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Enzymatic kinetic resolution of racemic 4-tetrahydropyranols by *Candida rugosa* lipase

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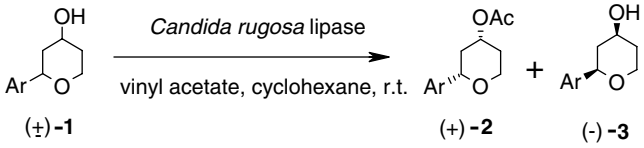
Abstract—Enzymatic kinetic resolution of (±)-hydroxytetrahydropyrans has been achieved for the first time by means of lipase-mediated transesterification to afford optically active (2*S*,4*R*)-tetrahydropyranyl acetates and (2*R*,4*S*)-tetrahydropyranols in excellent yields with high enantioselectivity. Absolute configurations of the tetrahydropyranyl acetates were assigned as (*S*) by chemical correlation.

Biocatalysts are very useful for the preparation of chiral drugs, fragrances and pheromones. The application of enzymes as biocatalysts in organic synthesis is well known. Lipases are the most widely applied enzymes for regio- and enantioselective biotransformations, because they are inexpensive, stable and easy to recycle. They direct the asymmetric course of many chemical transformations to produce chiral compounds in enantiomerically pure form. Lipase-catalyzed reactions have been applied to solve a number of synthetic problems, one of which is the kinetic resolution of diastereomeric and enantiomeric mixtures of primary and secondary alcohols.[1] Among various types of lipases, *Candida rugosa* lipase (CRL) is one of the most versatile and widely used enzymes for the resolution of esters and alcohols in both aqueous and organic media. In addition to stereoselective ester conversions, CRL can be used to perform regioselective and chemoselective acylations and deacylations and simple hydrolysis of esters under mild reaction conditions.[2]

The tetrahydropyran structure is a part of the internal backbone of various important carbohydrates, polyether antibiotics and marine macrolides.[3] In particular, optically active hydroxytetrahydropyrans are present as structural components in a number of natural products such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins and acutiphycins.[4,5] The Prins-cyclization is one of the most simple and straightforward approaches for the construction of the tetrahydropyran ring system.[6–8] However, there have been no precedents on the kinetic resolution of racemic tetrahydropyranols via lipase-mediated transesterification. Furthermore, there is no report on an asymmetric Prins-cyclization for the direct preparation of enantiomerically pure hydroxytetrahydropyrans.

In this Letter, we describe an enzymatic approach for the preparation of optically active hydroxytetrahydropyrans by means of kinetic resolution of racemic tetrahydropyranols using *C. rugosa* lipase (Scheme 1).

Racemic 4-hydroxytetrahydropyrans were easily prepared by the condensation of homoallylic alcohols with aldehydes via Prins-cyclizations.[8b] Accordingly, treatment of aryl aldehydes with but-3-en-1-ol in the presence of Amberlyst-15® in water resulted in the formation of 2-aryl-4-hydroxytetrahydropyrans in excellent yields. Subsequent kinetic resolution of the racemic tetrahydropyranols via lipase-mediated transesterification gave the (2*S*,4*R*)-tetrahydropyranyl acetates



Scheme 1.

Keywords: Kinetic resolution; Lipase; Tetrahydropyranols.
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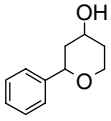
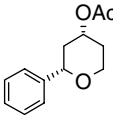
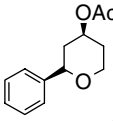
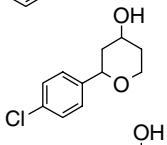
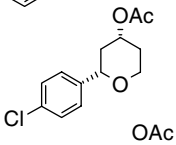
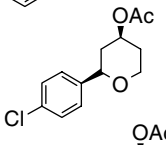
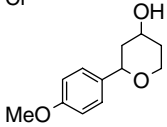
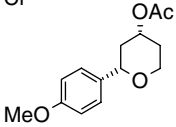
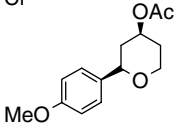
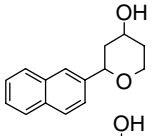
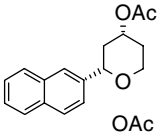
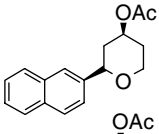
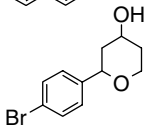
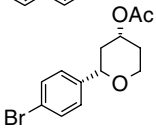
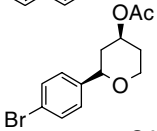
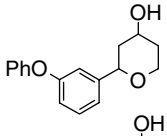
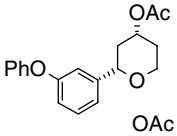
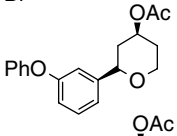
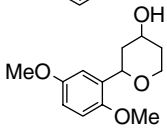
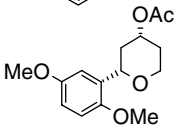
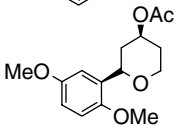
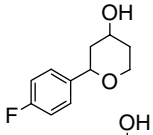
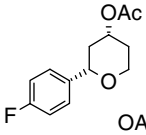
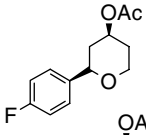
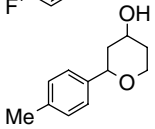
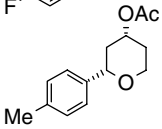
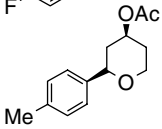
and the (2*R*,4*S*)-tetrahydropyranols. For example, treatment of (±)-2-phenyltetrahydro-2*H*-pyran-4-ol with *C. rugosa* lipase in the presence of vinyl acetate afforded (2*S*,4*R*)-2-phenyltetrahydropyranyl acetate and (2*R*,4*S*)-2-phenyl-tetrahydropyranol in a 1:1 ratio. Vinyl acetate was used as the acyl donor in this reaction. Among PPL and CRL lipases, *C. rugosa* lipase (CRL) was found to be most effective in terms of conversion and enantioselectivity. The enantiomeric excesses of the resulting acetates and unreacted alcohols were higher than 88%. Thus, the lipase derived from *C. rugosa* (CRL) proved to be the optimal biocatalyst in the resolution of (±)-tetrahydropyranols. As solvent, cyclohexane appeared to give the best results. All the products were characterized by ^{1}H NMR, IR, chiral HPLC and mass spectroscopy and also by comparison with authentic samples.[9] The absolute stereochemistry of (2*S*,4*R*)-2-phenyltetrahydropyranyl acetate was established by a comparison with diastereomerically pure product.[10] The scope and generality of the process is illustrated with respect to various tetrahydropyranols and the results are presented in Table 1.[11]

In summary, we describe a novel strategy to prepare optically active tetrahydropyranols via an enzymatic kinetic resolution of racemic 4-hydroxytetrahydropyrans using *C. rugosa* lipase. This is the first report on the preparation of chiral tetrahydropyranols from readily available racemic alcohols via lipase-induced transesterification.

Table 1. Kinetic resolution of tetrahydropyranols using *Candida rugosa* lipase

Entry	Substrate	Acetate **2**[a]	$[\alpha]_D^{25}$[b]	ee[c] (%)	Acetate **3**[d]	$[\alpha]_D^{25}$[b]	ee[c] (%)	Time (h)	Yield[e] (%)
a			21.2	98		−21.3	95	6	75
b			11.3	92		−9.8	87	6.5	79
c			21.7	90		−18.3	87	10	80
d			29.8	94		−27.9	89	9	85
e			19.6	88		−16.7	83	12	86
f			70.8	98		−62.1	90	8	81
g			5.8	92		−4.3	87	6	79
h			8.9	90		−7.5	87	9	82
i			13.9	92		−12.3	88	10	86

[a] All products were characterized by IR, NMR and mass spectroscopy.[9]
[b] Optical rotations were recorded in $CHCl_3$ (*c* 1.0).
[c] Enantiomeric excess of acetates determined using chiral HPLC.
[d] Alcohols were converted to their corresponding acetates so as to 'match' the optical rotations.
[e] Isolated and unoptimized yields.

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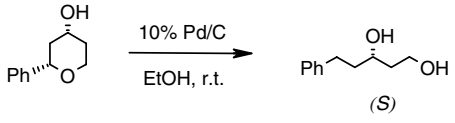

(S)

$[\alpha]_D^{25}$ +18.1 (*c* 0.4, $CHCl_3$)

11. *Experimental procedure*: A mixture of (±)-tetrahydropyranol (1 mmol) and vinyl acetate (1.5 mL) in cyclohexane (10 mL) was stirred with the enzyme *Candida rugosa* lipase, [(EC 3.1.1.3) type VII (20% w/w) supplied by Sigma–Aldrich] at room temperature for 6–12 h. The reaction mixture was filtered through a Celite pad. The combined filtrate and washings (ethyl acetate) were evaporated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column to furnish the corresponding diastereomerically pure acetate and alcohol in approximately 1:1 ratio. All the compounds were characterized by ^{1}H NMR, IR and mass spectroscopy. The enantiomeric excess of the product was determined using a Shimadzu high-performance liquid-chromatography (HPLC) system equipped with a chiral HPLC column (Chiralcel OD) and a UV detector at an absorbance of 225 nm. A solvent system of *n*-hexane and isopropanol (8:2) at a flow rate of 1.0 mL/min was used. Spectroscopic data for selected products: **2c**: *(2S,4R)-2-(4-methoxyphenyl)tetrahydro-2H-pyran-4-yl acetate*: Liquid, $[\alpha]_D^{25}$ +21.7 (*c* 1.0, $CHCl_3$, ee = 90%); IR (KBr): ν_{max} 2923, 2851, 1738, 1612, 1514, 1462, 1365, 1303, 1242, 1175, 1082, 1038, 910, 830, 769, 576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.17–4.85 (m, 1H), 4.30 (dd, J = 11.8, 2.3 Hz, 1H), 4.18 (ddd, J = 12.2, 5.1, 1.9 Hz, 1H), 3.95–3.50 (m, 4H), 2.23–1.85 (m, 5H), 1.82–1.50 (m, 2H); EIMS: *m/z*: 250, 190, 135, 83, 43, 29. *Compound* **2e**: *(2S,4R)-2-(4-bromophenyl)tetrahydro-2H-pyran-4-yl acetate*: Liquid, $[\alpha]_D^{25}$ +19.6 (*c* 1.0, $CHCl_3$, ee = 88%); IR (KBr): ν_{max} 2926, 2360, 1739, 1588, 1489, 1363, 1240, 1070, 1008, 820, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.47 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 5.09–4.85 (m, 1H), 4.30 (dd, J = 11.4, 2.1 Hz, 1H), 4.16 (ddd, J = 12.0, 5.0, 1.8 Hz, 1H), 3.59 (dt, J = 12.3, 2.1 Hz, 1H), 2.23–1.89 (m, 5H), 1.80–1.40 (m, 2H); EIMS: *m/z*: 299, 238, 185, 159, 77, 55, 43. *Compound* **2f**: *(2S,4R)-2-(3-phenoxyphenyl)-tetrahydro-2H-pyran-4-yl acetate*: Liquid, $[\alpha]_D^{25}$ +70.8 (*c* 1.0, $CHCl_3$, ee = 98%); IR (KBr): ν_{max} 2922, 2852, 1737, 1584, 1488, 1364, 1241, 1041, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39–7.19 (m, 3H), 7.10–6.80 (m, 6H), 5.09–4.83 (m, 1H), 4.35 (dd, J = 11.3, 2.0 Hz, 1H), 4.16 (ddd, J = 11.7, 4.9, 1.3 Hz, 1H), 3.60 (dt, J = 12.2, 2.0 Hz, 1H), 2.24–1.98 (m, 5H), 1.8–1.5 (m, 2H). EIMS: *m/z*: 312, 252, 197, 159, 121, 77, 55, 43. *Compound* **2g**: *(2S,4R)-2-(2,5-dimethoxyphenyl)tetrahydro-2H-pyran-4-yl acetate*: Liquid, $[\alpha]_D^{25}$ +5.8 (*c* 1.0, $CHCl_3$, ee = 92%); IR (KBr): ν_{max} 2920, 2851, 1739, 1499, 1465, 1367, 1241, 1085, 1041, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.05 (s, 1H), 6.69 (s, 2H), 5.1–4.9 (m, 1H) 4.65 (dd, J = 11.4, 2.1 Hz, 1H), 4.18 (ddd, J = 12.0, 5.0, 1.8 Hz, 1H), 3.82–3.5 (m, 7H), 2.35–1.90 (m, 5H), 1.80–1.50 (m, 2H); EIMS: *m/z*: 280, 189, 164, 77, 55, 43.