Decarboxylative Incorporation of α-Oxobutyrate and α-Oxovalerate into (*R*)-α-Hydroxyethyl- and n-Propyl Ketones on Reaction with Aromatic and α,β-Unsaturated Aldehydes in Baker's Yeast

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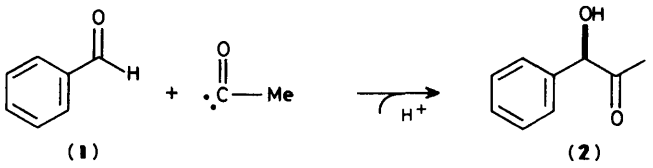
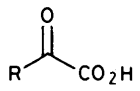
Decarboxylative incorporation of linear C_3, C_4, and C_5 α-oxo acids into (*R*) α-hydroxy ketones (**2**), (**9**) and (**10**) is observed when benzaldehyde (**1**) is incubated with baker's yeast; α,β-unsaturated aldehydes (**11**) and (**15**) with the C_3 and C_4 acids yield (*R*)-α-hydroxy methyl and ethyl ketones (**16**), (**20**), (**19**), and (**21**).

The well established[1] asymmetric acyloin-type condensation of benzaldehyde (**1**) to (*R*)-acetylphenylcarbinol (**2**) [useful intermediate in the manufacture of (−)-ephedrine] occurring in fermenting baker's yeast, is one of the most significant examples of enzymic transformations of non-conventional substrates, and has only recently found parallels in synthetic chemistry.[2,3] The identity of the enzyme(s) involved in the reaction is in question.[4,5] However, the formation of (**2**), in analogy with acetoin,[6] can be viewed (Scheme 1) as the consequence of the condensation of the 'active' form of

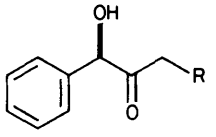


(1) (2)

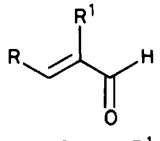
Scheme 1



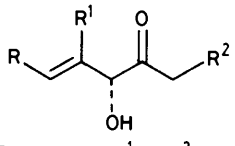
(3) R = Me
(4) R = CH_2Me
(5) R = CH_2CH_2Me
(6) R = $CHMe_2$
(7) R = C_6H_5
(8) R = 2-furyl



(9) R = Me
(10) R = CH_2Me



(11) R = C_6H_5; R^1 = H
(12) R = C_6H_5; R^1 = Me
(13) R = 2-furyl; R^1 = Me
(14) R = EtO_2C; R^1 = H
(15) R = EtO_2C; R^1 = Me

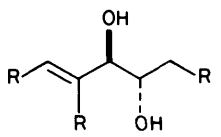


(16) R = C_6H_5; R^1 = R^2 = H
(17) R = C_6H_5; R^1 = Me; R^2 = H
(18) R = 2-furyl; R^1 = Me; R^2 = H
(19) R = C_6H_5; R^1 = H; R^2 = Me
(20) R = EtO_2C; R^1 = Me, R^2 = H
(21) R = EtO_2C; R^1 = R^2 = Me

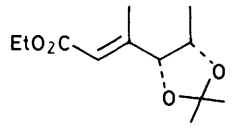
acetaldehyde formed by decarboxylative addition of pyruvate to thiamine pyrophosphate, with benzaldehyde, and the role of pyruvate as the C_2 donor has been established.[7] The same mechanism is expected to operate[8] with the baker's yeast-mediated conversion of aromatic α,β-unsaturated aldehydes (**11**)—(**13**) into (2*S*,3*R*)-methyl diols (**22**)—(**24**). However, under the fermentation conditions, the intermediate (3*R*)-hydroxyketones (**16**)—(**18**) are stereospecifically reduced to the diols actually isolated.

The wide synthetic significance[9] shown by the latter materials and the early observation that pyruvate decarboxylase (EC 4.1.1.1.) will accept as substrates α-oxoacids higher than pyruvic, led us to explore the possibility of obtaining in baker's yeast from the intermediates formed in the decarboxylation of these materials and suitable aldehydes, homologues of (**2**) and (**22**)—(**24**).

In the first set of experiments benzaldehyde (**1**) (16 g l^{-1}) was incubated with equimolecular amounts of the α-oxo acids (**3**)—(**8**) in the presence of *ca.* 15 fold excess of baker's yeast



(22) R = C_6H_5; R^1 = R^2 = H
(23) R = C_6H_5; R^1 = Me; R^2 = H
(24) R = 2-furyl; R^1 = Me; R^2 = H
(25) R = C_6H_5; R^1 = H; R^2 = Me
(26) R = EtO_2C; R^1 = Me; R^2 = H



(27)

(wet weight), washed with water[11]† at pH 5.5—6.0 and 23 °C. After 24—36 h the maximum conversion was reached. Extractive work up, chromatography and bulb-to-bulb distillation, afforded from the C_3, C_4, and C_5 linear α-oxo acids (**3**)—(**5**) the corresponding (*R*)-α-hydroxy ketones (**2**), $[\alpha]_D^{20}$ −380° (*c* 1, $CHCl_3$),[1] (**9**), $[\alpha]_D^{20}$ −395° (*c* 1, $CHCl_3$),[12] and (**10**), $[\alpha]_D^{20}$ −282° (*c* 1, $CHCl_3$).[13] The optical purity of these materials was determined by ^1H n.m.r. studies in the presence of $Eu(tfc)_3$ [tris(trifluoroacetylcamphorato)europium(III)] and comparison with synthetic racemic products and was shown to be >95% enantiomeric excess (e.e.). The yields ranged from 15 to 25%.‡ No condensation products were observed under the above conditions with the α-oxo acids (**6**)—(**8**).

Subsequently, the α,β-unsaturated aldehydes (**11**) and (**13**)—(**15**) were submitted to the above reaction conditions. In the presence of the α-oxo acids (**3**)—(**5**) with cinnamaldehyde (**11**) the formation of (**16**) and (**19**) from (**3**) and (**4**) was observed. The resulting α-hydroxy ketones were unstable[14] and were reduced *in situ* to the corresponding diols (**22**)[15] and (**25**),[8] in 20 and 15% yield respectively, by the addition of fresh baker's yeast and D-glucose. The aldehyde (**13**) afforded the (*R*)-hydroxy ketone (**18**) $[\alpha]_D^{20}$ −200.5° (*c* 1, MeOH), subsequently reduced, as above, to the (2*S*,3*R*) diol (**24**)[16] with (**3**) in 15% yield, but no transformation products were observed in the presence of (**4**) and (**5**). Futhermore, ethyl 3-methyl-4-oxo crotonate (**15**) yielded with (**3**) and (**4**) the α-hydroxy ketones (**20**) and (**21**) in 20 and 18% yield respectively. Product (**20**) was shown to be optically pure on the basis of the following evidence. Yeast reduction of (**20**) yields (4*R*,5*S*)-ethyl 3-methyl-4,5-dihydroxy-hex-2-enoate (**26**), $[\alpha]_D^{20}$ +12.3° (*c* 1, MeOH), converted [$Me_2C(OMe)_2$, toluene-*p*-sulphonic acid] into (**27**), $[\alpha]_D^{20}$ −61.6 (*c* 1, MeOH), in 68% overall yield. Identical material, prepared from optically pure (3*S*, 4*S*) 3,4-isopropylidenedioxypentan-3-one[13] by reaction with $Ph_3P{=}CHCO_2Et$, showed $[\alpha]_D^{20}$ −62°. Interestingly enough, a *ca.* 35% yield of (**26**) was obtained when to a mixture of 3% ethyl 3-methyl-4-oxo crotonate (**15**) and 5% D-gluclose in water at pH 5.5—6.0 and 23 °C fresh baker's yeast (10 fold excess) was added portionwise during 24 h. Optical purity and absolute configuration of (**21**) were not determined. No condensation products were observed with (**3**)—(**5**) when ethyl 4-oxo crotonate (**14**) was used as substrate.

Mechanistic considerations are outside the scope of the present note. Further work is in progress in order to better define the apparently subtle structural requirements for

† The use of carbohydrate-free yeast, reduces or prevents the extent of aldehyde reduction, and the formation of condensation products with the C_2 unit coming from pyruvate. When sodium pyruvate was added, hydroxy ketone (**2**) was obtained.

‡ Yields are not optimized.

acceptability by the enzyme(s) involved in this asymmetric C–C bond-forming reaction.

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