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Enzymes in Organic Synthesis: Remarkable Influence of a π System on the Enantioselectivity in PPL Catalysed Monohydrolysis of 2-Substituted 1,3-Diacetoxypropanes.

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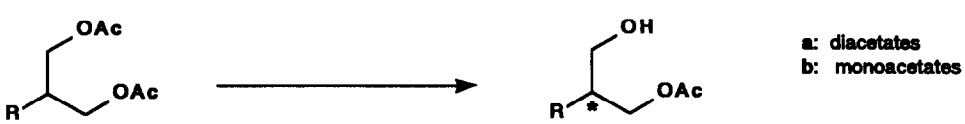
Abstract: The results of PPL catalysed monohydrolysis of a series of 2-substituted-1,3-diacetoxypropanes showed that alkinyl and (*E*) alkenyl substituents led to improvement of yield and enantioselectivity, compared to their saturated analogues. On the contrary, (*Z*) alkenyl substituents provoked a net reversal of asymmetric induction.

There is a notable interest in the use of enzymes as catalysts in the enantioselective synthesis of optically active compounds. However, although the synthetic utility of this methodology is amply demonstrated by the increasing number of reports in this field, rationalization of the results still proves challenging, since subtle changes in the substrate structure can often bring about great alterations in the enantiomeric excesses or in the chemical yields.[1] This fact can constitute sometimes a limit to an even wider application of this strategy and thus any information on the structure-stereospecificity relationship can give an useful contribution to the understanding of the active site topography.

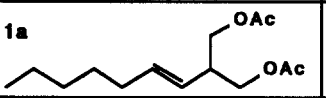
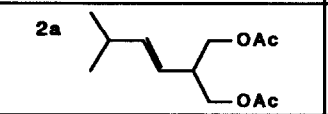
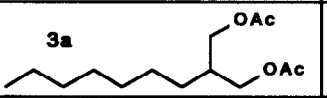
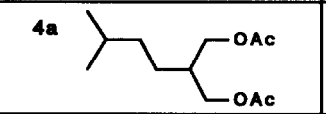
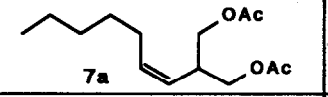
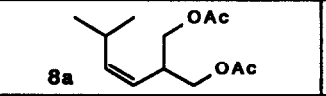
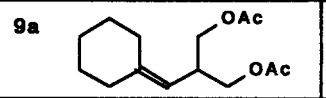
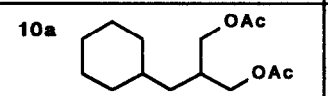
Recently a few results obtained by us[2] and others[1a,3] suggested that the presence of an unsaturation near the prochiral centre could play an important role in determining the enantioselectivity in monohydrolysis of prochiral diesters by means of hydrolytic enzymes.[4] Thus, in order to uncover the effect of different type of unsaturation near the prochiral centre we have now carried out a systematic study on the PPL catalysed monohydrolysis of 1,3-diacetoxypropanes substituted in 2 with alkyl, alkenyl, or alkinyl groups. This study would also be useful in establishing the best way for the obtainment of enantiomerically pure asymmetrized 1,3-propanediols substituted in 2 with hydrocarbon chains, to be used as new chiral building blocks,[5] and would greatly help the design of an empirical model for the quantitative and qualitative prediction, and for the explanation of induction in PPL-catalysed reactions.[6]

For this purpose we prepared a series of diacetates **1a-10a**[7,8,16] and examined their behaviour in PPL catalysed monohydrolyses. The Table shows the results obtained, displaying not only the enantiomeric excesses, but also other relevant features, like the percentage of monoacetate on the overall recovery of monoacetate +



1a-10a **1b-10b**

TABLE: PPL catalysed hydrolysis of diacetates 1a-10a[a]

Entry	Substrate	Solvent[b]	Initial rate/ Final rate[c]	% Mono-acetate[d]	Yield[e]	$[\alpha]_D$[f]	e.e.[g]	Configu-ration[h]
1	1a 	H_2O	1.49	66%	49%	-17.3	84%	S
2[i]		H_2O /*i*-Pr_2O	2.17	66%	63%	-21.8	95%	S
3		H_2O/*t*-BuOH	2.22	66%	59%	-19.8	93%	S
4	2a 	H_2O	5.26	78%	70%	-23.2	90%	S
5[i]		H_2O /*i*-Pr_2O	20	84%	75%	-25.3	97%	S
6		H_2O/*t*-BuOH	25	85%	71%	-23.2	88%	S
7	3a 	H_2O /*i*-Pr_2O	1.61	65%	56%	-7.87	70%	S
8	4a 	H_2O /*i*-Pr_2O	2	59%	47%	-8.56	72%	S
9	5a 	H_2O	1.52	62%	57%	-10.2	78%	S
10		H_2O /*i*-Pr_2O	1.27	56%	50%	-10.2	80%	S
11		H_2O/*t*-BuOH	1.89	67%	61%	-10.8	82%	S
12	6a 	H_2O	2.70	79%	67%	-10.0	82%	S
13		H_2O /*i*-Pr_2O	4.17	80%	65%	-10.4	85%	S
14		H_2O/*t*-BuOH	5.00	82%	71%	-10.4	88%	S
15	7a 	H_2O	1.52	48%	43%	+13.3	50%	R
16		H_2O /*i*-Pr_2O	1.47	40%	31%	+14.5	53%	R
17		H_2O/*t*-BuOH	2.38	48%	44%	+14.4	55%	R
18	8a 	H_2O	1.79	37%	25%	+4.7	21%	R
19		H_2O /*i*-Pr_2O	1.0	32%	20%	+2.2	15%	R
20	9a 	H_2O /*i*-Pr_2O	1.72	33%	29%	-19.0	67%	S
21	10a 	H_2O /*i*-Pr_2O	1.0	50%	45%	+ 0.1	2%	-

NOTES: **a)** All reactions were performed on 1-2 mmol scale at + 25°C using 110 mg of crude PPL (Sigma) and 7 cc of solvent for every mmol of diacetate. The pH was maintained constant at 7.00 by continuous addition of 1N NaOH from an autoburette. Reactions were stopped at 50% conversion, after consumption of 1 eq. of NaOH. Actual conversions were checked at ^{1}H n.m.r. and always found in the range 47-53%. Reactions were complete in 1-5 h. **b)** 0.02-0.05 M phosphate buffer was used; H_2O /*i*-Pr_2O were in the ratio 85:15; H_2O/*t*-BuOH were in the ratio 9:1. **c)** Determined by the rate of NaOH consumption. **d)** Molar percentage of monoacetate on the total recovery of monoacetate, diacetate, and diol, determined by ^{1}H n.m.r. of crude product or by weight of isolated products. **e)** Isolated yield after silica gel chromatography (see note 16). **f)** c 2 , $CHCl_3$. **g)** Determined at ^{1}H n.m.r. in the presence of Eu(hfc)$_3$, by integration of $CH_3C{=}O$ signals. **h)** Determined as described in note 15. **i)** These reactions were scaled up to 30-40 mmol without appreciable differences in yields and e.e.s.

diacetate + diol, and the initial rate/final rate ratio. These two data are closely related to the substrate selectivity and thence to the chemical yield.

The importance of the presence on an (*E*) double bond for the achievement of high enantioselection is evident by comparison of entries 2-7 and 15-18 a sensible decrease of e.e. is observed on passing from the

unsaturated to the saturated compounds. The improvement of asymmetric induction is not peculiar of the (*E*) alkenyl derivatives. Also the alkynyl compounds **5a** and **6a** (entries 9-14) afforded the corresponding monoacetates in higher e.e.s than the saturated analogues **3a** and **4a**. These results are furtherly confirmed by the dramatic difference in enantioselection between **9a** and **10a** (entries 20 and 21).

On the other hand, the examination of (*Z*) alkenyl diacetates **7a** and **8a** (entries 15-19) showed that the configuration at the double bond has a dramatic influence on both yield and stereoselectivity. The mere change of configuration from (*E*) to (*Z*) causes a reversal of enantioselection, as well as a decrease in substrate selectivity, initial to final rate ratio, and yield. To our knowledge this is the first example of such a dramatic effect on the enantioselectivity on changing the double bond configuration in an enzyme catalysed hydrolysis. Also the hydrolysis of compound **9a**, which possesses two identical substituents in *cis* and *trans* positions, proceeded with diminished substrate selectivity and stereoselectivity; in this case the preference for (*S*) isomer was maintained, although the e.e. was remarkably lower than for **1a** and **2a** (entry 20).

We have also studied the effect of added cosolvent: the addition of 15% *i*-Pr_2O furnished the best results in terms of yield and enantioselection for the (*E*) alkenyl derivatives, while for the alkynyl compounds best results were obtained in H_2O : *t*-BuOH 9:1. Interestingly the addition of *i*-Pr_2O, which was beneficial in the case of **1a**, **2a**, **5a**, and **6a**, increasing the percentage of (S) isomer and the yield, is detrimental for the (*Z*) alkenyl diacetates **7a** and **8a**, lowering the yield and, in the case of **8a**, again increasing the amount of minor (S) monoacetate.

Finally the Table allows a comparison between compounds where the double or triple bond bear different substituents. In the hydrolyses of (*E*) alkenyl and alkinyl diacetates the branched derivatives **2a** and **6a** proved to be superior to the straight chain analogues **1a** and **5a**: a slight increase in the enantioselection is accompanied by a marked improvement in substrate selectivity and yield, as well as in the initial to final rate ratio. In the case of **2a** (entries 5 and 6), the reaction proceeds with high substrate selectivity, almost stopping at 50% conversion.[14] Once again the effect of a branched substituent is opposite for the (*Z*) compounds, furtherly decreasing yield and e.e..

In regard to the synthesis of asymmetrized 2-substituted 1,3-propanediols, we may conclude that PPL catalysed monohydrolysis is a convenient method for obtaining directly 2-(*E*) alkenyl and 2-alkinyl derivatives. Although 2-alkyl and 2-(*Z*)-alkenyl compounds seem to be not directly accessible in satisfactory e.e.s from PPL catalysed hydrolysis, it should be pointed out that they are indeed easily accessible through hydrogenation of triple or (*E*) double bonds.[15] Application of 2-substituted asymmetrized 1,3-propanediols to the enantioselective synthesis of biologically active substances is in progress.

We wish to thank Chiara Ghiron for her collaboration in this work, and M.U.R.S.T. and C.N.R. for financial assistance.

REFERENCES AND NOTES

1) Representative examples: **a)** Nakada M., Kobayashi S., Ohno M., Iwasaki S., and Okuda S., *Tetrahedron Lett.*, 3951 (1988); **b)** Laumen K., and Schneider M., *Tetrahedron Lett.*, **1985**, *26*, 2073; **c)** Santaniello E., Chiari M., Ferraboschi P., and Trave S., *J.Org.Chem.*, **1988**, *53*, 1567; **d)** Zhou B., Gopalan A.S., Van Middlesworth F., Shieh W., and Sih C.J., *J.Am.Chem.Soc.*, **1983**, *105*, 5925; **e)** Nakamura K., Ushio K., Oka S., Ohno A., and Yasui S., *Tetrahedron Lett.*, **1984**, *25*, 3979.

2) **a)** Guanti G., Banfi L., and Narisano E., *Tetrahedron Lett.*, **1989**, *30*, 2697; **b)** Guanti G., Narisano E., Podgorski T., Thea S., and Williams A., *Tetrahedron*, in press.

3) Ramos Tombo G.M., Schaer H.P., Fernandez I Busquets X., and Ghisalba O., *Tetrahedron Lett.*, **1986**,

27, 5707;

4) For example 1,3-diacetoxy-2-phenylpropane gave 92% e.e. in PPL catalysed monohydrolysis[2b] while 1,3-diacetoxy-2-cyclohexyl-propane afforded only 60% e.e.;[3] moreover 1,3-diacetoxy-2-benzylpropane gave 61% e.e., compared to virtual no enantioselection for 1,3-diacetoxy-2-cyclohexylmethylpropane.[3]

5) For other preparations of asymmetrized 2-monosubstituted-1,3-propanediols *via* enzymatic methods see: **a)** Wang Y.F., and Sih C.J., *Tetrahedron Lett.*, **1984**, *25*, 4999; **b)** Kerscher V., and Kreiser W., *Tetrahedron Lett.*, **1987**, *28*, 531; **c)** Breitgoff D., Laumen K., and Schneider M.P., *J. Chem. Soc., Chem. Commun.*, **1986**, 1523; **d)** Eberle M., Egli M., and Seebach D., *Helv. Chim. Acta*, **1988**, *71*, 1; **e)** Terao Y., Murata M., Achiwa K., Nishio T., Akamatsu M., and Kamimura M., *Tetrahedron Lett.*, **1988**, *29*, 5173; **f)** Tsuji K., Terao Y., and Achiwa K., *Tetrahedron Lett.*, **1989**, *30*, 6189; **g)** Wang Y.F., Lalonde J.J;, Momongan M., Bergbreiter D.E., and Wong C.H., *J.Am.Chem.Soc.*, **1988**, *110*, 7200; **h)** Xie Z.F., Suemune H., and Sakai K., *J. Chem. Soc., Chem. Commun.*, **1988**, 1638; **i)** Ehrler J., and Seebach D., *Liebigs Ann. Chem.*, **1990**, 379; see also ref. 2b and 3.

6) Seebach (ref. 5i) has recently proposed a model for these reactions, which however does not give correct previsions in the case of acyclic compounds like those studied in this work. We thank prof. Seebach for sending us a reprint of his article.

7) Preparation of **1a** was already described (ref. 2a); **2a** was prepared in two steps from known diethyl *iso*-pentylidene malonate (ref. 9) : a) NaH, THF, 40°C, 7h, 72% (ref. 10); b) i: $LiAlH_4$, Et_2O, 4 h, T amb.; ii: Ac_2O, Et_3N, CH_2Cl_2, DMAP (0.05 eq.), 18h, R.T., 64%. This synthesis was carried out on 0.2 mol scale, without the need of chromatographic separations (only distillations were used). **9a** was prepared by a similar sequence in 38% overall yield from diethyl cyclohexylidenemalonate (ref. 9). **3a**, **4a**, and **10a** were prepared in 80-90% yield by hydrogenation (H_2, 10% Pd-C, EtOH) of **1a**, **2a**, and **9a** respectively.

8) **5a** and **6a** were prepared starting from *n*-heptine (Aldrich) or 3-methyl-1-butyne (ref. 11) through: a) *n*-BuLi, THF, 0°C; then -78°C, diacetoxyacetone (ref. 12), 91% for **5a** and 80% for **6a**. b) i: MsCl, Et_3N, CH_2Cl_2, -40°C→ -30°C, 3h; ii: $LiAlH_4$, Et_2O, -15°C, 3h (ref. 13); iii: Ac_2O, Et_3N, DMAP (0.05 eq.), CH_2Cl_2, R.T., 41% for **5a** and 43% for **6a**. **7a** and **8a** were prepared by hydrogenation of **5a** and **6a** (H_2, EtOH, Pd Lindlar, 2,6-lutidine, 95% for **7a** and 84% for **8a**).

9) Cope A.C., Hofmann C.M., Wyckoff C., and Hardenbergh E., *J.Am.Chem.Soc.*, **1941**, *63*, 3452.

10) Steinbeck K., Osterwinter B., *Tetrahedron Lett.*, **1979**, *20*, 861.

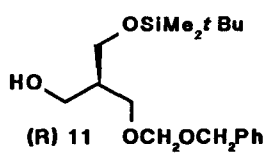
11) Miller H.N., Greenlee K.W., Derfer J.M., and Boord C.E., *J. Org. Chem.*, **1954**, *19*, 1883.

12) Bentley P.H., and McCrae W., *J.Org.Chem.*, **1970**, *35*, 2082.

13) Takemoto T., Fukaya C., and Yokoyama K., *Tetrahedron Lett.*, **1989**, *30*, 723, and references therein.

14) Since **2a** is also more easily prepared than **1a** (see note 7), we deem it the reagent of choice for the preparation of asymmetrized tris (hydroxymethyl)methane synthetic equivalents: see ref. 2a and G. Guanti, L. Banfi, and E. Narisano, *Tetrahedron Letters*, in press.

15) The assignment of absolute configuration of **1b** was already reported (ref. 2a). The configurations of **1b**, **2b**, and **9b** were correlated by their transformations into the same alcohol (R) **11**, by the following sequence: a) i: *t*-$BuMe_2SiCl$, DMF, imidazole; ii: 0.1 M KOH in abs. MeOH, R.T., 95% for **1b**, 87% for **2b**, 70% for **9b**; b) $PhCH_2OCH_2Cl$, $EtN(iPr)_2$, CH_2Cl_2, R.T., overnight, 84% for **1b**, 86% for **2b**, 77% for **9b**; c) i: O_3, CH_2Cl_2/MeOH, -78°C; then Me_2S →R.T.; then $NaBH_4$, 84% for **1b**, 92% for **2b**, 87% for **9b**. Correlation *via* optical rotation was not feasible, since **11** had $[\alpha]_D$ and $[\alpha]_{365} \approx 0°$. However ^1H n.m.r. examination of esters of **11** with both (R) and (S) Mosher acids, showed clearly that alcohols **11** obtained from **1b**, **2b**, and **9b** had the same absolute configuration. This analysis indicated also that the above described sequence of reactions was not racemizing. **1b**, **2b**, and **9b** were then correlated to **3b**, **4b**, and **10b** by hydrogenation (H_2, 10% Pd-C, EtOH). In the same way **5b**, **6b**, **7b**, and **8b** were correlated to **3b** and **4b** and thence to **1b** and **2b**. During these hydrogenations it is important to avoid unnecessary long reaction times and/or high catalyst quantities, in order to avoid small percentages of racemization.



16) All new compounds gave satisfactory elemental analyses, and were fully characterized by ^1H and ^{13}C n.m.r.