Synthesis of Desethanoqinghaosu, a Novel Analogue of the Antimalarial Qinghaosu

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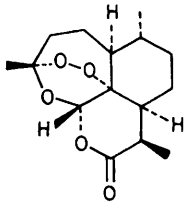
Desethanoqinghaosu, a novel potential antimalarial qinghaosu analogue containing the unique C–O–O–C–O–C–O–C=O (or cyclic peroxide lactone) moiety present in the natural product, has been synthesized from *R*-(+)-citronellal and its structure and stereochemistry have been verified from spectral data and a single-crystal *X*-ray analysis.

Two total syntheses[1,2] of qinghaosu [(**1**), arteannuin or artemisinin], a clinically useful antimalarial sesquiterpene lactone endoperoxide isolated from the Chinese drug Qinghao (*Artemisia annua*),[3,4] have recently been reported. Our previous studies[5] on structure–activity relationships and a programme of synthesis directed at the preparation of more active, simple analogues of (**1**) have led to the hypothesis that a requirement for the cyclic peroxide function to display antimalarial activity might involve the unique C–O–O–C–O–C–O–C=O moiety found in (**1**). We now report a stereoselective synthesis of desethanoqinghaosu (**2**), the first example of a simple analogue containing this structural feature.

As shown in Scheme 1, the synthesis of (**2**) involved an initial conversion of (*R*)-(+)-citronellal (**3**) into a dihydroxy compound (**4**) by known procedures.[6,7] Oxidation (70%) of (**4**) with Jones reagent followed by methylation (85%) with CH_2N_2 gave a ketomethyl ester (**5**). Wittig reaction of (**5**) with $MeOCH_2PPh_3Cl$ and Bu^nLi in dry Et_2O afforded an enol methyl ether (**6**) (40%). Photo-oxygenation[8] of a tetrahydrofuran (THF) solution of (**6**) with MeCHO in the presence of Rose Bengal at −70 to −78 °C under a bubbling stream of oxygen yielded a mixture of diastereoisomers [(**7a**) and (**7b**), (35%)], which were separated by h.p.l.c. ($MeCN:H_2O$ = 8 : 2, Nucleosil 100-C_{18}, 7 μm). The structures of (**7a**) and (**7b**) were elucidated by ^1H n.m.r. analysis,† and the stereochemistry of the former was confirmed by a single-crystal

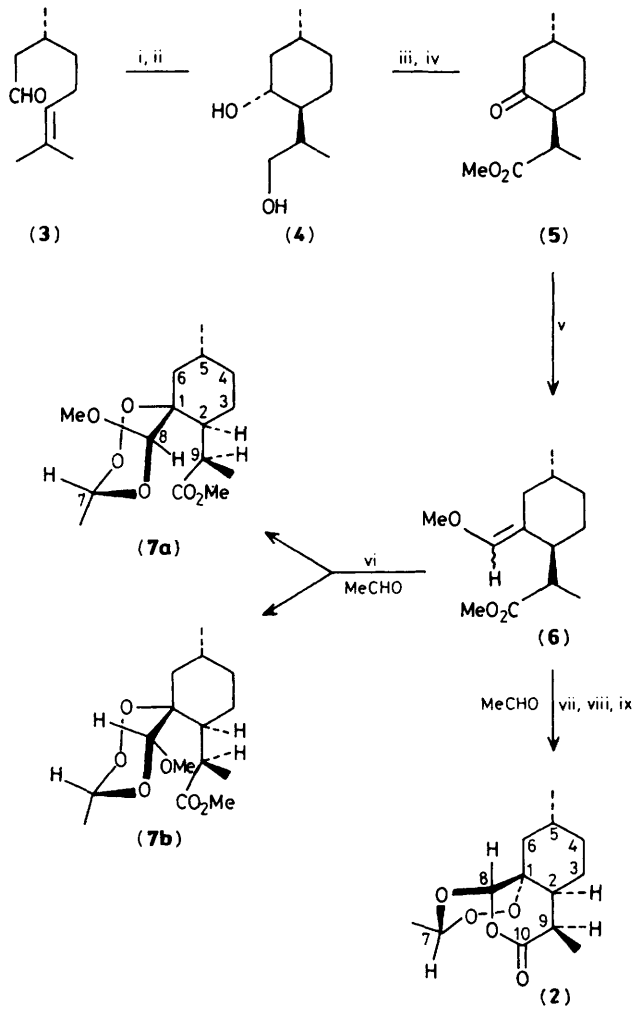


(**1**)

† *Spectroscopic data.* (**7a**): m.p. 88—89 °C (from $CHCl_3$/n-hexane); ^1H n.m.r.: δ 0.89 (3H, d, *J* 6.5 Hz, Me-5), 1.26 (3H, d, *J* 5.4 Hz, Me-7), 1.27 (3H, d, *J* 7.7 Hz, Me-9), 3.40 (3H, s, OMe-8), 3.62 (3H, s, CO_2Me-9), 3.80 (1H, dq, *J* 7.7 and 2.9 Hz, H-9), 4.79 (1H, s, H-8), and 5.61 (1H, q, *J* 5.5 Hz, H-7).

(**7b**): oil; ^1H n.m.r.: δ 0.88 (3H, d, *J* 6.4 Hz, Me-5), 1.21 (3H, d, *J* 7.1 Hz, Me-9), 1.36 (3H, d, *J* 5.7 Hz, Me-7), 3.48 (3H, s, OMe-8), 3.67 (3H, s, CO_2Me-9), 5.04 (1H, s, H-8), and 5.40 (1H, q, *J* 5.7 Hz, H-7).

(**2**): m.p. 95—96 °C (from MeOH/n-hexane); ^1H n.m.r.: δ 1.01 (3H, d, *J* 6.3 Hz, Me-5), 1.18 (3H, d, *J* 7.3 Hz, Me-9), 1.34 (3H, d, *J* 5.4 Hz, Me-7), 2.75 (1H, ddd, *J* 13.5, 3.9, and 1.8 Hz, H-2), 3.04 (1H, dq, *J* 7.3 and 3.9 Hz, H-9), 5.63 (1H, s, H-8), and 5.66 (1H, q, *J* 5.4 Hz, H-7).



Scheme 1. *Reagents and conditions*: i, $ZnBr_2$; ii, B_2H_6, $NaOH/H_2O_2$; iii, Jones reagent; iv, CH_2N_2; v, Bu^nLi, $MeOCH_2PPh_3Cl$; vi, $^1O_2$, Rose Bengal, THF, *hv*, −70 to −78 °C; vii, $^1O_2$, Rose Bengal, MeOH, *hv*, −70 to −78 °C; viii, HCl gas; ix, 60% $HClO_4$.

X-ray analysis (Figure 1).‡ Photo-oxygenation of a methanolic solution of (**6**) with MeCHO in the presence of oxygen and Rose Bengal at −70 to −78 °C followed by HCl gas treatment and acidic hydrolysis with 60% $HClO_4$ produced the target compound [(**2**), (15%)]. The complete structure and stereochemistry of (**2**) were elucidated by single-crystal *X*-ray analysis,‡ and ^1H n.m.r. spectroscopy.†

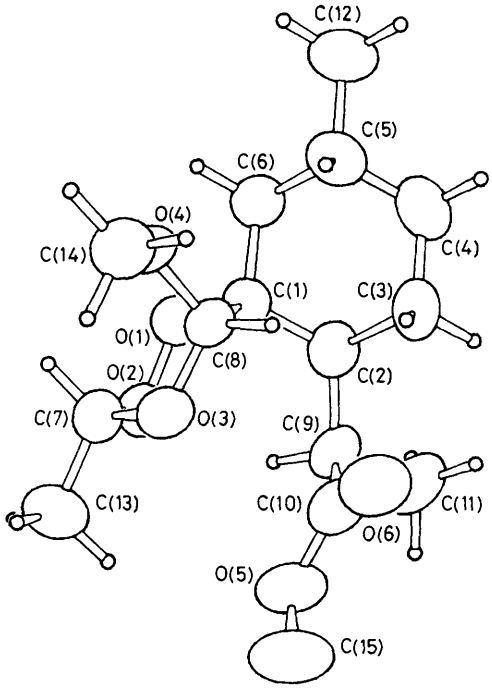


Figure 1. Structure and solid-state conformation of one of the molecules of (**7a**) in the asymmetric crystal unit; calculated hydrogen atom positions [C(15) hydrogens not defined by the analysis] are represented by small circles.

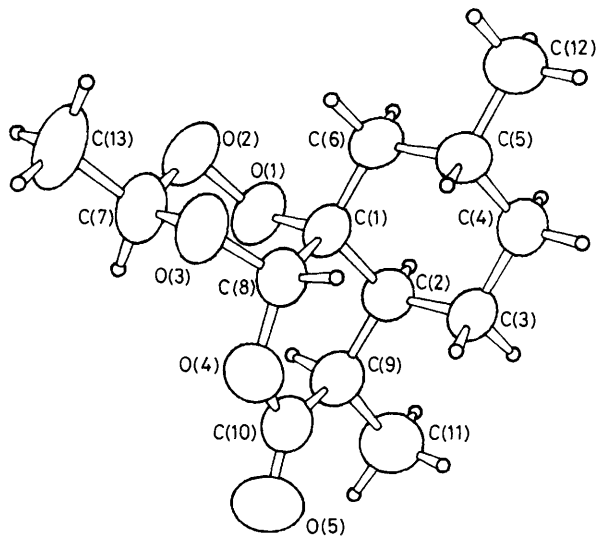


Figure 2. Structure and solid-state conformation of (**2**); small circles denote calculated hydrogen atom positions.

‡ *Crystal data*. (**7a**): $C_{15}H_{26}O_6$, M = 302.37, monoclinic, space group $P2_1$, a = 15.589(6), b = 9.494(4), c = 11.748(4) Å, β = 109.76(3)°, U = 1636.3 Å^3, Z = 4, D_c = 1.227 g cm^{-3}, μ(Cu-K_α) = 7.4 cm^{-1}.

(**2**): $C_{13}H_{20}O_5$, M = 256.30, monoclinic, space group $C2$, a = 19.944(6), b = 6.419(1), c = 10.721(2) Å, β = 93.31(2)°, U = 1370.2 Å^3, Z = 4, D_c = 1.242 g cm^{-3}, μ(Cu-K_α) = 7.5 cm^{-1}.

Intensity data [3104 and 1317 unique forms for (**7a**) and (**2**), respectively] were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-K_α radiation, λ = 1.5418 Å; incident-beam graphite monochromator; ω − 2θ scans, $\theta_{max.}$ = 67°). Data were corrected for the usual Lorentz and polarization effects; a decay correction was also necessary for (**7a**) which was unstable to *X*-irradiation. Both crystal structures were solved by direct methods. Initial non-hydrogen atom positions were derived from *E*-maps. Hydrogen atoms, save those on the ester methyl group of (**7a**), were located in difference Fourier syntheses. Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, O; calculated H positions) converged at R = 0.094, R_w = 0.114 for (**7a**) and R = 0.036, R_w = 0.049 for (**2**) over 2022 and 741 reflections, respectively, with $I > 3.0\,\sigma(I)$. Atomic co-ordinates, thermal parameters, and bond lengths and angles, have been deposited with the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Bioassay of (**2**), (**7a**), and (**7b**) as potential antimalarial agents is in progress.

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