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Enantioselective *Pseudomonas fluorescens (P. cepacia)* Lipase-Catalyzed Irreversible Transesterification of 2-Methyl-1,2-Diols in an Organic Solvent

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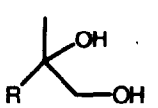
Abstract: The *Pseudomonas fluorescens (P. cepacia)* lipase-catalyzed irreversible transesterification of 2-phenyl-1,2-propanediol **1a** is not enantioselective, whereas the diols **1b** and **1c** are enzymatically resolved with the same procedure to (S)-**1b** and **1c** (>98 and 92% e.e.) and the (R)-acetates **2b** and **2c** (92% e.e.).

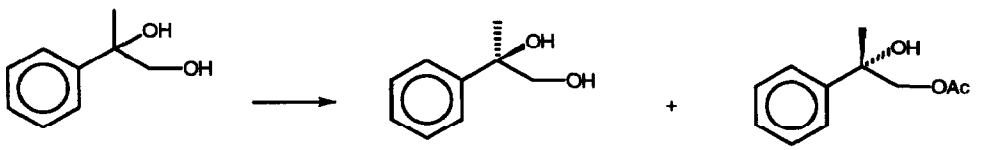
1,2-Diols can be found in many pharmaceuticals and synthetic intermediates[1] and several chemical and enzymatic approaches have been used to achieve the preparation of such compounds in enantiomerically pure forms.[2] A special class of these compounds is constituted by 2-methyl-1,2-diols **1** that contain a primary and a tertiary alcohol group and that could be interesting chiral synthons if prepared optically pure.[3] Among the vast array of biocatalytic methods for the preparation of enantiomerically pure compounds,[4] the lipase-catalyzed transesterification in organic solvents[5] has been frequently used to resolve racemic alcohols.[6] However, this method does not seem to apply satisfactorily to the resolution of 1,2-diols,[7,8] including a few 2-methyl-1,2-diols.[9] In contrast, a few α,α-disubstituted 1,2-diols were examined as substrates for a lipase-catalyzed resolution, that proceeded with high enantioselectivity.[10] We describe here the results of our study on the resolution of the diols **1a-c** under conditions of the irreversible transesterification with vinyl acetate in an organic solvent in the presence of *Pseudomonas fluorescens (P. cepacia)* lipase.[5] We investigated these diols, since we have collected many results on the resolution of several 2-substituted alkanols,[11] including some 2-substituted oxiranemethanols.[12] We were interested in the structural features of the diols **1a-c** which would permit the stereogenic center to be accepted by the enzyme so that an enantio- and regioselective enzymatic acylation could be achieved.



1

a. R = Ph
b. R = $PhCH_2$
c. R = $(CH_3)_2C{=}CHCH_2$

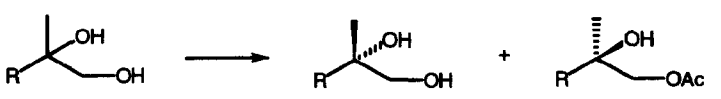
It has already been reported that the enzymatic resolution of 2-phenyl-1,2-propanediol **1a** using other conditions is not enantioselective[9a] and we repeated the enzymatic reaction with PFL and vinyl acetate in chloroform. The PFL-catalyzed transesterification of the diol **1a**[13] was very slow, since 31 and 69 hours were required to reach 40 and 60% conversion, respectively, to the acetate **2a**.[14] The low optical rotation for both (-)-**1a** and **2a** ($[\alpha]_D$ -0.7 in both cases)[15] suggested that a low e.e. was obtained for this resolution. This was confirmed by the 500 MHz ^{1}H-NMR spectra of the MTPA esters[16] of (-)-**1a** and of the alcohol **1a** obtained by hydrolysis of the (-)-acetate **2a** that showed a 10% e.e. in both cases.[17]



1a (R)-**1a** (S)-**2b**

10% ee

Since it could not be excluded that the racemization of the optically active diol **1a** had occurred in the reaction medium,[18] we subjected to the PFL-catalyzed transesterification the (R)-(-)-diol **1a** (92% e.e.)[19,20] and its optical rotation remained unchanged. This experiment ruled out the possibility of a chemical racemization and confirmed that the diol **1a** is not a suitable substrate for the PFL-catalyzed resolution. On the contrary, the enzymatic resolution of the racemic diols **1b** and **1c** proceeded with high enantioselectivity and in both cases the (S)-diols **1b** and **1c** [21] and the (R)-acetates **2b** and **2c** were obtained with e.e. between 92 and >98%, the only difference being in the reaction times.[22,23]



1b,c (S)-**1b,c** (R)-**2b,c**

Thus, the PFL-catalyzed transesterification also proceeds efficiently on a 2-methyl-1,2-diol as substrate, provided that some structural requirements are taken in consideration. In fact, the negative results of the diol **1a** confirms previous observations[20] that in the class of 2-substituted alkanols the phenyl ring directly bound to the stereogenic center exerts a sort of unfavourable electronic effect that influences the steric orientation of the groups at the active site of the enzyme.[24] As a result, the reaction proceeds with a very low enantioselectivity in a completely different fashion with respect to substrates as the diols **1b** and **1c** that are better recognized by the active site of the enzyme.

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References and Notes

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2. An overview of the most significant chemical and enzymatic approaches of interest to this topic is reported in a recently published detailed study; see: Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388.
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4. Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071.
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7. The enantioselectivity of the monoacylation step is apparently low and a sequential resolution of the diols is necessary to achieve high e.e. of the products (ref. 2).
8. Using the irreversible transesterification procedure on 2-phenyl 1,2-ethanediol and 3-phenyl-1,2-propanediol only 30% e.e. could be achieved and protection of the above diols as 2-methyl ethers did not enhance the enantioselectivity of the resolution beyond 62%.
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12. Ferraboschi, P.; Brembilla, D.; Grisenti, P.; Santaniello, E. *J. Org. Chem.* **1991**, *56*, 5478.
13. The diol **1a** was prepared by lithium aluminum hydride reduction of the corresponding epoxy alcohol, in turn obtained by epoxidation of 2-phenyl-2-propen-1-ol that could be prepared directly from benzoyl chloride only on millimolar scale. (Barluenga, J.; Concellon, J. M.; Fernandez-Simon, J. L.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 536). For larger scale, the required methylene alcohol was obtained (47% yield) starting from phenacyl alcohol protected as *t*-butyldimethylsilyl ether by reaction under a classic Wittig reaction and selective removal of the silyl moiety.
14. According to our experience, the highest e.e. for the unreacted alcohol was reached at 60% conversion to the acetate, whereas very high e.e. were obtained for acetate if the acetylation was stopped at 40%. Therefore, two separate runs were always necessary for the highest e.e. of the products.

15. For the enantiomerically pure (S)-(+)-**1a** the reported optical rotation is +8.99 (*c* 5.8 in diethyl ether); see: Eliel, E. L.; Freeman, J. P. *J. Am. Chem. Soc.* **1952**, *74*, 923.
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17. Although the e.e. values were low, the optical rotation of (-)-**1a** indicated the R configuration for the compound and the alcohol obtained by hydrolysis of the (-)- acetate **2a** showed by the 500 MHz ^{1}H-NMR analysis of the MTPA ester to be the enantiomer of (-)-**1a**. Note that the stereochemical outcome of the enzymatic resolution of the racemic **1a** is the opposite to that of the diols **1b** and **1c**.
18. We thank Professor H. Griengl (Graz University of Techonology, Austria) for this suggestion.
19. (R)-(-)-**1a** with $[\alpha]_D$ -8.3 (*c* 5.8 in diethyl ether) was prepared by lithium aluminum hydride reduction of (S)-(+)-2-phenyl oxiranemethanol acetate, $[\alpha]_D$ +42 (*c* 1.6 in chloroform) corresponding to 92% e.e., in turn obtained by the PFL-catalyzed resolution of the racemic epoxyalcohol. By the enzymatic transesterification of (R)-(-)-**1a**, the unreacted diol was isolated in 40% yield after 69 h and showed $[\alpha]_D$ -8 (*c* 5.8 in diethyl ether).
20. Results presented at the European Congress on Biocatalysis, Graz, Austria (September 1993). See also: Ferraboschi, P.; Casati, S.; De Grandi, S.; Grisenti, P.; Santaniello, E. *Biocatalysis* **1994**, *10*, 279.
21. The required diols **1b,c** were prepared by reduction with lithium aluminum hydride of the corresponding epoxyalcohols, in turn prepared essentially as described in Ref. 12. For the PFL-catalyzed resolution, to a solution of the diol (5 mmol) in dichloromethane (10 mL) vinyl acetate (1.9 mL, 20 mmol) and PFL (70 mg, 31.6 U/mg) were added and the mixture was kept under stirring at 30 °C for a time depending on the required conversion. At 60% conversion to the corresponding acetates, (S)-(-)-**1b** was obtained in 66 h (38% yield, >98% e.e.) and (S)-(-)-**1c** was isolated in 36% yield (15 h, 92% e.e.). For the assignment of the configuration, the optical rotation of (-)-**1b** was compared with the one reported in Ref. 12 and the diol (-)-**1c** was transformed into (R)-(+)-mevalonolactone (to be published).
22. At 40% acetylation, (R)-(+)-**2b** and (R)-(+)-**2c** were obtained in 8 and 4 h (40% yield, and 92% e.e. for both esters). The configuration was established through the optical rotations of the diols obtained by hydrolysis of the acetates.
23. The E values for **1b** and **1c** are 20 and 13, respectively, and are similar to those reported for three out of the five compounds described in ref. 10.
24. The stereochemical consequence of the stereoelectronic factors due to the presence of heteroatoms or phenyl groups at a stereogenic center have been already pointed out by several authors; see: (a) Foelsche, E.; Hickel, A.; Hönig, H.; Seufer-Wasserthal, P. *J. Org. Chem.* **1990**, *55*, 1749. (b) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. (c) Xie, Z. -F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry*, **1993**, *4*, 973. (d) Carrea, G.; De Amici, M.; De Micheli, C.; Liverani, P.; Carnielli, M.; Riva, S. *Tetrahedron: Asymmetry*, **1993**, *4*, 1063.

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