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SYNTHESIS OF THE TERPENOID ANTIBIOTIC LL-Z1271α

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The structural elucidation of the terpenoid antibiotic I, labelled LL-Z1271α, which has been isolated together with a minor amount of the related lactol II from the fermentation products of an Acrostalagmus species, has been recently reported[1]

This report deals with the synthesis of I from the (+)ketolactone IV, easily available by degradation of marrubiin[2-5]

Bromination of IV in glacial AcOH (with traces amount of HBr) gave the bromoketone V (95%), * m.p. 149-150°, $[\alpha]_D$+35.9°, λ_{max}^{EtOH} 310 nm (ε 80.3), which by treatment with 1,5-diazabicyclo[4.3.0]-5-nonene[6] smoothly gave the unsaturated ketone VI (90%), m.p. 96.5°, $[\alpha]_D$-5.23°, λ_{max}^{EtOH} 228 nm (ε 6400) .

Reaction of VI with lithium ethoxy-acetylide in THF afforded an ethynyl carbinol (90%), m.p. 150-151°, $[\alpha]_D$-219.6° to which we assigned structure VII as we can safely assume the attack from α-side to be the preferred one[5] .

The conjugate system present in I was easily made by very brief treatment of VII with conc H_2SO_4 in 95° EtOH . The reaction gave the conjugated ester VIII (65%), m.p. 116-118°, $[\alpha]_D$-307°, λ_{max}^{EtOH} 254 nm (ε 6300), besides a minor amount of the hydroxy ester IX[7] (28%), m.p. 92.5-93°, $[\alpha]_D$-94.8° .

The oxidation of VIII with SeO_2 (2.5 moles) in glacial AcOH afforded i) a lactol (the major product) m.p. 241-245°, $[\alpha]_D$-255.6°, λ_{max}^{EtOH} 257 nm (ε 15000) [lit.[1] m.p. 241-247°, $[\alpha]_D$ -256° , λ_{max}^{EtOH} 257 nm (ε 15400)], which has NMR and IR spectra identical to those reported for natural II[1] , too; ii) the lactone X, m.p. 191-193°, $[\alpha]_D$-323°, λ_{max}^{EtOH} 261 nm (ε 8750); iii) an

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* Satisfactory analyses were obtained for all compounds reported . M.p.'s were determined on a Kofler block and are uncorrected . Specific rotations were determined in chloroform solutions at room temperature .

acetate, m.p. 220-222°, $[\alpha]_D$-213°, λ_{max}^{MeOH} 258 nm (ε 12800) . Analysis of the NMR spectrum of this latter showed it to be XI, the C_{14}-epimer of the described III[1] . The C_{14} proton resonance, that occurs at δ 6.91 as a singlet * due to the very small allylic $J_{7,14}$ value[8], conclusively shows it to be pseudo-equatorial (α-oriented) ** .

The formation of XI requires the existence of an equilibrium between II and its C_{14}-epimer XII and, in addition, the preferential acetylation of this latter . However owing to the lacking of the C_9 and C_{12} syn-diaxial hydrogens in the lactol XII, the observed esterification of the epimer bearing the pseudo-axial 14-OH is not surprising .

The acetylation of II with pyridine/Ac_2O gave a 1:2 mixture of XI and of the known III . Fractional crystallization easily gave pure III, m.p. 205-206°, $[\alpha]_D$-136°, λ_{max}^{MeOH} 257 nm (ε 14000) [lit.[1] m.p. 205-210°, $[\alpha]_D$-145°, λ_{max}^{MeOH} 257 nm (ε 14000)], NMR and IR spectra identical to those reported[1] .

Treatment of XI, III or of their 1:2 mixture with HCl/MeOH almost quantitatively gave a 3:1 mixture of two epimeric methyl derivatives that were separated by PLC .

The major product was XIII, m.p. 153-155°, $[\alpha]_D$-250.6°, λ_{max}^{MeOH} 259 nm (ε 10000), NMR: δ 1.18 (3H,s), 1.32 (3H,s), 1.92 (1H,d,J=4,5 c/s), 3.53 (3H,s), 5.00 (1H,t), 5.54 (1H,s), 5.73 (1H,d,J=1,8 c/s), 6.34 (1H, double d), which clearly is the C_{14}-epimer of the minor product I, m.p. 215-217°, $[\alpha]_D$-201°, λ_{max}^{MeOH} 257 nm (ε 13100) [lit.[1] m.p. 214-215°, $[\alpha]_D$-203°, λ_{max}^{MeOH} 257 nm (ε 13500)], NMR and IR identical with those of the natural product .

As (±) ketolactone IV has been recently[11] synthetized , this work constitutes a total synthesis of the title compound .

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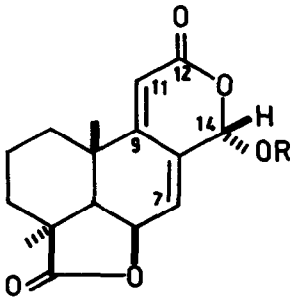
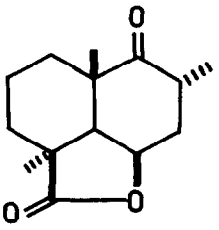
* In the NMR spectrum of the natural epimer III the C_{14} pseudo-axial proton appears at δ 7.02 as a triplet with $J_{7,14} \simeq 2,0$ c/s[1] .

** The C-CO-O-C grouping in X and III is assumed to be planar[9,10] .



I R=CH_3
II R=H
III R=Ac



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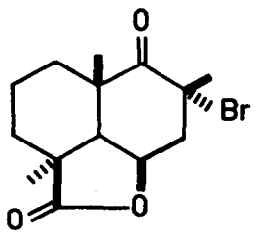
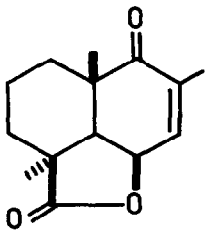
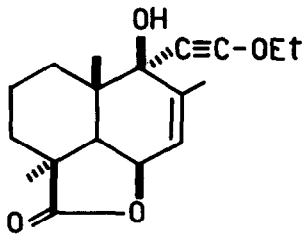


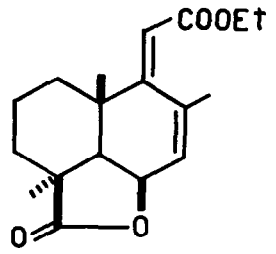
V



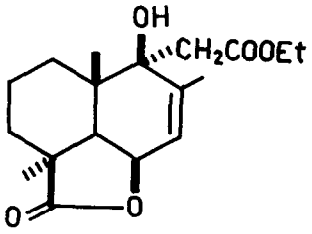
VI



VII



VIII



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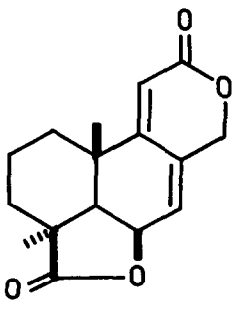
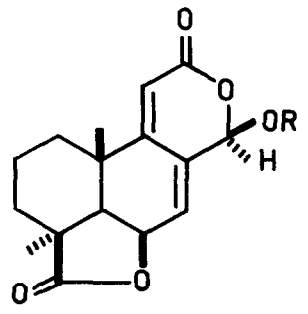


X



XI R=Ac
XII R=H
XIII R=CH_3

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