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# Accepted Manuscript




Dynamic kinetic resolution of 2-methyl-2-nitrocyclohexanol: Combining the intramolecular nitroaldol (Henry) reaction & lipase catalysed resolution

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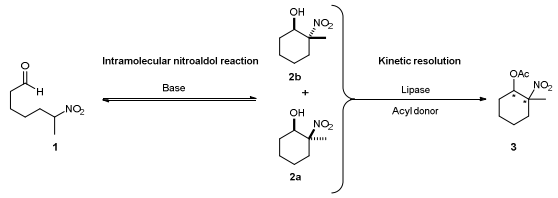
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## Graphic Abstract




Herein, we describe the development of a reversible intramolecular base catalysed Henry reaction coupled with the hydrolase mediated kinetic resolution with the view to selective acetylation of a single stereoisomer is described.

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# Dynamic Kinetic Resolution of 2-Methyl-2-nitrocyclohexanol: Combining the Intramolecular Nitroaldol (Henry) Reaction & Lipase Catalysed Resolution

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## Abstract

Efforts to combine the intramolecular nitroaldol reaction with lipase-catalysed resolution of the resulting nitroaldol adduct in a one-pot dynamic kinetic resolution (DKR) are described. Significant challenges were encountered in the combination of the two systems. *trans*-2-Methyl-2-nitrocyclohexyl acetate (±)-**3b** was isolated in excellent enantiopurity (>98% *ee*) *via* a sequential DKR sequence where the lipase-mediated resolution and base-mediated interconversion of 2-methyl-2-nitrocyclohexanol **2** were effected alternately, demonstrating the feasibility of this approach initially. Further work showed, for the first time, evidence that a DKR-type system is possible for **2**. Reaction engineering allowed the design of a sequential one-pot reaction system which furnished the products with excellent enantioselectivity, and good diastereoselectivity.


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**Keywords:**

Biocatalysis

Kinetic Resolution

Henry reaction

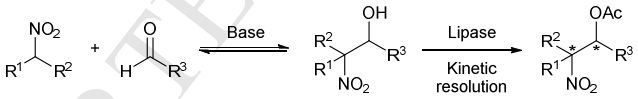
Dynamic Kinetic Resolution

Lipases

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# 1. Introduction

The Henry reaction is an important base-mediated transformation in organic chemistry leading to vicinal nitroalcohols (*Scheme 1*), which can be converted into a wide variety of synthetic intermediates, such as 1,2-aminoalcohols and α-hydroxycarboxylic acids.[1-3] Although the reaction is known for decades, stereo- and diastereoselective approaches leading to enantiomerically pure nitroalcohols are still challenging. Principal approaches to the catalytic asymmetric nitroaldol reaction, including transition metal- and organo-catalysed methods, have been reviewed in detail.[2, 4, 5] In the past decade, there has been an emergence of biocatalytic protocols to resolve the products of the Henry reaction due to their mild reaction conditions and high selectivity.[6] There are two distinct biocatalytic methods; direct enzyme-catalysed (hydroxynitrile lyases) asymmetric nitroaldol reaction[7] or initial chemical formation of the *β*-nitroalcohol product followed by enzymatic kinetic resolution of the resulting stereoisomers. The latter suffers from the limitation of attaining a maximum theoretical yield of 50%. In recent years, we have developed an effective protocol for kinetic resolution of 2-nitrocyclohexanol **5**.[8] In this study, we attempted to develop a dynamic kinetic resolution for compound **5**, and expanded it to 2-methyl-2-nitrocyclohexanol **2**.

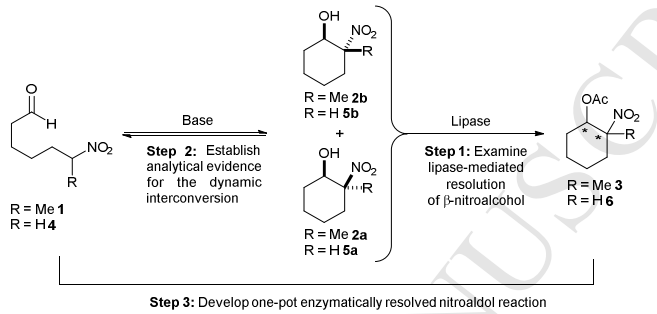



*Scheme 1 DKR of the nitroaldol through lipase catalysis*

Previously, Vongvilai *et al* have developed a procedure for the intermolecular dynamic kinetic resolution of β-nitroalcohols, but this was limited by the need to use a large excess of the nitroalkane in order to shift the equilibrium towards the formation of the product.[9, 10] In our current study, we have the added challenge of a second stereocentre, leading to potential complexity in stereocontrol.

Herein, we report our studies, combining the reversible intramolecular base-catalysed nitroaldol reaction of 6-nitroheptanal **1** with a one-pot lipase-mediated acetylation and kinetic resolution of the subsequent *β*-nitroalcohol **2** leading to 2-methyl-2-nitrocyclohexyl acetate **3** with moderate

diasteroselectivity but excellent enantiopurity (*Scheme 2*). Ideally, this DKR would provide exclusive access to a single stereoisomer of **3**. To date limited research has been carried out in this area, and while the viability of a one-pot reaction combining the Henry reaction with enzyme-mediated dynamic resolution has previously been described, it is evident that there are significant limitations to be overcome before this protocol has a broad synthetic utility.[9-11]



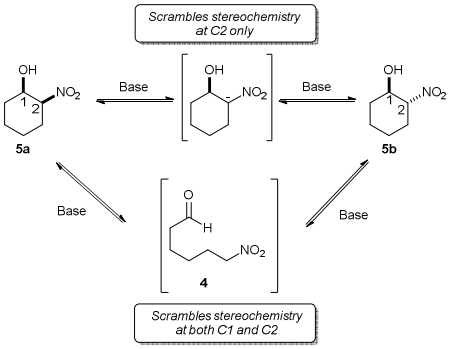

*Scheme 2 Stepwise investigation of the DKR of the intramolecular nitroaldol reaction through lipase catalysis*

## 2. Results and Discussion

### 2.1 Diastereoselective lipase-mediated transesterification

We have previously reported efficient kinetic bioresolution for both the *cis*- and *trans*-2-nitrocyclohexanols (±)-**5a** and (±)-**5b** *via* enzyme-mediated transesterification and ester hydrolysis.[8] While base-mediated interconversion of *cis*- and *trans*-2-nitrocyclohexanol (±)-**5a** and (±)-**5b** is readily established, initially believed to indicate reversible nitroaldol reaction, detailed investigation demonstrated that the interconversion was complicated due to competing epimerisation *via* deprotonation geminal to the nitro group (Scheme 3). Critically, when enantiopure *cis*- and *trans*-2-methyl-2-nitrocyclohexanol (±)-**5a** and (±)-**5b** are individually exposed to base, interconversion of (±)-**5a** and (±)-**5b** is seen but without stereochemical scrambling at C(1)OH centre. This can only be rationalised by deprotonation at the C(2)$NO_2$ centre, rather than a retro-Henry reaction. The interconversion of (±)-**5a** and (±)-**5b** *via* the reversible nitroaldol reaction is essential for a DKR approach as the alternative deprotonation pathway does not enable racemisation at the cyclohexanol

stereogenic centre but only affects the centre bearing the nitro substituent. The complication of the competing pathway prevented the development of a one-pot intramolecular nitroaldol reaction of 6-nitrohexanal **4** with dynamic kinetic lipase-mediated resolution of 2-nitrocyclohexanol **5** (*Scheme 2*).




*Scheme 3 Epimerisation pathway versus the reversible nitroaldol reactions*

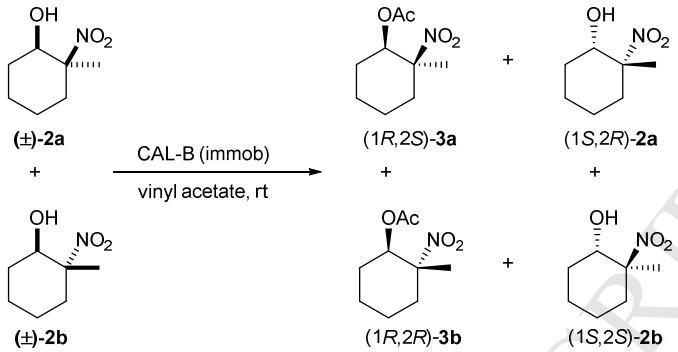
Therefore, use of a modified substrate, 2-methyl-2-nitrocyclohexanol **2**, was investigated, as it was envisaged that this would avoid base-mediated epimerisation at C2 due to the presence of the methyl moiety and, consequently, interconversion of the *cis*- and *trans*-2-methyl-2-nitrocyclohexanol (±)-**2a** and (±)-**2b** can only occur through ring opening and closing of the aldehyde 6-nitroheptanal **1**.

The bioresolution of an intramolecular nitroaldol reaction of 6-nitroheptanal **1** was investigated in a stepwise manner (**Scheme 2**). The first step in this study involved independent examination of the lipase-mediated kinetic resolution of the racemic *cis*- and *trans*-2-methyl-2-nitrocyclohexanols (±)-**2a** and (±)-**2b** identifying the most efficient lipase to perform this biotransformation enantioselectively and diastereoselectively. Ideally, for an efficient dynamic process, one enantiomer of either (±)-**2a** or (±)-**2b** would be efficiently and selectively acetylated. The alcohol substrates (±)-**2a** and (±)-**2b** were obtained by sodium borohydride reduction of 2-methyl-2-nitrocyclohexanone,[12, 13] while subsequent acetylation with acetic anhydride in DCM with pyridine & catalytic DMAP gave the novel racemic acetates (±)-**3a** and (±)-**3b**. The relative stereochemistry of (±)-**3a** was confirmed by X-ray crystallography. The optimum reaction conditions reported for the kinetic resolution of *cis*- and *trans*-2-nitrocyclohexanol (±)-**5a** and (±)-**5b** employing vinyl acetate as both solvent and acyl donor were applied in this study for the lipase-mediated transesterification of **2**.[8]

Following a screen using a targeted panel of lipases, several potential lead enzymes were identified (full detail included in SI). *Candida antartica* lipase B (immob) (CALB immob) was chosen as the lipase to continue the investigation as it gave moderate selectivity (5:1, after 12 hours) for acetylation of (±)-**2a** over (±)-**2b** as well as excellent enantioselectivity (>98% *ee*) for both diastereomers. **Table 1** shows the selectivity over time, with acetate (±)-**3b** being the preferred product initially, but with longer reaction times a relative increase in (±)-**3a** is observed as (±)-**2b** is depleated.

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Table 1 *Diastereoselective CAL-B (immob) mediated transesterification of* cis- *and* trans-*2-methyl-2-nitrocyclohexanol* ***(±)-2a*** *and* ***(±)- 2b*** *in vinyl acetate*




| Enzyme Source | Reaction Time | Alcohol **2** | | Acetate **3** | |
|---|---|---|---|---|---|
| | | *cis*-**2a** (%)[a] | *trans*-**2b** (%)[a] | *cis*-**3a** (%)[a] | *trans*-**3b** (%)[a] |
| CAL-B (immob) | 12 h | 44 | 38 | 3 | 15 |
| | 18.5 h | 43 | 36 | 4 | 17 |
| | 40.5 h | 41 | 30 | 6 | 23 |
| | 62.5 h | 27 (15% *ee*[b],[c]) | 30 (74% *ee*[b],[d]) | 11 (>98% *ee*[b],[e]) | 32 (>98% *ee*[b],[f]) |

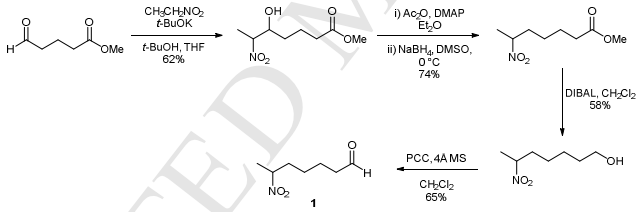
[a]Conversions were estimated by $^1$H NMR spectroscopy and were derived from integration of the $^1$H NMR spectrum of the mixture of the crude material. Starting material was an equimolar mixture of *cis*-**2a** and *trans*-**2b** [b]Enantiomeric excess [*ee* (%)] was determined by chiral HPLC analysis [Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 97:3, flow rate 0.75 mL/min, ambient temperature, injection volume 10 μL, λ = 209.8 nm]. [c]The principal enantiomer was (1*S*,2*R*)-*cis*-2-methyl-2-nitrocyclohexanol (1*S*,2*R*)-**2a**. [d]The principal enantiomer was (1*S*,2*S*)-*trans*-2-methyl-2-nitrocyclohexanol (1*S*,2*S*)-**2b**. [e]The principal enantiomer was (1*R*,2*S*)-*cis*-2-methyl-2-nitrocyclohexyl acetate (1*R*,2*S*)-**3a**. [f]The principal enantiomer was (1*R*,2*R*)-*trans*-2-methyl-2-nitrocyclohexyl acetate (1*R*,2*R*)-**3b**.

We also explored the use of acylating agents other than vinyl acetate (details included in SI) in conjunction with CAL-B (immob). While vinyl acetate and phenyl acetate performed equally well, including over longer reaction times (48 h), use of the higher boiling phenyl acetate did not offer any synthetic advantages and was difficult to separate from the product.

## 2.2 Dynamic interconversion process

Crucial to the success of the lipase-mediated DKR protocol is selection of the correct base. The fundamental requirement of the selected base is to mediate reversible ring closure of 6-nitroheptanal **1** and thus catalyse the dynamic interconversion process between the diastereomeric alcohols (±)-**2a** and (±)-**2b**. It was then envisaged that combination with the diastereoselective lipase-mediated transesterification (as discussed above) would lead to a one-pot DKR of the intramolecular nitroaldol reaction through lipase catalysis.

The novel aldehyde **1** was synthesised *via* a base-catalysed nitroaldol reaction with nitroethane and methyl 5-oxopentanoate. Subsequent reductive elimination of the *β*-nitroalcohol generated the nitroalkane.[14] Finally the aldehyde **1** was readily accessible *via* reduction of the ester (**Error! Reference source not found.**).

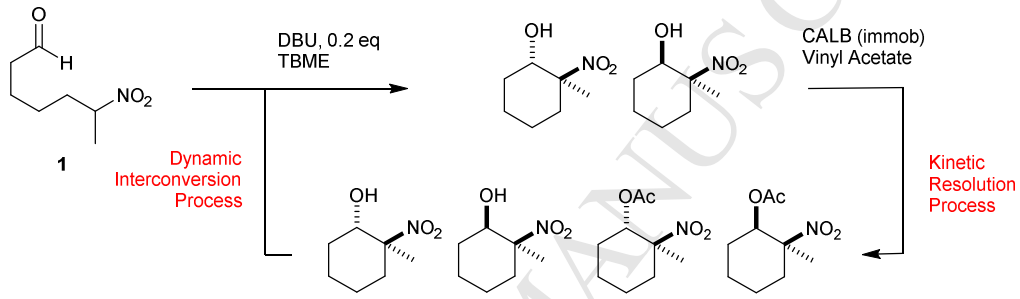



*Scheme 4 Synthesis of 6-nitroheptanal **1***

As vinyl acetate had been utilised for the lipase-mediated transesterification in both the analytical and synthetic-scale, the base-mediated investigation was effected in the same solvent to ultimately enable combination of the two processes in a single pot. Therefore, a series of bases was screened with 6-nitroheptanal **1** in vinyl acetate, (details in SI) and although there was evidence of a small amount of background chemical acylation, DBU was chosen as the base for the intramolecular Henry reaction.

## 2.3 Two-pot kinetic resolution process

A two-pot reaction was carried out, where the reaction mixture was alternately exposed to the cyclisation/interconversion conditions and the resolution conditions, with a work up in between to remove the previous catalyst (Scheme 5). This overcame the problem of competing chemical acylation, and base-lipase inhibition by physically separating the two reactions. This ultimately returned the preferred product (±)-**3a** with excellent enantiopurity (>98% *ee*) which made up 57% of the reaction mixture (see SI, Table 9).




*Scheme 5 Two-pot process*

## 2.4 Two-Pot System: Influence of Solvents and Immobilized Base

Details of early attempts to develop a one-pot process are described in the SI. Several problems were evident and needed to be overcome to effectively combine the two systems. The background chemical acylation was problematic in the presence of DBU, even at low concentrations. Accordingly, as use of vinyl acetate as the solvent was not viable in this process, reduced loading and the use of an organic solvent would need to be explored. Additionally, in one pot processes containing both the base and the lipase, neither the interconversion nor the resolution were effective due to interactions between the base and the lipase, leading to base-lipase inhibition.

It was decided to look again at the two separate transformations (the base-mediated interconversion and the resolution) and focus on optimising each part, building on insight generated at this point to address the unresolved problems. As one of the best bases for the interconversion was DBU,

immobilised DBU was explored to determine if a heterogenous base would overcome the problem of base-lipase inhibition, and to facilitate separation. Similarly, CAL-B (immob) was chosen as the lipase.

Solvent screens were carried out for both the interconversion, and the resolution processes separately. In addition to this, the vinyl acetate loading was initially reduced to 50 equivalents. We found that the resolution, mediated by CAL-B (immob), performed well in non-polar solvents (toluene & hexane) (See SI, Table 10, entries 1 & 2) while the interconversion is also conveniently favoured by these non-polar solvents (See SI, Table 11). Sampling was more reliable using toluene as solvent than using hexane, in which the substrates and products were poorly soluble. In addition, the rate of interconversion of (±)-**2a** to (±)-**2b** in toluene was increased relative to the rate in neat vinyl acetate. Interestingly, while the interconversion catalysed by DBU (immob) was sluggish in ethyl acetate (See SI, Table 11, Entry 6), this solvent furnished us with excellent diastereomeric discrimination (1:11) in the resolution step (See SI, Table 10, Entry 6).

Further decreasing concentration of vinyl acetate, as a solution in toluene, as anticipated, significantly reduced the issue of background chemical acylation (5 eq. of vinyl acetate gave <5% chemical acylation after 12 hours). Notably, the kinetic resolution was equally effective with vinyl acetate loading as low as 3 eq. of vinyl acetate in toluene as the earlier resolution with 50 eq. vinyl acetate in toluene.

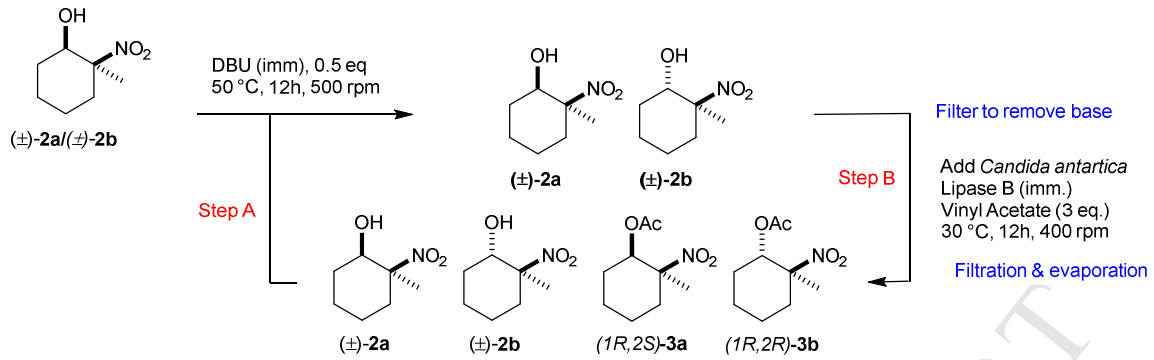
It was found that 30 °C was the optimum temperature for the resolution step. Although at higher temperature (50 °C) the enantioselectivity was still excellent, the diastereoselectivity was not maintained. The interconversion was more efficient at 50 °C than at the lower temperature, as anticipated.

## 2.5 Cycling System

Following this, a series of one-pot and two-pot reactions were attempted with the same solvent conditions for both the interconversion and the resolution. (See SI, Table 14).

The first reactions attempted examined the two processes at 50°C, without and with removal of the base before addition of the lipase by a simple filtration through Celite® (See SI, Table 14, Entry 1 & 2). This allowed us to carry out the interconversion first, to enrich a predominately (±)-**2a** sample to give us more of the enzymatically favoured (±)-**2b** diastereomer. A reaction was also carried out in which both catalysts were introduced at the same time (see SI, Table 14, Entry 3); inhibition of the base-mediated interconversion in the presence of the lipase was observed and this was overcome in entry 1 & 2 by delayed addition of the lipase. These experiments showed, for the first time, evidence of a dynamic system when both the base and the lipase were present together, albeit this required a time-delayed addition of the biocatalyst, key to the success of this system.

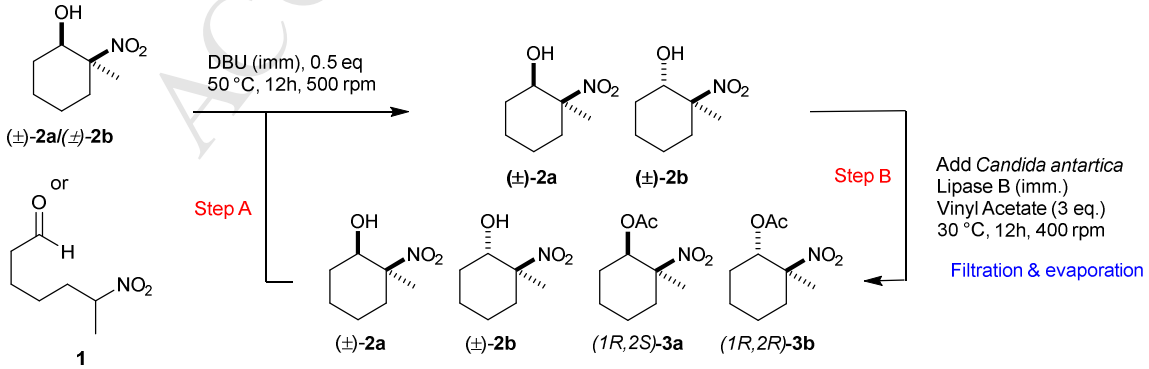
Further attempts to design the one-pot reaction focussed on a model circular flow system (Scheme 6), where each reaction was carried out in a separate vessel with the previous catalyst [DBU (immob) or CALB (immob)] removed by filtration before exposure to the next. This allowed us to carry out the two individual reactions while physically separating the two catalysts. The reaction mixture was cycled through each chamber in turn. Evaporation of the solvent and vinyl acetate from the reaction mixture prior to reexposure to the base was undertaken to avoid chemical acylation. Nevertheless, it was shown that when the evaporation step was omitted i.e. vinyl acetate was carried over to the DBU step, only a modest decrease in enantioselectivity was observed. Details of these reactions are included in the SI.




*Scheme 6 Cycling system, separating the catalysts*

Table 2 shows the optimised one-pot procedure (similar experiments shown in SI, Table 16) where the reaction material was alternately exposed to the interconversion conditions and the resolution conditions, and cycled through three times. It was found that the addition of the catalysts needed to be staggered, as DBU (immob) is less effective in the presence of CAL-B (immob) (see SI Table 16, Entry 3) . DBU (immob) was added first, in this case interconversion was carried out for 32 h at 50 °C for step 1A, although it was subsequently shown that 32 hours was not required and that the same (±)-**2a**: (±)-**2b** ratio (~36:64) was reached after only 18 hours; critically, due to staggered addition of reagents, it was possible to conduct the interconversion at 50 °C and then cool the reaction mixture to 30 °C for the lipase-mediated resolution, carried out in the same reaction vessel, with the vinyl acetate and the CAL-B (immob) added after the interconversion and cooling to 30 °C.

*Table 2 One-pot reaction*




| Entry | Step[a] | Alcohol 2[b] | Acetate 3[b] |
|---|---|---|---|

| | | *cis*-**2a** | *trans*-**2b** | *cis*-**3a** | *trans*-**3b** |
|---|---|---|---|---|---|
| **1** | 1A | 36 (4) | 64 (0) | 0 (-) | 0 (-) |
| | 1B | 18 (39) | 27 (>98) | 14 (>98) | 41 (>98) |
| | 2A | 16 (16) | 27 (7) | 17 (92) | 40 (97) |
| | 2B | 17 (16) | 25 (62) | 16 (97) | 43 (98) |
| | 3A | 9 (7) | 21 (13) | 19 (94) | 51 (97) |
| | 3B | 11 (55) | 17 (87) | 18 (97) | 53 (96) |

[a]Reaction conditions: Each step was 12 hours except **1a**, which was 32 hours. Step A was carried out at 50 °C, 500 rpm, Step B was carried out at 30 °C, 400 rpm. The reaction mixture was filtered through a plug of Celite® to remove the immobilised catalysts after the resolution (step B). 3 equivalents of vinyl acetate were added with the CAL-B (immob). [b]Expressed as a % estimated by integrating of the relevant $^1$H NMR signals. Numbers in parenthesis are % *ee* values, which were determined by chiral HPLC analysis [Daicel OJ-H, hexane/*i*-PrOH = 98.5:1.5, flow rate 0.5 ml/min, ambient temperature, injection volume = 10 µL, λ = 209.8 nm].

The final ratio of the products and substrates show, that, although not a traditional one-pot reaction, a modular circular system has been engineered, through extensive optimisation of the individual steps.

The starting material used was a mixture of (±)-**2a** and (±)-**2b** (87:13) instead of aldehyde **1**. In the presence of DBU only, aldehyde **1** will cyclise, and in this case, the mixture of nitroalcohols **2** or aldehyde **1** would be expected to give the same outcome under the conditions for step 1A.

These results are promising, showing, for the first time, a one-pot, dynamic system for the resolution of alcohol **2**. While this is not the desired one-pot reaction, it represents a significant move towards a one-pot procedure. In order to achieve this, several parameters were examined and their role evaluated. Filtration (after step B) is necessary to remove the immobilised catalysts, but does not need to be carried out after each step (A&B), only the end of each cycle (after step B). Sequential addition of the catalysts was found to be key to this one-pot procedure, where the immobilised base was added to the reaction mixture first, to allow interconversion to be carried out, followed by the introduction of the immobilised lipase, to carry out the resolution. While the evaporation step (after B) was shown to give better enantiopurity after three cycles as well as more product (~60% vs ~50%) than without vacuum step, it could be removed if necessary to simplify the procedure.

## 3. Conclusion

Significant progress has been made in the individual elements of the dynamic resolution process for *trans*-**3b**. Efficient kinetic resolution has been effected for both the *cis*-2-methyl-2-nitrocyclohexanol (±)-**2a** and *trans*-2-methyl-2-nitrocyclohexanol (±)-**2b**. CAL-B (immob) acelated both (±)-**2a** & (±)-**2b** in the ratio of ca. 10:30, with excellent enantioselectivity. Furthermore, the lipase-mediated transesterification of both (±)-**2a** and *trans*-**2b** have been performed on a preparative-scale yielding (1*S*,2*S*)-**2b**, (1*R*,2*S*)-**3a** and (1*R*,2*R*)-**3b** in excellent enantiopurity (≥98% *ee*). A series of bases has been screened and DBU was identified to mediate the intramolecular nitroaldol reaction and associated dynamic interconversion process. However, background chemical acetylation in the presence of vinyl acetate and lipase-mediated base inhibition presented significant barriers to the development of a one-pot DKR process. Clearly, screening a larger range of enzymes, both wild type and engineered enzymes, offers potential for an enhanced DKR protocol.

A sequential two-pot DKR process was developed whereby the dynamic interconversion process was performed independently of the lipase-mediated kinetic resolution. Good diastereoselectivity was observed with CAL-B (immob) and the transesterification of the *trans*-2-methyl-2-nitrocyclohexanol (±)-**2b** was the dominant kinetic resolution process. The *trans*–acetate (1*R*,2*R*)-**3b** was the major component (57%) of the reaction mixture and and isolated in excellent enantiomeric excess (≥98% *ee*).

Following this, the conditions were further explored, focussing on conditions which work for the individual parts. Conditions were developed which furnished us with a dynamic system albeit with poor efficiency. Key to this was the timing of the reagent addition, by first adding the base, to carry out the interconversion, then the lipase for the resolution, we successfully demonstrated a dynamic system was possible (Table 2).

Achieving DKR in the intramolecular nitroaldol is extremely challenging due to the number of competing processes arising. By careful exploration of the process conditions including variation of

biocatalyst, base and solvent we have demonstrated for the first time the feasibility of this process. In addition to careful analysis of the reaction conditions for each individual step in this process, introduction of the methyl group in (±)-**2a** and (±)-**2b** to avoid epimerisation *via* deprotonation as seen in (±)-**5a** and (±)-**5b** was critical to the success of this outcome. Investigation of the potential to enhance this through continuous flow is currently underway.

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# 4. Experimental Section

## 4.1 General procedures

Dichloromethane was distilled from phosphorus pentoxide. Ethanol was distilled from magnesium ethoxide. Infrared spectra were recorded as films on NaCl plates or as KBr discs. Melting points are uncorrected. NMR spectra were recorded on a 300 MHz or 600 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. $^1$H-$^1$H and $^1$H-$^{13}$C correlations were used to confirm the NMR peak assignments. HRMS was performed on a TOF instrument in electrospray ionization (ESI) mode; samples were made up in acetonitrile. Elemental analysis was performed using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Enantiomeric excess were measured by HPLC, using a Chiralcel® OJ-H column (5 × 250 mm) from Daicel Chemical Industries Limited. Mobile phase, flow rate, detection wavelength and temperature are included in the appropriate tables. HPLC analysis was performed on a Waters alliance 2690 separations module with a PDA detector. When only one single enantiomer could be detected, the enantiomeric excess is quoted as >98%. 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. $[\alpha]_D^{20}$is the specific rotation of a compound and is expressed in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. All lipases were kindly donated by Almac Sciences. Single crystal X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer fitted with an Oxford Cryosystems COBRA for controlling the sample temperature. Mo Kα radiation (λ = 0.7107 Å, graphite monochromator) was used for (±)-**3a** and Cu Kα radiation (λ = 1.5418 Å, doubly curved silicon crystal monochromator) was used for (1*R*,2*S*)-**3a**. Analysis was undertaken with the SHELX suite of programs[15] and diagrams prepared with Mercury 3.0.[16] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or they were located and refined with isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 969530 and 969531.

These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

### 4.2 Synthesis of racemic substrates

#### **4.2.1** 2-Methyl-2-nitrocyclohexanone[13]

2-Nitrocyclohexanone (2.50 g, 17.47 mmol) in dichloromethane (19 mL) was added in one portion to a stirred solution of tetrabutylammonium hydroxide (11.33 g, of a 40% aq. solution, 17.47 mmol) in water (17 mL) under nitrogen. The reaction mixture was stirred for 10 min, and then methyl iodide (4.4 mL, 69.87 mmol) was added in one portion. The reaction mixture was stirred vigorously for 36 h at room temperature. The reaction mixture was then transferred to a separating funnel and layers separated. The organic layer was washed with water (20 mL). The aqueous phase was extracted with dichloromethane (2 × 30 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure in an ice cold water bath. Diethyl ether (60 mL) was added to precipitate the tetrabutylammonium iodide salt, the solution was filtered and concentrated under reduced pressure in an ice cold water bath to give a crude mixture (1.54 g) of 2-methyl-2-nitrocyclohexanone and ring cleavage products, methyl 6-nitrohexanoate and methyl 6-nitroheptanoate (76:13:11 respectively) as an orange oil. Purification by column chromatography on silica gel using hexane/diethyl ether 97/3 as eluent gave the pure α-nitro ketone (0.78 g, 36%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2950, 2873, 1732, 1549; $\delta_H$ (600 MHz) 1.67 [3H, s, C(2)$CH_3$], 1.69-1.85 (4H, m, ring protons), 1.98-2.10 (1H, m, ring protons), 2.55-2.64 (2H, m, ring protons), 2.86-2.90 (1H, m, ring protons).

#### **4.2.2** 2-Methyl-2-nitrocyclohexanol **2**[12]

A solution of 2-methyl-2-nitrocyclohexanone (0.98 g, 6.24 mmol) in distilled ethanol (10 mL) was added dropwise over 10 min to a stirred suspension of $NaBH_4$ (0.24 g, 6.24 mmol) in distilled ethanol (25 mL) at 0 °C under nitrogen and stirring was continued for 5 h at 0 °C. The ice bath was then

removed and aqueous hydrochloric acid (10%) was added to adjust to pH 1. The solution was concentrated under reduced pressure and the resulting residue was partitioned between water (10 mL) and dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL), dried, filtered and concentrated under reduced pressure to give a crude mixture (0.72 g) of nitroalcohols **2a** and **2b** (41:59 respectively) as a yellow oil. Purification by column chromatography on silica gel using hexane/ethyl acetate 97/3 as eluent gave *cis*-2-methyl-2-nitrocyclohexanol **2a** (186.6 mg, 19%) as a light yellow low melting solid, m.p. 33-35 °C; $\nu_{max}$/cm$^{-1}$ (film) 3445, 2945, 1539, 1352; $\delta_H$ (600 MHz) 1.39-1.46 [1H, m, one of C(5)$H_2$], 1.48-1.52 [2H, m, C(4)$H_2$], 1.63 [3H, s, C(2)$CH_3$], 1.68-1.77 [3H, m, one of C(5)$H_2$, one of C(3)$H_2$ and one of C(6)$H_2$], 1.82-1.87 [1H, m, one of C(6)$H_2$], 2.43-2.48 [1H, m, one of C(3)$H_2$], 2.84 [1H, d, *J* 8.4, OH], 3.91 [1H, br s, C(1)H]; $\delta_C$ (150 MHz) 21.5 [$CH_2$, br, C(5)$H_2$], 21.9 [$CH_2$, C(4)$H_2$], 24.2 [$CH_3$, C(2)***C***$H_3$], 30.6 [$CH_2$, C(6)$H_2$], 32.9 [$CH_2$, br, C(3)$H_2$], 73.1 [CH, br, C(1)H], 91.5 [C, C(2)]; HRMS (ES+): Exact mass calculated for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0974 Found 160.0974. (more polar) *trans*-2-Methyl-2-nitrocyclohexanol (±)-**2b** (274.6 mg, 28%) was isolated as a white crystalline solid, m.p. 38-41 °C; (Found C, 53.06; H 8.17; N 8.62. $C_7H_{13}NO_3$ requires C, 52.82; H, 8.23; N, 8.80%); $\nu_{max}$/cm$^{-1}$ (KBr) 3376, 2947, 1538, 1340; $\delta_H$ (600 MHz) 1.33-1.47 [3H, m, one of C(4)$H_2$, one of C(5)$H_2$ and one of C(6)$H_2$], 1.61 [3H, s, C(2)$CH_3$], 1.70-1.73 [1H, m, one of C(4)$H_2$] 1.76-1.79 [1H, m, one of C(5)$H_2$], 1.86-1.91 [1H, m, one of C(3)$H_2$], 1.95-1.99 [1H, m, one of C(6)$H_2$], 2.13-2.16 [1H, m, one of C(3)$H_2$], 2.74 [1H, s, OH], 4.28-4.29 [1H, m, C(1)H]; $\delta_C$ (150 MHz) 16.3 [$CH_3$, br, C(2)***C***$H_3$], 22.1 [$CH_2$, C(4)$H_2$], 23.5 [$CH_2$, C(5)$H_2$], 30.6 [$CH_2$, C(6)$H_2$], 35.9 [$CH_2$, br, C(3)$H_2$], 72.4 [CH, C(1)H], 93.0 [C, C(2)].

***4.2.3*** *cis*-2-Methyl-2-nitrocyclohexyl acetate (±)-**3a**

*N*,*N*-Dimethylaminopyridine (DMAP) (2.0 mg, 0.02 mmol) was added to a stirring solution of *cis*-2-methyl-2-nitrocyclohexanol (±)-**2a** (131.8 mg, 0.83 mmol), acetic anhydride (0.5 mL, 5.80 mmol) and pyridine (0.3 mL, 3.39 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 21 h under nitrogen. A saturated aqueous solution of sodium bicarbonate (10

mL) was added and the mixture stirred for 30 min. The solution was transferred to a separating funnel and washed with a saturated aqueous solution of $CuSO_4$ (20 mL), water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (20 mL). The organic extract was dried, filtered and concentrated under reduced pressure to give crude acetate (±)-**3a** (145.8 mg, 88%) as a clear oil which solidified on cooling to a white crystalline solid which was sufficiently pure to use without further purification, m.p. 46-48 °C; $\nu_{max}/cm^{-1}$ (KBr) 2960, 1738, 1544, 1362; $\delta_H$ (300 MHz) 1.26–1.48 [3H, m, C(5)$H_2$ and one of C(4)$H_2$], 1.54-1.67 {4H, m containing 1.54 [3H, s, C(2)$CH_3$] and [1H, m, one of C(6)$H_2$]}, 1.70-1.82 [1H, m, one of C(4)$H_2$], 1.88-2.05 {5H, m containing 1.95 [3H, s, $COCH_3$] and [2H, m, one of C(6)$H_2$ and one of C(3)$H_2$]}, 2.22-2.32 [1H, m, one of C(3)$H_2$], 5.26-5.29 [1H, m, C(1)H]; $\delta_C$ (75.5 MHz) 18.6 [$CH_2$, C(5)$H_2$], 19.9 [$CH_3$, C(2)***C***$H_3$], 20.9 [$CH_2$, C(4)$H_2$], 22.1 [$CH_3$, CO***C***$H_3$], 25.8 [$CH_2$, C(6)$H_2$], 29.7 [$CH_2$, C(3)$H_2$], 72.4 [CH, C(1)H], 87.5 [C, C(2)], 168.6 [C, ***C***$OCH_3$]; HRMS (ES+): Exact mass calculated for $C_9H_{15}O_2$ [M-$NO_2$]$^+$ 155.1072 Found 155.1065.

A sample of (±)-**3a** suitable for single crystal X-ray diffraction was recrystallised from slow evaporation of deuterated solvent.

### ***4.2.4*** *trans*-2-Methyl-2-nitrocyclohexyl acetate (±)-**3b**

This was prepared following the procedure for **3a**, from DMAP (2 mg, 0.02 mmol), *trans*-2-methyl-2-nitrocyclohexanol (±)-**2b** (152.8 mg, 0.96 mmol), acetic anhydride (0.6 mL, 6.68 mmol) and pyridine (0.3 μL, 3.97 mmol) in dichloromethane (5 mL) to give the crude acetate (±)-**3b** (137.5 mg, 71%) as a light yellow oil which was sufficiently pure to use without further purification; $\nu_{max}/cm^{-1}$ (film) 2950, 1748, 1538, 1361; $\delta_H$ (300 MHz) 1.33–1.52 [3H, m, one of C(4)$H_2$, one of C(5)$H_2$ and one of C(6)$H_2$], 1.62-1.81 {5H, m containing 1.65 [3H, s, C(2)$CH_3$] and [2H, m, one of C(5)$H_2$ and one of C(4)$H_2$]}, 1.95-2.19 {6H, m containing 2.03 (3H, s, $COCH_3$) and [3H, m, C(3)$H_2$ and one of C(6)$H_2$]}, 5.50-5.55 [1H, m, C(1)H]; $\delta_C$ (75.5 MHz) 17.6 [$CH_3$, C(2)***C***$H_3$], 20.9 [$CH_3$, CO***C***$H_3$], 21.9, 22.7 [$CH_2$, C(5)$H_2$, and C(4)$H_2$], 28.1 [$CH_2$, C(6)$H_2$], 36.5 [$CH_2$, C(3)$H_2$], 73.9 [CH, C(1)H], 90.4 [C, C(2)], 169.5 (C, ***C***$OCH_3$); HRMS (ES+): Exact mass calculated for $C_9H_{15}O_2$ [M-$NO_2$]$^+$ 155.1072 Found 155.1072.

### 4.3 Lipase-mediated kinetic resolution

**4.3.1** *General procedure for the development of one-pot procedures: lipase-mediated transesterification of 2-methyl-2-nitrocyclohexanol (±)-**2a** or (±)-**2b** with vinyl acetate as acetylating agent and dynamic interconversion process (analytical scale)*

In a typical experiment, the following were added as appropriate to a solution of nitroalcohols (±)-**2a** and (±)-**2b** (typically 15 mg) in the appropriate solvent (10 mg/mL), DBU (immob) (0.5 eq.) (18 mg), vinyl acetate (50, 5 or 3 eq. as appropriate) and CAL-B (immob) (approx. 15 mg). The small test tube was sealed and agitated as appropriate for the specified length of time (generally 12 hours). The solutions were filtered through Celite® and concentrated under reduced pressure. The sample was analysed by $^{1}$H NMR spectroscopy, reconcentrated and dissolved in a mixture of isopropanol/hexane [10:90 (HPLC grade)] and enantioselectivity determined by chiral HPLC.

**4.3.2** *General procedure for the development of two-pot procedures: dynamic interconcverion process and lipase-mediated transesterification of 2-methyl-2-nitrocyclohexanol (±)-**2a** or (±)-**2b** with vinyl acetate as acetylating agent (analytical scale)*

In a typical experiment, DBU (immob) (0.5 eq., ~90 mg) was added to a solution of nitroalcohols (±)-**2a** & (±)-**2b** in toluene (5 mL, 10 mg/mL) and the test tube was sealed and shaken at 500 rpm for the required amount of time (generally 12 hours) at the specified temperature (usually 50°C). The reaction solution was filtered through Celite®, and concentrated under reduced pressure and redissolved in the appropriate amount of toluene.[1] CAL-B (immob) (18 mg/ 1 mL solvent) and vinyl acetate (3 eq) were added and the solution shaken at 400 rpm and 30°C) for 12h in a sealed test tube.

[1] Before concentration, a 0.5 mL sample (approx. 5 mg material) is removed, and the volume of toluene added after the concentration is equal to the volume of the reaction mixture after the sample is taken. e.g. after 12 hours the total volume will be 4.5 mL, because 1x 0.5 mL samples were taken.

The solution was filtered through a plug of Celite® and concentrated under reduced pressure if applicable. The samples were taken before each filtration and filtered through Celite®, concentrated under reduced pressure. The samples were analysed by $^{1}$H NMR spectroscopy, reconcentrated and dissolved in a mixture of isopropanol/hexane [10:90 (HPLC grade)] and enantioselectivity determined by chiral HPLC.

**4.3.3** *General procedure for the development of one-pot procedures: dynamic interconverion process and lipase-mediated transesterification of 2-methyl-2-nitrocyclohexanol (±)-**2a** or (±)-**2b** with vinyl acetate as acetylating agent (analytical scale) – cycling procedure*

In a typical experiment, immobilised DBU (0.5 eq., ~90 mg) was added to a solution of nitroalcohols (±)-**2a** & (±)-**2b** in toluene (5 mL, 10 mg/mL) and the test tube was sealed and shaken at 50°C, 500 rpm for the required amount of time. CAL-B (immob) (app 100 % *w*/*w*) and vinyl acetate (3 eq.) was added and the test tube was sealed, shaken at 400 rpm for 12 h at 30 °C. At the end of the cycle the solution was filtered through a plug of Celite® if appropriate and the filtrate was recycled through the process again. Before the addition of each reagent an aliquot (0.5 mL) was taken, filtered through Celite®, concentrated under reduced pressure. The samples were analysed by $^{1}$H NMR spectroscopy, reconcentrated and dissolved in a mixture of isopropanol/hexane [10:90 (HPLC grade)] and enantioselectivity determined by chiral HPLC.

**4.3.4** *Diastereoselective lipase-mediated transesterification of 2-methyl-2-nitrocyclohexanol* **2**

CAL-B (immob) (88.6 mg) was added to a equimolar mixture of *cis*- and *trans*-2-methyl-2-nitrocyclohexanol (±)-**2a** and (±)-**2b** (105.4 mg, 0.66 mmol) dissolved in vinyl acetate (5 mL). The reaction mixture was shaken at 750 rpm at room temperature. Reaction monitoring was conducted as follows; an aliquot (0.5 - 1 mL) of reaction mixture was isolated and filtered through Celite®, washed with ethyl acetate and concentrated under reduced pressure. The sample was analysed by $^{1}$H NMR spectroscopy. The final extraction following $^{1}$H NMR spectroscopy was dissolved in a mixture of

isopropanol/hexane [10:90 (HPLC grade)] and enantioselectivity determined by chiral HPLC. The results of the screen are summarised in **Table 1.**

### 4.4 Synthesis of 6-nitroheptanal 1

#### **4.4.1** Methyl 5-hydroxypentanoate[17]

Sulfuric acid (conc. 95-97%, 1 mL, 18.76 mmol) was added to a stirred solution of δ-valerolactone (15.00 g, 149.82 mmol) in methanol (269 mL). The reaction mixture was maintained at reflux while stirring for 48 h and then cooled to 0 °C and $NaHCO_3$ (1.90 g) added. The mixture was stirred for 10 min at 0 °C, then it was filtered through Celite® and the solvent removed under reduced pressure to give the crude methyl ester (19.12 g, 97%) as a milky white oil which was used without further purification; $\nu_{max}/cm^{-1}$ (film) 3418, 2954, 1732, 1441; $\delta_H$ (300 MHz) 1.53-1.62 [2H, m, C(3)$H_2$], 1.64-1.76 [2H, m, C(4)$H_2$], 2.36 [2H, t, *J* 7.4, C(2)$H_2$], 3.52 (1H, br s, OH), 3.61 [2H, t, *J* 6.3, C(5)$H_2$], 3.67 (3H, s, $OCH_3$).

#### **4.4.2** Methyl 5-oxopentanoate[17, 18]

Methyl 5-hydroxypentanoate (13.00 g, 98.36 mmol) was added to a solution of pyridinium chlorochromate (PCC) (31.50 g, 146.39 mmol) and crushed 4Å molecular sieves (4.80 g) in dichloromethane (473 mL) at 0 °C under nitrogen and allowed to warm slowly to room temperature. The mixture was stirred for 2 h and then diluted with diethyl ether (250 mL). The mixture was filtered through a sintered glass funnel containing a layer each of silica gel and Celite®. The filtrate was concentrated under reduced pressure and the residue redissolved in diethyl ether and the filtration process repeated to remove the remaining chromium residues. The resultant solution was concentrated under reduced pressure to produce the crude aldehyde (9.96 g) as a light yellow oil. Purification by vacuum distillation gave the aldehyde (6.44 g, 50%) as a clear oil; b.p. 34-49 °C at 0.1 mmHg (Lit.,[18] 80 °C at 0.2 mmHg); $\nu_{max}/cm^{-1}$ (film) 2936, 1733, 1198; $\delta_H$ (300 MHz) 1.91-2.01 [2H, quintet, *J* 7.2,

C(3)$H_2$], 2.38 [2H, t, *J* 7.2, C(2)$H_2$], 2.54 [2H, dt, *J* 1.2, 7.2, C(4)$H_2$], 3.68 (3H, s, $OCH_3$), 9.78 [1H, t, *J* 1.2, C(1)H].

**4.4.3** Methyl 5-hydroxy-6-nitroheptanoate[19]

Powdered potassium *tert*-butoxide (0.92 g, 8.21 mmol) was added to a solution of methyl 5-oxopentanoate (5.36 g, 41.22 mmol) and nitroethane (8.8 mL, 123.83 mmol) in *tert*-butanol:tetrahydrofuran (1:1, 50 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature overnight, and then diluted with diethyl ether (100 mL) and water (100 mL). The solution was transferred to a separating funnel and the layers were separated. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL). The combined aqueous layers were extracted with diethyl ether (2 × 200 mL) and the combined organic layers were dried, filtered, and concentrated under reduced pressure to give a crude equimolar mixture of nitro alcohol diastereomers (8.44 g) as a yellow oil. Purification by column chromatography on silica gel using hexane/ethyl acetate 90/10 as eluent gave a equimolar mixture of pure nitro alcohol diastereomers (5.25 g, 62%) as a light yellow oil; (Found C, 46.89; H 7.37; N 6.56. $C_8H_{15}NO_5$ requires C, 46.82; H, 7.37; N, 6.83%); $\nu_{max}/cm^{-1}$ (film) 3444, 2955, 1728, 1557, 1393; $\delta_H$ (300 MHz) 1.38-1.62 {5H, m containing 2 × d, 1.54 [1.5H, d, *J* 6.9, C(7)$H_3$ of 1 diastereomer], 1.55 [1.5H, d, *J* 6.9, C(7)$H_3$ of 1 diastereomer] and [2H, m, C(4)$H_2$ of 2 diastereomers]}, 1.63-1.96 [2H, m, C(3)$H_2$ of 2 diastereomer], 2.39 [2H, t, *J* 7.1, C(2)$H_2$ of 2 diastereomers], 2.91-2.95 (1H, OH, of 2 diastereomers), 3.68 (3H, s, $OCH_3$, of 2 diastereomers), 3.90-3.98 [0.5H, m, C(5)H, of 1 diastereomer], 4.14-4.21 [0.5H, m, C(5)H, of 1 diastereomer], 4.47-4.59 [1H, m, C(6)H of 2 diasteromers]. $\delta_C$ (75.5 MHz) 12.5, 16.1 [2 x $CH_3$, C(7)$H_3$ of 2 diastereomer], 20.3, 21.0 [2 x $CH_2$, C(3)$H_2$ of 2 diastereomer], 32.1, 32.3 [2 x $CH_2$, C(4)$H_2$ of 2 diastereomer], 33.3 [$CH_2$, C(2)$H_2$ of 2 diastereomers], 51.7 ($CH_3$, $OCH_3$ of 2 diastereomers), 71.7, 72.4 [2 x CH, C(5)H, of 2 diastereomers], 86.4, 87.7 [2 x CH, C(6)H, of 2 diastereomers], 174.0 [C, C(1) of 2 diastereomers].

**4.4.4** Methyl 5-acetoxy-6-nitroheptanoate[19] and methyl 6-nitroheptanoate [13]

A solution of an equimolar mixture of methyl 5-hydroxy-6-nitroheptanoate diastereomers (5.00 g, 24.37 mmol), DMAP (150 mg, 1.23 mmol), acetic anhydride (2.5 mL, 26.71 mmol) and diethyl ether (62 mL) was stirred for 4 h at room temperature under nitrogen and concentrated under reduced pressure to yield the crude equimolar mixture of nitro acetate diastereomers as a bright green oil; $\delta_H$ (300 MHz) 1.548 [1.5H, d, *J* 6.9, C(7)$H_3$ of 1 diastereomer] 1.554 [1.5H, d, *J* 6.9, C(7)$H_3$ of 1 diastereomer], 1.58-1.80 [4H, m, C(3)$H_2$ and C(4)$H_2$ of 2 diastereomers], 2.06 (1.5H, s, $COCH_3$ of 1 diastereomer) 2.09 (1.5H, s, $COCH_3$ of 1 diastereomer), 2.25-2.47 [2H, m, C(2)$H_2$ of 2 diastereomers], 3.68 (3H, s, $OCH_3$ of 2 diastereomers), 4.65-4.77 [1H, m, C(5)H of 2 diasteromers], 5.29-5.35 [1H, m, C(6)H of 2 diasteromers]. A suspension of $NaBH_4$ (0.68 g, 17.98 mmol) in dimethylsulfoxide (63 mL) was added dropwise to the crude nitro acetates at 0 °C under nitrogen and the solution was stirred overnight at room temperature. The reaction mixture was then acidified with aqueous hydrochloric acid (1M), extracted with diethyl ether (3 × 100mL), dried, filtered and concentrated under reduced pressure to yield the crude methyl ester (3.42 g, 74%) as a clear oil which was used without further purification; $\nu_{max}/cm^{-1}$ (film) 2953, 1738, 1552, 1361; $\delta_H$ (300 MHz) 1.26-1.44 [2H, m, C(4)$H_2$], 1.53 [3H, d, *J* 6.9, C(7)$H_3$], 1.61-1.80 [3H, m. C(3)$H_2$ and one of C(5)$H_2$], 1.92-2.13 [1H, m, one of C(5)$H_2$], 2.32 [2H, t, *J* 7.4, C(2)$H_2$], 3.67 (3H, s, $OCH_3$), 4.51-4.62 [1H, sym m, C(6)H].

**4.4.5** 6-Nitroheptan-1-ol[2]

DIBAL-H (38 mL, 38.00 mmol, 1M solution in hexanes) was added dropwise to a solution of methyl 6-nitroheptanoate (2.54 g, 13.45 mmol) in doubly distilled dichloromethane (100 mL) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 1 h, then warmed to −40 °C and stirred for a further 1 h. The temperature was then increased to −10 °C and the reaction carefully

[2] DIBAL-H selective reduction of methyl 6-nitroheptanoate to 6-nitroheptanal **1** lead to a mixture of products including the starting material, desired aldehyde **1** and 6-nitroheptan-1-ol. Due to the lack of selectivity methyl 6-nitroheptanoate was reduced completely to 6-nitroheptan-1-ol and subsequently oxidised to **1**.

quenched with aqueous hydrochloric acid (1M, 20 mL). Vigorous stirring and further addition of aqueous hydrochloric acid (1M, 20 mL) was required to degrade the gelatinous nature of the aluminium salt precipitate. The solution was transferred to a separating funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layer was washed with aqueous hydrochloric acid (1M, 100 mL), brine (100 mL), dried, filtered and concentrated under reduced pressure in an ice cold water bath to give the crude nitro alcohol (1.67 g) as a cloudy yellow oil. Purification by chromatography on silica gel using hexane/ethyl acetate 80/20 as eluent gave the pure nitro alcohol (1.26 g, 58%) as a clear oil; $\nu_{max}/cm^{-1}$ (film) 3365, 2940, 1553, 1391; $\delta_H$ (300 MHz) 1.26-1.48 [4H, m, C(3)$H_2$ and C(4)$H_2$], 1.52-1.61 {5H, m containing 1.53 [3H, d, *J* 6.6, C(7)$H_3$] and [2H, m, C(2)$H_2$]}, 1.64-1.79 [1H, m, one of C(5)$H_2$], 1.86 (1H, br s, OH), 1.96-2.08 [1H, m, one of C(5)$H_2$], 3.63 [2H, t, *J* 6.5, C(1)$H_2$], 4.52-4.63 [1H, sym m, C(6)H]; $\delta_C$ (75.5 MHz) 19.2 [$CH_3$, C(7)$H_3$], 25.2, 25.5 [2 x $CH_2$, C(3)$H_2$ and C(4)$H_2$], 32.2 [$CH_2$, C(2)$H_2$], 35.1 [$CH_2$, C(5)$H_2$], 62.5 [$CH_2$, C(1)$H_2$], 83.5 [CH, C(6)H]; HRMS (ES+): Exact mass calculated for $C_7H_{16}NO_3$ $[M+H]^+$ 162.1130 Found 162.1122.

**4.4.6** 6-Nitroheptanal **1**

PCC (2.00 g, 9.28 mmol) and crushed 3Å molecular sieves (0.42 g) were added to a solution of 6-nitroheptan-1-ol (0.68 g, 4.19 mmol) in doubly distilled dichloromethane (24 mL) under nitrogen at room temperature. Stirring was continued for 4 h. The reaction mixture was diluted with diethyl ether (100 mL) and filtered through a sintered glass funnel containing a layer each of Celite® and silica gel. The filtrate was concentrated under reduced pressure. The resulting oil was diluted with diethyl ether (40 mL), washed with water (2 × 50 mL), brine (50 mL), dried, filtered and concentrated under reduced pressure to give the crude aldehyde **1** (0.58 g) as a light brown oil. Purification by column chromatography on silica gel using hexane/ethyl acetate 90/10 as eluent gave the pure aldehyde **1** (0.44 g, 65%) as a clear oil; $\nu_{max}/cm^{-1}$ (film) 2943, 1724, 1549, 1392; $\delta_H$ (300 MHz) 1.27-1.47 [2H, m, C(4)$H_2$], 1.53 [3H, d, *J* 6.6, C(7)$H_3$], 1.59-1.82 [3H, m. C(3)$H_2$ and one of C(5)$H_2$], 1.94-2.12 [1H, m, one of C(5)$H_2$], 2.44-2.50 [2H, dt, *J* 1.2, 7.2, C(2)$H_2$], 4.51-4.63 [1H, m, C(6)H], 9.77 [1H, t, *J* 1.4

C(1)H]; $\delta_C$ (75.5 MHz) 19.2 [$CH_3$, C(7)$H_3$], 21.3 [$CH_2$, C(3)$H_2$], 25.2 [$CH_2$, C(4)$H_2$], 34.8 [$CH_2$, C(5)$H_2$], 43.4 [$CH_2$, C(2)$H_2$], 83.2 [CH, C(6)H], 201.8 [CH, C(1)H]; HRMS (ES+): Exact mass calculated for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0974 Found 160.0972.

**Supporting Information**

Chiral HPLC conditions and spectra for the separation of all four enantiomeric pairs (±)-**2a** and (±)-**2b** and (±)-**3a** and (±)-**3b** and copies of $^1$H and $^{13}$C NMR spectra of all novel compounds are available as Supporting Information. Details of supplementary experiments and results, as indicated throughout the manuscript, are also included in the Supporting Information.

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**Supplementary Information**

NMR Spectra and HPLC chromatograms are included in supplementary data, as well as additional results, as mentioned in the Results and Discussion

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