Tetrahedron Letters No. 29, pp 2489 - 2492, 1976. Pergamon Press. Printed in Great Britain.

X-RAY STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF STEMOLIDE, A NOVEL DITERPENE BISEPOXIDE[1]

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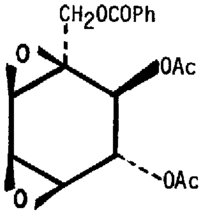
(Received in USA 16 April 1976; received in UK for publication 10 June 1976)

The isolation of the experimental anti-tumor compounds crotepoxide (**1**)[2] and the triptolides (**2** and **3**)[3] by Kupchan and his collaborators has stimulated further interest in the role of certain epoxides as cytotoxic agents.[4] We now report the isolation of stemolide (**4**), a novel diterpene bisepoxide which is closely related to the triptolides, from the leaves of *Stemodia maritima* (Scrophulariaceae).[5] Stemolide and the triptolides are the only known diterpenes possessing an 18(4→3) *abeo*-abietane skeleton.

Stemolide (**4**), $C_{20}H_{26}O_4$ (M^+330), m.p. 235-237^0, has i.r.($CHCl_3$, 1750 and 1675 cm.$^{-1}$) and Raman (neat, 1770 and 1690 cm.$^{-1}$) spectra which, in conjunction with u.v. absorption at 218 nm (EtOH, ε=12,500), are indicative of an α,β-unsaturated γ-lactone. The absence of olefinic absorptions in the 'H n.m.r. spectrum suggests that the olefinic group is tetra-substituted.

The 'H n.m.r. spectrum ($CDCl_3$,δ)[6] of stemolide displays signals at 0.96 (3H,s,20-$C\underline{H}_3$), 0.91 (6H,d,J=7Hz,16-and 17-$C\underline{H}_3$), 3.15 (1H,d,J=3Hz,11-$C\underline{H}$), 3.50 (1H,d,J=3Hz,12-$C\underline{H}$), and 4.68 (2H,m,19-$C\underline{H}_2$). In addition, the Fourier transform ^{13}C n.m.r. spectrum ($CDCl_3$,p.p.m. from TMS)[7] of stemolide is in accord with structure **4** with absorptions at 13.7 (q, C-20), 17.1 (q, C-16), 17.6 (t, C-6), 18.3 (q, C-17), 23.1 (t, C-14), 27.6 (t, C-1 and C-7), 31.6 (d, C-15), 32.0 (t, C-2), 34.3 (d, C-8), 37.0 (s, C-10), 44.3 (d, C-5), 49.7 (d, C-11), 54.4 (d, C-12), 57.1 (s, C-13), 66.1 (s, C-9), 70.2 (t, C-19), 124.3 (s, C-3), 162.0 (s, C-4), and 173.5 (s, C-18). Assignments are based on chemical shifts and off-resonance decoupled spectra, and are tentative for C-1, C-6, C-7, and C-14.



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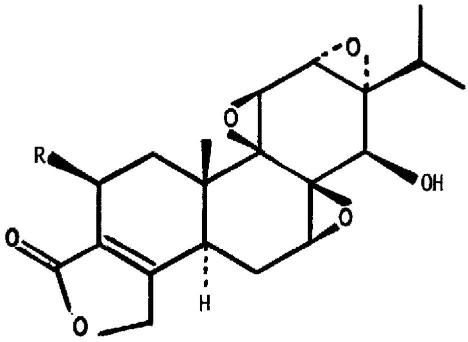
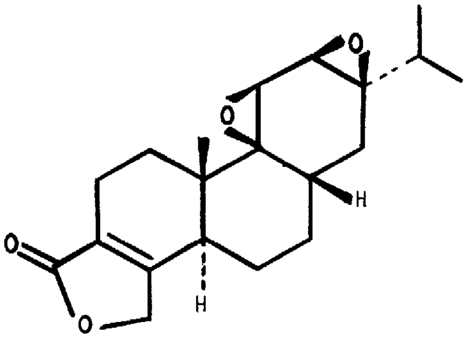




2, R=H (triptolide)

3, R=OH(tripdiolide)

4

The structure and absolute stereochemistry of stemolide were determined by X-ray crystallographic analysis. Crystals of **4** belong to space group $P2_12_12_1$, with a=11.305 (5), b=11.341 (8), c=13.540 (6) Å, and Z=4. Of a total of 2015 accessible reflections, which were measured on a computer-controlled four-circle diffractometer (θ-2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination), 1870 were considered observed [$I>2.5\sigma(I)$]. Application of a multiple solution procedure[8] with full-matrix least squares refinement (anisotropic and isotropic temperature parameters were used for non-hydrogen and hydrogen atoms respectively; hydrogens were held fixed at their calculated positions) led to the final discrepancy indices of R=0.046 and wR=0.055.

The absolute stereochemistry was established by taking into account the anomalous dispersion of oxygen ($\Delta f'=0.047$, $\Delta f''=0.032$). Two additional least squares refinements were made: in one the correct value of the imaginary part of the anomalous dispersion ($\Delta f''$) was used and in the other the sign of $\Delta f''$ was reversed (equivalent to refining the enantiomer). The configuration corresponding to the lower WR value (0.0554 _vs_. 0.0558) was taken as the absolute configuration, that corresponding to the higher WR value may be rejected at the 0.005 confidence level.[9] A stereoscopic drawing of **4** is shown in the Figure. The C.D. (dioxan, c=0.01M,25^{0}) of **4** gave $[\theta]_{254}$-4100, $[\theta]_{249}$-5200 and $[\theta]_{246}$-5225. The rotation of **4** was $[\alpha]_D^{25}$ -78°($CHCl_3$,c=1.0)

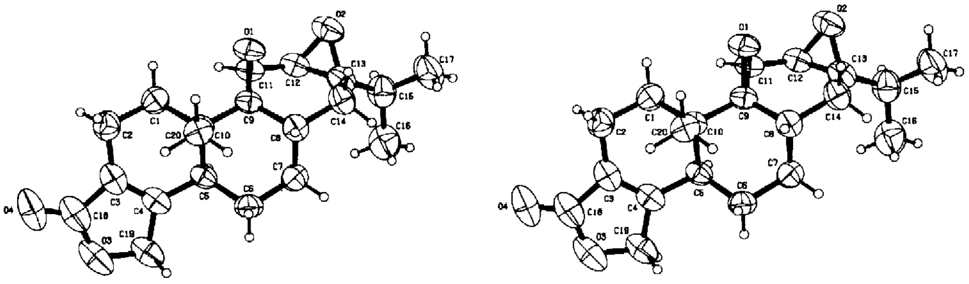
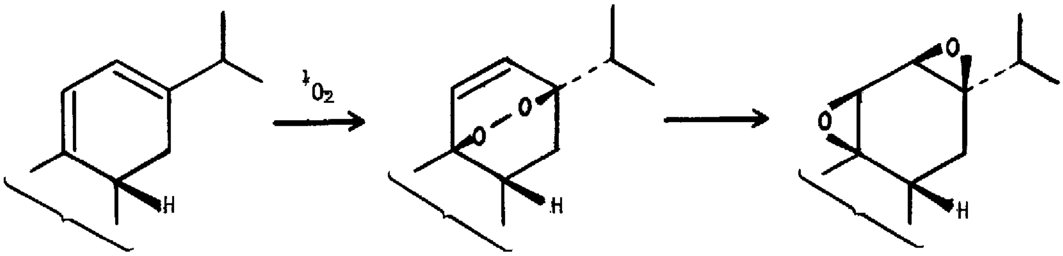


Figure. A stereoscopic view of stemolide (**4**).

Although nothing is known concerning the genesis of the epoxide groups in stemolide, one possibility involves reaction of singlet oxygen with a diene (A→B) followed by rearrangement of the resulting _endo_ peroxide (B→C).



A B C

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6. Assignments were aided by Eu(fod)$_3$ shift studies.

7. Recorded at 25.4 MHz on a Varian XL-100 instrument by Mr. R. G. Pitcher (Hoffmann-LaRoche, Nutley), to whom we are most grateful.

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