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Optically Active 6-Acetyloxy-2*H*-pyran-3(6*H*)-one Obtained by Lipase Catalyzed Transesterification and Esterification

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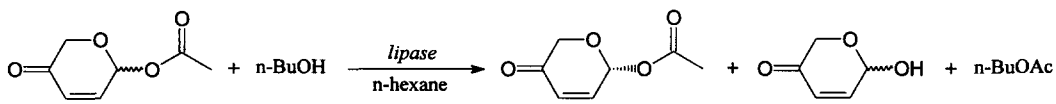
Abstract: Kinetic resolution of 6-acetyloxy-2*H*-pyran-3(6*H*)-one (**1**) is achieved by immobilized lipase PS on Hyflo Super Cell in organic solvents. Transesterification in hexane/n-butanol yields enantiomerically pure *R*-(-)-6-acetyloxy-2*H*-pyran-3(6*H*)-one, whereas esterification of 6-hydroxy-2*H*-pyran-3(6*H*)-one (**2**) with vinyl acetate by immobilized lipase PS gives the *S*-enantiomer with e.e.'s up to 76%.

Optically active pyranones are attractive chiral synthons in natural products chemistry, due to their multifunctional nature and diverse possibilities for enantioselective transformations, e.g. cycloadditions, enolate and acetal chemistry and conjugate addition reactions.[1] Optically pure pyranones are usually made from sugar derivatives such as tri-*O*-acetyl-D-glucal and di-*O*-acetyl-L-rhamnal via the Ferrier rearrangement.[2] Racemic acyl pyranones are readily accessible from furfuryl alcohols.[3] Few non-carbohydrate based routes to chiral pyranones are known.

In our group chiral pyranones have been investigated as chiral dienophiles and Michael acceptors.[1] These optically active pyranones were obtained by diastereomer separation using D-(-)-pantholactone as a chiral auxiliary. We now wish to describe the successful application of lipases in the (trans)esterification of 6-acetyloxy-pyranone (**1**) in organic solvents in an efficient route to either enantiomer of **1** without the need for a chiral auxiliary.

Over the past decade considerable attention has been devoted to the application of enzymes in the enantioselective synthesis of organic compounds.[4] Because of their stability, availability and broad specificity, lipases are the enzymes most frequently used in organic synthesis. The present work stems from excellent results recently obtained in our laboratories with the lipase catalyzed (trans)esterification of 5-acyloxy-2(5*H*)-furanones and pyrrolinones.[5,6]

Seventeen commercially available lipases[7] have been screened for their activity and stereoselectivity in the transesterification[8] of **1** (Scheme 1). The results for the most reactive lipases are shown in Table 1.



1 *R*-(-)-**1** **2**

SCHEME 1. Lipase catalyzed transesterification of 6-acetyloxy-2*H*-pyran-3(6*H*)-one (**1**).

TABLE 1. Transesterification of 6-Acetyloxy-2*H*-pyran-3(6*H*)-one (**1**) in Hexane/n-Butanol (3:1).

entry	lipase	reaction time[a] (h)	conversion (%)[b]	e.e. (%)[c]	E[9]	enantiomer[d]
1	PS	162	65	>99	>16	*R*-(-)
2	PS-HSC	9	65	99.1	16	*R*-(-)
3	AKG	233	65	84	7	*R*-(-)
4	CC	168	57	>99	>35	*S*-(+)
5	CC-HSC	238	32	27	5	*S*-(+)
6	CA	7	76	89	5	*R*-(-)

a) For amounts used, see ref. 8. b) Conversions are determined by GC analysis (Hewlett Packard 5890, HP-1 crosslinked methyl silicon gum column, 50m x 0.53mm) using n-decane as an internal standard. c) Enantiomeric excess is determined by chiral GC (Hewlett Packard 5890, Macherey-Nagel FS-Lipodex C column, 50m x 0.25 mm ID). d) Optical rotations were determined with a Perkin Elmer 241 polarimeter.

Since lipase PS (*Pseudomonas* sp.) is both active as well as enantioselective towards substrate **1** (entry 1) this lipase has been examined immobilized on Hyflo Super Cell (HSC).[10] This resulted (entry 2) in an enormous increase of activity with no significant change in selectivity. Lipase CC (*Candida cylindracea*, recently renamed *Candida rugosa*) shows a high selectivity (E>35) towards 6-acetyloxy-pyranone (**1**) and leads to the conversion of the *R*-enantiomer in contrast to lipases PS and AKG. Unfortunately, this transesterification with lipase CC shows poor reproducibility for unknown reasons. Lipase CA (*Candida antarctica*) is extremely active, but shows low enantioselectivity and completely transesterifies **1** within 24 hours.

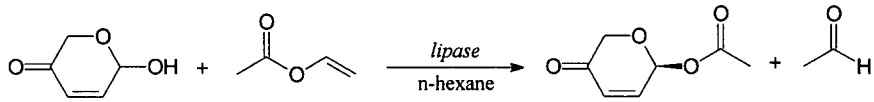
It is well known that solvents may influence the enantioselectivity of lipases when applied in kinetic resolutions of organic compounds.[5,11] In order to examine whether a change in solvent results in an increase in selectivity, nine solvents have been tested (Table 2) using lipase PS immobilized on HSC.[12]

TABLE 2. Solvent Effect on the Enantioselectivity of the Transesterification of **1** with Lipase PS-HSC.

entry	solvent	reaction time (h)	conversion (%)	e.e. (%)	E
1	t-butyl methyl ether	7	76	>99	>8
2	t-amyl alcohol	2	89	>99	>4
3	i-propyl alcohol	7	79	>99	>7
4	1,4-dioxane	48	62	99.8	26
5	toluene	48	65	98.6	15
6	dichloromethane	194	56	98	41
7	1,2-dichloroethane	48	51	86	27
8	cyclohexane	8.5	78	99.9	11
9	n-hexane	9	65	99.1	16

It is clear that the activity and enantioselectivity of immobilized lipase PS are affected by the solvent. Enantiomeric excesses (e.e.) of >99% can readily be obtained in almost all cases, but the activity of the lipase decreases on going from hexane to dichloromethane, the latter giving the highest selectivity (E=41).

The opposite *S*-enantiomer of 6-acetyloxy-2*H*-pyran-3(6*H*)-one (**1**) may be obtained from the lipase catalyzed esterification of 6-hydroxy-2*H*-pyran-3(6*H*)-one (**2**) with vinyl acetate (**3**) as acyl donor (Scheme 2) This approach is analogous to that used for the lipase catalyzed esterification of 5-hydroxy-furanones and pyrrolinones.[6] Only lipases that gave good results in the transesterification of **1** have been examined.[13]



2 **3** ***S*-(+)-1** **4**

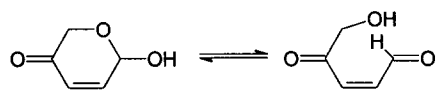
SCHEME 2. Lipase catalyzed esterification of 6-hydroxy-2*H*-pyran-3(6*H*)-one (**2**).

It has been shown that enantiomeric esterification is indeed possible in hexane as the solvent (Table 3). Although the enantiomeric excess of the **1** formed in the reaction with lipase PS is moderate, the esterification of 6-hydroxy-2*H*-pyran-3(6*H*)-one is complete. Again, immobilized lipase PS (entry 2) shows high activity.

TABLE 3. Esterification of 6-Hydroxy-pyranone (**2**).

entry	lipase	reaction time (h)	conversion (%)	e.e. (%)	enantiomer
1	PS	306	>99	76	*S*-(+)
2	PS-HSC	18	>99	76	*S*-(+)
3	AKG	306	93	79	*S*-(+)
4	CC	306	4	83	*R*-(-)
5	CC-HSC	285	29	56	*R*-(-)

The complete conversions in the esterification reaction indicate that hydroxy pyranone **2** (a hemiacetal) is in equilibrium with the aldehyde **5** and thus enables *in situ* racemization of structure **2** (Figure 1). Similar results have been obtained with the lipase catalyzed esterification of 5-hydroxy-furanone.[6] The enzymatic esterification of **2**, coupled to substrate racemization, comprises a highly efficient second order asymmetric transformation process[14] for complete conversion of **2**. Surprisingly, lipase CC shows scarcely any activity in this esterification. This seems to confirm the fact that lipase CC is more sensitive to deactivation with respect to enzyme stability and selectivity than lipase PS.[15] The lipase is presumably deactivated by the acetaldehyde (**4**) released in the reaction by formation of a Schiff base with lysine residues of the enzyme.

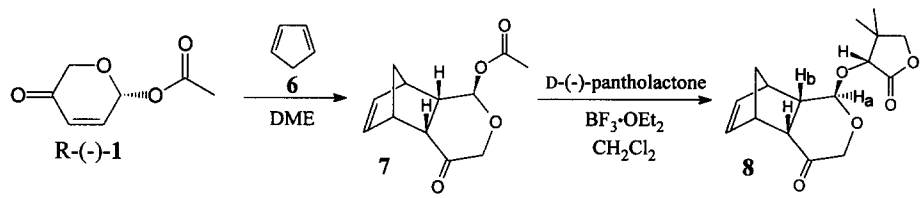


2 **5**

FIGURE 1. Racemization of hemiacetal **2**.

In order to determine the absolute configuration of enantiomerically pure 6-acetyloxy-2*H*-pyran-3(6*H*)-one, (-)-**1** was converted into **7** via a Diels-Alder reaction with cyclopentadiene (**6**) (Scheme 3). This adduct was then converted into the pantholactone derivative **8** by Lewis acid catalyzed transacetalization.[16] Compound **8** has

previously been prepared from the diastereoselective Diels-Alder addition of cyclopentadiene with (*R*)-6-D-pantholactoxy-2*H*-pyran-3(6*H*)-one and characterized as the *trans-endo* compound.[1] The Lewis acid catalyzed conversion of **7** into **8** takes place with retention of configuration (^{1}H-NMR) and the *trans* geometry with respect to H_a and H_b is assigned on basis of the coupling of H_a and H_b (J=5.6 Hz). Hence, based on the relative configuration of **8** and the absolute configuration of the pantholactone moiety, the *R*-configuration at the acetal carbon of **8** and **7** is established and therefore *R*-configuration in (-)-**1** is assigned. Furthermore, the spectroscopic data of **8** are identical to those of the compound prepared independently as reported previously.[1]



SCHEME 3.

In conclusion, enantiomerically pure pyranone **1** is now available as chiral synthon via an efficient asymmetric transesterification or esterification of pyranones involving a second order asymmetric transformation. Further enzymatic transformations with chiral pyranones are in progress.

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7. Lipases A, AKG, AY, CE, D, G, GC, L, M, N, PLE-A, PS, and R are from Amano; lipase CC, Hog Pancreatine lipase, and Pig Pancreas lipase from Sigma; lipase CA from NOVO.
8. A typical procedure is as follows: 10 mg of enzyme is added to 3 ml of a 0.1 M solution of 6-acetyloxy-2*H*-pyran-3(6*H*)-one in hexane/n-butanol (3:1) containing n-decane (0.079 M) as an internal standard. The suspension is stirred at room temperature for the time indicated in Table 1. At given intervals samples are taken, filtered over Celite in a Pasteur pipette and washed with CH_2Cl_2. The samples are then analyzed by GC for e.e. and conversion. With immobilized lipases (23% (w/w) on HSC) amounts are used that correspond to 10 mg of lipase.
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12. As in reference 8, but now 5 equivalents of n-butanol are used in the solvents indicated in the entries of Table 2, except for entry 9.
13. Enzyme (10 mg) is added to 3 ml of a 0.13 M solution of 6-hydroxy-2*H*-pyran-3(6*H*)-one in hexane/vinyl acetate (1.3:1) containing n-decane (0.081 M) as an internal standard. The suspension is stirred at room temperature for the time indicated in Table 3. At given intervals samples are taken, filtered over Celite in a Pasteur pipette and washed with CH_2Cl_2. The samples are then analyzed by GC for e.e. and conversion. With immobilized lipases amounts are used that correspond to 10 mg of lipase.
14. For recent examples see: ref. 6; Ward, R.S. *Tetrahedron: Asymm.* **1995**, *6*, 1475-1490; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Lett.* **1995**, *36*, 8493-8496.
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16. All new compounds showed spectroscopic and analytical data in accordance with the structures.

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