Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 5, pp. 1027-1030, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00116-6

Regio- and Enantioselective Properties of the Lipase-catalyzed Irreversible Transesterification of Some 2-Substituted-1,4-Butanediols in Organic Solvents

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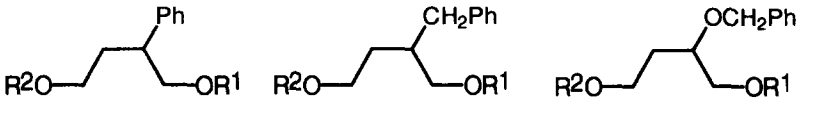
Abstract: The regioselectivity of the *Pseudomonas fluorescens (P. cepacia)* lipase (PFL)-catalyzed irreversible transesterification of 2-substituted-1,4-butanediols **1a-3a** has been studied and, in the case of **3a**, it has been shown that (R)- and (S)-diols are acylated with opposite regioselectivity.

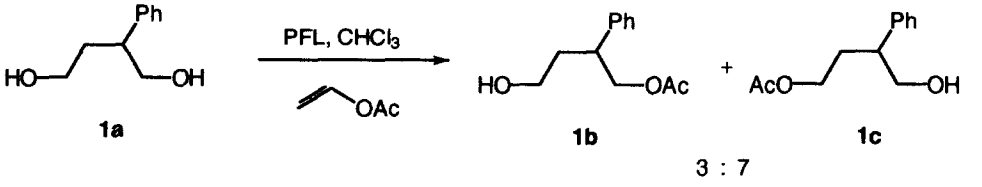
The lipase-catalyzed transesterification of a great variety of hydroxylated compounds is now a well established biocatalytic methodology for the synthesis of enantiomerically pure molecules.[1] A few reports on the regioselectivity of this reaction on dissymetric diols are also available in the recent literature.[2] We have been specially intrigued by the regioselectivity shown by the *Pseudomonas fluorescens (P. cepacia)* lipase (PFL) when the irreversible transesterification[3] of a few 2-substituted-1,4-butanediols was carried out with vinyl acetate in organic solvents.[4] Independently from the group present at position 2, the 1-hydroxy terminus was preferentially acylated and the stereochemical outcome of the reaction was the same as for other 2-substituted alkanols.[5] However, the small size substituents examined by us were properly chosen in view of some considerations on the expected stereochemical feature of the hydrophobic locus of the active site of PFL.[6] We now report on our studies on the same reaction catalyzed by PFL, using as substrates compounds bearing an aromatic moiety at the position 2. We considered this interesting because it has been already observed that, due to the probable presence of aromatic aminoacids at the active site, special electronic factors can influence the enantioselectivity of the enzymatic reaction.[6,7] We prepared the diols **1a-3a**[8] and subjected them to the lipase-catalyzed transesterification in chloroform, that we constantly have used as the organic solvent of the reaction.[9]



1 **2** **3**

a. $R^1 = R^2 = H$ **b.** $R^1 = Ac, R^2 = H$ **c.** $R^1 = H, R^2 = Ac$ **d.** $R^1 = R^2 = Ac$

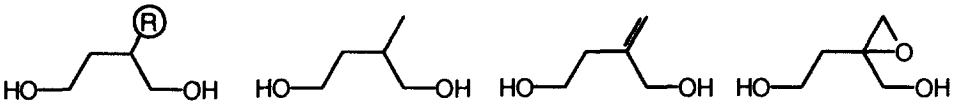
2-Phenyl-1,4-butanediol **1a** was preferentially acylated at the 4-hydroxy group with a slow reaction (10 days to reach a 83% conversion[10] to **1b** and **1c** in a 3:7 ratio[11]). The hydrolysis of the diacetate **1d** was much faster, but less regioselective (40 hours to reach a 63% conversion to a 4:6 ratio of **1b/1c**), thus affording preferentially the 4-acetate **1c**.[12]



1a **1b** **1c**

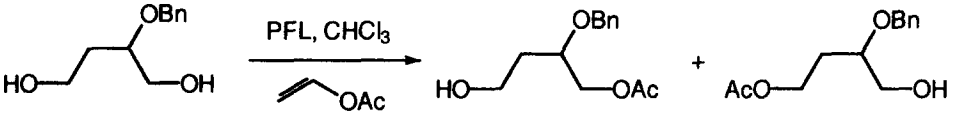
3 : 7

Changing the phenyl into a benzyl group, the enzymatic reaction on the diol **2a** was faster but virtually not regioselective (52 hours to a 50% of conversion into a **2b/2c** ratio 46 to 54). The regioselectivity of the reaction is opposite to that shown by previously examined diols **4-6**[4] and apparently the presence of the previous aromatic groups at the position 2 in the 1,4-butanediol framework renders the transesterification slow and the resulting regioselectivity profoundly altered.[13]



1a, 2a **4** **5** **6**

On the contrary, for the 2-benzyloxy diol **3a** the preferential formation of the 1-acetate **3b** is observed (in 27 hours, 90% of the diol was converted into a 75:25 ratio of **3b/3c**)[14] and the aqueous hydrolysis of the diacetate **3d** afforded a 2:8 ratio of **3b** and **3c** (4 h for 60% conversion). Thus, the enzymatic processes on the diol **3a** proceed as for the above mentioned compounds **4-6**.[4]

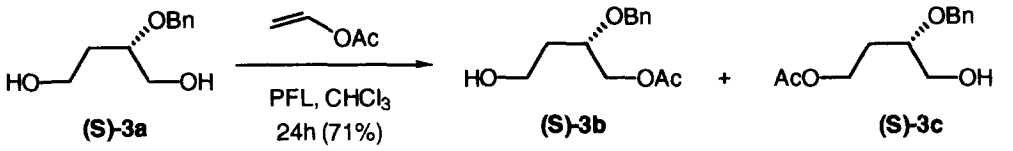


(R,S)-3a **3b** **3c**

75 : 25

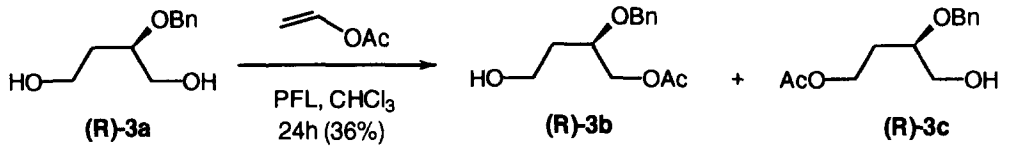
The enantioselectivity of the transesterification was relatively moderate, since for the unreacted diols **1a** and **3a** the ee was 50 and 70%, respectively.[15] Finally, in order to get a deeper insight into the reaction that had been performed on **3a** as a racemic mixture, we decided to investigate the transesterification of the

single enantiomers, namely (R)- and (S)-**3a**. Within the same time (24 h), (S)-**3a** was converted almost completely (95%) to diacetate **3d** (24%) and a 9:1 mixture of monoacetates **3b** and **3c** (71%) , whereas (R)-**3a** reached a 40% conversion to the diacetate **3d** (4%) and a 35:65 mixture of **3b** and **3c** (36%).[16]



(S)-3a (S)-3b (S)-3c

9 : 1



(R)-3a (R)-3b (R)-3c

35 : 65

This result shows that the two enantiomers of **3a** are acylated with opposite regioselectivity and explains the figures obtained using (R,S)-**3a** as substrate. It is also worth of mention that the transesterification of (S)-**3a** preferentially proceeds at C-1 and this result matches with the fact that also (S)-2-methyl alkanols are preferentially acylated by the same enzymatic reaction.[5,6]

Acknowledgements: This work has been financially supported by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and Consiglio Nazionale delle Ricerche (CNR, Programmi Finalizzati Chimica Fine). The technical assistance of Mrs. Antonella Molatore and Shahrzad Rezahelai is also gratefully acknowledged.

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7. The influence of π-electrons on the selectivity of lipase-catalyzed reaction has been already observed; see: (a) Lutz, D.; Güldner, A.; Thums, R.; Schreier, P. *Tetrahedron: Asymmetry*, **1990**, *1*, 783. (b) Foelsche,

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8. The diol **1a** was prepared in 90% yield from commercially available 2-phenylsuccinic acid, after esterification ($EtOH/H_2SO_4$) and $LiAlH_4$ reduction. For the preparation of the diol **2a**, the most fruitful synthesis started from 2-bromo-γ-butyrolactone that was converted (72%) into 2-benzylidene lactone *via* the intermediate α-phosphono derivative (Buechel, K. H.; Roechling, H.; Korte, F. *Justus Liebigs Ann. Chem.* **1965**, *685*, 10). Catalytic hydrogenation (10% Pd/C) to 2-benzyl lactone and $LiAlH_4$ reduction to the required diol **2a** proceeded in 50% yield. Finally, (R,S), (R) and (S)-**3a** were prepared from the corresponding malic acids, that were converted with diazomethane into the dimethyl esters and benzylated according to a literature method (Widmer, U. *Synthesis* **1987**, 568) in 60-70% yield of isolated product. Reduction to the required diols **3a** was quantitatively achieved with $LiAlH_4$.
9. We have always used chloroform or dichloromethane as solvent for our enzymatic reactions, because of the excellent enantioselectivity experimentally found. Recently, comparing different solvents we have confirmed that for these substrates chloroform is the best solvent.
10. A 60% conversion of **1a** has been achieved in 5 days and the ratio beween **2a** and **3a** was essentially the same.
11. The ratio between the two monoacetates was routinely assayed by GLC and, in order to unequivocally assign the structures of 1- and 4-acetates, a careful silica gel column chromatography allowed us to isolate some fraction containing a pure monoacetate. In the case of **1a**, the pure 4-acetate **1c** was isolated and the structure established by ^{1}H-NMR (500 MHz). Resonances at 3.68 (d, CH_2OH) and 3.85-4.05 ppm (m, CH_2OAc) were assigned after irradiation of the CH signal at 2.8-2.9 ppm. Similarly, for the 4-acetate **2c**, the resonances at 3.48-3.58 (m, CH_2OH) and 4.08-4.18 ppm (m, CH_2OAc) were assigned after irradiation of the CH signal at 1.9-2.0 ppm.
12. This result is in contrast to the observed reversed regioselectivity of the aqueous hydrolysis *versus* the transesterification; see, for example Ref. 4.
13. The enzymatic hydrolysis of the diacetate **2d** afforded in 15 hours a 35:65 mixture of monoacetates **2b** and **2c**.
14. The structure of 1-acetate for compound **3b** was established by ^{1}H-NMR (500 MHz) after isolation (silica gel column chromatography) and the resonances at 3.65-3.75 (m, CH_2OH) and 4.05-4.25 ppm (m, CH_2OAc) were assigned after irradiation of the CH signal at 3.75-3.85 ppm.
15. At 83% conversion of (R,S)-**1a** to the monoacetates, the unreacted diol (R)-(-)-**1a** was isolated (50% ee by optical rotation; for the value of pure (R)-**1a**, see: Bettoni, G.; Cellucci, C.; Tortorella, V. *J. Heterocycl. Chem.* **1976**, *13*, 1053). When (R,S)-**3a** was converted into the monoacetates (70%), the unreacted (R)-(+)-**3a** presented a 70% ee by comparison with literature data (Cardillo, G.; Orena, M.; Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501).
16. In 100 hours, a 83% conversion of (R)-**3a** to 64% of a 33:67 mixture of **3b** and **3c** and 18% of diacetate **3d** was observed.

(*Received in UK* 6 *March* 1995; *accepted* 21 *April* 1995)