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Enzymatic kinetic resolution of pantolactone: relevance to chiral auxiliary chemistry

Louise Haughton, Jonathan M. J. Williams* and Jochen A. Zimmermann

Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

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Abstract

Racemic pantolactone was converted into either enantiomerically enriched pantolactone acetate or pantolactone acrylate by an enzyme-catalysed kinetic resolution process. Pantolactone is known to be a good auxiliary for acrylate in the Diels–Alder reaction.

The enzyme-catalysed kinetic resolution of substrates by esterification or hydrolysis has found widespread application in the preparation of enantiomerically enriched building blocks.[1] Indeed, the preparation of chiral auxiliaries using such procedures has been reported. For example, Whitesell et al. have prepared their auxiliary using enzyme-catalysed kinetic resolution methodology.[2]

Enantiomerically pure pantolactone has been employed as a chiral auxiliary for acrylate in the highly diastereoselective Diels–Alder reaction with cyclopentadiene.[3] A brief report of the enzymatic resolution of pantolactone has been published.[4] Herein, we report our results on the resolution of pantolactone by enzyme-catalysed acylation, and the application of this methodology to the direct preparation of the acrylate derivative.

Treatment of racemic pantolactone **1** with vinyl acetate affords the corresponding pantolactone ester (*S*)-**2** with high enantioselectivity (Scheme 1). The CLEC (cross-linked enzyme crystal)[5] version of *Candida cylindracea* lipase (Altus 20) was found to be the most suitable of the enzymes screened.[6,7]

Since the acrylate derivative (*S*)-**3** can be used in subsequent chiral auxiliary-based chemistry, we wished to prepare this compound directly from the enzyme-catalysed reaction. In order to achieve this goal, we chose to employ vinyl acrylate as the acyl donor (Scheme 2). This acyl donor has not been widely employed in kinetic resolutions, although a few reports are available.[8] Of the enzymes screened, only the lipase from *Candida cylindracea* was effective,[7] and the reaction was optimised by variation of the solvent and the acyl donor concentration (Table 1). We again found that the CLEC enzyme Altus 20 was the most effective.

* Corresponding author.

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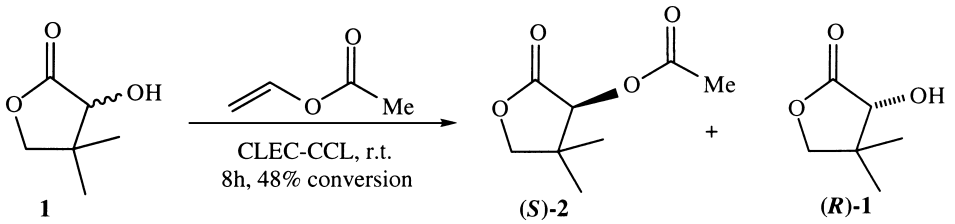
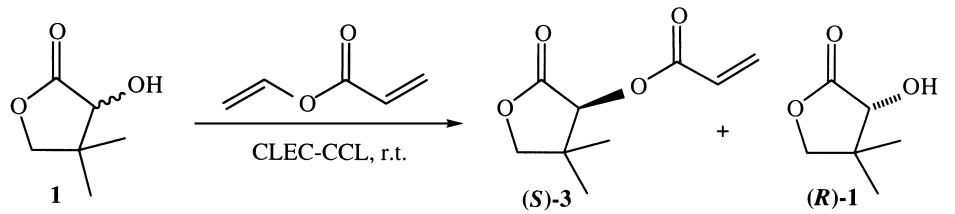


CLEC-CCL = Cross-Linked Enzyme Crystals of Candida Cylindracea Lipase (Altus-20)

Scheme 1. Conversion of pantolactone into pantolactone acetate



Scheme 2. Enzyme-catalysed pantolactone acrylate formation

Table 1
Variation of solvent and acyl donor concentration

Solvent[a,b]	Acyl donor	Conversion	(*R*)-1 ee[d]	(*S*)-3 ee[9]
^{t}BuOMe	0.5eq[e]	7%	5%	95%
^{t}BuOMe	1eq	27%	31%	94%
^{t}BuOMe	2eq	47%	75%	91%
^{t}BuOMe	3eq	50%	83%	89%
^{t}BuOMe	5eq	56%	94%	85%
Diisopropylether	3eq	32%	34%	93%
Diethylether	3eq	30%	30%	95%

[a] Other solvents, including toluene, MeCN, DCM, and $CHCl_3$ all gave lower reactivity and lower enantioselectivity.
[b] 20% w/w enzyme in 2ml solvent using 768μmol pantolactone.
[c] Conversion was determined by analysis of the NMR spectra of the crude product.
[d] Enantiomeric excess was determined by GC (gamma-dex column from Supelco, 110 °C, retention times (*R*)-**1**, 10.45 min, (*S*)-**1**, 10.91 min, (*R*)-**3**, 25.15 min, (*S*)-**3**, 26.45 min.

Variations in the temperature between 25°C and 45°C did not show a large effect on either the reaction rate or enantiomeric excess of the product (*S*)-**3**, but revealed that above 40°C polymerisation of the acyl donor was problematic. Nevertheless, an increase in the concentration of enzyme resulted in an acceleration of the reaction with the consequence that at high enzyme concentrations and long reaction times the enantiomeric excess of pantolactone acrylate decreased again (Table 2).

Table 2
Influence of enzyme concentration on reaction time and enantiomeric excess

w/w enzyme to pantolactone 1	Reaction time	Conversion	(*R*)-1 ee	(*S*)-3 ee[9]
5%	24h	11%	9%	94%
10%	24h	19%	14%	90%
15%	24h	49%	78%	91%
20%	8h	49%	88%	89%
20%	24h	56%	97%	84%
20%	48h	70%	100%	70%

The enantiomeric excess of the recovered starting material **1** and pantolactone acrylate **3** were monitored during the course of a reaction (20% w/w, enzyme to pantolactone) and the data are plotted in Fig. 1. It can be seen that at 50% conversion (after 8 h) the enantiomeric excess of both pantolactone **1** and the acrylate **3** were approximately 90% (somewhat lower than for the corresponding reaction to form the acetate).

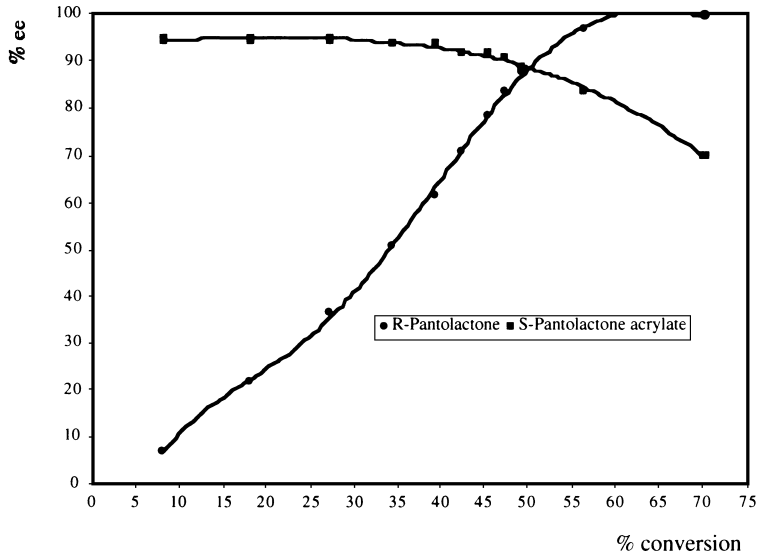
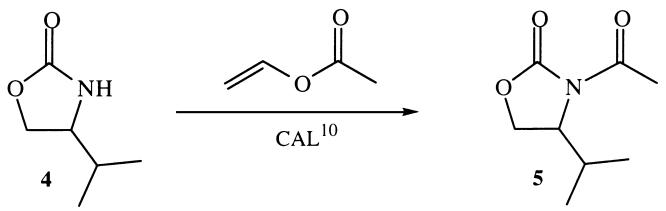


Figure 1. Kinetic study of enantiomeric excess versus conversion



Scheme 3. Enzyme-catalysed acyl oxazolidinone formation

The enzyme-catalysed acylation of a racemic Evans auxiliary **4** has also been performed using *Candida antarctica* lipase.[10] To the best of our knowledge, this is the first example of an enzyme-catalysed reaction involving an oxazolidinone, although we saw no kinetic resolution during the reaction (Scheme 3, Table 3). Hydrolysis of the acyl oxazolidinone **5** was also possible using *Candida antarctica* lipase in phosphate buffer:*t*BuOMe (80:20).

Table 3
Variations in acyl oxazolidinone formation

Solvent[a]	Temperature	Reaction time	Conversion[b]	ee[c](Product)
Vinyl acetate	40 °C	24h	83%	0%
Vinyl acetate	50 °C	24h	54%	0%
Vinyl acetate/^{t}BuOMe 1:1	40 °C	17h	38%	0%

[a] 50mg oxazolidinone and 10%w/w enzyme in 1ml solvent; other solvents gave worse results
[b] Conversion was determined by analysis of the ^{1}H NMR spectra
[c] Enantiomeric excess was determined by GC (beta-dex column from Supelco, 150 °C, retention times **4**, 8.12 and 9.49 min, **5**, 19.07 and 20.32 min.

In summary, pantolactone has been converted into the corresponding acetate in high enantiomeric excess by an enzyme-catalysed kinetic resolution strategy. Formation of the acrylate, which is useful in auxiliary controlled reactions, has been achieved using a similar strategy but with somewhat lower enantioselectivity.

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6. Altus 20 from Altus Biologics Inc., 40 Allston Street, Cambridge, MA 02139-4211, USA.
7. Using a gammadex column from Supelco, the pantolactone acetate enantiomers were separated at 110°C with retention times of 16.48 min (*R*) and 17.57 min (*S*). Other enzymes examined for the conversion of pantolactone into pantolactone acrylate include Altus 17 (CRL), lipases from *Candida antarctica*, *Pseudomonas cepecia*, and *Pseudomonas fluorescens*, and hog liver esterase and α-chymotrypsin, but none of these afforded any significant conversion.
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9. (a) (*S*)-Pantolactone acrylate (*S*)-**3** was separated from pantolactone by column chromatography (MeOH:toluene, 1:9); IR: 996 ν_{max}/cm^{-1} (C=C), 1634 (C=C), 1737 (O–CO–R), 1792 (R–O–CO–R, lactone), 2970/2935/2911/2879 (C–H); ^1H NMR: δ_H (400 MHz, $CDCl_3$) 1.14/1.23 (s, 3H, CH_3), 4.06 (d, 1H, J = 9.0 Hz, CH_2), 4.09 (d, 1H, J = 9.0 Hz, CH_2), 5.45 (s, 1H, CH), 5.98 (dd, 1H, J = 1.2 and 10.5 Hz, CH_2=), 6.23 (dd, 1H, J = 10.5 and 17.2 Hz, CH=), 6.53 (dd, 1H, J = 1.2 and 17.2 Hz, CH_2=); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 20.2/23.4 (CH_3), 40.7 (C), 75.4 (*CH), 76.5 (CH_2), 127.2 (CH=), 133.0 (CH_2=), 164.9 (CO), 172.4 (C=O); *m*/*z* (EI): 55 (100); *m*/*z* (isobutane CI): 185 (100), 85 (25), 100 (20). $C_9H_{12}O_4$ requires: C, 58.69%; H, 6.57%. Found: C, 58.70%; H, 6.63%. $[\alpha]_D^{23} = +9.5$ (*c* = 2, $CHCl_3$). (b) (*R*)-Pantolactone acrylate (*R*)-**3** was prepared for comparison purposes: Under nitrogen, acryloyl chloride (62.5 mmol, 5.65 g, 1.25 equiv.) was added over 1 h to a stirred cold (–24°C) solution of (*R*)-pantolactone (50.0 mmol, 6.50 g, 1 equiv.) and triethylamine (75.0 mmol, 7.60 g, 1.5 equiv.) in dry DCM (75 ml) and stirred at that temperature for 5 h. The organic layer was washed with 1 M HCl, sat. aq. $NaHCO_3$ and H_2O, followed by drying (over $MgSO_4$), evaporation and distillation, bp 88–90°C (0.85–0.90 mmHg), which afforded a colourless liquid (37.1 mmol, 6.79 g, 74%). $[\alpha]_D^{23} = -10$ (*c* = 2, $CHCl_3$).
10. *Candida antarctica* lipase (500kU, Chirazyme L-2 c.-f. C2, lyo) from Boehringer Mannheim.