Enantioselective lipase-catalyzed acetylation of β-lactam precursors of carbapenem antibiotics

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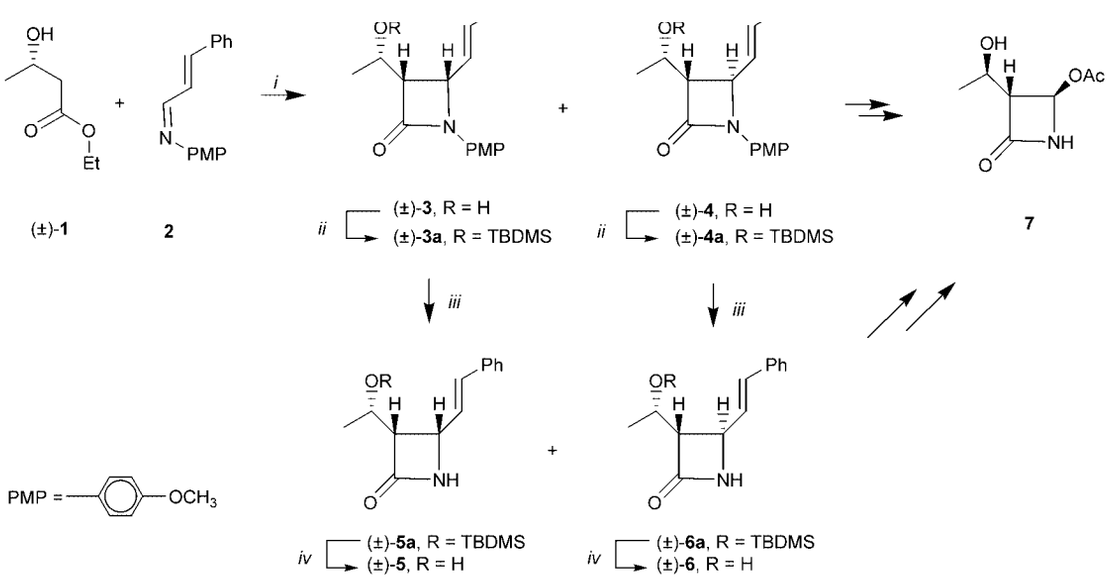
The Amano PS-lipase-catalyzed enantioselective acetylation in vinyl acetate of (±)-3-hydroxyethyl-β-lactams **3**–**6**, useful precursors of carbapenem antibiotics, proceeds with high enantioselectivity ($E > 98$) to afford the corresponding acetates **3b**–**6b** in optically pure form. The rate of acetylation is influenced by the relative stereochemistry of the C(3)–C(4) β-lactam carbon atoms, the *trans* isomers being transformed much faster than the *cis* ones. The stereochemical preference of the lipase-PS is for the (1′*R*,3*R*) enantiomers, as determined by chemical correlation. On the other hand, the lipase-PS-catalyzed hydrolysis of esters **3b**,**d** in phosphate buffer proceeds with low selectivity and at a lower rate.

Introduction

Hydrolytic enzymes, such as esterases, proteases and, in particular, lipases have received much attention because of their effectiveness in chemo-, regio- and enantio-selective transformations of structurally different acids, alcohols, amines, amides and esters, often performed in organic solvents.[1] However, in the literature, very few studies[2] deal with the lipase-catalyzed resolution of β-lactams: asymmetric synthesis is generally preferred for these heterocycles, and have been thoroughly investigated.[3] Nevertheless, owing to the growing interest in enantiomerically pure β-lactams as versatile intermediates for the asymmetric synthesis of bioactive molecules, such as proteinogenic and non-proteinogenic amino acids (β-lactam synthon method),[4] resolution methods are still desirable. For example, enantiopure 3-hydroxy-4-phenylazetidin-2-one,[5] a precursor of the C-13 side chain of Taxol, and 4-(4′-carboxyphenoxy)-3,3-diethylazetidin-2-one, a key intermediate in the synthesis of a potent human leukocyte elastase inhibitor, have been obtained by lipase-catalyzed resolutions.[6] In this paper, we report our findings relating to lipase-catalyzed optical resolution of 3-hydroxyethyl-β-lactams **3**–**6**, useful precursors of carbapenem antibiotics through the key intermediate **7**,[7] by lipase-catalyzed transformations; both the lipase-catalyzed processes, *i.e.* hydrolysis of the β-lactam esters and esterification of the alcoholic function, are studied.

Results and discussion

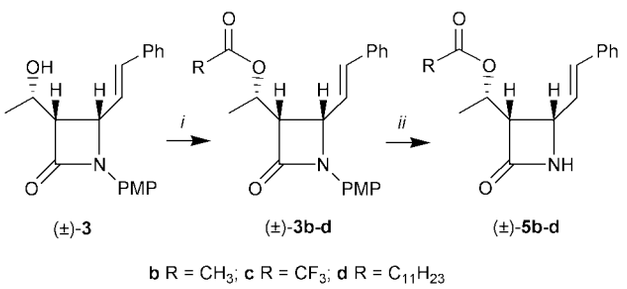
The β-lactams (±)-*cis*-**3** and -*trans*-**4** (Scheme 1) were synthesized according to the literature,[8] by condensation of racemic ethyl 3-hydroxybutanoate **1** and *N*-(*p*-methoxyphenyl)-cinnamylideneimine **2** promoted by lithium bis(trimethylsilyl)amide (LHMDSA); the reaction proceeds with a high degree of diastereoselection at C(3) of the azetidinone product, affording two diastereoisomers (45 : 55, respectively) which were separated by chromatography and crystallization (81% overall yield). The relative stereochemistry at C(3)–C(4) was assigned on the basis of the coupling constants ($^3J_{cis} > {}^3J_{trans}$); traces (<3%) of an epimeric β-lactam[8b] were detected in the crude



Scheme 1 *Reagents and conditions*: *i*, LHMDSA, THF, −78 °C; *ii*, TBDMSCl, DMAP, CH_2Cl_2; *iii*, CAN, CH_3CN; *iv*, TBAF, CH_2Cl_2.

reaction mixture, but not isolated. NH-β-lactams *cis*-**5** and *trans*-**6** were respectively obtained from **3** and **4** in 62 and 78% overall yield, by oxidative removal of the *p*-methoxyphenyl group (PMP) with ceric [cerium(IV)] ammonium nitrate (CAN)[9] performed on the *tert*-butyldimethylsilyl (TBDMS) ethers **3a** and **4a**.

Several commercially available lipases, such as CAL, CCL, PSL, AYL, PPL, PFL and ANL (see Experimental section) were tested for the lipase-catalyzed hydrolysis of esters **3b–d** and **5b**,**d** (Scheme 2). β-Lactam esters **3b–d** were obtained in



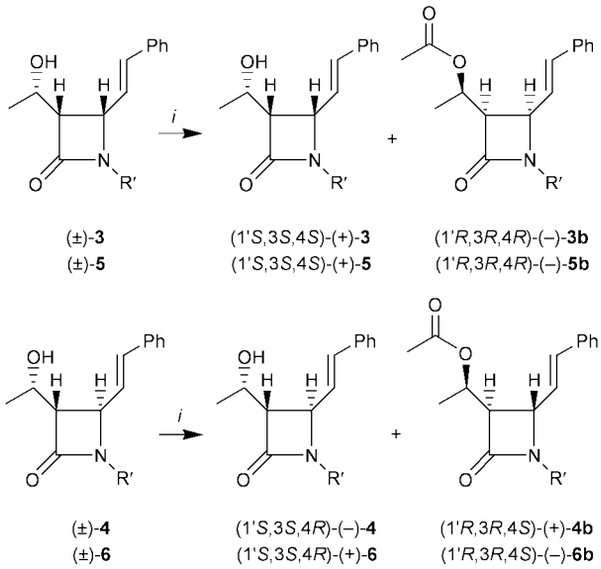
Scheme 2 *Reagents*: *i*, $(CH_3CO)_2O$, $(CF_3CO)_2O$ or $C_{11}H_{23}COCl$; *ii*, CAN, CH_3CN.

excellent yields (90–100%) by esterification of the alcoholic function of **3** with acetic anhydride (**3b**), with trifluoroacetic anhydride (**3c**) or with lauroyl chloride (**3d**), respectively. Compounds **5b**,**d** were synthesized from **3b**,**d** by oxidation with CAN in acetonitrile (66–70% yield); compound **5c** was not obtained from **3c** owing to fast hydrolysis of the trifluoroacetate in the reaction conditions.

In a typical experiment, the ester (50 mg) was dissolved in DMSO (0.5 mL) and diluted with phosphate buffer (pH 7.5; 5 mL); the lipase was added (50 mg) and the reaction mixture vigorously stirred at 37 °C until the desired conversion was reached (TLC). The reaction mixture was extracted with EtOAc and purified by chromatography, affording the unreacted ester and the reaction product, whose enantiomeric excesses (ees) were determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$† as chiral shift reagent (ees of compounds **3** and **5**, obtained by enzymic hydrolysis, were determined for the corresponding TBDMS derivatives **3a** and **5a**).

Trifluoroacetate **3c** displayed a high rate of hydrolysis in phosphate buffer even in the absence of the biocatalyst: the product of hydrolysis as well as the unreacted ester were consequently recovered in nearly racemic form. No catalytic activity was generally observed towards compounds **3b** and **5b**, with the exception of PSL, AYL and CAL, which displayed low activities (conv. < 10% after 4 days) and low selectivities (expressed as enantiomeric ratio,[10] $E < 8$). Even though the literature[5] reports that both the reaction rate and the selectivity of water-insoluble substrates can be improved by the use of co-solvents, no significant changes were observed using DMSO, THF, EtOH, CH_3CN or acetone as co-solvent.

Since lipases are known to display catalytic activity in a wide range of organic solvents,[1] we turned our attention to the lipase-catalyzed acetylation of β-lactam **3**, using vinyl acetate (VA) as acyl donor. The catalytic activities of all the lipases were tested in several solvents (hexane, toluene, diisopropyl ether, THF, $CHCl_3$, CH_3CN, VA), by adding the enzyme (5 mg) to a solution of the substrate (5 mg) in the selected solvent (1 mL containing 0.05 mL of VA) and stirring at 37 °C; the degree of conversion was estimated by TLC. Catalytic activity was observed for PSL, AYL and CAL in VA, with an acceptable rate for PSL. Therefore, we performed the optical resolution of β-lactams **3**, **4**, **5** and **6** in VA as solvent and acyl donor, using



Scheme 3 *Reagents and conditions*: *i*, VA, Lipase PS, 37 °C.

PSL as catalyst (Scheme 3); the results are summarized in Table 1.

The results show that the lipase PS catalyzes the acetyl transfer from VA to all the substrates with high enantioselectivity, as demonstrated by the values of *E*. The rate of the transesterification reaction is deeply influenced by the relative stereochemistry of the β-lactam ring: the *trans* stereoisomers **4** and **6** (entries 2, 4) are acetylated much faster than the *cis* isomers **3** and **5** (entries 1, 3) respectively, while slight variations are observed with respect to the N-substitution (entry 1 *vs*. 3, 2 *vs*. 4).

The stereochemical preference of the PS-lipase-catalyzed acetylation of (±)-**3**–**6** was determined by comparison of the optical rotations of the unreacted alcohols with those observed for the same compounds synthesized from optically active ethyl 3-hydroxybutanoate **1**. Condensation was therefore performed starting from (*S*)-(+)-**1**,[11] ee 85% (Scheme 4); chromatography of the crude residue afforded **3** and **4** as a mixure (55% yield). This mixture was purified by chromatography and treated with TBDMSCl and 4-(dimethylamino)pyridine (DMAP) in dichloromethane: careful chromatography gave diastereoisomerically pure (+)-**3a**, $[\alpha]_D = +133.4$, and (−)-**4a**, $[\alpha]_D = -45.8$.‡ Deprotection at oxygen (TBAF, CH_2Cl_2) afforded (+)-**3**, $[\alpha]_D = +138.7$, and (−)-**4**, $[\alpha]_D = -73.2$, while oxidative removal of the PMP group (CAN) and subsequent deprotection at oxygen (TBAF, CH_2Cl_2) afforded (+)-**5**, $[\alpha]_D = +11.9$, and (+)-**6**, $[\alpha]_D = +32.1$. Since the stereochemical pathway of the condensation between the dianion of (*S*)-(+)-**1** and imine **2** is known[8] to induce the (*S*) configuration at the C(3) stereocentre, *cis*-β-lactams (+)-**3** and (+)-**5** must have the (1′*S*,3*S*,4*S*) absolute configuration, while *trans*-β-lactams (−)-**4** and (+)-**6** must have the (1′*S*,3*S*,4*R*) absolute configuration. It follows therefore that lipase-PS catalyzes the acylation of (1′*R*,3*R*,4*R*)-*cis*-**3**, **-5** and (1′*R*,3*R*,4*S*)-*trans*-**4**, **-6** to the corresponding esters, while the unreacted substrates are recovered in the *cis*-(1′*S*,3*S*,4*S*)-**3**, **-5** and *trans*-(1′*S*,3*S*,4*R*)-**4**, **-6** absolute configuration, respectively.

We have thus shown that lipase-PS is much more enantioselective towards β-lactam esterifications in organic solvent with respect to ester hydrolysis in phosphate buffer: β-lactams **3**–**6**, useful precursors of carbapenem antibiotics, are acetylated in vinyl acetate with high enantioselectivity ($E > 98$) affording the corresponding acetates **3b**–**6b** in optically pure form; the reverse reaction of hydrolysis of **3b** occurs with lower selectivity ($E = 8$) and at a slower rate. The rate of acetylation is affected

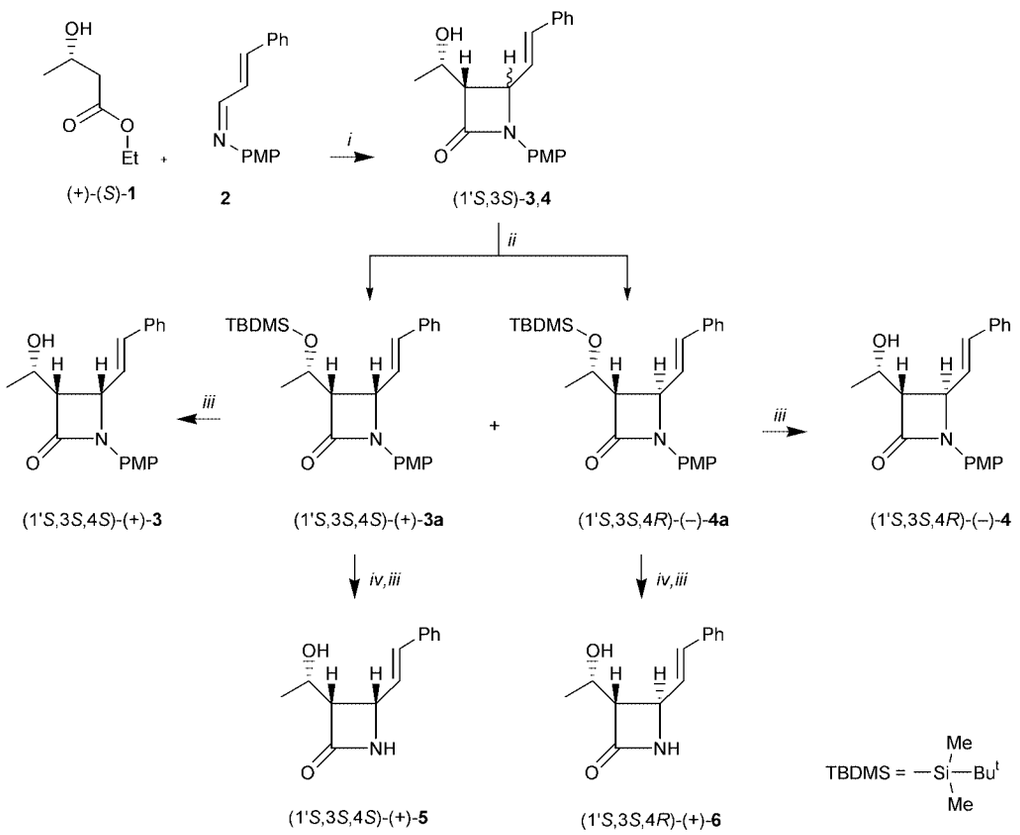
† Europium tris(heptafluorobutynylcamphorate).

‡ Units for specific optical rotations $[\alpha]_D$ are 10^{-1} deg cm^2 g^{-1}.

Table 1 Lipase-PS-catalyzed enantioselective acetylation of β-lactams (±)-**3**–**6**

	Remaining alcohol				Product						
Entry	Compd.	Yield (%)[a]	Abs. conf.[b]	ee (%)[c]	Compd.	Yield (%)[a]	Abs. conf.[b]	ee (%)[c]	Time (*t*/h)	*c* (%)[d]	*E*[d]
1	(+)-**3**	61	1′*S*,3*S*,4*S*	44	(−)-**3b**	29	1′*R*,3*R*,4*R*	>97	96	31	>100
2	(−)-**4**	47	1′*S*,3*S*,4*R*	>97	(+)-**4b**	49	1′*R*,3*R*,4*S*	>97	48	50	>100
3	(+)-**5**	69	1′*S*,3*S*,4*S*	41	(−)-**5b**	24	1′*R*,3*R*,4*R*	>97	170	30	98
4	(+)-**6**	49	1′*S*,3*S*,4*R*	>97	(−)-**6b**	42	1′*R*,3*R*,4*S*	>97	24	50	>100

[a] Isolated yield. [b] Determined by chemical correlation. [c] Determined by ^{1}H NMR in the presence of [Eu(hfc)$_3$]; compounds **3**–**6** were previously converted to **3a**–**6a**. [d] Calculated according to ref. 9.



Scheme 4 *Reagents and conditions*: *i*, LDA, THF, −78 °C; *ii*, TBDMSCl, DMAP, CH_2Cl_2; *iii*, TBAF, CH_2Cl_2; *iv*, CAN, CH_3CN.

by the C(3)–C(4) relative stereochemistry of the β-lactam-ring, the *trans* isomers **4** and **6** being transformed faster than the *cis* ones **3** and **5**. The stereochemical preference of lipase-PS is for the (1′*R*,3*R*) enantiomers, irrespective of the N-substituent or the C(4) configuration. The synthesis of the key precursor **7** of the carbapenem antibiotics from β-lactams **3**–**6** is described in the literature;[8] in order to obtain **7** in the required absolute configuration, the synthesis must start from the unreacted enantiomers (+)-**3**, (−)-**4**, (+)-**5** and (+)-**6**.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX-200 spectrometer. Chemical shifts are reported in δ-values from TMS as internal standard (s singlet, d doublet, m multiplet, q quartet, t triplet, br broad signal). Coupling constants (*J*) are given in Hz. Optical rotations were measured at 20 °C on a Perkin–Elmer 241 polarimeter and are measured in 10^{-1} deg cm^2 g^{-1}. GLC analyses were performed on a Hewlett-Packard 5890 A gas chromatograph on a DB-1 column (30 m × 0.53 mm id and 5 μm film phase) from J&W Scientific, with helium as carrier gas. The enantiomeric excesses (ees) of **1** and those of the β-lactams were determined from an analysis of the ^{1}H NMR spectra in $CDCl_3$ and in the presence of 1.5- to 3-fold excess of Eu(hfc)$_3$ as chiral shift reagent, after conversion to the corresponding TBDMS ether (compounds **3**–**6**) or directly (compounds **1**, **3**–**6b**, **3d**,**5d**). Mass spectra were determined on a Finnigan Mat SSQ A mass spectrometer (EI, 70 eV). Elemental analyses were performed with a Carlo Erba Elemental Analyzer 1110. Chromatographic purification of the compounds was performed on silica gel (φ 0.05–0.20 mm). Lipases from *Candida antarctica* (CAL), from *Candida cylindracea* (CCL), from porcine pancreas (PPL), from *Pseudomonas fluorescens* (PFL) and from *Aspergillus niger* (ANL) were purchased from Sigma, while Amano PS lipase (PSL) and AY lipase (AYL) were generously gifted by Amano Pharmaceutical Company. All enzymes were used without further purification. (*S*)-(+)-**1** (ee 85%),[11] racemic and optically active **3** and **4**[8] were prepared as described in the literature. Light petroleum refers to the fraction with distillation range 30–50 °C.

(1′*R**,3*R**,4*R**)-3-[1′-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)azetidin-2-one 3a and (1′*R**,3*R**,4*S**)-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)azetidin-2-one 4a

A mixture of β-lactams **3** and **4** (45:55 ratio; 1.464 g, 4.53 mmol) was dissolved in anhydrous CH_2Cl_2 (26 mL); DMAP

(1.659 g, 13.58 mmol) and TBDMSCl (1.364 g, 9.04 mmol) were added at room temperature under magnetic stirring and nitrogen atmosphere. After 40 h the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed successively with 5% HCl (25 mL) and water (20 mL), dried over $MgSO_4$, and rotary evaporated. Careful column chromatography (light petroleum–ethyl acetate 9:1) gave **3a** (0.790 g, 40%) as a white solid, mp 105–107 °C (from CH_2Cl_2) and **4a** (1.022 g, 52%) as a sticky oil.

3a: ^{1}H NMR: δ 0.09 (3H, s, MeSi), 0.10 (3H, s, MeSi), 0.91 (9H, s, Me_3C), 1.36 (3H, d, *J* 6.3, CH_3CH), 3.48 (1H, t, *J* 5.5, 3-H), 3.77 (3H, s, MeO), 4.26 (1H, dq, *J* 5.3, 6.3, C*H*Me), 4.69 (1H, dd, *J* 5.8, 8.6, 4-H), 6.47 (1H, dd, *J* 8.6, 16.1, C*H*CHPh), 6.77 (1H, d, *J* 16.1, C*H*Ph), 6.83 (2H, m, ArH), 7.25–7.45 (7H, m, ArH); *m*/*z* 437 (M^+, 10%), 380 (100), 366 (17), 262 (26), 231 (20), 157 (39), 115 (15), 73 (22) (Found: C, 71.2; H, 8.0; N, 3.1. $C_{26}H_{35}NO_3Si$ requires C, 71.4; H, 8.1; N, 3.2%).

4a: ^{1}H NMR: δ 0.10 (6H, s, MeSi), 0.85 (9H, s, Me_3C), 1.38 (3H, d, *J* 6.3, CH_3CH), 3.20 (1H, dd, *J* 2.4, 4.0, 3-H), 3.77 (3H, s, MeO), 4.31 (1H, dq, *J* 4.0, 6.3, C*H*CH$_3$), 4.54 (1H, dd, *J* 2.4, 8.1, 4-H), 6.29 (1H, dd, *J* 8.1, 15.9, C*H*CHPh), 6.74 (1H, d, *J* 15.9, C*H*Ph), 6.83 (2H, m, ArH), 7.20–7.50 (7H, m, ArH); *m*/*z* 437 (M^+, 8%), 380 (100), 366 (20), 262 (25), 231 (15), 157 (40), 115 (19), 73 (22) (Found: C, 71.1; H, 8.0; N, 3.1. $C_{26}H_{35}NO_3Si$ requires C, 71.4; H, 8.1; N, 3.2%).

(1′*R**,3*R**,4*R**)-3-(1′-Acetoxyethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)azetidin-2-one 3b

A solution of (±)-**3** (500 mg, 6.2 mmol) in pyridine (2.5 mL) and acetic anhydride (0.7 mL) was heated at 70 °C for 5 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed successively with 10% HCl (3 × 15 mL) and water (20 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (light petroleum–ethyl acetate 8:2), affording 507 mg of the title compound (90%) as a white solid, mp 144 °C; ^{1}H NMR: δ 1.44 (3H, d, *J* 6.4, CHCH_3), 2.08 (3H, s, CH_3CO), 3.60 (1H, t, *J* 5.8, 3-H), 3.80 (3H, s, MeO), 4.77 (1H, ddd, *J* 0.8, 5.8, 8.3, 4-H), 5.30 (1H, quintet, *J* 6.1, C*H*CH$_3$), 6.28 (1H, dd, *J* 8.3, 15.9, C*H*CHPh), 6.78 (1H, dd, *J* 0.8, 15.9, C*H*Ph), 6.86 (2H, m, ArH), 7.20–7.50 (7H, m, ArH); *m*/*z* 366 [(M + 1)$^+$, 15%], 365 (64), 305 (26), 236 (48), 216 (100), 174 (32), 173 (70), 158 (44), 149 (58), 131 (35), 115 (32) (Found: C, 72.5; H, 6.4; N, 3.6. $C_{22}H_{23}NO_4$ requires C, 72.3; H, 6.3; N, 3.8%).

(1′*R**,3*R**,4*R**)-1-(4′-Methoxyphenyl)-4-(2′-phenylethenyl)-3-[1′-(trifluoroacetoxy)ethyl]azetidin-2-one 3c

Trifluoroacetic anhydride (0.173 mL, 1.24 mmol) was added at room temperature to a stirred solution of (±)-**3** (100 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (1 mL). After 15 min the solvent was evaporated *in vacuo* and the crude oil (135 mg, 100%) was used without purification. ^{1}H NMR: δ 1.53 (3H, d, *J* 6.4, CHCH_3), 3.69 (1H, t, *J* 5.9, 3-H), 3.77 (3H, s, MeO), 4.82 (1H, ddd, *J* 0.6, 5.9, 8.2, 4-H), 5.43 (1H, quintet, *J* 6.3, C*H*CH$_3$), 6.21 (1H, dd, *J* 8.2, 16.0, C*H*CHPh), 6.78 (1H, d, *J* 16.0, C*H*Ph), 6.84 (2H, m, ArH), 7.20–7.45 (7H, m, ArH); *m*/*z* 419 (M^+, 16%), 270 (36), 157 (28), 156 (28), 149 (100), 141 (29), 129 (22), 115 (16).

(1′*R**,3*R**,4*R**)-3-[1′(Lauroyloxy)ethyl]-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)azetidin-2-one 3d

Lauroyl chloride (0.258 mL, 1.12 mmol) was added at 0 °C to a stirred solution of (±)-**3** (120 mg, 0.37 mmol) in pyridine (1.5 mL). The temperature was raised to 70 °C for 45 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed successively with 10% HCl (2 × 12 mL) and then with water (5 mL) and dried (Na_2SO_4). The filtered solution was concentrated and the crude product was purified by column chromatography (light petroleum–ethyl acetate 8:2), affording 176 mg of the title compound (94%) as a pale yellow solid, mp 144 °C; ^{1}H NMR: δ 0.93 (3H, t, *J* 6.4, CH_3CH$_2$), 1.20–1.35 (18H, m, CH$_2$), 1.40 (3H, d, *J* 6.8, CHCH_3), 2.29 (2H, dt, *J* 2.0, 7.5, CH_2CO), 3.57 (1H, dd, *J* 5.3, 5.8, 3-H), 3.76 (3H, s, MeO), 4.74 (1H, ddd, *J* 0.8, 5.8, 8.2, 4-H), 5.27 (1H, dq, *J* 5.3, 6.8, C*H*CH$_3$), 6.23 (1H, dd, *J* 8.2, 16.0, C*H*CHPh), 6.74 (1H, dd, *J* 0.8, 16.0, C*H*Ph), 6.83 (2H, m, ArH), 7.23–7.43 (7H, m, ArH) (Found: C, 75.8; H, 8.4; N, 2.7. $C_{32}H_{43}NO_4$ requires C, 76.0; H, 8.6; N, 2.8%).

(1′*R**,3*R**,4*R**)-3-[1′-(tert-Butyldimethylsilyloxy)ethyl]-4-(2′-phenylethenyl)azetidin-2-one 5a

A solution of **3a** (500 mg, 1.14 mmol) in CH_3CN (120 mL) was cooled at −12 °C, and an aqueous solution (60 mL) of CAN (1.24 g, 2.26 mmol) was added dropwise to the reaction mixture over a period of 5 min. The reaction mixture was stirred for 15 min before more solid CAN (625 mg, 1.14 mmol) was added. After an additional 15 min the reaction was quenched in saturated aq. $NaHCO_3$ (370 mL) and the mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and rotary evaporated. Column chromatography of the crude product (light petroleum–ethyl acetate 7:3) afforded **5a** (265 mg, 70%), ^{1}H NMR: δ 0.07 (3H, s, MeSi), 0.08 (3H, s, MeSi), 0.92 (9H, s, Me_3C), 1.29 (3H, d, *J* 6.3, CH_3CH), 3.40 (1H, dt, *J* 2.0, 5.5, 3-H), 4.19 (1H, dq, *J* 5.5, 6.3, C*H*CH$_3$), 4.35 (1H, ddd, *J* 0.4, 5.5, 7.6, 4-H), 5.88 (1H, br, NH), 6.40 (1H, dd, *J* 7.6, 15.9, C*H*CHPh), 6.60 (1H, d, *J* 15.9, C*H*Ph), 7.2–7.5 (5H, m, ArH); *m*/*z* 330 [(M − 1)$^+$, 1%], 316 (5), 288 (3), 274 (100), 230 (86), 157 (10), 129 (17), 115 (24), 75 (56) (Found: C, 68.6; H, 8.7; N, 4.1. $C_{19}H_{29}NO_2Si$ requires C, 68.8; H, 8.8; N, 4.2%).

(1′*R**,3*R**,4*R**)-3-(1′-Hydroxyethyl)-4-(2′-phenylethenyl)-azetidin-2-one 5

Tetrabutylammonium fluoride (946 mg, 3.62 mmol) was dissolved in anhydrous THF (4 mL) and added dropwise at room temperature to a stirred solution of **5a** (1.00 g, 3.02 mmol) in THF (10 mL). After 2 h, the solvent was evaporated off and the crude residue purified by column chromatography (light petroleum–ethyl acetate 1:1) to give **5** (635 mg, 97%) as a light yellow solid, mp 112–114 °C; ^{1}H NMR: δ 1.31 (3H, d, *J* 6.3, CH_3CH), 2.40 (1H, br, OH), 3.40 (1H, ddd, *J* 1.5, 5.5, 7.3, 3-H), 4.17 (1H, quintet, *J* 6.7, C*H*CH$_3$), 4.46 (1H, ddd, *J* 0.8, 5.5, 8.0, 4-H), 6.03 (1H, br, NH), 6.38 (1H, dd, *J* 8.0, 15.9, C*H*CHPh), 6.70 (1H, d, *J* 15.9, C*H*Ph), 7.23–7.50 (5H, m, ArH); *m*/*z* 217 (M^+, 3%), 185 (5), 156 (12), 155 (11), 141 (10), 139 (7), 128 (50), 113 (14), 87 (16), 69 (100), 55 (32) (Found: C, 72.0; H, 7.1; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.4%).

(1′*R**,3*R**,4*R**)-3-(1′-Acetoxyethyl)-4-(2′-phenylethenyl)-azetidin-2-one 5b

A solution of CAN (2.197 g, 4.0 mmol) in water (40 mL) was added over a period of 5 min to a stirred solution of **3b** (444 mg, 1.21 mmol) in CH_3CN (70 mL) cooled to 0 °C. After 30 min the reaction mixture was diluted with ethyl acetate (500 mL), washed successively with water (3 × 70 mL), aq. 5% $NaHCO_3$ (2 × 50 mL) and finally with brine (2 × 50 mL) and dried (Na_2SO_4). The solution was filtered, concentrated *in vacuo*, and the crude residue purified by column chromatography (light petroleum–ethyl acetate 7:3). Crystallization (CH_2Cl_2–pentane) afforded 208 mg of **5b** as a white solid (66%), mp 124–126 °C; ^{1}H NMR: δ 1.38 (3H, d, *J* 6.4, CH_3CH), 2.03 (3H, s, CH_3CO), 3.51 (1H, dt, *J* 1.5, 5.7, 3-H), 4.46 (1H, ddd, *J* 0.9, 5.7, 8.0, 4-H), 5.26 (1H, quintet, *J* 6.2, C*H*CH$_3$), 6.23 (1H, dd, *J* 8.0, 15.9, C*H*CHPh), 6.26 (1H, br, NH), 6.67 (1H, dd, *J* 0.9, 15.9, CHPh), 7.2–7.5 (5H, m, ArH); *m*/*z* 259 (M^+, 3%), 231 (8), 200 (17), 199 (27), 198 (20), 184 (30), 172 (27), 132 (100),

130 (80), 115 (30), 91 (17), 77 (18), 69 (29) (Found: C, 69.4; H, 6.5; N, 5.3. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%).

(1′*R,3*R**,4*R**)-3-[1′-(Lauroyloxy)ethyl]-4-(2′-phenylethenyl)-azetidin-2-one 5d**

The reaction was performed starting from **3d** (176 mg, 0.35 mmol) and following the procedure described for **5b**, affording 96 mg of **5d** (70%) as a white solid, mp 106–110 °C; ^{1}H NMR: δ 0.92 (3H, t, *J* 6.5, CH_3CH$_2$), 1.20–1.35 (18H, m, CH$_2$), 1.39 (3H, d, *J* 6.4, CH_3CH), 2.29 (2H, dt, *J* 2.8, 7.5, CH$_2$CO), 3.53 (1H, dt, *J* 1.6, 5.5, 3-H), 4.46 (1H, ddd, *J* 1.0, 5.7, 7.3, 4-H), 5.27 (1H, dq, *J* 5.4, 6.4, C*H*CH$_3$), 5.98 (1H, br, NH), 6.23 (1H, dd, *J* 7.3, 15.9, C*H*CHPh), 6.67 (1H, dd, *J* 1.0, 15.9, CHPh), 7.2–7.5 (5H, m, ArH); *m*/*z* 399 (M$^+$, 7%), 308 (4), 202 (17), 200 (100), 132 (61), 130 (15), 69 (17) (Found: C, 75.3; H, 9.4; N, 3.4. $C_{25}H_{37}NO_3$ requires C, 75.1; H, 9.3; N, 3.5%).

(1′*R,3*R**,4*S**)-3-[1′(*tert*-Butyldimethylsilyloxy)ethyl]-4-(2′-phenylethenyl)azetidin-2-one 6a**

Following the procedure described for **5a**, **4a** (544 mg, 1.24 mmol) afforded **6a** (365 mg, 89%). ^{1}H NMR: δ 0.10 (6H, s, Me$_2$Si), 0.90 (9H, s, Me$_3$C), 1.35 (3H, d, *J* 6.3, CH_3CH), 3.09 (1H, ddd, *J* 0.8, 2.5, 3.6, 3-H), 4.15–4.32 (2H, m, 4-H and C*H*CH$_3$), 5.93 (1H, br, NH), 6.25 (1H, dd, *J* 7.5, 15.8, C*H*CHPh), 6.61 (1H, d, *J* 15.8, C*H*Ph), 7.3–7.5 (5H, m, ArH); *m*/*z* 330 [(M − 1)$^+$, 1%], 316 (5), 288 (2), 274 (100), 230 (81), 157 (13), 129 (20), 115 (24), 75 (52) (Found: C, 68.5; H, 8.6; N, 4.0. $C_{19}H_{29}NO_2Si$ requires C, 68.8; H, 8.8; N, 4.2%).

(1′*R,3*R**,4*S**)-3-(1′-Hydroxyethyl)-4-(2′-phenylethenyl)-azetidin-2-one 6**

Following the procedure described for **5**, **6** (747 mg, 95%) was obtained from **6a** (1.20 g, 3.62 mmol). ^{1}H NMR: δ 1.36 (3H, d, *J* 6.4, CH_3CH), 2.05 (1H, br, OH), 3.03 (1H, ddd, *J* 0.7, 2.4, 6.1, 3-H), 4.12–4.20 (2H, m, 4-H and C*H*CH$_3$), 6.22 (1H, br, NH), 6.24 (1H, dd, *J* 7.6, 15.8, C*H*CHPh), 6.63 (1H, d, *J* 15.8, C*H*Ph), 7.22–7.45 (5H, m, ArH); *m*/*z* 217 (M$^+$, 5%), 185 (8), 156 (18), 155 (12), 141 (10), 139 (7), 128 (55), 113 (15), 87 (18), 69 (100), 55 (38) (Found: C, 71.7; H, 6.8; N, 6.2. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.4%).

Lipase-catalyzed acetylation of β-lactams 3–6

Lipase Amano PS (500 mg) was added to a solution of the selected β-lactam (500 mg) in vinyl acetate (25 mL) and the suspension vigorously stirred at 37 °C for the time reported in Table 1. For compounds **3** and **5**, which displayed a low degree of conversion, an additional 250 mg of enzyme was added after 48 h. Thereafter, the enzyme was removed by filtration, the solvent distilled *in vacuo*, and the residue chromatographed (light petroleum–ethyl acetate or diethyl ether–ethyl acetate) affording the acetate **3b–6b** along with the unreacted alcohol **3**–**6**, in the chemical and optical yields reported in Table 1.

Resolution of (±)-**3** afforded unreacted (+)-**3** (305 mg, 61%), $[a]_D$ +72.8 (*c* 1.1, CHCl$_3$) and (−)-**3b** (163 mg, 29%), $[a]_D$ −146.4 (*c* 0.9, CHCl$_3$).

Resolution of (±)-**4** afforded unreacted (−)-**4** (235 mg, 47%), $[a]_D$ −81.5 (*c* 1.3, CHCl$_3$) and (+)-**4b** (245 mg, 49%), $[a]_D$ = +79.1 (*c* 0.8, CHCl$_3$). **4b** ^{1}H NMR: δ 1.50 (3H, d, *J* 6.5, CH_3CH), 2.09 (3H, s, CH$_3$CO), 3.35 (1H, dd, *J* 2.5, 4.6, 3-H), 3.79 (3H, s, MeO), 4.45 (1H, dd, *J* 2.0, 8.2, 4-H), 5.41 (1H, dq, *J* 4.6, 6.5, C*H*CH$_3$), 6.30 (1H, dd, *J* 8.3, 15.9, C*H*CHPh), 6.76 (1H, d, *J* 15.9, C*H*Ph), 6.86 (2H, m, ArH), 7.20–7.50 (7H, m, ArH); *m*/*z* 366 [(M + 1)$^+$, 11%], 365 (60), 305 (30), 236 (43), 216 (100), 174 (29), 173 (65), 158 (45), 149 (55), 131 (39), 115 (27) (Found: C, 72.2; H, 6.2; N, 3.8. $C_{22}H_{23}NO_4$ requires C, 72.3; H, 6.3; N, 3.8%).

Resolution of (±)-**5** afforded unreacted (+)-**5** (345 mg, 69%), $[a]_D$ +4.1 (*c* 2.0, CHCl$_3$) and (−)-**5b** (143 mg, 24%), $[a]_D$ = −57.0 (*c* 0.9, CHCl$_3$).

Resolution of (±)-**6** afforded unreacted (+)-**6** (245 mg, 49%), $[a]_D$ +26.1 (*c* 1.0, CHCl$_3$) and (−)-**6b** (250 mg, 42%), $[a]_D$ = −51.9 (*c* 0.7, CHCl$_3$). **6b** ^{1}H NMR: δ 1.43 (3H, d, *J* 6.5, CH_3CH), 2.09 (3H, s, CH$_3$CO), 3.21 (1H, ddd, *J* 0.7, 2.6, 4.6, 3-H), 4.11 (1H, ddd, *J* 0.7, 2.2, 7.6, 4-H), 5.31 (1H, dq, *J* 4.6, 6.5, C*H*CH$_3$), 5.90 (1H, br, NH), 6.22 (1H, dd, *J* 7.6, 15.8, C*H*CHPh), 6.64 (1H, dd, *J* 15.8, C*H*Ph), 7.22–7.47 (5H, m, ArH); *m*/*z* 259 (M$^+$, 2%), 231 (10), 200 (15), 199 (25), 198 (23), 184 (33), 172 (31), 132 (100), 130 (78), 115 (32), 77 (13), 69 (24) (Found: C, 69.3; H, 6.4; N, 5.2. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%).

Chemical correlations

Optically active **3** and **4** were obtained from (*S*)-(+)-**1**, ee 85%,[11] as a mixture, following the procedure described in the literature.[8] Since column chromatography did not allow a satisfactory separation of the stereoisomers, the mixture (670 mg, 2.07 mmol), dissolved in anhydrous CH$_2$Cl$_2$ (10 mL) and in the presence of DMAP (506 mg, 4.14 mmol), was treated with TBDMS Cl (468 mg, 3.11 mmol) and stirred at room temperature for 40 h. Thereafter, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL) and washed with 5% HCl (10 mL); the organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. Careful column chromatography of the oily residue (light petroleum–ethyl acetate 9 : 1) afforded pure (1′*S*,3*S*,4*R*)-(−)-**4a** (447 mg, 54%) showing $[a]_D$ −45.8 (*c* 1.2, CHCl$_3$), ee 84%, 47 mg (5%) of a mixture of **4a**/**3a**, and (1′*S*,3*S*,4*S*)-(+)-**3a** (375 mg, 38%), $[a]_D$ +133.4 (*c* 1.9, CHCl$_3$), ee 85%.

(1′*S*,3*S*,4*S*)-(+)-**3a** (50 mg, 0.11 mmol), ee 85%, in anhydrous THF (1.5 mL) was treated with TBAF (72 mg, 0.27 mmol) at room temperature for 2 h; the solvent was evaporated under reduced pressure and the residue purified by column chromatography (light petroleum–ethyl acetate 1 : 1) to afford diastereoisomerically pure (1′*S*,3*S*,4*S*)-**3** (34 mg, 92%) showing $[a]_D$ +138.7 (c 1.0, CHCl$_3$). The same procedure performed on (1′*S*,3*S*,4*R*)-(−)-**4a** (50 mg, 0.11 mmol), ee 84%, afforded (1′*S*,3*S*,4*R*)-(−)-**4** (25 mg, 68%) showing $[a]_D$ −73.2 (*c* 1.0, CHCl$_3$). (+)-**3** and (−)-**4** presented the expected ^{1}H NMR and MS spectra.

Following the procedure described for **5b**, from (1′*S*,3*S*,4*S*)-(+)-**3a** (300 mg, 0.68 mmol), ee 85%, oxidative removal of the PMP group with CAN afforded crude **5a**, which was deprotected at oxygen (TBAF, CH$_2$Cl$_2$) to afford (1′*S*,3*S*,4*S*)-(+)-**5** (78 mg, 52%) showing $[a]_D$ +11.9 (*c* 1.2, CHCl$_3$). The same procedure performed on (1′*S*,3*S*,4*R*)-(−)-**4a** (350 mg, 0.80 mmol), ee 85%, afforded (1′*S*,3*S*,4*R*)-(+)-**4** (82 mg, 47%) showing $[a]_D$ +32.1 (*c* 2.0, CHCl$_3$).

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References

1 C. H. Wong and G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, 1995; R. A. Sheldon, *Chirotechnology: Industrial Synthesis of Optically Active Compounds*, Marcel Dekker, New York, 1993; S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1; 1998, 157; R. D. Schmid and R. Verger, *Angew. Chem., Int. Ed.*, 1998, **37**, 1608.

2 A. Basak, G. Bhattacharya and H. M. Bdour, *Tetrahedron*, 1998, **54**, 6529; P. Csomós, L. T. Kanerva, G. Bernáth and F. Fölöp, *Tetrahedron: Asymmetry*, 1996, **7**, 1789; H. Nagai, T. Shiozawa, K. Achiwa and Y. Terao, *Chem. Pharm. Bull.*, 1992, **40**, 2227.

3 L. Ghosez and Y. Marchand-Brynaert, *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, vol. 5.

4 I. Ojima and F. Delaloge, *Chem. Soc. Rev.*, 1997, **26**, 377.

5 R. Brieva, J. Z. Crich and C. J. Sih, *J. Org. Chem.* 1993, **58**, 1287.
6 R. J. Cvetovich, M. Chartrain, F. W. Hartner, C. Roberge, J. S. Amato and E. J. J. Grabowski, *J. Org. Chem.*, 1996, **61**, 6575.
7 A. H. Berks, *Tetrahedron*, 1996, **52**, 331 and references therein.
8 (*a*) G. I. Georg, J. Kant and H. S. Gill, *J. Am. Chem. Soc.*, 1987, **109**, 1129; (*b*) G. Cainelli, M. Panunzio, T. Basile, A. Bongini, D. Giacomini and G. Martelli, *J. Chem. Soc.*, *Perkin Trans. 1*, 1987, 2637.
9 R. Kronenthal, C. J. Han and M. K. Taylor, *J. Org. Chem.*, 1982, **47**, 2765.
10 C. J. Sih and S. H. Wu, *Top. Stereochem.*, 1989, **19**, 63.
11 B. Wipf, E. Kupfer, R. Bertazzi and H. G. W. Leuenberger, *Helv. Chim. Acta*, 1983, **66**, 485.

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