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TERPENES AND RELATED SYSTEMS. XIII.[1] REGIOSPECIFIC FRAGMENTATION OF PATCHOULOL: A SHORT SYNTHESIS OF α-BULNESENE

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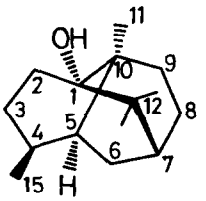
A utilitarian synthetic approach to the sesquiterpenoids consists of employing naturally occurring C_{15}-triisoprenoids as synthons.[2] This strategy envisages the selection of an abundantly available polycyclic sesquiterpene, bearing a latent carbocyclic framework and stereochemical disposition of the targeted molecule, which can be unmasked *via* a key bond-breaking operation. Routine manipulation of functional groups then completes the synthetic venture.[3] In particular bridged tricyclic sesquiterpenoids, derived *via* the biogenetic cyclization of simple mono- and bicyclic precursors, can unravel a variety of carbocyclic skeletons through suitably tailored chemical scission of strategic C-C bonds.[3] In pursuance of the above theme, we wish to report the creation[4] of *cis*-1-ketoeudesmanes **2** and **3**, with desired disposition of stereochemistry at four chiral centres, from readily available[5] tricyclic alcohol patchoulol **1**. Further elaboration of **2** completes a short synthesis[6-8] of the hydroazulenic sesquiterpene α-bulnesene **8**.

Refluxing (20 hr) a solution of patchoulol **1** (23 mmol) and lead tetraacetate (36 mmol) in 250 ml dry benzene (containing suspended $CaCO_3$) under N_2 blanket led to the formation of a 2:2:1 mixture of **2**, **3** and **4** in 50% yield. A combination of column chromatography and preparative TLC($AgNO_3$-silica gel and silica gel) resulted in the isolation of **2**, **3** and **4** in pure form and structural assignments to them follows from the complimentary spectral data summarized below:[9]

Compound **2**: $C_{15}H_{24}O$, ν_{max}(neat): 1710 (carbonyl), 3180, 1650 and 890 cm^{-1} (exocyclic methylene). PMR: δ0.98 (3H, d, $\underline{CH_3}$-$\overset{|}{C}$-H, J=7Hz), 1.2 (3H, s, $\underline{CH_3}$-$\overset{|}{C}$-), 1.68 (3H, br, s, $\underline{CH_3}$-$\overset{|}{C}$=$\overset{|}{C}$-), 4.65 (2H, br, s, $\underline{H_2C}$=$\overset{|}{C}$-).

Compound **3**: $C_{15}H_{24}O$, ν_{max}(neat): 1705 cm^{-1} (carbonyl). PMR: 1.04 (3H, d,



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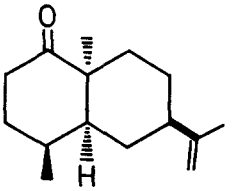

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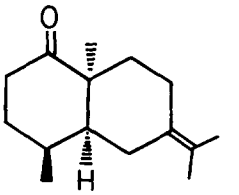

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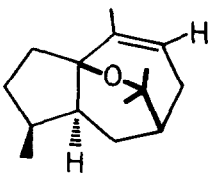

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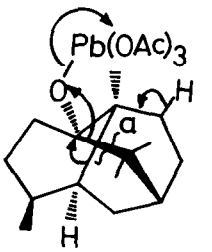

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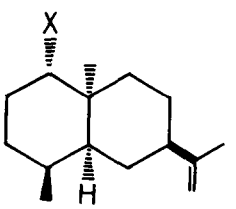

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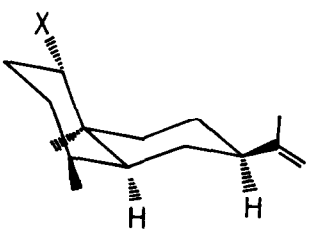

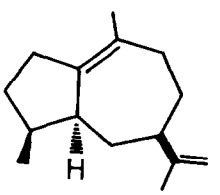

8

6. X = OH

7. X = OTs

$\underline{CH_3}$-C(H)-H, J=7Hz), 1.2 (3H, s, $\underline{CH_3}$-C(-)-), 1.64 (6H, br, s, $\underline{CH_3}$-C(-)=C(-)-$\underline{CH_3}$). The spectrum was transparent in the olefinic proton region.

Compound 4: $C_{15}H_{24}O$, ν_{max}(neat): 980, 998, 1060, 1110 cm^{-1} (ether). PMR: δ0.989 (3H, d, $\underline{CH_3}$-C(-)-H, J=7Hz), 0.95 & 1.04 (3H, s, $\underline{CH_3}$-C(-)-O), 1.76 (3H, br, s, $\underline{CH_3}$-C(-)=C(-)-), 5.41 (1H, br s, $\underline{H}$-C(-)=C(-)-). Addition of Eu(fod)$_3$ reagent (R/s = 0.105, molar ratio) led to following PMR chemical shifts: 1.02 (3H, d, $\underline{CH_3}$-C(-)-H, J=7Hz), 1.22 (6H, s, $\underline{CH_3}$-C(CH$_3$)(-)-O-), 1.85 (3H, br, s, $\underline{CH_3}$-C(-)=C(-)-), 5.5 (1H, br, $\underline{H}$-C(-)=C(-)-).

The cis fused eudesmane derivatives 2 & 3 are derived through the regiospecific cleavage of C_1-C_{12} bond (marked a) in lead ester 5 along precedented[10] lines. A competitive rearrangement process 5 (arrows) leads to the formation of the interesting guaioxide 4.

Reduction of 1-ketoeudesmane 2 with $NaBH_4$ in methanol (4 hr, 32°) resulted in the addition of the hydride from the less hindered β-face and alcohol 6 (ir: 3600, 1650 and 890 cm^{-1}; PMR: δ3.9, 1H, $\underline{H}$-C(-)-OH) was obtained in good yield. Tosylation of 6 with p-toluenesulphonylchloride-pyridine (7 days, 32°) gave the liquid tosylate 7 (1650, 1180, 1170 and 890 cm^{-1}) in quantitative yield. Solvolysis[11] of 7 in 0.5 molar potassium acetate in acetic acid (8 hr, 85°) gave α-bulnesene 8 identical (ir, pmr, tlc) with the natural specimen.

The availability of synthons 2 and 3 in one step from patchoulol 1 and the efficiency of the three step 2 → 8 transformation should provide a simple entry to several other functionalized perhydroazulenes of current interest[12] along these lines.

Acknowledgement: We wish to thank Dr. Sukh Dev, Malti-Chem Research Centre, Baroda for the pmr spectra of the compounds reported here and Professor C.H. Heathcock, University of California, Berkeley for the spectra of natural α-bulnesene.

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2. The utility of such a synthetic approach is fully substantiated by the number of short and elegant sesquiterpene syntheses emanating from santonin. A partial listing of these is reported.[3]

3. For an interesting example employing longifolene as synthon, see, G. Mehta and S.K. Kapoor, J. Org. Chem., 39, 2618 (1974); G. Mehta, S.K. Kapoor, T.N.G. Row and K. Venkatesan, Tetrahedron Lett., 2653 (1974).

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6. α-Bulnesene 8 has been previously synthesized through multi-step reaction sequence by Heathcock[7] and Piers.[8]

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