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REGIOSPECIFIC FUNCTIONALISATION OF HUMULENE

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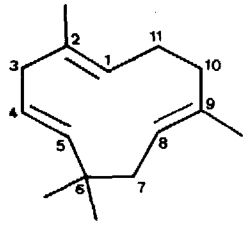
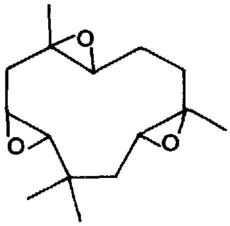
Cationic cyclisations initiated at the $\Delta^{4,5}$ double bond of humulene (1) have been invoked to rationalise the biogenesis of several classes of biologically-active sesquiterpenes. However, to date[1], all attempts to cyclise (1) *in vitro* have given products stemming from initial electrophilic attack at the most strained[2] ($\Delta^{1,2}$) double bond. In this connection we now report two solutions to the problem of functionalising the least reactive ($\Delta^{4,5}$) of the three double bonds of humulene.



(1)



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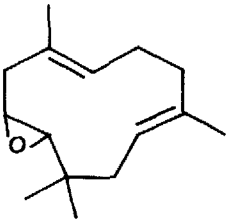

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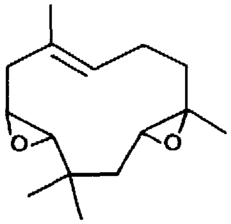

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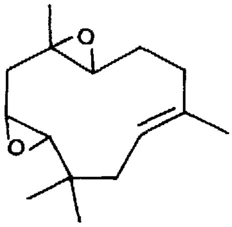

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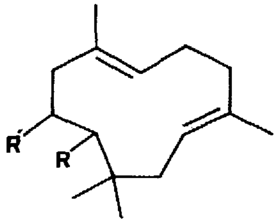
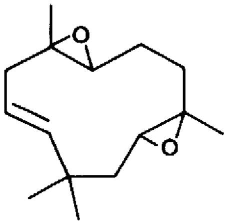


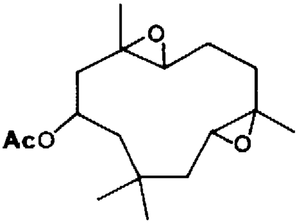
(6)

Treatment of the *tris*-epoxide[3] (2) in tetrahydrofuran with WCl_6/*n*-BuLi[4] in the molar ratio of (1:2:4) at 50° for 35-45 minutes gave the $\Delta^{4,5}$-epoxide[5] (3) in good yield accompanied by small amounts of humulene and the *bis*-epoxides (4) and (5). A corresponding reaction at lower temperature for a shorter time gave the same mixture but with the *bis*-epoxides predominating[6]. The structures[7] of the hitherto unknown *bis*-epoxides (4) and (5) follow from their high resolution m.s., i.r. and n.m.r. spectra[8] [(4), m.p. 75-76°, δ0.8 (3H,s). 1.05 (3H,s), 1.18 (3H,s), 1.7 (3H, broad s), 2.3-3.0 (3H,m), and 5.27 (1H, broad t); (5) an oil, δ0.75 (3H,s), 1.05 (3H,s), 1.3 (3H,s), 1.68 (3H, broad s), 2.3-2.8 (3H,m), and 5.15 (1H, broad dd)]. Both (4) and (5) can be readily converted into the *tris*-epoxide (2) on further epoxidation.

Reduction of (3) with either lithium aluminium hydride or lithium/ethylamine gave exclusively the 5-ol (6,R=OH; R'=H); m.p. 93-94°; n.m.r.[8] δ0.81 (3H,s), 1.05 (3H,s), 1.4 (3H, broad s), 1.57 (3H, broad s), 3.46 (1H, broad t), and 4.83 (2H,m).



(7)



(8)

When the known *bis*-epoxide[9] (7) was treated with WCl_6/*n*-BuLi in the molar ratio of (1:4:8) at 50° for 35-40 minutes, humulene (1) was obtained in 80% yield, whereas a molar ratio of (1:1:2) and the same reaction conditions gave a mixture of humulene and the $\Delta^{1,2}$- and $\Delta^{8,9}$-*mono*-epoxides[10] in the ratio of (1.5:1:7.5). Hydroboration/oxidation of (7), followed by acetylation, gave solely the acetate (8)[7], m.p. 141-142°, n.m.r.[8] δ1.0 (3H,s), 1.01 (3H,s), 1.3 (3H,s), 1.43 (3H,s), 2.0 (3H,s), 2.7-3.0 (2H,m), and 4.96 (1H,m). Deoxygenation of (8) under the former conditions noted above, followed by lithium aluminium hydride reduction, yielded the required alcohol (6, R=H, R'=OH), an oil n.m.r.[8] δ0.94 (3H,s), 1.04 (3H,s), 1.43 (3H, broad s), 1.58 (3H, broad s), 3.36 (1H,m), and 4.78 (2H,m).

Work is in progress on the *in vitro* and *in vivo* cyclisation of (6, R=H ; R'=OH and R=OH ; R'=H).

Acknowledgement

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