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On the Mode of Baker's Yeast Reduction of Benzylidenecyclohexanone

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***Abstract**: Baker's yeast reduction of benzylidene cyclohexanone 1 affords, as major transformation product, enantiomerically pure (S) carbinol 3, yielding in two steps (2S) 2-acetoxycyclohexanone 6, close to nearly racemic saturated ketone 4, whereas carbinol 5 and its enantiomer 8 can be obtained from 3 upon* $LiAlH_4$ *reduction upon baker's yeast reduction to 7, followed by inversion of configuration, respectively.*

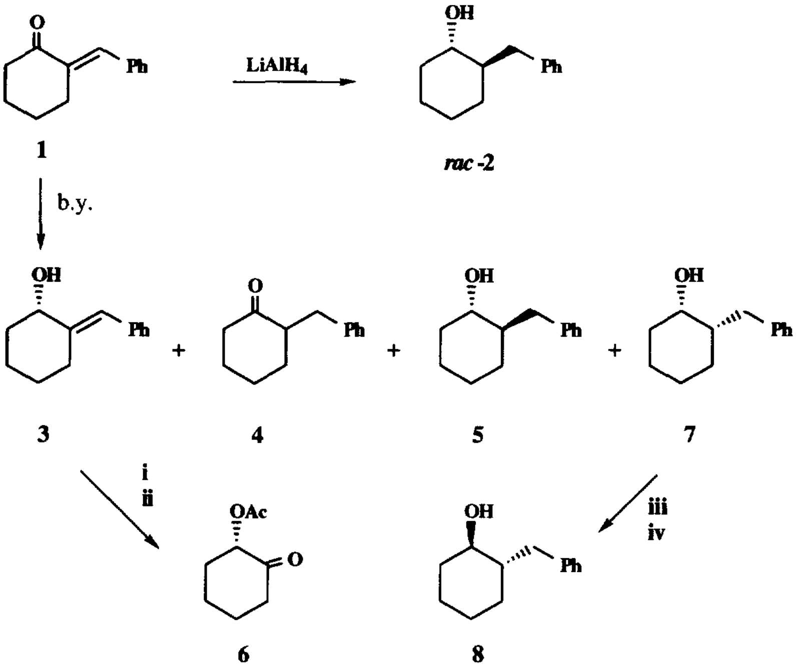
Recently it was reported that $LiAlH_4$ reduction of benzylidenecyclohexanone **1** gave, stereoselectively, the saturated *trans* carbinol **2** [1]. The ability of baker's yeast to reduce α,β-unsaturated carbonyl compounds, in a mode strongly dependent on structural features present, is well documented[2]. Accordingly, we undertook a comparative study of baker's yeast reduction of unsaturated ketone **1**[3]. This gave a mixture of unsaturated alcohol **3** and saturated ketone **4** in a ratio of 1:1.5. Also formed in traces amounts were saturated carbinols **5** and **7** . The overall yield (**3**+**4**+**5**+**7**) was 85%. The unsaturated carbinol **3** (m.p. 76-79°C) crystallised from a solution of the mixture in pentane ($[\alpha]_D^{20}$= -35.2° (c 1.2, $CHCl_3$)). This compound, obtained in 30% yield was found to be optically pure by ^1H NMR in the presence of $Eu(hfc)_3$ and by chiral HPLC (Chiralcel OD)[4], with racemic material obtained by $NaBH_4$ reduction of **1** as standard. The bioreduction product **3** was assigned the *S*-configuration by acetylation followed by ozonolysis to give the α-acetoxyketone **6** of known absolute configuration[5]. The saturated ketone **4** ($[\alpha]_D^{20}$= + 9.1° (c 1.3, $CHCl_3$)) proved to be nearly racemic (10% ee by ^1H NMR studies in the presence of chiral shift reagents).

Baker's yeast reduction of the racemic saturated ketone **4** under more forcing conditions[3] gave a mixture of *cis* and *trans* carbinols **7** and **5** in an overall yield of 80%. Compounds **7** (m.p. 67-70°C, $[]\alpha_D^{20}$= +28.2° (c 1, $CHCl_3$)) and **5** (m.p. 46-48°C, $[\alpha]_D^{20}$= +49.2° (c 1, $CHCl_3$) were formed in a ratio of 2:1.

The *trans*-carbinol **5** was identical in all respects with the product obtained by reduction of allylic alcohol **3** by $LiAlH_4$ in boiling THF, which, by analogy with conversion of unsaturated ketone **1** to saturated alcohol rac-**2**, was assumed to have the *trans*-configuration.

The major diastereoisomer **7**, from the baker's yeast reduction of **4**, was converted into the tosylate. Substitution of the tosylate group by acetate followed by hydrolysis gave the saturated alcohol **8**, which was shown to be the enantiomer of **5** by optical rotation measurements and chiral HPLC.

Accordingly, this single procedure provides access to the enantiomerically pure cyclohexanol derivatives **3**, **5**, **7**, and **8**[6].



i) Ac_2O/Pyr/r.t.; ii) O_3/CH_2Cl_2/-78 °C, then Ph_3P; iii) TsCl/Pyr; iv) CH_3COONa/DMF/reflux, then NaOH 1N, reflux

Scheme 1

These investigations, which are being extended in our laboratory to include related cyclopentanone derivatives, provide further examples of the usefulness of baker's yeast reductions in providing enantiomerically pure and highly functionalized small molecules useful as building blocks in organic synthesis.

References and Notes

1. Koch, K.; Smitrovich, J.H. *Tetrahedron Lett.*, **1994**, *35*, 1137.
2. Servi, S. *Synthesis*, **1990**, 1.
3. 50 g of substrate/1 kg baker's yeast/2 l tap water/100 g D-glucose/38-40 °C/5 h. Forcing conditions: 2 kg of yeast added in portions during 24 h.
4. Chiralcel OD, hexane/2-PrOH=95/5, 0.6 ml/min, UV=254 nm, retention times: 3R=15.4 min, 3S=20.36 min.
5. Harada, T., Wada, I., Oku, A.; *J.Org.Chem.* **1989**, *54*, 2599.
6. For a recent example of microbial reduction of α-substituted cyclic ketones see: Buisson, D.; Cecchi, R.; Lafitte, J.A.; Guzzi, U.; Azerad, R.; *Tetrahedron Lett.*, **1994**, *35*, 3091.

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