Enzymatic kinetic resolution of primary allenic alcohols. Application to the total synthesis and stereochemical assignment of striatisporolide A†

Jan Deska and Jan-E. Bäckvall*
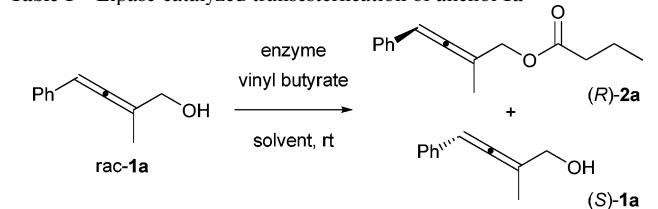
Crude *Porcine pancreatic* lipase was successfully used for the kinetic resolution of axially chiral primary allenic alcohols providing very high enantioselectivities with *E* values above 200. This simple access to optically active allenes was applied to the total synthesis of the fungal metabolite (–)-striatisporolide A, allowing its unambiguous stereochemical assignment.

During the past decade the use of allenes as synthetic intermediates has dramatically increased, and many useful transformations have been developed with this class of compounds.[1] An interesting feature of allenes is the axial chirality along the cumulated 1,2-diene system. Optically active allenes have been frequently used in stereoselective synthesis, but they are usually synthesized from enantioenriched precursors and preparation *via* kinetic resolution is rare. The few resolution methods described, both chemical[2] and enzymatic,[3] show compared to non-allene resolutions relatively poor enantioselectivities and a general lack of substrate scope, which makes them less attractive for synthetic applications. In order to overcome the issue of low selectivities we recently investigated the potential of tailor-made enzymes applying directed evolution strategies whereupon a mutant of *Pseudomonas aeruginosa* lipase was identified to catalyze the hydrolysis of an allenic *p*-nitrophenylester with very high enantioselectivity (*E* = 111).[4]

Herein we report on the use of cheap, commercially available *Porcine pancreatic* lipase as a biocatalyst for the highly enantioselective kinetic resolution of primary allenic alcohols by enzymatic transesterfication from vinyl esters in organic solvents. Choosing allenol **1a** as a model substrate for the investigation of the title reaction, we tested different lipases with precedent for good selectivities in the resolution of non-allenic primary alcohols.[5] While crude *Candida rugosa* lipase (CRL) yielded virtually racemic products both *Pseudomonas cepacia* (PCL) and *Pseudomonas fluorescens* (PFL) lipases showed slight enantiodiscrimination, however, no synthetically useful enantioselectivity was obtained (Table 1, entries 1–3). By far the best enantioselectivity was observed for *Porcine pancreatic* lipase (PPL), giving rise to highly enantioenriched transesterfication product (*R*)-**2a** with an *E*-value of 115 (Table 1, entry 4). Further improvement was achieved by variation of the solvent, where both 1,4-dioxane and diisopropyl ether afforded almost enantiopure butyrate with *E*-values higher than 200 (Table 1, entry 5 and 6). However, the use of 1,4-dioxane

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91, Stockholm, Sweden. E-mail: jeb@organ.su.se
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Table 1 Lipase-catalyzed transesterfication of allenol **1a**[a]

Entry	Enzyme[6]	Solvent	Time	% conv.	% ee$_{1a}$	% ee$_{2a}$	E[7]
1[b]	CRL	toluene	42h	35	5	9	1.3
2[b]	PCL	toluene	3h	52	71	65	9.8
3[b]	PFL	toluene	18h	39	46	73	10.0
4	PPL	toluene	24h	42	68	96.5	115
5	PPL	dioxane	24h	18	22	98.9	>200
6	PPL	$^iPr_2O$	24h	42	67	98.3	>200

[a] Reactions performed with 0.1 mmol **1a**, 0.5 mmol vinyl butyrate, 5 mg lipase in 2 ml of solvent at room temperature. Enantiomeric excesses were determined by HPLC analysis, conversions calculated from ee's. [b] 0.06 mmol (0.6 eq) vinyl butyrate used.

gave a significantly lower reaction rate (entry 5) compared to diisopropyl ether.
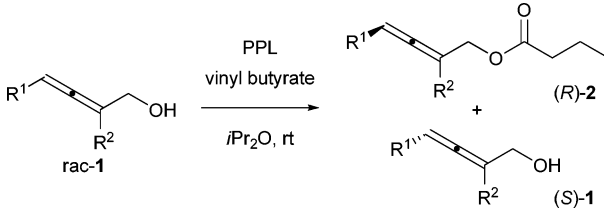
To explore the substrate scope of this synthetic method, a series of α-allenols with different substitution patterns at the chiral allene axis were subjected to the PPL-catalyzed kinetic resolution. Apparently, a substituent in the 2-position is crucial for the recognition by the protein since allene **1b** showed dramatically reduced selectivity together with a low reaction rate (Table 2, entry 2). On the other hand, increasing the steric demand in the 2-position by changing from methyl to ethyl (**1c**) affected the reaction only marginally and a high enantioselectivity was observed (Table 2, entry 3). The effect of variations at the aryl moiety in the 4-position of the allene remained minor and selectivity issues seem to depend on the substitution position rather than the character of the substituent. While *m*- and *p*-tolyl derivatives **1e** and **1f** showed high enantioselectivities with *E*-values of 176 and 102, respectively (Table 2, entries 5 and 6), the *o*-tolyl allenol **1d** gave a significantly lower selectivity (Table 2, entry 4). Halide-substituted derivatives **1g** and **1h** as well as the naphthalene derivative **1i** gave excellent results with *E* > 200 (Table 2, entries 7–9). In contrast, the alkenyl- and alkyl-substituted allenols **1j** and **1k** showed a considerably reduced enantioselectivity (Table 2, entries 10 and 11) and in order to obtain highly enantioenriched material, an attentive overacylation was required.

With the objective to verify the absolute configurations of the resulting products, alcohol (*S*)-**1a**, the non-reacting enantiomer in the PPL-catalyzed kinetic resolution, obtained in 97% ee by

Table 2 *Porcine pancreatic* lipase-catalyzed kinetic resolution of α-allenols[a]

Entry	R^1	R^2	Time	% conv.	% ee_{alc}	% ee_{but}	E^7
1	Ph	Me	24h	42	**1a**: 67	**2a**: 98.3	>200
2[b]	Ph	H	72h	25	**1b**: n.d.	**2b**: 76	9
3	Ph	Et	24h	39	**1c**: 61	**2c**: 97	127
4	*o*-Tol	Me	30h	19	**1d**: 21	**2d**: 94	40
5	*m*-Tol	Me	42h	43	**1e**: 74	**2e**: 97	176
6	*p*-Tol	Me	24h	46	**1f**: 82	**2f**: 95	102
7	*p*-Cl-Ph	Me	28h	49	**1g**: 96	**2g**: 97	>200
8	*p*-CF₃-Ph	Me	30h	10	**1h**: 23	**2h**: 99.2	>200
9	2-Naph	Me	31h	37	**1i**: 58	**2i**: 98.4	>200
10[b]	*i*Propenyl	Me	24h	30	**1j**: n.d.	**2j**: 81	13
11[b,c]	*n*Pentyl	Me	17h	59	**1k**: 97	**2k**: n.d.	23

[a] Reactions performed with 0.1 mmol **1**, 0.5 mmol vinyl butyrate, 5 mg PPL in 2 ml *i*Pr₂O at room temperature. Enantiomeric excesses were determined by HPLC analysis, conversions calculated from ee's. [b] Conversion was determined by ¹H-NMR. [c] Enantiomeric excess was determined by HPLC analysis of the corresponding *p*-nitrobenzoate.

careful overacylation, was cyclized to the corresponding dihydrofuran (*R*)-**3** by means of a silver-catalyzed cycloisomerisation with complete retention of the optical activity (Scheme 1). In order to obtain an authentic sample of the dihydrofuran with known configuration, racemic **4** was enzymatically resolved using *Candida antarctica* lipase type B as a biocatalyst. The enzymatic acylation of *rac*-**4** with this enzyme is known to give (*R*)-**5**[8] with the remaining alcohol being (*S*)-**4**. Etherification of (*S*)-**4** with 3-bromo-2-methylpropene and subsequent ring-closure metathesis[9] yielded (*S*)-**3** as a single enantiomer. Comparison of optical rotations and HPLC-chromatograms indicated (*R*)-configuration for the dihydrofuran originated from the chiral allene, as a
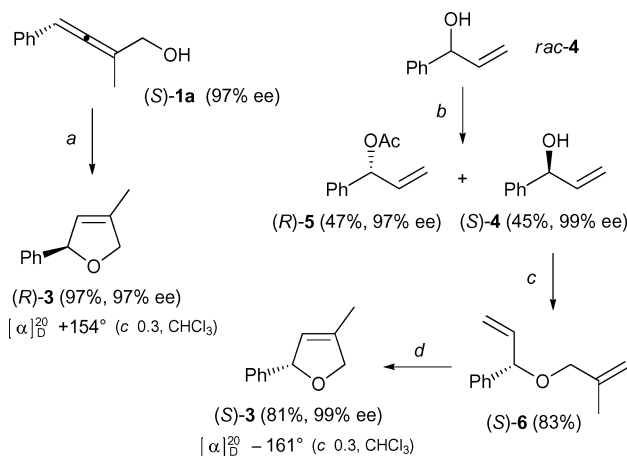
consequence (*S*)-configuration for the allenol ((*S*)-**1**).[10] The same observation regarding the stereochemical outcome was made for pentyl-substituted allenol (*S*)-**1k**.

In 2005 a series of fungal metabolites were isolated from an Australian *Penicillium striatisporum* strain, among them the new butenolide (−)-striatisporolide A (**7**),[11a] a double-bond regioisomer of the known γ-butyrolactone methylenolactocin (**8**)[14b] (Fig. 1). Both belong to the family of paraconic acids,[12] which have attracted a certain interest over the past few years due to their biological activities such as antifungal, antitumor and antibacterial effects. However, to date neither a synthetic approach towards striatisporolide A has been described nor could its absolute stereochemical configuration be determined.
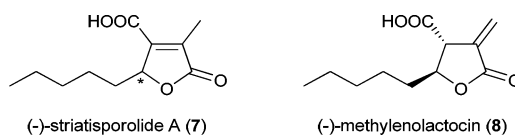
Fig. 1 Metabolites from *Penicillium* sp.

To emphasise the synthetic value of chiral allenes and our approach using the kinetic resolution of allenols we aimed for an enantioselective total synthesis of (−)-striatisporolide A starting from optically active (*S*)-**1k** (Scheme 2). Therefore enzymatically resolved (*S*)-**1k** (97% ee) from Table 1 was subjected to an iodocyclisation using *N*-iodosuccinimide as a halide source,[13] giving rise to 3-iodobutenolide (*S*)-**9**. Palladium-catalyzed methoxycarbonylation of vinyl iodide (*S*)-**9** afforded α,β-unsaturated methyl ester (*S*)-**10**[14] in high yield; a slightly elevated pressure (sealed tube) was required to achieve reasonable reaction rates. Finally, regioselective allylic oxidation using CrO₃/dimethylpyrazole[15] followed by an alkaline hydrolysis of the methylester yielded the desired natural product (*S*)-**7**. The spectral data from the synthetic striatisporolide A were identical with those reported from the natural source. Consistency of the specific rotations of (*S*)-**7**, $[\alpha]_D^{20}$ −25.2° (*c* 0.4, MeOH), and the natural striatisporolide A, $[\alpha]_D$ −24° (*c* 0.4, MeOH), allows the unambiguous assignment of the absolute configuration of the natural product.

Scheme 1 *Reagents and conditions:* (a) 10 mol% AgNO₃ on silica, pentane, rt, 3 h; (b) 0.5 eq vinyl acetate, 5 wt% Novozym 435, toluene, rt, 20 h; (c) 1.2 eq NaH, 1.2 eq 3-bromo-2-methylpropene, DMF, 0 °C, 3 h; (d) 5 mol% Grubbs' first generation catalyst, toluene, 80 °C, 5 h.
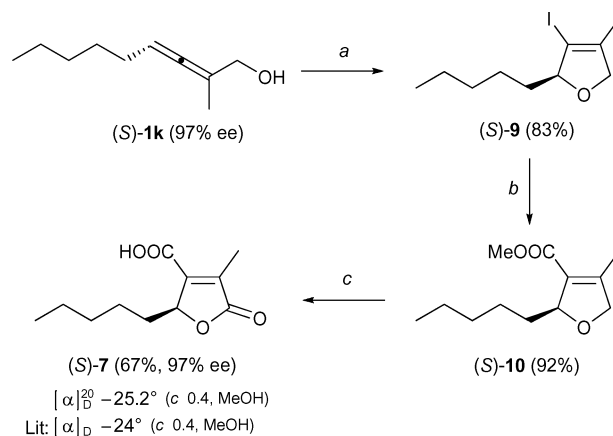

Scheme 2 *Reagents and conditions:* (a) 1.1 eq NIS, DCM, rt, 2 h; (b) CO (1 atm), 3 eq NEt₃, 5 mol% Pd(PPh₃)₄, MeOH, 85 °C, 20 h; (c) (i) 6 eq CrO₃, 6 eq 3,5-dimethylpyrazole, DCM, −20 °C, 6 h; (ii) 3 eq LiOH, THF/H₂O, 0 °C, 1 h.

In summary, a biocatalytic kinetic resolution of allenols using *Porcine pancreatic* lipase has been developed, which shows good to excellent enantioselectivity for a variety of different primary allenic alcohols. This approach was used as the enantiodetermining step in the synthesis of the fungal butenolide (–)-striatisporolide A. Work is in progress in our laboratory towards a dynamic kinetic resolution (DKR)[16] of allenes. We have previously reported on a novel racemization procedure for allenes that takes advantage of the reversible bromopalladation of the 1,2-diene moiety.[17] We are currently studying the combination of this racemization with the present enzymatic resolution in order to obtain a DKR.[18]

Acknowledgements

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