Enantioselective Reduction of Racemic Ketones by Yeast

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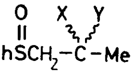
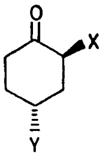
Summary Selective reductions of one enantiomer of simple racemic ketones have been observed with actively fermenting yeast; the method, which readily yields an optically active secondary alcohol and the recovered ketone in optically pure form, has led to the preparation of optically active sulphoxides and α-chloroketones.

It has been shown recently[1] that reductions of functionalised ketones by actively fermenting yeast (*Saccharomyces cerevisiae;* Fermex brand) yield the corresponding optically active alcohols in good chemical, and high optical, yields. Whilst enantioselective reactions in biological media are well known, they have not been reported in the reductions of simple racemic ketones with yeast, and we sought examples.

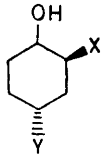
When 1-(phenylsulphinyl)acetone (**1**) was treated with actively fermenting yeast it was found that two β-hydroxysulphoxides were formed at vastly differing rates. The more rapidly formed alcohol, (R_{S},S_{C})-(+)-1-phenylsulphinylpropan-2-ol (**2**), $[\alpha]_{D}^{20}$ +321°, was formed in 50% yield after 30 h, whilst the less rapidly formed alcohol was present in trace amounts after 30 h and amounted to *ca.* 10% of the total mixture after 100 h. In spite of many attempts it was not possible to isolate a pure sample of this latter compound but enriched samples were strongly laevorotatory and showed similar spectral properties to those of alcohol (**2**). Hence it appeared to be either (S_{S},S_{C}) or (S_{S},R_{C})-1-phenylsulphinylpropan-2-ol. Finally, the sulphoxide ketone recovered from the reduction medium after 30 h had $[\alpha]_{D}^{20}$ −156°, and it was shown to be (*S*)-1-(phenylsulphinyl)-acetone (**3**).



(1) X,Y = O
(2) X = H, Y = OH



(4) X = Cl, Y = H
(5) X = OAc, Y = H
(6) X = OAc, Y = Bu^t



(7) X = Cl, Y = H
(9) X = OAc, Y = H
(11) X = OAc, Y = Bu^t

Reductions of the racemic cyclohexanones (**4**), (**5**), and (**6**) under similar conditions gave respectively (1*S*,2*R*)-(−)-2-chlorocyclohexanol (**7**), $[\alpha]_{D}^{20}$ −16·4° (32% yield) and (*S*)-(+)-2-chlorocyclohexanone (**8**), $[\alpha]_{D}^{20}$ + 33·8° (40%); 2-acetoxycyclohexanol (**9**), $[\alpha]_{D}^{20}$ +0·8° (40%) and (*R*)-(−)-2-acetoxycyclohexanone (**10**), $[\alpha]_{D}^{20}$ −85·1° (15%); and (1*R*,2*S*,4*S*)-(−)-2-acetoxy-4-t-butylcyclohexan-1-ol (**11**), $[\alpha]_{D}^{20}$ −48·6° (32%) and (2*R*,4*S*)-(+)-2-acetoxy-4-t-butylcyclohexanone (**12**), $[\alpha]_{D}^{20}$ +51·4° (40%).

Compounds (**2**) and (**3**) were demonstrated to be optically pure by observation of their ^{1}H n.m.r. spectra in the presence of Eu(TFC)$_3$.[2] The configuration at the sulphur atom in each case was assigned on the basis of o.r.d. and c.d. spectra,[3] whilst the configuration at the carbon atom in the alcohol (**2**) was determined by the method of Horeau.[4] The relative and absolute configurational assignments for compounds (**8**), (**10**), and (**12**) were made on the basis of ^{1}H n.m.r. and o.r.d. spectra; the relative configurations for compounds (**7**) and (**11**) were obtained from their ^{1}H n.m.r. spectra whilst oxidation of these alcohols with Jones' reagent gave the corresponding ketones which were shown to be enantiomeric to the ketones (**8**) and (**12**) respectively. Each of these optically active compounds was optically pure as judged by the above spectral criteria, except compound (**9**) which was shown to contain a mixture of the (+)- (77%) and (−)-isomers (23%). The fact that compound (**9**) was not optically pure was due to acyl exchange, well known with *cis*-hydroxyacetates under acidic conditions, and this was proven by observation of the racemisation of (**9**) under the reaction conditions.

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