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Pig Liver Esterase-catalyzed Hydrolyses of Racemic Diacetates of Bicyclic Compounds and Interpretation of the Enantiomeric Specificity of PLE

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Pig liver esterase-catalyzed hydrolyses of racemic diacetates of bicyclic compounds, bicyclo[2.2.1]heptanes, bicyclo[2.2.2]octanes, and bicyclo[3.2.1]octanes gave the optically active monoacetates and diacetates. The enantiomeric specificity of PLE toward diacetates of racemic diol substrates was analyzed by using the active site model.

One such hydrolytic enzyme that has received much current interest is pig liver esterase (PLE) which catalyzed the hydrolysis of a wide range of ester structures with considerable specificity.[1] However, a major disadvantage in planning the synthetic use of PLE is its seemingly unpredictable specificity. Recently, J. B. Jones and co-workers[2] proposed the active site model of PLE which can be used for analysis of the specificity of PLE toward methyl ester substrates. We here report PLE-catalyzed eantioselective hydrolyses of racemic diacetates of bicyclic compounds and interpretation of the enantiomeric specificity of PLE toward diacetates of racemic diol substrates by using the active site model.

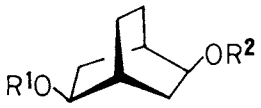
PLE-catalyzed hydrolyses of the racemic diacetates (2-3 mmol) prepared from the diols[3] were performed in 0.1 M (1 M=1 mol dm^{-3}) phosphate buffer solution (pH 8.0, 1-1.5 L) at room temperature and terminated at, or closs to 50%-of-hydrolysis point by extraction with dichloromethane. Absolute configurations of the products were confirmed by chemical correlation with known compounds. In typical experiments oxidation of (+)-2 with CrO_3 gave (-)-5-acetoxybicyclo[2.2.2]octan-2-one which was converted into the corresponding thioketal. Desulfurization of the thioketal with Raney nickel furnished the known acetate[4] (+)-(2S)-27. Treatment of (+)-(2S,5S)-2 and (-)-1 with $LiAlH_4$ giving (+)-(2S,5S)-3 and (-)-(2R,5R)-3, respectively assigned the (2R,5R) configuration to (-)-1. Similarly, the bicyclo[2.2.1]-heptane derivatives and the bicyclo[3.2.1]octane derivatives were converted into the known acetates[4] 29 and 31, respectively. Enantiomer excess (e.e.)

values of the products were determined by HPLC on the bis(phenylcarbamate) derivatives of the diols. The results are summarized in Table 1.

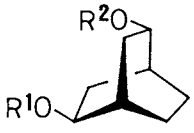
The stereoselectivities of the PLE-catalyzed hydrolyses of the diacetates are interpreted by using the model simplified the Jones' model.[2] Top perspective view and the size of the model are shown in Fig. 1. The important binding region for specificity determination is the hydrophobic pocket, H which interacts with the aliphatic hydrocarbon portions of a

Table 1. PLE-catalyzed Enantioselective Hydrolysis of Racemic Substrates

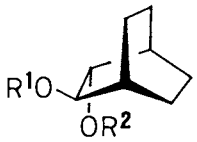
Substrate	Time/h	Products (% isolated yield)			E.e./%
(±)-1	4	(-)-(2R,5R)-1	(42)	26, (+)-(2S,5S)-2	(52) 21
(±)-4	211	(-)-(2R,5R)-4	(40)	66, (+)-(2S,5S)-5	(29) 84
		(-)-(2R,5R)-6	(7)	36	
(±)-7	4.5	(+)-(2S,3S)-7	(32)	85, (+)-(2R,3R)-8	(48) 82
(±)-10	3.5	(-)-(2R,5R)-10	(37)	13, (+)-(2S,5S)-11	(58) 10
(±)-13	33	(+)-(2R,5R)-13	(50)	15, (-)-(2S,5S)-14	(44) 19
(±)-16	48	(-)-(2R,5S)-16	(40)	17, (+)-(2S,5R)-17	(40) 17
(±)-19	205	(+)-(2S,8R)-19	(40)	8, (+)-(2R,8S)-20	(29) 87
				(+)-(2S,8R)-21	(22) 85
(±)-23	76	(+)-(2S,8S)-23	(44)	48, (+)-(2R,8R)-24	(28) 87
(±)-27	36	(-)-(2R)-27	(47)	9, (+)-(2S)-28	(48) 9
(±)-29	24	(-)-(2R)-29	(42)	2, (-)-(2S)-30	(42) 2



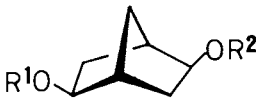
(+)-1 $R^1=R^2=Ac$
(+)-2 $R^1=H$ $R^2=Ac$
(+)-3 $R^1=R^2=H$



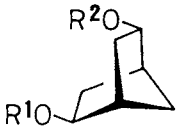
(+)-4 $R^1=R^2=Ac$
(+)-5 $R^1=H$ $R^2=Ac$
(+)-6 $R^1=R^2=H$



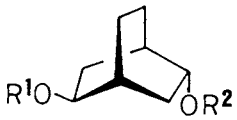
(-)-7 $R^1=R^2=Ac$
(+)-8 $R^1=H$ $R^2=Ac$
(+)-9 $R^1=R^2=H$



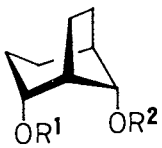
(+)-10 $R^1=R^2=Ac$
(+)-11 $R^1=H$ $R^2=Ac$
(-)-12 $R^1=R^2=H$



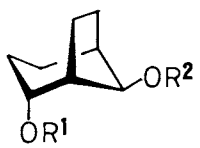
(-)-13 $R^1=R^2=Ac$
(-)-14 $R^1=H$ $R^2=Ac$
(-)-15 $R^1=R^2=H$



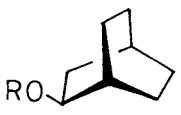
(+)-16 $R^1=R^2=Ac$
(+)-17 $R^1=H$ $R^2=Ac$
(+)-18 $R^1=R^2=H$



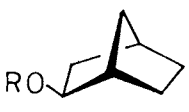
(-)-19 $R^1=R^2=Ac$
(+)-20 $R^1=H$ $R^2=Ac$
(-)-21 $R^1=Ac$ $R^2=H$
(+)-22 $R^1=R^2=H$



(-)-23 $R^1=R^2=Ac$
(+)-24 $R^1=H$ $R^2=Ac$
(-)-25 $R^1=Ac$ $R^2=H$
(+)-26 $R^1=R^2=H$



(+)-27 R=Ac
(+)-28 R=H



(+)-29 R=Ac
(-)-30 R=H

(-)-31

substrate. Two pockets of more polar character, P_1 and P_2 interact with the acetoxyl groups of a substrate and the catalytically essential region is the serine residue. The model is used to make predictions of the outcome of PLE-catalyzed enantioselective hydrolyses of racemic diacetates of bicyclic compounds by applying the following criteria. a) The acetoxyl group to be hydrolyzed is located in the P_1 pocket and the carbon atom of the carbonyl group must be placed in the serine sphere.

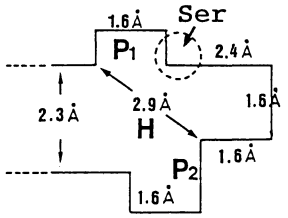


Fig. 1. Top perspective view of the model.

b) The unhydrolyzed acetoxyl group must be located in the P_2 pocket, and the enantioselectivities of the hydrolyses of diacetates being higher than those of the monoacetates 27 and 29 shows that the interaction of the unhydrolyzed group with the P_2 pocket seems to play an important role in determination of the orientation of a substrate. c) The aliphatic hydrocarbon portions of a bicyclic compound are bound into the H pocket. With racemic diacetates, the fit of each enantiomer is assessed separately in the same fashion and the enantiomer, the aliphatic hydrocarbon portions of which will be bound more efficiently into the H pocket, is preferentially hydrolyzed to give the monoacetate with PLE.

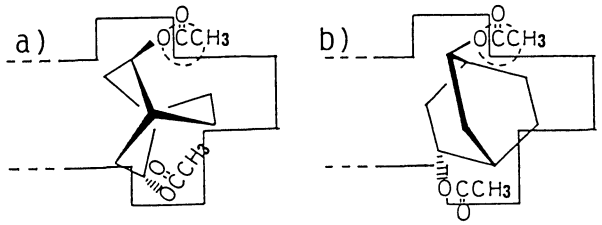


Fig. 2. Binding orientations. Figure a and b are illustrated for (2S,5S)-1 and (2R,5R)-1, respectively.

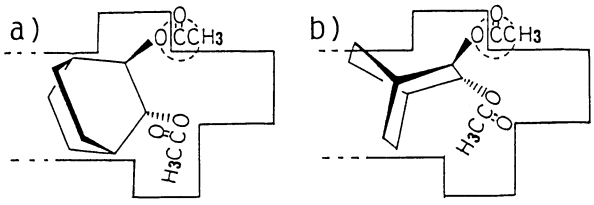


Fig. 3. Binding orientations. Figure a and b are shown for (2R,3R)-7 and (2S,3S)-7, respectively.

For diacetate 1 of C_2-symmetry, the acetoxyl group hydrolyzed and the nonhydrolyzable acetoxyl group are located in the P_1 and P_2 pocket, respectively, and the remaining hydrocarbon portions are placed in the H pocket. In the binding mode a, the aliphatic hydrocarbon portions fit well the H pocket and in the alternative binding mode b, a part of the hydrocarbon portions penetrates the wall of the pocket. The binding mode a is judged to be merely more favorable than the mode b and the monoacetate (+)-(2S,5S)-2 corresponding to the better complex fit (a) was experimentally obtained.

Similarly, in the case of 7, it is clear that the mode a is more favorable than the mode b. The stereoselectivity of the hydrolyses of the other diacetates 4, 10, and 13 are analyzed in the same manner.

In the cases of the diacetates of C_1-symmetry, four binding modes should be considered. Figure 4a shows (2R,8S)-19 bound into the active site with its acetoxyl group at C-2 in the P_1 pocket and Fig. 4d shows its antipode with the C-2 group in the P_1 pocket. The mode a is more favorable

than the mode d in which a part of the aliphatic portions is placed in the polar pocket. In the binding modes of 19 with its C-8 acetoxyl group in the P_1 pocket, the mode c is more favorable than b. Thus the diastereomers (+)-20 and (+)-21 were experimentally obtained. Similarly, in the case of 23, four binding modes 5a-d are depicted and only the mode a is favorable. In fact, (+)-(2R,8R)-24 was experimentally isolated as a sole monoacetate.

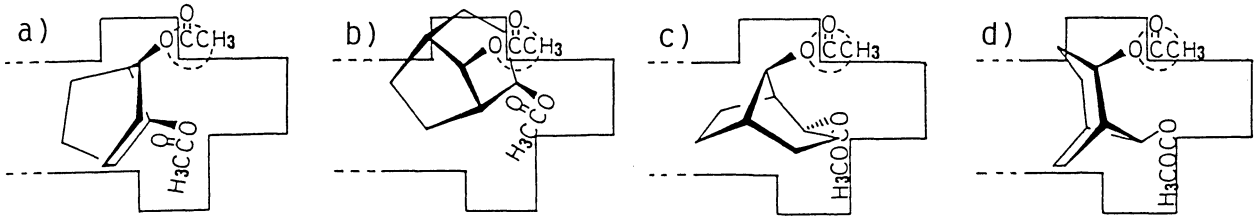


Fig. 4. Binding orientations. Figure a and b are illustrated for (2R,8S)-19 and the binding model c and d are shown for (2S,8R)-19.

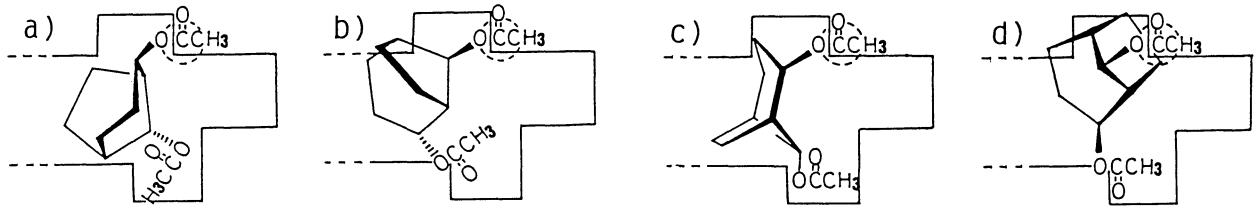


Fig. 5. Binding orientations. For (2R,8R)-23, the binding model a and b are illustrated and the binding model c and d are shown for (2S,8S)-23.

As mentioned here, the optically active diols of the bicyclic compounds were easily prepared by PLE-catalyzed enantioselective hydrolysis of the corresponding diacetates. The interpretation described above is used for diacetates of racemic diol substrates. When comparison between the advantage of the binding mode of each enantiomer is made, the model would help to predict the enantiomer of the monoacetate which is preferentially obtained by PLE-catalyzed enantioselective hydrolysis.

References

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