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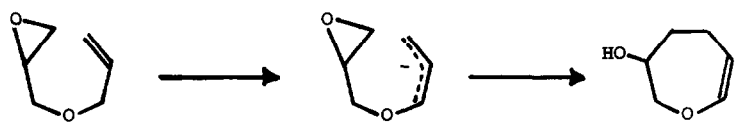
THE SCOPE OF A NEW APPROACH TO TETRAHYDROOXEPANOL SYNTHESIS

C.W. Bird* and N. Hormozi
Department of Chemistry, King's College London,
The Strand, London WC2R 2LS, U.K.

Abstract: The role of substituents in determining the preferential course of cyclisation of allyl glycidyl ethers to tetrahydrooxepanols rather than vinyloxetanylcarbinols has been studied.

The oxepane ring system is a key structural feature of an increasing number of biologically active natural products typified by the abortifacient diterpene, Zoapatanol, and the neurochemically important Brevetoxins. So far only (±)-Zoapatanol has been successfully synthesised[1] though the far more complex Brevetoxin B is clearly under siege[2]. The general topic of oxepane synthesis has also been addressed in a number of other recent publications[3].



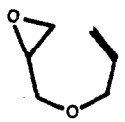
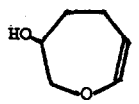
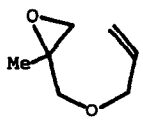
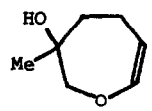
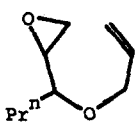
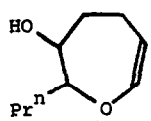
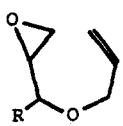
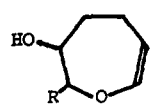
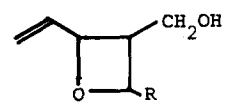
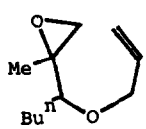
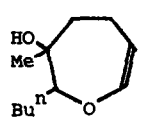
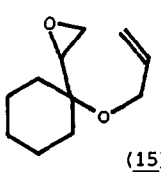
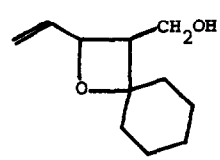
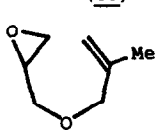
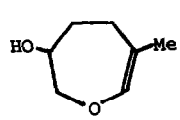
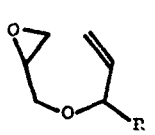
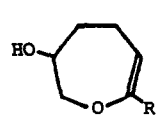
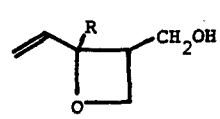
SCHEME

Inspection of the oxygenation pattern in the naturally occurring oxepanes led us to consider the use of the process indicated in the Scheme for their construction. A particular attraction of this route was the ready availability of appropriate chiral oxiranylcarbinol precursors[4]. Although it had been reported earlier[5] that the s-butyllithium promoted cyclisation of (1) yielded the oxetane (2), our preliminary experiments[6]

(1) (2)

showed that allyl glycidyl ether gave mainly the tetrahydrooxepanol (4) together with a little of the isomeric vinyloxetanylcarbinol (5)[7]. The intrinsic simplicity of this method of oxepane ring construction has encouraged us to explore further its generality and we summarise here our present results.

TABLE

Substrates	Products	
 (3)	 (4) 37%	 (5) 12%
 (6)	 (7) 37%	
 (8)	 (9) 30%	
 (10) R= N(6)-benzoyladenyl[8]	 (11) 10%	 (12) 10%
 (13)	 (14) (decomposed on attempted purification)	
 (15)	 (16) 47%	
 (17)	 (18) 42%	
 (19) R = $(CH_2)_4OSiMe_2Bu^t$	 (20) 7%	 (21) 53%

The allyl glycidyl ethers were mostly obtained either by base promoted reaction of allyl alcohols with epibromohydrin, or selective epoxidation of the appropriate diallyl ether. In view of the problems encountered with O-allylation of certain oxiranylcarbinols[9] the substrate (15) was prepared by O-propargylation of 1-vinylcyclohexanol, followed by epoxidation of the double bond and Lindlar hydrogenation of the triple bond. After extensive experimentation the optimum conditions for the cyclisation of these allyl glycidyl ethers were found to entail treatment at -78°C with 1.5 molar equivalents of s-butyllithium in tetrahydrofuran, containing 4% hexamethylphosphoric triamide, for 20 minutes followed by quenching with methanol. Under these conditions the formation of more complex products was minimised but generally resulted in the recovery of some unreacted substrate. No allowance has been made for this in recording the percentage yields in the Table, which includes one further example from the contemporary literature[8].

In accord with the preference for colinear alignment of the carbanionic centre and the breaking epoxide carbon-oxygen bond[9] only oxepane and/or oxetane formation was observed and none of the isomeric tetrahydrofurans was detected. As might have been anticipated substrates bearing methyl substituents on the γ-carbon of either the allyl or glycidyl moieties failed to undergo cyclisation. In only two of the cases we have examined so far has oxetane formation predominated. In the case of compound (19) it seems possible that intramolecular coordination of the side-chain oxygen could result in appreciable charge localisation on the α-carbon of the intermediary allyl carbanion. The reason for the exclusive formation of the oxetane (16) from (15) is not obvious but could be a manifestation of the Thorpe-Ingold effect[11].

Doubtless further experimentation will delineate with more precision the structural features governing the preferred pathway in such cyclisations. However, despite implications to the contrary[7], the results presented here indicate that oxepane rather than oxetane ring formation is the predominant mode of cyclisation.

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