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TETRAHEDRON: *ASYMMETRY*

Preparation of *S*-(−)-2-acetoxymethyl-2,5-dihydrofuran and *S*-(−)-*N*-Boc-2-hydroxymethyl-2,5-dihydropyrrole by enzymatic resolution

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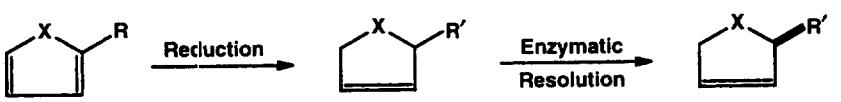
Abstract

The enzymatic kinetic resolution of 2-hydroxymethyl-2,5-dihydrofuran and -pyrrole derivatives has been studied. In particular, the acetylation of the primary alcohol as well as the hydrolysis and alcoholysis of the corresponding acetates were investigated in the presence of different lipases. The best results for the multi-gram preparation of *S*-(−)-2-acetoxymethyl-2,5-dihydrofuran [(*S*)-(−)-**2**] with 97% ee were obtained by the alcoholysis of **2** with *Candida antarctica*. The synthesis of *S*-(−)-*N*-Boc-2-hydroxymethyl-2,5-dihydropyrrole [(*S*)-(−)-**3**] with up to 98% ee was achieved by its irreversible acetylation catalysed by *Pseudomonas fluorescens* lipase.

As part of an ongoing project aimed at the stereoselective preparation of optically active furanoses and analogues, we envisaged the unsaturated molecules represented by the general structure III as suitable precursors (Scheme 1) and examined the lipase-mediated enzymatic resolution.[1] Our previous studies have already demonstrated the potential of the biocatalytic differentiation of 2,5-dihydrothiophene substrates II (X=S, R′=CH_2OAc).[2] The Type II heterocycles can be easily prepared from commercially available aromatic 2-carboxylic acids by Birch-reduction, followed by esterification and reduction according to literature procedures.[3,4]



I II III

X = O, NBoc, S R = CO_2H, CO_2Me R′ = CO_2H, CO_2Me, CH_2OH, CH_2OAc

Scheme 1.

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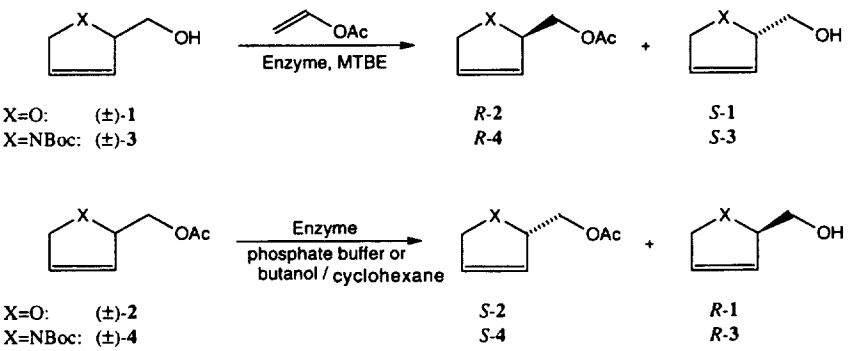
Initial attempts to resolve the racemic methyl esters were not encouraging. In fact, neither the enzymatic hydrolysis nor the alcoholysis with butanol in an organic solvent turned out to be successful. Of more than 10 tested enzymes only *Candida antarctica* B lipase (CAL) showed any enantiomeric excess for the ester. Therefore, the irreversible acetylation of the corresponding primary alcohols in an organic solvent and the hydrolysis/alcoholysis of the acetate were studied (Scheme 2), despite the usually observed difficulty in resolving the enantiomers of chiral primary alcohols via lipase-catalysed reactions.[5] The results of the screening[6] with lipases from *Candida antarctica*, *Pseudomonas fluorescens* (PFL) and *Pseudomonas cepacia* (PCL) are summarised in Table 1.[7] The efficiency of the kinetic resolution is assessed from the E-values of enantioselectivity as defined by Sih et al.[8]



Scheme 2.

While the enzymatic acetylation and hydrolysis of the dihydrofuran system proceeded with low selectivity,[9] the alcoholysis of racemic acetate **2** with butanol catalysed by CAL showed the highest enantioselectivity of all the reactions studied. The best results were obtained by lowering the temperature

Table 1
Results of the kinetic resolution of (±)-**1**, (±)-**2**, (±)-**3** and (±)-**4**[a]

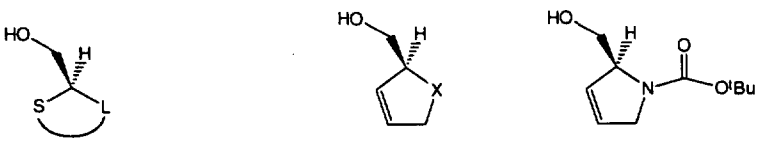
Entry	Starting material	Enzyme	Condition[b]	Time [h]	Conversion [%][c]	Alcohol/Acetate [% ee][d]	E
1	(±)-**1**	CAL	A	0.4	98	< 1	-
2	(±)-**1**	PFL	A	2.0	37	*S*-**1** 12	1.7
3	(±)-**1**	PCL	A	5.5	50	*S*-**1** 23	2.0
4	(±)-**3**	CAL	A	8	55	*S*-**3** 18	1.6
5	(±)-**3**	PFL	A	7	62	*S*-**3** 98	**18.4**
6	(±)-**3**	PCL	A	12	58	*S*-**3** 96	**21.0**
7	(±)-**2**	CAL	B	1.7	47	*S*-**2** 27	2.4
8	(±)-**2**	PFL	B	4.0	56	*S*-**2** 14	1.4
9	(±)-**2**	PCL	B	3.2	57	*R*-**2** 10	1.3
10	(±)-**2**	CAL	C	20	62	*S*-**2** 85	8.1
11	(±)-**2**	CAL	C, 3°C	33	66	*S*-**2** 97	**11.4**
12	(±)-**2**	PFL	C	46	52	*S*-**2** 16	1.6
13	(±)-**2**	PCL	C	46	51	*S*-**2** 5	1.2
14	(±)-**4**	CAL	C	96	60	*R*-**4** 49	3.1
15	(±)-**4**	PFL	C	96	58	*S*-**4** 24	1.8
16	(±)-**4**	PCL	C	96	54	*S*-**4** 53	4.4

a. unless otherwise stated all the reactions were carried out at room temperature b. A: 3 eq vinyl acetate, tert.butyl methyl ether B: 0.1 M phosphate buffer C: 10 eq butanol, cyclohexane c. determined by GC
d. determined by chiral GC / HPLC

to +3°C (entry 11).[10] Under these conditions it was possible to obtain *S*-(−)-acetate **2** essentially enantiomerically pure; the absolute configuration was assigned by the specific rotation value.[11]

In contrast to the above findings, the acetylation of dihydropyrrole (±)-**3** proceeded with high selectivity and provided the alcohol *S*-(−)-**3** in up to 98% e.e. (entries 5 and 6), whereas the alcoholysis of (±)-**4** showed only moderate to low selectivity (entries 14–16). This result is possibly due to an equilibrium state with butyl acetate acting as the acyl donor. The absolute configuration of *S*-(−)-*N*-Boc-2-hydroxymethyl-2,5-dihydropyrrole **3** was established after reduction of the double bond with H_2/Pd–C and comparison of the specific rotation value of *N*-Boc protected prolinol with literature data.[12]

The comparison between these findings and the results obtained for the enzymatic resolution of the analogous 2,5-dihydrothiophene **5** (Scheme 3), where in the best case an E value of 10.9 was achieved,[2] reveals that the additional side chain attached to nitrogen plays an important role for the specificity of the reaction. While in view of the sterically rather similar small (S)- and large (L)-residues (Scheme 3) the enantiomeric differentiation of 2,5-dihydrofuran and -thiophene derivatives (**1** and **5**) in the catalytic site of the enzyme is significant, the differentiation of the nitrogen heterocycle **3** is even better. This observation is most probably due to the larger spatial demand of X=NCO$_2$^{t}Bu.



S = small, L = large X = O: **1** X = S: **5** **3**

Scheme 3.

In conclusion, a highly efficient procedure for the lipase mediated kinetic resolution of 2-hydroxymethyl-2,5-dihydrofuran, -pyrrole and -thiophene derivatives has been achieved. These molecules are valuable building blocks[13] and further work is in progress focusing on the realisation of the synthetic applications of these chiral systems.

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