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Kinetic resolution of racemic 2-(2-furyl)-2-hydroxyethyl acetate in the presence of PS lipase

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Abstract

Kinetic resolution of racemic 2-(2-furyl)-2-hydroxyethyl acetate by transesterification with vinyl acetate in the presence of Amano PS lipase, yielding (1*R*)-1-(2-furyl)ethane-1,2-diol diacetate with 98% ee and (2*S*)-2-(2-furyl)-2-hydroxyethyl acetate with >99% ee, is described.

1. Introduction

The 2-furan-substituted ethane-1,2-diols with known configuration at C-1 can serve as chiral synthons in the preparation of modified D- or L-sugar moieties (azasaccharides, deoxyazasaccharides) and nitrogen heterocycles, such as carbacephems, unusual amino acids, piperidine and izidine alkaloids in aza-Achmatowicz reactions.[1] Quite recently we reported a method for the multigram scale preparation of homochiral (*S*)- and (*R*)-1-(2-furyl)ethanols from the racemic alcohol by acetylation with vinyl acetate in the presence of lipases.[2,3] These alcohols were converted to (1*S*)- and (1*R*)-(2,5-dihydro-2,5-dimethoxy-2-furyl)ethanols via electrochemical methoxylation.[4] The utility of these synthons in the preparation of D- and L-aminosugars daunosamine and ristosamine (3-amino-2,3,6-trideoxyhexoses) has recently been demonstrated.[5]

Herein we describe the enzymatic resolution of racemic 2-(2-furyl)-2-hydroxyethyl acetate (±)-**1** yielding homochiral mono- (*S*)-(−)-**1** and diacetyl (*R*)-(+)-**2** derivatives, new potential carbohydrate precursors (Scheme 1). These compounds can be converted to the corresponding hex-2-enopyranosid-4-uloses, intermediates in the preparation of 6-hydroxy analogues of daunosamine and ristosamine,[6] both D- and L-sequences, as well as chiral synthons in other natural product preparations following known synthetic pathways.[7,8]

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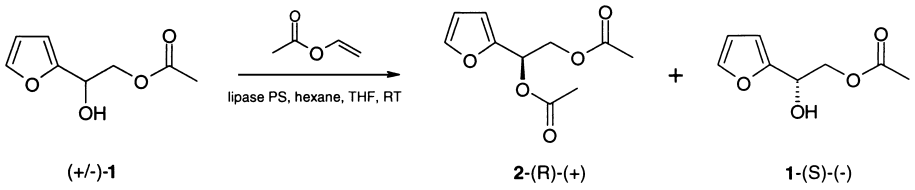

Scheme 1.

2. Results and discussion

Taking into account the similarity of the 2-(2-furyl)-2-hydroxyethyl acetate (±)-**1** structure to previously resolved racemic 1-(2-furyl)ethanol, our first trials were directed at the resolution of **1** via transesterification with vinyl acetate (1:5 molar ratio) in carbon tetrachloride in the presence of Lipozyme IM (immobilized lipase from *Rhizomucor miehei*).[2] Unfortunately for this substrate the enantioselectivity (E = 4) of Lipozyme IM was found to be insufficient to attain satisfactory enantiomer separation. Searching for a more selective lipase we performed screening experiments under the same conditions with other commercial enzymes, namely, porcine pancreas lipase (PPL) and microbial lipases: A (from *Aspergillus* sp.), AY (from *Candida rugosa*) and PS (from *Pseudomonas* sp.). With the exception of lipase A, which was inactive, all other lipases have shown the same direction of enantioselectivity, the (*R*)-enantiomer being acetylated faster than the (*S*). Moreover, the enantiopreference was the same as for 1-(2-furyl)ethanol,[2] which means that replacing methyl group in the side chain with hydroxymethyl group does not change the substrate arrangement in enzyme active site. The most promising results in preliminary tests have been found for lipase PS (Amano), which was the most active as well as being the most enantioselective. When the transesterification was carried out in carbon tetrachloride at ambient temperature for 24 h, 61% conversion was reached yielding pure enantiomer (*S*)-(−)-**1** and diacetate (*R*)-(+)-**2** of 63% ee (E = 22).

The absolute configuration of (*R*)-1-(2-furyl)ethane-1,2-diol diacetate (*R*)-(+)-**2** and (*S*)-2-(2-furyl)-2-hydroxyethyl acetate (*S*)-(−)-**1** was determined by conversion into corresponding diols by treatment with sodium methoxide in methanol, and comparison of sign of the specific rotation with literature data.[9] Enantiomeric excesses were determined by GC analysis of the reaction mixture using Chiraldex-GTA column, on which full separation of enantiomers of **2** and partial separation of the enantiomers of **1** could be achieved.

Although lipase PS has been sufficiently active, the enantioselectivity factor E = 22 is too low to attain resolution for both enantiomers in a single transesterification. Sometimes, changing the acyl donor results in a significant increase of enantioselectivity.[10] We checked this possibility by replacing vinyl acetate with more bulky isopropenyl acetate. The resolution was carried out in hexane, carbon tetrachloride and tetrahydrofuran. For hexane and carbon tetrachloride the lower enantioselectivities were observed (15–17 versus 22), while in tetrahydrofuran acetylation did not take place at all.

Another possibility for increasing enantioselectivity of PS lipase was searching for the proper solvent system ensuring a reasonable transesterification rate together with a high enantioselectivity. For several tested solvents of different polarity (hydrocarbons, chlorohydrocarbons, ethers) E ranged from 15 to 80. It is noteworthy that in polar solvents such as dioxane, 1,2-dimethoxyethane, or

acetone the transesterification rate is very low and conversion does not exceed 5%, while in hydrocarbons or chlorinated solvents it reaches 25–50% at the same time.

It is generally accepted that kinetic resolution of a racemic substrate for both pure enantiomers in a single process is possible when the enantioselectivity value is ca. 100 or higher. In our screening the highest enantioselectivity (E = 80) was reached in the mixture of hexane and tetrahydrofuran (4:1 ratio, v/v). Therefore this solvent mixture was chosen for preparative transesterifications on a multigram scale. The reaction proceeded with an acceptable rate yielding homochiral non-acetylated enantiomer (*S*)-(−)-**1** at 53% conversion. In order to obtain the second enantiomer of high purity we decided to perform deacetylation of (*R*)-(+)-**2** with ee > 80% into the corresponding enriched diol and again acetylate it with vinyl acetate in the presence of lipase PS. During diol acetylation the primary hydroxyl group is acetylated first, and then enantioselective acetylation of the secondary hydroxyl group proceeds. When ca. 80% conversion was reached, diacetate (*R*)-(+)-**2** of 98% ee was isolated.[11] We have found that lipase PS could be used in the transesterification process several times without change in enantioselectivity; however, activity somewhat decreased after each run.

Comparing our method to reported asymmetric dihydroxylation[12] of 2-vinylfuran in the presence of AD-mix, the yields are in the same range, 80–90%, but diols obtained via kinetic resolution using PS lipase are of higher purity, 98–99% ee versus 90–93% ee for dihydroxylation products. Moreover, experimental protocol for enzymatic resolution is extremely simple (stirring at room temperature, then filtration, evaporation and chromatography) and economic, because all chemicals — solvent, vinyl acetate and lipase — can be recycled in several runs.

3. Conclusions

A convenient and effective two-step procedure of kinetic resolution of 2-(2-furyl)-2-hydroxyethyl acetate by transesterification with vinyl acetate in the presence of PS lipase providing both homochiral enantiomers has been realised. These compounds can serve as chiral synthons in the preparation of D- and L-3-amino-2,3-dideoxyhexoses — aminosugars useful in anthracycline antibiotics synthesis.[13–15]

4. Experimental

4.1. General

Porcine pancreas lipase was purchased from Sigma. Lipases A, AY and PS were received from Amano Enzyme Europe Ltd and Lipozyme IM from Novo-Nordisk. Vinyl acetate was obtained from Fluka, all solvents reagent grade from POCH. All reagents were used as received. Preparative TLC was performed on Kieselgel 60 F_{254} plates from Merck. Enantiomeric excesses were determined by GC using Chiraldex G-TA column 30 m×0.25 mm with temperature program: isotherm. 70°C, 30 min, then to 135°C at 0.5°C/min. Retention times were as follows: (*S*)-**2** —119.45 min; (*R*)-**2** —120.72 min; (*S*)-**1** —130.55 min; (*R*)-**1** —131.48 min. Optical rotations were measured using Horiba or Autopol IV (Rudolph Research) polarimeters. NMR spectra were recorded using a Bruker 250 MHz spectrometer. All transesterifications were performed at room temperature with magnetic stirring.

4.2. (2S)-(2-Furyl)-2-hydroxyethyl acetate (S)-(−)-1

To the solution of 17.0 g (100 mM) of (±)-**1**, and 43.0 g (500 mM) vinyl acetate in the mixture of 80 ml hexane and 20 ml THF, 1.7 g of lipase PS (Amano) was added. The suspension was stirred at room temperature and progress of the reaction was monitored by GC. When 56% conversion was reached (3 days), enzyme was filtered, and solvents together with excess of vinyl acetate were evaporated under reduced pressure. The residue was chromatographed on silica gel impregnated with 1% (by weight) of sodium acetate. The column was eluted first with hexane and then with hexane/acetone mixture. After solvent evaporation from fractions containing diacetate (*R*)-**2**, 11.0 g of product with 82% ee was obtained. After solvent evaporation from fractions containing non-reacted substrate, 8.0 g (94%) of homochiral (*S*)-(−)-**1** (ee > 99% by CG) was obtained. (*S*)-(−)-**1**: $[\alpha]_D$ −22.3 (2.61, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.09 (s, 3H); 2.82 (s, 1H); 4.36 (d, J 7.5 Hz, 2H) 4.95 (t, J 7.5 Hz, 1H); 6.34 (m, 2H); 7.39 (m, 1H).

4.3. (1S)-(2-Furyl)ethane-1,2-diol

Sample of (*S*)-(−)-**1** after treatment with 0.05 M MeONa in methanol at room temperature overnight yielded quantitatively (*S*)-1-(2-furyl)-1,2-ethandiol, $[\alpha]_D$ −36.1 (2.72, CH_2Cl_2) (lit.[9] $[\alpha]_D$ −34.3).

4.4. (1R)-(2-Furyl)ethane-1,2-diol diacetate (R)-(+)-2

To 11.0 g (52 mM) of diacetate **2** (ee 82% *R*) obtained from the previous experiment, 50 ml of 0.05 M MeONa in methanol was added at room temperature and the mixture was left overnight. Then the solution was filtered through a silica pad and methanol evaporated under reduced pressure yielding 6.6 g of (*R*)-1-(2-furyl)-1,2-ethandiol (82% ee). To the diol dissolved in the mixture of hexane (40 ml) and THF (10 ml), 40 g (470 mM) of vinyl acetate and 0.5 g PS lipase were added. The suspension was stirred at room temperature and monitored by GC. When ca. 80% conversion was reached (3 days), enzyme was filtered, and solvents together with excess of vinyl acetate were evaporated under reduced pressure. The residue was chromatographed on silica gel as previously yielding 8.7 g (87%) of (*R*)-(+)-**2** (98% ee), $[\alpha]_D$ 107.7 (1.90, CH_2Cl_2); $[\alpha]_D$ 120.2 (0.44, $CHCl_3$) (lit.[16] $[\alpha]_D$ 117, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.06 (s, 3H); 2.09 (s, 3H); 4.45 (m, 2H); 6.11 (2d, J 5 Hz, 1H); 6.38 (m, 2H); 7.41 (m, 1H, and 1.7 g of almost racemic **1**).

4.5. (1R)-(2-Furyl)ethane-1,2-diol

Sample of (*R*)-**2** after treatment with 0.05 M MeONa in methanol at room temperature overnight yielded quantitatively (*R*)-1-(2-furyl)-1,2-ethandiol, $[\alpha]_D$ 35.2 (1.12, CH_2Cl_2) (lit.[9] $[\alpha]_D$ 36.7).

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