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A BIOGENETICALLY SIGNIFICANT CYCLIZATION OF HUMULENE-4,5-EPOXIDE

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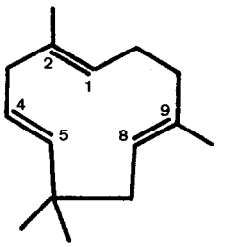
Abstract. Rearrangement of humulene-4,5-epoxide with boron trifluoride etherate leads to the formation of two tricyclic alcohols the structures of which are closely related to that of africanol; the X-ray structure of the p-bromobenzoate of one of the alcohols is reported.

Over the past decade humulene (1) has assumed greater significance in the sesquiterpene field as a result of its implication as the possible biogenetic precursor of an ever-increasing number of sesquiterpenoids, largely of fungal origin. Basically these sesquiterpenoids fall into five structural types, viz. the hirsutane, the protoilludane, the marasmane, the illudane and the africane groups. The important biogenetic feature of all these types is the proposed initial protonation of the $\Delta^{4,5}$ double bond of humulene to generate a cationic site (or its biolgoical equivalent) at C-4 which then acts as the trigger for the subsequent cyclization steps involving participation by the other two double bonds. To date all attempts to mimic these processes in vitro have been frustrated by the greater reactivity of the $\Delta^{1,2}$ double bond of humulene towards electrophilic attack.[2]

To circumvent this intrinsic problem we recently described a method of converting humulene indirectly into its 4,5-monoepoxide (2).[3] We now wish to report that acid-catalysed rearrangement of this epoxide does indeed provide a means of inducing a humulene derivative to undergo a cyclization in accord with one biogenetic postulate. Thus treatment of (2) with boron trifluoride etherate in ether leads to the formation of two alcohols (3, R = H_2) and (4) (in an approximate ratio of 1:1) in 70% yield. Compounds (3, R = H_2) and (4) were separated by SiO_2 - $AgNO_3$ column chromatography and their partial structures were deduced on the basis of their spectral and analytical data:-
(3, R = H_2), $C_{15}H_{24}O$,[4] m.p. 63-64.5°C $\nu_{max.}$ 3610, 3060, 1050, 1030, and 1010 cm^{-1}; δ 0.45-0.8 (3H,m), 0.9 (3H,s), 0.92 (3H,s), 1.00 (3H,s), 1.67 (3H,bs), and 3.23 (1H,d, J = 9.5Hz); (4), $C_{15}H_{24}O$,[4] b.p. 95 - 100°C/0.25mm, ν_{max} 3610, 3060, 3040, 1650, 1055, 1030, 1012, and 825 cm^{-1}; δ 0.3-0.9 (3H,m), 1.02 (9H,s), 1.64 (3H,bs), 3.21 (1H,d,J=8Hz), and 5.33 (1H,m). By INDOR and spin

decoupling experiments the carbinyl proton at δ3.23 in (3, R = H_2) was shown to couple with one of the cyclopropyl protons. A downfield shift of the three quaternary methyl signals together with a simplification of the cyclopropyl proton region was achieved in the presence of Eu(fod)$_3$ which revealed an ABMX system consonant with the partial structure (5). The four coupling constants (J_{AB}=-4.5, J_{AM}=8.5, J_{BM}=6.0, and J_{MX}=9.5±0.5Hz) were determined by spin decoupling and INDOR techniques. Taken in conjunction with the ^{13}C n.m.r. data[5] and mechanistic considerations (vide infra) structure (3, R = H_2) was assigned to this alcohol. This has been confirmed by an X-ray analysis of the p-bromobenzoate of (3,R=H_2)(m.p.53.5-55°C). Crystal data: $C_{22}H_{27}BrO_2$, monoclinic, $P2_1/c$, Z = 4, a = 14.43, b = 5.85, c = 26.48 Å, β = 114.5°; 2283 unique reflexions on layers h0-4l (857 with I>3σ (I)) were collected on a Stoe STADI-2 diffractometer (Mo-K_α radiation). The structure was solved by direct methods[6] with a present R factor of 7%.[7]



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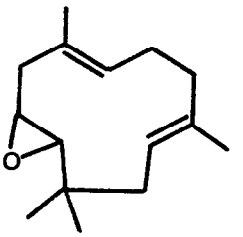

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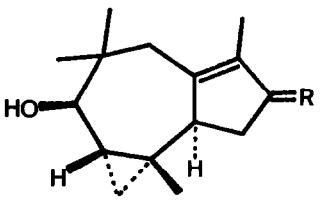

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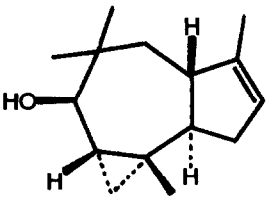

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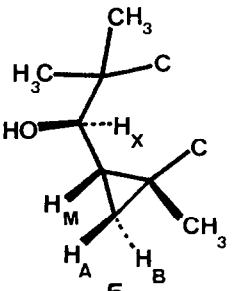

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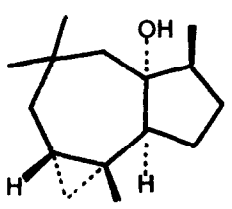
Using similar n.m.r. techniques structure (4)[8] was assigned to the isomeric alcohol. Both alcohols are closely related in structure and stereochemistry to africanol (6) and to its major dehydration product (7) which is also naturally-occurring.[9] Even more closely related is the angelate ester of (3, R = O) which was reported recently by Bohlmann and Zdero[10] although the suggested biogenesis starting from humulene-8,9-epoxide seems unlikely in view of our results.[11] The mechanism of formation of these two alcohols can be rationalised in terms of BF_3-assisted opening of the epoxide ring in (2) with subsequent cyclization steps involving

participation of the $\Delta^{1,2}$ and $\Delta^{8,9}$ double bonds as shown in (8). The observed stereochemistry in (3, R = H_2) [and most probably in (4)] is exactly that dictated by a conformer of (2) which matches that of the silver nitrate adduct of humulene itself.[12] Work is in progress to alter the relative nucleophilicities of the $\Delta^{1,2}$ and $\Delta^{8,9}$ double bonds in (2) in an attempt to divert the cyclization modes towards the other four structural types.



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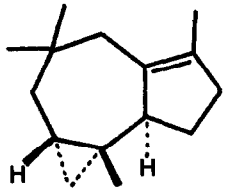

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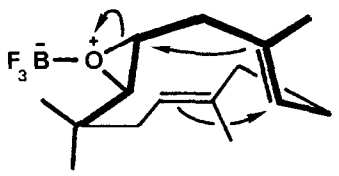

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References and Notes

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4. Accurate mass measurement.
5. The off-resonance ^{13}C n.m.r. spectrum shows singlets at δ 20.28, 39.29, 133.11, 135.25, doublets at δ 29.58, 54.33, 80.38, triplets at δ 21.94, 26.38, 37.72, 42.18, and quartets at δ 13.74, 20.21 (x2), and 27.74 p.p.m.; a completely unambiguous assignment of all these signals is not yet possible.
6. G.M. Sheldrick, 1976, SHELX-76 program for crystal structure determination, University of Cambridge, England.

7. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
8. The ring conjunction stereochemistry is thought to be trans based on mechanistic considerations.
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10. F. Bohlmann and C. Zdero, Phytochemistry, 1978, 17, 1669.
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