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Tuning lipase-catalysed kinetic resolution of 2-substituted thiophenes and furans: A scalable chemoenzymatic route to masked γ-bis-oxo-alcohols

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ABSTRACT

The demand for greener and applicable approaches aiming at the synthesis of optically active compounds as single enantiomers has seen a significant growth worldwide. Since most of the chemically synthesized compounds are produced as racemates their kinetic resolution has been of great interest. For this purpose a number of chemo-enzymatic approaches were proposed. One of such approaches, the use of isolated lipases, is a well-established alternative. Herein we report the kinetic resolutions of 2-Substituted five-membered heteroaromatic rings. By optimizing the reaction conditions it was possible to produce (2-hydroxy)-2-substituted furans and thiophenes in high enantiomeric ratio ($E > 200$). Thus, racemic mixtures of compounds with slight structural differences were resolved. The current chemo-enzymatic strategy has been applied to a scalable approach leading to the formation of the enantiopure (S)-2i a well-known building block used for the synthesis of bioactive natural compounds.

1. Introduction

Compounds containing five-membered heteroaromatic subunits are important synthetic intermediates for a variety of chemical and biochemical transformations, due to both their wide range of biological activity [1] and great versatility, as they are readily converted into other functional groups [2]. Thus efforts to develop alternative approaches for the introduction of this functionality into diverse organic substrates have been intensified. Although chiral methodologies to prepare secondary alcohols containing aromatic moiety is well established, the most general and commonly used asymmetric methods of their production include the addition of a reactive organometallic to the aldehydes using chiral auxiliaries [5] or hydrogenation of ketones catalysed by chiral ligands using boranes [6] or phosphines [7]. Alternatively, they can be prepared using chiral heavy metal complexes [8]. While catalytic chemical procedures can be found, commonly equimolar quantities of chiral auxiliary or metallic salts wastes are generated.

Therefore 2-substituted furans containing secondary alcohols should be considered as masked bis-oxo building blocks being useful intermediates which are readily converted into 1,4-dicarbonyl compounds and related derivatives. Since these compounds would be prepared asymmetrically, their use as chiral building blocks for the synthesis of bioactive compounds in their single enantiomer form is of great value. Examples are the total synthesis of biologically active macrolides such Citreofuran [3] and Pyrenophorin [4], prepared from the same chiral building block (S)-2i (Fig. 1).

Despite under natural conditions, where lipases can catalyse the hydrolysis of esters, their activity and specificity in organic solvents should be highlighted. Moreover, with the exclusion of water molecules hydrolysis is suppressed what has extended the range of their application in non-aqueous systems. Thus, a variety of lipases has been successfully used demonstrating their extraordinary capability as catalysts used in the transesterification of several unnatural substrates in chemo-enzymatic process. Therefore, the use of isolated lipases linked to the high demand for chiral intermediates in their single enantiomer form is on the rise.

Despite biocatalysis being a well-known efficient strategy to prepare enantioenriched secondary alcohols, very few of the published methods uses isolated lipases as catalyst in the synthesis of heteroaromatic compounds containing furans or thiophenes [9]. Besides, the major disadvantages of these methods are the requirement of high times of resolutions and the obtainment of compounds with a low enantiomeric ratio (E-value) [9a,c]. Hence, the develop-

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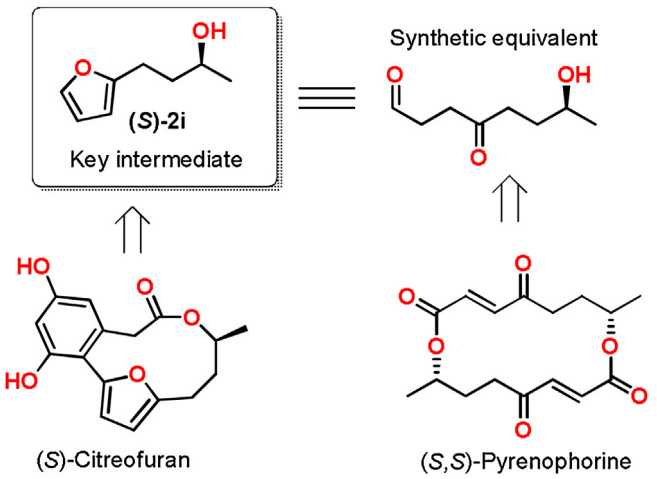


Fig. 1. Bioactive macrolides from furan (*S*)-2i.

ment of an efficient and general method aiming at the preparation of these compounds with high ee using shorter time is mandatory in order to overcome the drawbacks reported in literature.

For the above-mentioned reasons and to develop alternative methods for the asymmetric synthesis of considerable amounts of optically active 2-substituted α, β and γ-furans and thiophenes, we were interested in develop a general method with an aim to prepare furans and thiophenes containing enantiopure secondary alcohols. Thus a behavior study of five different lipases upon nine different substrates in enzymatic kinetic resolutions was done. Using the current method (*S*)-2i, a known key intermediate on the synthesis of natural products, was prepared in scalable quantity highlighting the potential of the process to be used.

2. Results and discussion

2.1. Preparation of racemic substrates 2a–i

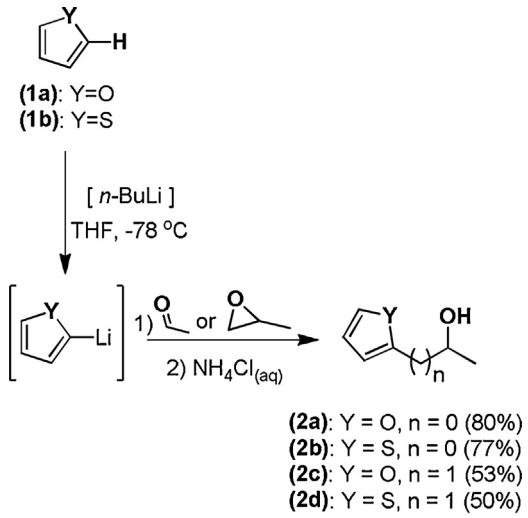
In order to prepare the racemic substrates 2a–d, a one-pot operation reaction based on literature-modified method was employed [10]. Thus, furan and thiophene were submitted to react with *n*-BuLi, through α-deprotonation reaction, followed by treatment of the in situ generated lithium salt with acetaldehyde or propylene oxide. For synthesizing the propargylic alcohol 2e, a commercially available ethynyl Grignard reagent was reacted with 2-furaldehyde (Scheme 1).

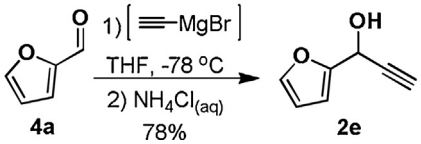
To synthesize the 2-substituted chain-extended analogs 2f–i a two-step sequence reaction based on literature modified method [11] was employed. Thus the enones **5**, prepared by Aldol reaction between dimethyl ketone and 2-furan or 2-thiophene carboxaldehydes, were subjected to react with $NaBH_4$, which have furnished the allylic alcohols 2f and 2g after reducing only the carbonyl moiety. For preparing the tetrahydro analogs 2h and 2i, 5 were treated with $LiAlH_4$, thus both the carbonyl and the C=C double bonds were reduced (Scheme 2).

With these short routes of achieving (Schemes 1 and 2), significant amounts of racemic substrates 2a–i could be prepared, for the further enzymatic studies.

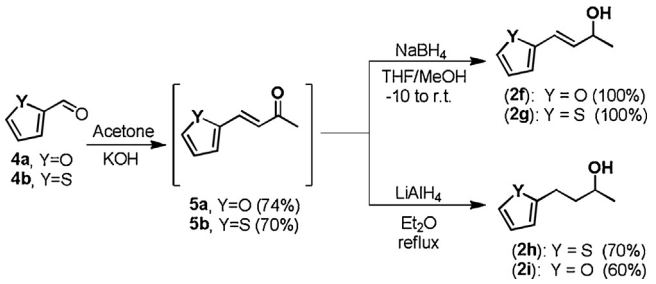
2.2. Enzymatic kinetic resolution

For the initial studies toward the enzymatic kinetic resolution, some experimental parameters such different solvents and temperatures were tested. From these results was possible to observe high influence on the enzyme activity upon substrate 2i against five different lipases at different conditions.





Scheme 1. Preparation of alcohols 2a–e.



Scheme 2. Preparation of alcohols 2f–2i.

Table 1
Screening based on conversion of (*R*/*S*)-2i.

Entry	Lipase	(*S*)-2i (*ee*)	(*R*)-3i (*ee*)	Time (min)	*C* (%)	*E*
1	CAL-B	>99%	>99%	15	50	>200
2	A12L-A	48%	73%	15	40	10
3	AE07	>99%	>99%	60	50	>200
4	A2AE011	96%	97%	120	50	>200
5	PCL-G	7%	>99%	15	6,5	<5

2.2.1. Screening of lipases

For the preliminary study, the screening of the lipases was conducted using 2i as model substrate, vinyl acetate as acyl donor and pure *n*-hexane as non-polar organic solvent. The progress of the resolution was accomplished by monitoring the consumption of the most reactive enantiomer on the racemate. For this, solid supported *Candida antarctica* lipase B chemically immobilized on acrylic resin (CAL-B) and the powder free enzymes: Amano Lipase G from *Penicillium camenberti* (PCL-G); Lipase A amano12 (A12L-A); lipase from *Pseudomonas stutzeri* (AE07) and lipase from *Alcaligenes* spp. (A2AE011) were used. The results from the enzymatic screening upon (*R*/*S*)-2i are depicted in Table 1.

Conditions (*R*/*S*)-2i (0.1 mmol), CAL-B (10 mg)[5 mg/mL], vinyl-acetate (0.1 mL), *n*-hexane (2.0 mL), 150 rpm, 25 °C.