupings. By analogy with a well-known fact that labdane-type diterpenes are biosynthesized (*5*) by cyclization of geranyl geraniol (VI) or its equivalents, one of the possible biogeneses of levantenolides would involve

cyclization of hypothetical keto acid (VII), presumed to arise in nature by oxidation at the C-1 and C-4 positions of geranyl geraniol. It is equally probable that C_4 oxidation would occur after cyclization of VI to a labdane-type intermediate such as labd-8,13-diene-15-oic acid (VIII).

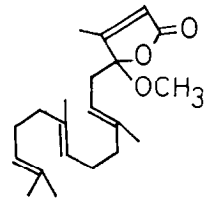
The biogenetic-type reaction involving the cyclization of hypothetical precursor VII and its equivalents was expected to lend itself to the stereospecific synthesis of the levantenolides. Verification of this expectation has been examined, and this paper describes the total synthesis of the levantenolides.



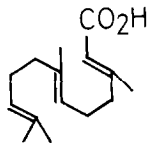
VIIb



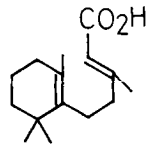
IX



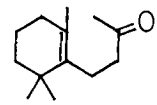
X



XI



XII



XIII

In considering an appropriate scheme for the synthesis of the precursor VII, we wished to utilize the closely related compounds (IX) and (X) instead of VII, since the precursor VII is considered to exist as a lactol form (VIIb) under laboratory conditions. The lactol grouping of VIIb would not be stable under the usual conditions, especially cyclization conditions to be described later, and acid treatment might cause dehydration before formation of the A/B ring system of levantenolide. Consequently, certain of our synthesis efforts were directed toward preparation of intermediates IX and X, which were expected to cyclize readily to the levantenolides. We turned our attention first to the preparation of IX, since the analogous acid-catalyzed partial cyclization of farnesic acid (XI) to monocyclofarnesic acid (XII) has been performed by Stork (*6*),

and the latter compound (XII) could be easily obtained from dihydro-β-ionone (XIII) by a Wittig reaction with triethylphosphono acetate and subsequent hydrolysis (*7*). Monocyclofarnesol (XIV), easily obtainable from XII, was chosen as a starting material for the preparation of the intermediate IX.

Synthesis and Cyclization of Intermediate IX

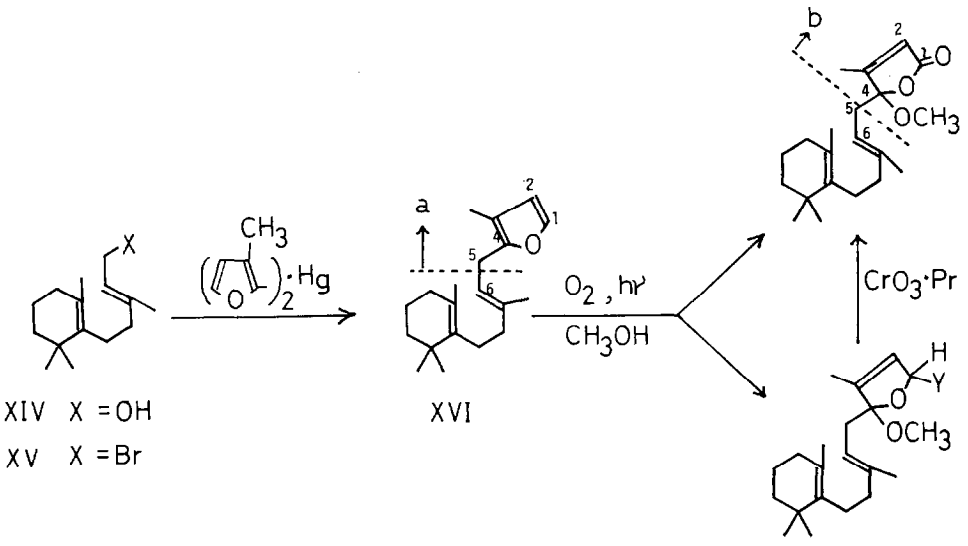
A simple and effective route to the intermediate IX was achieved by coupling of the monocyclofarnesyl group with 2-methylfuran and subsequent selective photo-oxidation of the furan moiety. Büchi has successfully brought about (*8*) the coupling reaction of 1-bromo-3-methyl-2-butene with 2-lithio-3-methylfuran to obtain rosefuran in 35% yield. We applied the above method to monocyclofarnesyl bromide (XV) which was obtained in a quantitative yield by treatment of monocyclofarnesol XIV with phosphorous tribromide. Reaction of XV with 2-lithio-3-methylfuran gave, however, no condensation product, but instead a mixture of hydrocarbons which was presumably derived from XV by dehydrobromination. When the coupling reaction was tried using 2,2′-di-3-methylfurylmercury instead of 2-lithio-derivative, the objective (XVI) was gained in 50% yield after purification by means of silica-gel column chromatography.

The addition product XVI was subjected to photo-oxidation (*9*) by passing oxygen gas through an absolute methanol solution, with three 20-W fluorescent lamps using eosine as sensitizer. Since compound XVI has many reactive sites, the progress of the photo-oxidation was followed by watching the disappearance of the starting material on the thin-layer plate, thus avoiding further oxidation (*10*). The photo-oxidation products consisted mainly of butenolide IX and more polar compounds, presumably acetal (XVII) and/or its peroxide (*9b*) (XVIII). The relative amount of IX was increased by addition of vanadium pentoxide during the photo-oxidation reaction. Although structures of XVII and XVIII were not precisely confirmed because of their difficulties of purification, the following evidence suggested the assigned structures. A mixture of photo-oxidation products was reduced by sodium iodide, and the reduction mixture, which showed the presence of hydroxyl in the ir spectrum, was oxidized with chromium trioxide to increase the amount of IX. The amount of liberated iodine differed greatly, depending on the photo-oxidation conditions. On a preparative scale, however, the mixture of photo-oxidation products was treated with chromium trioxide–pyridine complex (*11*), giving butenolide derivative IX in 60% yield after purification with silica-gel chromatography.

The structures of adduct XVI and its oxidation product IX were confirmed on the basis of physical evidence (*12*). In the mass spectrum of XVI, there appeared strong peaks at *m/e* 191 $(M\text{-}a)^+$ and 95 $(a)^+$, whereas IX showed the intense peaks at *m/e* 205 $(M\text{-}b)^+$ and 127 $(b)^+$, respectively. Formation of these fragment ions could be attributed to bond fission at C_5–C_6 in XVI and at C_4–C_5 in IX, respectively, as shown with dotted lines (*13*). These fragmentations are consistent with the assigned structures of compounds XVI and IX.

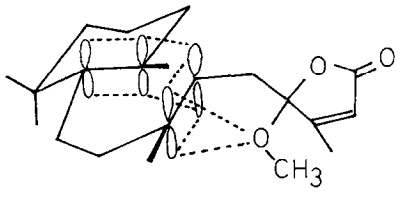
After several fruitless trials to find cyclization conditions, the reaction was achieved with stannic chloride in benzene solution at room temperature for 4 hr to afford a mixture of three major products (IV, V, and XIX), which were separated by recrystallization and repeated silica-gel column chromatographies in 30, 12, and 25% yield. Infrared and nmr spectra in chloroform solutions of the crystalline compounds IV and V were completely superimposable with those of natural α- and β-levantenolides, respectively. This cyclization reaction was subtle, and the yield of the products depended on the reaction conditions, especially the quality of stannic chloride. It is interesting

to note that the α-form predominates over the β-form, a relation similar to the natural proportion of α- and β-forms.

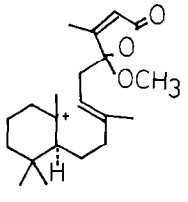


The structure of compound XIX follows from the physical evidence. The mass spectrum shows the strong peaks at *m/e* 205 $(M\text{-}b)^+$ and 127 $(b)^+$ which were also observed in IX and X. In addition, XIX underwent cyclization to α-levantenolide, although the major amount of the starting material remained unchanged when treated with stannic chloride at room temperature for 2 days or with dioxane-6N H_2SO_4 (13:1) at 90° for 24 hr.

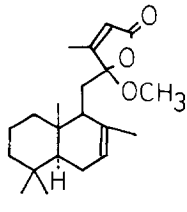
There is at present no basis for mechanistic conclusions, especially with regard to the question of whether the intramolecular interactions between the system of the carbon–carbon double bonds and lone pair electrons of methoxyl group are present or not in benzene solution, as shown with IXa. The reaction would be expected (*14*), however, to proceed via intermediate IXb which existed in equilibrium with IX. Since the methoxyl group of XIX was fairly stable under the cyclization conditions and the



IXa



IXb

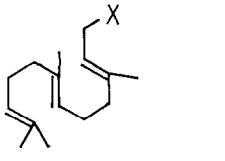


XIX

relative rate of conversion of IX to levantenolides was much faster than that of XIX, demethylation of the methoxyl group and simultaneous cyclization of the intermediate IXb would be more likely to result in the formation of levantenolides.

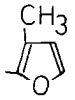
Synthesis and Cyclization of Intermediate X

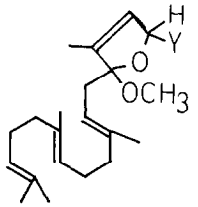
The intermediate X was prepared by the sequence of reactions previously used in the preparation of IX. *Trans,trans*-farnesol (*15*) was transformed to the corresponding bromo derivative (*16*) (XX), which was treated with 2,2′-di-3-methylfurylmercury to afford furano derivative (XXI) in 50% yield. Photo-oxidation of XXI furnished a



XX X = Br

XXI X =





XXII

mixture of X and XXII (Y = OH and/or O_2H), which was treated with chromium trioxide–pyridine complex. After purification by means of careful silica-gel chromatography, intermediate X was obtained in 30% yield. The yield of the photo-oxidation is probably not optimal, since only a single experiment was performed. The structures of the adduct and its oxidation product were deduced from the physical evidence, which was quite similar to that of monocyclic equivalents.

Similar treatment of X with stannic chloride at room temperature for 30 hr served to transform it to α- and β-levantenolides in 16 and 6% yield, respectively. The yield and rate of the cyclization of X are somewhat lower and slower than those of IX.

Thus the simple and stereoselective synthesis of levantenolides based on biogenetic considerations was performed, although this work does not signify establishment of the stereochemistry of the natural levantenolides.

EXPERIMENTAL

Nmr spectra were measured with varian A-60 spectrometer and the chemical shifts are expressed as ppm from an internal standard of tetramethylsilane. Ir and mass spectra were measured with Hitachi EPI-S2-type infrared, and Hitachi RMU-6D-type mass spectrometers, respectively. Melting points were measured with Tamura micro mp meter and are uncorrected.

Coupling Reaction of Farnesyl Bromides (XV and XX) with 2,2′-di-3-methylfurylmercury

To an anhydrous benzene solution (5 ml) of 2,2′-di-3-methylfurylmercury (1 g) was added 1.1 g of farnesyl bromide (XV) dissolved in 5 ml of absolute benzene. A catalytic amount of zinc–copper powder (ca. 20 mg) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture, after being diluted with ether, was washed with water and dried over magnesium sulfate. From the organic

layer was obtained a crude oil, which was passed through 50 g of silica gel column using cyclohexane as eluent to obtain oily furano derivative XVI in 50% yield. Similar treatment of XX afforded XXI in 51% yield. XVI: Found C, 83.72; H, 10.63 $C_{20}H_{30}O$ requires C, 83.86; H, 10.56 ir (film) 1513, 890, and 725 cm^{-1}; nmr (CCl_4) 0.97 (6H, s), 1.57 (3H, s), 1.92 (3H, s), 2.07 (3H, s), 3.20 (2H, d, $J = 7$, C_5-protons), 5.23 (1H, t, $J = 7$, C_6-*H*), 6.04 (1H, d, $J = 2$, C_2-*H*), and 7.17 ppm (1H, d, $J = 2$, C_1-*H*): mass 286 (M^+, mol wt = 286.44). XXI: Found C, 83.50; H, 10.46 ir (film) 1513, 887, and 725 cm^{-1}; nmr (CCl_4) 1.58 (6H, s), 1.93 (3H, s), 2.00 (6H, s), 3.22 (2H, d, $J = 7$, C_5-protons), 5.08 (3H, m), 6.03 (1H, d, $J = 2$, C_2-*H*) and 7.10 ppm (1H, d, $J = 2$, C_1-*H*); mass 286 (M^+).

Photo-oxidation of Furano Derivatives (XVI and XXI)

(A) *With vanadium pentoxide.* Oxygen was bubbled into a mixture of furano derivative XVI (660 mg), eosine (8 mg), and vanadium pentoxide (8 mg) in absolute methanol (50 ml) for 2 hr, during which time external irradiation with three 20-W fluorescent lamps was continued. Methanol was removed in vacuo to give residual oil, which was chromatographed on silica-gel column with mixed solvents of cyclohexane–isopropyl ether (6:1), affording butenolide derivative IX (oil) in 55% yield. Continuation of the chromatography with cyclohexane–isopropyl ether (1:1) afforded acetal (XVII) or its peroxide (XVIII) in ca. 10% yield, which was converted to IX with chromium trioxide–pyridine complex by similar treatment as described in method B.

(B) *Without vanadium pentoxide.* A mixture of XVI (1.5 g), eosine (20 mg) was photo-oxidized similarly for several hours, and the residual oil, obtained by evaporation of methanol, was taken up in benzene solution (40 ml). To the benzene solution was added chromium trioxide–pyridine complex (4.5 g) and the mixture was stirred at room temperature for 3 hr. The remaining powder was removed by decantation, and the organic layer was successively washed with 1 *N* hydrochloric acid and then water, dried with magnesium sulfate and evaporated to give crude oil. The latter was purified by silica gel chromatography to afford IX in 60% yield; 330 mg of XXI was similarly photo-oxidized following method B and X (oil) was isolated in 30% yield. IX: Found C, 76.01; H, 9.87; $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70 ir (film) 1770, and 1658 cm^{-1}; nmr (CCl_4) 0.93 (6H, s), 1.53 (3H, s), 1.90 (6H, s), 2.52 (2H, q, $J = 7$), 3.07 (3H, s), 4.88 (1H, t, $J = 7$, C_6-*H*), and 5.75 (1H, bs, C_2-*H*); mass 332 (M^+, mol wt = 332.47). X: Found C, 75.62; H, 9.62 ir (film) 1773, 1673, and 1658 cm^{-1}; nmr (CCl_4) 1.58 (6H, s), 1.64 (6H, s), 1.93 (3H, s), 3.13 (3H, s), 4.93 and 5.80 (olefinic protons).

Cyclization of IX, X, and XIX

A benzene solution (10 ml) of butenolide (IX) (100 mg) was cooled to 10°C, and 0.2 ml of stannic chloride was added. After 4 hr the reaction mixture was poured into ice water and extracted with ether. From the organic layer, after being washed with water and then dried over magnesium sulfate, was obtained crude oil, which was dissolved in *n*-hexane and kept in the refrigerator to give white crystals (IV). The residual oil, obtained from the mother liquor, was chromatographed on silica gel (50 times by weight of the oil) with mixed solvents of cyclohexane–isopropyl ether (5:1) to give further crops of IV, mp 192–194° (total 30%). Successive elution with the same solvent afforded V, mp 171–173° (12%). Physical data (ir, nmr, mass, and tlc) of IV and V were completely superimposable with those of natural α- and β-levantenolides, respectively. After removal of the crystalline IV and V, the eluted oil was combined and rechromatographed on silica gel (150 times by weight of the eluted oil) using the same solvent to separate the oily compound (XIX) with 25% yield.

To a benzene solution (4 ml) of XIX (40 mg) was added stannic chloride (0.2 ml), and the mixture kept at room temperature for 2 days. The reaction mixture showed the presence of the recovered material (XIX) (major) and α-levantenolide (minor) on silica-gel thin-layer chromatography developed by mixed solvents of benzene–isopropyl ether (5:1).

XIX (10 mg) dissolved in a mixture (1 ml) of dioxane–6 *N* H_2SO_4 (13:1) was warmed at 90° for 24 hr. Thin-layer chromatography of the reaction mixture showed the presence of XIX (major) and IV.

A mixture of X (70 mg), stannic chloride (0.2 ml), and benzene (7 ml) was kept at room temperature for 30 hr and the reaction mixture was poured into ice water. Following the same procedure as described in the cyclization of IX, IV and V were obtained in 16 and 6% yields after separation by silica-gel column chromatography.

Analyses, synthetic IV, found C, 75.21; H, 9.83. Synthetic V, found C, 75.31; H, 9.71; $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50. XIX: ir (film) 1773 and 1658 cm^{-1}; nmr (CCl_4) 0.87 (6H, s), 1.97 (3H, s), 2.00 (3H, s), 3.10 (3H, s), 5.36 (1H, bs), and 5.82 ppm (1H, bs); mass 332 (M^+, mol wt = 332.47).

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