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The Cyclization of Polyenes.[1] VII. The Cyclization of Labda-13-ene-8,12,15-triol

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12α-Hydroxy epimanoyl oxide[3] (I), a labdane-type diterpene, was isolated by Giles *et al.* from Turkish tobacco, which also produces diterpene lactones, α- and β-levantenolides[4] (II, III).

As we have already reported the synthesis of II and III on the basis of biogenetical consideration,[5] it does not seem absurd to expect the conversion of triol (IV) to I or its stereoisomers. This paper will describe the acid-catalyzed cyclization of IV.

The reduction of synthesized α-levantenolide (II) with lithium aluminum hydride afforded the relatively unstable triol (IV), which was then treated with several Lewis acids, such as iodine, *p*-toluenesulfonic, sulfuric, and camphorsulfonic acids, and stannic chloride under various conditions. The reactions were followed by silica-gel thin-layer chromatography using natural 12α-hydroxyepimanoyl oxide (I) as a reference. The treatment of IV with stannic chloride gave, among the examined acids, the simplest mixture, from this mixture an oily compound (V) was isolated in a 37% yield by silica-gel chromatography.

1) Part V of this series, T. Kato, S. Kanno, and Y. Kitahara, *Tetrahedron*, **26**, 4287 (1970).

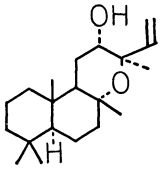
2) To whom inquiries regarding this paper should be addressed.

3) J. A. Giles, J. N. Schumacher, S. S. Mims, and E. Bernasek, *Tetrahedron*, **18**, 169 (1962).

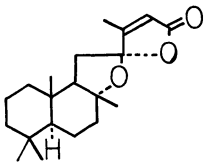
4) J. A. Giles, and J. N. Schumacher, *ibid.*, **14**, 246 (1961).

5) a) T. Kato, M. Tanemura, T. Suzuki, and Y. Kitahara, *Chem. Commun.*, **1970**, 28. b) M. Tanemura, T. Suzuki, T. Kato, and Y. Kitahara, *Tetrahedron Lett.*, **1970**. 1463.

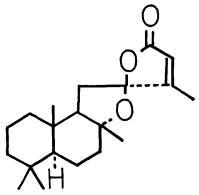
The gross structure of the product (V) was determined on the basis of the following observations. The NMR spectrum[6] of V exhibits signals of a doublet and a triplet at 4.05 and 5.48 ppm, with $J=7.2$ Hz due to C_{15}- and C_{14}-protons, a sharp singlet at 1.15 (C_8–Me), and broad multiplet at 4.77 (C_{12}–H). The hydroxyl group of V was easily oxidized with manganese dioxide to give the corresponding unsaturated aldehyde (VI), which showed a conjugated carbonyl group at 1672 cm^{-1} in the IR spectrum. The NMR spectrum of VI shows two kinds of formyl groups in *ca.* a 3: 1 ratio, indicating that VI is a mixture of either C_{12}-epimers or double-bond isomers at C_{13}–C_{14}. The former is more probable, since the 13-methyl group appears at 1.95 ppm, showing the *trans* relation of the methyl group with respect to the formyl group.[7] The destruction of the asymmetry at the 12 position of IV might occur prior to the ring formation.[8] Our objective, I, could not be isolated, although the formation, in quite a small amount, of a substance having the same R_f value on thin-layer chromatography with natural I was observed.



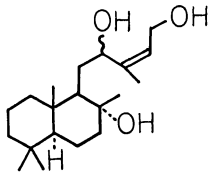
I



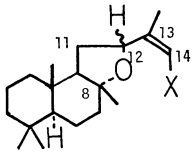
II



III



IV



V X = CH_2OH

VI X = CHO

6) NMR spectra were measured with Varian T-60 in carbon tetrachloride and expressed with ppm from an internal standard of tetramethylsilane.

7) M. Ohtsuru, M. Teraoka, K. Tori, and K. Takeda, *J. Chem. Soc.*, **1967**, 1033.

8) E. Wenkert and Z. Kumazawa, *Chem. Commun.*, **1968**, 140.

Experimental

Reduction of dl-α-*Levantenolide.* To a stirred, absolute ether solution (10 m*l*) of α-levantenolide (200 mg), we added lithium aluminum hydride (30 mg) under ice cooling. After stirring for an hour at 0°C, the reaction mixture was further stirred at room temperature for another hour and then poured onto ice water. Ether extracts from the reaction mixture were washed with cold hydrochloric acid and water, and then dried over magnesium sulfate in a refrigerator. Triol (IV) (200 mg) was thus obtained from the ether solution. Although the triol (IV), which should be stored in a refrigerator, could not be purified because of its unstability, the physical evidence supported the structure of the reduction product. NMR (δ) of the crude triol (IV) (D_2O was added) 1.13 (C_8–Me), 1.74 (C_{13}–Me), 4.05 (C_{15}-protons), 4.77 (C_{12}-proton), and 5.40 (C_{14}-proton). IR (film) 3400 cm^{-1} (strong), no absorption in the carbonyl region.

Cyclization of Triol (IV). Stannic chloride (0.1 m*l*) was added to a chloroform solution (10 m*l*) of the triol (200 mg) at −40——−60°C and the mixture was kept for an hour at the same temperature. The temperature of the reaction mixture was gradually raised to 25°C by removing the cooling bath. It took about an hour. After being diluted with ether, the ether solution was washed with aqueous sodium bicarbonate and then water, dried over magnesium sulfate, and then evaporated. The residued oil thus obtained was chromatographed on silica gel with a mixed solvent of benzene - isopropyl ether (8:1) to give V (70 mg). Found, C, 77.86; H, 10.85%. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18%.

Although four methyl groups at C_4, C_8, and C_{10} were observed as a sharp singlet in the NMR spectrum of V, the signals due to C_{12}-, C_{14}-, and C_{15}-protons appeared broadly, suggesting that the alcohol (V) is an epimeric mixture. NMR (δ), 0.85 (tert Me×2), 0.87 (tert Me), 1.15 (sharp s, C_8–Me), 1.73 (C_{13}–Me), 3.12 (bs, OH, disappeared on the addition of D_2O), 4.05 (bd, $J=7.2$ Hz, C_{15}–H_2), 4.77 (m, C_{12}–H), and 5.48 (br. t, $J=7.2$ Hz, C_{14}–H). IR (film), 3375 (OH), 1653 (C=C) cm^{-1}.

Oxidation of V. Active manganese dioxide (500 mg) was added to an ether solution (5 m*l*) of V (60 mg) and the reaction mixture was stirred for two hr at room temperature. The subsequent filtration and washing of the solid and evaporation of the combined ether afforded unsaturated aldehyde (VI).

The pair of doublets at 10.23 and 10.20 ppm, which appear in the ratio of 3: 1, corresponds to one formyl proton in the NMR spectrum of VI. The appearance of two kinds of formyl protons may be due to the presence of an epimeric mixture, which could not be separated by usual chromatography. VI; NMR (δ), 1.20 (s, C_8–Me), 1.95 (C_{13}–Me), 5.83 (bd, $J=7$ Hz, C_{14}–H), 10.23 (d, $J=7$ Hz), and 10.20 (d, $J=7$ Hz). IR (film) 1672 (conjugated formyl) cm^{-1}.

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