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FUNCTIONALIZATION AT C_{12} OF LABDANOLIC DITERPENES
SYNTHESIS OF α- AND β-LEVANTENOLIDE

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Several C_{12} oxygenated labdanolic diterpenes have been isolated in the last few years, principally from species of Nicotiana [1,2]. As, up to now, no efficient synthesis of these products have been reported and also considering that biogenetic routes to these compounds have been hypothesized from abienol through 12-keto intermediates, we have developed a method of preparing some C_{12} oxygenated labdanolic diterpenes starting from the readily available labdanolic acid 1a. An application of this method led us to a simple synthesis of α- and β-levantenolide.

Reduction of 1a with LAH gave the known diol 1b [3] which, by intramolecular cyclization with $Pb(OAc)_4/I_2$ in cyclohexane under reflux and irradiation with a 100w tungsten-filament lamp for 15 min, yielded a mixture (77%) of the two isomeric spiroketals 2a (75%) and 3a (25%) ($C_{20}H_{34}O_2$, M^+ 306), which was separated by preparative TLC on silica gel (C_6H_6-EtOAc, 95:5).

Compound 2a [4], m.p. 94-95° (acetone), $[\alpha]_D$ +47°, shows PMR signals at δ 3.84 (m, $W_{1/2}$ 18Hz, 2H-C_{15}) and 1.26 (s, Me-C_8). Its MS fragmentation pattern is analogous to that of spirostan sapogenins [5], the base peak (m/e 111) being represented by ion [a], a characteristic of spiroketals.

3a [4]: m.p. 158-160° (acetone), $[\alpha]_D$-42°; its MS is nearly identical to that of 2a and its PMR spectrum differs only in the position of the Me-C_8

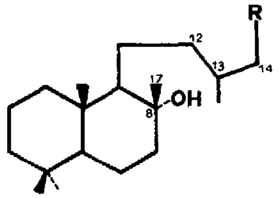
signal (δ 1.07). Adsorption on silica gel of 2a or 3a produces an equilibrium (3:1) between them.

The 12-keto compound 4 (amorphous, M^+ 348) was obtained by treating 2a or 3a with $Ac_2O/MeNH_2.HCl$ in pyridine under reflux for 2 hr. Its structure was determined on the basis of unequivocal spectral data: IR ν_{max}^{KBr} 3080, 1710, 885 cm^{-1}; PMR signals at δ 4.75, 4.35 (m, 2H-C_{17}) and 4.06 (t, J 6Hz, 2H-C_{15}). The principal fragments of its MS appear at m/e 190 and 101, ion [b] (40%) and base peak [$^+O{\equiv}C-CH(CH_3)-CH_2OH$] respectively.

Bromination of 2a or 3a with one equivalent of bromine in HOAc at 5° for 5 min proceeded regioselectively to give the same equimolecular mixture (80%) of only two monobromine compounds 2b[4] and 3b[4]. Both have $C_{20}H_{33}O_2Br$ molecular formula and their fragmentation patterns are nearly identical. 2b has m.p. 112-113° (MeOH), $[\alpha]_D$ +96°, and the principal signals in its PMR are at δ 4.02 (m, $W_{1/2}$ 18Hz, 2H-C_{15}), 1.82 (s, Me-C_{13}) and 1.26 (s, Me-C_8). In that of the other isomer 3b, m.p. 136-138° (MeOH, dec), $[\alpha]_D$ -83°, the Me-C_{13} and Me-C_8 are at δ 1.86 and 1.10 respectively.

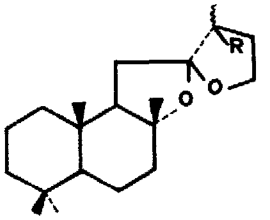
Dehydrobromination of 2b with potassium t-butoxide in C_6H_6-DMSO 4:1 at 0° for 30 min gave 5, while 3b afforded 6. The olefins 5 and 6, which are not stable enough to make physical constants, show the vinyl proton at δ 5.70 and 5.75 respectively, in their PMR spectra. These olefins are transformed quantitatively into the amorphous furan derivative 7 by adsorption on SiO_2. The PMR spectrum of 7 presents signals at δ 7.23, 6.15 (two furanic protons), 1.97 (s, Me-C_{13}) and 1.23 (s, Me-C_8).

By oxidation of 7 with m-chloroperbenzoic acid in $CHCl_3$[6], only a small quantity (4%) of α-levantenolide was obtained, a possibly biogenetic-type reaction[2]. A mixture (95%) of α- and β-levantenolide (40 and 60% respectively) was formed when the olefin 6 was oxidized with modified Collins reagent[7]. Stereospecificity was improved using NBS in dioxane/H_2O in the presence of $CaCO_3$[8] as oxidizer for 5 and 6. In the first case, the ratio between 8 and 9 was 4:1 while in the second, it was 3:7. In both cases the anomalous C_{12} isomer may be formed *via* the furan intermediate since 7 was also transformed



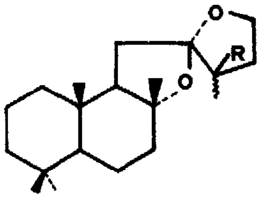
1a R = COOH

1b R = CH_2OH



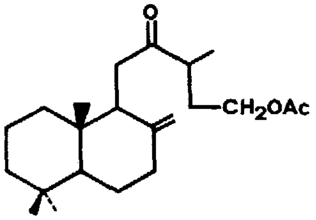
2a R = H

2b R = Br



3a R = H

3b R = Br



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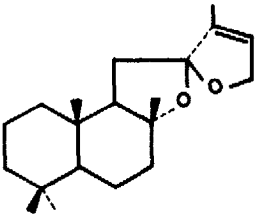

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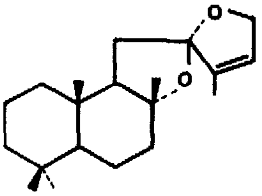

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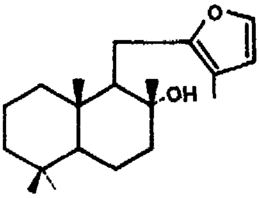

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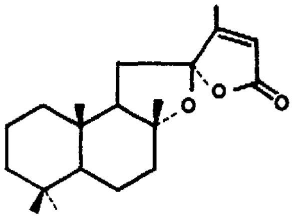

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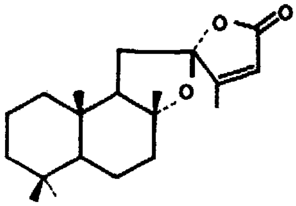

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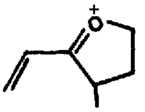
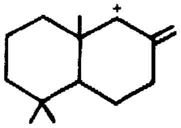


[a]



[b]

by this oxidation reaction to a mixture of 8 and 9.

The α- and β-levantenolide were identified by their physical constants, PMR, MS and the superimposability of their IR spectra.

All the new compounds gave correct elemental analysis. Optical activities were measured in $CHCl_3$ and PMR spectra in $CDCl_3$ (60 MHz).

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