# Modelling Vinyl Ether Formation in Rifamycin S

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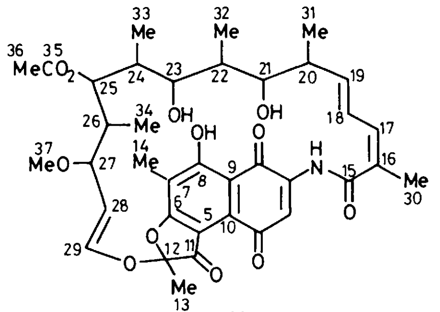
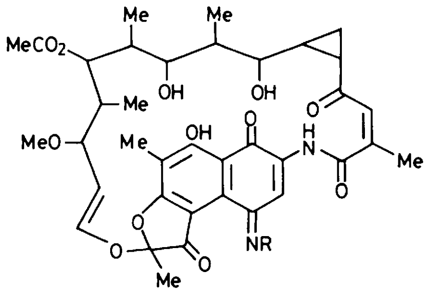
A novel radical-induced epoxide cleavage has been observed to model introduction of an oxygen atom into the ansa chain of rifamycin S.

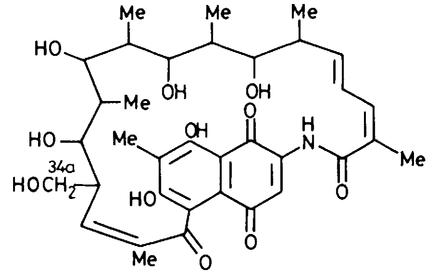
Ansamycin antibiotics, *e.g.* rifamycin S (**1**) and tolypomycin Y (**2**), are important and structurally very interesting natural products.[1] Rickards,[2] White,[3] and a Ciba–Geigy[4] team have uncovered many of the secrets of their biosyntheses, the really intriguing step of which is the introduction of an oxygen atom as a vinyl ether into the ansa chain conversion of rifamycin H (**3**) to (**1**) and subsequently to (**2**). It has been suggested[3a] that the oxygen may be introduced by way of an epoxide intermediate, or through a modified Baeyer–Villiger reaction, but no detailed explanation or precedent for these processes was proffered. Here we propose a detailed mechanistic rationale which allows oxygen insertion to be accomplished in



**(1)**



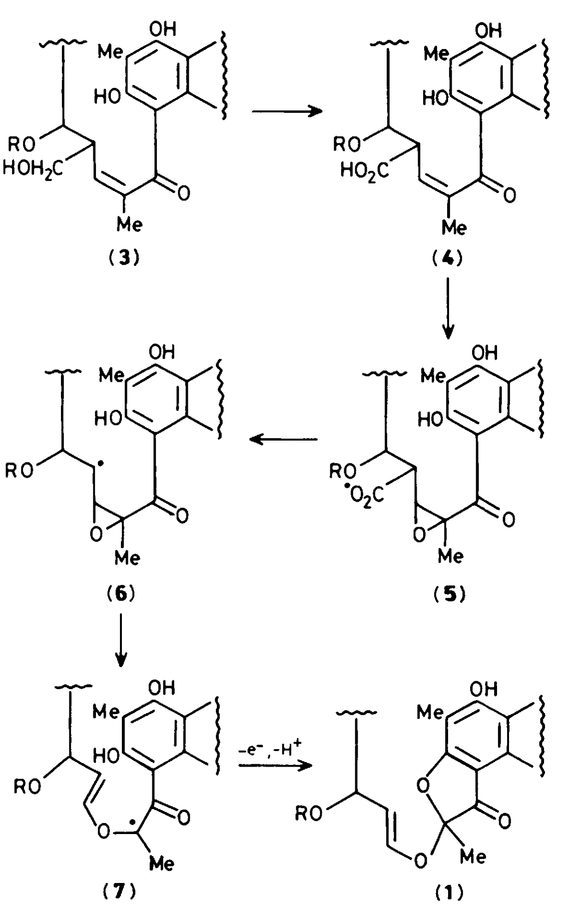
**(2)**



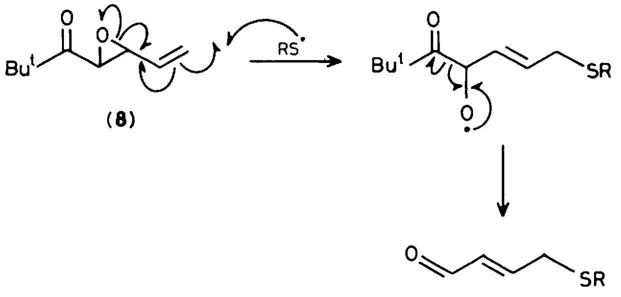
**(3)**

a chemically economical way,[5] together with a novel reaction which models *in vitro* the crucial and unprecedented step.

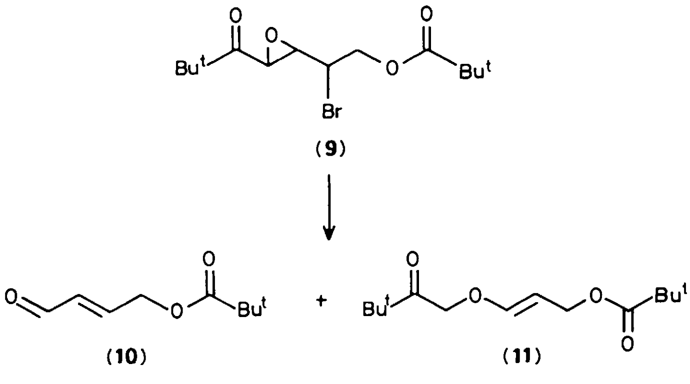
In the transformation of rifamycin H (**3**) to rifamycin S (**1**), C-34a is lost, and the isolation of oxidized forms of (**3**) in which this carbon is at the aldehyde or carboxylic acid oxidation levels has been taken to suggest that this carbon ends up as carbon dioxide.[3a,4a] Starting from the carboxylic acid (**4**), our radical mechanism for production of (**1**) is shown in Scheme 1. The crucial and unmodelled step features epoxide carbon–carbon bond cleavage (**6**) → (**7**). We have recently found[6] that fragmentation of epoxycarbonyl compounds (**8**) led to C–O bond cleavage within the epoxide and we were unable to detect vinyl ether products which would result from epoxide C–C bond cleavage (Scheme 2). We feared however that some vinyl ether product could have formed and decomposed during reaction. We have now studied an alternative radical cleavage substrate (**9**), prepared by reaction of (**8**) with *N*-bromosuccinimide (NBS) and potassium pivalate in pivalic acid. Reaction of (**9**) with tributylstannyl radicals led to the



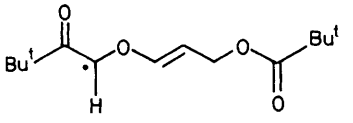
Scheme 1



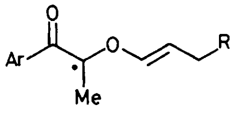
Scheme 2



Scheme 3



(12)



(13)

production of the α,β-unsaturated aldehyde (**10**) as major product (37%) but also the vinyl ether (**11**) as minor product (22%) (Scheme 3).[7] Although the vinyl ether is the minor product, this reaction occurs in the absence of enzymatic assistance which may be used to enhance C–C bond cleavage *in vivo*. Furthermore the radical (**12**) which is produced in our model system is on a less substituted carbon and hence is less stabilised than that in the rifamycin case (**13**) and we have already observed marked differences in the regioselectivity of radical-induced cleavages of other epoxides as a result of similar substitution differences.[8]

The above pathway is consistent with biosynthetic findings to date (*i.e.* we are not aware of rifamycin intermediates which have lost C-34a without incorporating oxygen as a vinyl ether, or of intermediates featuring an oxygen atom in the ansa chain but retaining C-34a). We believe that rifamycin S biosynthesis may thus be the first recognised natural example of the use of epoxide cleavage as an intramolecular radical indicator.[9]

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7 For other radical-induced epoxide cleavages leading to vinyl ether formation see: E. L. Stogryn and M. H. Gianni, *Tetrahedron Lett.*, 1970, 3025; M. Cook, O. Hares, A. Johns, J. A. Murphy, and C. W. Patterson, *J. Chem. Soc., Chem. Commun.*, 1986, 1419; for C–C bond cleavages of epoxides *via* non-radical routes see *e.g.* D. A. Whiting and P. Clawson, *Tetrahedron Lett*, 1987, **28**, 3155. This latter process is an unlikely candidate for the rifamycin oxygen insertion, since for an oxonium ylide to form, it is necessary to have two substituents present which are capable of highly stabilising the ylide; from the examples in the literature the substituents in the rifamycin case would not meet these criteria.

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