Lipase-Catalyzed Second-Order Asymmetric Transformations as Resolution and Synthesis Strategies for Chiral 5-(Acyloxy)-2(5*H*)-furanone and Pyrrolinone Synthons

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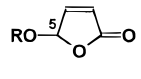
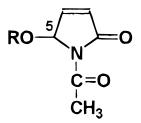
Abstract: By use of lipase R (Amano, *Penicillium roqueforti*) immobilized on Hyflo Super Cell it is possible to convert at ambient temperature 5-hydroxy-5*H*-furan-2-one (**5**) to acetic acid 5-oxo-2,5-dihydrofuran-2-yl ester (**1b**) by acylation with vinyl acetate in 1:1 cyclohexane−butyl acetate. At 90% conversion the enantiomeric excess of **1b** is 100%. This is an example of an enzyme-catalyzed second-order transformation whereby the unreactive enantiomer of **5** racemizes during reaction, allowing up to 100% conversion and obtainment of high enantiomeric excesses. The method is even more effective with 5-(acyloxy)-2(5*H*)-pyrrolinones. Racemic acetic acid 1-acetyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl ester (**2**) when treated with the lipase from *Candida antarctica* at ambient temperature in 3:1 *n*-hexane−butanol undergoes exactly 50% conversion to afford (+)-**2** in >99% enantiomeric excess. This is the unreactive enantiomer. The (−)-enantiomer is converted to the 5-hydroxy derivative **6**, which with *Candida antarctica* in 1:1 *n*-hexane−vinyl acetate at 69 °C (the temperature is higher to increase the rate of racemization) is transformed (100% conversion) to (−)-**2**, obtained in >99% enantiomeric excess. The scope of these second-order asymmetric transformations is discussed as well as procedures for optimalization of reaction conditions whereby transesterification strategies are combined with those of second-order asymmetric transformation.

Second-order asymmetric transformations[1] offer attractive processes for the complete conversion of a racemate into a single enantiomer.[2] Recently examples of enzymatic kinetic resolutions coupled to substrate racemization have been discovered.[3−5] We report here the application of separate aspects of this approach in kinetic resolution and enantioselective synthesis to achieve—using a single enzyme but only by variation of the technique—the directed synthesis of either enantiomer of interesting heterocyclic synthons. The approach leads to 5-(acyloxy)-2(5*H*)-furanones **1** and pyrrolinones **2**.



1a) R=C_2H_5CO, b) R=CH_3CO
3) (5*R*), R=l-menthyl
5) R=H



2) R=CH_3CO
4) (5*R*), R=$CH(CH_3)_2$
6) R=H

These classes of heterocycles are of proven potential as chiral synthons. The capacities of (5*R*)-(l-menthyloxy)-2(5*H*)-furanone (**3**) are nicely demonstrated in the flexible, one-pot syntheses of several lignans[6] and analogs of podophyllotoxins, potent lignan anticancer drugs.[7a] An asymmetric synthesis of analogs of the germination stimulant strigol, developed by Zwanenburg et al., depends on the availability of **3**.[7b] These examples complement a variety of other synthetic applications that have been reported.[8] The structurally related 5-isopropoxypyrrolinone **4**, prepared somewhat arduously from (*R*)-malic acid, is a source of optically active *N*-acyliminium ion precursors, and has been shown by Hiemstra and Speckamp to be an effective synthon for construction via stereoselective Diels−Alder cycloadditions of intermediates for the synthesis of gelsemine.[9]

Virtually all descriptions of applications of these chiral heterocyclic compounds are based on butenolide **3**, which contains the l-menthyl auxiliary, and **4** for which malic acid is required as a precursor. Avoidance of chiral auxiliaries and more direct routes to these chiral synthons would enhance their applicability. To this end we reported recently[10] that (+)-**1a**[11,12] can be obtained in 98% ee at 51% conversion (E >130) with lipase R (from Amano, source *Penicillium roqueforti*) and (−)-

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Scheme 1

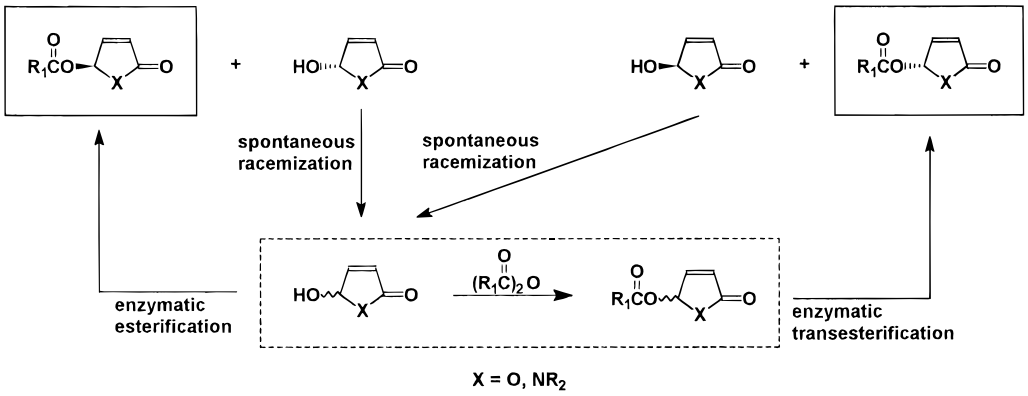
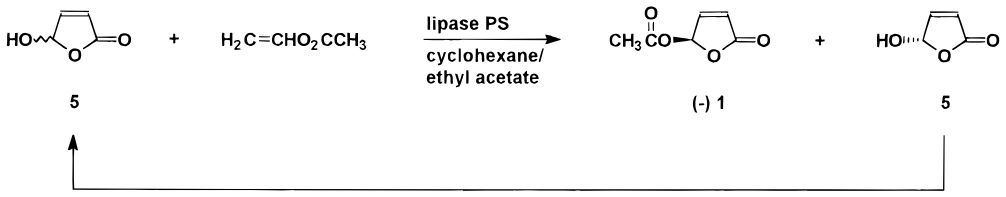


Table 1. Lipase-Catalyzed Esterification and Transesterification As Illustrated in Scheme 1

entry	reaction[a]	lipase[b]	time (h)	product	X	R_1	R_2	c^c (%)	ee[d] (%)
1	esterification	R	240	(−)-**1b**	O	CH_3		90	>99
2	esterification	PS	21	(−)-**1b**	O	CH_3		100	89
3	esterification	PS	21	(−)-**1a**	O	C_2H_5		100	83
4	transesterification	CAL	48	(+)-**7**	N	CH_3	CH_3	67	>99
5	transesterification	CAL	24	(+)-**2**	N	CH_3	$COCH_3$	50	>99
6	transesterification	CAL	48	(+)-**8**	N	C_2H_5	COC_2H_5	49	>99
7	transesterification	CAL	24	(+)-**9**	N	CH_3	COC_2H_5	49	>99
8	transesterification	CAL	24	(+)-**10**	N	C_2H_5	$COCH_3$	49	>99
9	esterification	CAL	18	(−)-**2**	N	CH_3	$COCH_3$	100	>99

[a] Solvent: for transesterification, *n*-hexane−1-butanol (3:1); for esterification entry 1, diethyl ether; entries 2 and 3, cyclohexane−butyl acetate (1:1); entry 9, vinyl acetate−*n*-hexane (1:1). Acyl donor (esterification): vinyl acetate or vinyl propionate. All reactions were performed at room temperature except for entry 9, which was performed at 69 °C. Monitoring and analysis carried out analogously to the procedure described in ref 10. [b] Commercial immobilized *C. Antarctica* lipase (CAL) was used; lipases R and PS were immobilized on Hyflo Super Cell.[13] [c] The conversion (*c*) was determined by chiral GC using *n*-decane or tridecane as an internal standard. [d] The ee was determined by chiral GC; >99% indicates that the other enantiomer could not be detected.



(1)

1a in 90% ee at 48% conversion (E > 200) with lipase AY (*Candida rugosa*) by means of catalyzed transesterification with 1-butanol in *n*-hexane.

We have now found that on use of lipase PS (Amano, *Pseudomonas fluorescens*), immobilized on Hyflo Super Cell,[13] the rate is increased dramatically. For example, on an 8.0 g scale complete conversion is obtained in about 4 h instead of the 8 days that would normally be required on this scale. As expected (+)-**1b** fails to react and is isolated chemically and enantiomerically pure in 64% yield based on a maximum conversion of 50% (see the Experimental Section). This enzyme clearly converts (−)-**1** to **5**, and the latter racemizes rapidly under the reaction conditions.

The observation of spontaneous in situ racemization offers an opportunity to carry out complete resolution by coupling the kinetic resolution to an asymmetric transformation (second-order asymmetric transformation). Therefore, the reverse reaction, i.e., esterification (eq 1) was investigated with lipase PS (one of the more reactive lipases) in vinyl acetate as solvent at 40 °C. However, the conversion to (−)-**1b** (ee = 82%) was only 33% complete after 10 days. For lipase R 28% conversion (ee > 98%) was found.

Some improvement in reactivity was obtained by systematic investigation of solvents; on use of the mixed solvent system cyclohexane−ethyl acetate (1:1), 100% conversion was obtained in 14 days and (−)-**1b** was formed in 86% ee. Again dramatic further improvement was obtained with immobilized lipase PS. Within 21 h in 1:1 cyclohexane−butyl acetate, 100% conversion was obtained and (−)-**1b** was obtained in 89% ee. Using lipase R at 90% conversion the ee of (−)-**1b** is >99%. The results are summarized in Table 1. Other acyl donors used with success were vinyl propionate (Table 1, entry 3), vinyl butanoate, and vinyl crotonate (neither illustrated).

This approach is even more successful with **2** prepared by reaction of 5-methoxy-2(5*H*)-furanone with NH_3 followed by acylation with acetic anhydride. With the lipase from *Candida antarctica* at 20 °C in 3:1 *n*-hexane−butanol **2** is converted (Table 1, entry 5) to the extent of 50% leaving (+)-**2** in >99% ee (eq 2).[14] Even on extended standing, the reaction proceeded no further. Both *N*-alkyl and *N*-acyl substituents as well as

(11) The absolute configuration of (+)-**1a** is thought to be *S* as illustrated. This is based on correlations carried out with the corresponding (+)-**1b**. Briefly, Diels−Alder cycloaddition with cyclopentadiene proceeds in the expected endo fashion and on the face of the alkene opposite the acyloxy group. Transacetalization of this cycloadduct either with methanol or with water leads to two adducts identical to those obtained from the cycloaddition followed by analogous transacetalization of (5*R*)-**3** except that the optical rotations are opposite. The configuration of (+)-**1b** is therefore *S* and (+)-**1a** also *S* by analogy.

(12) The lipase does not catalyze ring-opening of the lactone at a detectable rate.

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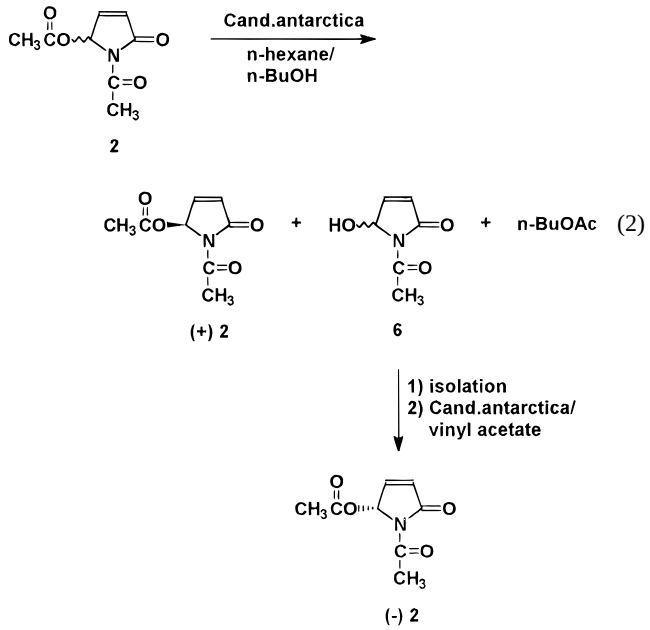

variations in acyl substituents at C5 are tolerated (see Table 1, entries 4−8).

The 5-hydroxy derivative **6**, also formed in 50% yield, partially racemized during the transesterification. Esterification of **6** (Table 1, entry 9) in *n*-hexane−vinyl acetate (1:1) at 69 °C (the higher temperature is needed to speed the rate of racemization relative to the rate of acylation) again with *C. antarctica* provides (−)-**2** within 18 h in 99% conversion and >99% ee!

By use of lipases in organic solvents, it is now possible to prepare in excellent yield and enantiomeric excess *either enantiomer* of the investigated butenolides or pyrrolinones either by transesterification ((+)-enantiomer) or by esterification of the 5-hydroxy derivatives ((−)-enantiomer) as is illustrated in Scheme 1. Complete transformation into either enantiomer is now achievable by (a) in situ racemization of the 5-hydroxy butenolide and 5-hydroxypyrrolinone followed by esterification with the appropriate anhydride combined with the enzymatic transesterification and (b) second-order asymmetric transformation.

To our knowledge this is the first description of a procedure to obtain directly—at reasonable rates of conversion—both enantiomers with a single enzyme simply by variation of the procedure. Useful synthons are now available via this approach, and the potential for application to other heterocyclic systems is most appealing.

Experimental Section

Immobilization of Lipases on Hyflo Super Cell. Lipases were immobilized following a literature procedure.[13] Lipase (1.5 g) and Hyflo Super Cell (5 g) were mixed. After adding 5 mL of a phosphate buffer of pH 7, the mixture was stirred well for 15 min. The enzyme slurry was spread on a Petri dish and allowed to dry in the air for 2 days.

General Procedure for the Lipase-Catalyzed Transesterifications of Pyrrolinones. A typical procedure is as follows: 10 mg of immobilized enzyme (CAL) was added to 3 mL of a solution of hexane−*n*-BuOH (3:1) containing 0.15 mmol of substrate and 8 mg of tridecane or *n*-decane (internal standard). Dichloromethane was added until the solution was clear (0−0.3 mL). The suspension was stirred at room temperature for the time indicated (Table 1). At given intervals samples of 0.3 mL were taken and filtered over Celite (1.0 cm in a Pasteur pipet). The Celite was washed with 0.5 mL of acetone, and the crude mixture was analyzed by GC for conversion and ee.

General Procedure for the Lipase-Catalyzed Esterifications. A typical procedure is as follows: 66 mg of immobilized lipase (or 20 mg of immobilized CAL) was added to 3 mL of a solution of the appropriate solvent containing 20 mg of substrate and 8 mg of the internal standard. To this mixture was added the appropriate vinyl ester (0.5 mL). The mixture was stirred at room temperature (only for compound **2** was it refluxed). At given intervals samples of 0.2 mL were taken and filtered over Celite (1.0 cm in a Pasteur pipet). The Celite was washed with CH_2Cl_2 or acetone, and the crude mixture was analyzed by GC for conversion and ee.

Transesterification of Acetic Acid 1-Acetyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl Ester (2). A solution of **2** (10.0 g, 54.6 mmol) in 1-butanol (100 mL) was added to 1 L of *n*-hexane−1-butanol (3:1). Immobilized CAL (1.82 g) was added, and the mixture was shaken at 20 °C for 40 h. The mixture was filtered over a glass filter (P3), and the enzyme was washed with acetone (it could be used again). The solution was concentrated in vacuo, the temperature not exceeding 25 °C. The white solid product mixture was separated by column chromatography (silica gel, ethyl acetate−*n*-hexane (1:1)). Pure **2** was obtained in 50% yield (5.02 g, 27.4 mmol) as almost white crystals: R_f 0.38; $[\alpha]_D$ +199° (*c* 1.00, $CHCl_3$); ee > 99% as estimated by chiral GC. ^{1}H NMR and ^{13}C NMR ($CDCl_3$) were identical to those of the racemate (see the supporting information). 1-Acetyl-5-hydroxy-1,5-dihydropyrrol-2-one (**6**) was obtained in 47% yield (3.61 g, 25.6 mmol), as almost white crystals: mp 90−91 °C; R_f 0.17; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H, NCOC*H*$_3$), 4.58 (br s, 1H, O*H*), 6.11 (d, J = 0.9 Hz, 1H, OC*H*N), 6.16 (d, J = 6.0 Hz, 1H, CH=C*H*CO), 7.12 (dd, J = 2.0, 6.0 Hz, 1H, C*H*=CHCO); ^{13}C NMR ($CDCl_3$) δ 24.29 (q, NCO*C*H$_3$), 81.63 (d), 128.16 (d), 147.48 (d), 167.79 (s), 171.31 (s); exact mass calcd for $C_6H_7NO_3$ 141.043, found 141.043. An analytical sample was sublimed (0.1 mmHg, 50 °C). Anal. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.92. Found: C, 51.14; H, 5.06; N, 9.90.

Transesterification of Acetic Acid 5-Oxo-2,5-dihydrofuran-2-yl Ester (1b). To a solution of **1b** (8.00 g, 56.3 mmol) in 1.5 L of *n*-hexane−1-butanol (3:1) was added immobilized (at pH 7 in a phosphate buffer)[10] lipase PS (3.0 g, 30% w/w). The mixture was stirred vigorously at room temperature and was monitored by capillary GC. After 4 h, the ee of (+)-**1b** was >99% and the stirrer was stopped. After standing for 15 min, the solution was decanted from the enzyme slurry and filtered through Celite. The solvent was removed by vacuum distillation at 10−15 °C, leaving a yellow oil (4.1 g), which was purified by flash chromatography (silica gel, ethyl acetate−*n*-hexane (1:3)) to give 2.6 g (64% yield based on 50% conversion) of a slightly yellow oil (**1b**), $[\alpha]_D$ + 25.4° (*c* 1.00, $CHCl_3$), which was pure as determined by NMR and GC.

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Supporting Information Available: Experimental procedures for the synthesis and characterization of **1a**, **1b**, acetic acid 1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl ester (**7**), 5-hydroxy-1,5-dihydropyrrol-2-one (**12**), **2**, **8**, **9**, and **10** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet: see any current masthead page for ordering information and Internet access instructions.

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(14) The absolute configuration is indicated as analogous to **1**; this remains to be proven.