

## SHIKIMATE-DERIVED METABOLITES <sup>1</sup>

### REVISED STRUCTURE AND TOTAL SYNTHESIS OF PIPOXIDE

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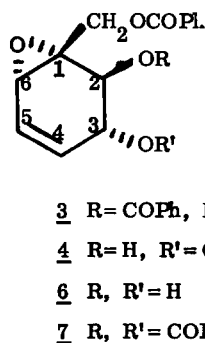
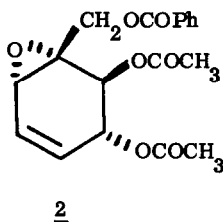
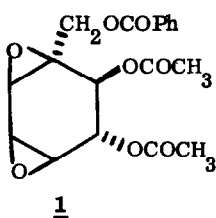
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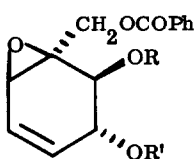
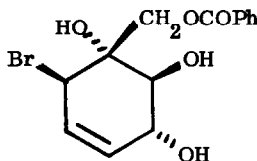
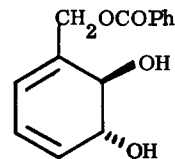
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The plant metabolites crotepoixide 1, <sup>3</sup> senepoxide 2, <sup>4</sup> and pipoxide 3 <sup>5</sup> belong to a family of highly oxygenated cyclohexane epoxides displaying an interesting spectrum of biological activity. Although several routes to racemic 1 and 2 have recently been described, a successful total synthesis of pipoxide has yet to be disclosed. <sup>6</sup>



We have discovered a more abundant source of pipoxide in the leaves of *Uvaria purpurea* (.15% purified yield, mp 152°,  $[\alpha]_D^{23} = +53^\circ$  ( $c = .02$ ,  $\text{CHCl}_3$ ); collected in Songkhla, Thailand) which provided material having physical properties identical with those previously reported.<sup>7</sup> However stereostructure 3 proposed for pipoxide in 1970<sup>5</sup> was not supported by our NMR measurements at 90 MHz, particularly in DMSO solution, which suggested that both the relative stereochemistry and the position of the secondary benzoate depicted in 3 must be revised. At the same time, ongoing synthetic work at Cornell resulted in unambiguous routes to the literature structure 3 and its regioisomer 4, confirming that neither was identical with the natural product. In this Letter we present convincing evidence that the correct structure of pipoxide is represented by 5.

5 R = H, R' = COPh10 R, R' = COPh89

Diol 6<sup>6</sup> was benzoylated under controlled conditions (1 equiv  $\text{PhCOCl}$ ,  $\text{Et}_3\text{N}$ ) to produce dibenzoate 4 [20%, NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.35-8.2 (2m, 10H, benzoates), 6.45 (dd,  $\text{H}_5$ ,  $J_{5,4} = 9$ ,  $J_{5,6} = 4$  Hz), 6.13 (ddd,  $\text{H}_4$ ,  $J_{4,5} = 9$ ,  $J_{4,3} = 5.3$ ,  $J_{4,6} = 1$  Hz), 5.58 (dd,  $\text{H}_3$ ,  $J_{3,4} = 5.3$ ,  $J_{3,2} = 2.5$  Hz), 5.18, 4.37 (AB q, C7 H's,  $J = 12$  Hz), 4.43 (d,  $\text{H}_2$ ,  $J_{2,3} = 2.5$  Hz), 3.46 (dd,  $\text{H}_6$ ,  $J_{6,5} = 4$ ,  $J_{6,4} = 1$  Hz)] along with tribenzoate 7 (40%).<sup>8</sup> Dibenzoate 3 was likewise obtained upon selective monotrifluoroacetylation at C3 of 6 followed by benzoilation and partial hydrolysis ( $\text{SiO}_2$ ) [15% overall from 6; NMR of 3:  $\delta$  ( $\text{CDCl}_3$ ) 6.28-6.43 (m, 2H, vinyl), 5.91 (d,  $\text{H}_2$ ,  $J_{2,3} = 2.5$  Hz), 4.83, 4.42 (AB q, 2H,  $J = 12$  Hz), 4.05-4.35 (broad m,  $\text{H}_3$ ), 3.68 (m,  $\text{H}_6$ )].<sup>8</sup> Clearcut differences were evident in the spectra and in chromatographic behavior of synthetic 3 and 4 and pipoxide. Moreover, exhaustive benzoilation of pipoxide furnished a tribenzoate<sup>8</sup> distinct from 7.

It seemed to us that pipoxide's  $\text{H}_2$ - $\text{H}_3$  coupling constant of 8 Hz was much closer to that found in crotepoxide ( $J_{2,3} = 9$  Hz, diaxial hydrogens) than in senepoxide ( $J_{2,3} = 2.5$  Hz) where  $\text{H}_2$  and  $\text{H}_3$  are diequatorial. On this basis, stereostructure 5 was formulated for pipoxide and verified both by x-ray

crystallography and by total synthesis.

Pipoxide crystallized in the monoclinic system with  $a = 8.885(1)$ ,  $b = 7.234(1)$ ,  $c = 13.994(1)$  Å and  $\beta = 98.75(1)^\circ$ . Systematic extinctions (0k0 missing if  $k = 2n + 1$ ) and the known chirality indicated space group  $P2_1$ . A calculated density of 1.27 ( $z = 2$ ) indicated one molecule of  $C_{21}O_6H_{18}$  per asymmetric unit. All unique diffraction maxima with  $2\theta \leq 114^\circ$  were collected on a fully automated four-circle diffractometer using graphite-monochromated  $CuK\alpha$  (1.54178 Å) radiation. After correction for Lorentz, polarization and background effects, 1293 (98%) of the 1314 reflections were judged observed. ( $F_o^2 \geq 3\sigma(F_o^2)$ ).

The structure was solved by direct methods using a multi-solution weighted tangent formula approach.<sup>9</sup> The weighted E synthesis corresponding to the most consistent set of phases showed 22 chemically reasonable atoms. The remaining non-hydrogen atoms were located on subsequent  $F_o$  synthesis. The positions of all the hydrogens were located on difference syntheses by searching at calculated values. Full matrix least squares refinement with anisotropic temperature factors for carbon and oxygen and isotropic temperature factors for hydrogen have converged to a final unweighted crystallographic residual of 0.036 for the observed reflections.<sup>10</sup>

Figure 1 is a computer-generated perspective drawing of the x-ray model of pipoxide. The epoxide and the C(2) hydroxyl are cis while the C(2) hydroxyl is trans to the C(3) benzoate group. The cyclohexene ring is quite flat with a mean distance from the least squares plane of 0.13 Å. Carbons (4), (5), (6) and (1) are approximately planar (0.08 Å mean deviation) and C(2) and C(3) are on opposite sides of this plane ( $\pm 0.24$  Å). The epoxide ring is inclined at ( $105^\circ$ ) to the C(5)-C(6)-C(1)-C(2) plane. The bond distances are in good agreement with those found for senepoxide and crotepoxide. The closest intermolecular contact is 2.85 Å for O(17)-O(19) indicating the presence of a weak hydrogen bond. All other distances for intermolecular contacts correspond to normal van der Waals interactions.

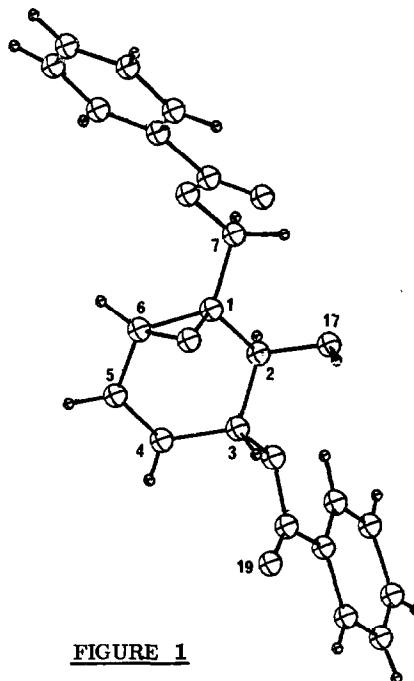


FIGURE 1

The synthesis of pipoxide's revised structure 5 began with epoxydiol 6 which cleanly formed bromohydrin 8 after 15 min exposure to 48% HBr-CHCl<sub>3</sub> [95% yield; m/e 343, 345 (M<sup>+</sup>)]<sup>8</sup>. Reduction of 8 (Zn, 1:1 HOAc:EtOH, 0°) furnished dienediol 9 [10%; δ 6.02 (m, 3H, vinyl)]<sup>8</sup>. Stereospecific and regiospecific monoepoxidation of 9 at the trisubstituted alkene (74%, MCPBA-CH<sub>2</sub>Cl<sub>2</sub>) and subsequent benzoylation yielded a racemic sample of 5 spectroscopically indistinguishable from naturally-occurring pipoxide.

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#### REFERENCES AND NOTES

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7. We are grateful to Dr. K. L. Dhar for providing an authentic sample of the original pipoxide. We also thank Professor E. J. Corey and Dr. Homer L. Pearce for recording its FT-NMR spectrum.
8. Satisfactory IR, NMR and mass spectral data were obtained for this compound.
9. All crystallographic calculations were done on a Prime 400 CPU operated by the Materials Science Center and Department of Chemistry, Cornell University. The program package has been described previously (J. Amer. Chem. Soc., **100**, 7079 (1978)).
10. Tables of fractional coordinates, thermal parameters, bond distances, bond angles and their errors have been deposited with the Cambridge Crystallographic Data Center.

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