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S-(-)-2-Acetoxymethyl-2,5-dihydrothiophene via Enzymatic Resolution

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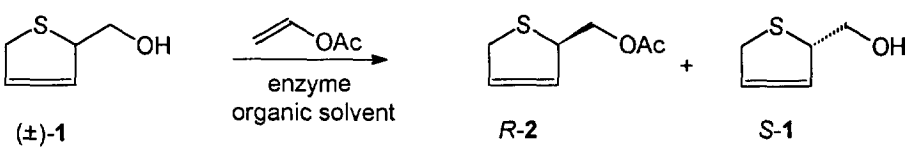
Abstract: For the resolution of (±)-2-hydroxymethyl-2,5-dihydrothiophene lipase-catalysed acetylation as well as hydrolysis and alcoholysis of the corresponding acetate were investigated, the best results being obtained in alcoholysis catalysed by lipase from *Pseudomonas fluorescens* with butanol in organic solvent.

Efficient enzymatic resolution[1] of racemic secondary alcohols is very common in organic synthesis. On the other hand the successful kinetic resolution of chiral primary alcohols like the title compound is rather rare[2]. In a project for the synthesis of thiasugars[3] and thionucleosides[3] we needed enantiomerically pure 2-hydroxymethyl-2,5-dihydrothiophene **1** and examined its enzymatic resolution. Compound **1** can be easily obtained from commercially available thiophene-2-carboxylic acid by Birch-reduction, esterification and reduction following literature procedures[4,5]. A first attempt to resolve (±)-2-hydroxymethyl-2,5-dihydrothiophene **1**, the irreversible acetylation (Scheme 1) with vinyl acetate in organic solvents, was not very encouraging (Table 1).



(±)-**1** *R*-**2** *S*-**1**

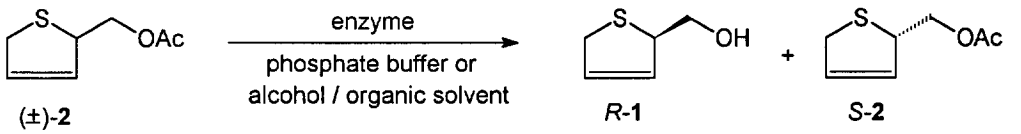
Scheme 1

From more than 15 tested hydrolytic enzymes only lipase from *Pseudomonas fluorescens* [PFL] (entry 1) and *Pseudomonas cepacia* [PCL] (entry 2) delivered some enantiomeric excess of the acetate. In spite of the fact that the results of the acetylation were not very promising we employed the enzyme-catalysed hydrolysis and alcoholysis of the (±)-2-acetoxymethyl-2,5-dihydrothiophene **2** (Scheme 2). The results are summarised in Table 2 and Table 3. Whereas the enzymatic hydrolysis of the acetate **2** also gave only moderate enantioselectivities of up to 72 % ee with lipase from *Pseudomonas fluorescens* (entry 1), the alcoholysis of the racemic acetate **2** showed the highest enantioselectivity of all tested reactions (Table 3).

Table 1. Results of the enzyme-catalysed acetylation of (±)-2-hydroxymethyl-2,5-dihydrothiophene **1**

entry	enzyme	temperature [°C]	solvent[a]	time [h]	conversion[b] [%]	*R*-acetate[c] [% ee]	E[6]
1	PFL	25	MTBE	39	24	74	8.4
2	PCL	25	MTBE	23	40	60	5.8
3	PFL	0	Hexane/CH_2Cl_2	15	23	77	9.6

a. MTBE = tert.butyl methyl ether b. Conversion determined by GC (SE-52) c. Enantiomeric excess determined by GC on FS-CYCLODEX beta-I/P



Scheme 2

Table 2. Results of the enzyme-catalysed hydrolysis[a] of (±)-2-acetoxymethyl-2,5-dihydrothiophene **2**

entry	enzyme	temperature [°C]	time [min]	conversion[b] [%]	*S*-acetate[b] [% ee]	E[b]
1	PFL	25	15	77	72	3.0
2	PCL	25	30	60	50	3.2

a. 0.1 m phosphate buffer b. see table 1

The best results were obtained[7] (Table 3) using butanol as the alcohol component and once again the lipase from *Pseudomonas fluorescens* (entries 1-3) and *Pseudomonas cepacia* (entry 4). Other alcohols like ethanol, hexanol, octanol and decanol were also examined, but their use lead either to lower ee-values or to recovery problems due to difficulties in separation of the acetate **2** from the alcohol. The enantiomeric excess depends on the amount of butanol (entry 2 and 3) as has been observed earlier[8].

Table 3. Results of the enzyme-catalysed alcoholysis of (±)-2-acetoxymethyl-2,5-dihydrothiophene **2**

entry	enzyme	alcohol	time [h]	conversion[a] [%]	*S*-acetate[a] [% ee]	E[a]
1	PFL	3 eq n-$C_4H_{10}O$	88	63	84	7.4
2	PFL	5 eq n-$C_4H_{10}O$	68	66	85	6.4
3	PFL	10 eq n-$C_4H_{10}O$	73	63	93	10.9
4	PCL	3 eq n-$C_4H_{10}O$	88	66	80	5.5

a. see table 1

With 10 equivalents of butanol in cyclohexane PFL catalysed alcoholysis leads to enantiomerically enriched *S*-(-)-acetate[9] **2** with 93 % ee after 63 % conversion in 31 % isolated yield. The hydrolysed (*R*)-2-hydroxymethyl-2,5-dihydrothiophene **1** was obtained in 55 % yield with only 54 % ee as determined after conversion into the corresponding acetate.

The absolute configuration of (-)-2-acetoxymethyl-2,5-dihydrothiophene **2** could be established by comparison with independently synthesized material. DCC-esterification of 2,5-dihydrothiophene-2-carboxylic acid and *R*-pantholactone led to diastereomers which were separated via HPLC[10]. The diastereomeric ester[11] which crystallised better was shown to possess the *S,R*-configuration **3** by X-ray crystallography[12]. A drawing of the structure is shown in Figure 1. After reduction with $LiAlH_4$ and acetylation, the product proved to be identical by GC and specific rotation value with the one from the enzymatic alcoholysis.

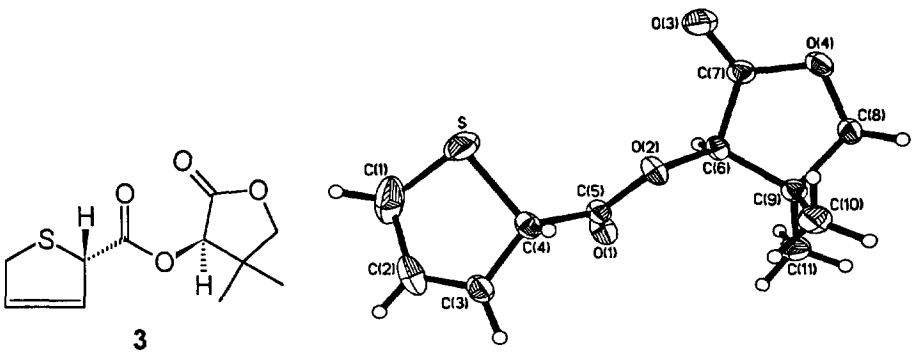


Figure 1

Although it is not yet possible to predict the enantiopreference of lipases towards primary alcohols on the basis of a general model[2], the observed unexpected selectivity could open the possibility for the resolution of other related 2,5-dihydroheterocycles which are useful intermediates in organic synthesis.

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7 General procedure: 500 mg of (±)-2-acetoxymethyl-2,5-dihydrothiophene and 150 mg of PFL in 20 ml cyclohexane were used.

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9 *S*-(-)-**2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s,3H), 3.73-3.78 (m,2H), 4.11-4.18 (m,2H), 4.42-4.44 (m,1H), 5.78-5.81 (m,1H), 5.92-5.95 (m,1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.2, 39.0, 54.1, 68.8, 129.9, 130.7, 171.0; $[\alpha]_D^{25}$ = -57.4 (c 1.75, $CHCl_3$).

10 RP-18 HPLC column; methanol/water:1/1.

11 *S,R*-**3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s,3H), 1.26 (s,3H), 3.82-3.95 (m,2H), 4.04-4.10 (m,2H), 4.93-4.96 (m,1H), 5.38 (s,1H), 5.91-5.94 (m,1H), 6.11-6.14 (m,1H); ^{13}C NMR (100 MHz $CDCl_3$): δ = 19.9, 23.3, 39.6, 40.6, 55.8, 75.8, 76.3, 126.8, 132.6, 170.8, 171.9; mp: 110-112 °C.

12 Additional crystallographic details may be obtained from Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, by quoting the deposit number CSD-405469, the authors and the literature reference.

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