The Preparation and Microbiological Hydroxylation of 10β,11-Oxido-4α,5α,7β-eremophilane

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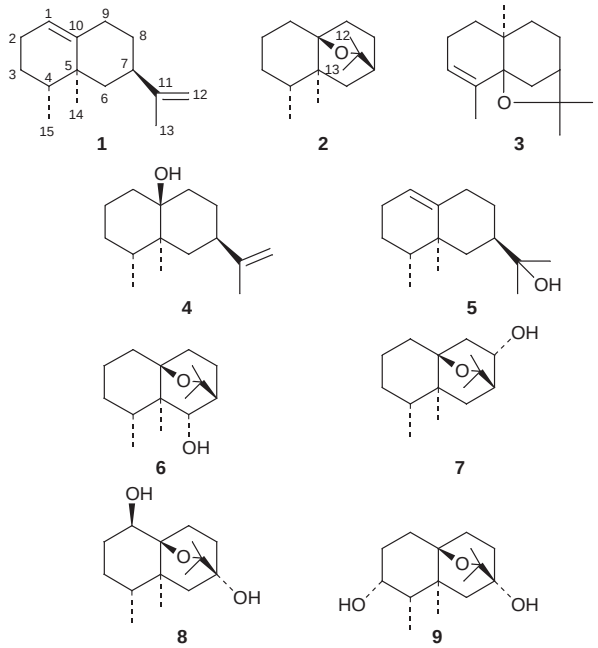
The preparation of 10β,11-oxido-4α,5α,7β-eremophilane by the oxymercuration of valencene, its microbiological hydroxylation at C-1, C-3, C-6, C-7 and C-8 by the fungus, *Mucor plumbeus*, and the X-ray crystal structures of two of the metabolites, are described.

The study of the microbiological hydroxylation of bridged polycyclic sesquiterpenoids provides a useful method of mapping the topology of microbial hydroxylases and thus of building a model to predict their scope. In the sesquiterpenoid series a transannular cyclic ether not only imposes a conformational rigidity on the structure but it may also act as a hydrogen bond acceptor. In this paper we report on the preparation of 10β,11-oxido-4α,5α,7β-eremophilane **2** from the readily available valencene **1**[1] and its hydroxylation by *Mucor plumbeus*. The formation of the ether bridge converts ring B of the eremophilane skeleton into a boat conformation.

Oxymercuration–demercuration[2] is a mild procedure for the hydration of double bonds and for making cyclic ethers from dienes.[4,5] Treatment of the diene, valencene **1** with mercuric acetate in aqueous tetrahydrofuran and reduction of the organomercury derivative with sodium borohydride gave four compounds: 10β,11-oxido-4α,5α,7β-eremophilane **2**, (42%), α-agarofuran **3** (2%),[7] 10β-hydroxy-4α,5α,7β-eremophil-11-ene **4** (2%) and 11-hydroxy-4α,5α,7β-eremophil-1(10)-ene (valerianol) **5** (20%).[9] Structure **2** has been assigned[6] to the fungal metabolite, hypodoratoxide, but the spectroscopic data are quite different and this assignment needs to be reconsidered.



Incubation of 10β,11-oxido-4α,5α,7β-eremophilane **2** with *Mucor plumbeus* afforded two monohydroxylated and two dihydroxylated products. The structures **6**–**9** of the metabolites were established by NMR spectroscopy and those for **6** and **8** were confirmed by X-ray crystallography (see Figs. 1 and 2).

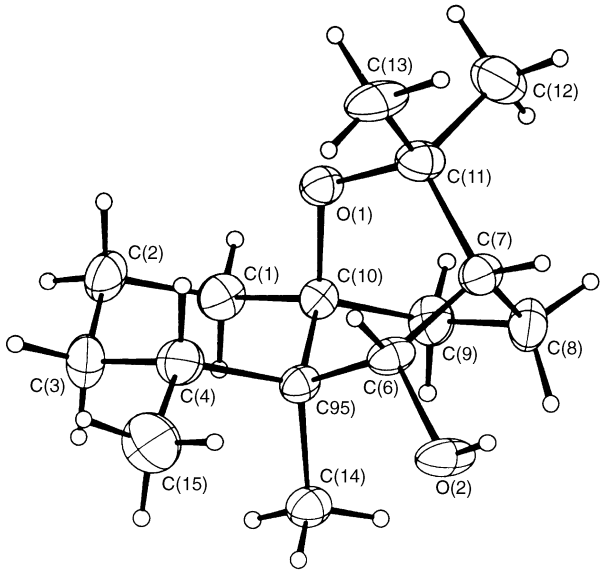


Fig. 1 X-Ray crystal structure of compound **6**

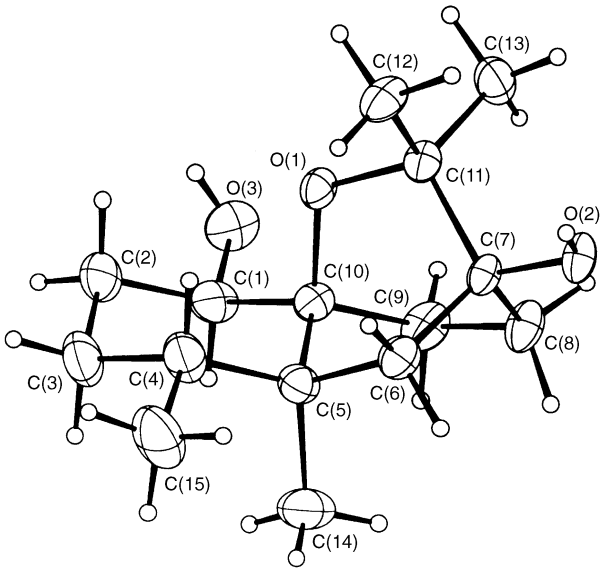


Fig. 2 X-Ray crystal structure of compound **8**

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10β,11-Oxido-4α,5α,7β-eremophilane **2** as a cyclic ether, is chemically relatively unreactive. However these microbiological hydroxylations provide access to centres on both rings A and B. An interesting feature of these hydroxylations is their apparent symmetry. In the case of the monohydroxylations of the ether, rotation around the O:C-10 axis relates C-6α and C-8α. Once hydroxylation has taken place at C-7, rotation around the O:C-7 axis relates C-1β with C-3α.

Crystal Data and Structure Determinations.—(*a*) *Compound* **6**. $C_{15}H_{26}O_2$, $M_r = 238.4$, monoclinic, space group $C2$ (no. 5), $a = 24.894(4)$, $b = 8.892(5)$, $c = 13.915(3)$ Å, $\beta = 113.94(2)^\circ$, $V = 2815(2)$ Å^3, $Z = 8$, $D_c = 1.13\,g\,cm^{-3}$, $F(000)$ 1056, $\lambda = 0.71073$ Å, $\mu = 0.07\,mm^{-1}$. Data were collected using a crystal of size $0.4 \times 0.4 \times 0.1$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 3679 reflections were collected for $2 < \theta < 28^\circ$ and $0 < h < 32$, $0 < k < 11$, $-18 < l < 16$. There were 3614 independent reflections and 3140 reflections with $I > 2\sigma(I)$ that were used in the refinement.

(*b*) *Compound* **8**. $C_{15}H_{26}O_3$, $M_r = 254.4$, trigonal, space group $P3_1$ (no. 144), $a = 13.161(3)$, $b = 13.161(3)$, $c = 7.136(3)$ Å, $\gamma = 120^\circ$, $V = 1070.4(5)$ Å^3, $Z = 3$, D_c $1.16\,g\,cm^{-3}$, $F(000) = 420$, $\lambda = 0.71073$ Å, $\mu = 0.08\,mm^{-1}$. Data were collected using a crystal of size $0.3 \times 0.3 \times 0.3$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 1972 reflections were collected for $2 < \theta < 28^\circ$ and $0 < h < 17$, $-17 < k < 0$, $0 < l < 9$. There were 1859 independent reflections and 1473 reflections with $I > 2\sigma(I)$ that were used in the refinement. There was no crystal decay and no absorption correction was applied. The structures were solved by direct methods using SHELXS-86[10] and SHELXL-93.[11] The non-hydrogen atoms were refined anisotropically by full matrix least squares on F^2. Hydrogen atoms were included in riding mode with $U_{iso} = 1.2U_{eq}(C)$ or $1.5U_{eq}(C)$ for methyl groups except for hydroxyl group H atoms which were located on a difference map and freely refined isotropic. For compound **6** there were two independent molecules of similar geometry arranged in pairs, forming a hydrogen bonded tetramer around the crystallographic two-fold rotation axis.

The final R indices were $R_1 = 0.043$, $wR_2 = 0.112$ and R indices (all data) $R_1 = 0.054$, $wR_2 = 0.127$. The goodness of fit on F^2 was 1.087 and the maximum shift to e.s.d. was 0.001. For compound **8** the final R indices were $R_1 = 0.050$, $wR_2 = 0.119$ and R indices (all data) $R_1 = 0.068$, $wR_2 = 0.133$. The goodness of fit on F^2 was 1.021 and the maximum shift to e.s.d. was 0.001. Tables of atomic coordinates, bond lengths and angles, anisotropic displacement factors and hydrogen atom coordinates are given in the appendix.

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Techniques used: ^{1}H and ^{13}C NMR, X-ray crystallography, IR, MS, microbiological transformation.

Tables: 2 (^{13}C NMR data)

References: 11

Appendix: Crystal data for **6** and **8**

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