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Substituent Control in the Synthesis of Tetrahydropyrans, Oxepanes and Oxocanes by Episulphonium Ion-Mediated Cyclisation

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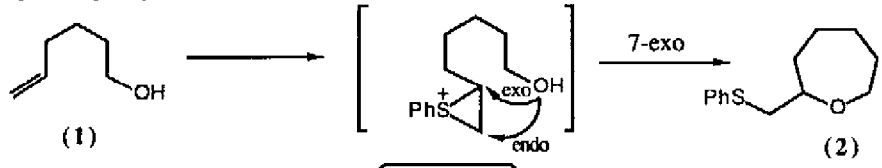
Key Words: tetrahydropyran; oxepane; oxocane; episulphonium ion; zoapatanol

Abstract: Cyclisation of the heptenols **(1)**, **(6a)**, **(6b)**, and **(6c)** to cyclic ethers *via* episulphonium ions has been studied and the effect of allylic substituents on the size of ring produced has been explored.

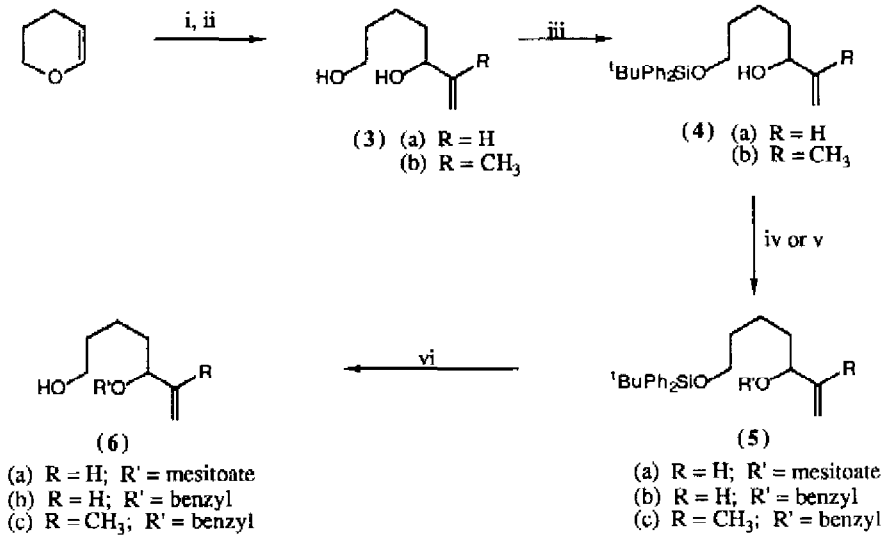
Recently, there has been considerable interest in the synthesis of cyclic ethers due to their widespread occurrence particularly in marine natural products. Thus the important neurotoxins, the brevetoxins[1] contain 6-, 7-, 8-, and 9-membered cyclic ethers and the metabolites of the red algae of the genus *Laurencia*[2] contain 8-membered cyclic ethers. The larger 8- and 9-membered rings present a particular challenge to the synthetic chemist and a limited number of methods for their synthesis have been published[3]. The elegant work of Nicolaou[4] is prominent in this area and in particular he has shown that the electronic nature of the substituents on vinyl epoxides can control the regioselectivity of ring opening[5]. In this manner, tetrahydrofurans, tetrahydropyrans, and oxepanes can be synthesised with a high degree of selectivity. As part of a project concerned with the synthesis of oxepanes related to zoapatanol[6] *via* episulphonium ion chemistry[7], we wish to report a similar effect which we believe will allow the controlled synthesis of cyclic ethers including oxocanes.

We have previously reported on the reaction of phenylthiomorpholine/triflic acid with unsaturated alcohols to generate cyclic ethers *via* episulphonium ions[8]. Under these conditions[9], hept-6-en-1-ol **(1)**[11] cyclised to give 2-(phenylthiomethyl)oxepane **(2)** in 80% yield with no trace of the oxocane (Scheme 1[12]).



Scheme 1

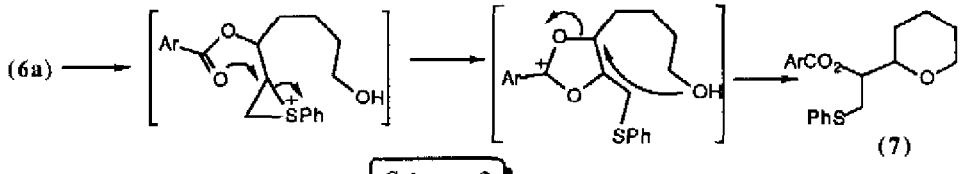
We next investigated the effect of allyic substituents on the cyclisation. The three substrates studied were synthesised as outlined in Scheme 2. Cyclisation of the mesitoate ester **(6a)** led to only one cyclic product **(7)** which was isolated in 30% yield. This structure was assigned on the basis of nmr spectroscopy,



Reagents: (i). HCl, H_2O, reflux. (ii). 2.5 equivalents $H_2CCII(R)MgBr$, ether, 0°C (43%). (iii). DBU, $Ph_2{}^tBuSiCl$, CH_2Cl_2 (85%). (iv). 2,4,6-trimethylbenzoyl chloride, pyridine, CH_2Cl_2 (93%). (v). $PhCH_2Br$, KH, Bu_4NI, THF (89%). (vi). Bu_4NF, THF (90%).

Scheme 2

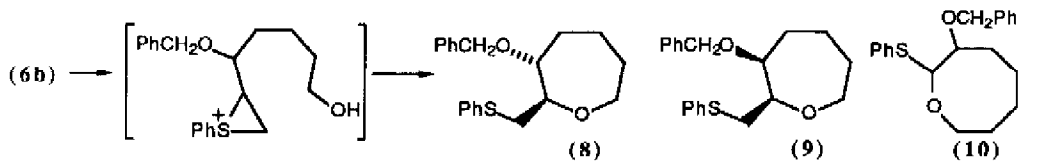
in particular the proton on the carbon carrying the mesitoate ester could be identified and was clearly coupled to the methylene carrying the phenylthio group. Both diastereomers were isolated in a 1:1 ratio. As expected, the cyclisation of **(6a)** proceeds through the dioxolonium ion derived from the episulphonium ion (Scheme 3) followed by a 6-*exo* cyclisation.



Scheme 3

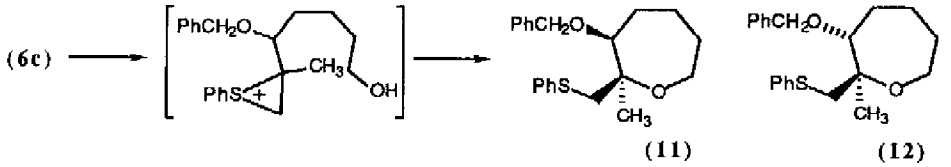
Cyclisation of the benzyl ether **(6b)** led to a mixture of products in a total yield of 70%. The *trans*- and *cis*-oxepanes **(8)** and **(9)** were obtained in 20% and 35% yields respectively whilst, unexpectedly, the oxocane **(10)** was obtained in 21% yield as one diastereoisomer. That none of these products contained a tetrahydropyran ring system was confirmed by treatment of **(7)** with $LiAlH_4$ followed by O-benzylation to produce O-benzylated tetrahydropyran. Further structural assignments were based on ^1H and ^{13}C nmr, in particular the phenylthio group in the oxepanes **(8)** and **(9)** was shown to be attached to a methylene carbon by ^{13}C nmr. The stereochemistry of the oxepanes **(8)** and **(9)** was confirmed by oxidation to the sulphones and observation of the coupling constants between H_2 and H_3 ($J_{2,3}$8.5 Hz for the *trans*-isomer and $J_{2,3}$2.6 Hz for the *cis*-isomer). It did not prove possible to determine the stereochemistry of the oxocane **(10)**. The formation of the oxocane in this reaction is surprising as such rings are usually difficult to form in cases where

there are no obvious conformational restraints. We believe the reason for this is that 7-*exo*-cyclisation of the episulphonium ion (Scheme 4) is slowed by the presence of the electron-withdrawing benzyloxy group which forces the episulphonium ion to carry a higher degree of positive charge on the terminal carbon than would otherwise be the case (e.g. cyclisation of (**1**))[13].



Scheme 4

Finally, cyclisation of (**6c**) carrying a methyl group on the carbon/carbon double bond occurred cleanly to give oxepanes (**11**) and (**12**) as a 3:2 mixture in 74% yield. The stereochemistry of the two isomers was determined after oxidation to the sulphones followed by nOe difference spectroscopy. This proved that the major isomer (**11**) possesses the *cis*-benzyloxy/phenylthiomethyl stereochemistry and the minor product is the *trans*-isomer (**12**). No trace of the oxocane isomer was observed in this cyclisation. This agrees with the analysis of the previous cyclisation. In this case, the extra methyl group helps to stabilise the incipient carbocation at the internal carbon of the alkene and counteracts the effect of the allylic benzyloxy group. Hence the 7-*exo* cyclisation is favoured. In order to see if dimethyl subsitution on the terminal end of the double bond forces the cyclisation to occur via the 8-*endo* mode to give the oxocane, we required the terminal dimethyl derivative of (**6**). However, attempts to prepare this compound *via* the route utilised for the other heptenols proved unsuccessful.



Scheme 5

In summary, we have shown that the regioselectivity of cyclisation of heptenols *via* episulphonium ions is subject to some electronic control. We believe this has considerable potential in the synthesis of complex cyclic ethers.

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