Desymmetrisation of 4,4-disubstituted cyclohexanones by enzyme-catalysed resolution of their enol acetates

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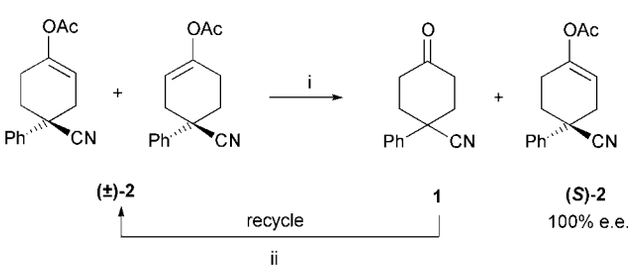
Enol acetates **3**–**10** derived from prochiral 4,4-disubstituted cyclohexanones can be resolved with *Pseudomonas fluorescens* lipase to give enantiomerically pure (>99% ee) enol esters by transesterification with *n*-BuOH. The product ketones are prochiral and can easily be recycled giving an overall desymmetrisation of the ketone. Highest selectivity was obtained for substrates containing a 4-cyano and 4-aryl or a 4-benzyloxy substituent. The methodology was compared to asymmetric deprotonation–enolate trapping using the chiral base (*S*,*S*)-bis(α-methylbenzyl)amide which gave low (54–64%) ee's for this class of ketones.

Introduction

The desymmetrisation of prochiral ketones has become an important method in asymmetric synthesis. The use of chiral lithium amides for the deprotonation of 4-substituted cyclohexanones and prochiral bicyclic ketones has been developed by Koga[1] and Simpkins[2] respectively.[3] High enantioselectivity has been achieved using a number of specialised chiral amines. However, in order to achieve high selectivity, the reactions are run at low temperatures (−78 °C or −100 °C) and require anhydrous conditions. The chiral silyl enol ethers which result from enolate trapping can provide a handle for maintaining the newly introduced asymmetry by oxidative cleavage or electrophilic addition. Baeyer–Villiger reactions using monooxygenase enzymes[4] and asymmetric copper and platinum catalysts[5,6] have also recently attracted attention 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 which can operate at ambient temperature are needed.

We recently reported the use of a lipase enzyme for the effective desymmetrisation of prochiral ketone 4-cyano-4-phenylcyclohexanone **1** (Scheme 1).[6] The racemic enol acetate **2**



Scheme 1 *Reagents and conditions*: i, *Pseudomonas fluorescens* lipase, THF, *n*-BuOH; ii, isopropenyl acetate, *p*-TsOH.

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 desymmetrisation of the prochiral ketone.

We now report the use of related enol acetate substrates derived from prochiral 4,4-disubstituted cyclohexanones to probe the structural requirements for enantioselectivity with this enzyme.

Results and discussion

In the preliminary work[6] we varied the chain length of the ester group of the substrate, the reaction solvent and the alcohol for transesterification. The nature of the ester group turned out not to affect the enantioselectivity of PFL so in all subsequent substrates we have employed the enol acetate. Tetrahydrofuran, toluene, diisopropyl ether and acetonitrile were tested as solvents and all gave approximately the same enantioselectivity with 1–2 equivalents of *n*-BuOH for the transesterification. Tetrahydrofuran was the solvent of choice since the reaction time (18 h) allowed us to closely monitor the progress of the reaction and stop it at an appropriate degree of conversion to recover a maximum yield of optically pure enol ester. It was found that the reaction needed to be run to 67% conversion to leave unreacted optically pure (100% ee) (*S*)-enol acetate **2**. In order to test the scope of this biotransformation for the production of chiral enol esters derived from 4,4-disubstituted prochiral cyclohexanones, we synthesized racemic enol acetates **3**–**10** as new substrates (Fig. 1). These were chosen with some synthetic targets in mind and to test the importance of the aromatic and cyano groups for selectivity. The enol acetate **3** was chosen since synthetic elaboration to a series of Pfizer NK-2 antagonists was envisaged and substrates **4** and **5** would further test the effect of substitution on or in the phenyl ring. Substrate **6** would test the requirement for the cyano group. Substrate **7** was chosen with the view to converting the chiral enol acetate to a chiral dione equivalent **11** by Tsuji[7] oxidative rearrangement to the enone followed by *cis* dihydroxylation of the alkene (Scheme 2). Cyanohydrins can be considered to be protected ketones and in compound **11** there exist two distinguishable ketones. The possibility of bi-directional synthesis is available by first reacting the free ketone and then unmasking the protected ketone or conversely protecting the free ketone, then unmasking and reacting the protected ketone. The bicyclic structure which results from the acetonide formation should

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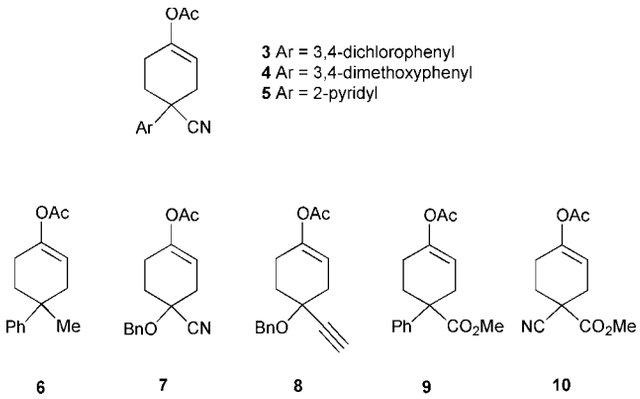
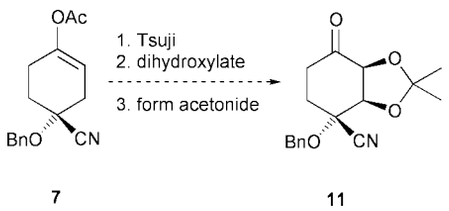


Fig. 1 New substrates for resolution by PFL-catalysed transesterification.



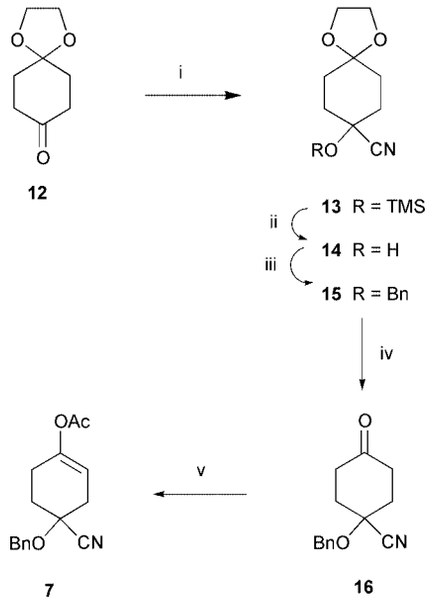
Scheme 2 Potential application of enol acetate **7** to make the chiral diketone equivalent **11** for bi-directional synthesis.

confer diastereocontrol upon subsequent nucleophilic addition to the ketone. Substrate **8** contains the acetylene group as an isosteric replacement for the cyano group to probe the need for the polar nitrogen in substrate **7**. Substrate **9** replaces the cyano with a polar ester group and substrate **10** replaces the aromatic group with the ester group.

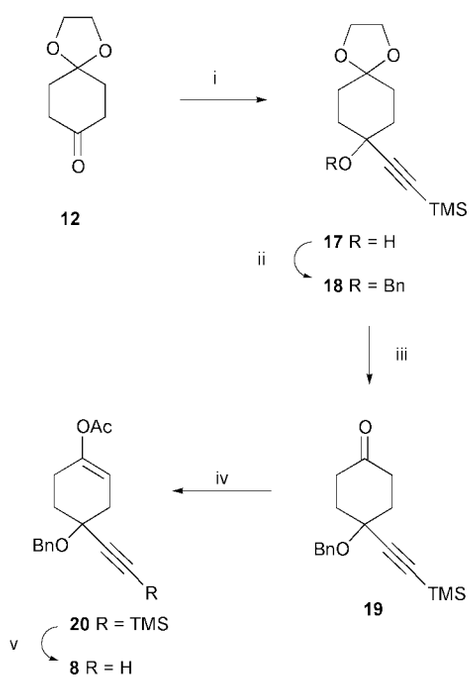
The cyclohexanone precursors to enol esters **3**–**5** and **9** and **10** were readily made using a procedure similar to that previously described by Dei[8] involving Michael addition of the appropriate arylacetonitrile or activated ester to methyl acrylate followed by Dieckmann cyclisation, hydrolysis and decarboxylation. 4-Methyl-4-phenylcyclohexanone, the precursor to enol acetate **6**, was made by reduction of 4-methyl-4-phenylcyclohex-2-en-1-one which was prepared according to the literature.[9] The enol acetates were prepared using either acetic anhydride with a catalytic amount of toluene-*p*-sulfonic acid or LiHMDS–acetic anhydride.

The enol acetate **7** was synthesised starting from the commercially available cyclohexane-1,4-dione monoethylene acetal **12** (Scheme 3). The TMS-cyanohydrin **13** was prepared in good yield from ketone **12** using trimethylsilyl cyanide in the presence of zinc chloride. The removal of both the TMS and acetal protecting groups simultaneously with strong acid gave the hydroxyketone. However all attempts to benzylate this met with failure and so it was decided to sequentially remove the two protecting groups, removing the acetal after benzylation of the secondary alcohol **14**. Treatment of TMS-cyanohydrin **13** with tetra-*n*-butylammonium fluoride and HCl (to minimise elimination of HCN; giving **12**) gave alcohol **14** in good yield. Subsequent benzylation with benzyl trichloroacetimidate and TMS-triflate gave the benzylated acetal **15**. Removal of the acetal protecting group was achieved by stirring in refluxing HCl to afford the ketone target **16**. The corresponding enol acetate **7** was formed in good yield using lithium hexamethyldisilazide–acetic anhydride.

The synthetic route to the enol acetate **8** was analogous to the route used for the synthesis of enol acetate **7** (Scheme 4). Reaction of the anion of TMS-acetylene with cyclohexane-1,4-dione monoethylene acetal **12** in THF gave the required alcohol **17** in moderate yield. A small amount (9%) of the desilylated acetylene was also isolated from this reaction, although the reason for this desilylation reaction is unknown. Benzylation



Scheme 3 *Reagents and conditions*: i, TMSCN, $ZnCl_2$, Et_2O, rt, 18 h (81%); ii, TBAF, THF, rt, 2 h (82%); iii, benzyl trichloroacetimidate, TMS-triflate, Et_2O, rt, 17 h (60%); iv, HCl, THF, reflux, 6 h (52%); v, LiHMDS, Ac_2O, THF, 0 °C, 1.5 h (81%).



Scheme 4 *Reagents and conditions*: i, TMS-acetylene, *n*-BuLi, THF, −10 °C, 5 h (49%); ii, benzyl trichloroacetimidate, TMS-triflate, Et_2O, rt, 5 h (60%); iii, HCl, THF, reflux, 2 h (42%); iv, LiHMDS, Ac_2O, THF, 0 °C, 1.5 h (88%); v, TBAF, THF, rt, 2 h (74%).

of the silylated compound **17** with benzyl trichloroacetimidate followed by removal of the acetal gave the required cyclohexanone **19**. The low yield (42%) in the second step was possibly caused by removal of the TMS group although the corresponding deprotected compound was not isolated. The enol acetate **20** was formed using LiHMDS and Ac_2O in good yield from ketone **19**. The final step involved deprotection of the TMS-acetylene moiety by stirring with TBAF in THF to give the target enol acetate **8** in 74% yield.

Results of biotransformations

Having screened around 25 lipases with substrate **2** in the early stages of this work we decided to use the commercially supplied

Table 1 Biotransformation of substrates **2**–**10** with *Pseudomonas fluorescens* lipase[a]

Substrate	R^1	R^2	Solvent	Conversion to ketone (%)	Ee of enol acetate (%)	*E*
2	Ph	CN	THF	64	>99	24
3	3,4-Cl_2Ph	CN	THF	70	>99	15
3	3,4-Cl_2Ph	CN	Toluene	52	61	6.5
4	3,4-$(MeO)_2$Ph	CN	THF	71	95	7.4
5	2-Pyridyl	CN	THF	84	93	2.2
5	2-Pyridyl	CN	Toluene	71	94	7
6	Ph	CH_3	Hexane	75	17	1.3
7	OBn	CN	THF	73	91	5.6
8	OBn	C_2H	THF	82	12	1.2
9	Ph	CO_2CH_3	THF	62	7	1.2
10	CN	CO_2CH_3	THF	30	0	—

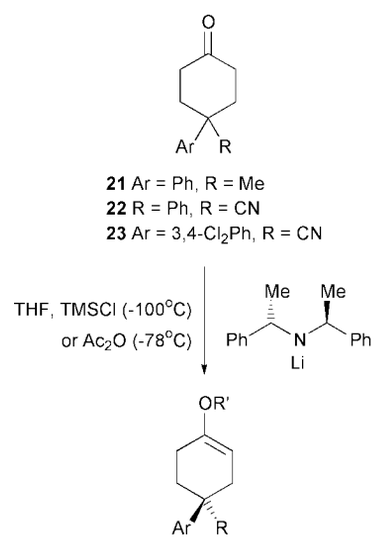
[a] Reactions were carried out in organic solvent, 1.2 eq. *n*-BuOH, 100 mg of enol acetate (10 mg ml^{-1}) and PFL (30 mg) at room temperature. Ee's determined by chiral HPLC, Chiralcel OJ and Chiralpak AD.

freeze-dried Amano PFL for all further studies with the new substrates. Under optimised conditions the enol acetate **2** was resolved to give enantiomerically pure enol ester (*S*)-**2** (>99% ee) after 67% conversion giving an enantiomeric ratio (*E*-value) of 24. The 3,4-dichlorophenyl substrate **3** was resolved with slightly reduced but satisfactory selectivity giving the enol ester (*S*)-**3** in >99% ee after 70% conversion to ketone ($E = 15$) (Table 1). The reaction in toluene was less selective ($E = 6.5$). The absolute configurations of enol acetates (*S*)-**2** and (*S*)-**3** were determined by X-ray crystal analysis of camphanic ester derivatives.[6,10] Substrates **4** and **5** were both resolved with similar enantioselectivity in THF and toluene respectively ($E = 7.4$ and 7). Evidently the active site of PFL can accommodate changes in the nature of the substitution on the phenyl ring of the substrate without affecting the selectivity significantly. The change in solvent requirement for optimum selectivity with substrate **5** may reflect small conformational changes in the enzyme in these solvents. We have previously shown that enol acetates derived from 4-methyl- and 4-phenylcyclohexanone did not undergo biotransformation in tetrahydrofuran but in hexane they were poorly resolved and reaction times were considerably longer.[6]

Substrate **6** containing both 4-phenyl and 4-methyl groups was transformed in hexane with very low selectivity ($E = 1.3$), supporting the finding with the earlier monosubstituted substrates that the cyano group is important for selectivity. This substrate was not transformed in THF. Incubation of the benzyl-protected cyanohydrin enol acetate **7**, in which the aromatic group is more remote from the chiral center, gave comparable ($E = 5.6$) but slightly diminished selectivity when compared to substrates **2** and **3**–**5**. However, these reactions have been run under unoptimised conditions and there is scope for improving the selectivity for this potentially useful substrate **7** by screening other enzymes or using immobilised PFL. In substrate **8** the 4-cyano group is replaced by the linear 4-acetylene group which would place similar steric demands on the enzyme active site but would lack the polarity which might be required for binding. Indeed the considerably lower selectivity ($E = 1.2$) with this substrate compared to substrate **7** confirms this. Earlier results showed that the rate of biotransformation of substrate **2** in acetonitrile was very slow (9 days for 62% conversion compared with 2.75–18 h in other solvents for 60–70% conversion).[6] This could result from a change in overall conformation of the enzyme or the stripping of essential water from the enzyme by the acetonitrile.

Substrate **9**, in which the cyano is replaced with the polar ester group, and **10** in which the aromatic is replaced with the ester group both gave very poor ($E = 1.2$) or no selectivity, with substrate **10** reacting very slowly. These results confirm the requirement for a cyano group at the 4-position for reasonable enantioselectivity with this enzyme. The absolute requirement for an aromatic group at the 4-position is less clear since substrates **6** and **9** and the previously studied monosubstituted 4-phenyl substrate were poorly resolved. Compound **10**, containing the cyano and ester groups in the 4-position was also a poor substrate suggesting the requirement for both 4-cyano and 4-aryl substituents.

The use of chiral lithium amides for the desymmetrisation of prochiral ketones is well developed for a number of substrate types. A range of chiral lithium amides have been developed which can, under appropriate conditions, give high enantiomeric selectivity for the silyl enol ether products. As a comparison we have examined a limited number of asymmetric deprotonation reactions with the prochiral ketone precursors to the current class of substrates using the lithium amide derived from the commercially available (*S,S*)-(−)-bis(α-methylbenzyl)-amine hydrochloride (Scheme 5). Honda[11] reported the asymmetric deprotonation of 4-phenyl-4-methylcyclohexanone **21** at −100 °C to give the (*S*)-silyl enol ether **24** in 71% ee and 81% yield. We have carried out this reaction on the 4-cyano-4-phenyl ketone **22** under the same conditions and obtained a slightly lower 64% ee and 64% yield of the enol ether **25**. We also carried out asymmetric deprotonations on ketones **22** and **23** with this base at −78 °C with an external acetic anhydride quench and obtained lower selectivity giving the corresponding (*R*)-enol acetates **2** and **3** with 54% and 57% ee respectively.



Scheme 5 Asymmetric deprotonation of ketones **21**–**23** using chiral lithium (*S,S*)-bis(α-methylbenzyl)amide.

Evidently enantioselectivities for these 4,4-disubstituted cyclohexanones are moderate and not preparatively useful for

chiral synthesis using the commercially available base. As enol esters can be regarded as enolate equivalents in the same way as silyl enol ethers, our enzymatic resolution method provides the best approach to obtaining these materials from this class of ketones. We have recently scaled up the resolution of enol ester **3** (10 g) and shown application of (*S*)-**3** in the synthesis of an important class of tachykinin NK-2 antagonists.[10] Although the resolutions are not optimal, the product ketone is not chiral and can be recycled, hence there is no loss of the 'unwanted' enantiomer normally associated with resolutions. *Pseudomonas fluorescens* lipase is commercially available in large (kg) quantities and the reactions are run at room temperature.

For the enzyme reactions the results show the importance of steric and electronic effects, both playing a crucial role in the enantioselective binding and turnover of this class of substrates with PFL. Obviously it will be important to screen more enzymes for subtrates not well resolved by PFL which has been used in this study. This can be readily done with the wide range of commercially available enzymes for a substrate of specific synthetic interest. We are currently showing synthetic application of some of these enol acetates as outlined above in addition to developing a one pot deracemisation strategy.

Experimental

General

Elemental microanalyses were performed in the departmental microanalytical laboratory. NMR spectra were recorded on a Gemini-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer. Chemical shifts are described in parts per million downfield shift from $SiMe_4$ and are reported consecutively as position (δ_H or δ_C), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, sep = septet, m = multiplet, and br = broad), coupling constant (*J*/Hz) and assignment (numbering according to the IUPAC nomenclature for the compound). ^{1}H NMR spectra were referenced internally on $CHCl_3$ (δ 7.27), ^{13}C NMR spectra were referenced on $CDCl_3$ (δ 77.5). IR spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. The samples were prepared as Nujol mulls between sodium chloride discs. The frequencies (ν) as absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard. Mass spectra and accurate mass measurements were recorded on a VG 70-070E, or a TRIO 1000. Major fragments were given as percentages of the base peak intensity (100%). Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. Flash chromatography was performed using Sorbsil C 60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography (TLC) was carried out on 0.25 mm pre-coated silica gel plates (Macherey-Nagel SIL g/UV_{254}) and compounds were visualised using UV fluorescence or permanganate. The solvents used were either distilled or of analytical reagent quality and light petrol ether refers to that portion boiling between 40 and 60 °C. THF was dried over sodium–benzophenone and distilled under nitrogen.

4-Cyano-4-phenylcyclohex-1-enyl acetate 2

To a stirred solution of 4-cyano-4-phenylcyclohexanone (0.50 g, 2.51 mmol) in dry THF (80 cm^3) at 0 °C under an argon atmosphere was added potassium *tert*-butoxide (6.0 cm^3, 3.00 mmol). The mixture was stirred at 0 °C for 30 min whereupon isopropenyl acetate (2.0 cm^3, excess) was added and the mixture stirred for a further 1 hour. The reaction was then quenched by the addition of ammonium chloride solution (50 cm^3) and ether (50 cm^3) was added. The organic layer was washed with water (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow solid, which was recrystallised from ether–hexane to give the title compound **2** as a white crystalline solid (0.57 g, 94%); mp 104–105 °C (Found: C, 74.54; H, 6.27; N, 5.78. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.26; N, 5.81%) (HRMS: found M^+, 241.10996. $C_{15}H_{15}NO_2$ requires 241.11026); ν_{max}(Nujol)/cm^{-1} 2235 (CN) and 1745 (CO); δ_H(300 MHz; $CDCl_3$) 2.12 (3 H, s, $AcCH_3$), 2.26–3.23 (6 H, m, H-3, H-5 and H-6), 5.49 (1 H, dd, *J* 3.9, *J* 4.4, H-2) and 7.22–7.50 (5 H, m, Ar-H); δ_C(75 MHz, $CDCl_3$) 20.9 ($AcCH_3$), 24.9, 32.8, 35.6 (C-3, C-5 and C-6), 40.5 (C-4), 110.8 (C-2), 122.2 (CN), 125.7, 128.2 and 129.1 (Ar-H), 139.1 (quaternary Ar), 148.0 (C-1) and 169.2 (CO); *m*/*z* (CI) 259 (100%, $[M + NH_4]^+$); *m*/*z* (EI) 241 (5%, M^+), 199 (53), 70 (100), 55 (23), 43 (80).

4-Cyano-4-phenyl-1-(trimethylsilyloxy)cyclohexene 25

To a stirred solution of (*S*,*S*)-(−)-bis(α-methylbenzyl)amine hydrochloride (0.20 g, 0.76 mmol) in dry THF (50 cm^3) at −20 °C under argon was added *n*-BuLi (1.0 cm^3, 1.67 mmol). The mixture was strirred for 30 min and then cooled to −100 °C whereupon TMSCl (0.06 g, 0.55 mmol) followed by ketone **1** (0.10 g, 0.55 mmol) in THF (5.0 cm^3) was added. The mixture was stirred for a further 1 h and then quenched by the addition of ammonium chloride solution (50 cm^3). Ether (50 cm^3) was added and the organic layer was washed with water (50 cm^3), 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 9 : 1 petrol–ethyl acetate) to give the title compound as a clear oil (0.087 g, 64%) with a 64% ee (Found: C, 70.86; H, 7.78; N, 5.11. $C_{16}H_{21}NOSi$ requires C, 70.80; H, 7.80; N, 5.16%); ν_{max}(neat)/cm^{-1} 2238 (CN) and 1747 (CO); δ_H(300 MHz; $CDCl_3$) 0.27 (9 H, s, TMS-CH_3), 2.12 (3 H, s, CH_3), 2.16–2.24 (3 H, m, CH_2), 2.59–2.63 (3 H, m, CH_2), 4.91 (1 H, dd, *J* 3.0, *J* 4.2, H-3) and 7.22–7.56 (5 H, m, Ar-H); δ_C(75 MHz, $CDCl_3$) 0.2 ($TMSCH_3$), 27.9, 33.0 and 36.1 (C-3, C-5 and C-6), 40.8 (C-4), 100.7 (C-2), 122.6 (CN), 125.7, 127.9 and 128.9 (Ar-H), 140.0 (quaternary Ar) and 150.4 (C-1); *m*/*z* (CI) 272 (35%, $[M + H]^+$) and 90 (100, $[C_3H_{10}OSi]^+$). HPLC Chiralpak AD, t_R 9.7 min, 11.2 min, eluent 9 : 1 hexane–isopropyl alcohol, flow rate 1 cm^3 min^{-1}, λ 220 nm.

Treatment of 4-cyano-4-phenylcyclohexanone with lithium (*S*,*S*)-bis(α-methylbenzyl)amide–acetic anhydride

4-Cyano-4-phenylcyclohexanone (50 mg, 0.25 mmol) was dissolved in THF (3.0 cm^3) and added to a solution of (*S*,*S*)-bis(α-methylbenzyl)amine hydrochloride (65 mg, 0.25 mmol) in THF (6.0 cm^3) and *n*-BuLi (1.6 M, 0.31 cm^3, 0.50 mmol) at −78 °C. The mixture was stirred for 10 min at −78 °C and Ac_2O (0.035 cm^3, 0.37 mmol) was added. The reaction was left to warm to room temperature over 1 h and quenched with a saturated solution of NH_4Cl before extraction with Et_2O and drying over $MgSO_4$ to yield the enol acetate (*R*)-**2** (30 mg) in 49% yield. HPLC showed an enantiomeric excess of 54%. HPLC Chiralcel OJ, t_R (*S*)-**2** 33 min, (*R*)-**2** 39 min, eluent: isopropyl alcohol–hexane (10 : 90), 1 cm^3 min^{-1}, λ 220 nm.

4-Cyano-4-(3′,4′-dichlorophenyl)cyclohex-1-enyl acetate 3

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 LiHMDS (97 cm^3 1 M solution in THF, 97 mmol). The mixture was stirred for 15 min whereupon acetic anhydride (10.6 cm^3) 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 cm^3) and ether was added (200 cm^3). The organic layer was washed with saturated ammonium chloride solution (3 × 300 cm^3) and brine (3 × 300 cm^3), 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 **6** as a white solid (20.00 g, 86%); 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^+ 309.03227. $C_{15}H_{13}Cl_2NO_2$ requires

309.03235); ν_{max}(neat)/cm^{-1} 2233 (CN) and 1755 (CO); δ_H(300 MHz, $CDCl_3$) 2.23 (3 H, s, $AcCH_3$), 2.23–2.67 (6 H, m, 2 × H-3, 2 × H-5 and 2 × H-6), 5.46 (1 H, s, H-2), 7.22–7.56 (3 H, 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, t_R (*R*)-**3** 15.5 min, (*S*)-**3** 20.9 min, eluent 100% EtOH, flow rate 0.5 cm^3 min^{-1}, λ 220 nm.

Treatment of 4-cyano-4-(3′,4′-dichlorophenyl)cyclohexanone with lithium (*S*,*S*)-bis(α-methylbenzyl)amide

The ketone (50 mg, 0.19 mmol) was treated with the chiral base lithium (*S*,*S*)-bis(α-methylbenzyl)amide as described above to yield the enol acetate (*R*)-**3** (30 mg) in 54% yield. HPLC showed an enantiomeric excess of 57%.

4-Cyano-4-(3′,4′-dimethoxyphenyl)cyclohex-1-enyl acetate 4

4-Cyano-4-(3′,4′-dimethoxyphenyl)cyclohexanone (260 mg, 1.00 mmol) was dissolved in isopropenyl acetate (2.0 cm^3, 18.10 mmol) in the presence of a catalytic amount of toluene-*p*-sulfonic acid. The mixture was heated under reflux for 18 h. The excess isopropenyl acetate was removed *in vacuo*. The product was dissolved in dimethyl ether (20.0 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (3 × 5.0 cm^3). The product was recrystallised from ethyl acetate to give a white solid **4** (240 mg, 80%); R_f (ethyl acetate–hexane, 1:1) 0.36; mp 99–100 °C (from ethyl acetate) (Found: C, 67.8; H, 6.38; N, 4.62. $C_{17}H_{19}NO_4$ requires C, 67.76, H, 6.36; N, 4.65%) (HRMS: found M^+, 301.1314. $C_{17}H_{19}NO_4$ requires 301.1317); ν_{max}($CDCl_3$)/cm^{-1} 2255 (CN) and 1755 (CO); δ_H(200 MHz; $CDCl_3$ 2.25–2.70 (6 H, m, H-3, H-5 and H-6), 3.86 and 3.89 (each 3 H, s, 2 × -OCH_3), 5.46 (1 H, s, H-2), 6.82–7.03 (3 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 20.9 ($AcCH_3$), 24.9, 33.0 and 35.8 (C-3, C-5 and C-6), 40.0 (C-4), 56.1 and 56.0 (2 × Ar-OCH_3), 109.3 (C-2), 110.9, 111.4 and 117.9 (C-2′, C-5′ and C-6′), 122.1 (CN), 132.2 and 149.1 (C-3′ and C-4′), 169.1 (CO); *m/z* (EI) 301 (M^+, 9%), 190 (10), 189 (100). HPLC Chiralpak AD, t_R 13.5 min and 14.9 min, eluent 100% EtOH, flow rate 0.5 cm^3 min^{-1}, λ 220 nm.

4-Cyano-4-(2′-pyridyl)cyclohex-1-enyl acetate 5

Enol acetate **5** was synthesised in an identical manner to that described for compound **4**, using 4-cyano-4-(2′-pyridyl)cyclohexanone (250 mg, 1.25 mmol). The crude residue was purified by column chromatography (eluent 1:1 ethyl ether–hexane) to yield the product enol acetate **5** as a white solid (193 mg, 64%); R_f (ethyl acetate–hexane, 1:1) 0.46; mp 92–93 °C (from ethyl acetate) (Found C, 69.31; H, 5.82; N, 11.55. $C_{14}H_{14}O_2N_2$ requires C, 69.41; H, 5.82; N, 11.56%) (HRMS: found M^+, 242.1052. $C_{14}H_{14}O_2N_2$ requires 242.1055); ν_{max}(neat)/cm^{-1} 2238.0 (CN) and 1755 (CO); δ_H(200 MHz; $CDCl_3$) 2.13 (3 H, s, $AcCH_3$), 2.27–3.07 (6 H, m, H-3, H-5 and H-6), 5.49 (1 H, br, H-2), 7.24 (1 H, m, Ar-H), 7.60–7.76 (2 H, m, Ar-H), 8.58 (1 H, d, *J* 4.7, H-3′); δ_C(75 MHz; $CDCl_3$) 20.9 ($AcCH_3$), 24.7, 31.9 and 39.9 (C-3, C-5 and C-6), 42.8 (C-4), 110.7 (C-2), 120.7, 123.0 and 137.2 (C-4′, C-5′ and C-6′), 147.2 (C-1), 149.7 (C-3′), 157.9 (C-1′), 169.1 (CO); *m/z* (EI) 242 (M^+, 4.46%), 200 ($M^+ - C_2H_2O$, 20.05), 199 ($M^+ - C_2H_3O$, 100), 183 (11.74), 181 (14.70), 172 (18.41), 171 (26.37), 144 (17.03), 142 (15.25), 131 (60.44), 118 (10.99), 104 (16.41), 79 (20.05), 43 (52.47). HPLC Chiralpak AD, t_R 11.5 min and 12.5 min, eluent 100% EtOH, flow rate 0.5 cm^3 min^{-1}, λ 250 nm.

4-Methyl-4-phenylcyclohex-1-enyl acetate 6

The enol acetate **6** was synthesised in an identical manner to that described for compound **4**, using 4-methyl-4-phenylcyclohexanone (0.50 g, 2.69 mmol) to yield the crude product as a yellow oil, which was purified by flash column chromatography on silica (eluent 10:1 petrol–ethyl acetate) to give the title compound **6** as a clear oil (HRMS: found $[M + NH_4]^+$, 248.16598. $C_{15}H_{22}NO_2$ requires 248.16563); ν_{max}(neat)/cm^{-1} 3032 (CH) and 1742 (CO); δ_H(300 MHz; $CDCl_3$) 1.32 (3 H, s, CH_3), 1.92–1.98 (2 H, m, 2 × H-5), 2.05 (3 H, s, Ac-CH_3), 2.13–2.24 (2 H, m, 2 × H-3), 2.51–2.54 (2 H, m, 2 × H-6), 5.43 (1 H, dd, *J* 6.6, *J* 5.1, H-2) and 7.15–7.38 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 21.0 ($AcCH_3$), 24.8, 34.9, 36.1 (C-3, C-5 and C-6), 27.9 (CH_3), 36.2 (C-4), 112.8 (C-2), 125.7, 125.9 and 128.3 (Ar-H), 146.2 (quat. Ar), 148.6 (C-1) and 169.5 (CO); *m/z* (CI) 248 (100%, $[M + NH_4]^+$) and 230 (50, $[M + H]^+$). HPLC Chiralcel OJ, t_R 7.8 min, 9.7 min, eluent 4:1 hexane–isopropyl alcohol, flow rate 1 cm^3 min^{-1}, λ 220 nm.

4-Benzyloxy-4-cyanocyclohex-1-enyl acetate 7

The enol acetate **7** was synthesised in an identical manner to that used for the synthesis of compound **3** using the ketone **16** (0.23 g, 1.01 mmol) to yield the crude product as a yellow oil, which was purified by flash column chromatography on silica (eluent 5:1 petrol–ethyl acetate) to give the title compound **7** as a yellow oil (0.22 g, 81%); mp 58.5–60.0 °C (HRMS: found $[M + NH_4]^+$, 289.15537. $C_{16}H_{21}N_2O_3$ requires 289.15522); ν_{max}(neat)/cm^{-1} 2230 (CN) and 1748 (CO); δ_H(300 MHz; $CDCl_3$) 2.19 (3 H, s, $AcCH_3$), 2.21–2.64 (6 H, m, C-3, C-5 and 2 × H-6), 4.66 (2 H, s, BnCH_2), 5.26 (1 H, m, 2 × H-2) and 7.24–7.39 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 23.9 (Ac-CH_3), 33.8, 34.9 and 36.6 (C-3, C-5 and C-6), 67.1 (BnCH_2), 72.5 (C-4), 110.0 (C-2), 126.1, 126.7 and 128.1 (Ar-H), 141.1 (quat. Ar), 149.2 (C-1) and 171.1 (CO); *m/z* (CI) 289 (100%, $[M + NH_4]^+$), 108 (10, $[C_7H_8O]^+$) and 91 (20, $[C_7H_7]^+$). HPLC Chiralcel OJ, t_R 43.1 min, 44.9 min, eluent 9:1 hexane–isopropyl alcohol, flow rate 1 cm^3 min^{-1}, λ 220 nm.

4-Benzyloxy-4-trimethylsilylethynylcyclohex-1-enyl acetate 20

The enol acetate **20** was synthesised in an identical manner to that described for enol acetate **7**, using ketone **19** (0.08 g, 0.27 mmol) to give the title compound after chromatography as a clear oil (0.08 g, 88%) (HRMS: found $[M + NH_4]^+$, 360.20058. $C_{20}H_{30}NO_3Si$ requires 360.19950); ν_{max}(neat)/cm^{-1} 1748 (CO); δ_H(300 MHz; $CDCl_3$) 0.02 (3 H, s, $TMSCH_3$), 1.98 (3 H, s, $AcCH_3$), 2.19–2.40 (3 H, m, H-3, H-5 and 2 × H-6), 4.46 (2 H, s, BnCH_2), 5.06 (1 H, dd, *J* 5.5, *J* 4.1, H-2) and 7.05–7.21 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 0.0 ($TMSCH_3$), 21.0 ($AcCH_3$), 24.5, 33.1 and 35.9 (C-3, C-5 and C-6), 66.3 (BnCH_2), 71.5 (C-4), 90.3 (C-1′), 106.3 (C-2′), 110.1 (C-2), 127.5, 127.9 and 128.4 (Ar-H), 139.1 (quat. Ar), 147.9 (C-1) and 169.3 (CO); *m/z* (CI) 360 (100%, $[M + NH_4]^+$), 235 (80, $[M + H - BnOH]^+$), 193 (65, $[M + H - CH_2CO - BnOH]^+$) and 91 (50, $[C_7H_7]^+$).

4-Ethynyl-4-benzyloxycyclohex-1-enyl acetate 8

To a stirred solution of enol acetate **20** (0.09 g, 0.26 mmol) in dry THF (10 cm^3) was added TBAF (0.52 cm^3, 0.52 mmol) and the mixture was stirred at rt for 1 h, whereupon ether (40 cm^3) was added and the reaction quenched by the addition of water (50 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude mixture was purified by flash column chromatography on silica (eluent 4:1 petrol–ethyl acetate) to give the title compound **8** as a yellow oil (0.05 g, 74%) (Found: C, 75.81; H, 7.00. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71%); ν_{max}(neat)/cm^{-1} 1747 (CO); δ_H(300 MHz; $CDCl_3$) 2.01 (3 H, s, $AcCH_3$), 2.18–2.25 (3 H, m, ring-CH_2), 2.41–2.47 (3 H, m, ring-CH_2), 2.55 (1H, s, H-2′), 4.50 (2 H, s, BnCH_2), 5.12 (1 H, dd, *J* 5.7, *J* 4.2, H-2) and 7.15–7.31 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 24.5, 33.5 and 35.3 (C-3, C-5 and C-6), 27.8 ($AcCH_3$), 65.9 (BnCH_2), 71.2 (C-4), 73.3 (C-2′), 90.3 (C-1′), 112.2 (C-2), 127.2, 127.8 and 128.8 (Ar-H), 140.0 (quat. Ar), 146.9 (C-1)

and 168.8 (CO); *m/z* (CI) 288 (100%, $[M + NH_4]^+$), 162 (30, $[M + H - BnOH]^+$), and 91 (80, $[C_7H_7]^+$). HPLC Chiralcel OJ, t_R 8.7 min, 9.8 min, eluent 95 : 5 hexane–isopropyl alcohol, flow rate 0.8 cm^3 min^{-1}, λ 220 nm.

4-Methoxycarbonyl-4-phenylcyclohex-1-enyl acetate 9

Enol acetate **9** was synthesised in an identical manner to that described for enol acetate **7**, using the corresponding ketone (0.12 g, 0.52 mmol) to give the title compound after chromatography (eluent 6 : 1 petrol–ethyl acetate) as a yellow oil (0.09 g, 64%) (HRMS: found $[M + H]^+$, 241.12899. $C_{16}H_{19}O_4$ requires 275.12828); ν_{max}(neat)/cm^{-1} 1741 and 1750 and 1740 (CO); δ_H(300 MHz; $CDCl_3$) 2.11 (3 H, s, $AcCH_3$), 2.20–2.76 (6 H, m, 2 × H-3, 2 × H-5 and 2 × H-6), 3.56 (3 H, s, CO_2CH_3), 5.10–5.22 (1 H, m, H-2) and 7.17–7.30 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 24.6 ($AcCH_3$), 31.3, 32.6 and 35.4 (C-3, C-5 and C-6), 49.7 (C-4), 52.9 (CO_2CH_3), 116.8 (C-2), 125.8, 127.9 and 128.4 (Ar-H), 142.0 (quat. ArC), 144.3 (C-1), 165.1 (CO_2CH_3) and 168.1 (AcCO); *m/z* (CI) 241 (100, $[M + NH]^+$). HPLC Chiralcel OJ, t_R 17.3 min, 19.2 min, eluent 9 : 1 hexane–isopropyl alcohol, flow rate 1 cm^3 min^{-1}, λ 220 nm.

4-Cyano-4-methoxycarbonylcyclohex-1-enyl acetate 10

The enol acetate **10** was synthesised in an identical manner to that described for enol acetate **7**, using the corresponding ketone (0.09 g, 0.50 mmol) to give the title compound after chromatography as a clear oil (0.085 g, 77%) (HRMS: found $[M + NH_4]^+$, 241.11890. $C_{11}H_{17}N_2O_4$ requires 241.11877); ν_{max}(neat)/cm^{-1} 2247 (CN), 1741 and 1748 (CO); δ_H(300 MHz; $CDCl_3$) 2.01 (3 H, s, $AcCH_3$), 2.30–3.01 (6 H, m, 2 × H-3, 2 × H-5 and 2 × H-6), 3.86 (3 H, s, CO_2CH_3) and 5.02–5.13 (1 H, m, H-2); δ_C(75 MHz; $CDCl_3$) 24.6 ($AcCH_3$), 30.3, 31.6 and 36.4 (C-3, C-5 and C-6), 45.7 (C-4), 52.7 (CO_2CH_3), 115.8 (C-2), 118.3 (CN), 147.3 (C-1), 169.1 (CO_2CH_3) and 170.1 (AcCO); *m/z* (CI) 241 (100, $[M + NH]^+$). HPLC Chiralcel OJ, t_R 22.2 min, 24.7 min, eluent 4 : 1 hexane–isopropyl alcohol, flow rate 1 cm^3 min^{-1}, λ 220 nm.

8-Trimethylsilyloxy-1,4-dioxaspiro[4.5]decane-8-carbonitrile 13

To a stirred solution of cyclohexanedione monoethylene acetal (5.00 g, 32.05 mmol) in dry ether (200 cm^3) under argon at rt was added $ZnCl_2$ (0.05 g, 0.36 mmol) and TMSCN (4.8 cm^3, 36.0 mmol). The mixture was stirred at rt for 18 h, whereupon the solvent was removed under reduced pressure to yield the crude product as a yellow oil, which was purified by flash column chromatography on silica (eluent DCM) to give the title compound **13** as a clear oil (6.60 g, 81%) (Found: C, 56.68; H, 8.30; N, 5.72. $C_{12}H_{21}NO_3Si$ requires C, 56.44; H, 8.29; N, 5.48%) (HRMS: found $[M + H]^+$, 256.13725. $C_{12}H_{22}NO_3Si$ requires 256.13690); ν_{max}(neat)/cm^{-1} 2246 (CN); δ_H(300 MHz; $CDCl_3$) 0.25 (9 H, s, $TMSCH_3$), 1.77–1.86 (4 H, m, H-7 and H-9), 2.00–2.11 (4 H, m, H-6 and H-10) and 3.94 (4 H, s, acetal-CH_2); δ_C(75 MHz; $CDCl_3$) 0.2 ($TMSCH_3$), 29.6 (C-7 and C-9), 35.5 (C-6 and C-10), 63.2 (C-2 and C-3), 67.6 (C-8), 105.8 (C-5) and 120.7 (CN); *m/z* (CI) 273 (20%, $[M + NH_4]^+$), 256 (100, $[M + H]^+$) and 229 (50, $[M + H - HCN]^+$).

8-Hydroxy-1,4-dioxaspiro[4.5]decane-8-carbonitrile 14

To a stirred solution of acetal **13** (2.00 g, 7.84 mmol) in dry THF (100 cm^3) at rt was added dilute HCl (0.5 cm^3) and TBAF (8.0 cm^3, 8.00 mmol). The mixture was stirred at rt for 2 h whereupon ether (100 cm^3) was added followed by sodium hydrogen carbonate solution (30 cm^3). The organic layer was washed with water (50.0 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a brown oil, which was purified by flash column chromatography on silica (eluent 3 : 1 petrol–ethyl acetate) to give the title compound **14** as a white solid (1.17 g, 82%) mp 56–58 °C (Found: C, 59.21; H, 7.28; N, 7.58. $C_9H_{13}NO_3$ requires C, 59.00; H, 7.15; N, 7.65%); ν_{max}(Nujol)/cm^{-1} 3267 (OH) and 2248 (CN); δ_H(300 MHz; $CDCl_3$) 1.65–1.74 (4 H, m, 2 × H-7 and H-9), 1.98–2.10 (4 H, m, 2 × H-6 and H-10), 2.46 (1 H, t, *J* 7.27, OH) and 3.89 (4 H, s, acetal-CH_2); δ_C(75 MHz; $CDCl_3$) 30.5 (C-7 and C-9), 35.2 (C-6 and C-10), 64.5 (C-2 and C-3), 67.8 (C-8), 107.0 (C-5) and 121.7 (CN); *m/z* (CI) 201 (1%, $[M + NH_4]^+$), 183 (1, $[M + H]^+$), 157 (50, $[M + H - HCN]$) and 99 (100).

8-Benzyloxy-1,4-dioxaspiro[4.5]decane-8-carbonitrile 15

To a stirred solution of acetal **14** (0.20 g, 1.10 mmol) in dry DCM (50.0 cm^3) at 0 °C under argon was added benzyl trichloroacetimidate (0.33 cm^3, 1.77 mmol) followed by trimethylsilyl triflate (0.04 cm^3, 0.20 mmol). The mixture was allowed to warm to rt and stirred for 17 h, whereupon the reaction was quenched by the addition of water (60 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow solid, which was purified by flash column chromatography on silica (eluent 7 : 1 petrol–ethyl acetate) to give the title compound **15** as a clear oil (0.18 g, 60%) (HRMS: found $[M + NH_4]^+$, 291.17104. $C_{16}H_{23}N_2O_3$ requires 291.17087); ν_{max}(neat)/cm^{-1} 2225 (CN); δ_H(300 MHz; $CDCl_3$) 1.75–1.82 (4 H, m, 2 H-7 and H-9), 2.07–2.14 (4 H, m, 2 × H-6 and H-10), 3.96 (4 H, s, acetal-CH_2), 4.67 (2 H, s, BnCH_2) and 7.26–7.36 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 30.3 (C-7 and C-9), 32.6 (C-6 and C-10), 64.5 (C-2 and C-3), 67.9 (BnCH_2), 73.5 (C-8), 107.0 (C-5), 119.9 (CN), 127.9, 128.1 and 128.6 (Ar-H) and 137.2 (quat. Ar); *m/z* (CI) 291 (100%, $[M + NH_4]^+$), 247 (10, $[M + H - HCN]^+$), 167 (10, $[M + H - OBn]^+$), 108 (5, $[C_7H_8O]^+$) and 91 (5, $[C_7H_7]^+$).

4-Benzyloxy-4-cyanocyclohexanone 16

To a stirred solution of acetal **15** (0.25 g, 0.92 mmol) in THF (50 cm^3) at rt was added 2 M HCl (30 cm^3) and the mixture was stirred for 6 h. The mixture was diluted with ether (90 cm^3) and sodium hydrogen carbonate solution (150 cm^3) was added slowly. The organic layer was washed with water (50 cm^3), 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 3 : 1 petrol–ethyl acetate) to give the title compound **16** as a clear oil (0.11 g, 52%) (HRMS: found $[M + NH_4]^+$, 247.14501. $C_{14}H_{19}N_2O_2$ requires 247.14462); ν_{max}(neat)/cm^{-1} 2238 (CN) and 1710 (CO); δ_H(300 MHz; $CDCl_3$) 2.17–2.25 (4 H, m, 2 × H-2), 2.56–2.60 (4 H, m, 2 × H-3), 4.48 (2 H, s, BnCH_2) and 7.22–7.41 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 33.7 (C-3 and C-5), 35.6 (C-2 and C-6), 67.6 (BnCH_2), 71.5 (C-4), 121.9 (CN), 126.9, 128.3 and 129.2 (Ar-H), 141.6 (quat. Ar) and 201.6 (CO); *m/z* (CI) 247 (100%, $[M + NH_4]^+$), 229 (5, $[M + H]^+$), 203 (10, $[M + H - HCN]^+$), 108 (55, $[C_7H_8O]^+$) and 91 (95, $[C_7H_7]^+$).

8-Trimethylsilylethynyl-1,4-dioxaspiro[4.5]decan-8-ol 17

To a stirred solution of trimethylsilylacetylene (1.00 g, 10.18 mmol) in dry THF (50.0 cm^3) at −10 °C under argon was added LiHMDS (11.0 cm^3, 11.0 mmol). The mixture was stirred for 30 min at −10 °C whereupon it was added *via* cannula to a solution of cyclohexane-1,4-dione monoethylene acetal **12** (1.60 g, 10.20 mmol) in THF (100 cm^3) at −10 °C under argon. The mixture was stirred for 3 h at −10 °C whereupon the reaction was quenched by the addition of ammonium chloride solution (160 cm^3) and ether added (200 cm^3). The organic layer was washed with water (150 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude mixture was purified by flash column chromatography on silica (eluent 4 : 1 petrol–ethyl acetate) to give two major components. The high running component, identified as alcohol **17**, was isolated as a clear oil (1.27 g, 49%) (HRMS: found $[M]^+$, 254.13399. $C_{13}H_{22}O_3Si$ requires 254.13378);

ν_{max}(neat)/cm^{-1} 3210 (OH); δ_H(300 MHz; $CDCl_3$) 0.15 (9 H, s, TMSCH_3), 1.66–1.72 (4 H, m, 2 × H-7 and H-9), 1.75–1.82 (5 H, m, OH and 2 × H-6 and H-10) and 3.79 (4 H, s, acetal-CH_2); δ_C(75 MHz; $CDCl_3$) 0.5 (TMSCH_3), 31.5 (C-7 and C-9), 37.2 (C-6 and C-10), 64.4 (acetal-CH_2), 67.7 (C-8), 88.5 (C-1′), 108.1 (C-2′) and 108.9 (C-5); *m*/*z* (EI) 254 (2%, $[M]^+$), 239 (40, $[M - CH_3]^+$), 226 (45, $[M - C_2H_4]^+$) and 181 (100, $[M - TMS]^+$).

The lower running component, identified as the desilylated analogue of alcohol **17**, was isolated as a clear oil (0.21 g, 9%) (HRMS: found $[M + H]^+$, 183.10237. $C_{10}H_{15}O_3$ requires 183.10212); ν_{max}(neat)/cm^{-1} 3227 (OH); δ_H(300 MHz; $CDCl_3$) 1.79–1.83 (4 H, m, 2 × H-7 and H-9), 1.90–1.95 (4 H, m, 2 × H-6 and H-10), 2.50 (1 H, s, H-10), 2.96 (1 H, br s, OH) and 3.94 (4 H, s, acetal-CH_2); δ_C(75 MHz; $CDCl_3$) 31.2 (C-7 and C-9), 36.9 (C-6 and C-10), 64.2 (acetal-CH_2), 66.9 (C-8), 72.0 (C-1′), 87.2 (C-2′) and 108.0 (C-5); *m*/*z* (CI) 183 (25%, $[M + H]^+$) and 165 (100, $[M + H - H_2O]^+$).

8-Benzyloxy-8-trimethylsilylethynyl-1,4-dioxaspiro[4.5]decane 18

To a stirred solution of alcohol **17** (0.48 g, 1.87 mmol) in dry ether (50.0 cm^3) at 0 °C under argon was added benzyl trichloroacetimidate (0.63 cm^3, 2.52 mmol) followed by trimethylsilyl triflate (0.08 cm^3, 0.40 mmol). The mixture was stirred at 0 °C and then allowed to warm to rt and stirred for a further 5 h, whereupon the reaction was quenched by the addition of water (30.0 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow solid, which was purified by flash column chromatography on silica (eluent 10 : 1 petrol–ethyl acetate) to give the title compound **18** as a clear oil (0.39 g, 60%) (HRMS: found $[M]^+$, 344.18104. $C_{20}H_{28}O_3Si$ requires 344.18073); δ_H(300 MHz; $CDCl_3$) 0.10 (3 H, s, TMSCH_3), 1.58–1.61 (4 H, m, 2 × H-7 and H-9), 1.82–1.85 (4 H, m, 2 × H-6 and H-10), 3.78 (4 H, s, acetal-CH_2), 4.40 (2 H, s, BnCH_2) and 7.06–7.20 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 0.1 (TMSCH_3), 31.1 (C-7 and C-9), 36.4 (C-6 and C-10), 64.5 (acetal-CH_2), 66.1 (BnCH_2), 68.2 (C-8), 88.7 (C-1′), 107.6 (C-2′), 108.3 (C-5), 127.4, 128.4 and 128.5 (Ar-H) and 138.1 (quat. Ar); *m*/*z* (EI) 344 (5%, $[M]^+$), 329 (10, $[M - CH_3]^+$), 271 (15, $[M - TMS]^+$) and 91 (100, $[C_7H_7]^+$).

4-Benzyloxy-4-trimethylsilylethynylcyclohexanone 19

To a stirred solution of acetal **18** (0.11 g, 0.32 mmol) in THF (20.0 cm^3) was added 0.1 M HCl (5 cm^3). The solution was heated under reflux for 2 h, whereupon 0.1 M NaOH was added followed by ether (50 cm^3). The organic layer was washed with water (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude mixture was purified by flash column chromatography on silica (eluent 3 : 1 petrol–ethyl acetate) to give the title compound **19** as a yellow oil (0.04 g, 42%) (Found: C, 72.34; H, 7.48. $C_{18}H_{24}O_2Si$ requires C, 72.03; H, 7.72%) (HRMS: found $[M]^+$, 300.15374. $C_{18}H_{24}O_2Si$ requires 300.15457); ν_{max}(neat)/cm^{-1} 1712 (CO); δ_H(300 MHz; $CDCl_3$) 0.02 (3 H, s, TMSCH_3), 1.95–2.04 (4 H, m, ring-CH_2), 2.29–2.36 (4 H, m, ring-CH_2), 4.50 (2 H, s, BnCH_2) and 6.99–7.20 (5 H, m, Ar-H); δ_C(75 MHz; $CDCl_3$) 0.1 (TMSCH_3), 34.5 (C-3 and C-5), 37.3 (C-2 and C-6), 66.5 (BnCH_2), 73.2 (C-4), 83.7 (C-1′), 107.4 (C-2′), 127.5, 128.0 and 128.5 (Ar-H), 139.1 (quat. Ar) and 181.0 (CO); *m*/*z* (EI) 300 (2%, $[M]^+$), 227 (5, $[M - TMS]^+$) and 91 (100, $[C_7H_7]^+$).

Typical biotransformation protocol

To a solution of enol acetate **2** (0.10 g, 0.41 mmol) in dry THF (10 cm^3) at 30 °C was added *n*-BuOH (0.046 cm^3, 0.50 mmol) and lipase from *Pseudomonas fluorescens* (30 mg). The solution was stirred for 6 h, until 65% conversion to ketone was observed by GC, whereupon the mixture was filtered through a Celite pad and the enzyme washed with dimethyl 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 enol acetate **2** as a white crystalline solid (29 mg, 29%); mp 100–101 °C; $[a]_D = +8.52$ ($c = 1.76$, $CHCl_3$).

Scale-up biotransformation procedure

The enol acetate **3** (10 g, 32.4 mmol), lipase from *Pseudomonas fluorescens* (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. t_R (*R*)-**3** 15.5 min, (*S*)-**3** 20.9 min, eluent 100% EtOH, 0.5 cm^3 min^{-1}. 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%) as a white solid; mp 148–150 °C; $[a]_D = +11.5$ ($c = 1.74$, $CHCl_3$). Other analytical data as reported above.

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