Enzymatic Hydrolysis of (±)-*trans*-1,2-Diacetoxycycloalkanes. A Facile Route to Optically-active Cycloalkane-1,2-diols

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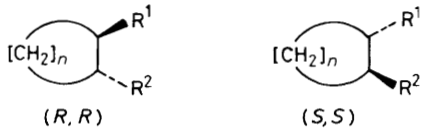
The racemic title compounds were resolved conveniently into the enantiomers with high optical purities by enzymatic hydrolysis in the presence of porcine liver esterase.

Hydrolytic enzymes are well known for their capability of enantiomer differentiation.[1] While optically-active carboxylic acids have been obtained frequently by enantioselective hydrolysis of racemic (or prochiral) esters,[2] the corresponding preparation of alcohols (or 1,2-diols) has received much less attention in the past.[3] In this communication we report the enzymatic hydrolysis of (±)-(**1c**), -(**2c**), and -(**3c**) in the presence of porcine liver esterase (PLE, E.C.3.1.1.1), a simple and facile preparative route to optically-active diols (**1a**), (**2a**), and (**3a**), which are potentially useful chiral auxiliaries and ligands (*e.g.* for hydrogenation catalysts[4] or chiral crown ethers[5]) [equations (1)—(3)].[6]

Table 1. Enzymatic hydrolysis of (±)-(**1c**), -(**2c**), -(**3c**), and -(**3b**) in the presence of PLE.

Entry	Substrate	Rel. rate	% Conversion	Products[a]	Mol%[b]	Abs. config.	% E.e.
1	(±)-(**1c**)	1	50	(**1a**)	10	(*S*,*S*)	>95[e]
				(**1b**)	49	(*R*,*R*)	>95[c]
				(**1c**)	41	(*S*,*S*)	>95[d]
2	(±)-(**2c**)	0.9	25	(**2a**)	<3	—	—
				(**2b**)	43	(*R*,*R*)	50[c]
				(**2c**)	54	(*S*,*S*)	54[d]
3			63	(**2a**)	37	(*S*,*S*)	50[e]
				(**2b**)	58	(*R*,*R*)	50[c]
				(**2c**)	5	—	—
4			74	(**2a**)	53	(*S*,*S*)	47[e]
				(**2b**)	46	(*R*,*R*)	63[c]
				(**2c**)	<1	—	—
5	(±)-(**3c**)	0.8	38	(**3a**)	24	(*R*,*R*)	>95[c]
				(**3b**)	31	(*R*,*R*)	58[c]
				(**3c**)	45	(*S*,*S*)	>95[e]
6			50	(**3a**)	41	(*R*,*R*)	>95[c]
				(**3b**)	26	—	0[c]
				(**3c**)	33	(*S*,*S*)	>95[f]
7	(±)-(**3b**)	0.02	44	(**3a**)	46	(*R*,*R*)	32[c]
				(**3b**)	54	(*S*,*S*)	26[c]

[a] For classical approaches to (*R*,*R*)-/(*S*,*S*)-(**2a**), -(**3a**) see ref. 9. [b] Determined by v.p.c.; chemical yields were 95% in the experiments with (±)-(**2c**) and -(**3c**), 78% with (±)-(**1c**). [c] Determined by v.p.c. on a chiral column [XE-60-L-valine-(*S*)-phenylethylamide]. [d] Determined by ^{1}H n.m.r. spectroscopy in the presence of Eu(tfc)$_3$. [e] Correlated with the diacetates *via* optical rotation after acetylation. [f] Correlated *via* optical rotation with the diacetate of (*R*,*R*)-(**3a**).



(**1**) Cyclobutane (n = 2)
(**2**) Cyclopentane (n = 3)
(**3**) Cyclohexane (n = 4)

a; R^1 = R^2 = OH **b**; R^1 = OAc, R^2 = OH **c**; R^1 = R^2 = OAc

$$(\pm)\text{-(1c)} \xrightarrow{i} (S,S)\text{-(1a)} + (R,R)\text{-(1b)} + (S,S)\text{-(1c)} \quad (1)$$

$$(\pm)\text{-(2c)} \xrightarrow{i} (S,S)\text{-(2a)} + (R,R)\text{-(2b)} + (S,S)\text{-(2c)} \quad (2)$$

$$(\pm)\text{-(3c)} \xrightarrow{i} (R,R)\text{-(3a)} + (\pm)\text{-(3b)} + (S,S)\text{-(3c)} \quad (3)$$

Reagents and conditions: i, PLE, 0.1 M phosphate buffer, pH 7.

In a series of experiments 15—30 mmol of (±)-(**1c**), -(**2c**), and -(**3c**) were suspended in 0.1 M phosphate buffer (20—40 ml, pH 7, T = 30 °C) and treated with 10 mg PLE (Boehringer, soluble or immobilized,[7] = 1000 units, standard Bu^{n}OAc). The rapidly decreasing pH, an indication of the beginning of hydrolysis, was kept constant during the reactions by continuous addition of 1 M NaOH solution from an autoburette. The reactions were terminated after the desired conversions (*cf.* Table 1) by removal of the enzyme and worked-up by continuous extraction with Et$_2$O. The crude product mixtures were analysed by v.p.c. (Carbowax 20 M, T = 130 °C) and isolated by flash chromatography on SiO$_2$ (Et$_2$O/Et$_2$O–EtOAc, 1 : 1). Enantiomeric purities were determined by (a) ^{1}H n.m.r. spectroscopy of the diacetates in the presence of tris(trifluorocamphorato)europium(III) (Eu(tfc)$_3$]; (b) v.p.c. of (**1b**), (**2b**), and (**3a,b**) on a chiral support (Table 1). The absolute configurations of (*S*,*S*)-(**1a**), -(**2a**), and (*R*,*R*)-(**3a**) were determined by the c.d. exciton chirality method[8] with the corresponding *p*-methoxybenzoates.

Yields, absolute configurations, and optical purities of the products are obviously dependent on the degree of conversion. Thus (±)-(**1c**) was resolved at 50% conversion into optically pure [>95% enantiomeric excess (e.e.)] (*R*,*R*)-(**1b**) and (*S*,*S*)-(**1c**) with only a small amount of (*S*,*S*)-(**1a**) being obtained. Hydrolysis of (±)-(**2c**) at low conversion (25%) again produces preferentially the monoacetate (*R*,*R*)-(**2b**) and the diacetate (*S*,*S*)-(**2c**), this time with only moderate optical yields (50% e.e.). At higher conversions (63—74%), however, practically no (*S*,*S*)-(**2c**) is isolated; only (*R*,*R*)-(**2b**) and (*S*,*S*)-(**2a**) are found. It is noteworthy that the absolute configurations of diols [(**1a**), (**2a**)] *and* diacetates [(**1c**), (**2c**)] are identical.

$$(\pm)\text{-(2c)} \xrightarrow{k_1} (R,R)\text{-(2b)} \xrightarrow{k_3} (R,R)\text{-(2a)} \quad (4)$$

$$(\pm)\text{-(2c)} \xrightarrow{k_2} (S,S)\text{-(2b)} \xrightarrow{k_4} (S,S)\text{-(2a)} \quad (5)$$

$$k_1 > k_2,\ k_4 > k_3$$

The results are most probably a consequence of the rate constants k_1—k_4, as illustrated for (±)-(**2c**) [equations (4) and (5)]. At low conversions, the product ratio is determined by $k_1 > k_2$. At higher conversions the product ratio is controlled by $k_4 > k_3$, (*S*,*S*)-(**2b**) being hydrolysed to the diol much more rapidly than (*R*,*R*)-(**2b**).

Reverse stereochemistry is observed for (±)-(**3c**). Regardless of the % conversion both (*R*,*R*)-(**3a**) and (*S*,*S*)-(**3c**) were obtained in optically pure form (>95% e.e.). Surprisingly, however, the monoacetate (*R*,*R*)-(**3b**) showed only moderate enantiomeric purity with a racemate being produced at 50% conversion. (±)-(**3b**) is also a substrate for PLE. In a very slow reaction (*R*,*R*)-(**3a**) and (*S*,*S*)-(**3b**) with low enantiomeric purities were isolated.

The change of absolute configuration and the lower enantioselectivity in the cyclopentane case closely parallel our previous results with PLE.[2†] From a preparative point of view the method described provides a facile route to (*R*,*R*)-(**1a**), -(**3a**) and (*S*,*S*)-(**1a**), -(**3a**) in enantiomerically pure form, the diacetates (*S*,*S*)-(**1c**) and -(**3c**) being readily converted into the diols (*S*,*S*)-(**1a**) and -(**3a**) with K_2CO_3 in MeOH. The preparation of (*R*,*R*)- and (*S*,*S*)-(**3a**) has been optimized on a molar scale and they are now readily available in 100 g quantities.

It is interesting to note that the corresponding *cis*-1,2-diacetoxycycloalkanols are converted exclusively into the corresponding monoacetates under these conditions. The products are, however, racemic, possibly due to rapid acyl-migration during work-up.

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† A detailed investigation of these systems is currently under way and further mechanistic discussions will be given in the full paper.

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