Stereochemical Course of the Reduction of Cinnamaldehyde and Cinnamyl Alcohol to 3-Phenylpropanol by Fermenting Baker's Yeast

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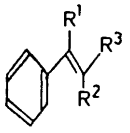
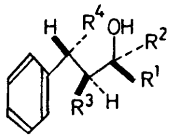
Summary Reduction of cinnamyl alcohol by fermenting baker's yeast proceeds with formal *trans* addition of hydrogen across the double bond, a *pro-R* hydrogen atom being introduced at position 2; (1*S*)-3-phenyl[1-$^2H_1$]propanol is obtained from [*formyl*-^{2}H]cinnamaldehyde and from [1-$^2H_2$]cinnamyl alcohol under the same conditions.

IN a study on the mechanism of enzymic transformations of the amino acid L-homoserine the four enantiomeric forms of 3-phenylpropanol asymmetrically labelled with isotopic hydrogen at positions 1 and 2 were needed as key synthetic intermediates.[1] We have therefore studied the steric course of the reduction of cinnamaldehyde and cinnamyl

alcohol to 3-phenylpropanol,[2] carried out by fermenting baker's yeast.

Thus, reduction of [*formyl*-^{2}H]cinnamaldehyde (**1**) to 3-phenylpropanol proceeded with the introduction at position 1 of a *pro-R* hydrogen atom, because ^{1}H-n.m.r. studies on the camphanoyl derivative of the saturated alcohol showed it to be the (1*S*)-isomer (**10**).[3] The unsaturated aldehyde (**1**) with purified yeast alcohol dehydrogenase, NAD^+, and ethanol gave (*E*)-(1*S*)[1-^{2}H]cinnamyl alcohol (**2**), free (by g.l.c.) from saturated alcohol.





(1) $R^1=R^2=H$; $R^3=CDO$

(2) $R^1=R^2=H$, $R^3=C(OH)H(D)$

(3) $R^1=H$; $R^2=D$, $R^3=CO_2H$

(4) $R^1=H$, $R^2=D$, $R^3=CH_2OH$

(5) $R^1=D$, $R^2=H$, $R^3=CH_2OH$

(6) $R^1=R^2=D$; $R^3=CD_2OH$

(7) $R^1=R^2=D$; $R^3=CO_2H$

(8) $R^1=H$; $R^2=Me$; $R^3=CH_2OH$

(9) $R^1=R^3=H$; $R^2=CH_2OH$

(10) $R^1=D$; $R^2=R^3=R^4=H$

(11) $R^1=R^2=H$; $R^3=D$

(12) $R^1=R^2=R^3=H$; $R^4=D$

(13) $R^1=R^3=R^4=D$; $R^2=H$

(14) $R^1=R^2=D$; $R^3=H$;

(15) $R^1=R^2=R^4=H$; $R^3=Me$

The steric course of the saturation of the double bond was determined using labelled (*E*)-cinnamyl alcohol as substrate. [α-^{2}H]Cinnamic acid (**3**), prepared by thermal decarboxylation of benzylidenemalonic acid which had been repeatedly dissolved in D_2O and freeze-dried, was converted *via* AlH_3 reduction of the ethyl ester into (*E*)-[2-^{2}H]cinnamyl alcohol (**4**) (96% $^2H_1$). The latter compound was reduced by yeast to the saturated alcohol, and oxidised (CrO_3 in acetic acid) to 3-phenylpropionic acid without deuterium loss. The latter compound upon ozonolysis yielded monodeuteriosuccinic acid. Mass spectrometric and o.r.d. measurements indicated it to contain 90 ± 10% of the (2*S*)-isomer, by comparison with an authentic sample,[4] thus suggesting that the 3-phenyl[2-^{2}H]propanol obtained in this reaction was the 2*S*-isomer (**11**), formed by stereospecific introduction of a *pro-R* hydrogen atom at position 2.

Repetition of the above-mentioned sequence starting with (*E*)-[3-^{2}H]cinnamyl alcohol (**5**) afforded 85 ± 10% of (2*R*)-[2-^{2}H]succinic acid, thus indicating that the biosynthetic 3-phenyl[3-^{2}H]propanol was the (3*R*)-isomer (**12**).

The above mentioned steric course was confirmed by experiments with [1,1,2,3-$^2H_4$]cinnamyl alcohol (**6**), which gave (1*S*,2*S*,3*R*)-3-phenyl[1,2,3-$^2H_3$]propanol (**13**) since the [2,3-$^2H_2$]succinic acid obtained from it was optically inactive, whereas the sodium salt of the intermediate dideuteriophenylpropionic acid showed a negative optical rotation of the same order of magnitude as that of the sample obtained from dideuteriocinnamic acid (**7**) using *Clostridium kluyveri* and hydrogen gas.[5] The steric course of the exchange of a deuterium atom at position 1 for a *pro-R* hydrogen atom, observed also using 3-phenyl[1-$^2H_2$]propanol (**14**) as substrate, was determined by n.m.r. studies,[3] and resulted in agreement with previous observations.[6]

Although (*E*)-2-methyl-3-phenylprop-2-en-1-ol (**8**) afforded (2*S*)-2-methyl-3-phenylpropanol (**15**) upon yeast reduction, (*Z*)-cinnamyl alcohol (**9**) was recovered unchanged even from experiments carried out under forcing conditions. A similar steric requirement has been observed recently with the enzyme-catalysed decarboxylation of cinnamic acid.[7]

The evidence therefore indicates a formal *trans* stereospecific addition of hydrogen atom across the double bond, a feature already observed in vegetal systems,[8] and the expected introduction of a *pro-R* hydrogen atom at position 1 in the reduction of the unsaturated aldehyde (**1**).

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