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REARRANGEMENT OF HUMULENE-8,9-EPOXIDE

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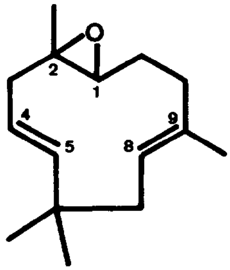
Abstract. Rearrangement of humulene-8,9-epoxide with tin(IV) chloride leads to the formation of a bicyclic alcohol, the structure of which is related to a rearrangement product of humulene itself.

The three mono-epoxides of humulene (1) - (3) are naturally-occurring[1] and therefore it is reasonable to propose that they may serve as the *in vivo* precursors of other bicyclic and tricyclic sesquiterpenoids. To date, *in vitro* cyclizations of two of these mono-epoxides have been studied. In the case of the 1,2-epoxide (1) acid-catalysed cyclization[2] leads to two principal tricyclic diols (4) and (5), the latter of which has been reported to be a constituent of hop oil.[3] More recently we[4] have studied the cyclization of the 4,5-epoxide (3) which, on treatment with boron trifluoride etherate, produces two tricyclic alcohols (6) and (7), the former of which is closely related to the naturally-occurring keto-angelate (8) recently isolated by Bohlmann and Zdero.[5]



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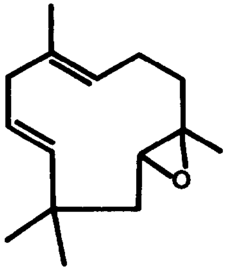

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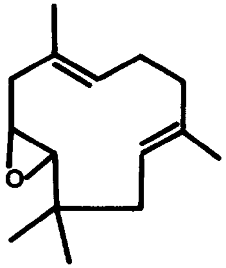

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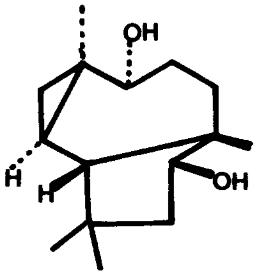

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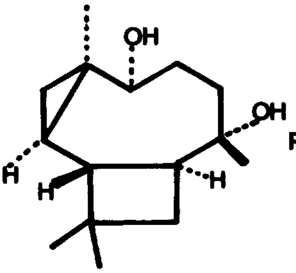

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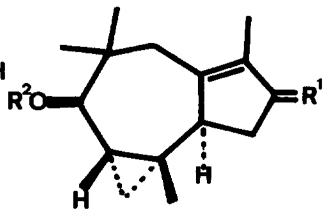
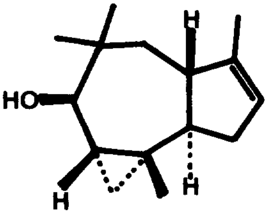


6 $R^1 = H_2, R^2 = H$

7 $R^1 = O$, R^2 Ang



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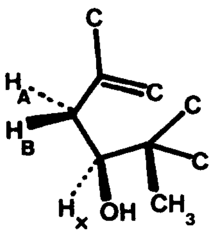
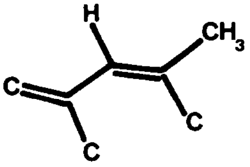
We now report that treatment of the 8,9-epoxide (2)^{1,6} with tin(IV) chloride in chloroform solution at -60°C for 15 minutes leads to the formation of one major alcohol, $C_{15}H_{24}O$, in 25% yield (a number of hydrocarbons are also produced in this reaction). The spectral data for this alcohol are: $\lambda_{max.}$(EtOH) 245nm (ε, 11,280); $\nu_{max.}$ 3620 and 1070 cm^{-1}; δ ($CDCl_3$) 0.89 (3H, s), 0.91 (3H, d, J = 7Hz), 0.94 (3H, d, J = 7Hz), 1.76 (3H, bs), 2.3-2.8 (5H, m), 3.83 (1H, X part of ABX system, $J_{AX} \sim J_{BX} \sim 9Hz$), and 5.90 (1H, bs); m/e 220 (100%), 205 (45%), 177 (33%), and 147 (46%).

A simplification of the nmr spectrum was achieved in the presence of $Eu(fod)_3$ and this, with the aid of double irradiation experiments, permitted the identification of the part structures (A) - (C). Taken in conjunction with the u.v. data and a mechanistic rationale (vide infra), these part structures could be assembled to produce (9) as the structure of the rearrangement product. This structure is, in fact, closely related to that of the bicyclic diene (10) obtained from humulene itself upon treatment with various acid catalysts.[7] In order to substantiate this structural similarity the alcohol (9) was converted into the corresponding ketone ($\nu_{max.}$ 1745cm^{-1}) with pyridinium chlorochromate. Treatment of the derived p-toluenesulphonylhydrazone with sodium borohydride in dioxane[8] gave the hydrocarbon (10) as the sole product and this proved to be identical (nmr, ir, ms, glc) to an authentic sample of the diene prepared from humulene.[7]



A



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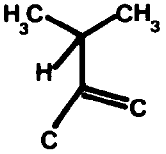

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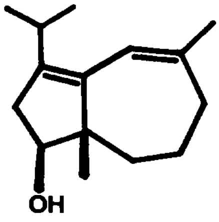

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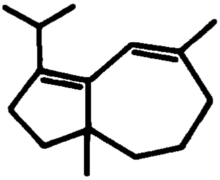

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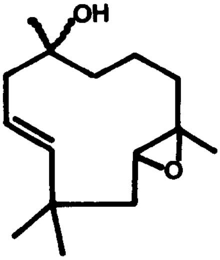

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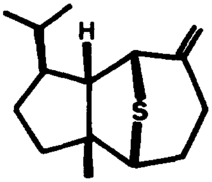
A probable mechanism for the formation of the alcohol (9) is depicted in the Scheme. Molecular models indicate that participation of the $\Delta^{4,5}$ double bond in the opening of the 8,9-epoxide can best be achieved after an initial isomerisation of the $\Delta^{1,2}$ double bond. In partial support of this hypothesis, humulol[3,7] was converted into the hydroxy-epoxide (11)[9] and tin(IV) chloride treatment of this compound [using identical conditions as used for (2)] gave the alcohol (9) in better yield, namely 40%. This mechanism parallels that proposed for the formation of (10) and other related compounds from humulene.[7] It is interesting to note that the carbon skeleton embodied in (9) is the same as that of the recently identified mintsulphide (12), a constituent of peppermint oil.[10]



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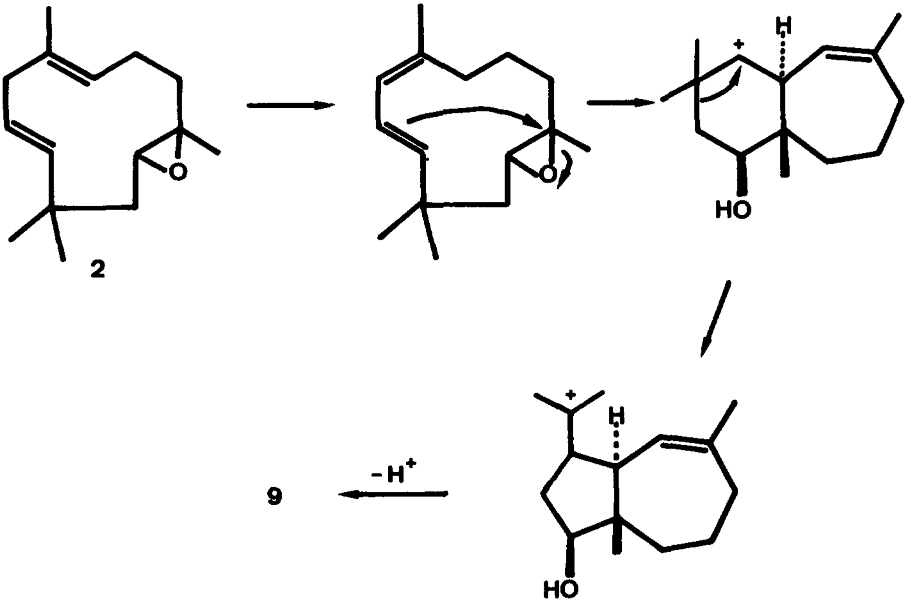

SCHEME

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References and Notes

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9. Obtained from humulol in 58% yield using one equivalent of m-chloroperoxybenzoic acid in the presence of aqueous sodium bicarbonate solution; $\nu_{max.}$ 3420 and 980 cm^{-1}; δ ($CDCl_3$) 1.04 (3H, s), 1.14 (3H, s) 1.23 (3H, s), 1.25 (3H, s), 2.6 - 2.85 (2H, m) and 5.25 (2H, m).
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