Lipase-catalyzed resolution and desymmetrization of 2-hydroxymethylaziridines

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The Amano PS lipase-catalyzed acetylation of 2-hydroxymethylaziridines **1a**–**e** has been investigated in order to evaluate the effect of ring substituents on the enantioselectivity of the reaction and to assess the stereochemical preference of the enzyme. *N*-Benzyl-3-substituted *cis*-aziridines displayed high enantioselectivity and higher *E* values were found when the bulkiness of the substituent in position 3 was increased. In contrast, the corresponding *trans* isomers showed only poor enantioselectivity, regardless of the steric hindrance of the substituent at C_3. Removal of the *N*-benzyl group proved to be detrimental to the enantioselectivity. In addition, desymmetrization of *meso* dimethanolic *cis*-aziridine **1f** was successfully accomplished, and the corresponding monoacetylated product **2f**, which is related to a key intermediate used in the total synthesis of the mitomycin antibiotic FR-900482, was obtained in excellent yield and nearly enantiomerically pure form. Moreover, the absolute configuration of enantiomerically pure *cis*-aziridines was determined by chemical correlation and/or chiroptical techniques, thus showing the stereochemical preference of Amano PS lipase for the *2S* enantiomer.

Introduction

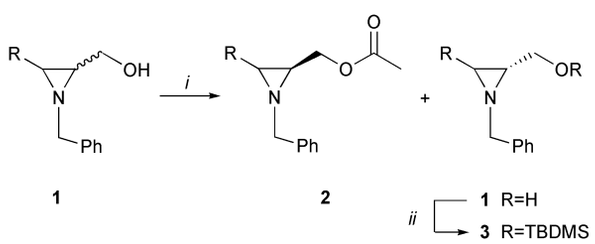
Aziridines are currently receiving a great deal of interest in modern organic synthesis as versatile building blocks for the preparation of a variety of important nitrogen-containing compounds.[1] In this respect, 2-hydroxymethylaziridines have been shown to represent useful substrates for carbonylative ring expansion to β-lactams, using $Co_2(CO)_8$ as the catalyst.[2] Along this line, we have recently applied this reaction in a novel approach to a precursor of the carbapenem antibiotic PS-5 from a suitable hydroxymethylaziridine, which was obtained in enantiomerically pure form by lipase-catalyzed acetylation.[3] In fact, lipases are among the most common biocatalysts used in organic synthesis, displaying a remarkable interfacial activity which makes them particularly suitable for enantioselective catalyzed reactions in aqueous suspensions, water–organic solvent mixtures, as well as in organic solvents.[4,5]

Aiming to evaluate the general applicability of the chemoenzymatic approach to enantiomerically pure β-lactams from hydroxymethylaziridines *via* enzymatic resolution followed by carbonylative ring expansion, we now wish to report our findings about the effect of ring substituents in the enantioselective Amano PS (from *Pseudomonas cepacia*) lipase-catalyzed acetylation of 2-hydroxymethylaziridines.

Results and discussion

Synthesis and enzymatic resolution

Aziridinemethanols **1a**–**e** (Scheme 1) were synthesized from the parent aziridinecarboxylates according to a well known procedure.[2] In a typical enzymatic resolution, the 2-hydroxymethylaziridine **1** (1 equiv.) was dissolved in *n*-hexane in the presence of vinyl acetate (5 equiv.), and Amano PS lipase was added in a 2 : 1 substrate–enzyme ratio (w/w). The resulting suspension was vigorously stirred at 37 °C for 0.6 to 20 h, depending on the aziridine (see Table 1), until the desired conversion, estimated by TLC, was reached. The enzyme was filtered off, the solvent removed *in vacuo* and the crude residue containing the acetylated product **2** was separated from the unreacted substrate **1** by column chromatography. However, the chromatographic separation proved to be much easier when the crude mixture was treated with TBDMSCl–DMAP in CH_2Cl_2 in order to convert the unreacted aziridine **1** into the corresponding silyl derivative **3**. Moreover, the determination of enantiomeric excess (ee) by ^{1}H NMR in the presence of (*R*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral shift reagent proved more reliable with silyl ethers **3** than with free hydroxymethylaziridines **1**. The results are shown in Table 1.



a R=H; **b** R=Me; **c** R=Et; **d** R=Ph; **e** R=CF_3; **f** R=CH_2OH

Scheme 1 *Reagents and conditions: i*, Amano PS lipase, vinyl acetate, *n*-hexane, 37 °C; *ii*, TBDMSCl, DMAP, CH_2Cl_2, rt.

On first inspection, all substrates were acylated by Amano PS lipase, albeit with different enantioselectivity. In particular, the enantiomeric ratio *E*[6] revealed a strict dependence on the *cis*/*trans* stereochemistry of the aziridine ring; high enantioselectivity was observed in the case of *cis* aziridines **1b**–**d** (entries 2–4), whilst the corresponding *trans* isomers (entries 5–7) gave very low *E* values. Moderate enantioselectivity was found for 3-unsubstituted aziridine **1a** (entry 1); the low yield observed for both substrate and product may be due to the high reactivity of 3-unsubstituted aziridines, which are well known to undergo nucleophilic ring opening.[2] As far as *cis* aziridines are concerned, the enantioselectivity is related to the steric hindrance of the substituent in position 3; in particular, when

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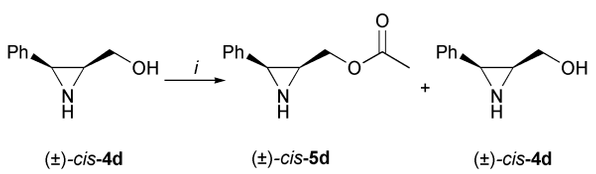
Table 1 Amano PS lipase-catalyzed enantioselective acetylation of 2-hydroxymethylaziridines **1a**–**f**

		Unreacted alcohol			Product					
Entry	R	Compound	Yield (%)	ee (%)	Compound	Yield (%)	ee (%)	*t*/h	*c*[a]	*E*[a]
1	H	(+)-**3a**	10	>97	(+)-**2a**	20	36	1.8[b]	0.73	8
2	Me	(−)-*cis*-**1b**	41	>97	(+)-*cis*-**2b**	46	86	2	0.43	55
3	Et	(+)-*cis*-**3c**	43	92	(+)-*cis*-**2c**	50	96	0.6	0.59	97
4	Ph	(−)-*cis*-**1d**	50	>97[c]	(+)-*cis*-**2d**	43	>98	20	0.50	>200
5	Me	(−)-*trans*-**3b**	27	31	(+)-*trans*-**2b**	37	24	1	0.56	2
6	Et	(+)-*trans*-**3c**	17	37	(−)-*trans*-**2c**	43	38	1.3	0.49	3
7	Ph	(+)-*trans*-**3d**	24	>30	(−)-*trans*-**2d**	29	N.d.	5	0.55[d]	<2
8	CF_3	(+)-*trans*-**1e**	48	65	(−)-*trans*-**2e**	48	67	7.5	0.49	10
9	CH_2OH	—	—	—	(+)-**2f**	96	>97	4.5		

[a] Calculated according to ref. 6. [b] A 1.5 : 1 ratio (mol/mol) of vinyl acetate-substrate was used. [c] Determined after chemical acetylation to (−)-*cis*-**2d**. [d] Calculated from the yield of the product and the unreacted alcohol.

moving from hydrogen to methyl, ethyl and, eventually, phenyl (entries 1–4), the *E* value increased accordingly, from 8 up to 200, and the same pattern was observed also for the chemical yields. In contrast, low *E* values and yields were obtained for *trans* aziridines, regardless of the substituent (entries 5–7), except for the trifluorinated derivative *trans*-**1e**, which showed moderate enantioselectivity (entry 8).

In order to evaluate the effect of the substituent at the nitrogen atom on the enantioselectivity, *N*-unsubstituted aziridine *cis*-**4d**, having the ring carbon substitution pattern that had shown the highest *E* value, was synthesized[2] and subjected to lipase-catalyzed resolution (Scheme 2). In this case,

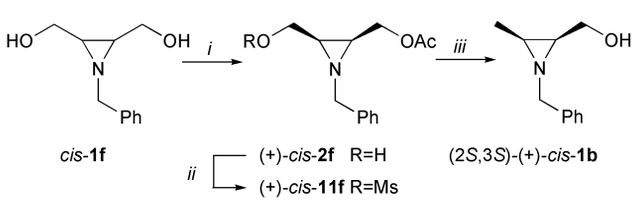


(±)-*cis*-**4d** (±)-*cis*-**5d** (±)-*cis*-**4d**

Scheme 2 *Reagents and conditions: i*, Amano PS lipase, vinyl acetate, 37 °C.

the acetylation rate dropped dramatically, thus highlighting the contribution of the *N*-benzyl substituent to the enzyme recognition; comparable reaction rates (18 h, 50% conversion) were obtained only when vinyl acetate was used as the solvent, however, racemic products (unchanged **4d** and acetylated **5d**) were recovered in moderate yield, along with a number of unidentified side products.

On the basis of the high enantioselectivity displayed by *cis* *N*-benzyl methanolic aziridines, we explored also the lipase-catalyzed desymmetrization of a *meso* analogue, namely *cis*-2,3-bis(hydroxymethyl)aziridine **1f** (Scheme 3), in



cis-**1f** (2*S*,3*S*)-(+)-*cis*-**1b**

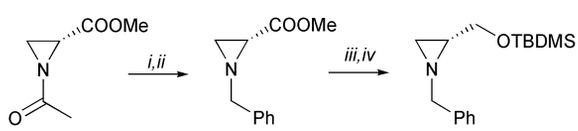
Scheme 3 *Reagents and conditions: i*, Amano PS lipase, vinyl acetate, *n*-hexane, 37 °C; *ii*, mesyl chloride, NEt_3, CH_2Cl_2, 0 °C; *iii*, LAH, THF, rt.

order to obtain the monoacetylated product **2f**, which is related to a key intermediate used in the total synthesis of the antibiotic FR-900482, a potent antineoplastic agent belonging to the mitomycins.[7,8] Aziridine **1f** was prepared from the corresponding bis-TBDMS derivative,[2,7] by a standard deprotection method.[9] Amano PS lipase catalyzed the formation of the monoacetate **2f**, which was recovered in excellent yield and nearly enantiomerically pure form (Table 1, entry 9).

Determination of absolute configurations

In order to assess the stereochemical preference of Amano PS lipase, the absolute configuration of the compounds was determined by chemical correlation and/or by comparison of chiroptical properties. In particular, aziridines that were recovered in enantiomerically pure form from the lipase-catalyzed acetylation (Table 1, entries 1–4, 9) were selected.

Aziridine (+)-**3a** was correlated with the configurationally known[10] *N*-acetyl-2-methoxycarbonylaziridine (2*R*)-(+)-**6** (Scheme 4); after removal of the *N*-acetyl group with *Candida*



(2*R*)-(+)-**6** (2*R*)-(+)-**7** (2*R*)-(+)-**3a**

Scheme 4 *Reagents and conditions: i*, *Candida cylindracea* lipase, phosphate buffer, pH 7.5, 37 °C; *ii*, $PhCH_2Br$, K_2CO_3, CH_3CN, reflux; *iii*, LAH, THF, −40 °C; *iv*, TBDMSCl, DMAP, CH_2Cl_2, −20 °C.

cylindracea lipase (CCL) in phosphate buffer at 37 °C, treatment with benzyl bromide in acetonitrile in the presence of K_2CO_3 afforded methyl *N*-benzylaziridine-2-carboxylate (+)-**7**, which was reduced with LAH to (+)-**1a** and finally converted into the TBDMS ether (+)-**3a** (25% yield in 4 steps). Therefore, the same 2*R* configuration can be assigned to (+)-**3a** and, consequently, 2*S* to (+)-**2a**.

The absolute configuration of 3-methylaziridine (+)-*cis*-**2b** was assigned by comparison of its chiroptical properties (CD and UV spectra) with the closely related and configurationally known 3-ethylaziridine (2*S*,3*S*)-(+)-*cis*-**2c**.[3] The CD and UV spectra are reported in Fig. 1. Both aziridines show a series of negative maxima in the 240–270 nm region which are related to the Cotton effect associated with the ^1L_b transition of benzene ring.[11] The close resemblance of the CD spectra allows us to extend the 2*S*,3*S* absolute configuration to the acetylated product 3-methyl-(+)-*cis*-**2b**; therefore, the configuration 2*R*,3*R* must be deduced for the unreacted substrate (−)-*cis*-**1b**.

Aziridine (−)-*cis*-**1d** was correlated with a phenylalanine derivative (Scheme 5). Reductive ring opening of (−)-*cis*-**1d** afforded *N*-benzylphenylalaninol (+)-**8** (59% yield), whose enantiomeric form (−)-**8** was obtained from phenylalanine methyl ester hydrochloride (2*S*)-(−)-**9** by reductive amination with benzaldehyde to (−)-**10** and subsequent reduction with LAH (Scheme 5). The same 2*S* configuration of (−)-**9** can therefore be assigned to (−)-**10** and (−)-**8**, thus allowing the assignment of the *R* absolute configuration to the C_2 stereocenter of (−)-*cis*-**1d**; the *cis* relationship in (−)-**1d** consequently assigns the *R* configuration to the C_3 stereogenic carbon. Thus, (−)-*cis*-**1d** has the 2*R*,3*R* absolute configuration, whereas the configuration 2*S*,3*S* can be inferred for the acetylation product (+)-*cis*-**2d**.

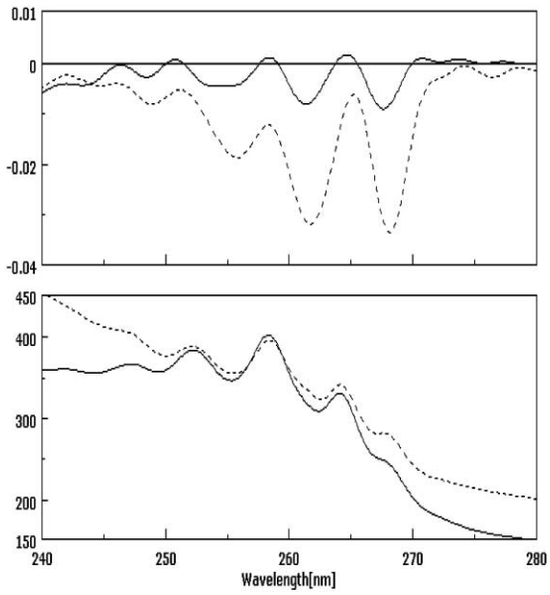
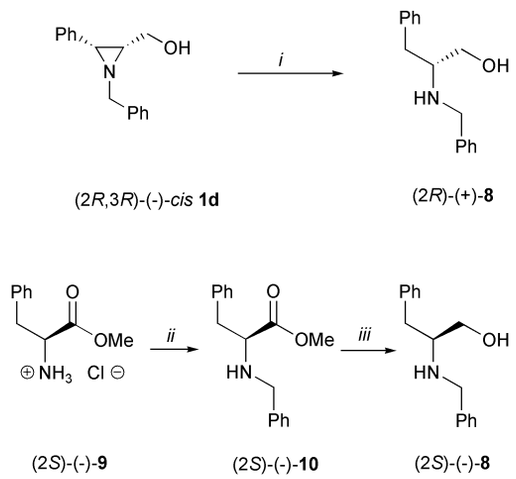


Fig. 1 Circular dichroism and electronic absorption spectra of (2*S*,3*S*)-(+)-*cis*-**2c**, ee 96% (straight line) and (+)-*cis*-**2b**, ee 86% (dashed line) recorded in *n*-hexane.



Scheme 5 *Reagents and conditions: i*, H_2, Pd–C, AcOH, MeOH, rt; *ii*, PhCHO, $NaBH_3CN$, MeOH, rt; *iii*, LAH, THF, rt.

The absolute configuration of (+)-*cis*-**2f** was determined by chemical correlation with compound (2*S*,3*S*)-(+)-*cis*-**1b** *via* the mesyl ester (+)-**11f** (Scheme 3). Aziridine (+)-*cis*-**2f** was treated with mesyl chloride in CH_2Cl_2 at 0 °C, affording (+)-*cis*-**11f** (81% yield) which was reduced with LAH at rt to the 3-methyl derivative (+)-*cis*-**1b**, thus assigning the 2*S*,3*S* absolute configuration to (+)-*cis*-**2f**.

The results of the configurational assignments are reported in Table 2 and clearly show the stereochemical preference of Amano PS lipase for the 2*S* enantiomer. A number of empirical rules have been proposed in the past to rationalize the stereopreference of lipases towards various substrates on the basis of the steric hindrance of the substituents;[5] in the case of secondary alcohols, the rule correctly predicts which enantiomer reacts faster with Amano PS lipase and shows that substrates which bear groups significantly different in size are resolved with higher enantioselectivity, and can be successfully applied over a range of structurally diverse substrates.[12] In contrast, such a stereochemical prediction is more difficult for primary alcohols, even though some attempts have been made in the case of five-membered *N*-containing heterocycles.[13] Nonetheless, their structural diversity with respect to the compounds described in the present contribution does not allow a meaningful comparison and makes any extension of these rules to methanolic aziridines quite arbitrary.

Table 2 Absolute configuration of selected aziridines from Amano PS lipase-catalyzed enantioselective acetylation

		Unreacted alcohol		Product	
Entry	R	Compd.	Abs.conf.	Compd.	Abs.conf.
1	H	(+)-**3a**	2*R*	(+)-**2a**	2*S*
2	Me	(−)-*cis*-**1b**	2*R*,3*R*	(+)-*cis*-**2b**	2*S*,3*S*
3	Et	(+)-*cis*-**3c**	2*R*,3*R*	(+)-*cis*-**2c**	2*S*,3*S*
4	Ph	(−)-*cis*-**1d**	2*R*,3*R*	(+)-*cis*-**2d**	2*S*,3*S*
5	CH_2OH	—	—	(+)-*cis*-**2f**	2*S*,3*R*

In summary, Amano PS lipase-catalyzed acetylation of 3-substituted 2-hydroxymethylaziridines allowed the preparation of methanolic *cis* aziridines in good chemical and enantiomeric yields, for both unreacted substrate and product; remarkably, higher enantioselectivity was found when the bulkiness of the substituent in position 3 was increased. *cis*-Aziridines **1** and **2** have been shown to represent useful substrates for the synthesis of β-lactams *via* Co-catalyzed carbonylative ring expansion,[2] thus making attractive such a chemo-enzymatic approach to enantiomerically pure *trans* β-lactams. In contrast, the corresponding *trans* isomers displayed poor enantioselectivity, regardless of the steric hindrance at C_3; in this respect, future work should investigate the influence of molecular geometry on the enantioselectivity by comparing different enzymes and solvents, in order to gain access to enantiomerically pure *trans* aziridines as well, which would be of value as substrates for carbonylation to *cis* β-lactams of high enantiomeric purity.

Experimental

^1H and ^{13}C NMR spectra were recorded for samples in $CDCl_3$ solution on a Bruker DPX-200 MHz spectrometer. Chemical shifts are reported in δ values from TMS as internal standard; coupling constants (J) are given in Hz. Optical rotations were recorded for samples in chloroform solution (unless otherwise stated) at 20 °C on a Perkin–Elmer 241 polarimeter and are in 10^{-1} deg cm^2 g^{-1}. GLC analysis were performed with a Hewlett–Packard 5890A gas chromatograph on a DB1 column (30 × 0.53 mm ID and 5 μm film) from J&W Scientific, with helium as the carrier gas. Mass spectra were determined on a Finnigan Mat SSQ 710A mass spectrometer (EI, 70 eV). CD and UV spectra of **2b** and **2c** were recorded for *n*-hexane solutions on a Jasco J710 spectropolarimeter (path length 1 cm) at concentrations of 4.8×10^{-3} and 5.7×10^{-3}, respectively. Elemental analyses were performed with a Carlo Erba Elemental Analyzer 1110. Chromatographic purification of the compounds was performed on silica gel (0.05–0.20 mm). Amano PS lipase was generously donated by Amano Pharmaceutical Company Ltd. (Nagoya, Japan) and used without further purification. *Candida cylindracea* lipase (CCL) was purchased from Sigma. Racemic hydroxymethylaziridines **1a**–**e** and **4d**, as well as *cis*-1-benzyl-2,3-bis(*tert*-butyldimethylsilyloxymethyl)aziridine, were synthesized as previously reported;[2] Amano PS lipase catalyzed acetylation of *cis*-**1c** has been already described.[3]

Determination of enantiomeric excess

The ee of compounds **2a**–**d** was determined by ^1H NMR analysis in the presence of (*R*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol as chiral shift reagent; in the case of hydroxymethylaziridines **1a**–**d**, conversion into the corresponding TBDMS ethers **3a**–**d**, as previously described,[2] was required, except for *cis*-(−)-**1d**, which was converted into the acetoxy derivative *cis*-(−)-**2d**. The ee of **2f** was determined after conversion into the mesyl ester **11f**. For compounds **1e**, **2e**, **4d** and **5d** the ee's were evaluated by use of a chiral B-DEX 120 column (30 m × 0.25 mm ID and 0.25 μm film) from Supelchem.

Amano PS lipase-catalyzed acetylation of hydroxymethylaziridines 1: general procedure

The hydroxymethylaziridine **1** (1 mmol) was dissolved in the minimum amount of THF (generally no more than 2 ml) and diluted with *n*-hexane (20 ml). Vinyl acetate (5 mmol) and Amano PS lipase (1 : 2 w/w with respect to the aziridine) were added and the resulting suspension was vigorously stirred at 37 °C for the time reported in Table 1. Thereafter, the enzyme was removed by filtration and carefully washed with anhydrous diethyl ether; the organic phases were combined and concentrated under reduced pressure. Depending on the chromatographic separation observed between the unreacted alcohol and the product of the enzymatic acetylation, the crude residue was directly chromatographed (method A) or treated with TBDMSCl to convert the unreacted alcohol into the corresponding TBDMS-ether (method B). In the latter case, the crude residue was dissolved in anhydrous CH_2Cl_2 (5 ml) and subsequently treated with DMAP (0.8 mmol) and TBDMSCl (0.6 mmol) under magnetic stirring at rt for 30 min. The mixture was diluted with further CH_2Cl_2 (5 ml), washed with water (5 ml) and brine (3 ml), and dried over $MgSO_4$. The solvent was distilled *in vacuo* and the residue chromatographed on silica gel [using the eluent reported below in square brackets], affording the product of the enzymatic acetylation **2** and the unreacted substrate as the *O*-TBDMS ether **3**.

1-Benzyl-2-hydroxymethylaziridine (1a). Resolution of (±)-**1a** (method B) afforded [diethyl ether–light petroleum 80 : 20] the unreacted substrate as 1-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)aziridine (2*R*)-(+)-**3a** (10%), $[\alpha]_D$ +4.6 (*c* 1.3, $CHCl_3$), ee > 97%, along with the acetylation product (2*S*)-(+)-**2a** (20%), $[\alpha]_D$ +11 (*c* 1.9, $CHCl_3$), ee 36%.

(2*S*)-(+)-**2a**: ^{1}H NMR: δ_H 1.57 (1H, d, *J* 6.4, CH_2 ring), 1.83 (1H, d, *J* 3.4, CH_2 ring), 1.85–1.96 (1H, m, C*H* ring), 2.00 (3H, s, COCH_3), 3.35 (1H, d, *J* 13.3, CH_2Ph), 3.64 (1H, d, *J* 13.3, CH_2Ph), 3.85 (1H, dd, *J* 11.6, 7.3, CH_2O), 4.23 (1H, dd, *J* 11.6, 4.4, CH_2O), 7.27–7.39 (5H, m, aromatic). MS, *m*/*z*: 205 (M^+, 5%), 204 (6), 190 (1), 175 (2), 162 (4), 146 (15), 144 (15), 132 (8), 114 (7), 91 (100), 77 (6), 72 (94), 65 (17), 43 (80). (Found: C, 70.4; H, 7.3; N, 6.8; $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%).

***cis*-1-Benzyl-2-hydroxymethyl-3-methylaziridine (*cis*-1b).** Resolution of (±)-*cis*-**1b** (method A) afforded [pure diethyl ether and finally diethyl ether–ethyl acetate 80 : 20] the unreacted substrate (2*R*,3*R*)-(−)-*cis*-**1b** (41%), $[\alpha]_D$ −3.9 (*c* 1.4, $CHCl_3$), ee > 97%, along with the acetylated product 1-benzyl-2-acetoxymethyl-3-methylaziridine (2*S*,3*S*)-(+)-*cis*-**2b** (46%), $[\alpha]_D$ +22.8 (*c* 2.6, $CHCl_3$), ee 86%. The ee of (2*R*,3*R*)-(−)-*cis*-**1b** was evaluated after conversion, under standard conditions, into the corresponding 1-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-methylaziridine (2*R*,3*R*)-(+)-*cis*-**3b** (84%), $[\alpha]_D$ +4.0 (*c* 2.7, $CHCl_3$), ee > 97%.

(2*S*,3*S*)-(+)-*cis*-**2b**: ^{1}H NMR: δ_H 1.25 (3H, d, *J* 5.6, CH_3CH), 1.69–1.82 (1H, m, CH_3CH), 1.83–1.91 (1H, m, C*H*CH_2), 2.01 (3H, s, COCH_3), 3.45 (1H, d, *J* 13.5, CH_2Ph), 3.65 (1H, d, *J* 13.5, CH_2Ph), 4.07 (1H, dd, *J* 11.7, 7.0, CH_2O), 4.18 (1H, dd, *J* 11.7, 5.5, CH_2O), 7.27–7.38 (5H, m, aromatic). MS, *m*/*z*: 218 ([M − 1]$^+$, 3%), 160 (16), 128 (22), 91 (64), 86 (100), 65 (15), 45 (49). (Found: C, 70.9; H, 7.7; N, 6.3. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%).

***trans*-1-Benzyl-2-hydroxymethyl-3-methylaziridine (*trans*-1b).** Resolution of (±)-*trans*-**1b** (method B) afforded [light petroleum–diethyl ether 70 : 30] the unreacted substrate as 1-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-methylaziridine (−)-*trans*-**3b** (27%), $[\alpha]_D$ −5.8 (*c* 3.1, $CHCl_3$), ee 31%, along with the acetylation product 1-benzyl-2-acetoxymethyl-3-methylaziridine (+)-*trans*-**2b** (37%), $[\alpha]_D$ +15.4 (*c* 3.1, $CHCl_3$), ee 24%.

(+)-*trans*-**2b**: ^{1}H NMR spectroscopy showed the presence of two invertomers (73 : 27), due to slow nitrogen inversion on the NMR timescale.[2] ^{1}H NMR major invertomer: δ_H 1.39 (3H, d, *J* 6.0, CH_3CH), 1.69–1.77 (1H, m, C*H*CH_2), 1.97 (3H, s, COCH_3), 2.16 (1H, dq, *J* 2.9, 6.0, CH_3CH), 3.53 (1H, d, *J* 13.8, CH_2Ph), 3.84 (1H, dd, *J* 11.6, 7.5, CH_2O), 3.86 (1H, d, *J* 13.8, CH_2Ph), 4.24 (1H, dd, *J* 11.6, 4.6, CH_2O), 7.32–7.44 (5H, m, aromatic); minor invertomer: δ_H 1.27 (3H, d, *J* 5.5, CH_3CH), 1.59–1.69 (1H, m, C*H*CH_2), 2.01 (3H, s, COCH_3), 2.19–2.31 (1H, m, CH_3CH), 3.62 (1H, d, *J* 13.9, CH_2Ph), 3.87 (1H, d, *J* 13.9, CH_2Ph), 4.20 (1H, dd, *J* 12.4, 8.2, CH_2O), 4.53 (1H, dd, *J* 12.4, 3.9, CH_2O), 7.25–7.33 (5H, m, aromatic). MS, *m*/*z*: 218 ([M − 1]$^+$, 2%), 204 (1), 176 (1), 160 (13), 132 (3), 128 (16), 91 (74), 86 (100), 77 (4), 65 (20), 58 (24), 43 (67). (Found: C, 71.1; H, 7.8; N, 6.3. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%).

***trans*-1-Benzyl-3-ethyl-2-hydroxymethylaziridine (*trans*-1c).** Resolution of (±)-*trans*-**1c** (method B) afforded [light petroleum–diethyl ether 70 : 30] the unreacted substrate as 1-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-ethylaziridine (+)-*trans*-**3c** (17%), $[\alpha]_D$ +11.1 (*c* 2.0, $CHCl_3$), ee 37%, along with the acetylated product 1-benzyl-2-acetoxymethyl-3-ethylaziridine (−)-*trans*-**2c** (37%), $[\alpha]_D$ −15.4 (*c* 4.2, $CHCl_3$), ee 38%.

(−)-*trans*-**2c**: ^{1}H NMR spectroscopy showed the presence of two invertomers (54 : 46), due to slow nitrogen inversion on the NMR timescale.[2] ^{1}H NMR major invertomer: δ_H 1.1 (3H, t, *J* 7.4, CH_2CH_3), 1.40–1.58 (2H, m, CH_3CH_2), 1.55–1.70 (1H, m, C*H*CH_2CH$_3$), 1.95 (3H, s, COCH_3), 2.20–2.31 (1H, m, C*H*CH_2O), 3.49 (1H, d, *J* 13.4, CH_2Ph), 3.85 (1H, dd, *J* 11.6, 7.4, CH_2O), 3.92 (1H, d, *J* 13.4, CH_2Ph), 4.21 (1H, dd, *J* 11.6, 4.8, CH_2O), 7.25–7.43 (5H, m, aromatic); minor invertomer: δ_H 0.85 (3H, t, *J* 7.5, CH_2CH_3), 1.68–1.86 (2H, m, CH_3CH_2), 1.55–1.70 (1H, m, C*H*CH_2CH$_3$), 2.02 (3H, s, COCH_3), 1.96–2.07 (1H, m, C*H*CH_2O), 3.55 (1H, d, *J* 13.6, CH_2Ph), 3.90 (1H, d, *J* 13.6, CH_2Ph), 4.24 (1H, dd, *J* 12.6, 5.2, CH_2O), 4.53 (1H, dd, *J* 12.6, 3.6, CH_2O), 7.25–7.43 (5H, m, aromatic). MS, *m*/*z*: 174 ([M − 59]$^+$, 4%), 160 (2), 142 (10), 100 (82), 91 (76), 72 (13), 65 (22), 54 (9), 43 (100). (Found: C, 72.2; H, 8.1; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%).

***cis*-1-Benzyl-2-hydroxymethyl-3-phenylaziridine (*cis*-1d).** Resolution of (±)-*cis*-**1d** (method A) gave [diethyl ether–light petroleum 60 : 40] the unreacted substrate (2*R*,3*R*)-(−)-*cis*-**1d** (49%), $[\alpha]_D$ −91.3 (*c* 0.8, $CHCl_3$), along with the acetylated product (2*S*,3*S*)-(+)-*cis*-**2d** (50%), $[\alpha]_D$ +85.6 (*c* 3.2, $CHCl_3$), ee > 97%. The ee of (2*R*,3*R*)-(−)-*cis*-**1d** was determined after conversion into (2*R*,3*R*)-(−)-*cis*-**2d** with acetic anhydride and DMAP at 60 °C for 40 min (93%), which showed $[\alpha]_D$ −81.4 (*c* 4.0, $CHCl_3$), ee > 97%.

(2*S*,3*S*)-(+)-*cis*-**2d**. ^{1}H NMR: δ_H 1.95 (3H, s, COCH_3), 2.26 (1H, ddd, *J* 7.6, 6.6, 5.2, C*H*CH_2), 2.93 (1H, d, *J* 6.6, PhC*H*), 3.69 (1H, d, *J* 13.4, CH_2Ph), 3.77 (1H, dd, *J* 11.8, 7.6, CH_2O), 3.80 (1H, d, *J* 13.4, CH_2Ph), 3.96 (1H, dd, *J* 11.8, 5.2, CH_2O), 7.22–7.49 (10H, m, aromatic). MS, *m*/*z*: 222 ([M − 59]$^+$, 2%), 190 (66), 148 (84), 130 (12), 120 (23), 91 (100), 77 (10), 65 (18), 43 (57). (Found: C, 76.7; H, 6.8; N, 4.9. $C_{18}H_{19}NO_2$ requires: C, 76.8; H, 6.8; N, 5.0%).

***trans*-1-Benzyl-2-hydroxymethyl-3-phenylaziridine (*trans*-1d).** Resolution of (±)-*trans*-**1d** (method B) afforded [light petroleum–diethyl ether 70 : 30] the unreacted substrate as 1-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-phenylaziridine (+)-*trans*-**3d** (24%), $[\alpha]_D$ +8.5 (*c* 3.1, $CHCl_3$), along with the acetylation product 1-benzyl-2-acetoxymethyl-3-phenylaziridine (−)-*trans*-**2d** (29%), $[\alpha]_D$ −36.5 (*c* 3.0, $CHCl_3$).

(−)-*trans*-**2d**: ^{1}H NMR spectroscopy showed broad and poorly resolved signals, indicating the presence of two invertomers at nitrogen[2] overlapped at the cohalescence. ^{1}H NMR: δ_H 2.00 (3H, s, COCH_3), 2.58 (1H, ddd, *J* 7.8, 4.4, 3.3,

C*H*CH_2), 3.18 (1H, br d, *J* 13.8, CH_2Ph), 3.27–3.40 (1H, br, PhC*H*), 3.55 (1H, br d, *J* 13.8, CH_2Ph), 3.75–4.43 (1H, br m, CH_2O), 4.35–4.68 (1H, br m, CH_2O), 7.25–7.45 (10H, m, aromatic). MS, *m*/*z*: 222 ([M − 59]$^+$, 2%), 190 (66), 148 (84), 130 (12), 120 (23), 91 (100), 77 (10), 65 (18), 43 (57). (Found: C, 76.9; H, 6.8; N, 4.9. $C_{18}H_{19}NO_2$ requires: C, 76.8; H, 6.8; N, 5.0%).

***trans*-1-Benzyl-2-hydroxymethyl-3-trifluoromethylaziridine (*trans*-1e).** Resolution of (±)-*trans*-**1e** (method A) gave [light petroleum–diethyl ether 50 : 50] the unreacted substrate (+)-*trans*-**1e** (48%), $[a]_D$ +11.6 (*c* 4.3, $CHCl_3$), ee 65%, along with the acetylated product 1-benzyl-2-acetoxymethyl-3-trifluoromethylaziridine (−)-*trans*-**2e** (48%), $[a]_D$ −18.1 (*c* 5.1, $CHCl_3$), ee 67%.

(−)-*trans*-**2e**. ^{1}H NMR spectroscopy showed broad and poorly resolved signals, indicating the presence of two invertomers at nitrogen.[2] ^{1}H NMR: δ_H 2.00 (3H, s, COCH_3), 2.23–2.46 and 2.78–2.90 (2H, br m, H ring), 3.65–4.07 (2H, br, CH_2Ph), 4.10–4.60 (2H, br m, CH_2O), 7.27–7.43 (5H, m, aromatic). MS, *m*/*z*: 273 (M$^+$, 8%), 214 (23), 200 (4), 144 (7), 140 (22), 104 (5), 91 (100), 77 (3), 65 (11), 43 (38). (Found: C, 57.2; H, 5.1; N, 5.2. $C_{13}H_{14}F_3NO_2$ requires: C, 57.1; H, 5.2; N, 5.1%).

***cis*-2-Hydroxymethyl-3-phenylaziridine (*cis*-4d).** Resolution of (±)-*cis*-**4d** (method A) afforded [diethyl ether–ethyl acetate 90 : 10] both the unreacted substrate *cis*-**4d** (30%) and the acetylated product *cis*-**5d** (31%) in racemic form.

(±)-*cis*-**5d**. ^{1}H NMR: δ_H 2.27 (3H, s, COCH_3), 3.05 (1H, dd, *J* 12.3, 6.1, C*H*CH_2), 3.47–3.56 (2H, m, CH_2O), 3.79 (1H, d, *J* 6.1, PhC*H*), 7.29–7.41 (5H, m, aromatic). MS, *m*/*z*: 190 ([M − 1]$^+$, 14%), 148 (51), 131 (63), 120 (25), 104 (51), 91 (41), 77 (19), 43 (100). (Found: C, 68.9; H, 6.8; N, 6.8. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%).

Synthesis and desymmetrization of aziridine 1f: *cis*-1-benzyl-2,3-bis(hydroxymethyl)aziridine (*cis*-1f)

Tetrabutylammonium fluoride (237 mg, 0.91 mmol) was added to a solution of *cis*-1-benzyl-2,3-bis(*tert*-butyldimethylsilyloxymethyl)aziridine[2] (165 mg, 0.39 mmol) in anhydrous THF (5 ml) and vigorously stirred at rt for 30 min. The solvent was removed under reduced pressure and the residue purified by column chromatography (ethyl acetate–methanol 95 : 5), affording *meso* aziridine *cis*-**1f** as a pale yellow solid (66 mg, 87%), which was crystallized from chloroform-*n*-pentane, affording the title compound as white crystals mp 105–106 °C. ^{1}H NMR: δ_H 1.90 (2H, br, CH_2OH), 1.90–2.11 (2H, m, C*H*CH_2), 3.59 (2H, s, CH_2N), 3.67 (2H, ddd, *J* 11.4, 6.0, 1.7, CH_2OH), 7.28–7.40 (5H, m, aromatic). MS, *m*/*z*: 193 (M$^+$, 1%), 192 (2), 176 (1), 162 (17), 102 (86), 91 (100), 84 (18), 74 (55), 65 (22). (Found: C, 68.2; H, 8.0; N, 7.3. $C_{11}H_{15}NO_5$ requires C, 68.4; H, 7.8; N, 7.25%).

For the enzymatic acetylation, Amano PS lipase (75 mg) and vinyl acetate (357 µl, 3.9 mmol) were added to a solution of aziridine *cis*-**1f** (150 mg, 0.8 mmol) and the resulting suspension was vigorously stirred at 37 °C. After 4 h 30 min, the reaction reached complete conversion (TLC); the catalyst was removed by filtration, the solvent evaporated *in vacuo* and the residue purified by column chromatography [ethyl acetate–methanol 95 : 5], affording (2*S*,3*R*)-(+)-*cis*-**2f** (96%) as a pale yellow sticky oil, which showed $[a]_D$ +25.9 (*c* 3.6, $CHCl_3$), ee > 97% (evaluated on the corresponding mesyl ester *cis*-**11f**).

(2*S*,3*R*)-(+)-*cis*-**2f**. ^{1}H NMR: δ_H 1.99–2.11 (2H, m, H ring), 2.02 (3H, s, COCH_3), 2.10 (1H, br, CH_2OH), 3.52 (1H, d, *J* 13.2, CH_2Ph), 3.66 (1H, d, *J* 13.2, CH_2Ph), 3.68–3.74 (2H, m, CH_2OH), 4.13–4.22 (2H, m, CH_2OAc), 7.29–7.39 (5H, m, aromatic). MS, *m*/*z*: 236 ([M + 1]$^+$, 1%), 235 (2), 204 (17), 176 (11), 162 (21), 144 (17), 134 (13), 102 (100), 91 (88), 84 (24), 74 (17). (Found: C, 66.3; H, 7.25; N, 5.9. $C_{13}H_{17}NO_3$ requires: C, 66.5; H, 7.3; N, 5.9%).

Chemical correlations: (2*S*,3*R*)-(+)-*cis*-2-acetoxymethyl-1-benzyl-3-methylsulfonyloxymethylaziridine (*cis*-11f)

A solution of mesyl chloride (29.5 µl, 0.374 mmol) in anhydrous CH_2Cl_2 (3 ml) was slowly added at 0 °C to a stirred solution of (+)-*cis*-**2f** (80 mg, 0.340 mmol) and triethylamine (71 µl, 0.510 mmol) in CH_2Cl_2; the resulting solution was allowed to react at rt for 4 h. Thereafter, the reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with water (4 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography [diethyl ether], affording (2*S*,3*R*)-(+)-*cis*-**11f** (81%) as a pale yellow oil, $[a]_D$ +7.6 (*c* 1.5, $CHCl_3$), ee >97%.

(2*S*,3*S*)-(+)-*cis*-**11f**: ^{1}H NMR: δ_H 2.02 (3H, s, COCH_3), 2.07–2.20 (2H, m, C*H*CH_2), 2.94 (3H, s, CH_3SO_2), 3.52 (1H, d, *J* 13.1, CH_2Ph), 3.66 (1H, d, *J* 13.1, CH_2Ph), 4.04–4.38 (4H, m, CH_2OAc + CH_2OMs), 7.28–7.42 (5H, m, aromatic). MS, *m*/*z*: 313 (M$^+$, 0.5%), 312 (1), 271 (1), 253 (3), 240 (2), 234 (3), 218 (12), 193 (8), 180 (33), 91 (100), 84 (9), 65 (7). (Found: C, 53.7; H, 6.1; N, 4.5. $C_{14}H_{19}NO_5S$ requires C, 53.65; H, 6.2; N, 4.5%).

(2*S*,3*S*)-(+)-*cis*-1-Benzyl-2-hydroxymethyl-3-methylaziridine (*cis*-1b)[14]

A 1.0 M $LiAlH_4$ solution in THF (0.4 ml) was slowly added dropwise to a stirred solution of (2*S*,3*R*)-(+)-*cis*-**11f** (58 mg, 0.185 mmol) in freshly distilled anhydrous THF (2 ml) at rt under a flow of nitrogen. After 1 h TLC analysis showed the total disappearance of the starting material; the reaction mixture was cooled to 0 °C and carefully quenched by the dropwise addition of water (35 µl), followed by 0.15 M NaOH solution (35 µl). The white inorganic precipitate was filtered off and washed with abundant ethyl ether; the filtrate was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue which was subjected to column chromatography [diethyl ether], affording (2*S*,3*S*)-(+)-*cis*-**1b** (56%), $[a]_D$ +4.0 (*c* 0.9, $CHCl_3$), ee > 97%. (Found: C, 74.2; H, 8.6; N, 7.8. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9%).

(2*R*)-(+)-1-Benzyl-2-methoxycarbonylaziridine (7)[15]

Lipase from *Candida cylindracea* (250 mg) was added to a suspension of (2*R*)-(+)-*N*-acetyl-2-methoxycarbonylaziridine (**6**),[10] ee 36% (500 mg, 3.52 mmol) in phosphate buffer (pH 7.5, 0.1 M, NaCl 0.1 M, 25 ml) and stirred at 37 °C for 3 h, until TLC analysis showed complete deacetylation. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated at atmospheric pressure. The crude residue containing the *N*-unsubstituted derivative was dissolved in anhydrous acetonitrile (5 ml); potassium carbonate (724 mg, 5.25 mmol) and benzyl bromide (461 µl, 3.87 mmol) were added and the resulting mixture was refluxed for 2 h. After addition of water (30 ml) and extraction with ethyl ether (3 × 30 ml), the pooled phases were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography on silica gel [light petroleum–diethyl ether 50 : 50, then diethyl ether] gave the *N*-benzylaziridine (2*R*)-(+)-**7** as a light yellow oil (417 mg, 62% overall yield), $[a]_D$ +28.5 (*c* 2.2, $CHCl_3$). (Found: C, 69.1; H, 6.8; N, 7.2. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%).

(2*R*)-(+)-1-Benzyl-2-(*tert*-butyldimethylsilyloxymethyl)aziridine (3a)

According to the procedure already described,[2] reduction of (2*R*)-(+)-**7** with 1.0 M $LiAlH_4$ solution in THF at −40 °C, and subsequent silylation with TBDMS-Cl, afforded the desired (2*R*)-(+)-**3a** (40% overall yield), $[a]_D$ +2.0 (*c* 4.0, $CHCl_3$), ee 40%.

(2*R*)-(+)-2-Benzylamino-3-phenylpropan-1-ol (8)

A solution of (2*R*,3*R*)-(−)-*cis*-**1d** (101 mg, 0.42 mmol), $[\alpha]_D$ −91.3, ee > 98%, in methanol (3 ml) and acetic acid (0.5 ml) was stirred at rt with 10% Pd-on-carbon (10 mg) under hydrogen (1 atm) until absorption of the required volume (11 ml in 30 min). The catalyst was then removed by filtration and the solution poured into saturated $NaHCO_3$ (10 ml). The resulting mixture was extracted with diethyl ether (3 × 5 ml) and the collected organic phases dried over $MgSO_4$. After filtration and rotary evaporation, the crude residue was purified by column chromatography [ethyl acetate–methanol 95 : 5], affording (2*R*)-(+)-**8** (59% yield), $[\alpha]_D$ +9.0 (*c* 2.7, $CHCl_3$). ^{1}H NMR: δ_H 2.21 (2H, br, O*H* + N*H*), 2.80 (1H, dd, *J* 13.9, 7.4 PhCH_2CH), 2.88 (1H, dd, *J* 13.9, 6.5, PhCH_2CH), 3.00 (1H, dddd, *J* 7.4, 6.5, 5.3, 3.8, C*H*NH), 3.40 (1H, dd, *J* 10.8, 5.2, CH_2OH), 3.69 (1H, dd, *J* 10.8, 3.8, CH_2OH), 3.82, (2H, s, NHCH_2Ph), 7.18–7.39 (10H, m, aromatic). MS, *m*/*z*: 242 ([M + 1]$^+$, 1%), 241 (0.5), 224 (2), 210 (38), 150 (93), 91 (100), 77 (4), 65 (12). (Found: C, 79.5; H, 8.0; N, 5.8. $C_{16}H_{19}NO$ requires C, 79.7; H, 7.9; N, 5.8%).

(2*S*)-(−)-Methyl 2-benzylamino-3-phenylpropanoate (10)

Benzaldehyde (141 µl, 1.391 mmol) was added to a magnetically stirred solution of L-phenylalanine methyl ester hydrochloride (2*S*)-(−)-**9** (300 mg, 1.39 mmol) in anhydrous methanol (9 ml); powdered 3 Å molecular sieves (1 g) were added and the resulting suspension allowed to react for 24 h at rt. The molecular sieves were filtered off and $NaBH_3CN$ (88 mg, 1.40 mmol) in anhydrous methanol (2 ml) was slowly added at 0 °C. After 35 min the mixture was diluted with water (30 ml), extracted with ethyl acetate (3 × 15 ml) and the combined organic phases were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by chromatography [ethyl acetate–methanol 80 : 20], affording (2*S*)-(−)-**10** (51%) as a pale yellow oil, $[\alpha]_D$ −8.8 (*c* 1.6, $CHCl_3$). ^{1}H NMR: δ_H 1.85 (1H, br, N*H*), 3.00 (2H, d, *J* 6.6, CH_2CH), 3.59 (1H, t, *J* 6.6, C*H*CH_2), 3.67 (1H, d, *J* 13.2, PhCH_2NH), 3.69 (3H, s, COOCH_3), 3.86 (1H, d, *J* 13.2, PhCH_2NH), 7.17–7.52 (10H, m, aromatic). MS, *m*/*z*: 270 ([M + 1]$^+$, 0.1%), 221 (3), 210 (18), 178 (85), 91 (100), 65 (5). (Found: C, 75.8; H, 7.0; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1, N 5.2%).

(2*S*)-(−)-2-Benzylamino-3-phenylpropan-1-ol (8)

1.0 M $LiAlH_4$ solution in THF (0.7 ml) was slowly added dropwise to a stirred solution of (2*S*)-(−)-**10** (95 mg, 0.353 mmol) in freshly distilled anhydrous THF (3 ml) at rt under a flow of nitrogen. After 45 min, when TLC analysis showed the total disappearance of the starting material; the reaction mixture was cooled to 0 °C and carefully quenched by the dropwise addition of water (100 µl), followed by 0.15 M NaOH solution (100 µl). The white inorganic precipitate was filtered off and washed with abundant ethyl ether; the filtrate was dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a residue which was subjected to column chromatography [diethyl ether], affording (2*S*)-(−)-**8** (42%), $[\alpha]_D$ −9.9 (*c* 3.5, $CHCl_3$). (Found: C, 79.7; H, 7.9; N, 5.7. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N, 5.8%).

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