The Stereocontrolled Formation of 1,2,3-Triols by Yeast-mediated Transformation of α-Keto Epoxides

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3-Phenyl-2,3-epoxy ketones are transformed using baker's yeast into the corresponding 1,2,3-triols as one pure diastereoisomer (*S,S,S* and *R,R,R*) formed by *syn* ring opening of the epoxide after first reduction of the carbonyl group; the reaction results in the epoxy-oxygen becoming the mid OH group of the triol, implicating enzyme attack at the C-3 in the ring-opening reaction.

We have demonstrated elsewhere that α,β-unsaturated amides are readily epoxidised using lithium *tert*-butylhydroperoxide and that these epoxides are efficiently transformed into the corresponding epoxy ketones by action of organolithium compounds.[1] Furthermore, these ketones are converted into various types of products dependent upon the nature of the substituents by the action of baker's yeast.[2] Herein, we examine the remarkable stereocontrolled reaction of 1-phenyl-1,2-epoxy ketones with yeast, which yields 1,2,3-triols involving a *syn* ring opening of the epoxide and reduction of the ketone to give a single diastereoisomer in racemic form (Scheme 1).

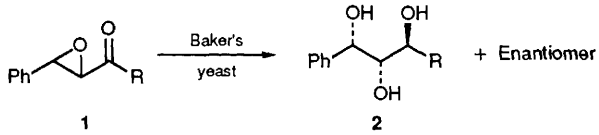
This transformation has several notable features: (*i*) The presence of bulky groups in the keto-substituent considerably slows the reaction. However, in no case has any intermediate been observed when the reaction was monitored at five-hourly intervals.

(*ii*) No reaction occurred in the absence of yeast, and pure, freshly cultured *Saccharomyces cerevisiae* gave identical results to the commercial yeast.†

(*iii*) That only one diastereoisomer was produced was indicated by the fact that a synthetic sample of the triols (prepared by permanganate hydroxylation of styryl n-butyl ketone followed by sodium borohydride reduction of the resulting dihydroxy ketone to give a mixture of the two diastereoisomers **2d** and **2d'**) showed double peaks for each carbon in their ^{13}C NMR spectra while all the products in Scheme 1 showed single peaks.

(*iv*) X-Ray crystallography‡ of the triol **2d** indicated that the compound was the *R,R,R* and *S,S,S* racemate, indicating *syn* ring opening of the epoxide ring.

(*v*) When a mixture of two diastereoisomers of the epoxy alcohol **3**§ was treated with yeast in the above manner, the



1 **2**

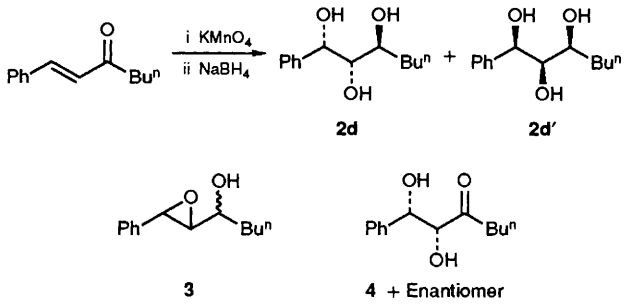
R	Yield (%)	Unchanged **1** (%)
a Et	51	
b Pr^n	74	
c Pr^i	22	54
d Bu^n	74	
e Bu^s	39	29
f Bu^t	13	67

Scheme 1

† The reactions were carried out as follows: The epoxy ketone (1.0 g) was added to actively fermenting yeast (12.5 g), sucrose (20.0 g) and water (200 ml) at 30 °C under anaerobic conditions. After 24 h a further aliquot of sucrose was added and after 48 h the total mass was continuously extracted with chloroform.

‡ The X-ray crystallography was kindly conducted by Dr J. L. M. Dillen.

§ The epoxy alcohols **3** were made by reduction of the epoxy ketone **1e** with sodium borohydride.

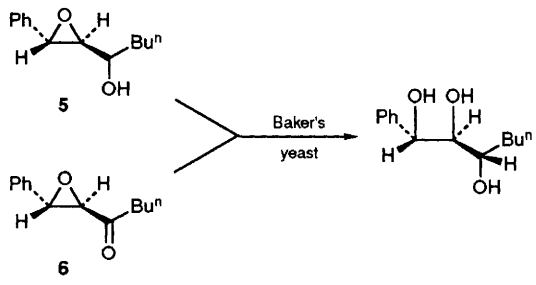


same diastereoisomer of the triol **2d** as derived from the ketone **1d** resulted, albeit in reduced yield (62%). However, the dihydroxy ketone **4** was unchanged on yeast treatment. This suggests that reduction of the ketone precedes ring opening of the epoxide but that the resultant epoxy alcohol does not exist as an enzyme-free intermediate.

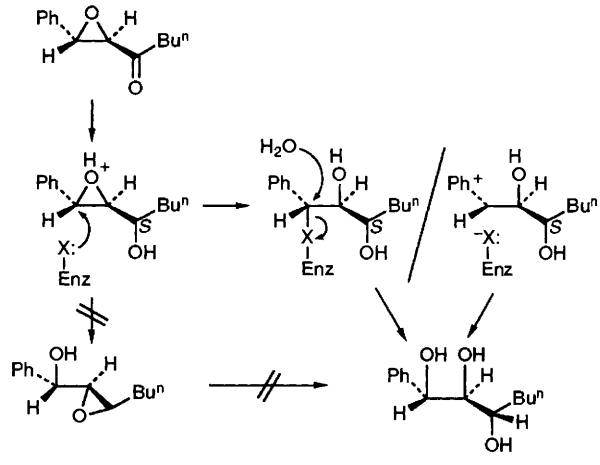
(*vi*) The homochiral (1*S*,2*S*,2*R*)-epoxy alcohol **5** [prepared from cinnamaldehyde by sequential treatment with butylmagnesium bromide, then L-(+)-diisopropyl tartrate–*tert*-butyl hydroperoxide] and the corresponding homochiral (1*S*,2*R*)-epoxy ketone **6** (prepared by oxidation of the above alcohol **5** with pyridinium dichromate) both gave essentially the same product, the (1*S*,2*S*,3*S*)-triol, on treatment with yeast (Scheme 2). Thus, no racemisation process is involved and it would appear that either one enzyme is capable of ring opening both enantiomers of the epoxide at equal rates stereospecifically (unusual but not without precedent[3]) or two enzymes exist that specifically open the two enantiomers—in either instance a remarkable feat.

(*vii*) When the epoxy ketone **2d** labelled with ^{18}O on the epoxide oxygen [prepared by treatment of benzaldehyde with ^{18}O-labelled water (97–98% isotopic purity) followed by a Darzens reaction with *N*,*N*-diethyl-2-chloroacetamide and potassium *tert*-butoxide. The epoxyamide was converted into the epoxy ketone in the manner already described[1]] was treated with yeast the resulting triol was obtained with no loss of label and with ^{18}O solely on the middle OH group (as shown by the known upfield ^{13}C NMR shift[4a–d] of carbons attached to ^{18}O and by mass spectral analysis¶). The unambiguous assignment of both the ^1H and ^{13}C NMR signals of all the relevant nucleii of **2d** were established by homo- and hetero-nuclear 2D correlation.[4a,b] This result implies that the ring opening of the epoxide must involve either a double inversion of C-1 of the triol or the involvement of an ion-pair, resulting in retention of configuration at C-1 (Scheme 3). The latter mechanism seems probable in that triol formation does not occur if the phenyl substituent is replaced by an alkyl group, supporting a benzyl cation intermediate. In any event, the involvement of a Payne rearrangement[5] in the formation of the triol is ruled out by this labelling experiment (Scheme 3).

¶ The mass spectrum of the triol **2d** does not show a molecular ion. However, the triol labelled with ^{18}O showed an M–H_2O peak at *m/z* 208 showing the retention of the label (43% of the peak at *m/z* 206 for the ^{16}O analogue). Furthermore, a peak at *m/z* 139 (43% of that at 137) characteristic of the ion $PhCHOHCH^{18}OH^+$, but *not* one at *m/z* 109 ($PhCH^{18}OH^+$) supports the argument for the label being on the central carbon of the triol function.



Scheme 2



Scheme 3

In conclusion, we have shown that 3-phenyl-2,3-epoxy ketones are transformed into 1,2,3-triols in a highly stereospecific manner involving *syn* ring opening of the epoxide—to our knowledge an unprecedented process. In view of the unusual mechanistic implications it is now intriguing to discover whether one or two enzymes are employed to ring open the two enantiomeric epoxides.

Received, 21st September 1992; Com. 2/05047A

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