Synthesis and NMR studies of key intermediates to a new class of β-lactam: the trinems

Carla Marchioro,* Giorgio Pentassuglia,* Alcide Perboni and Daniele Donati

Glaxo Wellcome S.p.A., Medicines Research Centre, via Fleming 4, 37135 Verona, Italy

An efficient synthesis of the four isomeric epoxides 4a–d, key compounds to the trinem ring system, starting from (3*R*,4*R*,1′*R*)-(+)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one 6a is described. All the intermediates have been characterized by means of NMR techniques.

β-Lactam antibiotics are important antibacterial agents because of their high potency and broad spectrum of activity usually accompanied by low levels of toxicity.[1] Because of this, research over recent years has been focused on discovering novel β-lactams from natural sources (*e.g.* cephalosporins, monobactams, carbapenems), by semisynthesis of new derivatives from naturally occurring sources (*e.g.* penicillins, cephalosporins, carbapenems) and by design of novel classes of compounds (*e.g.* penems, carbacephalosporins, oxacephalosporins).[2] Recently a new family of totally synthetic β-lactam antibiotics, the trinems (formerly referred to as tribactams, Fig. 1, **1**) has been discovered in our laboratories.[3] These compounds possessed both very broad antibacterial activity and high stability to most clinically relevant β-lactamases. From the structural point of view, the main feature of the members of this class is the presence of a third ring, C, fused to the bicyclic nucleus of carbapenems; this can be 5–7 membered, carbocyclic or a heteroatom-containing ring. Our research activities have been particularly focused on exploiting derivatives where C is a 6-membered carbocyclic ring substituted at C-4 (Fig. 1, **2**). In particular sanfetrinem (GV104326) **3a** and its metabolically labile ester GV118819 '**3b**' have shown a particularly good biological profile and have been selected for development studies.[4]

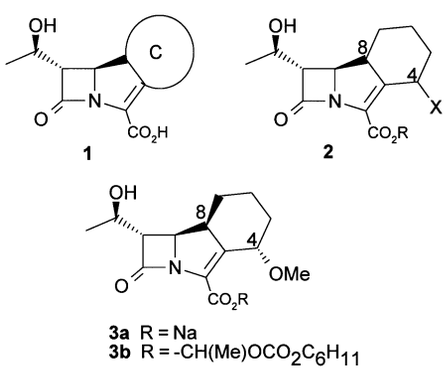


Fig. 1

As both antibacterial activity and biological stability of trinems **2** were found to be dependent on the absolute configuration at the stereogenic centres at C-4 and C-8, the identification of efficient and stereoselective routes to these compounds would allow us to synthesize more efficiently other derivatives. On this basis, we identified the isomeric epoxides **4a–d** (Fig. 2) as advanced key intermediates.

Compounds **4a–d** can react with nucleophiles to give α-substituted cyclohexanols **5** (where, for example, **5a** and **5b** represent the epoxide ring opening of **4a** with methylamine and methanol, respectively) which could be converted into 4-substituted trinems **2** through well established procedures (for example, see Scheme 1 for compound **3a**).[3a,5]

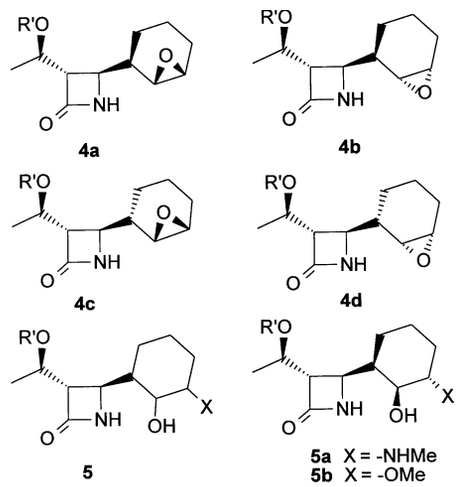
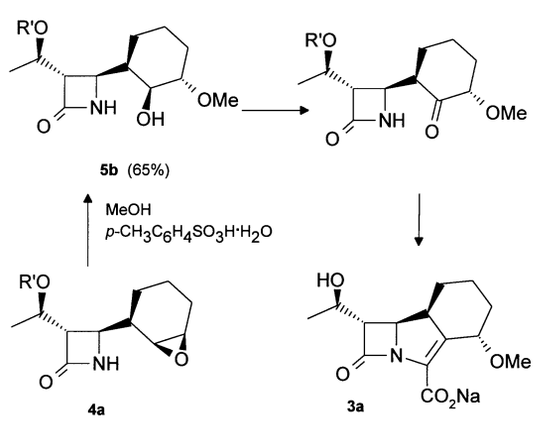


Fig. 2



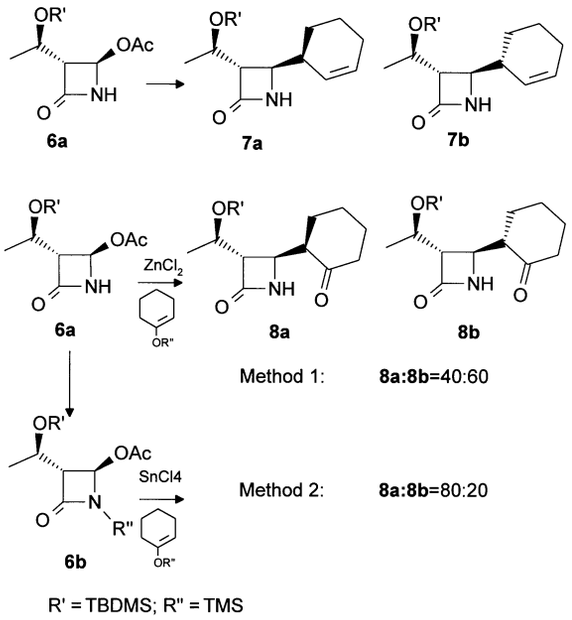
Scheme 1

Results and discussion

Synthesis

In early studies we succeeded in the direct cyclohexenylation of commercially available 4-acetoxyazetidinone **6a**[6] with cyclohexenyl bromide in the presence of zinc dust in anhydrous tetrahydrofuran (THF), to obtain an inseparable mixture of cyclohexenyl derivatives **7a**,**b**[7a] (Scheme 2). A 4:1 mixture of **7a**:**7b** was also obtained through an intramolecular Sakurai-type reaction.[7b]

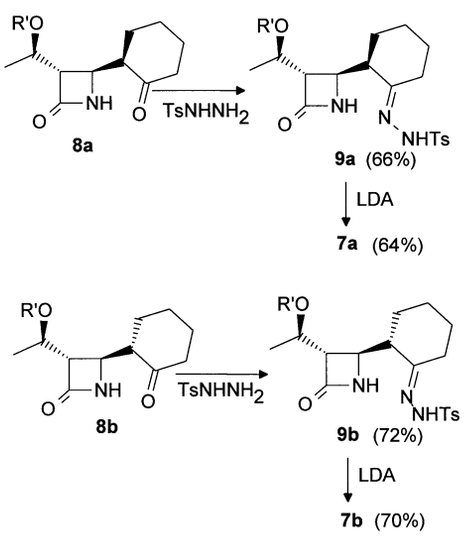
In order to obtain pure isomers of **7a** and **7b** a less direct route was thus preferred. It has previously been demonstrated[3c] that 1-(trimethylsilyloxy)cyclohexene reacts with the 4-acetoxyazetidinone **6a** in the presence of a number of catalysts, but



Scheme 2

most preferably zinc chloride, to give a 40:60 mixture of the ketoazetidinones **8a**,**b** in 90% overall yield from **6a**. We were able to change the diastereoisomer ratio by changing the reaction conditions. Protection of **6a** at the lactam nitrogen with a trimethylsilyl group gave **6b** that was reacted with 1-(trimethylsilyloxy)cyclohexene in the presence of tin(IV) chloride to give, after work-up and removal of the trimethylsilyl group, an 80:20 mixture of isomers **8a**,**b** in 95% overall yield from **6a** (Scheme 2). The ketoazetidinone **8a** could be obtained in 55% yield after crystallization of the crude reaction mixture.

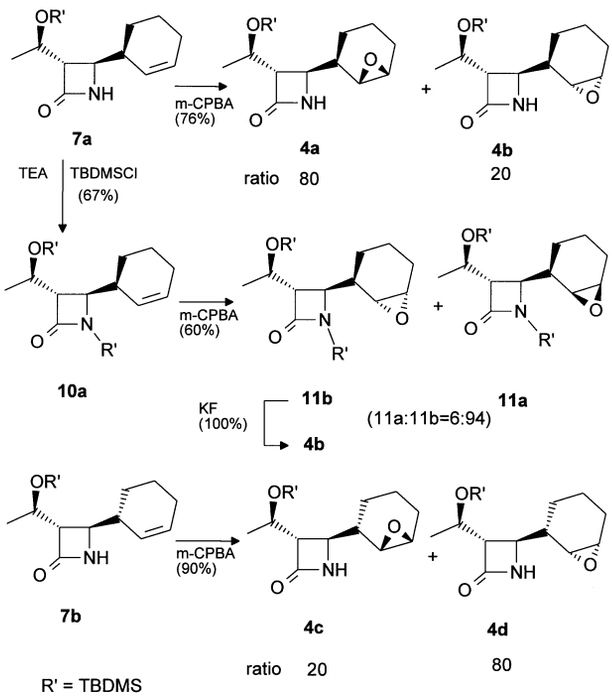
Compounds **8a** and **8b** were then separately transformed into the tosylhydrazones **9a** and **9b** in good yield (Scheme 3). It is



Scheme 3

worth noting that only the *E* isomer of the hydrazones could be isolated, although traces of the *Z* isomers could be detected by careful NMR analysis of the reaction mixtures.

Both hydrazones **9a** and **9b** were successfully transformed into cyclohexenyl derivatives in 64 and 70% yield, respectively, according to the well established Shapiro procedure.[8] Epoxidation of **7a** (3-chloroperoxybenzoic acid, dichloromethane, 23 °C) gave an 80:20 mixture of isomers **4a** and **4b** that could be easily separated by flash chromatography (for the structural assignment of epoxides **4a** and **4b** see next paragraph). The same reaction conditions were used for **7b** and, in this case, a 20:80 mixture of epoxides **4c** and **4d** was isolated (Scheme 4).



Scheme 4

In order to explain this stereochemical outcome we hypothesized the formation of a hydrogen bond between the lactam hydrogen and the peracid as reported by Roush[9] and by Kocovský.[10]

This was indirectly supported through the epoxidation of the *N*-*tert*-butyldimethylsilyl derivative **10a** (Scheme 4). Thus, reaction of **10a** with 3-chloroperoxybenzoic acid gave a mixture of the epoxides **11a** and **11b** in a 6:94 ratio and 60% yield. The absolute configurations at the stereogenic centres for **11b** were established by conversion into **4b** after removal of the silyl protecting group.

All the epoxides were found to undergo regioselective ring opening with a number of nucleophiles, such as methanol and methylamine, allowing the introduction of a variety of substituents on the trinem structure. In the case of the epoxide **4a** the regiochemistry of the reaction is consistent[11] with a preference for a ring-opening to give a *trans*-diaxial product such as **5**; for the epoxide **4b**, however, the substituent at C-3′, for steric reasons, directs nucleophile attack to C-1′.

Compound **4a** has been most widely studied because its reaction with methanol allowed the stereoselective introduction of a methoxy group and gave an intermediate that could be easily transformed into sanfetrinem and GV118819. In the same way[12,3c] we were able to open regioselectively the epoxide **4a** with amines, alcohols and thiols in order to evaluate the microbiological profile of the corresponding 4-substituted trinems.

NMR Studies

The complete proton and carbon assignments for compounds **4a–d**, **7a–b**, **8a–b** and **9a–b** were relatively straightforward and were made with the combined results of several experiments: ^{1}H NMR, ^{13}C NMR, ^{1}H–^{13}C NMR correlation (gHMQC, gHSQC) and gCOSY; in addition, the structures have been investigated by means of NOE techniques. The reference numbering is given in Fig. 3.

The description of the complete proton and carbon assignments for compound **4a** serves as an example. The ^{1}H NMR signal assignments were made first *via* the sequential correlations observed from the gCOSY spectra. The protons H-3 and H-4 (δ 3.77, dd, *J* 2.4, 6.8 Hz) showed a strong correlation in the

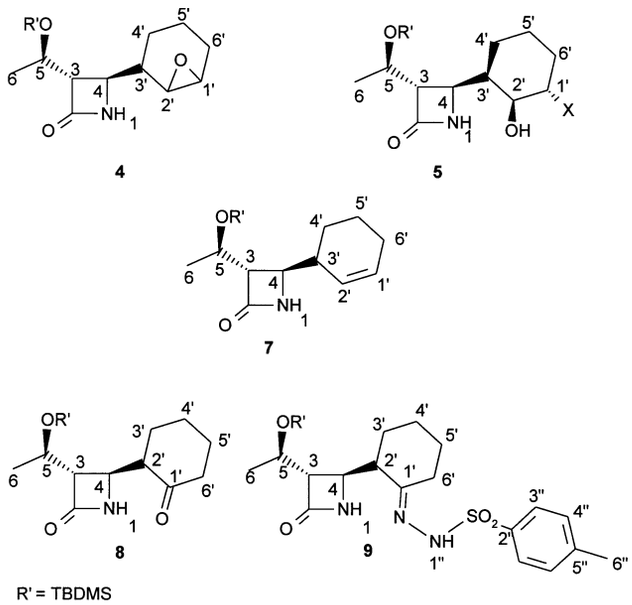


Fig. 3

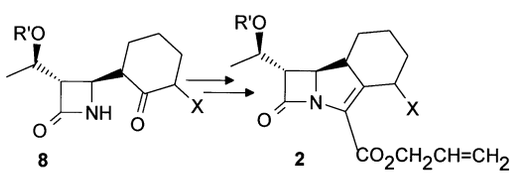
gCOSY spectrum, as expected. Proton H-4 was also coupled to H-3′ (δ 2.0) and this one was correlated to H-2′ and both the H-4′ protons: from these all of the aliphatic protons were readily identified. The axial and equatorial protons were assigned through their coupling constants and chemical shifts.

^{13}C NMR signals were then ascribed through gHMQC (gradient heteronuclear multiple quantum correlation) and gHSQC (gradient heteronuclear single quantum correlation).

The stereochemistries in the series **4a–d** were studied by means of NOE experiments. All the observed NOEs, together with a suggestion for the solution conformation are reported in Fig. 4: in the case of compound **4a** the configuration at C-3′ was confirmed from the presence of NOE enhancements between H-3 and H-3′ and between H-4 and H-2′; these findings, together with the same enhancements after irradiation of H-3, suggest a rotation around the C(4)–C(3′) bond and the configurations at H-2′ and H-1′ were also based upon the comparison of NOE data of compounds **4a** and **4b**.

The stereochemistries were also confirmed by the chemical transformation of **4a** to compound **3a**, as reported in Scheme 1.

The relative configuration at C-2′ in compounds **8a** and **8b** was unequivocally established through conversion into com-



Scheme 5

pounds related to the structure (**2a** and **2b**, where X = H, Scheme 5)†,[3a] and relative NOE studies while the stereochemistries at C-3 and C-4 are derived from the coupling constant value, *i.e.* $J_{3,4}$ = 2.2 Hz.[13]

† **2a**: δ_H 1.25 (3 H, d, 11-Me), 1.35 (1 H, m, 7-H$_{ax}$), 1.84 (2 H, m, 2 × 6-H), 1.92 (2 H, m, 2 × 5-H), 1.96 (1 H, m, 7-H$_{eq}$), 2.05 (1 H, m, 4-H$_{ax}$), 2.86 (1 H, m, 8-H), 3.15 (1 H, dd, *J* 3.0 and 6.5, 10-H), 3.45 (1 H, m, 4-H$_{eq}$), 4.15 (1 H, dd, *J* 3.0 and 10.0, 9-H), 4.20 (1 H, m, 11-H), 4.70 (2 H, m, C*H*$_2$CH=CH$_2$), 5.30 (2 H, m, CH$_2$CH=C*H*$_2$) and 5.95 (1 H, m, CH$_2$C*H*=CH$_2$). **2b**: δ_H 1.25 (1 H, m, 7-H$_{ax}$), 1.33 (3 H, d, 11-Me), 1.70 (1 H, m, 6-H), 1.75 (1 H, m, 5-H$_{ax}$), 1.85 (1 H, m, 6-H), 2.10 (1 H, m, 5-H$_{eq}$), 1.96 (1 H, m, 7-H$_{eq}$), 2.35 (1 H, m, 4-H$_{ax}$), 2.89 (1 H, m, 8-H), 3.13 (1 H, dd, *J* 2.8 and 7.6, 10-H), 3.44 (1 H, m, 4-H$_{eq}$), 3.71 (1 H, dd, *J* 2.8 and 6.6, 9-H), 4.20 (1 H, m, 11-H), 4.80 (2 H, m, C*H*$_2$CH=CH$_2$), 5.33 (2 H, m, CH$_2$CH=C*H*$_2$) and 5.95 (1 H, m, CH$_2$C*H*=CH$_2$).

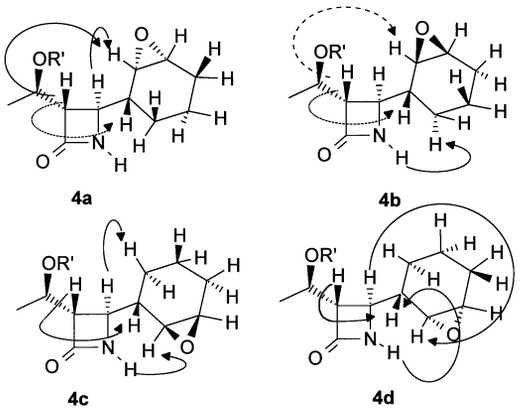


Fig. 4

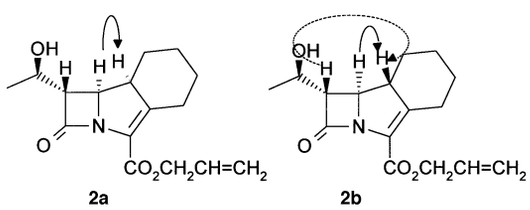


Fig. 5

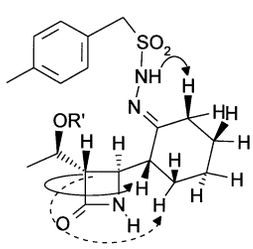


Fig. 6

In both isomers, saturation of H-8 results in a strong NOE enhancement in the signal of H-9 in compound **2a** and in the case of the epimer, **2b**, in a strong enhancement in the H-10 signal in addition to a small effect on the H-9 signal (Fig. 5).

The two isomers **8a** and **8b** also show significant differences in their chemical shifts. Comparing the proton chemical shifts, characteristic differences can be observed between the H-4 signals of the two isomeric compounds: in the case of **8a**, the signal is at about 4.1 ppm while in compound **8b** the signal is at about 3.6 ppm. This trend in the chemical shifts difference can be observed also in compounds **9a** and **9b**: respectively, 4.0 and 3.6 for their H-4 chemical shifts. The configuration of the double bond of both compounds is derived from the NOE experiments: in the case of **9a** saturation of the lower field aromatic protons results in enhancements in H-1 and H-4, saturation of the upper field aromatic protons in an enhancement of the H$_{eq}$-6′ signal, irradiation of H-4 results in an enhancement of H-3, H-1, H-2′ and in the lower field aromatic protons. Irradiation of H-3 results in an enhancement of H-2′, H$_{eq}$-3′, H-5 and H-4 and a smaller effect on the aromatic region. The most relevant result is from saturation of H$_{eq}$-6′: an NOE enhancement is evident on the NH of the Ts group, H$_{eq}$-4′ and H$_{eq}$-5′; irradiation of H-2′ gives enhancement on H-3, H-4 and H$_{eq}$-5′ and in the upper field aromatic region. From all these results, the structure in Fig. 6 is derived.

Moving to the compounds **7a** and **7b** there are no significant differences in the chemical-shift values, and the coupling constant $J_{4,3'}$ value (7.4 Hz in **7a** and 8.6 Hz in **7b**), suggests a close steric similarity between the two compounds.

Experimental

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Solvents were distilled under a nitrogen atmosphere from sodium benzophenone ketyl (THF), CaH_2 (triethylamine, DMF) or P_2O_5 (CH_2Cl_2). Zinc chloride, $ZnCl_2$, was fused *in vacuo* before use. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping in a phosphomolybdic acid solution followed by heating. Flash chromatography was performed on E. Merck silica gel (230–400 mesh).[14] Melting points are uncorrected and were determined with a capillary melting point apparatus. IR spectra were recorded in $CDCl_3$ solution unless otherwise indicated and are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 500 MHz, ^{13}C NMR were recorded at 100.57 or at 75.43 MHz: all the spectra were collected in $CDCl_3$ at 25 °C; *J* values are given in Hz. In the ^1H NMR spectra, chemical shifts are reported in ppm with respect to residual $CHCl_3$ at 7.26 downfield from TMS while in the carbon NMR spectra, the central signal (δ 77.0) ^{13}C resonance of $CDCl_3$ was used as internal reference. NMR assignments are assisted by NOE and 2D- techniques. For the numbering systems used in the NMR assignments, see Fig. 3.

Mass spectra were recorded in FAB (70 eV) mode using 3-nitrobenzyl alcohol as matrix. All optical rotations [*a*] values were obtained in CH_2Cl_2 solution, at the sodium D line, at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*)-1′-oxocyclohexan-2′-yl]azetidin-2-one 8a and (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(2′*S*)-1′-oxocyclohexan-2′-yl]azetidin-2-one 8b

Method 1. To a solution of 4-acetoxyazetidinone **6a** (2.85 g, 9.91 mmol) and zinc chloride (2.50 g, 18.34 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise a solution of 1-(trimethylsilyloxy)cyclohexene (2.12 ml, 10.90 mmol) in dry CH_2Cl_2 (20 ml). The resulting reaction mixture was stirred for 3 h after which further 1-(trimethylsilyloxy)cyclohexene (0.25 ml, 1.28 mmol) in dry CH_2Cl_2 (2 ml) was added to it and stirring was continued for 1 h. The solution was washed with brine, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 7:3 mixture of cyclohexane and ethyl acetate to afford **8a** (1.18 g) and **8b** (1.77 g) (ratio **8a**:**8b** = 40:60, total yield 90%).

Compound **8a**: white solid; mp 105–107 °C; [*a*] +33.9 (*c* 0.54) (Found: C, 62.62; H, 9.54; N, 4.22. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3418s, 1757s and 1707s; δ_H 0.06 [3 H, s, $(Me_3C)Me_2Si$], 0.08 [3 H, s, $(Me_3C)Me_2Si$], 0.87 [9 H, s, $(Me_3C)Me_2Si$], 1.24 (3 H, d, *J* 6.5, 5-Me), 1.69 (3 H, m, 3′-H_{ax}, 5′-H_{ax}, 4′-H_{ax}), 1.96 (1 H, m, 4′-H_{eq}), 2.15 (2 H, m, 5′-H_{eq} and 3′-H_{eq}), 2.36 (1 H, m, 6′-H_{ax}), 2.43 (1 H, m, 6′-H_{eq}), 2.56 (1 H, m, 2′-H), 2.88 (1 H, dd, *J* 2.3 and 5.5, 3-H), 4.10 (1 H, dd, *J* 2.3 and 3.5, 4-H), 4.19 (1 H, m, 5-H) and 5.75 (1 H, br s, NH); δ_C(100.57 MHz) −4.95, −4.20 [2 × $(Me_3C)Me_2Si$], 17.97 [$(Me_3C)Me_2Si$], 22.55 (C-6), 24.66 (C-4′), 25.77 [$(Me_3C)Me_2Si$], 27.64 (C-5′), 27.76 (C-3′), 42.37 (C-6′), 49.35 (C-2′), 52.59 (C-4), 60.58 (C-3), 65.97 (C-5), 168.58 (C-2) and 211.57 (C-1′) [Found (HRMS): *m*/*z* 326.215 980. Calc. for (MH^+): 326.215 148]; *m*/*z* 326 (MH^+, 28%), 310 (20) and 268 (100).

Compound **8b**: white solid; mp 107–109 °C; [*a*] +40.1 (*c* 0.57) (Found: C, 62.54; H, 9.72; N, 4.24. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3423s, 1755s and 1707s; δ_H 0.07 [3 H, s, $(Me_3C)Me_2Si$], 0.08 [3 H, s, $(Me_3C)Me_2Si$], 0.86 [9 H, s, $(Me_3C)Me_2Si$], 1.22 (3 H, d, *J* 6.5, 5-Me), 1.42 (1 H, m, 3′-H_{ax}), 1.65 (2 H, m, 4′-H_{ax} and 5′-H_{ax}), 1.95 (1 H, m, 4′-H_{eq}), 2.10 (1 H, m, 5′-H_{eq}), 2.16 (1 H, m, 3′-H_{eq}), 2.33 (1 H, m, 2′-H), 2.40 (1 H, m, 6′-H_{ax}), 2.42 (1 H, m, 6′-H_{eq}), 2.70 (1 H, m, 3-H), 3.63 (1 H, dd, *J* 2.18 and 9.92, 4-H), 4.18 (1 H, m, 5-H) and 6.12 (1 H, br s, NH); δ_C(75.43 MHz) −4.86, −4.51 [2 × $(Me_3C)Me_2Si$], 17.79 [$(Me_3C)Me_2Si$], 22.78 (C-6), 24.60 (C-4′), 25.65 [$(Me_3C)Me_2Si$], 27.46 (C-5′), 31.07 (C-3′), 41.89 (C-6′), 50.77 (C-2′), 55.57 (C-4), 63.15 (C-3), 65.51 (C-5), 167.88 (C-2) and 212.05 (C-1′) [Found (HRMS): *m*/*z* 326.213 44. Calc. for (MH^+): 326.215 148]; *m*/*z* 326 (MH^+, 10%), 310 (14), 268 (84) and 126 (100).

Method 2. To a solution of 4-acetoxyazetidinone **6a** (45.2 g, 157.0 mmol) in CH_2Cl_2 (400 ml) were added at 0 °C triethylamine (33 ml, 237 mmol) and trimethylsilyl chloride (25 ml, 197 mmol). The resulting reaction mixture was stirred at room temperature for 1 h after which it was washed with pre-cooled water and brine, dried (Na_2SO_4) and evaporated to give **6b** (55 g, 97%) which was used without further purification; δ_H 0.02 [6 H, s, $(Me_3C)Me_2Si$], 0.22 (9 H, s, Me_3Si), 0.8 [9 H, s, $(Me_3C)Me_2Si$], 1.18 (3 H, d, *J* 5.7, 5-Me), 2.04 (3 H, s, OCOMe), 3.08 (1 H, m, 3-H), 4.15 (1 H, m, 5-H) and 6.08 (1 H, d, *J* 1.0, 4-H).

To a vigorously stirred solution of tin(IV) chloride (20.5 ml, 175 mmol) in dry acetonitrile (250 ml), cooled at −40 °C was added dropwise a solution of **6b** (55 g, 152 mmol) in dry acetonitrile (150 ml). During the addition the temperature was maintained <−25 °C; a solution of 1-(trimethylsilyloxy)cyclohexene (41 ml, 210 mmol) was then rapidly added to the reaction mixture which was then stirred for 1 h. After this it was diluted with diethyl ether, washed with pre-cooled 10% aqueous NaOH, dried (Na_2SO_4) and evaporated. The residue was dissolved in methanol (300 ml) and stirred for 30 min in the presence of silica gel (30 g) and triethylamine (1 ml). The silica gel was filtered off and the filtrate evaporated to give **8a** and **8b** (48 g, 95%) (ratio **8a**:**8b** = 80:20). The mixture was recrystallized from light petroleum to give pure **8a** (28 g, 55%).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-{[(2′*R*)-1′-(4-methylphenylsulfono)hydrazono]cyclohexan-2′-yl}azetidin-2-one 9a

To a solution of **8a** (1 g, 3.0 mmol) in glacial acetic acid (30 ml) was added toluene-*p*-sulfonylhydrazine (0.63 g, 3.38 mmol). The resulting reaction mixture was stirred for 3 h, diluted with CH_2Cl_2 (80 ml), neutralized with 5% aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 7:3 mixture of diethyl ether and light petroleum to afford **9a** (1 g, 66%) as a white solid; mp 95–96 °C; [*a*] +78.90 (*c* 0.73) (Found: C, 58.17; H, 8.10; N, 8.24. $C_{24}H_{39}N_3O_4SSi$ requires C, 58.37; H, 7.98; N, 8.51%); ν_{max}/cm^{-1} 3306s and 1755s; δ_H 0.04 [3 H, s, $(Me_3C)Me_2Si$], 0.06 [3 H, s, $(Me_3C)Me_2Si$], 0.87 [9 H, s, $(Me_3C)Me_2Si$], 1.04 (3 H, d, *J* 6.5, 5-Me), 1.46 (1 H, m, 3′-H_{ax}), 1.47 (2 H, m, 4′-H_{ax} and 5′-H_{ax}), 1.81 (1 H, m, 3′-H_{eq}), 1.82 (1 H, m, 6′-H_{ax}), 1.90 (1 H, m, 5′-H_{eq}), 1.92 (1 H, m, 4′-H_{eq}), 2.35 (1 H, m, 2′-H), 2.45 (3 H, s, 5″-Me), 2.55 (1 H, m, 6′-H_{eq}), 2.82 (1 H, dd, *J* 2.5 and 5.2, 3-H), 4.00 (1 H, dd, *J* 2.5 and 6.5, 4-H), 4.10 (1 H, m, 5-H), 5.60 (1 H, br s, NH), 7.34 (2 H, m, 4″-H), 7.46 (1 H, br s, 1″-NH) and 7.81 (2 H, m, 3″-H); δ_C(100.57 MHz) −5.10, −4.39 [2 × $(Me_3C)Me_2Si$], 17.84 [$(Me_3C)Me_2Si$], 21.52 (C-6″), 22.33 (C-6), 23.81 (C-4′), 25.68 [$(Me_3C)Me_2Si$], 25.85 (C-5′), 26.31 (C-3′), 26.80 (C-6′), 46.14 (C-2′), 49.85 (C-4), 59.62 (C-3), 65.63 (C-5), 128.06 (C-3″), 129.65 (C-4″), 135.15 (C-2″), 144.35 (C-5″), 161.32 (C-1′) and 168.54 (C-2); *m*/*z* 494 (MH^+, 29%), 436 (25) and 319 (100).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-{[(2′*S*)-1′-(4-methylphenylsulfono)hydrazono]cyclohexan-2′-yl}azetidin-2-one 9b

Following the same procedure as described for the synthesis of **9a**, **9b** (0.16 g, 72%) was obtained from **8b** (0.15 g, 0.45 mmol); mp 187–189 °C; [*a*] +67.6 (*c* 0.61) (Found: C, 58.51; H, 8.05; N, 8.52. $C_{24}H_{39}N_3O_4SSi$ requires C, 58.37; H, 7.98; N, 8.51%); ν_{max}/cm^{-1} 3304s and 1753s; δ_H 0.085 [s, 3 H, $(Me_3C)Me_2Si$], 0.095 [s, 3 H, $(Me_3C)Me_2Si$], 0.93 [s, 9 H, $(Me_3C)Me_2Si$], 1.19 (1 H, m, 3′-H_{ax}), 1.20 (3 H, d, *J* 6, 5-Me), 1.38 (1 H, m, 5′-H_{ax}), 1.49 (1

H, m, 4′-H_{ax}), 1.75 (1 H, m, 6′-H_{ax}), 1.84 (1 H, m, 4′-H_{eq}), 1.90 (1 H, m, 5′-H_{eq}), 1.96 (1 H, m, 3′-H_{eq}), 2.09 (1 H, m, 2′-H), 2.46 (3 H, s, 5″-Me), 2.63 (1 H, m, 3-H), 2.64 (1 H, m, 6′-H_{eq}), 3.60 (1 H, dd, *J* 2.0 and 9.5, 4-H), 4.17 (1 H, m, 5-H), 5.68 (1 H, br s, NH), 7.22 (1 H, br s, 1″-NH), 7.35 (2 H, m, 4″-H) and 7.82 (2 H, m, 3″-H); δ_C(100.57 MHz) −4.81, −4.47 [2 × (Me_3C)Me_2Si], 18.06 [(Me_3C)Me_2Si], 21.71 (C-6″), 22.69 (C-6), 24.47 (C-4′), 25.54 (C-5′), 25.85 [(Me_3C)Me_2Si], 26.57 (C-6′), 30.33 (C-3′), 49.65 (C-2′), 51.32 (C-4), 62.90 (C-3), 65.33 (C-5), 128.13 (C-3″), 129.81 (C-4″), 135.07 (C-2″), 144.74 (C-5″), 161.26 (C-1′) and 167.84 (C-2); *m*/*z* 494 (MH^+, 100%), 436 (27) and 319 (18).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(3′*S*)-cyclohex-1′-en-3′-yl]azetidin-2-one 7a[15]

To a stirred solution of LDA [prepared from dry diisopropylamine (1.35 ml) and a 1.6 M solution of butyllithium in hexanes (5.7 ml)] was slowly added at −40 °C a solution of **9a** (1.12 g, 2.27 mmol) in dry THF (20 ml). The reaction mixture was slowly warmed to −20 °C and maintained at 0 °C for 1 h. After this it was added to pre-cooled 5% aqueous HCl (20 ml) and extracted with ethyl acetate (2 × 40 ml). The combined organic phases were washed successively with 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 1:1 mixture of diethyl ether and light petroleum to afford **7a** (0.45 g, 64%) as a white solid.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(3′*R*)-cyclohex-1′-en-3′-yl]azetidin-2-one 7b

Following the same procedure as described for the synthesis of **7a**, **7b** (0.17 g, 70%) was obtained from **9b** (0.50 g, 1 mmol); mp 98–100 °C; [*α*] +62.8 (*c* 0.67) (Found: C, 66.07; H, 10.20; N, 4.52. $C_{17}H_{31}NO_2Si$ requires C, 65.95; H, 10.11; N, 4.53%); ν_{max}/cm^{-1} 3418s and 1755vs; δ_H 0.10 [3 H, s, (Me_3C)Me_2Si], 0.11 [3 H, s, (Me_3C)Me_2Si], 0.90 [9 H, s, (Me_3C)Me_2Si], 1.26 (3 H, d, *J* 6.4, 5-Me), 1.34 (1 H, m, 4′-H_{ax}), 1.54 (1 H, m, 5′-H_{ax}), 1.77 (1 H, m, 5′-H_{eq}), 1.83 (1 H, m, 4′-H_{eq}), 2.00 (2 H, m, 2 × 6′-H), 2.23 (1 H, m, 3′-H), 2.83 (1 H, m, 3-H), 3.46 (1 H, dd, *J* 2.1 and 8.6, 4-H), 4.20 (1 H, m, 5-H), 5.58 (1 H, dd, *J* 9.9 and 2.0, 2′-H), 5.85 (1 H, m, 1′-H) and 5.91 (1 H, br s, NH); δ_C(75.43 MHz) −4.34, −3.34 [2 × (Me_3C)Me_2Si], 18.07 [(Me_3C)Me_2Si], 20.97 (C-5′), 22.87 (C-6), 24.99 (C-6′), 25.37 [(Me_3C)Me_2Si], 25.87 (C-4′), 39.61 (C-3′), 55.12 (C-4), 62.93 (C-3), 65.33 (C-5), 126.54 (C-1′), 129.76 (C-2′) and 169.02 (C-2); *m*/*z* 310 (MH^+, 20%), 294 (8) and 110 (100).

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

To a solution of **7a** (0.24 g, 0.77 mmol) in CH_2Cl_2 (10 ml) was added dropwise at 0 °C a solution of 3-chloroperoxybenzoic acid (assay 55%; 0.3 g, 0.96 mmol) in CH_2Cl_2 (10 ml). The solution was warmed to room temperature, stirred for 3 h and then washed with 10% aqueous Na_2SO_3, 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 1:1 mixture of diethyl ether and light petroleum to afford **4b** (0.05 g) followed by an 8:2 mixture of the same solvents to afford **4a** (0.13 g) (ratio **4a**:**4b** = 80:20, total yield 76%).

Compound **4a**: white solid; mp 134–136 °C; [*α*] −35.1 (*c* 0.61) (Found: C, 62.99; H, 9.61; N, 4.19. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3413s and 1757vs; δ_H 0.07 [6 H, s, (Me_3C)Me_2Si], 0.87 [9 H, s, (Me_3C)Me_2Si], 1.22 (2 H, m, 5′-H_{ax} and 4′-H_{ax}), 1.26 (3 H, d, *J* 6.0, 5-Me), 1.40 (1 H, m, 5′-H_{eq}), 1.55 (1 H, m, 4′-H_{eq}), 1.86 (1 H, m, 6′-H_{ax}), 1.96 (1 H, m, 6′-H_{eq}), 2.00 (1 H, m, 3′-H), 3.01 (1 H, m, 3-H), 3.12 (1 H, m, 2′-H), 3.16 (1 H, t, *J* 4.1, 1′-H), 3.77 (1 H, dd, *J* 2.4 and 6.8, 4-H), 4.22 (1 H, m, 5-H) and 5.97 (1 H, br s, NH); δ_C(100.57 MHz) −5.0, −4.3 [2 × (Me_3C)Me_2Si], 17.90 [(Me_3C)Me_2Si], 19.9 (C-5′), 21.1 (C-4′), 22.6 (C-6), 23.3 (C-6′), 25.7 [(Me_3C)-Me_2Si], 38.9 (C-3′), 51.8 (C-1′), 53.2 (C-2′), 53.3 (C-4), 62.4 (C-3), 65.3 (C-5) and 168.5 (C-2); *m*/*z* 326 (MH^+, 33), 310 (10), 268 (72) and 126 (100).

Compound **4b**: white solid; mp 96–98 °C; [*α*] −20 (*c* 0.59) (Found: C, 62.63; H, 9.64; N, 4.31. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3414s and 1757vs; δ_H 0.08 [3 H, s, (Me_3C)Me_2Si], 0.09 [3 H, s, (Me_3C)Me_2Si], 0.88 [9 H, s, (Me_3C)Me_2Si], 0.90 (1 H, m, 4′-H_{ax}), 1.27 (3 H, d, *J* 6.5, 5-Me), 1.43 (2 H, m, 2 × 5′-H), 1.62 (1 H, m, 4′-H_{eq}), 1.69 (1 H, m, 6′-H_{ax}), 1.99 (1 H, m, 3′-H), 2.10 (1 H, m, 6′-H_{eq}), 2.93 (1 H, dd, *J* 2.2 and 6.4, 3-H), 3.08 (1 H, m, 2′-H), 3.16 (1 H, m, 1′-H), 3.55 (1 H, dd, *J* 2.2 and 8.4, 4-H), 4.13 (1 H, m, 5-H) and 6.00 (1 H, br s, NH); δ_C(100.57 MHz) −5.10, −4.64 [2 × (Me_3C)-Me_2Si], 16.73 (C-5′), 17.72 [(Me_3C)Me_2Si], 22.84 (C-6), 24.50 (C-6′), 24.61 (C-4′), 25.62 [(Me_3C)Me_2Si], 38.49 (C-3′), 52.16 (C-2′), 52.58 (C-1′), 54.15 (C-4), 62.90 (C-3), 66.0 (C-5) and 168.12 (C-2); *m*/*z* 326 (MH^+, 28%), 268 (61) and 126 (100).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1′*R*,2′*S*,3′*S*)-1′,2′-epoxycyclohexan-3′-yl]azetidin-2-one 4c and (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1′*S*,2′*R*,3′*S*)-1′,2′-epoxycyclohexan-3′-yl]azetidin-2-one 4d

Following the same procedure as described for the synthesis of **4a** and **4b**, from **7b** (1.44 g, 4.62 mmol) was obtained **4c** (0.28 g) eluting with a 1:1 mixture of diethyl ether and light petroleum and **4b** (1.13 g) by continuing the elution with an 8:2 mixture of the same solvents (ratio **4c**:**4d** = 20:80, total yield 90%).

Compound **4c**: mp 129–131 °C; [*α*] +3.90 (*c* 0.64) (Found: C, 62.40; H, 9.70; N, 4.20. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3414s and 1757vs; δ_H 0.07 [3 H, s, (Me_3C)Me_2Si], 0.08 [3 H, s, (Me_3C)Me_2Si], 0.87 [9 H, s, (Me_3C)Me_2Si], 0.91 (1 H, m, 4′-H_{ax}), 1.20 (1 H, m, 4′-H_{eq}), 1.22 (3 H, d, *J* 6.0, 5-Me), 1.38 (1 H, m, 2 × 5′-H), 1.68 (1 H, m, 6′-H_{ax}), 1.99 (1 H, m, 3′-H), 2.10 (1 H, m, 6′-H_{eq}), 2.88 (1 H, dd, *J* 2.0 and 5.5, 3-H), 2.91 (1 H, m, 2′-H), 3.20 (1 H, m, 1′-H), 3.62 (1 H, dd, *J* 2.0 and 8.3, 4-H), 4.21 (1 H, m, 5-H) and 6.18 (1 H, br s, NH); δ_C(100.57 MHz) −4.85, −4.29 [2 × (Me_3C)-Me_2Si], 17.10 (C-5′), 17.94 [(Me_3C)Me_2Si], 22.86 (C-6), 24.51 (C-4′), 24.83 (C-6′), 25.75 [(Me_3C)Me_2Si], 38.95 (C-3′), 52.58 (C-1′), 52.84 (C-2′), 53.15 (C-4), 62.94 (C-3), 65.30 (C-5) and 168.55 (C-2); *m*/*z* 326 (MH^+, 33%), 310 (10), 268 (76) and 126 (100).

Compound **4d**: mp 76–78 °C; [*α*] +18.7 (*c* 0.71) (Found: C, 63.11; H, 9.63; N, 4.35. $C_{17}H_{31}NO_3Si$ requires C, 62.71; H, 9.62; N, 4.30%); ν_{max}/cm^{-1} 3414s and 1757vs; δ_H 0.04 [6 H, s, (Me_3C)-Me_2Si], 0.86 [9 H, s, (Me_3C)Me_2Si], 1.22 (3 H, d, *J* 6.5, 5-Me), 1.25 (1 H, m, 4′-H_{ax}), 1.26 (1 H, m, 5′-H_{ax}), 1.34 (1 H, m, 5′-H_{eq}), 1.51 (1 H, m, 4′-H_{eq}), 1.85 (2 H, m, 2 × 6′-H), 1.88 (1 H, m, 3′-H), 2.80 (1 H, m, 3-H), 3.12 (1 H, m, 2′-H), 3.21 (1 H, m, 1′-H), 3.63 (1 H, dd, *J* 2.2 and 9.2, 4-H), 4.16 (1 H, m, 5-H) and 6.51 (1 H, br s, NH); δ_C(100.57 MHz) −4.83, −4.33 [2 × (Me_3C)Me_2Si], 17.91 [(Me_3C)Me_2Si], 19.17 (C-5′), 21.73 (C-4′), 22.78 (C-6), 23.38 (C-6′), 25.75 [(Me_3C)Me_2Si], 39.77 (C-3′), 52.59 (C-1′), 52.71 (C-2′), 52.75 (C-4), 63.72 (C-3), 65.49 (C-5) and 168.91 (C-2); *m*/*z* 326 (MH^+, 15%), 310 (7), 268 (61) and 126 (100).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1′*S*,2′*S*,3′*R*)-(1′-methoxy-2′-hydroxycyclohexan-3′-yl]-azetidin-2-one 5b

To a solution of **4a** (0.1 g, 0.3 mmol) in methanol (10 ml) was added at 0 °C toluene-*p*-sulfonic acid monohydrate (0.01 g, 0.05 mmol). The solution was warmed to room temperature and stirred for 2 h, after which it was diluted with diethyl ether (60 ml), washed with 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with an 8:2 mixture of diethyl ether and light petroleum to afford **5b** as a white foam (0.07 g,

65%); [α] −4.6 (*c* 0.54) (Found: C, 60.14; H, 10.00; N, 3.90. $C_{18}H_{35}NO_4Si$ requires C, 60.45; H; 9.88; N, 3.92%); ν_{max}/cm^{-1} 3418s and 1753s; δ_H 0.10 [6 H, s, $(Me_3C)Me_2Si$], 0.90 [9 H, s, $(Me_3C)Me_2Si$], 1.29 (3 H, d, *J* 6.0, 5-Me), 1.45 (1 H, m, 4′-H_{ax}), 1.52 (2 H, m, 2 × 5′-H), 1.66 (2 H, m, 4′-H_{eq} and 6′-H_{ax}), 1.74 (1 H, m, 6′-H_{eq}), 1.85 (1 H, m, 3′-H), 2.96 (1 H, dd, *J* 2.5 and 6.0, 3-H), 3.34 (1 H, m, 1′-H), 3.35 (3 H, s, OMe), 3.66 (1 H, dd, *J* 2.25 and 7.04, 4-H), 3.89 (1 H, m, 2′-H), 4.20 (1 H, m, 5-H) and 5.83 (1 H, br s, NH); δ_C(100.57 MHz) −4.53, −4.23 [2 × $(Me_3C)Me_2Si$], 18.09 [$(Me_3C)Me_2Si$], 19.04 (C-5′), 21.73 (C-4′), 22.83 (C-6), 23.74 (C-6′), 25.82 [$(Me_3C)Me_2Si$], 40.11 (C-3′), 53.71 (C-4), 56.33 (OMe), 61.91 (C-3), 66.45 (C-5), 70.01 (C-1′), 79.05 (C-2′) and 168.52 (C-2); *m*/*z* 358 (MH^+, 51%), 300 (91) and 158 (100).

(3*S*,4*R*)-1-*tert*-Butyldimethylsilyl-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(3′*S*)-cyclohexan-3′-yl]azetidin-2-one 10a

To a solution of **7a** (0.5 g, 1.62 mmol) in DMF (3 ml) were added triethylamine (0.21 ml, 2.1 mmol) and *tert*-butyldimethylchlorosilane (0.29 g, 1.95 mmol). The resulting reaction mixture was stirred for 4 h and then diluted with diethyl ether, washed with water, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 9:1 mixture of hexane and ethyl acetate to afford **10a** (0.46 g, 65%) as a white solid; ν_{max}/cm^{-1} 1732vs ; δ_H 0.06 [3 H, s, $(Me_3C)Me_2Si$], 0.07 [3 H, s, $(Me_3C)Me_2Si$], 0.20 [3 H, s, $(Me_3C)Me_2Si$], 0.26 [3 H, s, $(Me_3C)Me_2Si$], 0.88 [9 H, s, $(Me_3C)Me_2Si$], 0.96 [9 H, s, $(Me_3C)Me_2Si$], 1.22 (3 H, d, *J* 6.3, 5-Me), 1.22 (1 H, m), 1.5 (1 H, m), 1.8 (2 H, m), 2.00 (2 H, m), 2.5 (1 H, m), 2.79 (1 H, dd, *J* 2.4 and 2.6, 3-H), 3.51 (1 H, dd, *J* 2.7 and 2.4, 4-H), 4.02 (1 H, m, 5-H), 5.7 (1 H, m) and 5.83 (1 H, m).

(3*S*,4*R*)-1-*tert*-Butyldimethylsilyl-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1′*R*,2′*S*,3′*R*)-1′,2′-epoxycyclohexan-3′-yl]azetidin-2-one 11a and (3*S*,4*R*)-1-*tert*-butyldimethylsilyl-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1′*S*,2′*R*,3′*R*)-1′,2′-epoxycyclohexan-3′-yl]azetidin-2-one 11b

To a solution of **10a** (0.42 g, 1.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0 °C a solution of 3-chloroperoxybenzoic acid (assay 55%; 0.37 g, 0.97 mmol) in CH_2Cl_2 (5 ml). The solution was warmed to room temperature and stirred for 3 h, after which it was washed with 10% aqueous Na_2SO_3, 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography eluting with a 95:5 mixture of hexane and ethyl acetate to afford **11a** (0.015 g) and **11b** (0.25 g) (ratio **11b**:**11a** = 94:6, total yield 60%).

Compound **11a**: colourless oil; δ_H 0.07 [3 H, s, $(Me_3C)Me_2Si$], 0.08 [3 H, s, $(Me_3C)Me_2Si$], 0.17 [3 H, s, $(Me_3C)Me_2Si$], 0.29 [3 H, s, $(Me_3C)Me_2Si$], 0.86 [9 H, s, $(Me_3C)Me_2Si$], 0.96 [9 H, s, $(Me_3C)Me_2Si$], 0.96 (1 H, m), 1.28 (3 H, d, *J* 6.2, 5-Me), 1.72–1.2 (4 H, m), 2.11 (1 H, m), 2.23 (1 H, m), 2.88 (1 H, dd, *J* 2.1 and 8.4, 3-H), 3.02 (1 H, m), 3.14 (1 H, m), 3.74 (1 H, dd, *J* 2.1 and 4.8, 4-H) and 4.02 (1 H, m, 5-H).

Compound **11b**: colourless oil; δ_H 0.06 [3 H, s, $(Me_3C)Me_2Si$], 0.09 [3 H, s, $(Me_3C)Me_2Si$], 0.27 [3 H, s, $(Me_3C)Me_2Si$], 0.30 [3 H, s, $(Me_3C)Me_2Si$], 0.88 [9 H, s, $(Me_3C)Me_2Si$], 0.95 [9 H, s, $(Me_3C)Me_2Si$], 1.27 (3 H, d, *J* 6.25, 5-Me), 1.45 (3 H, m), 1.69 (2 H, m), 2.22–2.08 (2 H, m), 2.80 (dd, *J* 7.0 and 2.5, 3-H), 3.12 (1 H, m), 3.20 (1 H, m), 3.56 (1 H, t, *J* 2.5 and 3.0, 4-H) and 4.04 (1 H, m, 5-H).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1′*S*,2′*R*,3′*R*)-1′,2′-epoxycyclohexan-3′-yl]azetidin-2-one 4b

To a solution of **11b** (0.145 g, 0.28 mmol) in methanol (2 ml) was added at 0 °C potassium fluoride (0.05 g, 0.86 mmol). The solution was warmed to room temperature and stirred for 15 min, after which it was diluted with diethyl ether, washed with saturated NH_4OH and brine, dried (Na_2SO_4) and evaporated to give **4b** (0.092 g, 100%).

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References

1 (*a*) O. A. Mascaretti, C. E. Boschetti, G. O. Danelon, E. G. Mata and O. A. Roveri, *Curr. Med. Chem.*, 1995, 441; (*b*) R. Southgate and N. F. Osborne, in *Chemotherapeutics and Disease Control*, ed. Mary Howe-Grant, Wiley, New York, 1993, pp. 232–258; (*c*) J. Roberts, ref. 1(*b*), pp. 259–313; K. R. Lindner, D. P. Bonner and W. H. Koster, ref. 1(*b*), pp. 338–360; (*d*) R. J. Ponsford, ref 1(*b*), pp. 360–389.

2 (*a*) R. Wise, *Antimicrob. Newsl.*, 1990, **7**, 73; (*b*) G. Franceschi, E. Perrone, M. Alpegiani, A. Bedeschi, C. Della Bruna and F. Zarini, in *Recent Advances in the Chemistry of β-Lactam Antibiotics*, eds., P. H. Bentley and R. Southgate, RSC, London, 1989, pp. 222–246; (*c*) G. Pentassuglia, G. Tarzia, D. Andreotti, C. Bismara, R. Carlesso, D. Donati, G. Gaviraghi, A. Perboni, A. Pezzoli, T. Rossi, B. Tamburini and A. Ursini, *J. Antibiot.*, 1995, **48**, 399; (*d*) T. N. Salzmann, F. P. DiNinno, M. L. Greenlee, R. N. Guthikonda, M. L. Quesada, S. M. Schmitt, J. J. Herrmann and M. F. Woods, in *Recent Advances in the Chemistry of β-Lactam Antibiotics*, ed. P. H. Bentley and R. Southgate, The Royal Society of Chemistry, London, 1989, pp. 171–189; (*e*) R. D. G. Cooper, in *The Chemistry of β-Lactams*, ed. M. I. Page, Chapman and Hall, 1992, p. 272; (*f*) E. W. Colvin, in *The Chemistry of β-Lactams*, ed. M. I. Page, 1992, pp. 325–347; (*g*) C. E. Newall, *Spec. Publ.-R. Soc. Chem.*, 1989, **70** (Recent Adv. Chem. β-Lactam Antibiot.), 365–380; (*h*) J. H. C. Nayler, *Trends Biochem. Sci.*, 1991, **16**, 234; (*i*) J. E. Baldwin and E. Abraham, *Nat. Prod. Rep.*, 1988, **5**, 129; (*l*) R. Herranz, *Farm. Clin.*, 1986, **3**, 548; (*m*) D. P. Bonner and R. B. Sykes, *Med. Microbiol.*, 1984, 171; (*n*) T. Okonogi, S. Shibahara, Y. Murai, S. Inouye, S. Kondo and B. G. Christensen, *Heterocycles*, 1990, **31**, 797.

3 (*a*) B. Tamburini, A. Perboni, T. Rossi, D. Donati, D. Andreotti, G. Gaviraghi, R. Carlesso and C. Bismara, EP 0416953 A2/1991 (*Chem. Abstr.*, 1992, **116**, 235337t); (*b*) A. Perboni, T. Rossi, G. Gaviraghi, A. Ursini and G. Tarzia, WO 9203437/1992 (*Chem. Abstr.*, 1992, **117**, 7735m); (*c*) A. Perboni, B. Tamburini, T. Rossi, D. Donati, G. Tarzia and G. Gaviraghi, in *Recent Advances in the Chemistry of Anti-Infective Agents*, ed. P. H. Bentley and R. Ponsford, The Royal Society of Chemistry, Cambridge, 1992, pp. 21–35.

4 E. Di Modugno, I. Erbetti, L. Ferrari, G. L. Galassi, S. M. Hammond and L. Xerri, *Antimicrob. Agents Chemother.*, 1994, **38**, 2362.

5 I. Yuji and H. Koichi, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1363.

6 (3*R*,4*R*,1′*R*)-(+)-4-Acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl-azetidin-2-one **6a** is commercially available from the Aldrich Chemical Company Inc., Milwaukee, WI.

7 (*a*) A. Perboni and C. Bismara, unpublished results; (*b*) C. Bismara, R. Di Fabio, D. Donati, T. Rossi and R. J. Thomas, *Tetrahedron Lett.*, 1995, **36**, 4283.

8 (*a*) R. H. Shapiro, *Org. React.*, 1976, **23**, 405; (*b*) P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 1717.

9 W. R. Roush, J. A. Straub and R. J. Brown, *J. Org. Chem.*, 1987, **52**, 5127.

10 P. Kocovský and I. Starý, *J. Org. Chem.*, 1990, **55**, 3236.

11 M. D. Threadgill and P. Webb, *J. Chem. Soc., Chem. Commun.*, 1991, 269.

12 (*a*) G. Pentassuglia, A. Perboni, G. L. Araldi, D. Donati, A. Ursini, G. Tarzia, A. Pezzoli, R. Carlesso, E. De Magistris and G. Gaviraghi, *Proceedings of the 1st Int. Symposium*: *Recent Advances in the Chemistry of Anti-Infective Agents*, Cambridge, 1992, p. 14; (*b*) M. E. Tranquillini, G. L. Araldi, D. Donati, G. Pentassuglia, A. Pezzoli and A. Ursini, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1683.

13 F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, 1981, **46**, 2208.

14 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

15 T. Rossi, S. Biondi, S. Contini, R. J. Thomas and C. Marchioro, *J. Am. Chem. Soc.*, 1995, **117**, 9604.

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