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Chiral enol acetates derived from prochiral oxabicyclic ketones using enzymes

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Abstract

Racemic enol acetates **2–4** and **9** derived from prochiral 8-oxabicyclo[3.2.1]oct-6-en-3-ones have been resolved with good enantioselectivity (E=45, 47, 48 and 7.8, respectively) using silica-adsorbed *Humicola* sp. lipase and the absolute configuration of enol acetate **2** was determined by X-ray crystallographic analysis of the camphanyl derivative **13**.

The desymmetrization of prochiral ketones has become an important method for asymmetric synthesis. The use of chiral lithium amides for the asymmetric deprotonation of 4-substituted cyclohexanones and prochiral aza-and oxa-bicyclic ketones has been developed by Simkins, Koga and others.[1–3] Baeyer–Villiger monooxygenase enzymes have shown promise for the desymmetrization of prochiral and *meso* cyclohexanones[4] although the scale of these reactions is limited by the availability of the enzymes and the expense of the requisite co-factors. Recently, a copper-based asymmetric Baeyer–Villiger catalyst has been reported by Bolm which utilizes molecular oxygen and an aldehyde.[5] Chiral lithium amide desymmetrization of 8-oxabicyclic[3.2.1]ketones has shown significant promise giving intermediates for the synthesis of natural products such as lasonolide A[6] and the acetyl choline agonist (−)-anatoxin a.[7]

We now report the use of a silica-adsorbed lipase for the highly efficient resolution of enol acetates derived from 1,5-disubstituted 8-oxabicyclic[3.2.1]oct-6-en-3-ones[8] as an alternative strategy. The ketones which result from lipase transesterification can be recycled chemically to the enol acetate resulting in a net desymmetrization of the ketone over several cycles (Scheme 1).[9]

Initial screening of oxabicyclic substrates **1–9** identified a lipase from *Humicola* sp. to be the best biocatalyst (where R=larger than H) for the resolution by transesterification with *n*-butanol in hexane (Scheme 2, Table 1). Enol acetates **1** and **5** with no bridgehead substitution were not resolved by this enzyme. Introduction of bridgehead methyl groups in substrate **2** resulted in reasonable selectivity using the freeze dried enzyme. However, use of the same enzyme which had been pre-adsorbed onto silica gel at pH 7, according to a recently described procedure,[10] resulted in a dramatic increase in reaction

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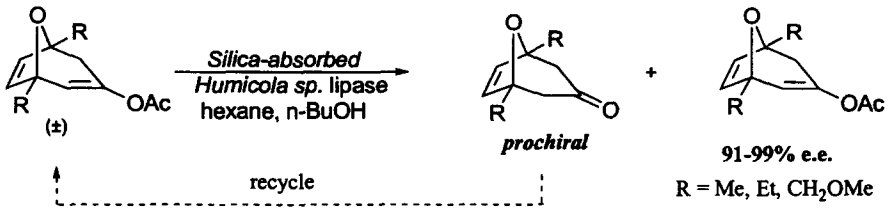
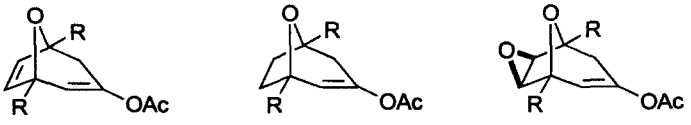


Scheme 1.

rate (110 min vs 82 h for ca. 50% conversion). We used dry *n*-butanol instead of *n*-propanol to carry out the dehydration washing step after decanting the adsorbed enzyme since this is the alcohol used in our transesterification reaction.[11] Hence, for accuracy we have used the acronym BREP (butanol rinsed enzyme preparation).



1 R = H
2 R = Me
3 R = Et
4 R = CH_2OMe

5 R = H
6 R = Me
7 R = Et
8 R = CH_2OMe

9

Scheme 2.

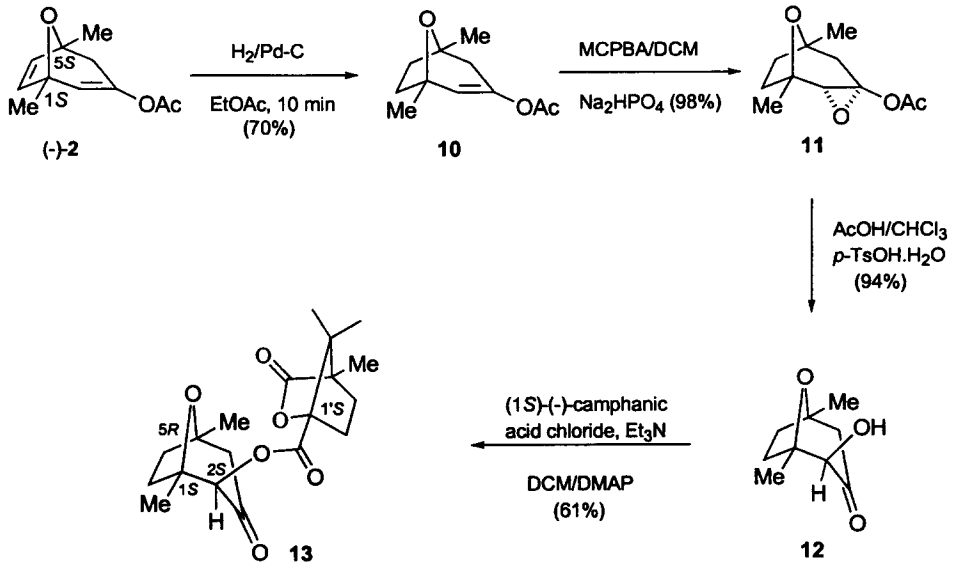
Enantiomerically pure enol ester (*S*)-**2** ($[\alpha]_D$=−53.5) was isolated in 30% yield after chromatography. Biotransformation of related substrates **3** and **4** with the BREP gave a similar level of enantioselectivity (E=47 and 48). However the closely related saturated substrates **5–8** were transformed with much lower selectivity. From these results it is clear that the active site of the enzyme can tolerate quite a wide variation at the bridgehead positions of the substrates but both reaction rate and selectivity are severely compromised upon saturation of the alkene in the 6,7-position of the ring system. Interestingly, intermediate but still useful selectivity (E=7.8) was observed with the epoxide substrate **9** in which case it was necessary to run the reaction to 70% completion to leave highly enriched (95% ee) unreacted epoxy enol acetate **9**. In order to determine the absolute configuration of the enantiomerically pure enol acetate (−)-**2** it was selectively hydrogenated and epoxidized to give exclusively the *endo* epoxide **11** in high yield (Scheme 3). Acid-catalyzed rearrangement of compound **11** gave the α-hydroxyketone **12** as a single diastereoisomer with the hydroxy group in the axial position, presumably by intramolecular delivery of the acetate carbonyl with concomitant ring opening of the protonated epoxide followed by hydrolysis of the α-acetoxy group. Reaction with (1*S*)-(−)-camphanic acid chloride under standard conditions led to the isolation of the ester derivative **13** which was then re-crystallized from *tert* butyl methyl ether to obtain crystals suitable for X-ray analysis.[12]

The crystal structure obtained (Fig. 1) confirms the axial orientation of the 2-camphanic ester group and by reference to the known 1(*S*) chiral centre in the camphanic acid shows the oxabicyclic ketone in compound **13** to possess the 1(*S*), 5(*R*)-configuration. This in turn allows us to determine the configuration of the biotransformation product **2** as 1(*S*), 5(*S*). The 1,5-disubstituted chiral enol acetates described here can serve as chiral enolate equivalents and have not been previously available using chiral lithium amide methodology. In addition, the good enantioselectivity (E=>45) for three of the substrates makes recycling the prochiral ketone a viable approach to achieving a net desymmetrization and we are currently focusing on this aspect of the reaction.

Table 1
Lipase resolution of enol acetates **1–9** with *Humicola* sp. lipase

Substrate enol acetate	Enzyme type	Rxn time	Conversion (%)	Isolated Ketone (%)	Isolated Yield of enol acetate (%)	E.e.(%) enol acetate	E
1	Freeze dried	24h	51	-	-	0	-
2	Freeze dried	82h	55	-	-	83	-
2	BREP*	110mins	49	36	37	84	45
2	BREP	1h	67	36	30	>99	-
3	BREP	19h	51	23	40	91	47
4	Freeze dried	5days	0	-	-	-	-
4	BREP	48h	53	46	32	96	48
5	Freeze dried	28h	25	-	-	0	
6	BREP	31h	51	-	-	42	3.5
7	BREP	30h	0	-	-	-	-
8	BREP	28h	35	37	53	12	-
9	BREP	3h	70	31	23	95	7.8

*BREP = *n*BuOH rinsed enzyme preparation. Reactions were run using substrate (0.052M), enzyme (60mg/mM substrate) and nBuOH (2eq.) in dry hexane. Chiral analysis was done using a Chiralpack AD column eluting with hexane/*iso*-propanol.



Scheme 3.

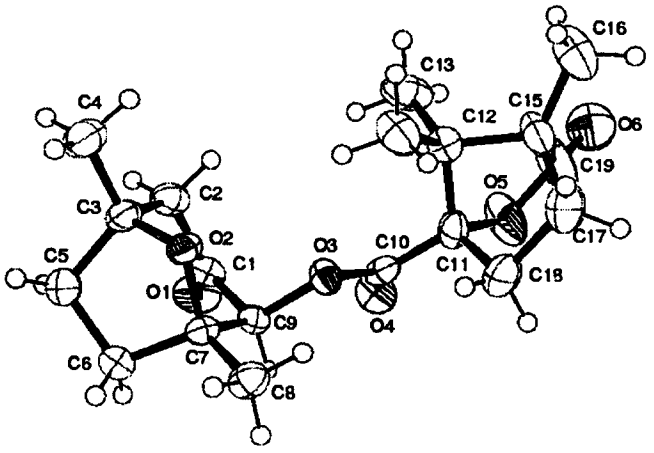


Figure 1.

Acknowledgements

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11. Typical experimental procedure: *Humicola* sp. lipase (190 mg) was dissolved in tris-HCl buffer (pH 7, 64 cm^3). To this solution was added silica gel (3.2 g) and the mixture shaken at room temperature for 2 h. The mixture was allowed to settle and the aqueous phase decanted, ensuring that the silica remained wet at all times. Dry butanol (3×40 cm^3) was added, rinsed and decanted. Dry hexane (3×40 cm^3) was added, rinsed and decanted. Dry hexane (40 cm^3) was added and the suspension added to the enol acetate (±)-**2** (760 mg, 3.92 mmol). To the mixture was added dry butanol (0.72 cm^3, 7.84 mmol) and the mixture allowed to stir at 25°C for 1 h. The mixture was filtered through Celite, and the filtrate concentrated in vacuo to yield a crude mixture which was separated using flash column chromatography on silica with 5% ethyl acetate/40–60% petroleum ether as the eluent to give the prochiral ketone (290 mg, 49%) and the enol acetate (−)-**2** of >99.5% ee (230 mg, 30%) as a yellow oil $[\alpha]_D$ −53.5 (*c* 8.0 in $CHCl_3$); (HRMS: found $[M+H]^+$ 195.10237. $C_{11}H_{15}O_3$ requires 195.10212); υ_{max} (neat)/cm^{-1} 1759 (CO); δ_H (300 MHz; C_6D_6; Me_4Si) 1.29 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.66 (3H, s, $COCH_3$), 1.83 (1H, dd, *J* 17 and 1.5, CH_{2endo}), 2.45 (1H, dd, *J* 17 and 1.8, CH_{2exo}), 5.43 (1H, d, *J* 5.7, CH=), 5.81 (1H, d overlapping, *J* 1.8 and 1.5, CH=CO) and 5.99 (1H, d, *J* 5.4, CH=); δ_c (75.5 MHz; C_6D_6; Me_4Si) 20.8 (CH_3), 22.0 (CH_3), 24.4 (CH_3), 36.8 (CH_2), 82.1 (C), 83.3 (C), 121.9 (CH), 131.6 (CH), 141.4 (CH), 147.7 (C) and 168.6 (C); *m/z* (CI) 212 (100%, $[M+NH_4]^+$), 195 (37, $[M+H]^+$).
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