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Chemoenzymatic preparation of intermediates for the taxol side chain and analogs

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Abstract. In the present study, optically active cis and trans α-hydroxy-β-lactams were prepared by Baker's yeast reduction of a racemic α-keto-β-lactam and by the hydrolysis of a racemic α-acetoxy β-lactam with the resting cells of *Bacillus Subtilis*.

Introduction

Semi-synthetic taxol and its analogs, such as taxotere, have received significant attention from medicinal and synthetical chemists (1). Taxol and taxotere are well-known anticancer drugs (1). The side chains for these compounds can be derived from α-hydroxy-β-lactams (2). In the present study, we describe findings from our chemoenzymatic approaches to optically pure 3-hydroxy-4-phenyl-azetidinones.

Materials and methods

Acetoxy β-lactam, 3-keto β-lactam, Baker's yeast (*Saccharamyces Cerevisiae*, type 3), sodium hydroxide, acetic anhydride, pyridine, methanol, p-toluenesulfonyl chloride, DMSO, *Bacillus Subtilis*.

Results

Reduction of α-keto-β-lactam (1,3) with Baker's yeast (*Saccharamyces Cerevisiae*, type 3) with methanol as the energy source produced a mixture of two α-lactams (2 and 3) in a 3:1 ratio in an overall yield of 50% (Scheme 1). Proton NMR studies showed that 2 was a cis β-lactam and 3 was its trans isomer. The corresponding acetates 4 and 5 were studied by proton NMR spectroscopy using an optically active shift reagent, and it was found that the cis isomer 4 was of low optical purity (ee 25%), while the trans isomer was optically pure. We have prepared by a chemical sequence the cis (-)-1-(p-anisyl)-3-hydroxy-4-phenyl-2-azetidinone of a known absolute configuration, as shown by the stereostructure 6 (4). The corresponding tosylate 7 was subjected to an SN2 reaction with sodium acetate in DMSO solution to obtain the trans α-acetoxy-β-lactam 8 (Scheme 2). Saponification provided the trans α-hydroxy-β-lactam of stereostructure 9. The yeast reduction of product 3 was found to be identical with 9 in all respects, thereby establishing its absolute configuration as in 3. The racemic form of 12 has been synthesized recently as an intermediate for taxol analogs (1).

Acylation of a racemic alcohol and the deacylation of a racemic ester under the influence of a lipase or a micro-organism are biotransformations that can lead to compounds of high optical purity (5). Sih *et al* reported that certain lipases are capable of acetylating alcohol groups using vinyl acetate as the acyl donor (5). After preliminary experiments, we discovered that *Bacillus Subtilis* can be utilized for the enzymatic hydrolysis of the acetoxyl group in 10. Thus, 50 mg of 10 (Ar, para anisyl) in tetrahydrofuran solution was added to a suspension of *Bacillus Subtilis* in a phosphate buffer of pH 7.0. After 96 h, the cells were removed by centrifugation and the supernatant was worked up in the usual way. Chromatography of the organic fraction over a silica gel column provided an α-hydroxy-β-lactam 11 in 42% yield and the starting acetate 4 in 40% yield. To facilitate comparison, 11 was converted to the acetate 12, and 4 was saponified to 2 (Scheme 3). Proton NMR studies using chiral shift reagent $Pr(hfc)_3$ indicated that 12 and 4 were optically pure and were the antipodes of each other (6).

Discussion

The use of non-aqueous media for enzymatic reactions has become the subject of study for the preparation of optically active compounds from readily available racemic substrates (7-11). Optically pure cis and trans-β-lactams that are present in taxol can be prepared in this way, making the method very useful. The chemoenzymatic methods described here should be applicable to 3-hydroxy- or 3-keto-2-azetidinones with various aryl groups at positions 1 and 4. In view of our recent work on the synthesis and biological evaluation of anticancer β-lactams, this method of enzymatic hydrolysis of the acetoxy-group and the reduction of the keto-group should prove useful (12-14).

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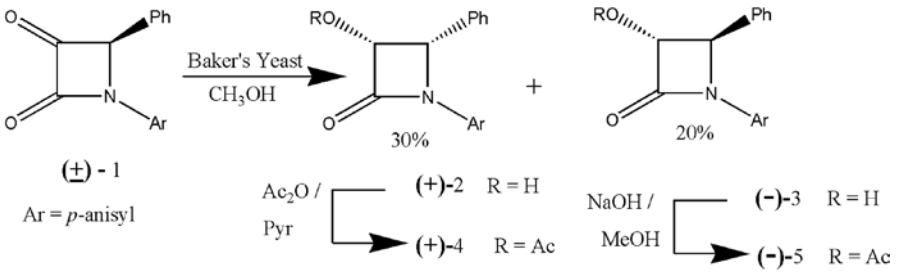
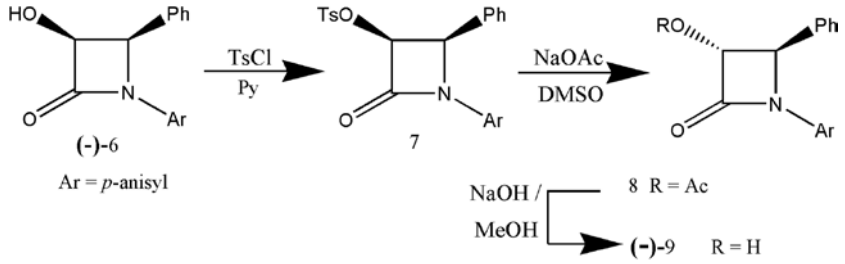
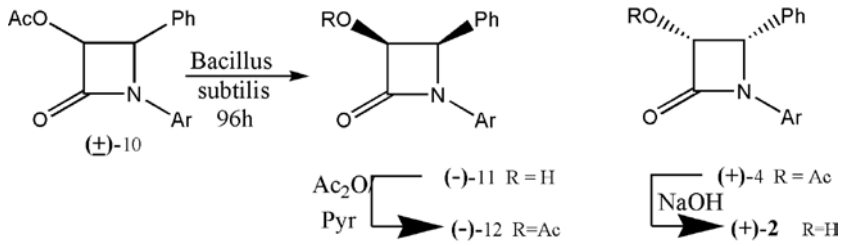


Scheme 1.



Scheme 2.



Scheme 3.

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