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BAKER'S YEAST-MEDIATED HYDROGENATION OF 2-SUBSTITUTED ALLYL ALCOHOLS: A BIOCATALYTIC ROUTE TO A NEW HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (R)-2-METHYL ALKANOLS

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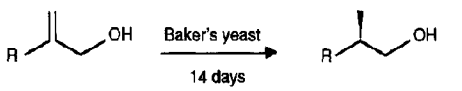
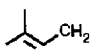
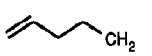
Abstract. The biohydrogenation of 2-substituted allyl alcohols **1a-c** proceeds enantioselectively (95-98% ee) to afford (R)-2-methyl alkanols **2a-c**.

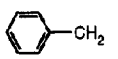
The use of baker's yeast as chiral reducing agent has been shown to be extremely versatile for the enantioselective preparation of optically pure compounds.[1] Several examples of hydrogenation of carbon-carbon double bonds have been described, although most results refer to unsaturated carbonyl groups.[2] In this context, the asymmetric reduction of the double bond in α-methylene ketones has received scant attention,[3] probably because easy syntheses of these compounds are not available. In connection to our studies on lipase-catalyzed transesterifications of 2-substituted oxiranemethanols,[4] we prepared 2-susbstituted allyl alcohols **1a-c** by diisobutylaluminum hydride (DIBAL) reduction of the corresponding unsaturated esters, in turn prepared by a described method.[5]



1 (R)-2

a. R = 

b. R = 

c. R = 

d. R = 

Following a different route,[6] we prepared also the alcohol **1d**, which differs from the previous ones because the double bond is conjugated with the phenyl group. The above allyl alcohols **1a-d** were chosen as representative substrates for baker's yeast-mediated biohydrogenation, since this biocatalytic route should lead to an easy preparation of chiral 2-methyl alkanols **2** which are useful intermediates in organic synthesis.[7] The biohydrogenation of **1a-c** required 14 days[8] affording, after purification, the (+)-2-methyl alkanols **2a-c** in 40-45% yield.[9] As established by ^{1}H-NMR analysis

(500 MHz) of the corresponding MTPA esters,[10] the three alkanols **2a-c** were nearly enantiomerically pure (98, 95 and 96% ee, respectively). We found that the alcohol **1d** is not a substrate for the baker's yeast biotranformation in the same experimental conditions. At longer times (21-25 days) only trace amounts of more polar compounds were formed. The (R)-configuration of the alcohol **2c**, $[\alpha]_D$ +10 (*c* 1.15 in benzene) was established by comparison with the optical rotation reported for (R)-**2c**.[11] The same (R)-configuration was established for **2b** by the 500 MHz ^{1}H-NMR spectrum of its MTPA ester.[12] For (+)-**2a**, $[\alpha]_D$ +0.56 (*c* 1.4 in CH_2Cl_2), the same configuration was established by ozonolysis-reduction conversion to the known (R)-2-methyl-1,4-butanediol.[13] It is worth mentioning that, although the reduction of other unsaturated compounds may proceed with high enantioselectivity, in many instances the stereochemical outcome and the optical purity of the products are dependent on the geometry and substitution of the double bond.[14] This is not the case of the baker's yeast-mediated biohydrogenation of 2-substituted allyl alcohols **1a-c**, which may now constitute a new access to enantiomerically pure 2-methyl alkanols.[15]

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8. A yeast/substrate ratio (g/mmol) 40/1 was used in the incubation of **1a**, whereas for **1b** and **1c** a 30/1 ratio was necessary.
9. The ratio of saturated *versus* the unsaturated alcohols **2a-c**/**1a-c** was generally 9:1 and for an easier purification the unreacted allylic alcohol was oxidized by means of MnO_2.
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12. The resonances of the CH_2O moiety in the spectrum of the MTPA ester of (+)-**2b**, $[\alpha]_D$ +1.14 (*c* 1.4 in CH_2Cl_2), were superimposable to all the other (R)-2-methyl alkanols prepared by lipase-catalyzed resolution of racemic alcohols. See, for instance: Ferraboschi, P.; Grisenti, P.; Manzocchi, A.; Santaniello, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1159.
13. The optical rotation of the enantiomerically pure (R)-2-methyl-1,4-butanediol has been reported: Feringa, B. L.; de Lange, B.; de Jong, J. C. *J. Org. Chem.* **1989**, *54*, 2471.
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15. The yeast-mediated biohydrogenation-oxidation of a sulfur containing allyl alcohol (compound **1**, R=PhSCH$_2$CH$_2$) has been reported to yield the corresponding (R)-2-methyl acid: Sato, T.; Hanayama, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 2197. Also from our incubations we found some acidic compound, which was not isolated or characterized.

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