Pergamon

Tetrahedron 57 (2001) 8193–8202

TETRAHEDRON

Chemoenzymatic synthesis of a tachykinin NK-2 antagonist

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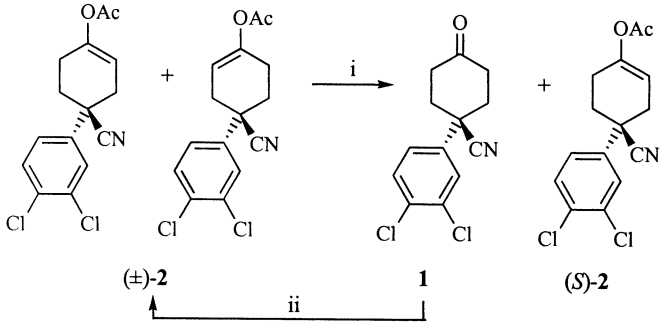
Received 8 June 2001; revised 2 July 2001; accepted 26 July 2001

Abstract—A non-peptide tachykinin antagonist has been synthesized in a short and efficient four step sequence starting from a chiral enol acetate, which was obtained in enantiomerically pure form by resolution using a lipase catalysed transesterification reaction. The biotransformation was optimized in terms of solvent, temperature and immobilization method used. Oxidative cleavage of the (+)-enol acetate to give the key aldehyde ester intermediate could be achieved indirectly by oxidative rearrangement to an enone followed by Baeyer–Villiger oxidation and ring opening, or by epoxidation, rearrangement and oxidative cleavage or most directly by ozonolysis. X-Ray crystallographic analysis of a camphanic ester derivative of an ester alcohol confirmed that the absolute configuration of the enol acetate was (*S*). © 2001 Published by Elsevier Science Ltd.

1. Introduction

The desymmetrization of prochiral ketones to obtain chiral enolates or lactones has become an important method in asymmetric synthesis. Chiral lithium amides have been employed by Koga,[1] Simpkins[2] and others for the deprotonation of 4-substituted cyclohexanones and prochiral bicyclic ketones.[3] However, in order to achieve high selectivity, specialised chiral amines may be required and the reactions are run at low temperatures (−78°C or −100°C) under anhydrous conditions. The chiral silyl enol ethers that result from enolate trapping can provide a handle for maintaining the newly introduced asymmetry by oxidative cleavage or electrophilic addition. Asymmetric Baeyer–Villiger reactions can be carried out using monooxygenase enzymes[4] and asymmetric copper and platinum catalysts[5,6] but suffer from low substrate concentrations and moderate enantioselectivities, respectively. Despite recent progress, methods to achieve this type of transformation which are amenable to scale-up using commercially available catalysts that can operate at ambient temperature are required.

We recently reported the use of a lipase enzyme for the effective desymmetrization of prochiral ketone 4-cyano-4-(3,4-dichlorophenyl)cyclohexanone **1** (Scheme 1).[7,8] The racemic enol acetate **2** derived from ketone **1** was resolved using Amano *Pseudomonas fluorescens* lipase (PFL) to give unreacted enantiomerically pure (100% ee) (*S*)-enol acetate **2** and recovered ketone **1**, the product of the lipase transesterification. Unlike most enzyme kinetic resolutions this reaction has the advantage that the prochiral ketone can be chemically recycled leading to greater than 50% yields of enantiopure enol ester after several cycles, constituting a desymmetrization of the prochiral ketone.



Scheme 1. *Reagents and conditions*: (i) *Pseudomonas fluorescens* lipase, THF, *n*BuOH; (ii) isopropenyl acetate, pTsOH.

Keywords: enol acetate; NK-2 antagonist; lipase; enone; ozonolysis.
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0040–4020/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4020(01)00796-7

The sensoneuropeptide tachykinins, which include substance P and neurokinins A and B, are distributed in the peripheral and central nervous systems and are known to be involved in neurologic inflammation, pain transmission and bronchoconstriction.[9] The effects of these tachykinins are mediated through the activation of NK-1, NK-2 and NK-3 receptors and new antagonists are being sought as a means of controlling pain and inflammation. Pfizer have developed a class of non-peptidic neurokinin NK-2 antagonists generally consisting of an (*S*)-4-aryl-4-dialkylaminoethyl-N-alkyl δ-lactams such as structure **3** (Scheme 2).[10]

We now report full details of the optimization of the biotransformation of the enol ester **2** and the synthesis of a representative member of this class of tachykinin NK-2 antagonists.

2. Results and discussion

Our original retrosynthesis of the lactam **3** involved, as the final step, reductive cyclisation[11] of the nitrile ester **4** which would be made by reductive amination of aldehyde **5**. This aldehyde would be derived by ring opening and oxidation of the lactone **6** which we envisaged could be made by asymmetric Baeyer–Villiger oxidation of the cyclohexanone **1** using a monooxygenase enzyme.[4] Alternatively the enol lactone **7** might be accessible from the enone **8** by regioselective Baeyer–Villiger oxidation according to a similar transformation reported by Schultz.[12] This would present the correct aldehyde oxidation state for subsequent reductive amination.

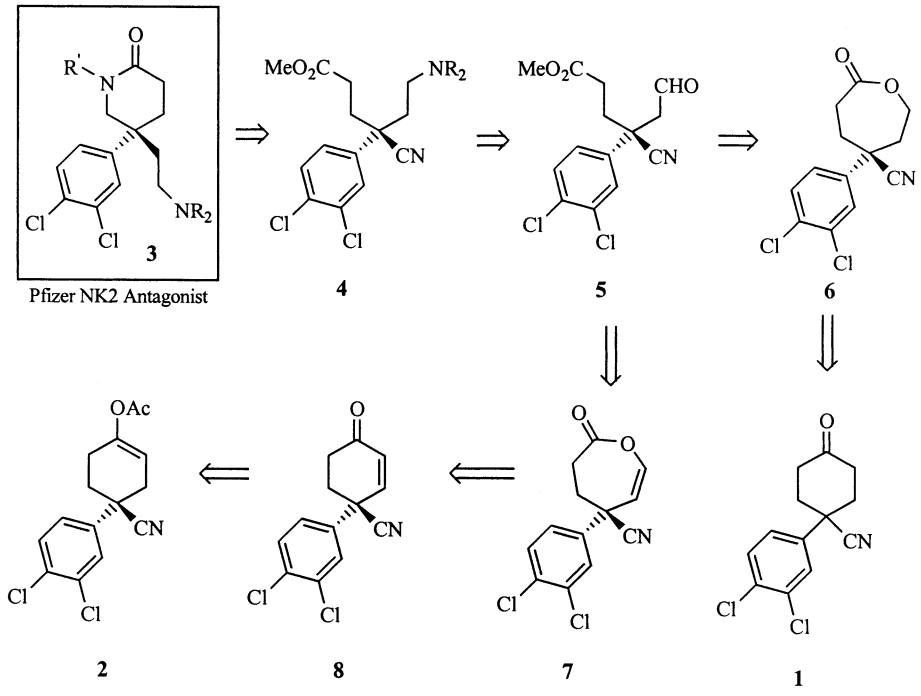
We had previously used Tsuji's bimetallic oxidative rearrangement of an enantiomerically pure enol acetate to obtain an enone with no loss of enantiomeric purity and so envisaged making enone **8** in the same way.[13]

Unfortunately the prochiral ketone **1** was not a substrate for cyclohexanone monooxygenase, 2,5-diketocamphane monooxygenase (MO1) or 3,4,4-trimethylcyclopent-2-enone acetic acid monooxygenase (MO2), enzymes known to give chiral lactones from prochiral or racemic cyclohexanones.[4,14] We therefore focussed our attention on the alternative route involving the optically pure enol acetate **2** as the starting material.

2.1. Optimization of the biotransformation for the preparation of (*S*)-(+)-2

In an attempt to ensure that we had found optimum conditions for the biotransformation we screened a range of enzymes, varied the solvent and reaction temperature and examined a range of immobilisation methods. Our initial screen in toluene and THF identified eight lipases.[8] Reactions in toluene were generally faster than those in THF but selectivity was lower. *Pseudomonas fluorescens* lipase was the best enzyme in terms of reaction rate and selectivity giving the enol acetate **2** in >99% ee after 70% conversion in 8.5 h (E=15) in THF. The same reaction in toluene gave an E value of 6.5. The PFL reaction was then carried out in a range of solvents (Table 1). THF turned out to be the optimal solvent with E values ranging from 1 in phosphate buffer to 15 for THF.

Immobilisation of enzymes can provide advantages such as increased activity and selectivity and can also facilitate downstream processing. We had previously shown that the rate and enantioselectivity of *Humicola* lipase in hexane, when used for the transesterification of enol acetates derived from prochiral oxabicyclic [3.2.1] ketones, was greatly improved by prior adsorption of the enzyme onto flash



Scheme 2.

Table 1. Variation in selectivity of PFL catalysed transesterification of substrate **2** with solvent

Solvent	Time (h)	Conversion (%)	ee (%)	*E*
THF	3.5	70	>99	15
EtOAc	2.5	41	48	9
Dioxane	4	72	94	7
Toluene	4	52	61	6.5
Et_2O	1	66	85	6
CH_3CN	6.5	52	53	5
Hexane	6.5	55	5.7	1
Buffer	2.5	56	0	1

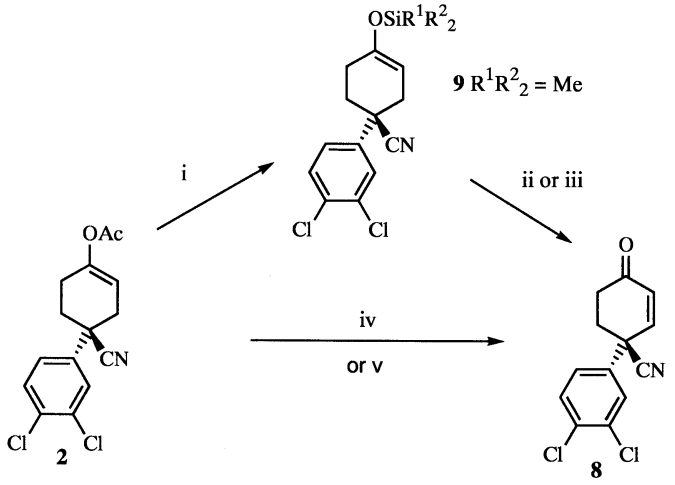
silica.[15,16] Use of silica adsorbed PFL in THF gave no improvement in enantioselectivity and reaction times were considerably longer (9 days for 20% conversion cf. 3.5 h for 70% conversion with freeze dried non-adsorbed enzyme). Covalent attachment of PFL to the polymer Eupergit C gave more encouraging results in that, although enantioselectivity was unaffected, the rate was increased (2.5 h for 68% conversion cf. 3.5 h with non-immobilised enzyme) and the immobilised enzyme could be easily removed and re-used with no noticable loss in activity. It was decided to carry out the large-scale biotransformations to obtain the material required for the synthesis using Eupergit C-immobilised PFL in THF with *n*-BuOH at room temperature for the transesterification. The reaction was carried out on 10 g of racemic enol aceate **2** to yield, after chromatography, 2.8 g (28% yield) of enol acetate (+)-(*S*)-**2** of high enantiomeric excess.

2.2. Synthesis of the NK-2 antagonist 3

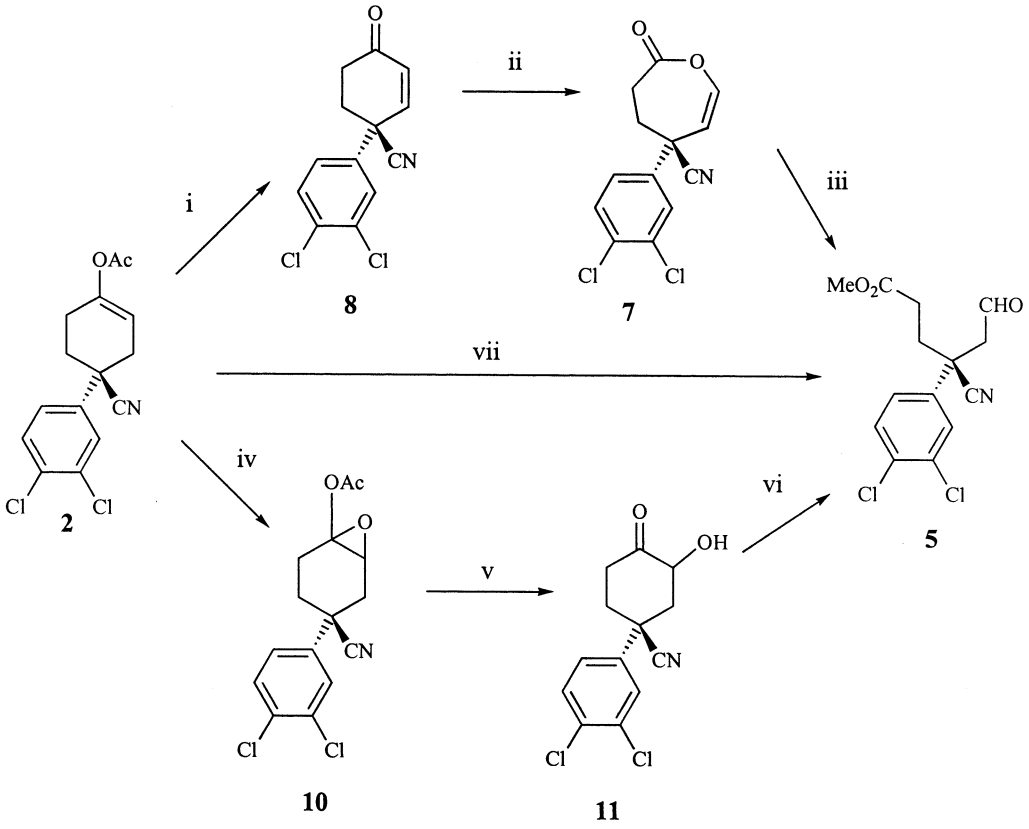
For the synthesis of the enone **8** directly from enol acetate **2** we found Tsuji's method capricious in that, although yields of 65% were obtainable, they were difficult to reproduce. We therefore considered three alternative procedures (Scheme 3). Firstly, treatment of the enol acetate **2** with methyl lithium and phenyl selenyl chloride followed by oxidative elimination with H_2O_2 gave enone **8** in a poor 35% yield. The TMS enol ether **9** could be made in 66% yield by treatment of the enol acetate **2** with methyl lithium followed by trimethyl silyl chloride. Subsequent treatment of enol ether **9** with PhSeCl followed by oxidative elimination with H_2O_2 afforded the enone **8** in 52% yield over 2 steps. Evans et al. reported the formation of α,β-unsaturated ketones from the corresponding triisopropyl silyl enol ethers by direct dehydrogenation using ceric ammonium nitrate at 0°C in DMF.[17] We subjected the TMS enol ether **9** to these conditions but this gave a low (6%) yield of the enone **8**, perhaps owing to the lability of the TMS group under these conditions. Increasing the size of the groups on silicon gave a progressive increase in yield (28% for TBDMS and 32% for $^{i}Pr_3Si$) but yields for the formation of the silyl enol ether substrates were progressively worse with an increase in size of the silane. Overall, we found Tsuji's oxidative rearrangement to be the highest yielding, but the success of this transformation was highly dependent on the purity of the reagents used.

For the conversion of the enol acetate **2** to the ester aldehyde **5** three approaches were tried (Scheme 4). Enone **8** underwent regioselective Baeyer–Villiger oxidation with pertrifluoroacetic acid prepared in situ, according to the procedure reported by Schultz whereby trifluoroacetic anhydride is reacted with urea–hydrogen peroxide in dichloromethane in the presence of sodium hydrogen phosphate.[12]

Under these conditions the enol lactone **7** produced is stable and could be isolated in 80% yield. The enol lactone **7** could be ring opened using basic methanol to provide the aldehyde ester **5** in 60% yield. Alternatively, epoxidation of the enol acetate followed by rearrangement and oxidative cleavage gave the same aldehyde ester **5** in lower overall yield. Finally, much more direct was the ozonolysis of enol acetate **2** in methanol/dichloromethane to give, after reductive workup with DMS or Ph_3P, the aldehyde ester **5** in 62% yield. Although the yield was disappointing, it was reproducible and the directness of this method was preferable to the other approaches. In order to confirm the suspected (*S*)-configuration of the 4-position of the enol acetate (+)-**2** we converted the aldehyde (−)-**5** into the crystalline camphanic ester derivative **13** via alcohol **12** shown in Scheme 5. Crystallisation of the ester **13** from propan-2-ol gave crystals suitable for X-ray analysis.[7] By reference to



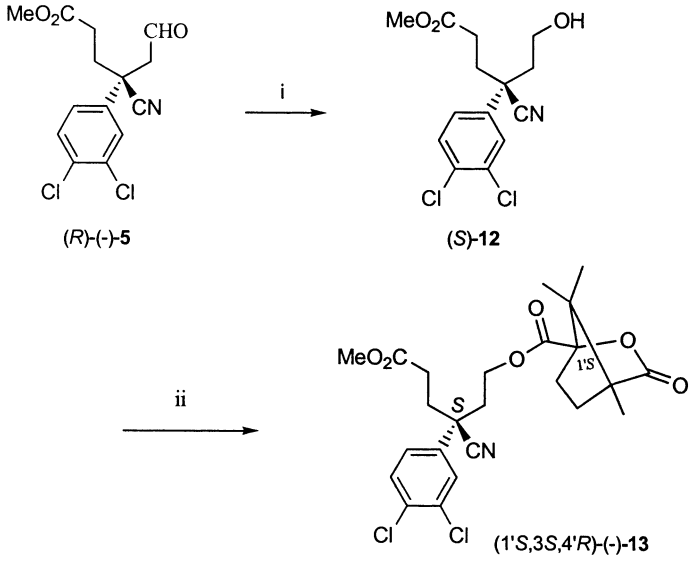
Scheme 3. *Reagents and conditions*: (i) MeLi, THF, TMSCl (57%); (ii) PhSeCl, DCM then H_2O_2 (52%); (iii) CAM, DMF, 0°C; (iv) $Pd(OAc)_2$, $MeOSnBu_3$, allyl methyl carbonate, MeCN (65%); (v) MeLi, THF, PhSeCl, 0°C then H_2O_2 (35%).



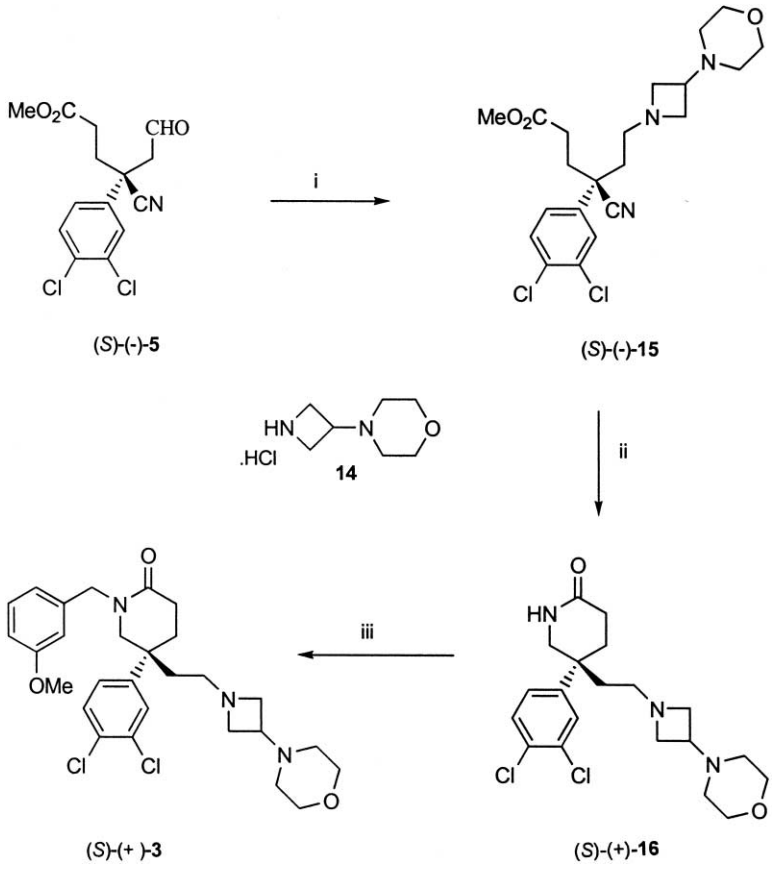
Scheme 4. *Reagents and conditions*: (i) $Pd(OAc)_2$, dppe, $MeOSnBu_3$, allyl methyl carbonate, MeCN (65%); (ii) UHP, $(CF_3CO)_2O$, Na_2HPO_4 DCM (80%); (iii) MeOH, K_2CO_3 (60%); (iv) MCPBA, Na_2HPO_4, DCM (72%); (v) $CHCl_3$, CH_3CO_2H (74%); (vi) $NaIO_4$, MeOH (58%); (vii) O_3, MeOH, DCM then Ph_3P (62%).

the 1′(*S*) camphanyl moiety the absolute configuration of the cyano substituted center was determined to be (*S*), thus confirming the configuration of the enol acetate (+)-**2** as (*S*) required for the synthesis of the NK-2 antagonist **3**.

To complete the synthesis of the NK-2 antagonist **3** required reductive amination of the aldehyde (−)-**5** ester followed by lactam formation and N-benzylation. Reductive amination with morpholinoazetidine[18] hydrochloride **14** under hydrogenation conditions (Pd-C/H_2) was not successful. The presence of the triethylamine used to release the free azetidine amine from its hydrochloride salt or the resultant triethylamine hydrochloride may have poisoned the palladium catalyst. However, prior formation of the imine between **14** and (−)-**5** in THF in the presence of triethylamine followed by reduction with sodium triacetoxyborohydride afforded the intermediate (−)-**15** in 91% overall yield. The reductive cyclization of (−)-**15** to give lactam



Scheme 5. *Reagents and conditions*: (i) $NaB(OAc)_3H$, AcOH, <20°C (72%); (ii) (−)-1(*S*)-camphanic acid chloride, DMAP, Et_3N, DCM (83%).



Scheme 6. *Reagents and conditions*: (i) (a) (**14**), THF, Et_3N, rt, (b) $NaB(OAc)_3H$, Et_3N (91%); (ii) H_2, Raney Ni, MeOH, 45°C (97%); (iii) KH, 3-methoxybenzylbromide, DMF,18-C-6, 0°C, (28%).

(+)-**16** was acheived in 97% yield using hydrogenation and Raney Nickel. Fortunately, no dechlorination of the aromatic ring was observed under these conditions. Lactam **16** underwent N-benzylation to furnish the target NK-2 antagonist (+)-**3** in 28% yield (Scheme 6).

In attempts to improve this step we used valerolactam as a model substrate. This underwent benzylation cleanly with 3-methoxybenzyl bromide or chloride using KOH/DMSO/10% H_2O or NaOH/18-crown-6/DMF in yields of 75 and 72%, respectively. However, when these conditions were applied to the lactam **16**, low yields resulted. The morpholinoazetidine group may undergo N-benzylation and the resulting alkylammonium species may not be efficient alkyl donors or may undergo ring cleavage leading to more polar products.

In summary, the enantiomerically pure (*S*)-enol acetate **2** was obtained by enantioselective transesterification with *Pseudomonas fluorescens* lipase under optimized conditions. The enol acetate was converted to enone **8** using Tsuji's conditions with no loss of enantiomeric purity and subsequent Baeyer–Villiger oxidation gave regioselective oxygen insertion towards the alkene, giving the enol lactone **7**. Ozonolysis of the enol acetate **2** proved to be the most direct way to access the required ester aldehyde intermediate **5** for subsequent elaboration to the target NK-2 antagonist (*S*)-**3** in a short and efficient four step synthesis. As previously stated, the ketone product of the biotransformation is prochiral and can easily be separated and chemically recycled, thus providing greater than 50% yield of the chiral enol ester over several cycles. We are currently developing an in situ method for this recycling which will be reported elsewhere.

3. Experimental

3.1. General

Elemental analysis, NMR spectra, infrared spectra, mass spectra and accurate mass measurements were obtained and recorded were recorded as previously described.[19] Melting points were taken on a gallemkamp melting point apparatus and are uncorrected. Optical rotations $[\alpha]_D$ (concentration in g/100 mL, solvent) were recorded on an Optical Activity A1000 polarimeter at 589 nm. GC analysis was performed on a DANI 3800 gas chromatograph equipped with an Altech Econo-Cap SE-30 column. Samples were prepared as 5–10% solutions in EtOAc and were analysed at temperatures between 150 and 300°C. HPLC analysis was performed on a Waters 2690 separations module equipped with a Daicel Chiralpak AD or Chiracel OJ column. Samples were recorded using a Waters 996 photodiode array detector. Integration was performed using Waters Millenium[32] software.

3.1.1. 4-Cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate 2. To a stirred solution of 4-cyano-4-(3′,4′-dichlorophenyl)cyclohexanone (20 g, 75 mmol) in dry THF

(400 mL) at −78°C under argon was added LHMDS (97 mL 1M, 97 mmol). The mixture was stirred for 15 min, whereupon acetic anhydride (10.6 mL) was added and the mixture allowed to warm to rt for 1 h. The reaction was quenched by the addition of ammonium chloride solution (100 mL) and ether was added (200 mL). The organic layer was washed with saturated ammonium chloride solution (3×300 mL) and brine (3×300 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil, which was purified by flash column chromatography on silica (eluent 2:1 hexane/diethyl ether) to give the title compound **2** (20 g, 86%) as a white solid, mp 153–154°C. (Found C, 57.81; H, 4.18; N, 4.48. $C_{15}H_{13}Cl_2NO_2$ requires C, 58.08; H, 4.22; N, 4.52%) (HRMS: found M^+ 309.0322. $C_{15}H_{13}{}^{35}Cl_2NO_2$ requires 309.0323); ν_{max}(neat) 2233 (CN), 1755 (CO); δ_H (300 MHz, $CDCl_3$) 2.23 (3H, s, $AcCH_3$), 2.23–2.67 (6H, m, 2×H-3, 2×H-5 and 2×H-6), 5.46 (1H, s, H-2) 7.22–7.56 (3H, Ar); δ_C (75 MHz, $CDCl_3$) 20.9 ($AcCH_3$), 24.6, 32.7, 35.4 (C-3, C-5, and C-6), 40.0 (C-4), 110.5 (C-2), 121.5 (CN), 125.3, 128.1 and 131.1 (C-2′, C-5′, C-6′), 132.8, 133.5 and 139.6 (C-1′, C-3′ and C-4′), 148.1 (C-1), 169.3 (C=O); *m/z* (EI) 309 (3%, M^+), 267 (11), 70 (69), 43 (100). HPLC Chiralpak AD, R_T (*R*)-3 15.5 min, (*S*)-**3** 20.9 min, eluent 100% EtOH, flow rate 0.5 mL/min, λ 220 nm.

3.2. Typical biotransformation protocol

To a solution of enol acetate **2** (100 mg, 0.41 mmol) in dry THF (10 mL) at 30°C was added *n*-BuOH (0.046 mL, 0.50 mmol) and lipase from *Pseudomonas fluorescens* (30 mg). The solution was stirred for 3.5 h, until 65% conversion to ketone was observed by GC, whereupon the mixture was filtered through a celite pad and the enzyme washed with diethyl ether. The filtrate was concentrated under reduced pressure to give the crude product as a yellow solid which was purified by flash column chromatography on silica (eluent 5:1 petrol/ethyl acetate) to give the enantiomerically pure (>99% ee) enol acetate **2** (29 mg, 29%)as a white crystalline solid, mp 148–150°C.

3.3. Scale-up biotransformation procedure

The enol acetate **2** (10 g, 32.4 mmol), *Pseudomonas fluorescens* lipase, Amano (8 g) and *n*-BuOH (5.21 mL, 64.7 mmol) were stirred in THF at room temperature for 9.5 h whereupon HPLC (Chiralpak AD) indicated 100% ee for the enol acetate. R_T (*R*)-**2** 15.5 min, (*S*)-**2** 20.9 min, eluant 100% EtOH, 0.5 mL/min. The solution was filtered through a glass sinter funnel, the residual enzyme washed with tetrahydrofuran and the solvent removed by evaporation under reduced pressure. The crude residue was purified by flash column chromatography (eluent 1:2 diethyl ether/petroleum ether) to give the ketone (7 g) and the (*S*)-enol acetate **3** (2.8 g, 28%, >99% ee) as a white solid, mp 148–150°C, $[\alpha]_D$=+11.5 (*c*=1.74 in $CHCl_3$). Other analytical data as reported above.

3.3.1. 4-Cyano-4-(3,4-dichlorophenyl)-1-(trimethylsilyloxy) cyclohexene 9. A solution of 4-cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate **2** (200 mg, 0.83 mmol) in THF (10 mL) was added to a solution of 1.4 M methyl lithium in diethyl ether (1.36 mL, 1.91 mmol) at 0°C. The reaction was cooled to −78°C, trimethylsilyl chloride (225 mg, 2.07 mmol) was added and the mixture allowed to warm to room temperature over 1 h. The reaction was quenched with saturated ammonium chloride solution (20 mL), ether was added (10 mL) the organic layer was washed with water (3×10 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica (petroleum ether/diethyl ether, 7:1) to yield the product **9** (101 mg, 45%) as a white solid. Mp 72°C. (Found C, 56.68; H, 5.63; H, 4.14; M^- 339.0611. $C_{16}H_{19}N^{35}Cl_2OSi$ requires C, 56.47; H, 5.63; N, 4.11%; 339.0613); ν_{max}(film) (cm^{-1}) 2238 (CN); δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.20 (9H, s, CH_3), 2.14–2.57 (6H, m, H-3, H-5 and H-6), 4.89 (1H, t, *J*=2.1 Hz, H-1), 7.13 (1H, dd, J_o=8.5 Hz, J_m=2.2 Hz, H-6′), 7.25 (1H, d, J_o=8.5 Hz, H-5′) and 7.35 (1H, d, J_m=2.2 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 0.21 (3×CH_3), 27.69, 33.02 and 35.92 (C3, C5 and C6), 40.36 (C4), 100.09 (C2), 121.89 (CN), 125.37, 128.02 and 130.89 (C2′, C5′and C6′), 132.44, 133.24 and 140.20 (C1′, C3′ and C4′) and 150.50 (C1); *m/z* (EI) 339 (9%, $[M]^+$), 142 (95), 127 (100), 75 (38) and 73 (30).

3.3.2. 4-Cyano-4-(3,4-dichlorophenyl)cyclohex-2-enone 8. *Method A*: To a solution of 4-cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate **2** (150 mg, 0.4 mmol) in dry CH_3CN (5 mL) was added palladium acetate (6.7 mg, 0.03 mmol), *bis*(diphenylphosphino)ethane (12 mg, 0.03 mmol) and allylmethylcarbonate (0.07 mL, 0.62 mmol) and the mixture was stirred for 30 min at room temperature. Tributyltin methoxide (0.03 mL, 0.12 mmol) was then added and the mixture heated under reflux for 18 h. The solution was filtered through celite and dichloromethane (15 mL) was added. The organic layer was washed with saturated ammonium chloride solution (3×15 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash column chromatography on silica (hexane followed by diethyl ether/hexane, 1:1) to yield the product **8** (77.4 mg, 65%) as a colourless oil. R_f (ethyl acetate/hexane, 1:1) 0.62. (Found M^+ 265.0065. $C_{13}H_9{}^{35}Cl_2NO$ requires 265.0061); ν_{max}(film) (cm^{-1}) 2239 (CN), 1693 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.13–2.86 (4H, m, H-5 and H-6), 6.33 (1H, d, *J*=9.9 Hz, H-3), 6.80 (1H, d, *J*=9.9 Hz, H-2) and 7.24–7.54 (3H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 34.65 and 37.63 (C5 and C6), 42.25 (C4), 118.41 (CN), 125.48, 128.31 and 131.52 (C2′, C5′ and C6′), 132.49 (C3′), 133.73 and 134.03 (C3′ and C4′), 137.91 (C1′), 143.61 (C2) and 195.22 (C1); *m/z* (EI) 265 (44%, $[M]^+$), 237 (82), 202 (23), 267 (32), 239 (57)and 174 (100).

Method B: A solution of phenylselenyl chloride (100 mg, 0.53 mmol) in dichloromethane (3 mL) was added to a stirred solution of silyl enol ether **9** (100 mg, 0.29 mmol) in dichloromethane (3 mL) at −78°C. After 10 min the mixture was warmed to room temperature and dichloromethane (30 mL) was added. The solution was washed with a saturated solution of sodium hydrogen carbonate (2×25 mL) and a saturated solution of sodium chloride (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The α-phenylselenide was isolated from the crude. (Found M^+ 418.9733.

$C_{19}H_{15}{}^{35}Cl_2NO^{76}Se$ requires 418.9723); ν_{max}(film) (cm^{-1}) 2238 (CN), 1719 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.16–3.08 (6H, m, H-3, H-5 and H-6), 4.61 (1H, dd, J=6, 7.2 Hz, H-2), 7.21–7.60 (8H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 37.38, 38.38 and 45.28 (C3, C5 and C6), 44.34 (C4), 48.76 (C2), 120.08 (CN), 124.91, 128.55 and 131.30 (C2′, C5′ and C6′), 126.55 (C1″), 127.72, 129.59 and 135.19 (C2″, C3″, C4″, C5″ and C6″), 133.32, 133.75 and 137.94 (C1′, C3′ and C4′) and 203.24 (C═O); *m/z* (EI) 429 (0.4%, 2×^{37}Cl and ^{82}Se $[M]^+$), 427 (3, ^{35}Cl, ^{37}Cl and ^{82}Se $[M]^+$), 425 (12, ^{35}Cl, ^{37}Cl and ^{79}Se $[M]^+$), 423 (19, 2×^{35}Cl and ^{79}Se $[M]^+$), 421(9, 2×^{35}Cl and ^{78}Se $[M]^+$), 420 (3, 2×^{35}Cl and ^{77}Se $[M]^+$), 419 (3, 2×^{35}Cl and ^{76}Se $[M]^+$), 268 (13), 266 (21), 158 (20), 155 (20), 140 (18), 77 (28) and 55 (100). The crude was dissolved in dichloromethane (10 mL) and cooled to −40°C, hydrogen peroxide (0.2 mL) was added and the mixture was warmed to room temperature and stirred over 2 h. Dichloromethane (20 mL) was added and the mixture was washed with a saturated solution of sodium hydrogen carbonate (2×25 mL) and a saturated solution of sodium chloride (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. Flash column chromatography on silica (diethyl ether/hexane, 1:1) yielded the product **8** (40 mg, 52%) whose spectral data was consistent with that previously observed.

Method C: 4-Cyano-4-(3,4-dichlorophenyl)cyclohexanone **1** (2.5 g, 7.5 mmol) was dissolved in THF (30 mL) and the solution was cooled to −78°C under N_2. A solution of 1M LiHMDS in THF (10 mL, 10.0 mmol) was added and the mixture stirred for 10 min. TIPSCl (3 mL, 14.0 mmol) was added and the mixture left to warm to room temperature over 1 h. The reaction was quenched with saturated $NaHCO_3$ solution (70 mL) and the product extracted with diethyl ether (3×70 mL). The organic layers were combined and dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica (petroleum ether/diethyl ether, 7:1) to yield the product TIPS enol ether (1.2 g, 37%) as a white solid. (Found M^+ 423.1547. $C_{22}H_{31}N^{35}Cl_2OSi$ requires 423.1552); ν_{max}(film) (cm^{-1}) 2238 (CN); δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.99–1.53 (21H, m, 3×C*H*(CH_3)$_2$), 2.15–2.20 (6H, m, H-3, H-5 and H-6), 4.88 (1H, m, H-2), 7.35 (1H, dd, J_o=8.5 Hz, J_m=2.1 Hz, H-6′), 7.47 (1H, d, J_o=8.5 Hz, H-5′) and 7.57 (1H, d, J_m=2.1 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 12.60 (3×*C*H(CH_3)$_2$), 17.95 (3×CH(*C*H_3)$_2$), 27.61, 33.04 and 36.00 (C3, C5 and C6), 40.27 (C4), 98.73 (C2), 122.05 (CN), 125.41, 128.07 and 130.91 (C2′, C5′ and C6′), 132.43 and 133.26 (C3′ and C4′), 140.37 (C1′) and 150.74 (C1); *m/z* (EI) 427 (1%, 2×^{37}Cl $[M]^+$), 425 (3, ^{37}Cl and ^{35}Cl $[M]^+$), 423 (5, 2×^{35}Cl $[M]^+$), 384 (12, 2×^{37}Cl $[M-C_3H_7]^-$), 382 (55, ^{37}Cl and ^{35}Cl $[M-C_3H_7]^+$), 380 (82, 2×^{35}Cl $[M-C_3H_7]^+$), 357 (12, 2×^{37}Cl $[M-C_3H_7-HCN]^+$), 355 (56, 357 (12, ^{37}Cl and ^{35}Cl $[M-C_3H_7-HCN]^+$) and 353 (100, 2×^{35}Cl $[M-C_3H_7-HCN]^+$). $(NH_4)_2Ce(NO_3)_6$ (724 mg, 1.32 mmol) was added to a solution of the 4-cyano-4-(3′,4′-dichlorophenyl)-1-(triisopropylsilyloxy)cyclohexene (250 mg, 0.59 mmol) in DMF (6 mL) at 0°C. The mixture was stirred for 18 h and the reaction quenched with saturated sodium hydrogen carbonate solution (25 mL). The product was extracted with diethyl ether (3×25 mL) and the organic layers where combined and washed with lithium chloride solution (3×25 mL). The crude product was purified by flash column chromatography on silica to yield the product **8** (50 mg, 32%) whose spectral data was consistent with those previously observed.

3.3.3. 5-Cyano-5-(3′,4′-dichlorophenyl)-4,5-dihydro-3*H*-oxepin-2-one 7. 4-Cyano-4-(3′,4′-dichlorophenyl)cyclohex-2-enone **8** (54 mg, 0.20 mmol) and urea hydrogen peroxide (100 mg, 2.0 mmol) were dissolved in dichloromethane (5 mL) with sodium hydrogen phosphate (259 mg, 1.8 mmol) under nitrogen. The mixture was cooled to 0°C and the trifluoroacetic anyhydride (0.07 mL, 0.5 mmol) was added. Urea hydrogen peroxide (50 mg, 1.0 mmol) and trifluoroacetic anhydride (0.07 mL, 0.5 mmol) were added. The mixture was stirred at room temperature for 12 h and then quenched with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3×50 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The product was obtained as colourless oil **7** (40 mg, 80%). (Found 281.0005. $C_{13}H_9{}^{35}Cl_2NO_2$ requires 281.0010); ν_{max}(film) (cm^{-1}) 2240 (CN), 1771 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.22 (1H, m, H_{ax}-4), 2.54 (1H, m, H_{ax}-3), 2.89–3.08 (2H, m, H_{eq}-3 and H_{eq}-4), 5.10 (1H, dd, J=7.7, 1.6 Hz, H-4), 6.51 (1H, d, J=7.7 Hz, H-3), 7.30 (1H, dd, J_o=8.4 Hz, J_m=2.3 Hz, H-6′), 7.35 (1H, d, J_o=8.4 Hz, H-5′) and 7.58 (1H, d, J_m=2.3 Hz, H-2′); δ_C (75 MHz, $CDCl_3$; Me_4Si) 31.36 and 34.29 (C6 and C7), 46.52 (C5), 109.29 (C3), 119.70 (CN), 125.40, 128.25, and 131.44 (C2′, C5′ and C6′), 133.73, 134.00 and 138.00 (C1′, C3′ and C4′), 140.64 (C4) and 168.77 (CO); *m/z* (EI) 281 (1, 2×^{35}Cl $[M]^+$), 255 (17), 253 (28), 190 (11), 84 (22) and 55 (100).

3.3.4. 4-Cyano-1,2-epoxy-4-(3′,4′-dichlorophenyl)cyclohexyl acetate 10. 4-Cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate **2** (54 mg, 0.17 mmol) and sodium hydrogen phosphate (101 mg, 0.7 mmol) were dissolved in dichloromethane (10 mL), the mixture was cooled to 0°C and *m*-chloroperbenzoic acid (247 mg, 1.4 mmol) was added. The reaction was left to warm to room temperature. The reaction was quenched with water (30 mL) and extracted with dichloromethane (3×50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The product **10** was isolated as a white solid as an inseparable mixture of diastereoisomers (41 mg, 72%). For the major diastereoisomer (Found M^- 325.0277; $C_{15}H_{13}N^{35}Cl_2O_3$ requires 325.0272); ν_{max}(film) (cm^{-1}) 2238 (CN), 1755 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.89–2.81 (6H, m, H-3, H-5 and H-6), 2.11 (3H, s, CH_3), 3.50 (1H, d, J=4.8 Hz, H-2), 7.29 (1H, dd, J_o=8.5 Hz, J_m=2.4 Hz, H-6′), 7.48 (1H, d, J_o=8.5 Hz, H-5′) and 7.55 (1H, d, J_m=2.4 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 21.02 (CH_3), 24.76, 30.25 and 37.33 (C3, C5 and C6), 39.92 (C4), 55.20 (C2), 81.14 (C1), 120.78 (CN), 124.96, 127.81 and 131.18 (C2′, C5′ and C6′), 132.93 and 133.56 (C3′ and C4′), 139.55 (C1′) and 169.10 (C═O); *m/z* (EI) 325 (1%, $[M]^+$), 199 (13), 197 (27), 55 (18) and 43 (100, CH_3CO).

3.3.5. 2-Hydroxy-4-cyano-4-(3′,4′-dichlorophenyl)cyclohexanone 11. The 4-cyano-1,2-epoxy-4-(3,4-dichlorophenyl)cyclohexyl acetate **10** (50 mg, 0.15 mmol) was

dissolved in chloroform (10 mL) and acetic acid (0.26 mL) and a catalytic amount of *p*-toluensulfonic acid (7 mg, 0.04 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogencarbonate solution (20 mL) and extracted with dichloromethane (3×20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica (petroleum ether/ethyl acetate, 2:1) to yield the product **11** (32 mg, 74%) as a white solid. The product was a 5:1 mixture of diastereoisomers. For the major isomer (Found M^+ 283.0167; $C_{13}H_{11}N^{35}Cl_2O_2$ requires 283.0164); ν_{max}(film) (cm^{-1}) 3438 (OH), 2238 (CN), 1727 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.97–3.02 (6H, m, H-3, H-5 and H-6), 3.52 (1H, br, OH), 4.61 (1H, q, J=6.3 Hz, H_{ax}-2), 5.59 (1H, q, J=6.2 Hz, H_{eq}-2), 7.28 (1H, dd, J_m=2.2 Hz, J_o=8.5 Hz, H-6′), 7.46 (1H, d, J_o=8.5 Hz, H-5′) and 7.53 (1H, d, J_m=2.2 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 36.09, 38.02 and 42.42 (C3, C5 and C6), 72.12 (C2), 41.89 (C4), 120.31 (CN), 124.86, 127.69 and 131.38 (C2′, C5′ and C6′), 133.45, 133.85 and 137.88 (C1′, C3′ and C4′) and 207.31 (CO); *m/z* (EI) 287 (2%, 2×^{37}Cl $[M]^+$), 285 (9, ^{37}Cl and ^{35}Cl $[M]^+$), 283 (15, 2×^{35}Cl $[M]^+$), 241 (10), 226 (11) and 197 (100).

3.3.6. Methyl 4-cyano-(3,4-dichlorophenyl)-6-oxo-hexanoate 5. *Method A*. The 4-cyano-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate **2** (100 mg, 0.3 mmol) was dissolved in methanol/dichloromethane, 1:4 (10 mL). The mixture was cooled to −78°C and O_3/O_2 was bubbled through the solution. After 1 h the flow of O_3/O_2 was stopped and O_2 was bubbled through until the solution became colourless. Triphenylphosphine (125 mg, 0.48 mmol) was added to the reaction mixture and left to stir for 18 h under nitrogen. The solvent was removed in vacuo and the crude was purified by flash column chromatography on silica (ethyl acetate/hexane, 1:1) to yield the product as a colourless oil **5** (62 mg, 62%). (Found C, 53.30; H, 4.38; N, 4.24. $C_{14}H_{13}O_3N^{35}Cl_2$ requires C, 53.52; H, 4.17; N, 4.46%); ν_{max}(film) (cm^{-1}) 2241 (CN), 1730 (CO); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.02–2.49 (4H, m, H-2 and H-3), 3.16 (2H, s, H-5), 3.61 (3H, s, $-OCH_3$), 7.30, 7.46 and 7.51 (3H, m, H-2′, H-5′ and H-6′) and 9.62 (1H, s, H-6); δ_C (75 MHz; $CDCl_3$; Me_4Si) 29.57 and 35.29 (C2 and C3), 42.22 (C4), 52.01 (C5), 52.16 (CH_3), 119.68 (CN), 125.38, 128.09 and 131.41 (C2′, C5′ and C6′), 133.36, 133.97 and 136.40 (C1′, C3′ and C4′), 171.88 (C1) and 195.68 (C6); *m/z* (EI) 313 (1.5%, $[M]^+$), 298 (17), 283 (12), 210 (100) and 197 (50).

3.3.7. (*R*)-(−)-Methyl 4-cyano-4-(3′,4′-dichlorophenyl)-6-oxo-hexanoate 5. The title compound (*R*)-(−)-**5** was synthesized in an identical manner to that above using (*S*)-(+)-4-cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate (+)-**2** (1.0 g, 3.2 mmol) to yield, after purification by flash column chromatography on silica (ethyl acetate/hexane, 1:1), the product (*R*)-(−)-**5** (610 mg, 60%) as a colourless oil. $[\alpha]_D$=−7.5 (c=2.0 in chloroform) whose spectral data was consistent with the data previously observed.

Method B. Sodium periodate (45 mg, 0.21 mmol) was added to a solution of the hydroxy-ketone **11** (32 mg, 0.14 mmol) in methanol (3 mL) at 0°C and the reaction was stirred for 18 h. The reaction was quenched with water (5 mL) and the methanol removed in vacuo. The aqueous layer was extracted with dichloromethane (10 mL), the organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash column chromatography on silica (ethyl acetate/hexane, 1:3) to yield the product **5** (20 mg, 58%) as a colourless oil whose spectral data was consistent with the data previously observed.

3.3.8. (*S*)-Methyl 4-cyano-4-(3′,4′-dichlorophenyl)-6-hydroxyhexanonoate 12. Sodium triacetoxyborohydride (339 mg, 1.6 mmol) was added to a solution of the (−)-ester aldehyde **5** (138 mg, 0.44 mmol) in acetic acid (20 mL) at 20°C. After 2.5 h the reaction was quenched with water (20 mL) and extracted with dichloromethane (3×30 mL). The organic layers were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica (hexane/ethyl acetate, 1:1) to yield the product (*S*)-**12** (100 mg, 72%) as a colourless oil. (Found M^+ 315.0428. $C_{14}H_{15}NCl_2O_3$ requires 315.0429); ν_{max}(film) (cm^{-1}) 3297 (OH), 2250 (CN), 1738 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.11–2.55 (6H, m, H-2, H-3 and H-5), 3.50–3.68 (2H, m, H-6), 3.63 (3H, s, CH_3O), 7.28 (1H, dd, J_o=8.5 Hz, J_m=2.5 Hz, H-6′), 7.49 (1H, d, J_o=8.5 Hz, H-2′) and 7.53 (1H, d, J_m=2.5 Hz, H-5′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 29.8, 35.85 and 42.69 (C2, C3 and C5), 44.76 (C4), 51.94 (C6), 59.05 (OCH_3), 120.65 (CN), 125.30, 128.07 and 131.18 (C2′, C5′ and C6′), 132.82, 133.68 and 137.27 (C3′, C4′ and C1′) and 172.20 (CO); *m/z* (EI) 315 (11%, $[M]^+$), 284 (15), 239 (48), 210 (55), 197 (66), 173 (23) and 74 (100).

3.3.9. (1′*S*,3*S*,4′*R*)-(−)-(4′,7′,7′)-Trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]heptane-1′-carboxylic acid 3-cyano-3-(3″,4″-dichlorophenyl)-5-methoxycarbonyl-pentanyl ester (−)-13. (*S*)-Camphanyl chloride (115 mg, 0.53 mmol) and triethylamine (0.17 mL, 1.23 mmol) were added to a solution of the (*S*)-methyl 4-cyano-4-(3′,4′-dichlorophenyl)-6-hydroxyhexanoate **12** (100 mg, 0.32 mmol) in dichloromethane (2 mL). DMAP (13 mg, 0.041 mmol) was added and the mixture was stirred at room temperature for 2 h whereupon the reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The organic layers were combined and washed with saturated sodium chloride solution (3×10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica (hexane/ethyl acetate, 1:1) to yield the product (−)-**13** (130 mg, 83%) as a white crystalline solid which was crystallized from 2-propanol. Mp 143.0–144.0°C; (Found C, 58.27; H, 5.47; N, 2.77; M^+ 495.1219. $C_{24}H_{27}N^{35}Cl_2O_6$ requires C, 58.07; H, 5.48; N, 2.82%, 495.1215); $[\alpha]_D$=−22 (c=1 in chloroform); ν_{max}(film) (cm^{-1}) 2256 (CN), 1791 (C=O) and 1739.0 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.93 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.62–2.55 (10H, m, H-2, H-4, H-5, H-5′and H-6′), 3.63 (3H, s, CH_3O), 4.13–4.30 (2H, m, H-6) and 7.24–7.54 (3H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.63 (CH_3), 16.71 (2×CH_3), 28.88, 29.78, 30.51, 35.90 and 38.80 (C2, C4, C5, C5′ and C6′), 44.84 (C3), 51.96 (CH_3O), 54.24 and 54.73 (C4′ and C7′), 61.43 (C1), 90.81

(C1′), 120.04 (CN), 125.34, 131.51 and 133.27 (C2″, C5″ and C6″), 133.27, 133.93 and 136.46 (C1″, C3″ and C4″), 167.29, 171.97 and 177.85 (3×CO); *m/z* (EI) 497 (1%, ^{37}Cl and ^{35}Cl $[M]^+$), 495 (2, 2×^{35}Cl $[M]^+$), 316 (2), 298 (7), 210 (11), 136 (94), 134 (86) and 109 (100).

3.3.10. (4*S*)-(−)-Cyano-4-(3′,4′-dichlorophenyl)-6-*N*-morpholinoazetidine-hexanoic acid methyl ester 15. (*R*)-(−)-Methyl 4-cyano-4-(3′,4′-dichloropheyl)-6-oxo-hexanoate **5** (180 mg, 0.57 mmol), morpholinoazetidine hydrochloride (98 mg, 0.54 mmol) and triethyl amine (0.064 mL) were stirred in THF (10 mL) for 30 min at room temperature under an atmosphere of nitrogen. Sodium triacetoxyborohydride (160 mg, 0.74 mmol) was added followed by acetic acid (0.04 mL) and the reaction was stirred for 3 h. The reaction was quenched with saturated sodium hydrogen carbonate solution (5 mL) and the product extracted with dichloromethane (3×10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash column chromatography on silica (dichloromethane/methanol, 9:1) to yield the product (−)-(*S*)-**15** (227 mg, 91%) as a colourless oil. $[\alpha]_D$=−17.6 (*c*=2 in chloroform). (Found $[M+H]^-$ 440.1521. $C_{21}H_{27}{}^{35}Cl_2N_3O_3$ requires 440.1507); ν_{max}(film) (cm^{-1}) 2220 (CN) and 1738 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.87–3.71 (21H, m, 10×H-2, H-3, H-5, H-6, H-2″, H-3″, H-4″, H6″, H-7″, H-9″ and H-10″), 3.62 (3H, s, CH_3O) and 7.22–7.29 (3H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 29.86, 35.82, 38.23, 50.15, 55.11, 58.38, 66.55 (C2, C3, C5, C6, C2″, C4″, C6″, C7″, C9″ and C10″), 45.30 (C4), 51.87 (CH_3), 55.52 (CH), 120.55 (CN), 125.28, 128.12 and 131.18 (C2′, C5′ and C6′), 132.76, 133.66 and 137.35 (C1′, C3′ and C4′) and 172.23 (CO); *m/z* (CI) 442 (85%, ^{37}Cl and ^{35}Cl $[M+H]^+$), 440 (100, 2×^{35}Cl $[M+H]$ and 406 (20).

3.3.11. (5*S*)-(+)-5-(3′,4′-Dichlorophenyl)-5-(2″-*N*-morpholinoazetidinethyl)-piperidin-2-one 16. (−)-(4*S*)-4-Cyano-4-(3,4-dichlorophenyl)-6-*N*-morpholinoazetidine-hexanoic acid methyl ester (−)-**15** (180 mg, 0.41 mmol) was dissolved in methanol (20 mL) and Raney Nickel (18 mg) was added followed by NH_4OH (0.10 mL). The mixture was heated under reflux for 18 h under an atmosphere of hydrogen. The solution was cooled and filtered through celite and the methanol was removed in vacuo. The residue was dissolved in dichloromethane (20 mL), washed with a saturated solution of $NaHCO_3$ (3×20 mL). The solution was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica (dichloromethane/methanol, 10:1) to yield the product (*S*)-(+)-**16** (166 mg, 97%), whose spectral data was consistent with the data previously observed. $[\alpha]_D$=+7.2 (*c*=2.2 in chloroform). (Found $[M+H]^+$ 412.1545. $C_{20}H_{28}{}^{35}Cl_2N_3O_2$ requires 412.1558); ν_{max}(film) (cm^{-1}) 1667 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.57–3.70 (23H, m, H-3, H-4, H-6, H-1″, H-2″, H-morpholinoazetidine), 6.78 (1H, br, NH), 7.14 (1H, dd, J_o=8.4 Hz, J_m=2.1 Hz, H-6′), 7.37 (1H, d, J_m=2.2 Hz, H-2′) and 7.42 (1H, d, J_o=8.4 Hz, H-5′); δ_C (75 MHz; $CDCl_3$; Me_4Si) 28.19, 32.30, 37.76, 49.98, 50.19, 54.44, 58.48 and 66.53 (C3, C4, C6, C1″, C2″ and CH_2–morpholinoazetidine), 38.92 (C5), 55.55 (CH–morpholinoazetidine), 125.86, 128.61 and 130.77 (C2′, C5′ and C6′), 131.04, 133.08 and 142.66 (C1′,C3′ and C4′) and 171.69 (C═O); *m/z* (CI) 414 (25%, ^{37}Cl and ^{35}Cl $[M+H]^+$), 412 (38, 2×^{35}Cl $[M+H]^+$), 380 (32), 378 (88), 344 (39), 145 (36), 114 (100), 88 (83) and 52 (75).

3.3.12. (5*S*)-(+)-5-(3′,4′-Dichlorophenyl)-1-(3‴-methoxybenzyl)-5-(2″-*N*-morpholinoazetidin ethyl)-piperidin-2-one 3. A dispersion of 60% sodium hydride in oil (20 mg, 0.25 mmol) was washed with hexane and added to a solution of (5*S*)-5-(3,4-dichlorophenyl)-5-(2-*N*-morpholinoazetidinethyl)-piperidin-2-one (+)-**16** (70 mg, 0.17 mmol) in DMF (1 mL) at 0°C under an atmosphere of nitrogen. 18-Crown-6 (0.05 mL, 0.25 mmol) was added and the mixture was stirred for 10 min. whereupon *m*-methoxybenzyl bromide (0.02 mL, 0.17 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 7 h. The reaction was quenched with water (5 mL) and the product extracted with ethyl acetate (3×10 mL). The organic layers were combined and washed with saturated sodium chloride solution (3×20 mL) and water (3×20 mL). The solvent was removed in vacuo, dried and the crude product was purified by flash column chromatography on silica (dichloromethane/methanol, 9:1) to yield the title product (*S*)-(+)-**3** (25 mg, 28%) as a colourless oil. (Found $[M+H]^+$ 532.2133. $C_{28}H_{36}N_3O_3Cl_2$ requires 532.2133). $[\alpha]_D$=+42 (*c*=1.5 in chloroform); ν_{max}(film) (cm^{-1}) 1633 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.34–3.68 (23H, m, C*H*$_2$ and C*H*), 3.69 (3H, s, CH_3O), 4.31 (1H, d, *J*=14 Hz, benzylic-H), 4.83 (1H, d, *J*=14 Hz, benzylic-H), 6.75–6.86 (3H, m, Ar-H), 7.03–7.04 (1H, m, Ar-H), 7.22–7.30 (3H, m, Ar-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.81, 32.36 and 39.51 (C3, C4 and C1″), 38.42 (C5), 50.18 (CH_3O), 50.28, 54.25, 54.85, 55.22 and 58.43 (C6, C2″, C4″, C8″, C6″, C12″ and C-benzylic), 55.58 (C5″), 66.50 (C9″ and C11″), 113.37, 114.27, 120.99 and 129.73 (C2‴, C4‴, C5‴ and C6‴), 125.61, 128.32 and 130.51 (C2′, C5′and C6′), 130.87, 132.04 and 142.39 (C1′, C3′ and C4′), 138.04 (C1‴), 159.95 (C3‴) and 168.78 (C═O); *m/z* (FAB) 535 (1%, 2×^{37}Cl $[M]^+$), 533 (1, ^{37}Cl and ^{35}Cl $[M]^+$), 531 (1, 2×^{35}Cl $[M]^+$), 121 (13), 113 (100) and 98 (11).

3.3.13. *N*-(3-methoxybenzyl)piperidin-2-one 18. A solution of valerolactam **17** (200 mg, 2.0 mmol) and sodium hydride (150 mg, 3.0 mmol) in xylene (10 mL) was heated to reflux. The *m*-methoxybenzyl chloride (0.3 mL) in xylene (2 mL) was added dropwise and mixture was heated under reflux for 18 h. The reaction was quenched with water (20 mL), the xylene was removed in vacuo and the aqueous layer was extracted with dichloromethane (3×20 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash column chromatography on silica (petroleum ether/ethyl acetate, 1:2) to yield the product **18** (270 mg, 62%) as a colourless oil. (Found M^+ 219.1260. $C_{13}H_{17}NO_2$ requires 219.1259); ν_{max}(film) (cm^{-1}) 1644 (C═O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.70–1.81 (4H, m, H-4 and H-5), 2.42–2.46 (2H, m, H-3), 3.15–3.19 (2H, m, H-6), 3.76 (3H, s, CH_3O), 4.55 (2H, s, H-benzylic), 6.76–6.80 (3H, m, Ar-H) and 7.21 (1H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 21.21, 23.01 (C4 and C5), 32.24 (C3), 47.16 (C-Bn), 49.87 (C6), 55.05 (CH_3), 112.71, 113.62, 120.31, 129.56, 139.01 and 159.98 (C-ar) and 169.86 (C═O); *m/z* (EI) 219 (71%, $[M]^+$), 204 (3, $[M-CH_3]^+$), 134 (22), 122 (100), 121 (57).

Acknowledgements

We are grateful to the University of Liverpool and Pfizer Ltd for a studentship (M. L. E. H.), BBSRC for a PDRA (G. A.) and to Amano Enzyme Europe Ltd for kind donation of *Pseudomonas fluorescens* lipase.

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