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STEREOSELECTIVE SYNTHESIS OF CYCLIC ETHERS VIA BROMINE ASSISTED EPOXIDE RING EXPANSION

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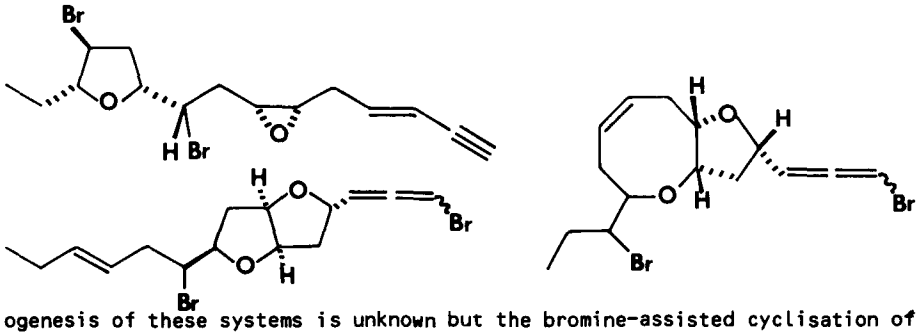
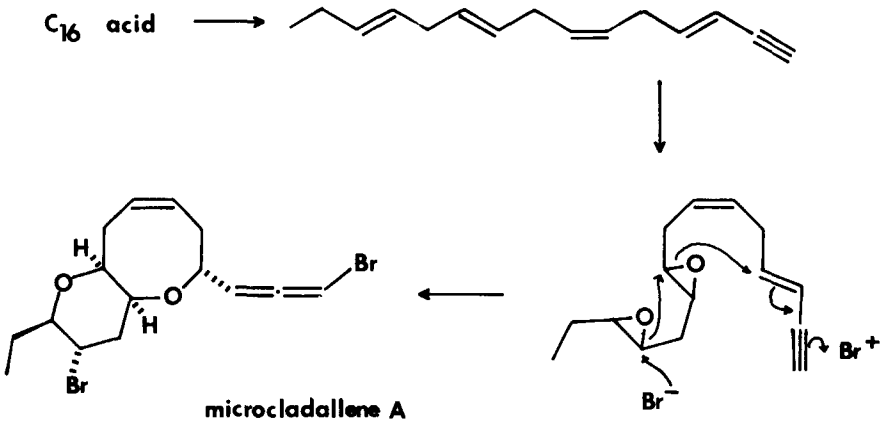
Summary: 9-Oxabicyclo[6.1.0]non-4-ene reacts with bromine to give stereoselectively trans,trans-2,6-dibromo-9-oxabicyclo[3.3.1]nonane and trans,trans-2,5-dibromo-9-oxabicyclo[4.2.1]nonane.

Many dibrominated sesquiterpenes containing ether linkages have been isolated from the red algal genus Laurencia;[1-5] three examples are illustrated below.



The biogenesis of these systems is unknown but the bromine-assisted cyclisation of unsaturated epoxides, originally proposed by Bu'Lock,[6] has recently been invoked as a possible biosynthetic route to microcladallene A.[5]



Although the cyclisations of unsaturated epoxides by mercury (II) electrophiles[7] and of unsaturated episulphides by halogens[8] have been established, a bromine-assisted cyclisation of unsaturated epoxides has no chemical precedent as far as we are aware.

We wish to report a bromine-mediated transformation of unsaturated epoxides into dibrominated cyclic ethers. Treatment of 1,5 cyclo-octadiene 1 with one equivalent of bromine at $0^{o}C$ gave trans-1,2-dibromocyclo-oct-5-ene which was oxidised with mCPBA to the expected product 4,5-dibromo-9-oxa-bicyclo[6.1.0]nonane 2. Oxidation of 1 with one equivalent of mCPBA to give 3 followed by bromination in carbon tetrachloride at $0^{o}C$, however, led to a 1.22:1 mixture of trans,trans isomers of 2,6-dibromo-9-oxabicyclo [3.3.1]nonane 6 and 2,5-dibromo-9-oxabicyclo [4.2.1]nonane 7. The products 6 and 7 were identified by comparison of their spectroscopic properties with literature data[9-12] and the product ratio was determined from the $^{13}C-\{^{1}H\}$ spectrum of the mixture. No other diastereoisomers of 6 or 7 were detected. A mechanism involving neighbouring group participation by the epoxide oxygen in the opening of the bromonium ion 4 to give the oxonium species 5 is consistent with the observed stereoselective formation of only trans,trans-6 and 7.

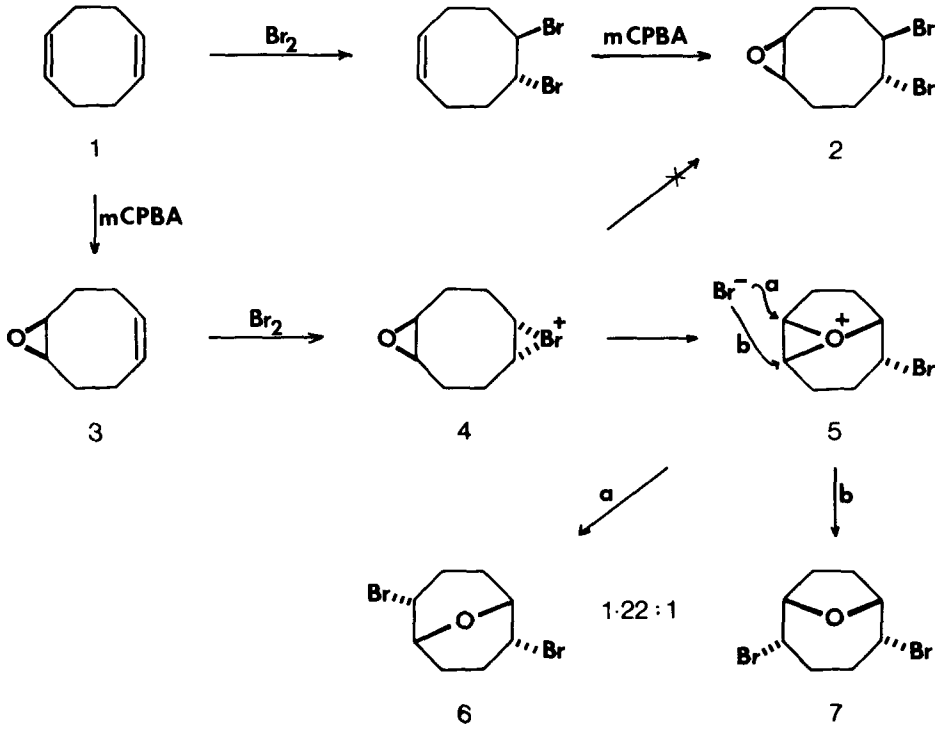
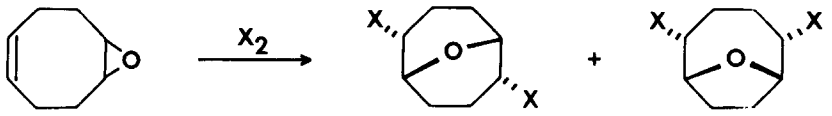


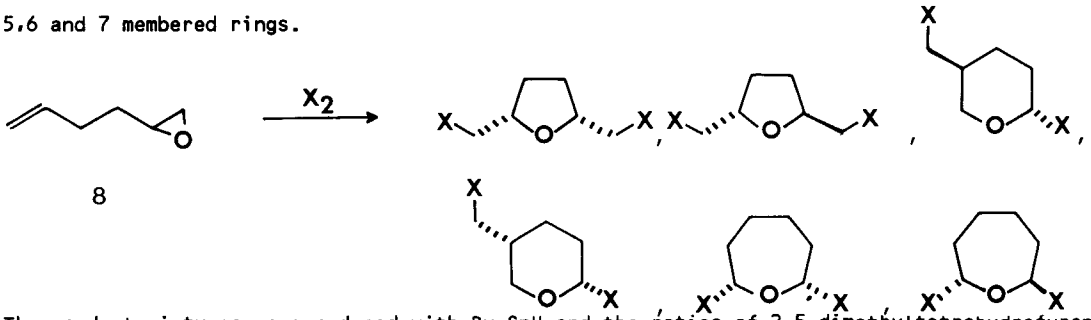
Table 1 records the ratios of dihalogenated bicyclic ethers obtained on treatment of 3 with halogen under various conditions.

Table 1: Halogenation of 9-oxabicyclo[6.1.0]non-4-ene 3.



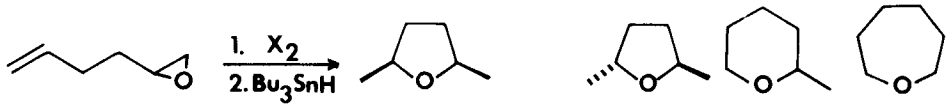
X_2	Temp	Solvent	Ratio 6:7
Br_2	0°C	CCl_4	1.2:1
Br_2	20°C	CH_3CN	1:1.3
Br_2	-78°C	CH_2Cl_2	1.7:1
I_2	20°C	CH_3CN	1.7:1

Investigations into the reactivity of 1,2-epoxyhex-5-ene 8 indicate that this bromine-assisted cyclisation is a general phenomenon, independent of the conformation of the cyclo-octane ring. Halogenation of 1,2-epoxyhex-5-ene 8 leads to products containing 5,6 and 7 membered rings.



The product mixtures were reduced with Bu_3SnH and the ratios of 2,5-dimethyltetrahydrofuran (cis and trans) : 2-methyltetrahydropyran : oxepane determined by g.c. analysis (See Table 2). These ratios are assumed to reflect the ratios of dihalogenated products obtained.

Table 2: Cyclisation of 1,2-epoxyhex-5-ene 8



X_2	Temp.	Solvent					
Br_2	20°C	CCl_4		75		20	5
Br_2	-78°C	CH_2Cl_2	25		35	40	0
I_2	20°C	CH_3CN	60		20	20	0

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