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ENZYME-CATALYSED ESTERIFICATION OF (±)-*trans*-CYCLOHEXANE-1,2-DIMETHANOL

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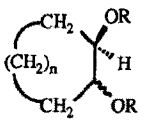
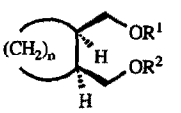
Abstract: The (*S*),(*S*)-diesters (8), (10) and (12) have been obtained from the diol (±)-(6) in Lipozyme®-catalysed esterification reactions.

Introduction and Background Information

Enantiomerically pure cycloalkane-1,2-diols are of interest in the synthesis of optically active crown ethers[1] and as ligands in asymmetric synthesis.[2] The enzymatic modification of cycloalkane diols (1) and diacetates (2) has been investigated in detail.[3]



(1) R = H
(2) R = $COCH_3$



(3) n = 1-4; $R^1 = R^2 = COCH_3$
(4) n = 1-6; $R^1 = COCH_3$; $R^2 = H$
(5) n = 3-6; $R^1 = R^2 = H$

Similarly the hydrolysis of the diacetates (3) using porcine pancreatic lipase, pig liver esterase or *Pseudomonas* sp allowed access to the alcohols (4).[4] Some members of the same series of monoesters are available by selective acylation of the diols (5) using SAM-2 (a lipase from *Pseudomonas*) in vinyl acetate as the solvent. Using either the hydrolysis or the esterification methodology the alcohols (4) were obtained in states of high optical purity.

We now report our investigation into the provision of (±)-*trans*-cyclohexane-1,2-dimethanol (6)[5] (or the corresponding diesters) in optically active form.

Results and Discussion

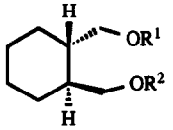
The diol (6) was esterified using different acyl donors and enzyme catalysts at 30 °C over several periods of time (Table). In most runs monoesters and diesters were produced and these were obtained in pure states along with unreacted diol. The esters obtained were hydrolysed and the optical purity of the diols obtained were assessed by g.c. using a chiral stationary phase.

Table

Enzymatic Esterification of Diol (6)

Run	Starting Material	Catalyst*	Acid or ester (equiv.)	Time	Yield	(Compound) Percentage Yield (Enantiomeric excess)		
						Diol	Monoester	Diester
1	(6)	PPL	n-$C_7H_{15}CO_2H$ (2)	48	70	(6) 85 (6)	(7) 15 (8)	-
2	(6)	PFL	n-$C_7H_{15}CO_2H$ (2)	24	71	(6) 24 (22)	(7) 30 (40)	(8) 46 (32)
3	(6)	CVL	n-$C_7H_5CO_2H$ (2)	168	80	(6) 4 (4)	(7) 40 (4)	(8) 56 (4)
4	(6)	Lipozyme®	n-$C_7H_{15}CO_2H$ (1)	2	68	(6) 42 (9)	(7) 53 (9)	(8) 5 (NA)
5	(6)	Lipozyme®	n-$C_7H_5CO_2H$ (1)	6	78	(6) 36 (23)	(7) 52 (0)	(8) 12 (83)
6	(6)	Lipozyme®	n-$C_7H_{15}CO_2H$ (1)	24	62	(6) 7 (26)	(7) 63 (32)	(8) 30 (84)
7	(6)	Lipozyme®	n-$C_7H_{15}CO_2H$ (2)	24	69	-	(7) 67 (38)	(8) 33 (83)
8	(7)	Lipozyme®	n-$C_7H_{15}CO_2H$ (1)	6	86	-	(7) 72 (30)	(8) 28 (80)
9	(7)	Lipozyme®	n-$C_7H_{15}CO_2H$ (2)	6	88	-	(7) 75 (28)	(8) 25 (76)
10	(6)	Lipozyme®	vinyl acetate (solvent)	6	88.5	(6) 44 (38)	(9) 46 (57)	(10) 10 (83)
11	(6)	Lipozyme®	$[CH_2CH_2CO_2Me]_2$ (1)	336	95	(6) 46 (14)	(11) 39 (8)	(12) 15 (35)

*PPL: porcine pancreatic lipase; PFL: *Pseudomonas fluorescens* lipase; CVL: *Chromobacterium viscosum* lipase; Lipozyme: immobilised *Mucor miehei* lipase from Novo



(6) $R^1 = R^2 = H$
(7) $R^1 = COC_7H_{15}$; $R^2 = H$
(8) $R^1 = R^2 = COC_7H_{15}$
(9) $R^1 = COCH_3$; $R^2 = H$
(10) $R^1 = R^2 = COCH_3$
(11) $R^1 = CO(CH_2)_4CO_2Me$
(12) $R^1 = R^2 = CO(CH_2)_4CO_2Me$

Immobilised *Mucor miehei* lipase (Lipozyme) proved to be the most effective catalyst. Thus esterification of the diol (±)-(6) with octanoic acid in hexane using Lipozyme® as the catalyst gave a smooth conversion into the monoester of low optical purity and a slower conversion of the mono-ester into the (*S*),(*S*)-diester of good optical purity (*ca.* 83% e.e.).[6]

The fact that the second stage of the esterification process conferred the stereoselectivity was confirmed by subjecting racemic monoester (7) to the same biotransformation (Table; Runs 8 and 9).

The latter process had an E value *ca.* 10. The esterification of the diol (6) using Lipozyme in hexane containing vinyl acetate produced much the same picture (Table; Run 10) *i.e.* the diol was rapidly converted into monoester of modest optical purity and subsequently the monoester was converted into (*S*),(*S*)-diester.

An initial attempt to obtain polyester units from the diol (6) and dimethyl adipate was not very successful (Table; Run 11). Monoester (11) and diester (12) both of low optical purity were obtained; GPC analysis indicated the presence of polymeric materials of molecular weight *ca.* 800 and › 1000 but these were not analysed further.

In summary the (*S*),(*S*)-diesters (8) and (10) and hence the (*S*),(*S*)-diol (6) can be obtained in good optical purity (*ca.* 83% e.e.) in a fast biotransformation using octanoic acid as an acylating agent.

Experimental

General method for the enzymatic esterification of (±)-*trans*-1,2-cyclohexane dimethanol (6) with octanoic acid.- A reaction mixture of (±)-*trans*-1,2-cyclohexane diol (6) (288 mg, 2 mmole), octanoic acid (288 mg, 2 mmole) and Lipozyme® (200 mg) in anhydrous hexane (10 ml) was shaken under argon in the incubator at 30 °C (220 rev/min) for 24 h. The mixture was filtered and the filtrate was washed with a 0.5 M aqueous solution of sodium hydroxide, followed by deionised water. The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Chromatography

over silica gel with ethyl acetate-petroleum (1:1) as the eluent products gave monoester (7), δ_H (250 MHz, $CDCl_3$) 4.06 (2H, m, CH_2O) ester), 3.60 (2H, d, J 6.6, CH_2OH), 2.28 (2H, t, J 7.5, -$COCH_2$-), 1.88 (1H, s, OH), 1.74 (4H, m, 2 x 3-H, 2 x 6-H), 1.60 (4H, m), 1.26 (14 H, m), 0.92 (3H, m, Me); δ_C ($CDCl_3$) 173.99 (C, C=O), 67.45, 65.65 (CH_2, C-O), 42.13, 38.51 (CH, C-1, C-2), 34.39, 34.33, 31.64, 29.85, 29.50, 29.09, 28.87, 25.80, 25.71, 24.98, 22.55 (CH_2, C-ester group, C-3, C-4, C-5, C-6), 13.99 (CH_3). ν_{max} (film, cm^{-1}) 3453 (OH), 1735 (C=O). Found: $M+H^+$, 271.2273. $C_{16}H_{30}O_3$ requires M+H 271.2273. The diester (8) was obtained from later fractions δ_H (250 MHz, $CDCl_3$), 4.04 ((4H, m, CH_2O), 2.28 (4H, t, J 7.5, -$COCH_2$-), 1.66 (10 H, m), 1.28 (20 H, m), 0.88 (6H, m, CH_3). δ_C ($CDCl_3$), 173.79 (C, CO), 66.96 (CH_2, C-O), 38.99 (CH, C-1, C-2), 34.34, 31.65, 29.63, 29.13, 28.90, 25.58, 24.98, 22.58 (CH_2, C-ester group, C-3, C-4, C-5, C-6), 13.99 (CH_3). ν_{max} (film, cm^{-1}) 1735 (C=O). Found $M+H^+$ 397.3318. $C_{24}H_{44}O_4$ requires 397.3318.

Hydrolysis of the esters (7) and (8). A solution of the ester in a 2% solution of potassium carbonate in MeOH was stirred at room temperature and the reaction was monitored by tlc. After completion of the reaction, the solvent was evaporated. Chromatography on silica gel with ethyl acetate-petroleum (1:1) as the eluent yielded the diol (6). The optical purity of the diol was determined using a Philips Pye Unicam gas chromatograph, equipped with a chiral FS-lipodex A column (25 m, 25 mm), oven temperature 110 °C, injector temperature 170 °C, detector temperature 260 °C; retention time (*S*)(*S*)-isomer-(6) 33.68 min., (*R*)(*R*)-isomer-(6) 37.28 min.

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