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ENZYMATIC PREPARATION OF OPTICALLY ACTIVE α AND β-HYDROXYALDEHYDES

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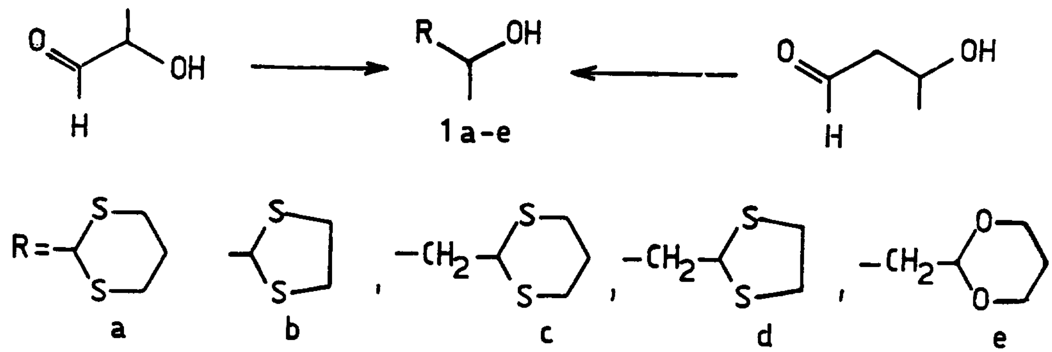
Abstract: Resolution of protected α and β-hydroxyaldehydes 1a-e, chiral building blocks in the synthesis of natural products, was easily achieved by lipase-catalyzed stereoselective hydrolysis of corresponding acetic or butyric ester derivative

Optically active α and β-hydroxyaldehydes are useful chiral building blocks in the synthesis of natural products such as S,S(+) and R,R(-) grahamimycin A_1[1a], rhodinose[1b], exo-(+)-brevicomin[1c], amino sugars[1d].
These chiral synthons are generally obtained from natural precursors or by microbial reduction of synthetic substrates such as α and β-keto-thioacetals.[2a]
Both these methods allow a simple preparation of only one enantiomer, the antipode is sometimes difficult to achieve without using sophisticated and expensive procedures.
In this paper we report a new approach to the enzymatic preparation of both enantiomers of protected α and β-hydroxyaldehydes.
It involves lipase-catalyzed stereoselective hydrolysis of the corresponding carboxylic esters.
α-hydroxy-propionaldehyde and β-hydroxy-butyraldehyde were chosen as model compounds (SCHEME 1).

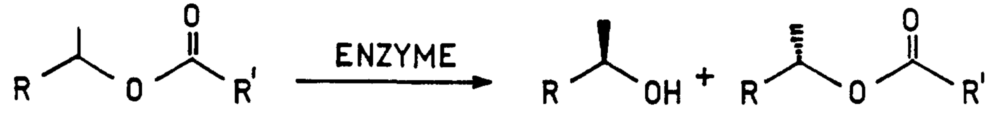


SCHEME 1

Our experiments showed that when the aldehydic group was converted to 1,3-dithian (1a,c), 1,3-dithiolan (1b,d) or 1,3-dioxan (1e) optical resolution was easily achieved by lipase-catalyzed hydrolysis of the corresponding acetic or butyric ester derivatives.

Compounds 1a-e were prepared from the corresponding α and β-hydroxyaldehydes dimethyl acetals by condensation with 1,3 propandiol, 1,3 propandithiol and 1,2 ethandithiol in benzene in the presence of PTSA.

Acetates and butyrates of racemic protected hydroxyaldehydes were subjected to stereoselective enzymatic hydrolysis (SCHEME 2).



2-3 a-e (R,S) → 1a-e (R) + 2-3 a-e (S)

2 : R' = Me
3 : R' = nPr

SCHEME 2

Although several commercially available hydrolytic enzymes were tested only three lipase preparations, namely lipase Amano P, lipase Amano CES from <u>Pseudomonas</u> and lipase from <u>Chromobacterium viscosum</u>, gave satisfactory results.[3]

Lipase-catalyzed hydrolysis of 2,3-a,e were carried out at pH 7 and the pH was maintained constant by the addition of 0.5 N aqueous NaOH. The reactions were stopped at different degrees of conversion.

Alcohols and esters were recovered and purified as indicated in the experimental section.

The enantiomeric excesses (ee's) of the optically active alcohols were determined by NMR and GLC analysis.

The ee's of the esters were determined after alkaline hydrolysis to the corresponding alcohols.

The absolute configuration of the alcohols 1a and 1c were determined by comparison of the measured optical rotation with literature data[2a-1a] and for alcohols 1b,1d and 1e on the basis of specific rotation of their O-benzyl-

hydroxy aldehydes derivatives whose absolute configurations are well estabilished.[1d,8]
Table 1 , summarizes the results obtained by asymmetric hydrolysis of 2,3-a,e using Lipase Amano P.[4]

TABLE 1. Enzymatic resolution of alcohols 1a-e

Racemic substrate	time (h)	conv. %	Alcohol yield %	Alcohol $[\alpha]_D^{25}$	Alcohol conf.	Alcohol ee%	Ester yield %	Ester $[\alpha]_D^{25}$	Ester conf.	Ester ee%[l]
2a	18	46	35	+5.75[b]	R[d]	99[h]	40	-20.0	S	93
3a	14	46	34	+5.45	R	95	41	-15.6	S	92
2b	18	49	37	-4.85[c]	R[e]	99[h]	40	+1.50	S	95
2c	17	48	35	-24.5[c]	R[f]	99[h]	40	-5.60	S	95
3c	20	49	40	-23.4	R	95	36	-1.10	S	94
2d	22	48	36	-27.4[c]	R[g]	95[h]	40	+11.8	S	95
2e	28	40	25	+3.65[c]	S[g]	26[i]	35	-3.40	R	11
3e	24	55	30	-3.80	R	27	30	+20.8	S	11

a) All the reactions were performed in 0.01 N phosphate buffer, pH 7 (40 ml) at 30 °C; substrate, 10 mmoles; enzyme, 0,4 g Lipase Amano P. b) (C=1, MeOH) c) (C=1, $CHCl_3$). d) The specific rotation for (R)-1-(1,3-dithian-2-yl)-1-ethanol is $[\alpha]_D$+5.8 (MeOH).[2a] e) Determined on the basis of the specific rotation of (R)-O-benzyl-lactaldehyde[1d] after O-benzylation and deprotection of aldehydic group[7]. f) The specific rotation for (S)-1-(1,3-dithian-2-yl)-2-hydroxy propane is $[\alpha]_D$ +24.7 (C=2, $CHCl_3$).[1a] g) Determined on the basis of the specific rotation of (R)-O-benzyl-3-hydroxybutyraldehyde[8] after O-benzylation and deprotection of aldehydic group.[7] h) Estimated by ^1H NMR using $Eu(hfc)_3$. i) Estimated by GLC analysis of the corresponding diastereomeric phenyl-ethyl carbamate.[9] l) Determined on the basis of the optical purity of the alcohol obtained from the ester by alkaline hydrolysis.

It is worth noting that both (R) and (S) forms of hydroxythioacetals 1a-d with high optical purity (>95% ee) were obtained in good yields using lipase.
It was found that these enzymes were preferentially active on the R

enantiomer; consequently at the end of the reaction, the remaining esters were enriched in the S form and the alcohols were produced in the R form. Moreover the stereospecificity of the hydrolysis was not influenced by the chain length of the acid moiety.

Conversely when carboxylic esters of β-hydroxyacetals 1e were used as substrates, lipases displayed good hydrolytic activity again but the stereoselectivity was much lower (20-30% ee).

This fact suggests that the enantioselectivity of lipase catalyzed hydrolysis of these compounds greatly depends on the lipophilicity of the protecting group (hydrophobicity ratio between 1,3-dithiane and 1,3-dioxane obtained by using theoric hydrophilic fragmental constant[6] results 3/1).

This observation could be potentially interesting as a method of choice of protective groups on substrates to be enzymatically hydrolysed stereoselectively.

EXPERIMENTAL SECTION

The optical rotation was measured with a Perkin Elmer 241 polarimeter. ^1H NMR spectra were recorded in $CDCl_3$ solution [$(CH_3)_4Si$ as internal standard] on a BRUKER AM 300 instrument. GLC analyses were carried out on a CARLO ERBA HRGC 5300 chromatograph with a 2 m x 4 mm SP 2100 3% column at 100-250 °C and with a flame ionization detector. The optical purity of compound 1e was determined with a 0.32 mm x 25 m OV 1 capillary column at 150-300 °C of the diasteromeric amide.[7] Lipase Amano P and Lipase Amano CES were purchased from Amano Chemical Co., Lipase from <u>Chromobacterium</u> <u>Viscosum</u> was purchased from Tojo Jozo (Japan).

Synthesis of racemic alcohols 1a-b

The following procedure is representative.

1,3 propandithiol (4,7 g, 49.2 mmol) was added to a stirred solution of 2-hydroxy propionaldehyde dimethylacetal (5.9 g, 49.2 mmol) in benzene (50 ml) containing PTSA (50 mg). The solution was stirred at 80°C for 6 hours, washed with 5% aqueous sodium hydroxyde and successively with water.

The organic phase was dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 7/3 hexane ether as eluant afforded 4.9 g of 2-(1-hydroxyethyl)-1,3-dithiane (1a); ^1H NMR ($CDCl_3$) δ= 1.25 (3H, d), 1.60-2.18 (2H, m), 2.35-3.02 (5H, m), 3.50-3.55 (1H, m), 4.00 (1H, d); anal. calculated for $C_6H_{12}S_2O$: C, 43.87 H, 7.36 found: C, 43.85 H, 7.33.

The procedure above described, employing 1,2-ethandithiol instead of 1,3-

propandithiol, has been used to prepare 2-(1-hydroxyethyl)-1,3-dithiolane (1b); ^{1}H NMR ($CDCl_3$) δ= 1.30 (3H, d), 2.48 (1H, s), 3.13-3.31 (4H, m), 3.65-3.71 (1H, m), 4.40 (1H, d); anal. calculated for $C_5H_{10}S_2O$: C, 39.97 H, 6.71; found: C, 39.99 H, 6.74.

Synthesis of racemic alcohols 1c-e

The following procedure is representative.
1,2-ethandithiol (3.76 g, 40.0 mmol) was added to a stirred solution of 3-hydroxy butyraldehyde dimethylacetal (5.28 g, 40.0 mmol) in benzene (50 ml) containing PTSA (50 mg). The solution was stirred at 80°C for 6 hours, washed with 5% aqueous sodium hydroxyde and successively with water.
The organic phase was dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 7/3 hexane ether as eluant afforded 4.0 g of 1-(1,3-dithiolan-2-yl)-2-hydroxypropane (1d); ^{1}H NMR ($CDCl_3$) δ= 1.21 (3H, d), 1.85-2.07 (3H, m), 3.18-3.30 (4H, m), 3.94-4.00 (1H, m), 4.64-4.70 (1H, t); anal. calculated for $C_6H_{12}S_2O$: C, 43.87 H, 7.36 found: C, 43.85 H, 7.33.
The procedure above described, employing 1,3-propandithiol and 1,3-propandiol instead of 1,3-benzene, has been used to prepare 1-(1,3-dithian-2-yl)-2-hydroxypropane (1c); ^{1}H NMR ($CDCl_3$) δ= 1.20 (3H, d), 1.65-2.45 (5H, m), 2.60-3.15 (4H, m), 3.95-4.00 (1H, m), 4.12 (1H, t); anal. calculated for $C_7H_{14}S_2O$: C, 47.15 H, 7.91; found: C, 47.19 H, 7.88.; and 1-(1,3-dioxan-2-yl)-2-hydroxypropane (1e); ^{1}H NMR ($CDCl_3$) δ= 1.20 (3H, d), 1.60-2.50 (4H, m), 3.07 (1H, br. s), 3.65-4.31 (5H, m), 4.95 (1H, t); anal. calculated for $C_7H_{14}O_3$: C, 57.51 H, 9.65; found: C, 57.49 H, 9.62.

Synthesis of racemic esters 2-3 a-e

The following procedure is representative.
To a magnetically stirred solution of 2-(1-hydroxyethyl)-1,3-dithiane (1a) (24mmol) and pyridine (31 mmol) in ethyl ether (30 ml) was added acetyl chloride (30 mmol) at 0°C over a 15 min period. The reaction mixture was stirred an additional 5h at room temperature and then washed with water(30 ml) saturated sodium carbonate solution (20 ml) and water (20 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 2-(1-acetoxyethyl)-1,3-dithiane (2a) (75%). ^{1}H NMR ($CDCl_3$) δ 1.25 (3H,d), 1.6-2.15 (3H,m), 2.35-3.0 (4H,m), 3.5-3.55 (1H,m), 3.9 (1H,t).
2-(1-butyryloxyethyl)-1,3-dithiane (3a) : 80% yield , ^{1}H NMR ($CDCl_3$) δ 0.85 (3H,t), 1.20 (3H,d), 1.40-2.21 (6H,m), 2.35-3.04 (6H,m), 3.45-3.55 (1H,m), 3.85 (1H,t)
2-(1-acetoxyethyl)-1,3-dithiolane (2b) : 70% yield , ^{1}H NMR ($CDCl_3$) δ 1.25 (3H,d), 2.1 (3H,s), 3.1-3.3 (4H,m), 3.64-3.7 (1H,m), 4.42 (1H,d)

1-(1,3-dithian-2-yl)-2-acetoxypropane (2c) : 75% yield , ^{1}H NMR (CDCl$_3$
1.25 (3H,d), 1.6-2.4 (7H,m), 2.6-3.15 (4H,m), 3.92-3.98 (1H,m), 4.1 (1H,t)

1-(1,3-dithian-2-yl)-2-butyryloxypropane (3c) : 75% yield , ^{1}H NMR (CDCl$_3$) δ 0.9 (3H,t), 1.22 (3H,d), 1.45-2.3 (6H,m), 2.38-3.07 (6H,m), 3.9-3.96 (1H,m), 4.09 (1H,t)

1-(1,3-dithiolan-2-yl)-2-acetoxypropane (2d) : 80% yield , ^{1}H NMR (CDCl$_3$) δ 1.22 (3H,d), 1.85-2.1 (5H,m), 3.15-3.27 (4H,m), 3.95-4.0 (1H,m), 4.66-4.72 (1H,t)

1-(1,3-dioxan-2-yl)-2-acetoxypropane (2e) : 70% yield, ^{1}H NMR (CDCl$_3$) δ 1.2 (3H,d), 1.55-2.45 (7H,m), 3.6-4.26 (5H,m), 4.95 (1H,t)

1-(1,3-dioxan-2-yl)-2-butyryloxypropane (3e) : 70% yield, ^{1}H NMR (CDCl$_3$) δ 0.9 (3H,t), 1.22 (3H,d), 1.45-2.45 (6H,m), 2.5-3.15 (2H,t), 3.63-4.29 (5H,m), 4.96 (1H,t)

Lipase catalyzed hydrolysis of esters 2-3 a-e

The following procedure is representative. To a magnetically stirred solution of 2-(1-acetoxyethyl)-1,3-dithiane (2a) (2.06 g, 10 mmol) in 0.01 phosphate buffer (40 mL) at 30°C was added lipase P Amano (0.4 g) and the mixture was mantained at pH 7 with 0.5 N aqueous NaOH by using a pH stat. The hydrolysis was stopped at 46% conversion (18 h). The reaction mixture was extracted witl ethyl acetate (3x60 mL), and the organic layer was dried over sodium sulfate and evaporated to dryness. Chromatography on silica gel with n-exane/ethyl acetate (90:10) afforded 0.57 g (35%) of R-(+)-2-(1-hydroxyethyl)-1,3-dithiane (1a) $[\alpha]_D^{25}$= +5.75° (c 1, MeOH) and 0.82 g (40%) of S-(-)-2-(1-acetoxyethyl)-1,3-dithiane (2a) $[\alpha]_D^{25}$= -20.0° (c 1, CHCl$_3$).

Optically active alcohols 1b-e and corresponding esters have been prepared using the above procedures (Table 1).

Alkaline hydrolysis of esters 2-3 a-e

The following procedure is representative. An ethanolic solution (10 mL) of (S)-(-)-2-(1-acetoxyethyl)-1,3-dithiane (2a) (0.8 g, 3.9 mmol) obtained from the above described lipase catalyzed hydrolysis was treated for 5 h at 50°C with KOH (0.22 g, 3.9 mmol). Water (10 mL) was added and the reaction mixture was extracted with ethyl ether (3x15 mL). The organic extract was washed, dried over sodium sulfate, evaporated to dryness and purified on silica gel with 70:30 hexane/ether as eluant to give 0.38 g (60%) of (S)-(+)-2-(1-hydroxyethyl)-1,3-dithiane (1a) : 93% e.e.; $[\alpha]_D^{25}$= +23.3° (c 1, CHCl$_3$).

Optically active alcohols 1b-e were prepared from the corresponding enzimatically produced esters using the above procedure.

Synthesis of (R)-(+)-(O)-benzyl-lactaldehyde from optically active 1b

To a magnetically stirred suspension NaH (55%) (0.88 g, 20.1 mmol) in anidrous tetrahydrofurane (10 mL) was added dropwise (R)-(-)-2-(1-hydroxyethyl)-1,3-dithiolane (1b) (2.325 g, 15.5 mmol) at 0°C over a 0.5 h period. The reaction mixture was stirred an additional 6 h at room temperature and then benzyl bromure (2.65 g, 15.5 mmol) was added. The resulting mixture was shaken at 60°C for 4 h, diluted with water (10 mL) and extracted with ether (2x50 mL).Organic phase was dried ($MgSO_4$) and evaporated in vacuum. Chromatography on silica gel with 90:10 n-hexane/ether as eluant afforded 1.3 g (35%) of 2-(1-(O)-benzylethyl)-1,3-dithiolane.

2(1-(O)-benzylethyl)-1,3-dithiolane (1.3 g, 5.4 mmol) was dissolved in aceton (15 mL) containing water (1.5 mL) and methyl iodide (1.53 g, 10.8 mmol).The resulting solution was then heated under reflux for 24 hr, evaporated in vacuum, diluted with ether (50 mL) and washed with water (30 mLx2). Organic phase was dried ($MgSO_4$) and evaporated. Chromatography on silica gel with 1:1 n-hexane/ether afforded 274 mg (31%) of (R)-(+)-(O)-benzyl lactaldehyde $[\alpha]_D^{25}$ = + 64.0 (neat) [Lit.: = + 61.5 neat]. ^1H NMR ($CDCl_3$) δ 1.25 (3H,d), 3.8-4.38 (1H,m), 4.6 (2H,s), 7.35 (5H,s), 9.8 (1H,d). Anal. calculated for $C_{10}H_{12}O_2$: C, 73.15 H, 7.36 found: C, 73.0 H, 7.4

Synthesis of (R)-(O)-benzyl-3-hydroxybutyraldehyde from (R)-1-(1,3-dithiolan-2-yl)-2-hydroxypropane 1d

(R)-(O)-benzyl-3-hydroxybutyraldehyde has been prepared from (R)-1-(1,3-dithiolan-2-yl)-2-hydroxypropane (1d) using the procedure described above in 35% yield, $[\alpha]_D^{25}$= - 36.5° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25 (3H,d), 2.2-2.75 (2H,m), 3.75-4.33 (1H,m), 4.56 (2H,s), 7.35 (5H,s), 9.55 (1H,br,s). Anal. calculated for $C_{11}H_{14}O_2$: C, 74.13 H, 7.92 found: C, 74.25 H,7.98.

(R)-(O)-benzyl-3-hydropxybutyraldehyde from (R)-1-(1,3-dioxan-2-yl)-2-hydroxypropane 1e

(R)-(O)-benzyl-3-hydroxybutyraldehyde has been prepared using the procedure described above in from (R)-1-(1,3-dioxan-2-yl)-2-hydroxypropane (1e) in 30% yield except that the deprotection of acetal group has been done in diluted HCl according to P.A. Grieco et al.[10]

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3) In the hydrolysis of 1-5,a-b, lipase from porcine pancreas (Sigma) gave no reactions at all, lipase from Candida cylindracea (Sigma) was stereospecific.

4) Similar results have been obtained with lipase Amano CES and lipase from Chromobacterium viscosum.

5) Hydrophobicity ratio between 1,3-dithiane and 1,3-dioxane obtained by using theoric hydrophylic fragmental constant[6] results 3/1.

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8) (R)-(-)-O-benzyl-3-hydroxybutyraldehyde $[\alpha]_D^{25}$ = -37.9° (c=1, $CHCl_3$)has been prepared from (R)-1-(1,3-dithian-2-yl)-2-hydroxypropane 1c after benzylation and deprotection of the aldehydic group.[7]

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