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Enzymatic resolution of a 1,2-cyclic sulphite glycerol derivative

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Abstract

cis-2-Oxo-5-hydroxymethyl-1,3,2-dioxathiolane **2a** can be efficiently resolved by a lipase from *Pseudomonas cepacia*-catalysed acylation reaction with vinylbutyrate. Compound **2a** was directly prepared from glycerol in one step. This first lipase-catalysed resolution of a cyclic sulphite derivative provides a potentially useful activated chiral synthon.

1. Introduction

Chiral glycerol derivatives have been widely used as chiral synthons for the preparation of a large variety of enantiomerically pure and biologically active compounds such as β-blockers,[1] phospholipids[2] and many others.[3] They can be obtained either from the chiral pool starting from D-mannitol,[4] L-serine[5] or ascorbic acid.[3c] Although some chemical methods have been investigated from glycerol itself,[6] most of the studies use enzymatic methodology.[7,8] As a prochiral compound, glycerol can be desymmetrised by phosphorylation catalysed by glycerol kinase.[8] However, it is more convenient to start from a derivative of glycerol such as 2-*O*-benzylglycerol or 1,3-diacyl-2-*O*-benzylglycerol which can lead to monoesters by lipase catalysis.[9] Although desymmetrisation of a glycerol derivative appears as the most elegant enzymatic way, it is not the most convenient for further applications, since it can increase the number of deprotection steps. Numerous publications have appeared on the resolution of racemic derivatives of glycerol.[3d,7,10–14] In this case of course, only 50% chemical yield for one enantiomer can be isolated, but this is not really an inconvenience, due to the low price of the starting material. Moreover, both enantiomers can often have useful applications. As a primary alcohol, the first glycerol derivative to be resolved was glycidol,[11] but most of the studies have concerned the resolution of hydroxymethyl-1,3-dioxolanes, especially 2,2-dimethylhydroxymethyl-1,3-dioxolane (solketal)[12] or 2,2-dialkylhydroxymethyl-1,3-dioxolane[7,13] and glycerol-2,3-carbonate.[14] Apart from

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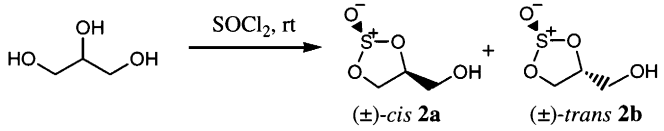
glycidol, all derivatives used are unactivated compounds, so that their utilisation as chiral synthons implies deprotection and activation steps.

It occurred to us that obtaining chiral cyclic sulphites and sulphates of glycerol could be of interest. Indeed, the chemistry of cyclic sulphites and sulphates has been well documented in recent years.[15] These compounds undergo regioselective ring opening with nucleophiles, cyclic sulphates being even more reactive than epoxides.[2c] Cyclic sulphates prepared from other chiral derivatives of glycerol have already been described, providing precursors of natural products.[2c,16]

In this paper, we describe the resolution of *cis*- and *trans*-glycerol-1,2-cyclic sulphites **2a** and **2b** (Scheme 1) by lipase-catalysed transesterification. To our knowledge no other cyclic sulphite has previously been resolved by hydrolases.



Scheme 1.

2. Results and discussion

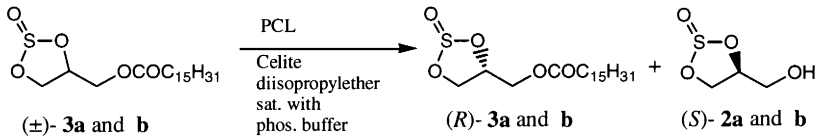
2.1. Sulphite synthesis

Compounds **2** (Scheme 1) have previously been obtained from glycerol by reaction of dimethylsulphite.[17] An improved method is described here where racemic glycerol 1,2-cyclic sulphites **2a** and **2b** (Scheme 1) were readily prepared from glycerol by the action of thionylchloride ($SOCl_2$).

Adding $SOCl_2$ diluted in anhydrous dichloromethane directly to pure glycerol at 0°C enabled us to isolate the desired compounds in 78% yield after bulb to bulb distillation. Distillation under vacuum through a Widmer column afforded a fraction containing only the *cis*-isomer pure in 57% yield while a mixture of the *cis*- and *trans*-isomers always constituted the other fractions.[18] As distillation was not a suitable operation for isolation of the *trans*-isomer, **2b** was purified by column chromatography in 34% yield.

2.2. Lipase catalysed hydrolysis of palmitate *3*

As with other esters of glycerol,[19] acyl sulphites such as **3** (Scheme 2) are prone to rearrangement. Indeed, in a preliminary assay we observed that the acetyl group migrated on the secondary alcohol function and the cyclic sulphite formed a six-membered ring. As it is known that esters of long chain acids are the most stable,[3d] we started with hydrolysis of the palmitoyl derivative. In the first experiments, several hydrolases were investigated for enantioselective hydrolysis of the mixture of **3a** and **3b**.



Scheme 2.

Nine lipases and one esterase were screened but only the lipase from *Pseudomonas cepacia*[20] gave low but significant enantioselectivity. The results concerning this lipase are reported in Table 1. Substrates and products were purified by column chromatography and the enantiomeric excess was determined by chiral GC. The yields were calculated on the basis of the conversion value.

Table 1
Pseudomonas cepacia lipase-catalysed hydrolysis of **3** (mixture of *cis* and *trans*) in diisopropyl ether saturated with phosphate buffer

T °C	t, h	product (*S*)	yield[a] (%)	ee[b] *cis* (%)	ee[c] *trans* (%)	substrate (*R*)	yield[a] (%)	ee[b] *cis* (%)	ee[c] *trans* (%)	conv *cis*[d] (%)	conv *trans*[d] (%)	E_{cis}[e]	E_{trans}[e]
24	14	**2**	90	22	16	**3**	83	48	62	69	79	2	2
0	72	**2**	92	23	40	**3**	80	14	30	38	43	3	3

[a]After flash chromatography, 100% at corresponding conversion. [b]Determined by chiral GC on the alcohol function; [c]Determined by chiral GC on the acetate derivative. [d]Calculated from ee, see ref 21. [e]See ref 7 and ref. cited therein.

The enantiomeric ratio (*E*) as a measure of the efficiency of the enzyme for each isomer *cis* and *trans* was calculated from the measured *ee* according to Sih et al.[21] In control experiments, the reaction did not proceed without the enzyme. Different solvents were tested such as acetone, dichloromethane, ether, benzene and diisopropyl ether. This last solvent provided the best enantioselectivity. Decreasing temperature, which is often known to increase enantioselectivity of a lipase, did not really improve the selectivity significantly. The *E* values for each isomer slightly increased but not significantly enough for further application of the hydrolysis step.

2.3. *Absolute configuration*

The absolute configuration was assigned by chemical correlation (Scheme 3), since for the moment, no empirical rule allows prediction of the fast reacting enantiomer when the stereocentre bears an oxygen atom.[22]

(*R*)-(+)-**3** (*S*)-(-)-**4**

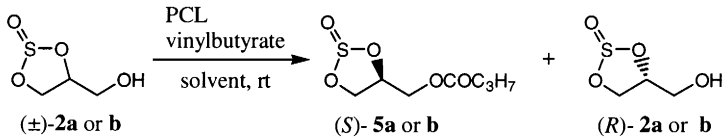
Scheme 3.

The remaining substrate (+)-**3** was refluxed with lithium azide in DMF. After hydrolysis, **4** was isolated and had a negative specific rotation. Comparison of this value with the data given in the literature for diol **4**[23] enabled us to assign the *R*-configuration to (+)-**3**. As generally seen for such glycerol derivatives, the faster reacting enantiomer in the lipase hydrolysis step is the (*S*) form.[7,12–14]

2.4. Pseudomonas cepacia *lipase-catalysed acylation by vinylbutyrate*

Considering our previous results, the resolution was then tested by transesterification. The experiments were carried out on each isomer with PCL (Scheme 4). It was found that the reactions were very slow when the acylating reagent was vinylpalmitate so we decided to work with vinylbutyrate. No transposition side reaction was observed.

The enzyme was immobilised on Celite in the presence of sucrose.[24] Several solvents were tested and the results are reported in Table 2 for the *cis*-isomer **2a** and in Table 3 for the *trans*-isomer **2b**. In control experiments, the reaction did not proceed without the enzyme.



(±)-**2a** or **b** (*S*)- **5a** or **b** (*R*)- **2a** or **b**

Scheme 4.

Table 2
Pseudomonas cepacia lipase-catalysed acylation of **2a** in the presence of vinylbutyrate in various solvents

solvent	T°C	t, h	product (*S*)	yield[a] (%)	ee[b] *cis* (%)	substrate (*R*)	yield[a] (%)	ee[b] *cis* (%)	conv[c] (%)	E[c]
CH_2Cl_2	24	6	**5a**	85	91	**2a**	81	24	21	26
$CHCl_3$	23	28	**5a**	86	86	**2a**	78	18	17	16
THF	24	23	**5a**	80	53	**2a**	80	34	39	4
iPr_2O	23	25	**5a**	87	73	**2a**	85	36	33	9
Et_2O	23	6	**5a**	81	80	**2a**	77	25	24	11

[a]After flash chromatography, 100% at corresponding conversion. [b]Determined by chiral GC on the alcohol function. [c]Calculated from ee, see ref 21.

Table 3
Pseudomonas cepacia lipase-catalysed acylation of **2b** in the presence of vinylbutyrate in various solvents

solvent	T°C	t, h	product (*S*)	yield[a] (%)	ee[b] *trans* (%)	substrate (*R*)	yield[a] (%)	ee[b] *trans* (%)	conv[c] (%)	E[c]
CH_2Cl_2	25	49	**5b**	85	17	**2b**	76	19	53	2
$CHCl_3$	24	200	**5b**	87	26	**2b**	75	5	16	2
*t*BuOMe	24	6.5	**5b**	82	21	**2b**	80	5	19	2
iPr_2O	25	23	**5b**	85	25	**2b**	81	14	36	2

[a]After flash chromatography, 100% at corresponding conversion. [b]Determined by NMR with $Eu(hfc)_3$ on the alcohol function. [c]Calculated from ee, see ref 21.

The reactions were monitored by TLC and the ester products and residual substrates were purified by column chromatography. The *ee* values were measured by chiral GC for the *cis*-isomer and by NMR for the *trans*-isomer. As seen in the hydrolysis step, the lipase reacted preferentially with the *S*-enantiomer.

Concerning the *cis*-isomer, the highest *E* values were obtained in halogenated solvents. Similar results have been described by Pallavicini et al. on a glycerol carbonate derivative.[14] *Pseudomonas fluorescens* acylated their glycerol derivative in chloroform with *E*=16. The results in Table 2 also demonstrate that successful enantioselective acylation of **2a** is possible when PCL is used in dichloromethane. As the reactions do not stop at 50% conversion, these conditions could afford a good preparative method for the resolution of the alcohol **2a**: 91% *ee* was observed after 21% conversion rate for the ester, the reaction could be continued over 50% leading to almost enantiomerically pure (*R*)-**2a**.

Concerning the *trans*-isomer, no noticeable differences for *E* values were observed when the reaction was performed in different solvents. The enantioselectivities are too low for synthetic applications.

As shown by the results listed in Tables 2 and 3, **2a** and **2b** are not resolved with the same efficiency by the lipase from *P. cepacia*. The acylation proceeded with significantly better enantioselectivities on the *cis*-isomer. Such discrimination between two isomers has already been observed in the case of asymmetrical disubstituted cyclic acetals of glycerol[7]. But this is not an inconvenience since this isomer **2a**, contrary to **2b**, can be easily obtained pure from glycerol by simple distillation.

3. Conclusion

Once more for a glycerol derivative, *P. cepacia* lipase was selected for an enzymatic resolution and has shown a preference for the *S*-enantiomer. Halogenated solvents have given a favourable influence for the enantioselectivity.

Although primary alcohol compounds are not the most favourable situation for enzymatic resolution, the lipase from *P. cepacia*-catalysed enantioselective acylation (E=26) of cyclic sulphite **2** can afford an efficient preparation of (*S*)-**5** and (*R*)-**2a**. This is the first resolution of cyclic sulphite via lipase-catalysed reaction. This enantiomerically enriched synthon can be used directly for synthetic application.

4. Experimental

4.1. General

Pseudomonas cepacia lipase (PCL) was purchased from Fluka. All reagents were of commercial quality and were purchased from Aldrich or Lancaster. Solvents were distilled over an appropriate desiccant and stored under argon. TLC plates of silica gel 60 F254 from Merck and Merck silica gel for column chromatography 60/230–400 and 60/40–63 mesh were used. Mps are uncorrected. Optical rotations were measured with a Jasco Dip-370 polarimeter. IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC400 spectrometer. Mass spectra were obtained on a Hewlett–Packard 5989 A spectrometer. GC analysis was carried out on a Delsi Nermag chromatograph.

4.2. 4-Hydroxymethyl-2-oxo-1,2,3-dioxathiolanes *2a* and *2b*

Thionylchloride ($SOCl_2$, 5 mL, 69 mmol) in 7.5 mL of anhydrous CH_2Cl_2 were added dropwise over 5 mL of freshly distilled glycerol (69 mmol) cooled to 0°C. When the addition stopped, the mixture was stirred at room temperature for 24 h. After evaporation of the solvent, the reaction mixture was neutralised with Amberlite IRA 93 in methanol. The mixture was filtrated and concentrated under vacuum. Bulb to bulb distillation (135°C, 0.7 mmHg) gave **2** as a colourless oil in 78% yield containing a mixture of 35% *cis* and 65% *trans* (based on NMR). To isolate **2a**, distillation of crude **2** on a Widmer column under reduced pressure was necessary. The first fraction collected from 57 to 59°C (0.02 mmHg) gave **2a** in 57% yield (5.46 g). The second fraction collected over 60°C (0.02 mmHg) was constituted by a mixture of **2a** and **2b**. The crude mixture of **2a** and **2b** was submitted to column chromatography on silicagel (97:3, CH_2Cl_2:MeOH). Compound **2b** was isolated in 34% yield.

For **2**: IR (neat) 950, 1200, 1470, 3650 cm^{-1}; MS (EI) *m/z*: 139 $(M+H)^+$, 121, 107, 75, 57. For **2a** *cis*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (1H, dd, J=3, 10 Hz, OH), 3.79 (1H, ddd, J=3, 10, 13 Hz, H_{6B}), 4.04 (1H, ddd, J=3, 6, 13 Hz, H_{6A}), 4.50 (1H, dd, J=8, 8 Hz, H_{5B}), 4.73 (1H, dd, J=8, 8 Hz, H_{5A}), 4.83 (1H, dddd, J=3, 6, 8, 8 Hz, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.7 (C_6), 67.5 (C_5), 83.8 (C_4). For **2b** *trans*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (1H, dd, J=6 Hz, OH), 3.76 (1H, m, ABX, H_{6B}), 3.89 (1H, m, ABX, H_{6A}), 4.34 (1H, dd, J=6, 8 Hz, H_{5B}), 4.73 (1H, dd, J=7, 8 Hz, H_{5A}), 5.05 (1H, m, J=5, 5, 6, 10 Hz, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.2 (C_6), 68.3 (C_5), 80.2 (C_4).

4.3. 4-Palmitoyloxymethyl-2-oxo-1,2,3-dioxathiolane **3a** and **3b**

To a solution of sulphite alcohol **2** (690 mg, 5 mmol) and DMAP (6 mg, 0.05 mmol) in 20 mL of anhydrous pyridine was added palmitoylchloride (1.65 g, 6 mmol). The mixture was stirred for 4 h at room temperature. After concentration, the crude compound was submitted to flash chromatography (80:20, cyclohexane:ethyl acetate). Palmitate **3** was isolated in 95% yield (1.789 g) as a white wax (64:36 *trans*:*cis* based on NMR). Mp 43–44°C, IR (neat) 910, 1210, 1300, 1465, 1710 cm^{-1}; MS (EI) *m/z*: 376 $M^{+\cdot}$, 312. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9 (6H, t, J=7 Hz, *cis* and *trans* CH_3), 1.25 (48H, m, *cis* and *trans* $(CH_2)_{12}$), 1.76 (4H, m, *cis* and *trans* CH_2), 2.75 (4H, q, J=7 Hz, *cis* and *trans* CH_2CO), 4.23 (2H, m, ABX, H_6 *trans*), 4.28 (1H, dd, J=5, 9 Hz, H_{5B} *trans*), 4.36 (1H, dd, J=5, 12 Hz, H_{5B} *cis*), 4.55 (3H, m, H_{5A} and 2 H_6 *cis*), 4.72 (1H, m, H_4 *cis*), 4.77 (1H, dd, J=7, 9 Hz, H_{5A} *trans*), 5.15 (1H, dddd, J=5, 7, 10, 11 Hz, H_4 *trans*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3 *cis* and *trans*), 22.7, 24.8, 29.5, 31.9, 34.0 (CH_2 *cis* and *trans*), 62.2 (C_6 *trans*), 62.9 (C_6 *cis*), 68.3 (C_5 *cis*), 68.4 (C_5 *trans*), 77.7 (C_4 *trans*), 80.2 (C_4 *cis*), 173.3 (C=O). Anal. calcd: C, 60.64; H, 9.63; S, 8.51. Found: C, 60.54; H, 9.92; S, 8.46.

4.4. Enzymatic hydrolysis

Racemic palmitate **3** (1.33 mmol), *P. cepacia* lipase (1 mg, 609 U) and Celite (50 mg) were added to diisopropyl ether (20 mL) saturated with 0.05N phosphate buffer (pH 7.0) and the reaction mixture was stirred at room temperature (24°C) or at 0°C. The reaction was monitored by TLC. The solid enzyme preparation was filtered and washed with ether and the organic layer was concentrated in vacuo. Purification by flash column chromatography (cyclohexane:ethyl acetate, 60:40) gave the alcohol (−)-(*S*)-**2**. Then unreacted ester (+)-(*R*)-**3** was separated from palmitic acid by flash column chromatography (CH_2Cl_2:MeOH, 98:2).

The *ee* values of the *cis* form were determined by gas chromatography on a FS Lipodex E column on the alcohol function. Thus, alcohol **2** was directly injected and the unreacted palmitate ester **3** was injected after hydrolysis.

The *ee* values of the *trans* form were determined after derivatisation of the alcohol **2** with acetic anhydride in the presence of DMAP and pyridine before the gas chromatography analysis. The palmitate ester **3** was hydrolysed and acetylised before measurement. For **2** and **3** the spectroscopic data were in accordance with the racemic samples. For **2** $[\alpha]_D^{25}=-8$ and for **3** $[\alpha]_D^{25}=+12$ (experiment at 24°C).

4.5. Absolute configuration: (−)-(2S)-3-azidopropane-1,2-diol

To a solution of 125 mg (0.33 mmol) of ester (+)-**3** in 2 mL of DMF, 50 mg (1 mmol) of LiN_3 were added. The mixture was refluxed for 12 h. The solvent was removed under reduced pressure. The residue was treated with 5 mL of water and extracted with 3×10 mL of ethyl acetate. The organic fractions were collected, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was pure enough for the next step.

To a solution of 111 mg of the intermediate in 4 mL of MeOH, 3 mg of MeONa were added. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (CH_2Cl_2:MeOH, 95:5). The diol was isolated in 58% yield (22 mg). $[\alpha]_D^{25}=-3$ (*c* 0.020, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (2H, m, H_3), 3.60 (1H, dd, J=11.5, 6 Hz, H_{1B}), 3.70 (1H, dd, J=11.5, 3.5 Hz, H_{1A}), 3.88 (1H, m, H_2), 3.6–4.0 (2H, s large, OH).

4.6. General procedure for enzymatic acylation of **2a** and **2b**

Before use, lipase from P. *cepacia* was dissolved in phosphate buffer (0.1 M, pH=7.5) in the presence of sucrose (4%, w/w), followed by adsorption on Celite. The lipase preparation thus obtained contained 1% (w/w) of lipase.

The racemic alcohol **2a** or **2b** (1.45 mmol) was dissolved in 10 mL of the selected dry solvent, 1.45 mmol of vinylbutyrate and 20 mg of the lipase preparation were added. The suspension was stirred at room temperature and the reaction followed by TLC. The solid enzyme preparation was filtered off, washed with the solvent and the organic layer was concentrated in vacuo. Flash chromatography (cyclohexane:ethyl acetate, gradient 80:20 to 40:60) afforded (*S*)-**5** and unreacted alcohol (*R*)-**2**.

The *ee* values of the *cis* form were determined by gas chromatography on a FS Lipodex E column on the alcohol function. Thus, unreacted alcohol **2a** was directly injected and the product ester **5a** was injected after hydrolysis.

The *ee* values of the *trans* form were determined by NMR using $Eu(hfc)_3$ as chemical shift reagent on the alcohol function. Thus, the product ester **5b** was hydrolysed before measurement. For **5a** and **5b**: IR (neat) 961, 1208, 1462, 1740 cm^{-1}. MS EI *m/z*: 209 ($M+H^+$), 71, 43. Anal. calcd: C, 40.37; H, 5.80; S, 15.40. Found: C, 40.41; H, 5.88; S, 15.47. (*S*)-**5a**: colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7 Hz, CH_3), 1.67 (2H, m, CH_2), 2.35 (2H, t, J=7 Hz, CH_2), 4.35 (1H, dd, J=5, 12 Hz, H_{5B}), 4.53 (3H,m, H_{5A} and 2 H_6), 4.71 (1H, m, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 18.3 (CH_2), 35.8 (CH_2), 62.8 (C_6), 68.2 (C_5), 80.2 (C_4), 173.1 (C=O). $[\alpha]_D^{25}=-34$ (experiment in CH_2Cl_2). (*S*)-**5b**: colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J=7 Hz, CH_3), 1.65 (2H, m, CH_2), 2.35 (2H, t, J=7 Hz, CH_2), 4.21 (2H, d, J=5 Hz, H_6), 4.27 (1H, dd, J=5, 9 Hz, H_{5B}), 4.75 (1H, dd, J=6, 9 Hz, H_{5A}), 5.13 (1H, dddd, J=5, 6, 7, 9 Hz, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 18.3 (CH_2), 35.8 (CH_2), 62.2 (C_6), 69.0 (C_5), 77.1 (C_4), 173.0 (C=O). $[\alpha]_D^{25}=-16$ (experiment in CH_2Cl_2)

The spectroscopic data for (*R*)-**2a** and **2b** were in accordance with the data for racemic **2a** and **2b**. For **2a** $[\alpha]_D^{25}=+8$ (experiment in CH_2Cl_2) and for **2b** $[\alpha]_D^{25}=+7$ (experiment in CH_2Cl_2).

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