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Enzyme-promoted kinetic resolution of acetoxymethyl aryl sulfoxides

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ABSTRACT

A simple and efficient method of the synthesis of enantiomerically enriched, unknown acetoxymethyl aryl sulfoxides has been developed which is based on an enzyme-catalyzed hydrolysis of racemic substrates under the kinetic resolution conditions. The hydrolysis was performed not only in a buffer solution but also in diisopropyl ether in the absence of the external water added to give in some cases the products with ee up to 98%. The enantioselectivity of both procedures was dependent on the enzyme used and the aryl substituent, being lower for *p*-tolyl than for phenyl. A comparative asymmetric synthesis based on the oxidation of the corresponding sulfides using chiral oxidizing reagent turned out to be inferior to the method described. Absolute configuration of the newly synthesized compounds was ascribed on the basis of CD spectra.

1. Introduction

Chiral sulfoxides are the most important group of compounds among a vast number of various types of organosulfur compounds. At the beginning, optically active sulfoxides were mainly used as model compounds in stereochemical studies [1]. At present, enantiopure sulfoxides play an important role as auxiliaries in asymmetric synthesis [2,3] and chiral ligands in enantioselective catalysis (for selected recent examples see [4–10]). Moreover, a few drugs which contain stereogenic sulfur in a sulfoxide unit are applied in the pharmaceutical industry, such as omeprazole [11] or modafinil [12,13]. Therefore, a lot of effort has been devoted to the preparation of optically active sulfoxides, mainly via asymmetric oxidation of the corresponding sulfides [2,14,15] and stereospecific transformation of enantiopure diastereomeric sulfinates [2].

Among many different methods of the synthesis of enantiomerically enriched compounds, which are now available, those employing enzymes are becoming more and more attractive [16]. Enzymes accept and stereoselectively recognize stereogenic and prostereogenic centers located not only on carbon but also on heteroatoms [17], among them on sulfur [6,18]. Hence, many examples of their use in the preparation of chiral non-racemic heteroatom derivatives have been reported [17].

In 1995 Rayner et al. [19] demonstrated the utility of optically active α-acetoxymethyl sulfides for an enantioselective synthesis of lamivudine **3**. They found out that the lipase-catalyzed hydrolysis of various racemic α-acetoxymethyl sulfides **1** was both chemoselective (only the acetate group was hydrolyzed) and stereoselective. As a result of the kinetic resolution, enantiomerically enriched unreacted starting compounds were recovered, but the hydrolysis products **2** were lost due to decomposition. In this way, the product yields could not exceed 50% (Scheme 1). The product (*R*)-**1** ($R = CH_2CH(OEt)_2$) was finally transformed into lamivudine **3** [20].

When the reverse procedure was applied, i.e. the enzymatic acetylation of racemic **2**, formed in situ from the appropriate aldehydes and thiols, the reaction proceeded under the conditions of dynamic kinetic resolution and gave enantiomerically enriched acetates **1** with ee's up to 95% (Scheme 2). It must be mentioned that the racemization of the initially formed substrates **2** occurred only in the presence of silica.

Having this in mind, we have decided to check whether a similar procedure could be applied in the kinetic resolution of acetoxymethyl sulfoxides **4**, in which the stereogenic center would be located on the sulfinyl sulfur atom and not on the α-carbon atom. This seemed particularly interesting, since the anion of optically active **4** could be considered as a chiral acyl anion equivalent (synthon) **5** (Scheme 3). For another example of such a synthon see [21].

2. Experimental

2.1. General

The synthesized products were purified by column chromatography on silica gel. Solvents were dried using general procedures and distilled prior to use. The NMR spectra were recorded in $CDCl_3$

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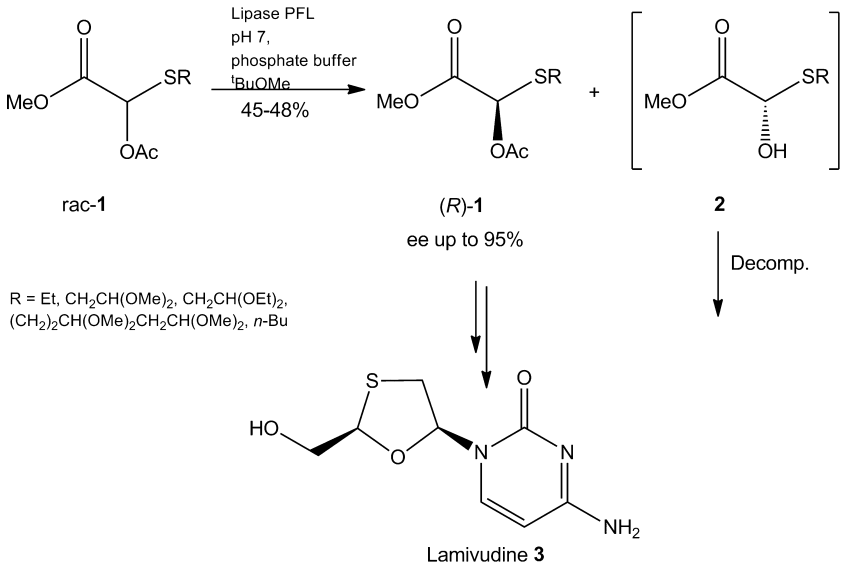
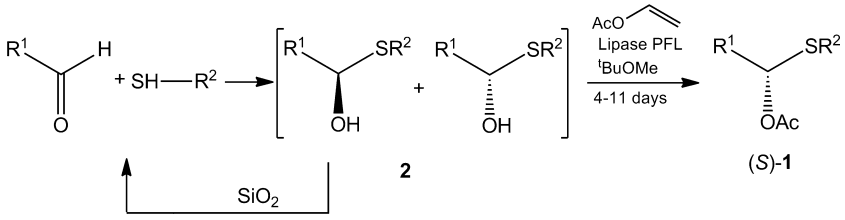
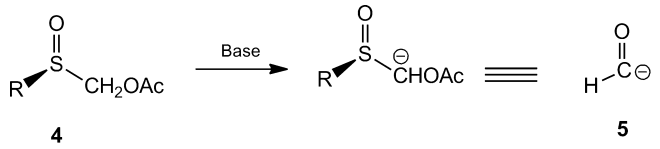


Scheme 1. Chemoenzymatic synthesis of lamivudine.



Scheme 2. Dynamic kinetic resolution of α-hydroxymethyl sulfides.



Scheme 3. Chiral acyl anion equivalent.

with a Bruker AC 200 spectrometer. The chemical shifts (δ) are expressed in ppm, the coupling constants (J) are given in Hz. Optical rotation values were measured on a Perkin-Elmer-241 photopolarimeter for the sodium D line at 20 °C. Mass spectra were recorded with a Finnigan MAT 95 Voyager Elite spectrometer.

Enzymes: PLE – pig liver esterase, FLUKA, 134 U/mg; α-CT – α-Chymotrypsin, SIGMA–ALDRCH, >40 U/mg; PFL – lipase from *Pseudomonas fluorescens*, SIGMA, ≥160 U/mg; AK – lipase from *P. fluorescens*, AMANO, >20 U/mg; PS – lipase form *Pseudomonas cepacia*, AMANO, >30 U/mg; CAL-B (Novozym 435) – lipase acrylic resin form *Candida antarctica*, SIGMA, 10 U/mg; AH – lipase AH (AMANO).

2.2. Synthesis of acetoxymethyl aryl sulfides *8* – Pummerer reaction [22]

A solution of sulfoxide **7** (0.013 mol) in acetic anhydride (10 mL) was refluxed until the starting material completely disappeared (about 4 h) (TLC chloroform–methanol 15:1). Then to the reaction mixture chloroform (5 mL) was added. The organic layer was washed with water (10 mL), 5% aqueous solution of potassium bicarbonate (10 mL) and water (10 mL) and dried over anhydrous $MgSO_4$. After filtration of the drying agent and evaporation of the solvent the pure products **8** were obtained in the yield of 86–95%.

Acetoxymethyl *p*-tolyl sulfide **8a**: ^{1}H NMR ($CDCl_3$): δ = 2.09 (s, 3H), 2.34 (s, 3H), 5.36 (s, 2H), 7.24 (AA′BB′, 4H).

Acetoxymethyl phenyl sulfide **8b**: ^{1}H NMR ($CDCl_3$): δ = 2.11 (s, 3H), 5.41 (s, 2H), 7.27–7.48 (m, 5H).

2.3. Synthesis of acetoxymethyl aryl sulfoxides *4*

2.3.1. Method A

To a solution of the corresponding sulfide **8** (4.2 mmol) in acetonitrile (10 mL) was added iodosobenzene (0.931 g, 4.2 mmol) and Montmorillonite K 10 (0.931 g). The mixture was stirred at room temperature until the substrate completely disappeared (TLC chloroform–methanol 15:1). Then the reaction mixture was filtered through Celite. After evaporation of the solvent, the crude product was purified by column chromatography using chloroform and then chloroform–methanol 150:1 as eluent. Sulfoxides **4** were obtained in the yield of 87–89%.

2.3.2. Method B

To a solution of the corresponding sulfide **8** (0.03 mol) in dichloromethane (100 mL) was slowly added dropwise *m*-chloroperbenzoic acid (7.1 g, 0.03 mol) in dichloromethane (10 mL) at −20 °C. The mixture was stirred at room temperature until the substrate completely disappeared (TLC dichloromethane–methanol 15:1). Then the reaction mixture was extracted with 5% aqueous solution of sodium hydrogencarbonate (3× 10 mL) and dried over anhydrous $MgSO_4$. After filtration of the drying agent and evaporation of the solvent, the crude product was purified by column chromatography using dichloromethane and then dichloromethane–methanol 150:1 as eluent. Sulfoxides **4** were obtained in the yield of 85–89%.