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Preparation of Highly Enantiopure Pyridylethanols by Baker's Yeast Reductions.

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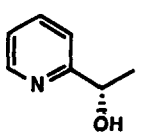
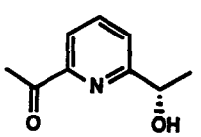
Abstract: Bakers' yeast is used to prepare **3a**, **4a** and **5a** in high enantiomeric purity by addition of allyl alcohol to the reaction. The double reduction of 2,6-diacetylpyridine **2** with bakers' yeast leads to **5a** with essentially complete enantiomeric purity predicted to be 99.97%ee.

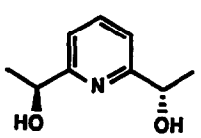
Bakers' yeast (*Saccharomyces cerevisiae*) has been used widely as a method for achieving asymmetric reductions of ketones.[1] By its very nature however bakers' yeast will often reduce ketones with moderate enantioselectivities as it is known to contain several dehydrogenase activities.[2] These dehydrogenases have contradictory stereoselectivities, the relative activities of which depend on the substrates presented to them.[2] This paper reports the methods we have used to achieve high enantioselectivity in the generation of pyridylethanols **3a**, **4a** and **5a**[3] using bakers' yeast.



3a

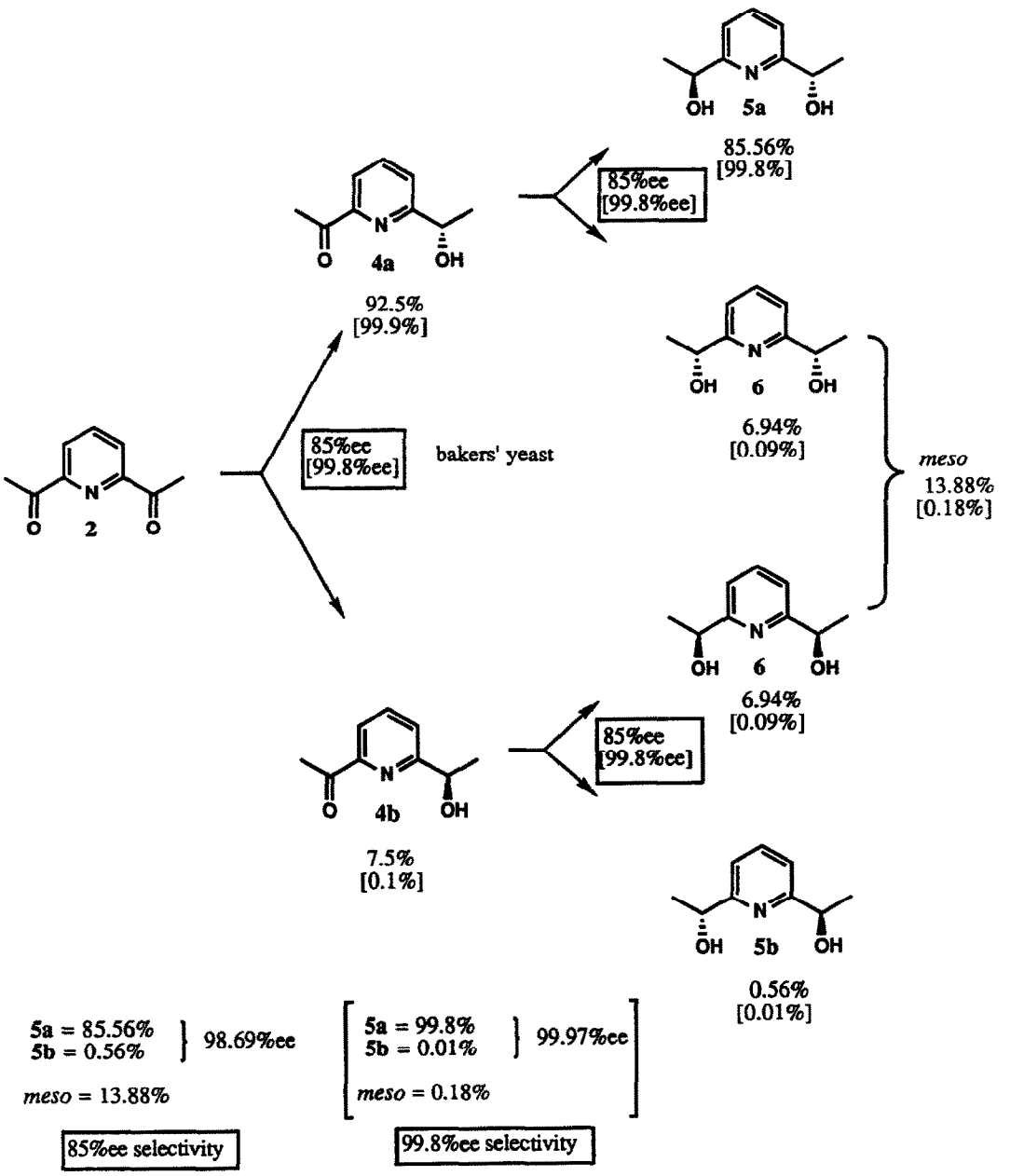


4a



5a

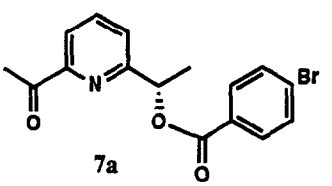
Reduction[4] of 2-acetylpyridine **1** with fermenting yeast gave pyridylethanol **3a** in 85%ee.[5] This transformation was previously achieved by a Japanese group[6] in 96%ee, however the discrepancy in selectivity almost certainly reflects the variation of yeast sources used. In order to improve the enantioselectivity we investigated the addition of allyl alcohol to the reaction. It had previously been reported[7] that addition of α,β-unsaturated carbonyl



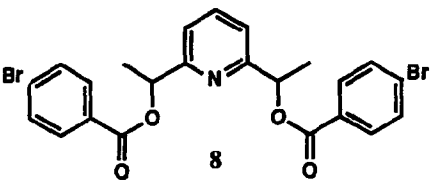
Scheme Overall stereochemical profile of the double yeast reduction of **2** at 85%ee. Square bracketed figures represent the distribution at 99.8%ee, which approximates closely the allyl alcohol modification.

compounds, or their corresponding allyl alcohols, to yeast reductions can improve the stereoselectivity and allyl alcohol proved to be one of the most successful additives in this regard. Accordingly, allyl alcohol (0.5equiv w.r.t **1**) was added to the fermenting yeast reaction and in the event substantially improved the enantioselectivity. (S)-Pyridylethanol **3a** (>95%ee)[5] was recovered 35% yield, $[\alpha]_D^{20}$ = -29.14, (c4.94,$CHCl_3$).[8]

We then investigated reduction of the bifunctional substrate, 2,6-diacetylpyridine **2**. Complete mono reduction of **2** using yeast was achieved after 24 hours and gave **4a** in 67% yield with 85%ee.[5] This is the same moderate enantioselectivity observed for **3**. Again however, addition of allyl alcohol (0.25equiv w.r.t **2**) to the reaction proved expedient and improved the enantiomeric purity of **4a** to 99.8%ee, $[\alpha]_D^{20}$ = -7.5,(c1.5, $CHCl_3$), after derivatisation as its *p*-bromobenzoate ester **7a** and quantitative chiral HPLC analysis[12]. When the reaction without allyl alcohol was allowed to continue, then the second acetyl group underwent reduction. This was a slow transformation which after 5 days gave a mixture of the mono-reduced products **4** and the doubly reduced DL-**5** and *meso*-**6** diols in the ratio 70:26:4. The diols **5** and **6** were easily separated from **4** by chromatography and were isolated in 15% yield. Derivatisation of the diol mixture as its di-*p*-bromobenzoate esters **8** allowed us to more easily assess the diastereomeric DL:*meso* ratio by ^{1}H-NMR as 87:13.



7a



8

Our interpretation of the stereochemical profile of this reaction follows from a recent analysis of the reductions of symmetrical bifunctional systems[10] and is illustrated in the Scheme. The first reduction has a stereoselectivity of 85%ee. In view of the fact that we obtain 13% of the *meso* product **6** from the yeast reaction, we can say with some confidence that the second reduction has a similar stereoselectivity to the first, ie. 85%ee. It follows from the Scheme that the enantiomeric excess of **5a** over **5b** is therefore 98.69%. The *meso* component is easily removed by recrystallisation of **8** and thus **8a** can be obtained in >98.7%ee[11]. It should also be noted that recrystallisation will adventitiously remove residual traces of **8b**. When allyl alcohol (0.25mol equiv) was added to the double yeast reduction the situation improved further and none of the *meso* diastereoisomer was detectable when the diol product **5a** ($[\alpha]_D^{20}$ = -26.84 , (c2.98, $CHCl_3$)) was converted to **8**. Quantitative chiral HPLC analysis of **8** demonstrated that the material was essentially the single enantiomer, **8a** with an optical purity of >99.92%ee. X-ray analysis of a crystal of (S,S) **8a** confirmed its absolute stereochemistry[13]. The very high %ee is to be expected in view of the enantiomeric purity of **4a** (99.8%ee) recovered after the first reduction. It can be predicted from the Scheme [bracketed figures], assuming that both reductions proceed with a similar selectivity, that the ultimate purity of **5a** will be 99.97%ee! This is close to the experimental value obtained for **8a** (>99.92%ee).

Acknowledgements; We thank the SERC and Glaxo Group Research Ltd., for a CASE studentship (DB), and Mr Robert J. Boughtflower (G.G.R.) for chiral HPLC analysis.

Notes and References

1. For a comprehensive review of bakers' yeast transformations in organic synthesis see S. Servi, *Synthesis*, 1990, 1.
2. W-R Shieh, A.S. Gopalan and C.J. Sih, *J. Am. Chem. Soc.*, 1985, **107**, 2993.
3. Compound numbers suffixed with **a** refer to the L- or (S) configuration and those suffixed with **b** to the D- or (R) configuration.
4. *Typical Bakers' yeast reduction*; To a suspension of yeast (*S. cerevisiae*, Type 1, Sigma Chem. Co.)(50g) in an aqueous solution of glucose (100g/150ml) at 35°C was added ketones **1** or **2** (30mM) and allyl alcohol (15mM or 7.5mM). Two aliquots of aqueous glucose (100g/150ml) were then introduced after 2 and 4 hours and the reaction left to stir at 35°C for either 24 hours (mono-reduction) or 5 days (di-reduction). In every case the products were recovered after extraction into diethyl ether and purification by column chromatography over silica.
5. The %ee values for **3a** and **4a** were determined, after conversion to their corresponding acetates, by ^{1}H-NMR and chiral shift analysis using [Eu(hfc)3]. This method is only reliable to 95%ee.
6. M. Takeshita, K. Terada, N. Akutsu, S. Yoshida and T. Sato, *Heterocycles*, 1987, **26**, 3051.
7. K. Nakamura, Y. Kawai, S. Oka and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 875; K. Nakamura, K. Inoue, K. Ushio and S. Oka, *Chem. Letts.*, 1987, 679.
8. The absolute stereochemistry of (-) **3** has been established as the (S) enantiomer **3a** by M. Imuta and H. Ziffer, *J. Org. Chem.*, 1978, **43**, 3530. Literature rotation data for **3a**; Ref 6, 96%ee, $[\alpha]_D^{20}$ = -25, c1.5; Ref 9, >95%ee, $[\alpha]_D^{20}$ = -26.4, (c1.34, $CHCl_3$).
9. R. Seemayer and M. P. Schneider, *Tetrahedron Asymmetry*, 1992, **3**, 827.
10. K. Soai, H. Hori and M. Kawahara, *J. Chem. Soc., Chem. Commun.*, 1992, 106.
11. Selected analytical data for **8a**. mp 154-154.5°C, $[\alpha]_D^{20}$ = +70.18, (c1.71, $CHCl_3$).
12. Chiral HPLC analysis of **7a** and **8a** were carried out using a Chiracel OD column in hexane : ethanol (98:2). In the racemate **8b**, *meso* **8** and **8a** were clearly resolved in the expected ratio of 1:2:1. For biotransformed mixtures, accurate %ee values were determined by intergration after spiking with a known amount (0.5%) of racemate.
13. Crystal data: (S,S) **8a**, $C_{23}H_{19}Br_2NO_4$, M = 533.22, orthorhombic, $P2_12_12_1$, a = 6.945 (1), b = 15.923(3), c = 19.898(6)Å, V = 2200(2)Å^3, λ =1.54178Å, z =4, D_c = 1.61g cm^{-3}, F(000) = 1064, μ(Cu-Kα) = 4.95mm^{-1}. Siemens R3m/V diffractometer, 2989 independent reflections measured ($3 < 2\theta < 115°$) of which 1964 reflections has $I > 3.0\ \sigma(I)$. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0050\ |F_o|^2]^{-1}$, refinement converged at R 0.078, R_w 0.083, goodness of fit = 1.24. The eta test of Rogers[14] [η = 1.0(1)] was used to determine the absolute configuration of the molecule.
Full details of the crystal structure have been deposited at the Cambridge Data Centre.
14. D. Rogers, *Acta Cryst.*, 1981, **A37**, 734.