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STUDIES ON THE TOTAL SYNTHESIS OF TRIPTOLIDE. II.
THE C-RING FUNCTIONALITY OF TRIPTONIDE.

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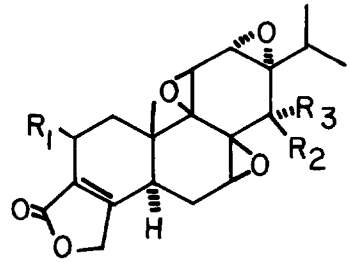
The isolation of triptolide (1), tripdiolide (2) and triptonide (3) by Kupchan and co-workers provided the first recognized diterpenoid triepoxides.[1] Of particular interest is the antileukemic activity of 1 and 2 and the hypothesis that the hydroxyl-assisted addition of nucleophiles to the 9,11-epoxide of 1 and 2 may mimic the mechanism by which they exert their antileukemic activity.[1]

Previously we have reported a stereospecific synthesis of 4 as an intermediate for the construction of the C-ring functionality in 1-3.[2] We report herein epoxidation studies with 4 and synthesis of 10 with C-ring functionality and stereochemistry corresponding to 3.

Reaction of 4 with t-butyl hydroperoxide in the presence of a catalytic amount of Triton B in benzene (45°, 48 hours) afforded, after preparative layer chromatography, pure 5 (89%).[3] Less than 5% of isomer 6 was present. The corresponding epoxidation of 4 with H_2O_2 in basic methanol gave a 1:2 mixture of 5 and 6, respectively. Sodium borohydride reduction of 5 afforded pure epimer 7 (100%, mp 170-172°)[4] the pmr spectrum of which suggests -O-H····π interaction[5] between the C-14 hydroxyl group and the C-9-C-11 double bond since the hydroxyl hydrogen appears as a doublet, J=11 Hz.[6] Epoxidation of 7 with m-chloroperbenzoic acid (CH_2Cl_2,Na_2CO_3 buffer) afforded 8 (37%, mp 180 - 181°) in which the stereochemistry of the new epoxide group was assigned β on the basis of the pmr spectrum in which the C-14 hydroxyl hydrogen appears as a doublet, J=11.6 Hz.[6]

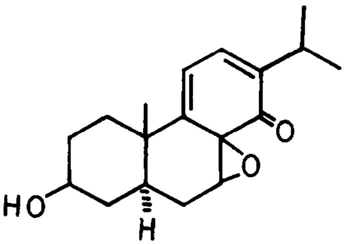
The structure and stereochemistry of 7, and consequently 5, 6, and 8, were determined by x-ray crystallographic analysis[7] of a crystal that contained one mole of solvent per mole of 7 on recrystallization from CH_2Cl_2. The crystals were monoclinic, space group



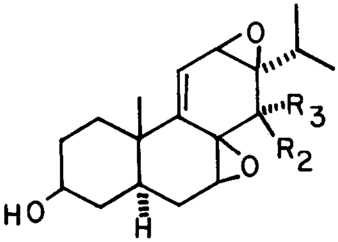
$\underline{1}$, $R_1 = H, R_2 = OH, R_3 = H$

$\underline{2}$, $R_1 = OH, R_2 = OH, R_3 = H$

$\underline{3}$, $R_1 = H, R_2{-}R_3 = O$

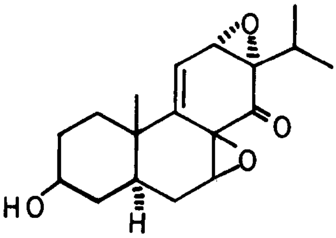


$\underline{4}$

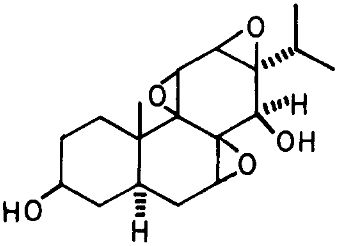


$\underline{5}$, $R_2{-}R_3 = O$

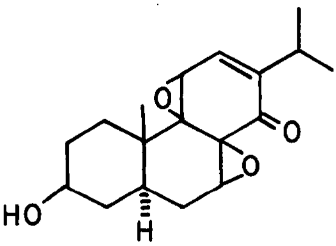
$\underline{7}$, $R_2 = OH, R_3 = H$



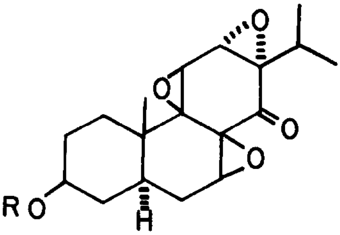
$\underline{6}$



$\underline{8}$



$\underline{9}$



$\underline{10}$, $R = H$

$\underline{11}$, $R = ClCH_2\overset{O}{C}-$

$P2_1/c$, with a = 9.939 (1), b = 21.974 (3), c = 9.482 (1) Å,β = 105.92 (1)°, and d_{calcd} = 1.305 g cm^{-3} for z = 4. A total of 2685 reflections were measured for θ < 57°, of which 1774 were considered to be observed [$I > 2.5\ \sigma(I)$]. The final discrepancy indices were R = 0.061 and wR = 0.063. The final difference map had no peaks greater than ±0.2 e A°$^{-3}$.

Epoxidation of 4 with *m*-chloroperbenzoic acid in CH_2Cl_2 afforded a mixture from which 9 (mp 165-167°) could be obtained in 32% yield by preparative layer chromatography. Further epoxidation of 9 with H_2O_2 in basic methanol gave 10 (63%, mp 160 - 161°) with the C-ring functionality and stereochemistry of 3.

The structure and stereochemistry of 10 were determined by x-ray crystallographic analysis[7] of chloroacetate ester 11. The crystals were monoclinic, space group $P2_1/c$, with a = 6.786 (4), b = 10.548 (4), c = 27.616 (10), A,β = 91.74 (4)°, and d_{calcd} = 1.334 g cm^{-3} for z = 4. Of the 2676 independent reflections for θ < 57°, 1674 were considered observed. The final discrepancy indices were R = 0.068 and wR = 0.065. There were no peaks greater than ±0.2 e A^{-3} on the final difference map.[9]

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REFERENCES

1. S.M. Kupchan, W.A. Court, R.G. Dailey, Jr., C.J. Gilmore and R.F. Bryan, *J. Amer. Chem. Soc.*, 94, 7194 (1972);
   S.M. Kupchan and R.M. Schubert, *Science*, 185, 791 (1974).
2. F.T. Sher and G.A. Berchtold, *J. Org. Chem.*, 42, 2569 (1977).
3. Satisfactory spectral data have been obtained for all new compounds reported.
4. The reduction of 1 with $NaBH_4$ affords a mixture of epimers in which the α-alcohol predominates (ref. 1).
5. L. Ananthasubramanian and S.C. Bhattacharyya, *J. Chem. Soc. Perkin II*, 1821 (1977).
6. Both 1 and 2 contain a hydrogen-bonded 9,11-epoxy-14-hydroxy system in which the hydroxyl hydrogen appears as a doublet, J = 11 Hz (ref. 1).
7. The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu K α radiation, θ - 2θ scans, pulse height discrimination) and were corrected for absorption. The structure was solved by a multiple solution procedure (ref. 8) and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined.
8. G. Germain, P. Main and M.M. Woolfson, *Acta Cryst.*, A27, 368 (1971).

9. The crystal used for the structure analysis was twinned. It was possible to distinguish the two reciprocal lattices, which were resolved except for the h=4n levels. The intensity data were measured for one member of the twin. The 0kl data were assigned a separate scale factor because of overlap of symmetry equivalent reflections from the other member of the twin. The 4kl data were discarded due to overlap of non-equivalent reflections of the twin. A total of 1398 observed reflections were used for the refinement.

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