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CYCLISATIONS OF ALLYLOXY RADICALS

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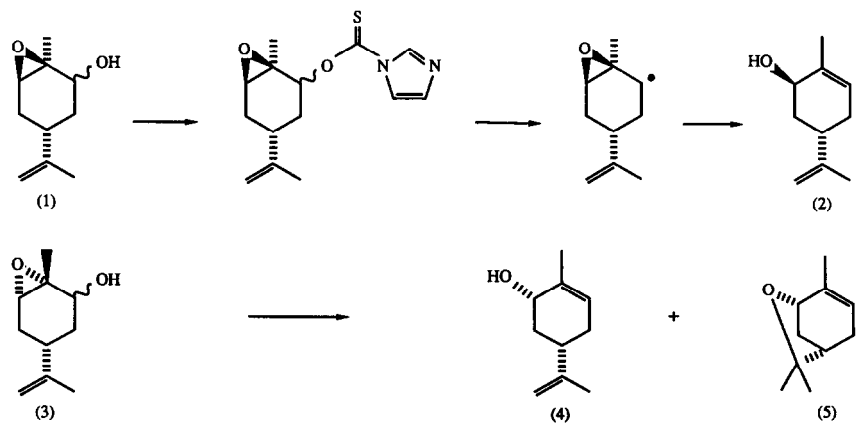
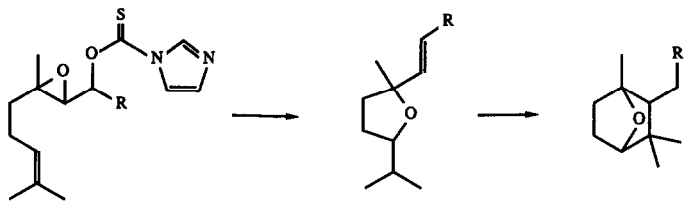
Summary. The scope of the cyclisation of allyloxy radicals onto carbon-carbon multiple bonds has been investigated.

In 1981, Barton, Hay Motherwell and Motherwell reported a convenient alternative to the Wharton reaction.[1] Their initial example involved the smooth conversion of the epoxyalcohol (1) into (+)-trans carveol (2). The isomeric epoxy alcohol (3) produced (+)-cis-carveol (4), but under certain conditions the bicyclic ether (5) was also observed. They found that the amount of this ether could be minimised by inverse addition. We were attracted by the formation of the cyclic ether and wondered whether conditions could be found to maximise the amount of cyclisation and whether such cyclisations would provide stereoselective routes to tetrahydrofurans and tetrahydropyrans, systems which are widely found in natural products with profound biological activities.[2,3] Here we report initial answers to these questions.



For a study of tetrahydrofuran formation we chose the epoxides (6), easily prepared from geraniol and citral. Slow addition of solutions of tributylstannane and azobisisobutyronitrile to refluxing solutions of (6) led to the products (7) and (8). The initial cyclised radical (10) may have its 2- and 5-alkyl substituents cis or trans, and (8) presumably arises by further cyclisation of the cis isomer as shown. The diastereomers of (7c) were separated by chromatography and the major isomer subjected to an n.O.e. investigation which showed that the isopropyl and vinyl groups were trans on the ring. The isomers of (7a) and (7b) were not separable, but by analogy we assume the major diastereoisomer to be trans in both cases. The cyclisations to form tetrahydrofuran radicals (10) are thus diastereoselective and the diastereoisomer ratio for the isolated products (7b) and (7c) are improved by further reaction of the appropriate cis (10) to give (8).

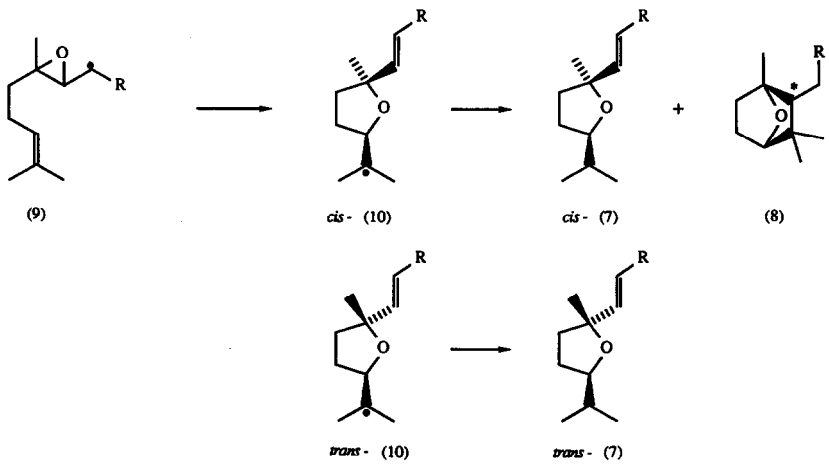
We are currently investigating the stereochemistry of the carbon marked "*" in (8). The exo stereochemistry is found naturally in farnesiferol C (11)[4].



(6a) R = H
(6b) R = Me
(6c) R = n-Bu

(7a) 14%
(7b) 53%
(7c) 63%

(8a) 0%
(8b) 14%
(8c) 22%



(9)

cis- (10)

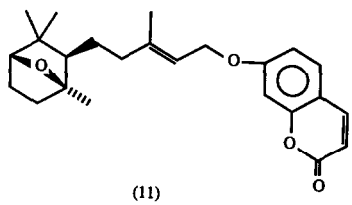
cis- (7)

(8)

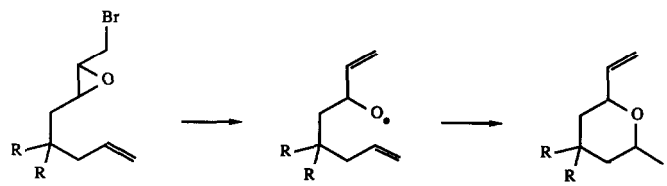
trans- (10)

trans- (7)

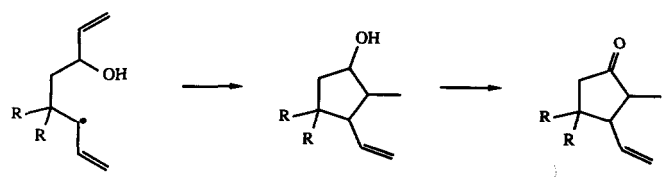
We next chose to study the substrate (12) to see if tetrahydropyran formation could be effected. The desired product (14) was isolated from this reaction in 27% yield. ^{1}H n.m.r. studies indicate this to be a very stereoselective cyclisation (with diastereomer ratio > 10:1) with the product having methyl and vinyl groups cis being predominant. The second product isolated from this reaction was (16) (32%), present as a mixture of diastereoisomers. This product results from transfer of a hydrogen atom[5] in (13) to give the stabilised allylic radical (15) which subsequently cyclises. The 400 MHz ^{1}H n.m.r. spectrum of (16) was highly complex, but the structural assignment was confirmed by pyridinium chlorochromate oxidation to (17) in 75% yield. Hence this example shows that two pathways from the intermediate radical (13) can be followed with equal facility; a current task is to explore the factors which can bias this in favour of one of the two possible routes.



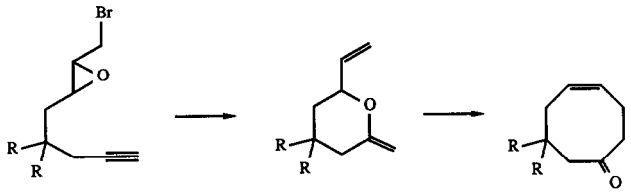
(11)



(12) R = CO_2Et (13) (14)



(15) (16) (17)



(18) R = CO_2Et (19) (20)

We felt this radical cyclisation could have applications other than for the synthesis of tetrahydrofurans and tetrahydropyrans, and an initial taste for this resulted from treatment of the alkyne (18) with tributyl tin radicals. This gave rise to a product (19) which was sensitive to silica chromatography; this compound rearranged smoothly in refluxing xylene to the cyclooctenone (20) in 65% yield. The Claisen rearrangement has been used extensively in synthesis[6], but this radical approach makes the preparation of exocyclic vinyl ethers such as (19) an extremely facile process. This strategy thus demonstrates exciting possibilities for synthesis of products containing difficultly accessible medium-sized rings.

We thank the S.E.R.C. for support.

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