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ENANTIOSELECTIVE HYDROLYSIS OF CIS -1,2-DIACETOXYCYCLOALKANEDIMETHANOLS:ENZYMATIC PREPARATION OF CHIRAL BUILDING BLOCKS FROM PROCHIRAL MESO -SUBSTRATES[1] .

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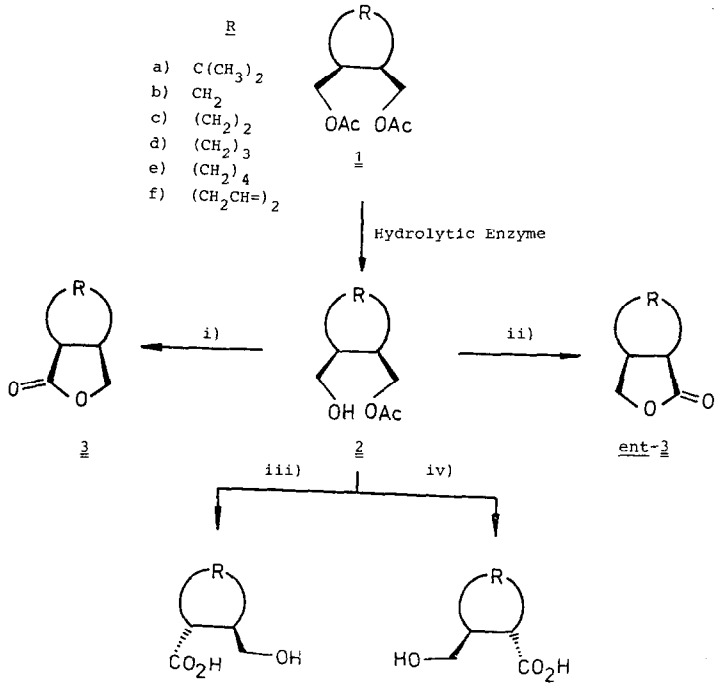
Summary : The enzymatic hydrolysis of the prochiral title compounds 1a - f in presence of porcine liver esterase (PLE) and lipase from porcine pancreas (PPL) was studied, resulting in the preparation of the chiral monoacetates 2b - f with high (72-99%e.e.) enantiomeric purities.

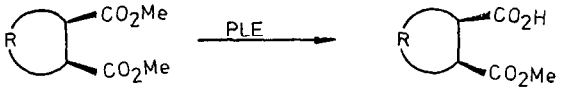
Enantioselective hydrolysis of the prochiral title compounds 1a - f would afford versatile chiral building blocks for numerous applications including natural products synthesis. Regardless of the resulting absolute configurations, the monoesters 2a - f could serve as potential precursers for all possible enantiomers of these systems by selective group transformations as exemplified in Scheme I .



Scheme I

i) Oxidation ; ii) Protection - Hydrolysis - Oxid. ; iii) Oxidation, Isomerisation ; iv) Protection - Hydrolysis - Oxidation, Isomerisation

Enzymes, nature's chiral reagents, are well known to transform prochiral meso -substrates into chiral molecules by enantiotopous group differentiation. Porcine liver esterase (E.C. 3.1.1.1) is not only known in this regard for its high enantioselectivity, but also for accepting a broad range of structurally different substrates. In fact, we could demonstrate in an earlier paper of this series, that several cis -1,2-Dimethylcycloalkanedicarboxylates (5) are transformed with high enantioselectively into the chiral monoesters (6) by this reagent (eq. 1) [2].

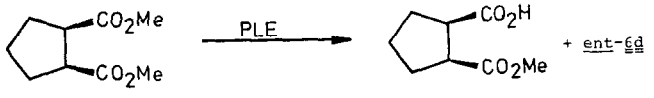


(1)

5a - f 6a - f

R: CMe_2; CH_2; $(CH_2)_2$; $(CH_2)_3$; $(CH_2)_4$; $(CH_2CH=)_2$

To our disappointment, however, one molecule in this series , Methyl(hydrogen)-1,2-cyclopentanedicarboxylate 6d (R= $(CH_3)_2$) was not available by this method, the PLE-catalyzed hydrolysis of the diester (5d) leads essentially to the racemate 6d and ent -6d (eq. 2).



(2)

5d 6d

While enzymes have been used frequently in the past to convert carboxylic esters with prochiral acid components[3] , the hydrolysis of esters with prochiral alcohol components like 1a - f has received much less attention [4].

Because of the convenient accessibility of the starting materials by reduction of the available esters (5) and with the aim of using cheap, commercially available, lipases for enantioselective transformations, we studied the enzymatic hydrolyses of 1a - f in presence of both PLE and lipase from porcine pancreas (PPL).

Accordingly, 10 m Mol of 1a - f were suspended in 0.1 M phosphate buffer (25 ml, pH 7, T=25 °C) and treated with either 5 mg PLE (Boehringer, soluble or immobilized [1] , = 500 units, standard n-BuOAc) or 200 mg PPL (Sigma, Type II, 2400 units, standard triacetin). The initial saponification was indicated by a rapid decrease of pH which was maintained constant at pH 7 by continous addition of 1N NaOH solution from an autoburette. Whereas in the case of PLE the reactions had to be terminated by removal of the enzyme, with PPL essentially only one ester group is saponified and the reactions terminate after the consumption of 1 equiv.of NaOH.

All reactions were worked up by continous extraction with Et_2O and the products purified conveniently by rapid flash chromatography (SiO_2,Et_2O), followed by distillation. Enantiomeric purities were determined by"optishift" 250 MHz ^{1}H-NMR-experiments in presence of Eu(tfc)$_3$ .The results are summarized in the table.

TABLE ENZYMATIC HYDROLYSIS OF 1a - f IN PRESENCE OF PLE AND PPL

SUBSTRATE	PRODUCT	ENZYME	YIELD (%) [a]	$[\alpha]_D^{20}$	Enantiomeric ratio [b] (% e.e.)
1a	(+) - 2a	PLE	69	5.3 °	60 : 40 (20)
	(-) - 2a	PPL	75	-10.3 °	70 : 30 (40)
1b	(+) - 2b	PLE	54	7.7°	72 : 28 (44)
	(+) - 2b	PPL	94	12.6 °	86 : 14 (72)
1c	(±) - 2c	PLE	62	±0 °	50 : 50 (0)
	(-) - 2c	PPL	97	- 1.5 °	94 : 6 (88)
1d	(+) - 2d	PLE	40	0.8 °	54 : 46 (8)
	(-) - 2d	PPL	94	-8.2 °	93 : 7 (88)
1e	(-) - 2e	PLE	31	-0.9 °	52 : 48 (4)
	(-) - 2e	PPL	81	- 19.1 °	89 : 11 (78)
1f	(+) - 2f	PLE	43	7.6 °	70 : 30 (40)
	(-) - 2f	PPL	96	- 19.4 °	>99 : 1 [c] (>99)

a) Yields are for isolated products ; in presence of PLE 2a - f are hydrolized partially into the corresponding diols ; b) determined by ^{1}H-NMR (250 MHz) in presence of Eu (tfc)$_3$; c) enantiomerically pure by ^{1}H- NMR , also by comparison of $[\alpha]_D^{20}$ with (+) - 2f .

Clearly both the chemical and optical yields obtained with PPL are far superior to those achieved with PLE.With the former, chemical yields were usually around 95% or better for isolated products with the exception of 2a (75%). Equally high were the enantiomeric purities obtained with PPL (again with the exeption of 2a) with values of 72 - 99 % e.e.
We were especially pleased to find that now also the cyclopentane system was obtained with excellent 86% e.e.

In contrast to the very low chemical and optical yields obtained with PLE, the results with PPL are highly attractive from a synthetic point of view. Since both the starting materials and the "reagent" are readily and cheaply available this seems at present the most attractive route to the chiral building blocks 2b - 2f. Whereas 2f was obtained enantiomerically pure [5], it seems also possible to obtain optically pure derivatives of 2b - e by recrystallisation. This could also be achieved at a suitable step in a synthetic sequence towards a selected target molecule. There seems to be no obvious limit as to the scale of these reactions, especially since all products are obtained with very high yields and are purified by simple flash chromatography and distillation. We are therefore presently optimising all reactions on a molar scale. Since none of the compounds 2a - f has, to our best knowledge, ever been prepared before[6] , the absolute configurations still have to be determined. This correlation of 2a - f with the known lactones [2,7] 3 and ent -3 and their transformation into other useful chiral building blocks is currently underway in our laboratory.

EXPERIMENTAL.

(-)- cis-1-Acetoxymethyl-2-hydroxymethylcyclobutane (2c):
2.0 g (10 mmol) 1c [8] were suspended in 0.1 M phosphate puffer (30 ml, pH 7, T=25° C) and treated with 200 mg PPL (Sigma Type II, crude (steapsin), 2300 units, standard triacetin). The mixture was stirred (magnetic stirrer) and the pH was kept constant during the hydrolysis by continous addition of 1N NaOH-solution from an autoburette. After addition of 9,95 ml 1N NaOH (30 h; 9,1 ml after 20 h) the reaction mixture was purified by flash chromatography (SiO_2, Et_2O, 30 min.) and bulb to bulb distilled to yield 1,53 g (97%) of 2c; $[\alpha]_D^{20}$ = -1,5° (c=4.23 $CHCl_3$).

ACKNOWLEDGEMENTS.

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