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STRUCTURES OF β-SENEPOXIDE, TINGTANOXIDE, AND THEIR DIENE PRECURSORS. CONSTITUENTS OF *UVARIA FERRUGINEA*.[1]

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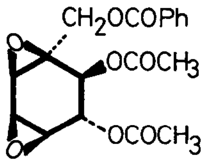
Summary: β-Senepoxide 9, Tingtanoxide 10, and their diene precursors 7 and 8 were isolated from *Uvaria ferruginea* (Annonaceae). Their structures and absolute configurations were deduced using spectroscopy and chemical correlations with compounds of known stereostructures.

Recent work[2,3] has revealed that plants in the *Uvaria* genus are a rich source of cyclohexene epoxides and derivatives thereof. Interestingly, until 1979 only three compounds, ie. Crotepoxide 1,[4] Senepoxide 2,[5] and Pipoxide 3a[6] had been isolated from nature, and thus represent only a small class of plant metabolites. Subsequent isolation of zeylena 4[3] provided further insight into the biogenesis[7] of these compounds, with the suggestion that 4 is formed from an enzyme catalysed 2+4 cyclo-addition reaction of the hypothetical diene intermediate 5.[3] Since then, our work on *Uvaria purpurea* has led to the discovery of the first of such an intermediate, the "missing link", diene 6[8] and we now wish to report the isolation of further diene intermediates 7 and 8 together with their epoxidised products, β-Senepoxide 9[9] and Tingtanoxide 10, from *Uvaria ferruginea*, or "Tingtang" as the plant is known in northeastern Thailand.



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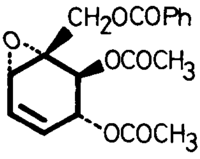

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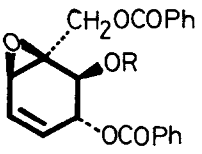
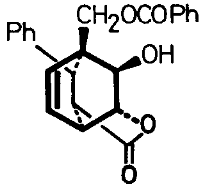


3 a, R=H
b, R=$COCH_3$

Hexane extraction of the dried roots of *Uvaria ferruginea* (collected from northeastern Thailand) afforded, after purification by column chromatography (silica gel, ethyl acetate: hexane = 1:5) followed by PLC (silica gel, benzene), 7, 8, 9, and 10 in 0.005, 0.006, 0.05, and 0.08% purified yields respectively.



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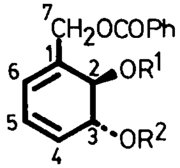
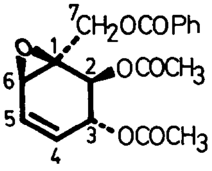


5 R^1=H, R^2=COCH=CHPh
6 R^1=H, R^2=COPh
7 R^1 = R^2=$COCH_3$
8 R^1=$COCH_3$, R^2=COPh



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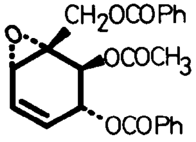

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Structural similarities between the two dienes 7 and 8 were apparent from their spectroscopic data.[10] The NMR spectrum of 7 [$[\alpha]_D^{28}$ -233° (c 0.38, $CHCl_3$); IR ($CHCl_3$) 1730, 1740 cm^{-1}; λ_{max}^{EtOH} 264 nm (ε 6,470)] showed the presence of two acetates (δ 2.03, 2.05, singlets), one benzoyl (δ 7.32-8.13, m) and a two proton singlet (δ 4.89) for the C-7 methylene group, while the spectrum of 8 [$[\alpha]_D^{28}$-298° (c 0.37, $CHCl_3$); IR ($CHCl_3$) 1720, 1740 cm^{-1}; λ_{max}^{EtOH} 264 (ε 7,080)] indicated the presence of one acetate (δ 2.02, s), two benzoyls (δ 7.30-8.11, m) and a methylene at δ 4.91. Evidence for the relative stereochemistry at C-2 and C-3 in 7 and 8 was also obtained from their NMR spectra, with 7 displaying the signals of H-2 and H-3 at δ 5.78 (d, J=6 Hz) and 5.45 (dd, J=6 and 3.5 Hz) and 8 displaying the corresponding signals at δ 6.08 (d, J=6.5 Hz) and 5.76 (dd, J=6.5 and 3.5 Hz), which indicated a *trans*- relationship at C-2 and C-3 for both compounds. The Mass Spectra (EI) of 7 and 8 were very similar in pattern and also very informative. The diene 7 showed a mass ion, m/e at 330 (6%) and the ions 270 (M^+ -CH_3COOH, 20%), 228 (M^+ -CH_3COOH -CH_3CO, 100%), 210 (M^+ -2xCH_3COOH, 15%), and 208 (M^+ -PhCOOH, 10%) were detected. Similarly the diene 8 with the mass ion of 392 (0.5%) gave the following fragment ions: 332 (M^+ - CH_3COOH, 10%), 270 (M^+ -PhCOOH, 7%), 228 (M^+ -PhCOOH -CH_3CO, 100%), and 148 (M^+ -2xPhCOOH, 14%). At this stage, although the *trans*- relative stereochemistry at C-2 and C-3 in both 7 and 8 had been deduced, their absolute stereostructures as well as the positions of the -$OCOCH_3$ and -OCOPh groups in 8 were not yet secured. These were subsequently proved unambiguously by chemical correlations which will be discussed later.

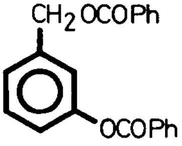
β-Senepoxide 9, mp. 72-73° C, [$[\alpha]_D^{25}$ +62° (c 0.55, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1} broad; λ_{max}^{EtOH} 273 (ε 1,140), 280 (ε 930); MS, 346 (M^+, 2.5%), 303 (M^+ -CH_3CO, 7%), 226 (M^+ -2xCH_3COOH, 3%), 122 (PhCOOH, 35%), and 105 (PhCO, 100%)] displayed a very interesting NMR spectrum. The two acetates resonated at δ 2.02 and 2.12, the C-7 methylene protons appeared as an AB system at δ 4.36 and 4.62 (J=12.5 Hz), and the only benzoyl group showed a multiplet at δ 7.40-8.12. Protons attached to C-6, C-5, and C-4 of the cyclohexene-epoxide nucleus appeared at δ 3.57 (dd, J=4, 2 Hz), 6.07 (ddd, J=10, 4, 2 Hz), and 5.76 (dt, J=10, 2 Hz) respectively. However, the most informative absorptions in the NMR spectrum of 9 were the resonances of the protons at C-2 (δ 5.68, d, J=8.5 Hz) and C-3 (δ 5.52, dt, J=8.5, 2 Hz) whose coupling constant (8.5 Hz) allowed assignment[2,11] of the steric $-CH_2OCOPh$ group to the α-side of the molecule, hence the epoxide ring to the β- side as shown in 9.

On the other hand, the NMR spectrum[12] of Tingtanoxide 10 [$[\alpha]_D^{28}$ -306° (c 6.31, $CHCl_3$); IR ($CHCl_3$) 1720, 1740 cm^{-1}; λ_{max}^{EtOH} 273 (ε 1,900), 280 (ε 1,400); MS, 408 (M^+, 2.5%), 348 (M^+ $-CH_3COOH$, 2%), 286 (M^+ -PhCOOH, 1%), 122 (PhCOOH, 12%), 105(PhCO, 100%)] was almost identical to the reported spectrum of Senepoxide 2[5,9] except for the presence of two benzoyl and only one acetyl groups (instead of vice versa). The value of the C-2, C-3 protons' coupling constant (2.5 Hz) dictated the α- stereochemistry of the epoxide ring.[2,11] Also, the NMR spectrum of 10 was clearly different from that of Pipoxide acetate 3b [$[\alpha]_D^{28}$ +9° (c 4.38, $CHCl_3$)] prepared by direct acetylation of Pipoxide 3a.[2]

Acetylation (CH_3COCl, Et_3N, CH_2Cl_2, RT., 12 hr) of (-)1,6 Desoxypipoxide 6 of known absolute stereochemistry[8] (previously isolated from *Uvaria purpurea*) afforded the aromatic product 11 (64%)[13] and the diene 8 [27%, $[\alpha]_D^{28}$ -285° (c 0.2, $CHCl_3$)] identical in all respects with the natural product. Epoxidation (MCPBA, CH_2Cl_2, 0°, 5 hr) of the natural 8 yielded Tingtanoxide 10 [$[\alpha]_D^{27}$ -221° (c 0.1, $CHCl_3$), 17%], Pipoxide acetate 3b (20%), and the 4,5-epoxide 12 (40%).[14]

Moreover, epoxidation of the diene 7 under the same reaction conditions gave β-Senepoxide 9 [21%, $[\alpha]_D^{28}$ +60° (c 0.12, $CHCl_3$)], Senepoxide 2 [4%, $[\alpha]_D^{28}$ -185° (c 0.11, $CHCl_3$)],[15] and 13 (29%).[14]

Since the absolute configurations of Senepoxide 2 and Pipoxide 3a are already known these results establish not only the positions of the $-OCOCH_3$ and -OCOPh groups in the diene 8 and the epoxide 10 but also the absolute stereochemistry of the natural products 7, 8, 9, and 10.



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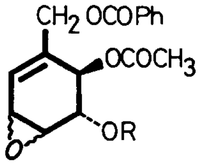
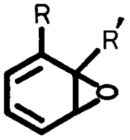


12, R=COPh
13 R=COCH3



14 a,R=CH2OCOPh,R'=H
b,R=H, R'=CH2OCOPh

The isolation of these four compounds from *Uvaria ferruginea* is particularly interesting from the view-point of cyclohexene-epoxide biosynthesis. It has been proposed[3] that cyclohexene-epoxides arise from epoxidation of diene intermediates (ie. 5 - 8) which, in turn, are products from the ring opening of arene-oxides 14a or 14b.[3] The detection of 7 - 10 within the same plant is therefore of biosynthetic significance since it provides strong evidence for the proposed pathway.

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9. It should be noted that 9 is infact the epoxide stereoisomer of the well known Senepoxide 2, here arbitrarily assigned as α-Senepoxide, hence 9 becomes β-Senepoxide.
10. Optical rotations (except for 9) were determined with a Bellingham and Stanley Model D Polarimeter; UV spectra were recorded with a Shimadzu (UV-240) UV-Visible Spectrophotometer; IR spectra were recorded with a Beckman IR 20A Spectrophotometer; MS were recorded with a DuPont 21-490B GC-MS instrument, and the Varian EM 360L Spectrometer was used for the low resolution NMR. Elemental analysis were performed by The Department of Science Service, Ministry of Science, Technology, and Energy. Although compounds 7, 8, and 10 were analytically pure we were unable to induce crystallization.
11. G.R.Schulte, B.Ganem; K.Chantrapromma, M.Kodpinid, K.Sudsuansri, Tetrahedron Lett., 23, 289 (1982).
12. NMR of 10: δ 2.06 (s, $OCOCH_3$), 3.48 (dd, J=3.5, 1.5 Hz, H_6), 4.28, 4.85 (AB system, J=12.5 Hz, $2xH_7$), 5.41 (dd, J=2.5, 4.5 Hz, H_3), 5.67 (d, J=2.5 Hz, H_2), 6.06 (ddd, J=9.5, 4.5, 1.5 Hz, H_4), 6.38 (dd, J=9.5, 3.5 Hz, H_5), 7.25-8.11 (m, 2xOCOPh).
13. Identified by direct comparison with a synthetic sample. Compound 11 is probably derived from 8 by elimination of acetic acid.
14. Two epoxide stereoisomers of 12 were isolated in 15% and 25%, but 13 was obtained as a single stereoisomer. The stereochemistry of the epoxide rings in these compounds have not yet been determined.
15. We have also isolated Senepoxide 2 from this same plant material (0.001% yield based on the dry weight of the roots of *U.ferruginea*).

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