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STUDIES ON HIGHLY OXIDIZED CYCLOHEXANES. CONSTITUTION OF A NEW KEY METABOLIC INTERMEDIATE.

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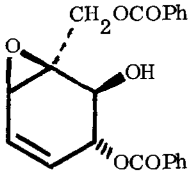
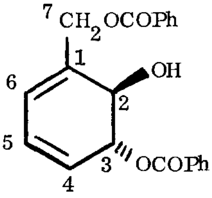
Summary: The absolute stereostructure of (-)1,6 desoxypipoxide (2), a new plant metabolite of biosynthetic significance was assigned by spectral interpretation and chemical correlation with (+)pipoxide (1).

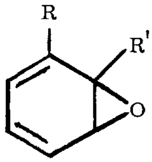
In the preceeding paper[1] we have unambiguously assigned absolute stereochemistry to several novel polyoxygenated cyclohexane metabolites, including (+)pipoxide (1). The biogenesis of these unusual compounds remains unknown, although hypothetical pathways involving arene oxides 3a[2,3] and 3b[3] have been suggested. In support of these proposals we wish to report the discovery and structure elucidation of (-)1,6 desoxypipoxide (2), a key intermediary metabolite isolated from Uvaria purpurea.



1



2



3a a $R=CH_2OCOPh$
$R'=H$
b $R=H$
$R'=CH_2OCOPh$

Specimens of the cosmopolitan shrub U. purpurea were collected near Songkhla, Thailand. Extraction of finely ground root with hexane, followed by silica gel column chromatography (ethyl acetate/hexanes, 1:1) furnished impure fractions of a new substance. Recrystallization afforded white needles, mp 90-91°C (benzene/hexane), $[\alpha]^{25}_{D}$ -276° (C 0.145, $CHCl_3$), in 0.0083% yield from wet root material. Spectroscopy indicated the presence of two benzoates [1720 cm^{-1}; λ^{EtOH}_{max} 229 nm (ε 25,450); δ 7.3 to 8.1 (10 H, complex)], hydroxyl [3590 and 3490 cm^{-1}; δ 2.72 (1 H, exchangeable)], and a trisubstituted homoannular diene [λ^{EtOH}_{max} 267 nm (ε 8,900), λ^{calc}_{max} 268 nm (Woodward's rules); δ 6.16 (2H, m) and 5.98 (1H, br ddd, J=8.5, 3.5, 2 Hz)].[4] The molecular formula, $C_{21}H_{18}O_5$, was ascertained from the highest peak in the CI mass spectrum, m/z 229

(M+H$^+$-benzoic acid) and was consistent with above mentioned functionality distributed about a 6-membered carbocyclic ring. Detailed stereochemical features were next adumbrated by double resonance studies.

Proton NMR decoupling experiments at 300 MHz clearly indicated two independent contiguous spin systems, exclusive of the benzoate groups. In the larger spin system, irradiation of the one proton resonance at δ 5.77 (H-3) caused signals δ 4.68 (H-2) and 5.98 (H-4) to collapse to a broad singlet and a doublet of doublets, respectively. Irradiating a 2 proton signal at δ 6.16 (H-5 and H-6) collapsed signal δ 5.98 to a broad doublet with 3.5 Hz residual coupling constant. Addition of D_2O to the sample eliminated the broad signal at δ 2.72 and sharpened the H-2 doublet at δ 4.68 ($\underline{J}$=7.5 Hz), thus indicating a secondary hydroxyl group. The smaller proton spin system consisted of the C-7 methylene appearing as an AB system, δ 5.11 (1H, d, $\underline{J}$=13.2 Hz) and 4.98 (1H, d, $\underline{J}$=13.2 Hz). Attaching the primary benzoate to C-1 thus completed the gross structure for (-) desoxypipoxide (2). Final confirmation of absolute configuration in 2 was obtained by its conversion to (+) pipoxide (1) with mCPBA [synthetic (+) -1 : $[\alpha]_D^{20}$ + 36.3° ($\underline{C}$ 0.67, $CHCl_3$); natural (+)-1 : $[\alpha]_D^{20}$ + 37.9° ($\underline{C}$ 0.16, $CHCl_3$)].[5]

Intermediary metabolite 2 maybe envisioned as arising from directed addition of benzoic acid to 3. Similarly, addition of cinnamic acid to arene oxide 3 would afford an intermediate triene that could furnish zeylena[3] by an enzyme-catalyzed intramolecular Diels-Alder reaction. The existence of arene oxide 3 may be difficult to prove, since such highly reactive species are in equilibrium with their oxepin valence tautomers and are usually converted to aromatic compounds under both acidic and basic conditions.[6]

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2) B. Ganem, G.W. Holbert, Bioorg. Chem., 6, 393 (1977).

3) S. D. Jolad, J. J. Hoffmann, K. H. Schram, J. R. Cole, M. S. Tempesta, R. B. Bates, J. Org. Chem., 46, 4267 (1981).

4) Other spectral data: CIMS (methane) m/z 229 (M+H$^+$-benzoic acid, 17%), 211 (M+H$^+$-benzoic acid-H_2O, 34%), 123 (benzoic acid + H^+, 58%), 107 (C_7H_7O, base), and 79 (11%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, br dd, $\underline{J}$=7.5, 3.5 Hz), AB system 5.11 (1H, d, $\underline{J}$=13.2 Hz) and 4.98 (1H, d, $\underline{J}$=13.2 Hz), and 4.68 (1H, br d, $\underline{J}$=7.5 Hz); IR ($CHCl_3$) 3030, 1605, 1455, 1320, 1270, 1110, 1070, 1030, and 950 cm^{-1}.

5) All other spectral data were identical with natural (+) pipoxide (2).

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