Tetrahedron: *Asymmetry* 21 (2010) 1011–1016

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Efficient kinetic bioresolution of 2-nitrocyclohexanol

Sinead E. Milner [a], Maude Brossat [b], Thomas S. Moody [b], Curtis J. Elcoate [a], Simon E. Lawrence [a], Anita R. Maguire [c,*]

[a] *Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland*
[b] *Biocatalysis Group, Almac Sciences, David Keir Building, Stranmillis Road, Belfast, BT9 5AG, United Kingdom*
[c] *Department of Chemistry & School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland*

ARTICLE INFO

Article history:
Received 4 May 2010
Accepted 11 May 2010
Available online 21 June 2010

This paper is dedicated to the memory of Sir Allen McClay and his commitment to the enhancement of human health and science from the island of Ireland.

ABSTRACT

The kinetic bioresolution of 2-nitrocyclohexanol **1** was investigated by screening a range of hydrolases both for enantioselective transesterification and for enantioselective hydrolysis of the corresponding acetate. By appropriate choice of biocatalyst and conditions, both enantiomers of *cis* and *trans* 2-nitrocyclohexanol **1** can be accessed in enantiopure form.

1. Introduction

2-Nitro alcohols constitute an important class of organic molecules as they are readily transformed into key synthetic intermediates, including 2-amino alcohols and α-hydroxy carboxylic acids, which are important chiral building blocks of many biologically active natural and synthetic products.[1–3] Access to enantiopure nitro alcohols has been principally achieved via the asymmetric Henry reaction. The first asymmetric synthesis of nitroalcohols via the Henry reaction was reported in 1992 employing a chiral metal catalyst,[4] and there has been considerable development in this approach.[5]

Despite the dramatic development of enantioselective synthesis and chromatographic separation methods, bioresolution still remains one of the most inexpensive and operationally simple methods for producing pure enantiomers on a large scale in the chemical industry. Typically the reactions are carried out under ambient and neutral conditions.[6]

The employment of a biocatalytic approach to the resolution of 2-nitro alcohols clearly has potential as hydrolase-catalysed kinetic resolutions have proved to be an efficient technique for the preparation of enantiomerically enriched compounds of this type.[7] By the appropriate choice of conditions and biocatalyst, access to the various stereoisomers of secondary alcohols can often be achieved with excellent enantiocontrol and across a wide range of substrates.[8]

To the best of our knowledge, the sole report of hydrolase-mediated kinetic bioresolution of 2-nitrocycloalkanols involved the kinetic resolution of *trans*-2-nitrocyclohexyl butyrate.[9]

Four biocatalysts were examined in the study but only the results of *Candida cylindracea* were reported. Low yields of 2-nitrocyclohexanol **1** were obtained with 20% of (*S*,*S*)-2-nitrocyclohexanol **1b** following hydrolysis of the butyrate ester and 40% (*R*,*R*)-2-nitrocyclohexanol **1b**. Enantioselectivity was high in the case of (*R*,*R*)-2-nitrocyclohexanol **1b** >98% ee. However, only 85% ee of the opposite enantiomer (*S*,*S*)-2-nitrocyclohexanol **1b** was achieved. While this preliminary study had limited success, herein we report potential access to all four enantiomers of 2-nitrocyclohexanol **1** via hydrolase-catalysed hydrolysis of 2-nitrocyclohexyl acetate **2** or hydrolase-catalysed transesterification of 2-nitrocyclohexanol **1** as shown in (Scheme 1).

2. Results and discussion

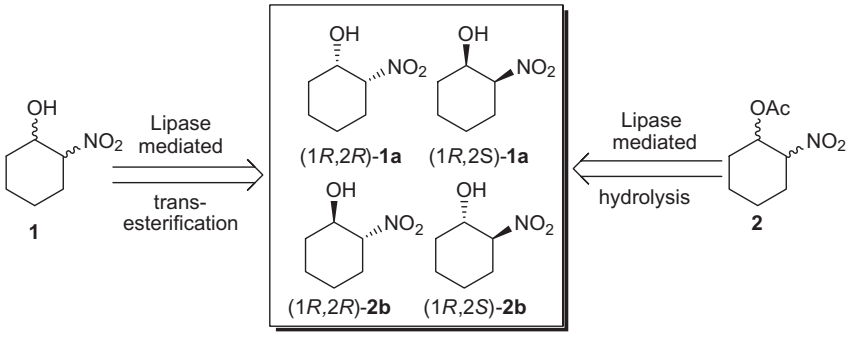
2.1. Kinetic bioresolution

The hydrolase-mediated kinetic bioresolution of both *cis*-**1a** and *trans*-2-nitrocyclohexanol-**1b** has been explored. The diastereomeric 2-nitrocyclohexanols were synthesised by sodium borohydride reduction of 2-nitrocyclohexanone **3** followed by chromatographic separation of the diastereomers (±)-**1a** and (±)-**1b** and 1-nitrocyclohex-1-ene **4**, (0.17:1:0.24, respectively) which forms as a byproduct of this reduction, but is readily removed by chromatography (see Scheme 2).

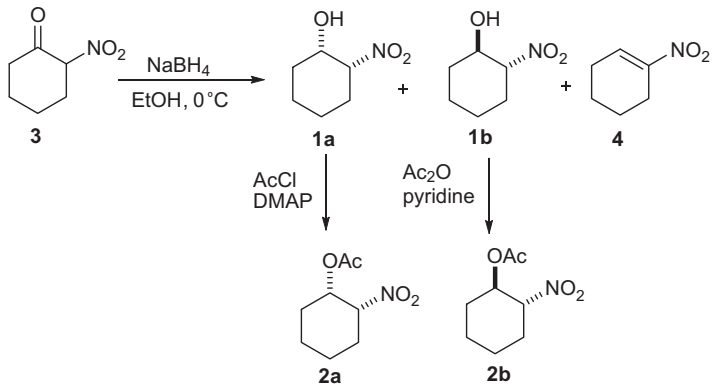
Racemic *trans*-2-nitrocyclohexyl acetate (±)-**2b** was prepared by acetylation in acetic anhydride, pyridine and a catalytic amount of dimethylaminopyridine (DMAP). However, the *cis* diastereomer (±)-**2a** required the use of acetyl chloride and an excess of DMAP. Assignment of the relative stereochemistry of the diasteromeric alcohols was enabled through comparison of the NMR data with those reported in the literature[10] and was confirmed by the

* Corresponding author. Tel.: +353 21 4901693; fax: +353 21 4901770.
E-mail address: a.maguire@ucc.ie (A.R. Maguire).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.05.006



Scheme 1. Potential access to all four enantiomers of 2-nitrocyclohexanol **1** via hydrolase-catalysed kinetic resolution.



Scheme 2. Preparation of racemic (±)-2-nitroalcohols **1** and racemic (±)-2-nitroacetates **2** employed in this study.

X-ray structure of (*R*,*R*)-*trans*-2-nitrocyclohexyl acetate (−)-**2b**. Once the racemic starting materials were prepared a chiral HPLC method was developed in order to determine the efficiency of the hydrolase-catalysed reaction with a single injection shown in (Fig. 1). Initially, experiments focused on the hydrolase-mediated transesterification of the *trans* isomer (±)-**1b** and the results of the study are summarised in (Table 1).

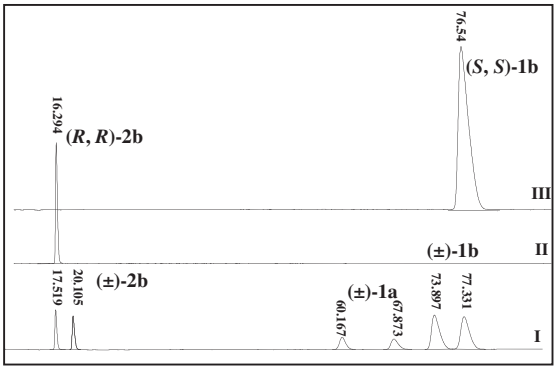


Figure 1. HPLC traces **I**: A racemic mixture of (±)-*trans*-2-nitrocyclohexylacetate **2b** and *trans* and *cis*-2-nitrocyclohexanol (±)-**1a** and (±)-**1b**, respectively. **II**: Enantiopure (*R*,*R*)-*trans*-2-nitrocyclohexyl acetate (-)-**2b** and **III**: Enantiopure (*S*,*S*)-*trans*-2-nitrocyclohexanol (+)-**1b** (conditions in experimental Section 4.2).

A number of hydrolase-catalysed acetylation conditions were examined employing a range of solvents, (ethyl acetate, *tert*-butylmethyl ether) and acyl donors, (vinyl acetate, ethyl acetate, vinyl benzoate, vinyl propionate, vinyl butyrate and isopropenyl acetate) with negligible conversions in each case. When one equivalent of vinyl acetate was employed as acyl donor with *tert*-butylmethyl ether as solvent, limited conversions were observed (<10%). However, the use of vinyl acetate as solvent and acyl donor led to the desired kinetic resolution as summarised in (Table 1).

It is clearly seen in (Table 1) that the efficiency of the kinetic resolution of (±)-**1b** varies enormously depending on the biocatalyst, which highlights the importance of screening a range of hydrolases for a specific transformation. From this screening the optimum biocatalysts for this biotransformation are *Pseudomonas fluorescens* and immobilised *Candida antarctica* lipase B.

Based on the efficient resolution achieved in the transesterification of the *trans* isomer (±)-**1b**, attention focused next on the *cis* isomer (±)-**1a** employing the optimised conditions with (±)-**1b**, that is, using vinyl acetate as solvent and acyl donor (Table 2).

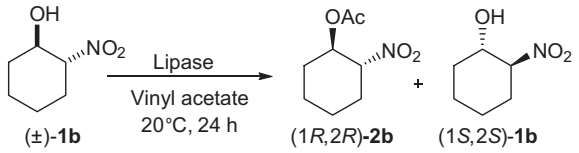
In general the efficiency of the transformation of (±)-**1a** is higher than that of the *trans* isomer (±)-**1b** and again by appropriate choice of biocatalyst it is possible to obtain the alcohol (1*S*,2*R*)-**1a** and acetate (1*R*,2*S*)-**2a** in enantiopure form.

Preparative scale transacetylation of (±)-*trans*-2-nitrocyclohexanol **1b** (2.94 mmol) was then performed with *P. fluorescens* which led to a 50% conversion after 28 h with the production of both enantiomers in >99% ee (Fig. 1). The enantiopure acetate (1*R*,2*R*)-**2b** was produced in 49% yield after column chromatography and the alcohol (1*S*,2*S*)-**1b** was produced in 48% yield.

A crystal structure determined the absolute configuration of the *trans*-2-nitrocyclohexyl acetate **2b** isolated from the scale up to be (1*R*,2*R*)-**2b** as expected[10] (see Fig. 2).

The large scale transesterification of *cis*-2-nitrocyclohexanol (±)-**1a** was next performed. Excellent enantioselectivity (>99% ee) was achieved in the production of both the acetate (1*R*,2*S*)-**2a** and the alcohol (1*S*,2*R*)-**1a**. However, upon separation of the enantioenriched products on silica gel, decomposition of the *cis* acetate (1*R*,2*S*)-**2a** to 1-nitrocyclohex-1-ene **4** was observed and neither **1a** nor **2a** could be isolated analytically pure. Therefore, while the absolute stereochemistry of **1a** and **2a** has not been confirmed it

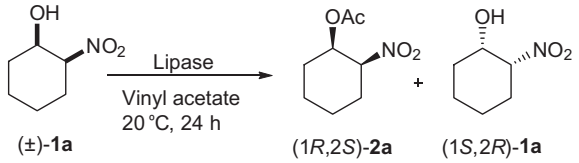
Table 1
Hydrolase-mediated transesterification of (±)-*trans*-2-nitrocyclohexanol **1b** in vinyl acetate



Enzyme strain	Conversion[a] (%)	**2b** (1*R*,2*R*) % ee	**1b** (1*S*,2*S*) % ee	*E*
Candida cylindracea C1	45	>98	80	244
Candida cylindracea C2	26	–	–	–
Rhizopus oryzae	0	–	–	–
Alcaligenes spp.	37	98	53	168
Pseudomonas cepacia	39	>98	46	156
Pseudomonas stutzeri	59	69	89	15
Rhizopus spp.	7	–	–	–
Rhizopus niveus	0	–	–	–
Aspergillus niger	0	–	–	–
Alcaligenes spp.	50	>98	91	>400
Pseudomonas cepacia P2	8	>98	6	105
Mucor javanicus	2	–	–	–
Penicillium camembertii	0	–	–	–
Pseudomonas fluorescens	50	>98	>98	>400
Mucor meihei	17	>98	32	272
Candida antarctica (lipase B)	49	>98	98	>400
Porcine pancrease II (Aldrich)	Trace	–	–	–
Pig liver esterase	0	–	–	–

[a] Conversions were determined by ^{1}H NMR spectroscopy of the crude products.

Table 2
Hydrolase-mediated transesterification of (±)-*cis*-2-nitrocyclohexanol **1a** in vinyl acetate



Enzyme strain	Conversion[a] (%)	**2a** (1*R*,2*S*) % ee	**1a** (1*S*,2*R*) % ee	*E*
Candida cylindracea C1	81	>98	>98	>400
Candida cylindracea C2	3	–	–	–
Pseudomonas cepacia P1	13	>98	16	232
Pseudomonas stutzeri	53	>98	>98	>400
Rhizopus niveus	0	–	–	–
Alcaligenes spp.	47	>98	88	>400
Pseudomonas cepacia	14	–	–	–
Mucor javanicus	0	–	–	–
Penicillium camembertii	0	–	–	–
Pseudomonas fluorescens	50	>98	>98	>400

[a] Conversions were determined by ^{1}H NMR spectroscopy of the crude products.

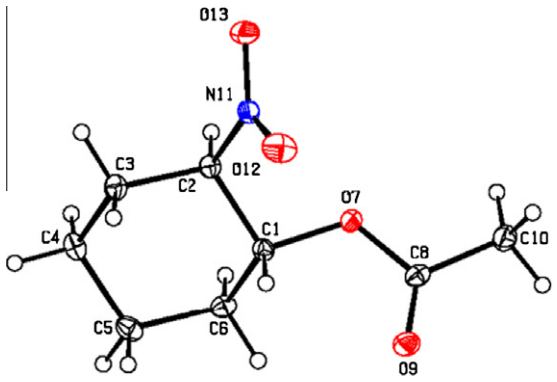


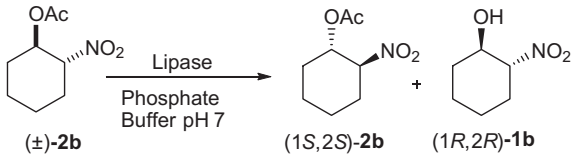
Figure 2. Crystal structure of (1*R*,2*R*)-*trans*-2-nitrocyclohexyl acetate (−)-**2b**. Atomic displacement ellipsoids are drawn at the 30% probability level.

has been assigned by analogy to the results obtained with the *trans*-**1b** isomer and is consistent with the expected stereochemical outcome.

The alternative approach of the hydrolase-mediated hydrolysis of the *trans* acetate **2b** was next explored using the series of hydrolases, the results of which are summarised in (Table 3).

Efficient kinetic bioresolution in the hydrolysis is observed with a number of hydrolases *C. cylindracea* C1, *Pseudomonas stutzeri*, *Alcaligenes* spp. and *Pseudomonas cepacia* P2. With the less efficient biocatalysts, in most instances, the alcohol formed has high enantiopurity, but the acetate is recovered with poor enantioselectivity, due to the limited extent of reaction. However, with two of the biocatalysts *C. cylindracea* C2 and *Aspergillus niger* the hydrolysis proceeds with poor stereocontrol, with the alcohol **1b** recovered with poor enantiopurity.

Table 3
Hydrolase-mediated hydrolysis of (±)-*trans*-2-nitrocyclohexanol **1b** in phosphate buffer



Enzyme strain	Conversion[a] (%)	Acetate-**2b** (1*S*,2*S*) % ee	Alcohol-**1b** (1*R*,2*R*) % ee	*E*
Candida cylindracea C1	52	>98	91	158
Candida cylindracea C2	72	100	45	16
Rhizopus oryzae	3	–	–	–
Alcaligenes spp.	48	88	93	80
Pseudomonas cepacia P1	47	88	99	>400
Pseudomonas stutzeri	50	96	92	94
Rhizopus spp.	4	–	–	–
Rhizopus niveus	2	–	–	–
Aspergillus niger	65	49	26	2.6
Alcaligenes spp.	53	99	97	>400
Pseudomonas cepacia P2	51	99	99	>400
Penicillium camembertii	>1	–	–	–
Mucor meihei	15	16	89	20
Porcine pancrease II	13	11	85	13
Porcine pancrease II	22	26	99	256
Pig liver esterase	44	75	97	148

[a] Conversions were determined by ^{1}H NMR spectroscopy of the crude products.

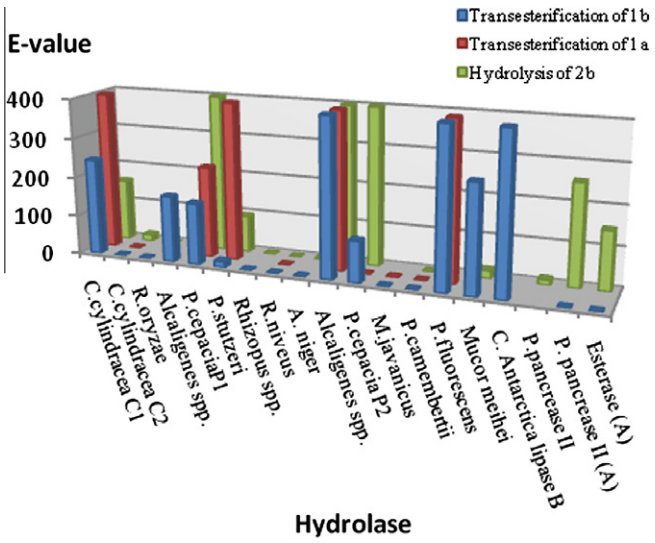


Figure 3. Plot of *E*-value versus hydrolase for **1a**, **1b** and **2a**.

Interestingly, while there is some similarity in the profiles of the efficiency of the kinetic resolution of each of the biocatalysts (Fig. 3) in the transesterification and hydrolysis processes there are also significant variations. For example, use of *P. stutzeri* leads to very efficient kinetic resolution in the transesterification of *cis*-2-nitrocyclohexanol (±)-**1a** but under the same conditions the resolution of *trans*-2-nitrocyclohexanol (±)-**1b**, is very limited.

3. Conclusion

Efficient kinetic bioresolution of both *cis* and *trans*-2-nitrocyclohexanol **1a** and **1b**, respectively, can be achieved through ester hydrolysis or hydrolase-mediated transesterification. Through the appropriate selection of biocatalyst, three of the four isomers (1*R*,2*R*)-**1b**, (1*S*,2*S*)-**1b** and (1*S*,2*R*)-**1b** were obtained directly, while hydrolysis of (1*R*,2*S*)-**2a** would potentially lead to (1*R*,2*S*)-**1b** although this is complicated by competing elimination.

4. Experimental

4.1. General procedures

A Bruker Avance 300 MHz NMR spectrometer was used to record ^{1}H (300 MHz) NMR spectra. ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 589 nm in a 10-cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^t$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}. All hydrolases used for these biotransformations were obtained from Almac Sciences. All reagents are analytical grade and purchased from Sigma–Aldrich chemical company.

4.2. Chiral HPLC analysis

Enantiomeric purity of **1** and **2** was determined by chiral HPLC analysis on a Chiralcel OJ-H column (5 × 250 mm) purchased from Daicel Chemical Industries, Japan. Mobile phase was 1% *iso*propanol in hexane; flow rate 0.9 mL/min; detection wavelength 209.8 nm. HPLC analysis was performed on a Waters alliance 2690 separations module with a PDA detector. All solvents employed were of HPLC grade.

4.3. Experimental procedures

4.3.1. Nitrocyclohexanol 1a and 1b[9]

2-Nitrocyclohexanone **3** (5.00 g, 0.035 mol) in ethanol (50 mL) was added dropwise over 10 min to a stirred suspension of $NaBH_4$ (1.32 g, 0.035 mol) in ethanol (150 mL) at 0 °C under nitrogen and stirring was continued for 5 h at 0 °C. The ice bath was removed and 10% HCl was added to adjust to pH 1. The solution was concentrated in vacuo and the resulting residue was partitioned between water (50 mL) and dichloromethane (50 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL) and the

combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture (3.89 g) of nitroalcohols **1a**, **1b** and nitrocyclohexene **4** (0.17:1:0.24, respectively) as a yellow oil. Purification by column chromatography using a (3–25%) ethyl acetate hexane gradient as eluant gave 1-nitrocyclohex-1-ene **4** as a yellow oil (490 mg, 11%); δ_H (400 MHz, $CDCl_3$) 1.60–1.67 (2H, sym m), 1.74–1.82 (2H, sym m), 2.30–2.38 (2H, sym m), 2.54–2.61 (2H, sym m), 7.31–7.35 (1H, sym m). (less polar) (±)-*cis*-2-nitrocyclohexanol **1a** (520 mg, 10%); δ_H (300 MHz, $CDCl_3$) 1.19–2.31 (8H, m), 2.57 (1H, d, *J* 3.9), 4.34–4.41 (1H, m), 4.51 (1H, br s) and (±)-*trans*-2-nitrocyclohexanol **1b** (2.54 g, 50%); δ_H (300 MHz, $CDCl_3$) 1.12–1.46 (3H, m), 1.70–1.89 (3H, m), 2.04–2.17 (1H, m), 2.25–2.40 (1H, m), 2.85 (1H, br s), 4.06 (br s), 4.18–4.42 (1H, m).

4.3.2. (±)-*cis*-2-Nitrocyclohexyl acetate 2a[11]

(±)-*cis*-2-Nitrocyclohexanol **1a** (1.00 g, 6.88 mmol) and acetyl chloride (5.0 mL, 0.07 mol) were stirred in CH_2Cl_2 (35 mL) under nitrogen and *N*,*N*-dimethylaminopyridine (1.2 mg, 10.32 mmol) was added and stirring was continued at room temperature for 12 h. Aqueous $NaHCO_3$ (satd, 20 mL) was added and the mixture was transferred to a separation funnel. The aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a crude acetate **2a** (0.90 g, 70%) δ_H NMR (300 MHz, $CDCl_3$) 1.30–1.45 (1H, m), 1.49–1.66 (3H, m), 1.89–2.00 (1H, m), 2.08 (3H, s), 2.11–2.19 (3H, m), 4.42–4.49 (1H, m), 5.56–5.61 (1H, m). (7% *trans* acetate **2b** was observed in the product). Purification was not possible due to the partial formation of the elimination product **4** on exposure to silica gel.

4.3.3. (±)-*trans*-2-Nitrocyclohexyl acetate 2b[11]

N,*N*-Dimethylaminopyridine (12.9 mg, 0.10 mmol) was added to a stirring solution of (±)-*trans*-2-nitrocyclohexanol **1b** (1.54 g, 10.6 mmol), acetic anhydride (7.0 mL) and pyridine (3.5 mL) in dichoromethane (35 mL). The mixture was stirred at room temperature for 20 h under nitrogen. Aqueous $NaHCO_3$ (satd) (20 mL) was added to quench the reaction. The solution was transferred to a separating funnel and washed with aqueous $CuSO_4$ (satd), water, aqueous $NaHCO_3$ (satd) and brine (30 mL each) and dried over $MgSO_4$. The resultant solution was concentrated in vacuo to produce the acetate **2b** as a white crystalline solid; mp 40–42 °C, (1.65 g, 83%). δ_H (300 MHz, $CDCl_3$) 1.26–1.55 (3H, m), 1.75–1.94 (3H, m), 2.01 (3H, s), 2.17–2.28 (1H, m), 2.32–2.42 (1H, m), 4.46–4.57 (1H, m), 5.17–5.26 (1H, ddd appears as a dt, *J* 4.8, 10.5).

4.3.4. Hydrolase-mediated transesterification of (±)-*trans*-2-nitrocyclohexanol 1b with vinyl acetate as solvent and acyl donor

A standard solution of (±)-*trans*-2-nitrocyclohexanol **1b** (360 mg, 2.48 mmol) in vinyl acetate (18 mL) was prepared and aliquots (1 mL, 0.14 M, 0.13 mmol of **1b**) were dispensed into 18 test tubes. A spatula tip of enzyme (~5-10 mg) was added, shaken at 750 rpm for 24 h at room temperature and 40 °C for a further 3 h. The solution was filtered and concentrated in vacuo. The sample was analysed by ^{1}H NMR spectroscopy, reconcentrated and dissolved in a mixture of hexane:*iso*-propyl alcohol (90:10 HPLC grade) and enantioselectivity determined by chiral HPLC. The results of the screening are summarised in (Table 1).

4.3.5. Hydrolase-mediated transesterification of (±)-*cis*-2-nitrocyclohexanol 1a with vinyl acetate as both acyl donor and solvent

A standard solution of (±)-*cis*-2-Nitrocyclohexanol **1a** (200 mg, 1.37 mmol) in vinyl acetate (10 mL) was prepared and aliquots (1 mL, 0.14 M, 0.13 mmol of **1a**) were dispensed into 10 test tubes. A spatula tip of each enzyme (~5–10 mg) was added and this was shaken at 750 rpm for 24 h at room temperature and 40 °C for 3 h. The solution was filtered and concentrated in vacuo. The sample was analysed by ^{1}H NMR spectroscopy, reconcentrated and dissolved in a mixture of hexane:*iso*-propyl alcohol (90:10 HPLC grade) and enantioselectivity determined by chiral HPLC. Enantiomeric excess was only determined for conversions above 10%. The results of the screening are summarised in (Table 2).

4.3.6. Hydrolase-mediated hydrolysis of (±)-*trans*-2-nitrocyclohexylacetate 2b

A standard solution of (±)-*trans*-2-nitrocyclohexylacetate **2b** (320 mg, 1.70 mmol) in *tert*-butylmethyl ether (4 mL) was prepared and aliquots (250 μL, 0.42 M, 0.10 mmol of **2b**) were dispensed between 16 test tubes. Phosphate buffer (1 mL) at pH 7 and a spatula tip of enzyme (~5-10 mg) were added to each test tube which was then sealed and shaken at 750 rpm for 24 h at room temperature. Diethyl ether (1 mL) was added and the layers were separated. The organic layer was filtered and concentrated in vacuo. The crude product was analysed by ^{1}H NMR spectroscopy, reconcentrated and dissolved in a mixture of hexane:*iso*-propyl alcohol (90:10 HPLC grade) and enantioselectivity determined by chiral HPLC. The results of the screening are summarised in (Table 3).

4.3.7. Preparative scale transesterification of (±)-*trans*-2-nitrocyclohexanol 1b

P. fluorescens (80 mg) was added to (±)-*trans*-2-nitrocyclohexanol (830 mg, 5.71 mmol) in vinyl acetate (10 mL) and this was shaken at 750 rpm for 28 h at room temperature. The solution was filtered through a pad of Celite and the mother liquor concentrated in vacuo to produce a clear oil (932 mg). Purification by column chromatography using (3–25%) ethyl acetate in hexane gradient as eluant gave acetate (1*R*,2*R*)-**2b** as a white crystalline solid; mp 41–43 °C, $[\alpha]_D^{20} = -40.65$ (*c* 1.0, CH_2Cl_2), >98% ee, (520 mg, 97%) and (1*S*,2*S*)-**1b** $[\alpha]_D^{20} = +48.6$ (*c* 1.0, CH_2Cl_2), >98% ee, lit.[9] $[\alpha]_D^{20} = +43.3$ (*c* 1.0, CH_2Cl_2) 85% ee, (400 mg, 96%). ^{1}H NMR spectra were identical to those of the racemic materials previously prepared.

A sample of (1*R*,2*R*)-**2b** was recrystallised from a dichloromethane hexane (50:50) mixture. X-ray diffraction measurements for **2b** were made on a Bruker APEX II DUO diffractometer using graphite-monochromatised MoKα radiation (λ = 0.71073 Å) and cooled with an Oxford Cryosystems COBRA fitted with a N_2 generator. All calculations were made using the APEX2 software,[12,13] and the diagrams prepared using PLATON.[14] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC No. 771829. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was carried out with the financial support of IRCSET and Pfizer. Nuala Maguire and Tom O' Mahony are acknowledged for their technical assistance.

References

1. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
2. Groger, H. *Adv. Synth. Catal.* **2001**, *343*, 547–558.
3. Noboru, O. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
4. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.
5. Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.

6. (a) Moody, T. S.; Taylor, S. J. C. *Speciality Chem.* **2009**, *Jan*, 51–53; (b) Moody, T. S.; Taylor, S. J. C. *Sp2 Mag.* **2009**, *Dec*, 30–32; (c) Ou, L.; Xu, Y.; Ludwig, D.; Pan, J.; Xu, J. H. *Org. Process Res. Dev.* **2008**, *12*, 192–195; (d) Park, O.-J.; Lee, S.-H.; Park, T.-Y.; Chung, W.-G.; Lee, S.-W. *Org. Process Res. Dev.* **2006**, *10*, 588–591; (e) Yazbeck, D.; Derrick, A.; Panesar, M.; Deese, A.; Gujral, A.; Tao, J. *Org. Process Res. Dev.* **2006**, *10*, 655–660.
7. (a) Bornscheuer, U. R.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*, 2nd ed.; John Wiley & Sons, 2006; (b) Moody, T. S.; Brossat, M.; Taylor, S. J. C.; Wiffen, J. W. *Tetrahedron: Asymmetry* **2009**, *18*, 2112–2116; (c) Brossat, M.; Moody, T. S.; de Nanteuil, F.; Taylor, S. J. C.; Vaughan, F. *Org. Process Res. Dev.* **2009**, *13*, 706–709.
8. Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140.
9. Honig, H.; Seuferwasserthal, P.; Fulop, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2341–2345.
10. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665; Kazlauskas, R. J. *Trends Biotechnol.* **1994**, *12*, 464–472.
11. Borisenko, A. A.; Nikulin, A. V.; Wolfe, S.; Zefirov, N. S.; Zyk, N. V. *J. Am. Chem. Soc.* **1984**, *106*, 1074–1079.
12. APEX2 v2009.3-0, Bruker AXS, 2009.
13. Sheldrick, G. M. *Acta Cryst. A* **2008**, *64*, 112–122.
14. Spek, A. L. *PLATON*; University of Utrecht: The Netherlands, 2000.