Tetrahedron Letters No. 29, pp 2691 - 2694.
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0040-4039/79/0715-2691$02.00/0

GERMACRA-1(10),4-DIENE-CIS-6,12-OLIDES: A NOVEL STEREOCHEMICAL GROUP OF NATURAL SESQUITERPENIC LACTONES FROM URSINIA ANTHEMOIDES (L.) POIRET[1]

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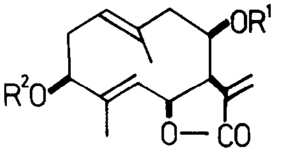
Abstract. New stereochemical group of germacranolides - germacra-1(20),4-diene-cis-6,12-olides - was identified on the basis of ^{1}H-NMR and X-ray analysis.

Several years ago the isolation of three new sesquiterpenic lactones from the above-ground parts of the species Ursinia anthemoides (L.) POIRET (Family Compositae, Tribe Anthemidae) was published, which were named ursiniolide A ($C_{22}H_{28}O_7$, m.p. 140-142 °C, and $[\alpha]_D^{20}$ -237°), ursiniolide B ($C_{24}H_{32}O_9$, m.p. 152-154 °C, $[\alpha]_D^{20}$ -217°), and ursiniolide C ($C_{20}H_{26}O_6$, m.p. 173-175 °C)[2]. The fundamental structural aspects of these substances followed from the elemental composition, IR spectra, mass spectra, and especially from a detailed analysis of the IR and ^{1}H-NMR spectra[3,4] which showed that in all cases γ-lactones of germacra-1(10),4-dienolides were involved, differing only in the number and character of the ester groups, and that the structure expressed by formula I (ursiniolide A), II (ursiniolide B), and III (ursiniolide C) should be assigned to them. These structures are now supported by the X-ray analysis of ursiniolide A.

The conformation in the solution is characterized by the following facts: a) pyrolysis of ursiniolide B (carried out directly in a sealed NMR-sample-tube at 210 °C under nitrogen) afforded the usual Cope's product IV; b) NOE-experiments indicated that both endocyclic double bonds were trans, i.e., that it was an E,E-isomer; c) Under this assumption (b) it follows from the observed values of allylic couplings $|J_{7,13}$ (transoid)$|$ = 2 - 2.2, $|J_{7,13}$ (cisoid)$|$ = 1.9 - 2 that it must be a cis-lactone. According to the generalized lactone rule[5,6] $|J_{7,13}$ (lactone type S)$| \geqslant 3 > |J_{7,13}$ (lactone type A)$|$, the constants $J_{7,13}$ imply a pseudorotational A-type of lactone ring. In the case of the E,E-isomer of germacra-1(10),4-diene-6-12-olides the following situation is typical: the trans lactones are of type S while the cis-lactones are of type A. On the contrary $|J_{7,13}| = 3.3$ and $|J_{7,13'}| = 3.2$ Hz were found in elemanolide IV. These values now indicate the pseudorotational type S of the lactone ring. This fact is in accordance with the cis-configuration of the lactone-ring. In cis-lactones bound to a six-membered ring the S-type is typical of the chair conformation with an axial $C_{(7)} - C_{(11)}$ bond[5]. In fact the realization of such chair-like conformation is also supported by the value of $J_{5,6} = 12$ Hz indicating a diaxial configuration of $H_{(5)}$ and $H_{(6)}$. All these aspects lead to the assumption that the ten-membered homocycle has in solution a chair-boat conformation represented schematically by formula V, and the elemanolide IV has the chair-conformation VI. A change of the boat conformation of the fragment $C_{(5)}$-- ... -- $C_{(10)}$ in compound V to the chair conformation in compound VI, accompanied by a change in the conformation of the lactone ring from type A to type S, energetically disfavours the reversible path VI ⟶ V in consequence of the different geometry of the transition state. This would permit an easy explanation of the observed quantitative formation of VI.

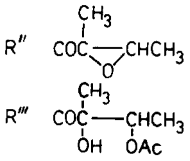


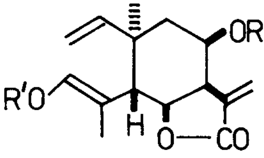
I $R^1 = R''$, $R^2 = R'$

II $R^1 = R'''$, $R^2 = R'$

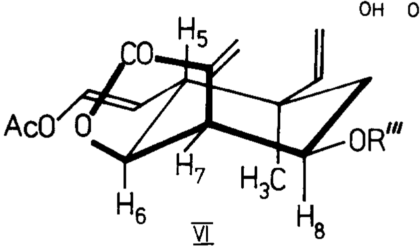
III $R^1 = R''$, $R^2 = H$

R' · Ac

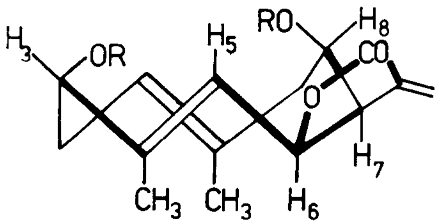




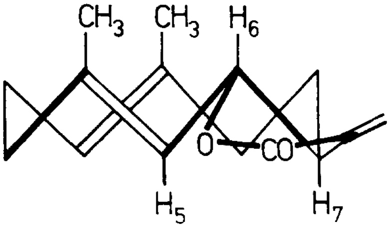
IV



VI



V



VII

X-Ray analysis[4] was carried out for ursiniolide A. The compound crystallized from butyl alcohol as a monohydrate. Diffraction-pattern indicated space group $P4_1$ or its enantiomer $P4_3$. Unit cell parameters: a=b=13.921 (2), c=11.187 (1) A. The structure was solved by direct methods from intensity data collected on a Syntex $P2_1$ diffractometer, and the least-squares adjustment of the atomic parameters converged to R 0.043 over 1321 reflections. The calculations were carried out in arbitrarily chosen $P4_1$ space group. A perspective view of the molecule is shown in Figure 1.

In the solid state the ten-membered trans-trans germacradiene ring adopts a chair-boat conformation with syn-orientation of the two methyl groups (C(14) and C(15)) on the α-face of the macrocycle. The five-membered lactone ring is cis-fused to the ten-membered ring and adopts a distorted half-chair conformation.

We propose the absolute configuration of ursiniolides on the basis of CD studies. In contrast to E,E-isomers of the series of 7 H-germacra-1(10),4-diene-trans-6,12-olides (substances of the costunolide type) with cross-conjugated double bonds of the type $({}^{15}D_5, {}_1D^{14})^6$, and having CD maxima about 220 nm in the positive region, the CD curves of ursiniolides have maxima at a similar wave-length in the negative region. This is in agreement with the assumed conformation of type $({}_{15}D^5, {}^1D_{14})^6$, since in the 7αH-series both trans-annular conformations of the double bonds are pseudoenantiomeric (compare the symbolic crown-representations of 7αH-E,E-isomers of the chair-boat conformation of ursiniolides V and the chair-conformation of costunolide VII). Hence, it is very probable that ursinolides belong to the series of 7αH-germacranolides, too.

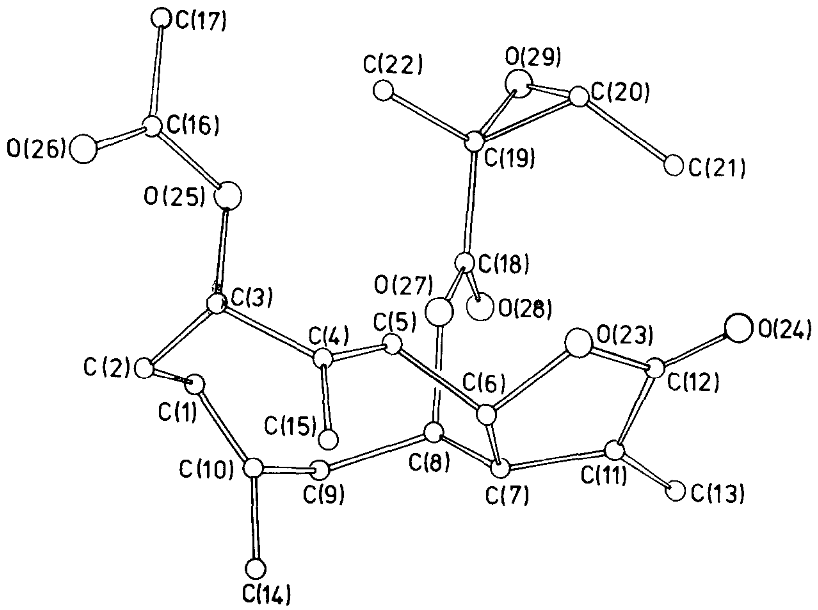


Fig. 1. View of the α-face of the molecule of ursiniolide A.

So far about 92 germacranolides have been described among which about 75 have a lactone group closed at C(6), and of which 71 have been characterized as trans-lactones (4 compounds do not have the stereochemistry of the lactone group determined). About 17 germacranolides with a lactone closure at C(8) have been described so far, among which 13 substances have a trans-annelated lactone group, and only 2 have a cis-annelated lactone ring (in the case of 2 compounds the stereostructure of their lactone ring is as yet undetermined). From these rough statistics it follows that cis-lactones in the series of germacranolides are very rare, and ursiniolides are the first germacranolides described with a lactone ring closed at C(6) and cis-annelated to a ten-membered homocycle.

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   Ursiniolid A: 5.72 bd ($\underline{H}_5$; $J_{5,6}$ = 11; $J_{5,15}$ = 1.4), 5.35 dd ($\underline{H}_6$; $J_{6,5}$ = 11; $J_{6,7}$ = 7), 3.38 bd ($\underline{H}_7$; $J_{7,6}$ = 7; $J_{7,8}$ = 1 - 3), 5,1 - 5.45 ($\underline{H}_1$, $\underline{H}_3$, $\underline{H}_8$), 2.78 ba ($\underline{H}_9$; $J_{9,9'}$ = 15), 5.78 d ($\underline{H}_{13}$, $J_{13,7}$ = 1.9; $J_{13,13'}$ = 0), 6.36 d ($\underline{H}_{13}$; $J_{13,7}$ = 2) 1.46 bd ($\underline{H}_{14}$; $J_{14,1}$ = 1.2); 1.81 bd ($\underline{H}_{15}$; $J_{15,5}$ = 1,4), 2.00; CH_3CH  $C(CH_3)$-CO-(1.61s(3H); 1.22 d (3H; J = 5.35); 3.03 q (1H; J = 5.35)).
4. A complete description of the X-ray and NMR results will be published separately.
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(Received in UK 24 April 1979)