Stereocontrol in organic synthesis using silicon-containing compounds. A formal synthesis of (±)-thienamycin

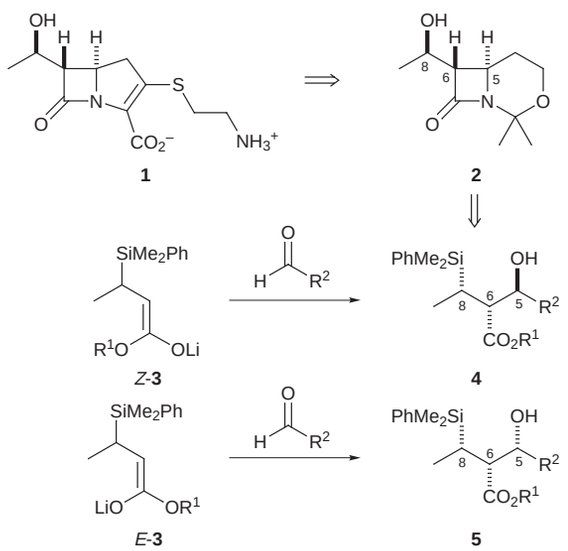
Ian Fleming * and Jeremy D. Kilburn

Department of Chemistry, Lensfield Road, Cambridge, UK CB2 1ZW

The lithium enolate *Z*-11 derived from methyl 3-dimethyl(phenyl)silylbutanoate reacts with the *N*-silylimines of cinnamaldehyde 12, of 3-trimethylsilylpropynal 18, and of 3-trimethylsilylpropenal 19 to give β-lactams with a high level of stereoselection in favour of the *cis* isomers 13, 20 and 21, respectively. The dimethyl(phenyl)silyl group in the *N*-benzyldihydro derivative of the β-lactam 13 was converted into a hydroxy group by protodesilylation followed by peracid oxidation. The aldol product 24 of acetaldehyde with the same enolate *Z*-11 was converted into the corresponding *O*-benzyl hydroxamate 25, which gave the *trans*-β-lactam 26 by a Mitsunobu reaction. A similar aldol reaction using 3-dimethyl(phenyl)silylpropanal and the lithium *Z*-enolate derived from benzyl 3-dimethyl(phenyl)silylbutanoate gave the aldol 32, which was converted successively by way of the *O*-benzyl hydroxamate 33 and the *trans*-β-lactam 34 into the disilylated *trans*-β-lactam 35. Silyl-to-hydroxy conversion of both silyl groups and *N*,*O*-acetonide formation gave the known intermediate 36. Another Mitsunobu reaction with formic acid gave the C-8 epimer 2, which has previously been converted into (±)-thienamycin 1.

Introduction

Thienamycin[1] **1** has often been used as a test of synthetic methodology, exciting several syntheses,[2] either of the antibiotic itself or, more commonly, of a precursor like the β-lactam **2** that has already been converted famously into



Scheme 1

the antibiotic.[3] We chose thienamycin because the functionality and the relative stereochemistry of the three adjacent stereogenic centres, C-8, C-6 and C-5 in the precursor **2** (thienamycin numbering), appeared to be easily derived from the array of functional groups set up by an aldol reaction of an enolate having a β-silyl group, a reaction we had already studied in some detail.[4] In summary, we found that both stereochemical relationships in the products **4** or **5** of an aldol reaction between an enolate *Z*-**3** or *E*-**3**† and an aldehyde are well controlled—the relative stereochemistry between C-8 and C-6 is always the same because attack takes place *anti* to the silyl group in the low energy conformation of the enolate—and that between C-6 and C-5 depends upon the constraints of the cyclic transition structure, and hence upon the geometry of the enolate double bond. An essential feature of this plan was the eventual conversion, with retention of configuration, of the silyl group into a hydroxy, allowing us to keep the groups on C-5 and C-8 well differentiated, but exposing us to the test of whether a β-lactam would survive the conditions necessary for the silyl-to-hydroxy conversion.[5]

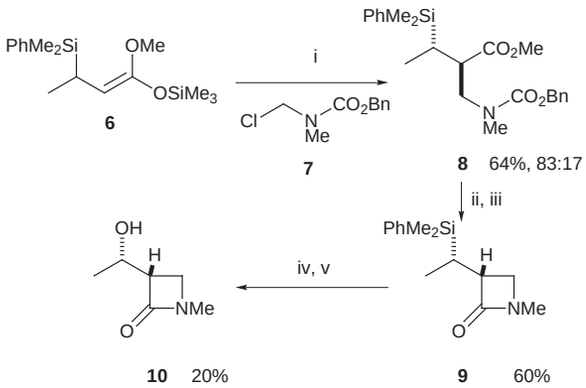
What remained was to choose R^1 and R^2, and to decide upon the best sequence for introducing the nitrogen atom. One possibility was to use an imine in place of the aldehyde, and another was to use a nitrogen nucleophile to displace the oxygen function on C-5, in which case there was then the choice of whether the β-lactam should be made after the nitrogen atom was attached to C-5, or whether the nitrogen should already be joined to the carbonyl group. We eventually chose the last of these sequences but we did look at the first as well. We record our work in full here, including the exploratory work on model compounds, having reported only the synthesis itself in a preliminary communication.[6]

Results and discussion

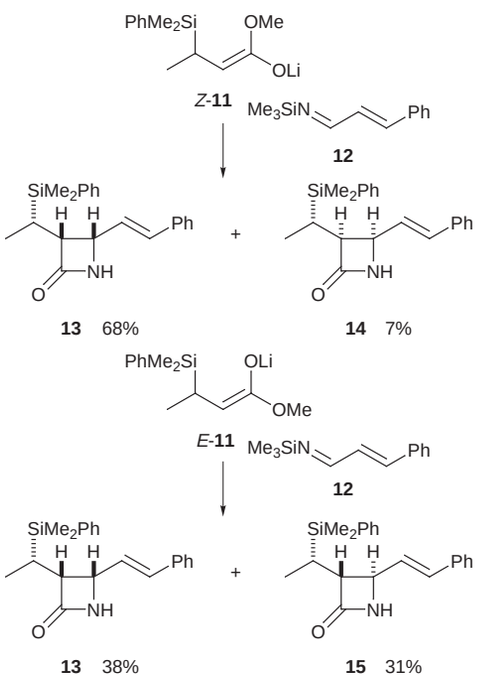
It would clearly be most simple to use the approach based on the reaction of an imine with the enolate, since the nitrogen atom would then already be attached to C-5. We carried out a simple version of this idea using the silyl enol ether **6** and the chloromethyl carbamate **7**, which gave an 83:17 mixture of the two diastereoisomeric products of a Mannich-like reaction,[7] presumably in favour of the isomer **8** (Scheme 2). Removal of the protecting group and cyclisation, gave the pair of β-lactams rich in the isomer **9**. This was our first opportunity to test whether a β-lactam was compatible with the conditions for the silyl-to-hydroxy conversion. We found, in one run with a low yield using our earlier method, now much improved,[8] that we obtained the mixture of alcohols rich in the isomer **10**.

Even more efficient is the direct reaction of a lithium enolate with an imine giving a β-lactam directly.[9] We therefore prepared the *Z*-enolate[4] *Z*-**11** and captured it with the imine **12**, giving, as the only identifiable products, the pair of β-lactams **13** and **14** in favour of the former (Scheme 3). These products were separable, and their ^{1}H NMR spectra showed that both were

† To match our full paper on aldol reactions,[4] we use the strict CIP description of geometry.

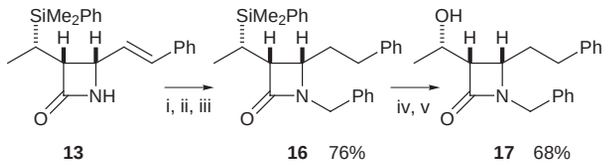


Scheme 2 *Reagents*: i, $TiCl_4$; ii, H_2, Pd/C; iii, LDA; iv, BF_3·2AcOH; v, MCPBA

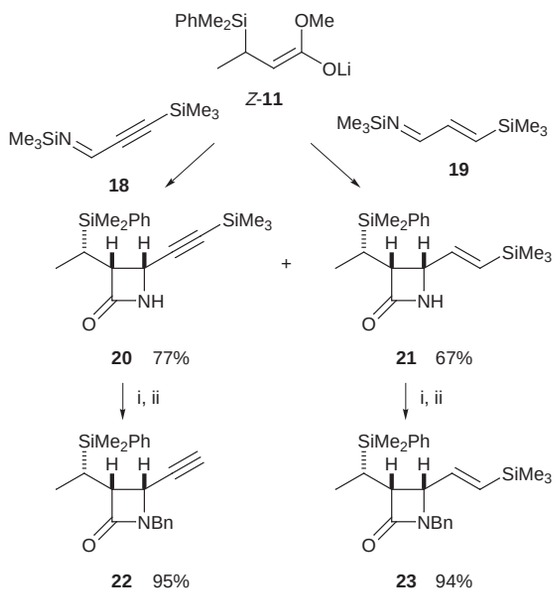


Scheme 3

cis-disubstituted in the β-lactam ring, as expected by analogy with the aldol reactions *Z*-**3** ⟶ **4**. Conjugate addition of the silylcuprate reagent to methyl crotonate is known to give largely the *E*-enolate *E*-**11**,[4] and trapping this ought, by analogy with the aldol reactions *E*-**3** ⟶ **5**, to have given largely the *trans*-disubstituted β-lactam **15**. In practice, it gave a nearly equal mixture of β-lactams, one of which was the same as the major product **13** from the earlier reaction, and the other **15** was *trans*-disubstituted. *E*-Enolates in general have proved to be less stereoselective in their aldol reactions than the *Z*-enolates, but this was one of our most disappointing results. This problem has been overcome more recently by Palomo and Aizpurua, using the same *E*-enolate *E*-**11** but using the imine derived from methyl glyoxalate and *p*-anisylamine to trap it.[10] We assign the relative configuration between C-8 and C-6 on the well supported presumption that the major products arise from the imines attacking the enolate *anti* to the silyl group. Using the major adduct **13**, we carried out the sequence of reactions that made the β-lactam **17**, with the silyl-to-hydroxy conversion **16** ⟶ **17** taking place in reasonably good yield (68%) once the double bond had been removed (Scheme 4). We were now confident that a β-lactam would present no difficulties in the silyl-to-hydroxy conversion, and were further reassured by some closely similar work of Hart's using a benzaldehyde-derived imine in place of our cinnamaldehyde-derived imine.[11]



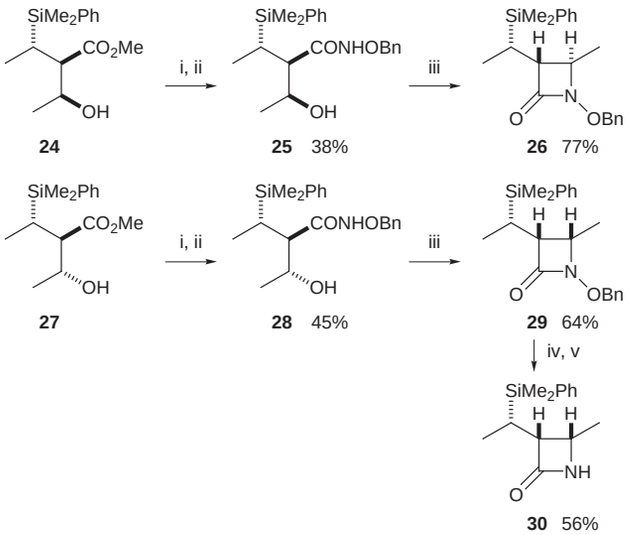
Scheme 4 *Reagents*: i, NaH; ii, BnBr; iii, H_2, Pd/C; iv, BF_3·2AcOH; v, $MeCO_3H$, Et_3N



Scheme 5 *Reagents*: i, NaH; ii, BnBr

Since the thienamycin precursor **2** needed a two-carbon chain attached to C-5, we also carried out similar reactions with the two imines **18** and **19** (Scheme 5), and protected the major products **20** and **21** by benzylation to give the β-lactams **22** and **23**, in which the former had somewhat surprisingly lost the silyl group (Scheme 5). We were unable to convert the acetylene **22** into an acetic acid side-chain by hydroboration–oxidation,[12] and, although the vinylsilane **23** gave a mixture of the diastereoisomeric epoxides with peracid, we were unable to hydrolyse it to recognisable products, let alone to the aldehyde we expected.[13] We were no more successful with a diol derived from the vinylsilane **23** by treatment with osmium tetroxide—it did not give recognisable products of β-elimination either in acid[14] or base,[15] nor did its diacetate give an enol acetate with fluoride ion.[16]

However, the β-lactams in all these reactions, except for the minor product **15**, were *cis*-disubstituted in the ring, like some of the olivanic acids[17] that we might have chosen as our targets, whereas thienamycin, which we did choose, is *trans*-disubstituted. β-Lactams with *cis*-disposed substituents are even more easily set up by the reaction of an imine with a ketene, prepared *in situ* from an acid chloride,[18] and this approach has been extended to acid chlorides carrying a β-silyl group.[10] We solved the problem of setting up *trans*-disposed substituents by turning to the alternative strategy, basing our work on that of Miller.[19] This involved making the benzyl hydroxamate **25** from the ester **24** that we had made in our earlier work on diastereoselective aldol reactions.[4] We made the benzyl hydroxamate **25**, by condensing *O*-benzyl hydroxylamine and the acid derived from the ester **24** using the water-soluble carbodiimide. Mitsunobu reaction on the benzyl hydroxamate gave the β-lactam **26**, in which the inversion of configuration at C-6 has set up the two substituents with a *trans* relationship (Scheme 6). A similar sequence starting with the diastereoisomeric ester **27** gave the isomeric β-lactam **29**, proving that the reaction was stereospecific. We used this product to confirm that debenzylation and cleavage of the N–O bond could easily

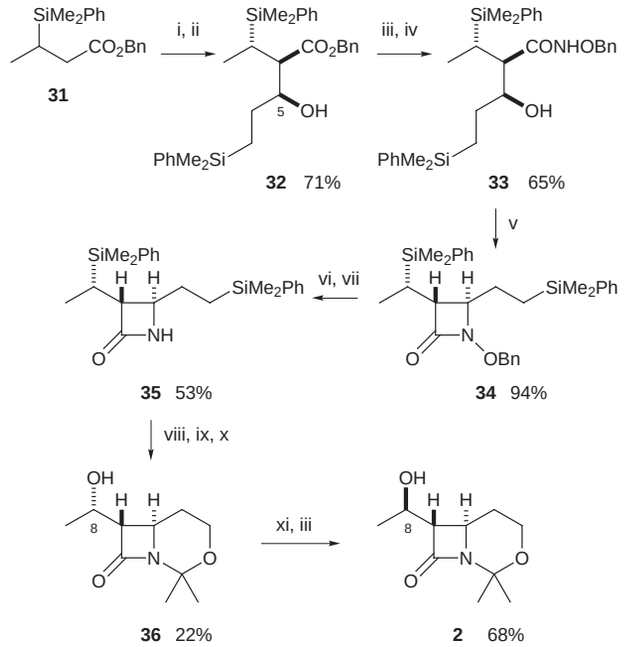


Scheme 6 *Reagents*: i, NaOH; ii, NH_2OBn, $Me_2N(CH_2)_3N{=}C{=}NEt$ (WSC); iii, $EtO_2CN{=}NCO_2Et$, Ph_3P; iv, H_2, Pd/C; v, $TiCl_3$

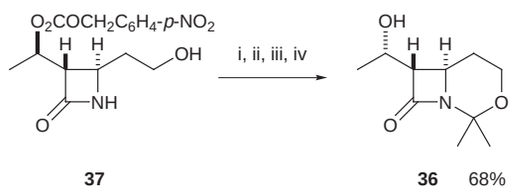
be accomplished **29** ⟶ **30** without disturbing the silyl group. This completed our model work, and we turned to the synthesis itself.

In view of our disappointment trying to develop the two-carbon side chains in Scheme 5, we needed a 3-carbon aldehyde that would already carry at the β-position an oxygen function. While this might have been possible with a protected 3-hydroxypropionaldehyde without serious risk of β-elimination, we chose to avoid the risk altogether, and use a silyl group for a second time as a hydroxy surrogate. The aldehyde we chose was β-phenyldimethylsilylpropionaldehyde, which we prepared by rhodium-catalysed hydrosilylation[20] of allyl trimethylsilyl ether, followed by oxidation of the alcohol to the aldehyde using pyridinium dichromate.[21] Conjugate addition of the silylcuprate reagent to benzyl crotonate gave the ester **31**, and aldol reaction of the *Z*-enolate derived from this compound with the β-silylated propionaldehyde gave the ester **32** as the major diastereoisomer, as expected from our earlier work.[4] Hydrogenolysis and reaction of the carboxylic acid with *O*-benzylhydroxylamine gave the hydroxamate **33** (Scheme 7). Miller's Mitsunobu reaction then gave the β-lactam **34**, and removal of the benzyloxy group gave the β-lactam **35**. At this stage we had only enough material to carry through one run in low yield, but we were able to convert both silyl groups to hydroxys in the one operation to give a highly polar diol, which we protected immediately as the acetonide **36**. This was a known compound, which had already been used in the synthesis of 8-epithienamycin.[3] It proved to be identical to an authentic sample prepared from the known β-lactam **37**[3] (Scheme 8), and it could be converted into the thienamycin precursor **2** by a Mitsunobu reaction, using formic acid as the nucleophile (Scheme 7). Formic acid was particularly helpful in this case, because the formate ester of the alcohol **2** was easier to hydrolyse than most esters, and it has been used before with β-lactams in order to avoid the easy β-elimination.[22]

As usual, our methods for stereocontrol could have been tailored to the synthesis of any of the diastereoisomers. Some of the olivanic acids could, in principle, have been made from one of the methods creating a β-lactam with *cis*-substituents, and they could also have been made by the route shown in Scheme 7, since the diastereoisomer of the ester **32** was produced by conjugate addition of the silylcuprate to benzyl crotonate, and trapping the *E*-enolate with the same aldehyde, although with a lower degree (70:30) of stereoselectivity at C-5. The inversion of configuration at C-8, although perhaps somewhat inelegant here, means that the C-8 epimers can be synthesised, both in the thienamycin series, and in the olivanic



Scheme 7 *Reagents*: i, LDA; ii, $PhMe_2Si(CH_2)_2CHO$; iii, H_2, Pd/C; iv, NH_2OBn, WSC; iv, $EtO_2CN{=}NCO_2Et$, Ph_3P; vi, H_2, Pd/C; vii, $TiCl_3$; viii, $BF_3{\cdot}2AcOH$; ix, $MeCO_3H$; x, $Me_2C(OMe)_2$, TsOH; xi, $EtO_2CN{=}NCO_2Et$, Ph_3P, HCO_2H



Scheme 8 *Reagents*: i, $Me_2C(OMe)_2$, TsOH; ii, H_2, Pd/C; iii, $EtO_2CN{=}NCO_2Et$, Ph_3P, HCO_2H; iv, NaOH

acid series, where both epimers are found among the natural products.

Experimental

Ether refers to diethyl ether.

Methyl 3-dimethyl(phenyl)silyl-2-(*N*-methylaminomethyl)-butanoate

Using the method of Danishefsky,[7] titanium tetrachloride (9 mmol) in dichloromethane (10 cm^3) was added to the carbamate **7**[23,24] (2.13 g, 10 mmol) in dichloromethane (10 cm^3) at −78 °C under nitrogen. A solution of the crude *E*-silyl enol ether **6** (9 mmol) in dichloromethane (10 cm^3) was immediately added and the mixture stirred for 1 h at −78 °C. The reaction was quenched with water (20 cm^3), extracted with ether (3 × 25 cm^3) and the combined organic extracts evaporated under reduced pressure. Flash column chromatography [SiO_2, light petroleum (bp 60–80 °C)–EtOAc, 10:1], gave a diastereoisomeric mixture of methyl 3-dimethyl(phenyl)silyl-2-(*N*-methyl-*N*-benzyloxycarbonylaminomethyl)butanoate **8** and its diastereoisomer (2.36 g, 64%) as an oil; R_f (hexane–EtOAc, 2:1) 0.51. The benzyl carbamates **8** and its diastereoisomer (2.05 g, 5 mmol) and palladium (10% on charcoal, 250 mg) in methanol were stirred under a hydrogen atmosphere for 3 h. The mixture was filtered through Celite and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc), gave a mixture of the (2*RS*,3*SR*) and (2*RS*,3*RS*) esters as an oil; R_f (hexane–EtOAc, 2:1) 0.21; ν_{max}(neat)/cm^{-1} 3400 (NH) and 1725 (C=O); $\delta_H(CDCl_3)$ (2*RS*,3*SR*) major isomer 7.53–7.32 (5 H, m, Ph), 3.57 (3 H, s, OMe), 2.92–2.42 (3 H, m,

C*H*CO_2Me and CH_2NHMe), 2.31 (3 H, s, NMe), 1.44 (1 H, dq, *J* 5 and 8, C*H*SiMe_2Ph), 0.94 (3 H, d, *J* 8, MeC), 0.32 (3 H, s, Si$Me_A$$Me_B$) and 0.31 (3 H, s, Si$Me_A$$Me_B$); δ_H($CDCl_3$) (2*RS*, 3*RS*) minor isomer 3.58 (3 H, s, OMe) and 0.97 (3 H, d, *J* 7, MeC); *m*/*z* 279 (3%, M^+) and 135 (100, $PhMe_2Si$) (Found: M^+, 279.1648. $C_{15}H_{25}NO_2Si$ requires *M*, 279.1655). The ratio of isomers 83 : 17 was determined by integration of the OMe and MeC signals in the ^{1}H NMR.

***N*-Methyl 3-[1-dimethyl(phenyl)silylethyl]azetidin-2-one 9**

The mixture of esters (560 mg, 2.0 mmol) in dry THF (2 cm^3) was added to a stirred solution of LDA, freshly prepared by addition of *n*-butyllithium (1.6 mol dm^{-3} in hexane, 2.25 cm^3, 3.6 mmol) to diisopropylamine (0.5 cm^3, 3.6 mmol) in dry THF (15 cm^3) under nitrogen, at −78 °C. After 1 h, distilled water (0.05 cm^3) was added and carbon dioxide was passed through the solution for 10 min. The solvent was evaporated under reduced pressure and the crude material taken up in ether (20 cm^3). The solution was washed with distilled water, the aqueous layer extracted with ether (2 × 20 cm^3), and the combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Flash column chromatography gave a mixture of the (3*RS*,1′*SR*)-azetidinone **9** and its (3*RS*,1′*RS*) diastereoisomer (300 mg, 61%) as an oil; R_f (hexane–EtOAc, 2 : 1) 0.48; ν_{max}(neat)/cm^{-1} 1750 (C=O); δ_H($CDCl_3$) (3*RS*,1′*SR*) major isomer 7.50–7.33 (5 H, m, Ph), 3.27 (1 H, m, CHCO), 3.01 (1 H, t, *J* 5, C$H_A$$H_B$NMe), 2.79 (1 H, dd, *J* 2 and 5, C$H_A$$H_B$NMe), 2.74 (3 H, s, NMe), 1.49 (1 H, dq, *J* 4 and 7, C*H*SiMe_2Ph), 0.95 (3 H, d, *J* 7, MeC), 0.30 (3 H, s, Si$Me_A$$Me_B$) and 0.28 (3 H, s, Si$Me_A$$Me_B$); δ_H($CDCl_3$) (3*RS*,1′*RS*) minor isomer 7.51–7.32 (5 H, m, Ph), 3.08 (1 H, m, CHCO), 3.02 (1 H, t, *J* 5, C$H_A$$H_B$NMe), 2.71 (3 H, s, NMe), 2.68 (1 H, dd, *J* 2 and 5, C$H_A$$H_B$NMe), 1.26 (1 H, dq, *J* 9 and 6, C*H*SiMe_2Ph), 1.18 (3 H, d, *J* 6, MeC), 0.33 (6 H, s, SiMe_2); *m*/*z* 232 (22%, M − Me) and 135 (100, $PhMe_2Si$) (Found: M − Me, 232.1168. $C_{14}H_{21}NOSi$ − Me requires *M*, 232.1158). The ratio of the (3*RS*,1′*SR*)- and (3*RS*,1′*RS*)-azetidinones was identical to the ratio of starting amines.

***N*-Methyl 3-(1-hydroxyethyl)azetidin-2-one 10**

Boron trifluoride–acetic acid complex (0.42 cm^3, 3 equiv.) was added to a solution of the *N*-methylazetidinone **9** and its diastereoisomer (250 mg, 1 mmol) in dichloromethane (5 cm^3) and the mixture stirred under nitrogen for 3 h. Aqueous sodium hydrogen carbonate (saturated, 30 cm^3) was added and stirring continued for 10 min. The mixture was diluted with ether and the aqueous layer removed. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a diastereoisomeric mixture of the crude *N*-methyl-3-[1-fluoro(dimethyl)silyl]azetidin-2-one (190 mg, 100%). *m*-Chloroperbenzoic acid (535 mg, 3.1 mmol) and triethylamine (110 mg, 1 mmol) were added to a stirred solution of the fluorosilane (190 mg, 1 mmol) in ether (10 cm^3). Hydrochloric acid (1 mol dm^{-3}, 10 cm^3) was added and the aqueous layer washed with ether. The combined organic extracts yielded the starting fluorosilane (90 mg, 47%). The aqueous layer was basified with sodium hydroxide and extracted with ethyl acetate (3 × 25 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Preparative thin layer chromatography (SiO_2, EtOAc), gave a mixture of the (3RS,1′RS) and (3RS,1′SR)-*hydroxyethylazetidinones*, (25 mg, 20%) as an oil; R_f (hexane–EtOAc, 1 : 1) 0.23; ν_{max}($CDCl_3$)/cm^{-1} 3400 (OH) and 1735 (C=O); δ_H($CDCl_3$) (2*RS*,3*RS*) major isomer 4.03 (1 H, quintet, *J* 6, C*H*OH), 3.31–3.20 (2 H, m, C$H_A$$H_B$NMe and CHCO), 3.07 (1 H, dd, *J* 2 and 5, C$H_A$$H_B$NMe), 2.83 (3 H, s, NMe), 1.96 (1 H, br s, OH), 1.29 (3 H, d, *J* 6, MeC); δ_H($CDCl_3$) (3*RS*,1′*SR*) minor isomer 4.18 (1 H, quintet, *J* 6, C*H*OH) and 1.27 (3 H, d, *J* 6, MeC); *m*/*z* 129 (10%, M^+), 114 (49, M − Me) and 57 (100, C_2H_3NO) (Found: M^+, 129.0784. $C_6H_{11}NO_2$ requires *M*, 129.0790). The ratio of the (3*RS*,1′*RS*) to the (3*RS*,1′*SR*)-azetidinone was identical to the ratio of the corresponding starting azetidinones.

(*E*)-(3*RS*,4*SR*)-3-[(*SR*)-1-Dimethyl(phenyl)silylethyl]-4-(2-phenylethenyl)azetidin-2-one 13 and (*E*)-(3*SR*,4*RS*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-(2-phenylethenyl)azetidin-2-one 14

Cinnamaldehyde (2.90 g, 22 mmol) in THF (20 cm^3) was added dropwise to a stirred solution of lithium bis(trimethylsilyl)-amide (freshly prepared by the addition of *n*-butyllithium (1.6 mol dm^{-3} in hexane, 13.8 cm^3, 22 mmol) to 1,1,1,3,3,3-hexamethyldisilazane (3.54 g, 22 mmol) in THF (30 cm^3) under nitrogen at −78 °C, and the solution stirred for 45 min. The resulting cold solution of *N*-trimethylsilylimine **12** was used directly. Methyl 3-dimethyl(phenyl)silylbutanoate (4.13 g, 17.5 mmol) in THF (20 cm^3) was added to a stirred solution of LDA, freshly prepared by addition of *n*-butyllithium (1.6 mol dm^{-3} in hexane, 12.5 cm^3, 20 mmol) to diisopropylamine (2.8 cm^3, 20 mmol) in THF (50 cm^3), under nitrogen at −78 °C, over a period of 10 min, and the solution stirred for 30 min. The *N*-trimethylsilylimine **12** was transferred, by double-ended needle, to the lithium enolate and the mixture stirred at −78 °C for 45 min. The cold bath was removed and stirring continued for a further 1.5 h while the mixture was allowed to warm to room temperature. The solution was diluted with ether (200 cm^3), and washed sequentially with hydrochloric acid (1 mol dm^{-3}), water and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) gave the *azetidinone* **13** (4.0 g, 68%) as an oil; R_f (hexane–EtOAc, 1 : 1) 0.44; ν_{max}(CCl_4)/cm^{-1} 3400 (NH) and 1760 (C=O); δ_H($CDCl_3$) 7.65–7.20 (10 H, m, Ph), 6.62 (1 H, d, *J* 16, PhC*H*), 6.24 (1 H, dd, *J* 16 and 7, PhCH=C*H*), 5.90 (1 H, br s, NH), 4.31 (1 H, dd, *J* 5 and 7, C*H*NH), 3.24 (1 H, ddd, *J* 1, 5 and 12, CHCO), 1.35 (1 H, dq, *J* 12 and 7, C*H*SiMe_2Ph), 0.83 (3 H, d, *J* 7, MeC), 0.46 (3 H, s, Si$Me_A$$Me_B$) and 0.40 (3 H, s, Si$Me_A$$Me_B$); *m*/*z* 335 (15%, M^+), 320 (7, M − Me) and 135 (100, $PhMe_2Si$) (Found: M^+, 335.1701. $C_{21}H_{25}NOSi$ requires *M*, 335.1705), and the *azetidinone* **14** (390 mg, 7%) as an oil; R_f (hexane–EtOAc, 1 : 1) 0.37; ν_{max}(CCl_4)/cm^{-1} 3400 (NH) and 1755 (C=O); δ_H($CDCl_3$) 7.61–7.25 (10 H, m, Ph), 6.45 (1 H, d, *J* 16, PhC*H*), 5.99 (1 H, dd, *J* 7 and 16, PhCH=C*H*), 5.93 (1 H, br s, NH), 4.18 (1 H, dd, *J* 6 and 7, C*H*NH), 3.50 (1 H, ddd, *J* 1, 6 and 7, CHCO), 1.37–1.17 (1 H, m, C*H*SiMe_2Ph), 1.21 (3 H, d, *J* 7, MeC), 0.34 (3 H, s, Si$Me_A$$Me_B$) and 0.31 (3 H, s, Si$Me_A$$Me_B$); *m*/*z* 335 (12%, M^+), 320 (5, M − Me) and 135 (100, $PhMe_2Si$) (Found: M^+, 335.1710. $C_{21}H_{25}NOSi$ requires *M*, 335.1705).

Reaction of the *N*-trimethylsilylimine 12 with the enolate *E*-11

Methyl crotonate (300 mg, 3 mmol) in dry THF (5 cm^3) was added dropwise to the stirred silyl cuprate reagent (3.3 mmol, based on CuCN) under nitrogen at −78 °C, and the stirring continued for 2.5 h. The *N*-trimethylsilylimine **12** (3.3 mmol) (prepared as described in the previous experiment) was transferred by double-ended needle to the lithium *E*-enolate and the mixture stirred at −78 °C for 45 min. The cold bath was removed and stirring was continued for 1.5 h while the mixture was allowed to warm to room temperature. Aqueous ammonium chloride (25 cm^3) was added and the mixture extracted with ether. The organic extracts were washed with aqueous ammonium chloride and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) gave the previously prepared (3*RS*,4*SR*, 1′*SR*)-azetidinone **13** (380 mg, 38%) and (*E*)-(3RS,4RS)-3-[(SR)-1-*dimethyl*(*phenyl*)*silylethyl*]-4-(2-*phenylethenyl*)*azetidin*-2-*one* **15** (310 mg, 31%) as an oil; R_f (hexane–EtOAc, 2 : 1) 0.43; ν_{max}(CH_2Cl_2)/cm^{-1} 3400 (NH) and 1760 (C=O); δ_H($CDCl_3$) 7.49–7.27 (10 H, m, Ph), 6.46 (1 H, d, *J* 16, C*H*Ph), 6.04 (1 H,

dd, *J* 8 and 16, C*H*=CHPh), 5.87 (1 H, br s, NH), 3.95 (1 H, dd, *J* 2 and 8, C*H*NH), 3.06 (1 H, ddd, *J* 1, 2 and 4, CHCO), 1.55 (1 H, dq, *J* 4 and 7, C*H*SiMe$_2$Ph), 1.11 (3 H, d, *J* 7, MeC), 0.35 (3 H, s, Si*Me*$_A$Me$_B$) and 0.31 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 335 (19%, M$^+$), 320 (4, M − Me) and 135 (100, PhMe$_2$Si) (Found: M$^+$, 335.1691. $C_{21}H_{25}NOSi$ requires *M*, 335.1705).

N-Benzyl-(*E*)-(3*RS*,4*SR*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-(2-phenylethenyl)azetidin-2-one

The azetidinone **13** (1.44 g, 4.3 mmol) was added dropwise to a stirred suspension of sodium hydride (4.5 mmol) in THF (20 cm^3) and DMF (10 cm^3) under nitrogen. After stirring for 15 min, benzyl bromide (770 mg, 4.5 mmol) was added and stirring continued for 1 h. The mixture was poured into ethyl acetate (50 cm^3) and washed with water (4 × 20 cm^3) and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) gave the N-*benzylazetidinone* (1.45 g, 80%) as an oil; R_f (hexane–EtOAc, 5:1) 0.30; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1740 (C=O) and 1500 (Ph); $\delta_H(CDCl_3)$ 7.62–7.19 (15 H, m, Ph), 6.52 (1 H, d, *J* 16, PhC*H*=CH), 6.11 (1 H, dd, *J* 9 and 16, PhCH=C*H*), 4.66 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph), 4.07 (1 H, dd, *J* 5 and 9, C*H*CH=CHPh), 3.98 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph), 3.16 (1 H, dd, *J* 5 and 12, C*H*CO), 1.35 (1 H, dq, *J* 12 and 7, C*H*SiMe$_2$Ph), 0.79 (3 H, d, *J* 7, *Me*CH), 0.48 (3 H, s, Si*Me*$_A$Me$_B$) and 0.41 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 425 (2%, M$^+$), 410 (9, M − Me), 334 (12, M − C_7H_7) and 135 (100, PhMe$_2$Si) (Found: M$^+$, 425.2172. $C_{28}H_{31}NOSi$ requires *M*, 425.2175).

N-Benzyl-(3*RS*,4*SR*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-(2-phenylethyl)azetidin-2-one 16

The 4-(2-phenylethenyl)-2-azetidinone (220 mg, 0.52 mmol) and palladium on charcoal (10%, 20 mg) in methanol (5 cm^3) was stirred under a hydrogen atmosphere until the uptake of hydrogen was completed. The mixture was filtered through Celite, and evaporated under reduced pressure. Flash column chromatography (hexane–EtOAc) gave the 4-(2-*phenylethyl*)-*azetidin*-2-*one* **16** (209 mg, 95%) as an oil; R_f (hexane–EtOAc, 5:1) 0.30; $\nu_{max}(CCl_4)$/cm^{-1} 1740 (C=O) and 1605 (Ph); $\delta_H(CDCl_3)$ 7.62–6.88 (15 H, m, Ph), 4.62 (1 H, d, *J* 15, NC*H*$_A$H$_B$Ph), 4.25 (1 H, d, *J* 15, NCH$_A$C*H*$_B$Ph), 3.55 (1 H, ddd, *J* 4, 5 and 9, CHN), 3.06 (1 H, dd, *J* 5 and 11, CHCO), 2.61 (1 H, ddd, *J* 7, 10 and 13, CH$_2$C*H*$_A$H$_B$Ph), 2.44 (1 H, ddd, *J* 7, 10 and 13, CH$_2$CH$_A$*H*$_B$Ph), 1.89–1.76 (2 H, m, C*H*$_2$CH$_2$Ph), 1.30 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.82 (3 H, d, *J* 7, *Me*CH), 0.47 (3 H, s, Si*Me*$_A$Me$_B$) and 0.42 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 426 (4%, M − H), 412 (7, M − Me), 336 (10, M − C_7H_7) and 135 (100, PhMe$_2$Si) (Found: M − H, 426.2242, $C_{28}H_{33}NOSi$ − H requires *M*, 426.2253).

N-Benzyl-(3*RS*,4*RS*)-3-[(*RS*)-1-hydroxyethyl]-4-(2-phenylethyl)azetidin-2-one 17

Boron trifluoride acetic acid complex (0.1 cm^3) and the dimethyl(phenyl)silylazetidinone **16** (200 mg, 0.47 mmol) were stirred in dichloromethane (5 cm^3) under nitrogen for 1 h at room temperature. Aqueous sodium hydrogen carbonate (saturated, 2 cm^3) was added and stirring continued for 10 min. The mixture was diluted with ethyl acetate and the aqueous layer removed. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude fluoro(dimethyl)silane (165 mg). Peracetic acid (40% in AcOH, 1 cm^3) and triethylamine (46 mg, 0.45 mmol) were added to a stirred solution of the crude fluorosilane in THF (2 cm^3) and methanol (2 cm^3) under nitrogen. After stirring for 4 h the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexane–EtOAc) gave the *hydroxyethylazetidinone* **17** (100 mg, 68%) as needles, mp 131–133 °C (from hexane–EtOAc); $\nu_{max}(CDCl_3)$/cm^{-1} 3600 (OH), 1740 (C=O) and 1605 (Ph); $\delta_H(CDCl_3)$ 7.39–6.93 (10 H, m, Ph), 4.64 (1 H, d, *J* 16, NC*H*$_A$H$_B$Ph), 4.28 (1 H, d, *J* 16, NCH$_A$C*H*$_B$Ph), 4.10 (1 H, dq, *J* 5 and 6, C*H*OH), 3.62 (1 H, dt, *J* 5 and 6, C*H*NCH$_2$Ph), 3.18 (1 H, t, *J* 5, CHCO), 2.53 (2 H, m, CH$_2$C*H*$_2$Ph), 2.06 (1 H, br s, OH), 2.01 (2 H, m, C*H*$_2$CH$_2$Ph) and 1.36 (3 H, d, *J* 6, Me); *m*/*z* 309 (2%, M$^+$) and 91 (100, C_7H_7) (Found: C, 77.5; H, 7.50; N, 4.47; M$^+$, 309.1735. $C_{20}H_{23}NO_2$ requires C, 77.6; N, 7.49; N, 4.53%; *M*, 309.1729).

(3*RS*,4*RS*)-3-[(*SR*)-1-Dimethyl(phenyl)silylethyl]-4-trimethylsilylethynylazetidin-2-one 20

This was prepared in the same way as the β-lactam **13** from 3-trimethylsilylprop-2-ynylidenetrimethylsilylamine **18** [prepared (78%), bp 149–150 °C, from 3-trimethylsilylprop-2-yn-1-al[25,26]] and methyl 3-dimethyl(phenyl)silylbutanoate. Flash column chromatography (SiO_2, hexane–EtOAc) gave 4-*trimethylsilylethynylazetidin*-2-*one* (77%) as prisms, mp 76–78 °C (from hexane); $\nu_{max}(CDCl_3)$/cm^{-1} 3400 (NH), 2200 (C≡C) and 1745 (C=O); $\delta_H(CDCl_3)$ 7.61–7.25 (5 H, m, Ph), 6.04 (1 H, br s, NH), 4.26 (1 H, d, *J* 5, C*H*NH), 3.16 (1 H, ddd, *J* 1, 5 and 11, CHCO), 1.58 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.97 (3 H, d, *J* 7, *Me*CH), 0.46 (3 H, s, Si*Me*$_A$Me$_B$), 0.42 (3 H, s, SiMe$_A$*Me*$_B$) and 0.18 (9 H, s, SiMe$_3$); *m*/*z* 329 (3%, M$^+$), 314 (20, M − Me) and 135 (100, PhMe$_2$Si) (Found: C, 65.7; H, 8.25; N, 4.10; M$^+$, 329.1632. $C_{18}H_{27}NOSi_2$ requires C, 65.6; H, 8.27; N, 4.25%; *M*, 329.1632).

(*E*)-(3*RS*,4*SR*)-3-[(*SR*)-1-Dimethyl(phenyl)silylethyl]-4-(2-trimethylsilylethenyl)azetidin-2-one 21

This was prepared in the same way as the β-lactam **13** from 3-trimethylsilylprop-2-enylidenetrimethylsilylamine **19** (prepared from 3-trimethylsilylprop-2-en-1-al[25,26]) and methyl 3-dimethyl-(phenyl)silylbutanoate. Flash column chromatography (SiO_2, hexane–EtOAc) gave the *azetidinone* **21** (67%) as plates, mp 105.5–107.5 °C (from hexane); ν_{max}(neat)/cm^{-1} 3250 (NH), 1750 (C=O) and 1610 (Ph); $\delta_H(CDCl_3)$ 7.61–7.27 (5 H, m, Ph), 6.11 (1 H, dd, *J* 5 and 19, C*H*=CHSiMe$_3$), 6.00 (1 H, d, *J* 19, CH=C*H*SiMe$_3$), 5.92 (1 H, br s, NH), 4.14 (1 H, t, *J* 5, C*H*NH), 3.17 (1 H, ddd, *J* 1, 5 and 11, C*H*CO), 1.28 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.78 (3 H, d, *J* 7, MeCH), 0.46 (3 H, s, Si*Me*$_A$Me$_B$) and 0.40 (3 H each, Si*Me*$_2$Ph) and 0.09 (9H, s, SiMe$_3$) (Found: C, 65.6; H, 9.00; N, 4.30. $C_{18}H_{29}NOSi_2$ requires: C, 65.2; H, 8.81; N, 4.2%) (Found: M$^+$, 331.1775. $C_{18}H_{29}NOSi_2$ requires *M*, 331.1788); *m*/*z* 331 (1%, M$^+$), 316 (36, M − Me), 258 (18, M − SiMe$_3$), 254 (30, M − C_6H_5) and 135 (100, PhMe$_2$Si).

N-Benzyl-(3*RS*,4*RS*)-4-ethynyl-3-[(*SR*)-1-dimethyl(phenyl)-silylethyl]azetidin-2-one 22

N-Benzylation of 4-trimethylsilylethynylazetidinone **20** in the same way as the *N*-benzylation of the azetidinone **13** gave the N-*benzylazetidinone* **22** (95%) as prisms, mp 60–62 °C (from hexane); $\nu_{max}(CCl_4)$/cm^{-1} 3300 (C≡C–H), 2200 (C≡C), 1740 (C=O), 1600 and 1580 (Ph); $\delta_H(CDCl_3)$ 7.62–7.22 (10 H, m, Ph), 4.73 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph), 4.05 (1 H, dd, *J* 2 and 5, C*H*NCH$_2$Ph), 4.02 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph), 3.08 (1 H, dd, *J* 5 and 11, CHCO), 2.45 (1 H, d, *J* 2, C≡CH), 1.56 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.94 (3 H, d, *J* 7, *Me*CH), 0.47 (3 H, s, Si*Me*$_A$Me$_B$) and 0.42 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 347 (2%, M$^+$), 332 (16, M − Me) and 135 (100, PhMe$_2$Si) (Found: C, 75.8; H, 7.17; N, 4.07; 347.1711. $C_{22}H_{25}NOSi$ requires C, 76.0; H, 7.25; N, 4.03%; 347.1705).

N-Benzyl-(*E*)-(3*RS*,4*SR*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-trimethylsilylethenylazetidin-2-one 23

N-Benzylation of 4-trimethylsilylethynylazetidinone **21** in the same way as the *N*-benzylation of the azetidinone **13** gave the N-*benzylazetidinone* **23** (94%) as an oil; R_f (hexane–EtOAc, 2:1) 0.45; ν_{max}(neat)/cm^{-1} 1740 (C=O); $\delta_H(CDCl_3)$ 7.60–7.18 (10 H, m, Ph), 5.91 (1 H, dd, *J* 2 and 19, C*H*SiMe$_3$), 5.90 (1 H, dd, *J* 5 and 19, C*H*=CHSiMe$_3$), 4.53 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph), 4.00 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph), 3.89 (1 H, dt, *J* 2 and 5,

C*H*NCH$_2$Ph), 3.07 (1 H, dd, *J* 5 and 12, C*H*CO), 1.28 (1 H, dq, *J* 12 and 7, C*H*SiMe$_2$Ph), 0.74 (3 H, d, *J* 7, *Me*CH), 0.46 (3 H, s, Si*Me*$_A$Me$_B$), 0.40 (3 H, s, SiMe$_A$*Me*$_B$) and 0.04 (9 H, s, SiMe$_3$); *m*/*z* 421 (1%, M$^+$), 406 (15, M − Me), 348 (15, M − SiMe$_3$), 330 (6, M − C$_7$H$_7$) and 135 (100, PhMe$_2$Si) (Found: M$^+$, 421.2261. C$_{25}$H$_{35}$NOSi$_2$ requires *M*, 421.2257).

_N_-Benzyl-(3*RS*,4*RS*)-4-[(*E*)-1,2-epoxy-2-trimethylsilylethyl]-3-[(*SR*)-1-dimethyl(phenyl)silylethyl)azetidin-2-one

m-Chloroperbenzoic acid (270 mg, 1.5 mmol) was stirred with 4-trimethylsilylethenylazetidinone **23** (400 mg, 0.95 mmol) in dichloromethane (15 cm^3) under nitrogen for 20 h. The mixture was washed with aqueous sodium hydrogen sulfite (5 cm^3), aqueous sodium hydrogen carbonate (5 cm^3), brine (5 cm^3), dried (MgSO$_4$) and evaporated under reduced pressure. Flash column chromatography (SiO$_2$, hexane–EtOAc) gave the *epoxysilane* (380 mg, 92%) as a (59:41) mixture of the (3*RS*,4*RS*,1′*SR*,1″*RS*,2″*RS*) and (3*RS*,4*RS*,1′*SR*,1″*SR*,2″*SR*) isomers; R_f (hexane–EtOAc, 2:1) 0.40; ν_{max}(CCl$_4$)/cm^{-1} 1740 (C=O); δ_H(CDCl$_3$) 7.63–7.13 (5 H, m, Ph, both isomers), 4.72 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph, both), 4.16 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph, major isomer), 3.88 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph, minor isomer), 3.33–2.84 (3 H, m, CHC=O, C*H*NCH$_2$Ph and C*H*CHSiMe$_3$, both), 2.03 (1 H, d, *J* 3, C*H*SiMe$_3$, minor), 1.95 (1 H, d, *J* 3, C*H*SiMe$_3$, major), 1.47–1.23 (1 H, m, C*H*SiMe$_2$Ph, both), 0.94 (3 H, d, *J* 7, *Me*CH, minor), 0.83 (3 H, d, *J* 7, *Me*CH, major), 0.50 (3 H, s, Si*Me*$_A$Me$_B$, major), 0.44 (3 H, s, SiMe$_A$*Me*$_B$, major), 0.49 (3 H, s, Si*Me*$_A$Me$_B$, minor), 0.44 (3 H, s, SiMe$_A$*Me*$_B$, minor), 0.06 (9 H, s, SiMe$_3$, minor) and 0.04 (9 H, s, SiMe$_3$, major); *m*/*z* 422 (11%, M − Me), 346 (15, M − C$_7$H$_7$) and 135 (100, PhMe$_2$Si) (Found: M − Me, 422.1979. C$_{25}$H$_{35}$NO$_2$Si$_2$ requires *M*, 422.1971).

_N_-Benzyl-(3*RS*,4*RS*)-4-(1,2-dihydroxy-2-trimethylsilylethyl)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]azetidin-2-one

The 4-trimethylsilylethenylazetidinone **23** (560 mg, 1.33 mmol) was stirred with osmium tetroxide (385 mg, 1.5 mmol) in pyridine (15 cm^3) for 16 h under nitrogen at room temperature. Aqueous sodium hydrogen sulfite (saturated, 10 cm^3) was added and stirring continued for 3 h. The mixture was extracted with ether (3 × 20 cm^3). The combined organic extracts were washed with hydrochloric acid (1 mol dm^{-3}, 20 cm^3), brine (20 cm^3), dried (MgSO$_4$) and evaporated under reduced pressure. Flash column chromatography (SiO$_2$, hexane–EtOAc) gave the (3RS,4RS,1′SR)-*diol* (570 mg, 94%), as a single isomer (>95:5 de), as an oil; R_f (EtOAc) 0.69; ν_{max}(neat)/cm^{-1} 3450 (OH) and 1730 (C=O); δ_H(CDCl$_3$) 7.65–7.16 (10 H, m, Ph), 4.54 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph), 4.25 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph), 3.74–3.71 (2 H, m, C*H*NBn and C*H*OHCHOHSiMe$_3$), 3.30 (1 H, s, C*H*OHSiMe$_3$), 3.15 (1 H, m, CHCO), 2.60 (1 H, br s, OH), 1.63 (1 H, br s, OH), 1.44 (1 H, m, C*H*SiMe$_2$Ph), 0.98 (3 H, d, *J* 7, MeC), 0.47 (6 H, s, Si*Me*$_2$Ph) and 0.03 (9 H, s, SiMe$_3$); *m*/*z* 438 (2%, M − OH), 322 (21, M − C$_5$H$_{13}$O$_2$Si), 135 (100, PhMe$_2$Si) and 91 (84, C$_7$H$_7$) (Found: M − OH, 438.2300. C$_{25}$H$_{37}$NO$_3$Si$_2$ − OH requires *M*, 438.2284).

_N_-Benzyl-(3*RS*,4*RS*)-4-(1,2-diacetoxy-2-trimethylsilylethyl)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]azetidin-2-one

Triethylamine (66 mg, 0.65 mmol), 4-dimethylaminopyridine (1 mg), acetic anhydride (66 mg, 0.65 mmol) and the dihydroxyazetidinone (120 mg, 0.26 mmol) were stirred in dichloromethane (10 cm^3) for 3 h. The mixture was washed with hydrochloric acid (1 mol dm^{-3}, 10 cm^3), brine (10 cm^3), and dried (MgSO$_4$). After evaporation under reduced pressure, flash column chromatography on (SiO$_2$, hexane–EtOAc) gave the *diacetoxyazetidinone* (110 mg, 77%) as a single diastereoisomer, as an oil; R_f (hexane–EtOAc, 2:1) 0.25; ν_{max}(neat)/cm^{-1} 1730 (C=O); δ_H(CDCl$_3$) 7.64–7.13 (10 H, m, Ph), 5.36 (1 H, dd, *J* 4 and 6, C*H*OAcCHOAcSiMe$_3$), 5.09 (1 H, d, *J* 6, C*H*OAcSiMe$_3$), 4.71 (1 H, d, *J* 15, C*H*$_A$H$_B$Ph), 4.04 (1 H, d, *J* 15, CH$_A$*H*$_B$Ph), 3.56 (1 H, dd, *J* 4 and 5, C*H*NCH$_2$Ph), 3.06 (1 H, dd, *J* 5 and 11, C*H*CONH), 2.08 (3 H, s, OAc), 2.00 (3 H, s, OAc), 1.61 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.90 (3 H, d, *J* 7, *Me*CH), 0.47 (3 H, s, Si*Me*$_A$Me$_B$), 0.45 (3 H, s, SiMe$_A$*Me*$_B$) and −0.12 (9 H, s, SiMe$_3$); *m*/*z* 539 (1%, M$^+$), 480 (100, M − OAc) and 322 (42, M − C$_9$H$_{17}$O$_4$Si) (Found: M$^+$, 539.2531. C$_{29}$H$_{41}$NO$_5$Si$_2$ requires *M*, 539.2523).

(2*RS*,3*SR*)-3-Dimethyl(phenyl)silyl-2-[(*SR*)-1-hydroxyethyl]-butanoic acid

The hydroxy ester **24**[4] (800 mg, 2.86 mmol) and aqueous sodium hydroxide (1 mol dm^{-3}, 10 cm^3) were stirred in 1,4-dioxan (5 cm^3) at 50 °C for 24 h. The mixture was washed with ethyl acetate, acidified with hydrochloric acid (3 mol dm^{-3}) and extracted with ethyl acetate (3 × 30 cm^3). The combined organic layers were washed with brine, dried (MgSO$_4$) and evaporated under reduced pressure to give the *acid* (720 mg, 95%), as an oil; R_f (hexane–EtOAc, 1:1) 0.25; ν_{max}(neat)/cm^{-1} 3600–2500 (COOH), 3400 (OH) and 1705 (C=O); δ_H(CDCl$_3$) 7.59–7.31 (5 H, m, Ph), 4.02 (1 H, dq, *J* 7 and 6, C*H*OH), 2.60 (1 H, t, *J* 7, C*H*CO$_2$H), 1.51 (1 H, quintet, *J* 7, C*H*SiMe$_2$Ph), 1.21 (3 H, d, *J* 6, *Me*CHOH), 1.03 (3 H, d, *J* 7, *Me*CHSi), 0.34 (3 H, s, Si*Me*$_A$Me$_B$) and 0.33 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 233 [5%, M − (Me + H$_2$O)] and 135 (100, PhMe$_2$Si) (Found: M − CH$_5$O, 233.0987. C$_{14}$H$_{22}$O$_3$Si − CH$_5$O requires *M*, 233.0997).

(2*RS*,3*SR*)-3-Dimethyl(phenyl)silyl-2-[(*RS*)-1-hydroxyethyl]-butanoic acid

This was prepared similarly from the hydroxy ester **27**[4] to give the *acid* (97%), as an oil; R_f (hexane–EtOAc, 1:1) 0.18; ν_{max}(neat)/cm^{-1} 3600–2500 (COOH) and 1705 (C=O); δ_H(CDCl$_3$) 7.54–7.25 (5 H, m, Ph), 4.03 (1 H, dq, *J* 4 and 7, C*H*OH), 2.31 (1 H, dd, *J* 4 and 9, C*H*CO$_2$H), 1.56 (1 H, dq, *J* 9 and 7, C*H*SiMe$_2$Ph), 1.21 (3 H, d, *J* 7, *Me*CHOH), 1.07 (3 H, d, *J* 8, *Me*CHSi), 0.34 (3 H, s, Si*Me*$_A$Me$_B$) and 0.31 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 233 (4%, M − CH$_5$O) and 135 (100, PhMe$_2$Si) (Found: M − Me − H$_2$O, 233.1001. C$_{14}$H$_{22}$O$_3$Si − Me − H$_2$O requires *M*, 233.0997).

***O*-Benzyl (2*RS*,3*SR*)-2-[(*SR*)-1-hydroxyethyl]-3-dimethyl-(phenyl)silylbutanohydroxamate 25**

Using the method of Miller,[19] the hydroxy acid (700 mg, 2.64 mmol), *O*-benzylhydroxylamine hydrochloride (625 mg, 3.93 mmol) and an aqueous solution of 1-ethyl-3-[3-dimethylamino)-propyl]carbodiimide hydrochloride (780 mg) were stirred in dimethylformamide (25 cm^3) and water (25 cm^3), and the pH was maintained at 4–5 by the addition of hydrochloric acid (1 mol dm^{-3}) for 2 h. The mixture was extracted with ethyl acetate (3 × 20 cm^3), the combined organic layers were washed with hydrochloric acid (3 mol dm^{-3}) and aqueous sodium hydrogen carbonate, dried (MgSO$_4$) and evaporated under reduced pressure. Flash column chromatography (SiO$_2$, hexane–EtOAc) gave the *hydroxamate* **25** (390 mg, 40%) as needles, mp 124–126 °C (from hexane–EtOAc); ν_{max}(CCl$_4$)/cm^{-1} 3400 (OH) and 1670 (C=O), δ_H([^{2}H$_6$]DMSO) 10.08 (1 H, br s, NH), 7.60–7.30 (10 H, m, Ph), 4.87 (2 H, s, C*H*$_2$Ph), 4.01 (1 H, dq, *J* 9 and 6, C*H*OH), 3.78 (1 H, br s, OH), 2.15 (1 H, dd, *J* 5 and 9, C*H*CONH), 1.62 (1 H, dd, *J* 5 and 8, C*H*SiMe$_2$Ph), 1.11 (3 H, d, *J* 6, *Me*CHOH), 0.97 (3 H, d, *J* 8, *Me*CHSi), 0.43 (3 H, s, Si*Me*$_A$Me$_B$) and 0.37 (3 H, s, SiMe$_A$*Me*$_B$) (Found: C, 67.90; H, 7.90; N, 3.58. C$_{21}$H$_{29}$NO$_3$Si requires C, 67.88; H, 7.87; N, 3.77%); *m*/*z* 326 (5%, M − C$_2$H$_5$O), 135 (75, PhMe$_2$Si) and 91 (100, C$_7$H$_7$) (Found: M − C$_2$H$_5$O, 326.1558. C$_{21}$H$_{29}$NO$_3$Si − C$_2$H$_5$O requires *M*, 326.1576).

***O*-Benzyl (2*RS*,3*SR*)-2-[(*RS*)-1-hydroxyethyl]-3-dimethyl-(phenyl)silylbutanohydroxamate 28**

This was prepared in the same way as the hydroxamate **25** from the hydroxy acid to give the *hydroxamate* **28** (46%) as needles, mp 130–132 °C; ν_{max}(CCl$_4$)/cm^{-1} 3400 (OH) and 1680 (C=O),

δ_H([$^2H_6$]DMSO) 10.17 (1 H, br s, NH), 7.65–7.25 (10 H, m, Ph), 4.89 (1 H, d, *J* 11, CH_AH_BPh), 4.84 (1 H, d, *J* 11, CH$_A$$H_B$Ph), 4.01 (1 H, quintet, *J* 6, C*H*OH), 3.88 (1 H, br s, OH), 2.15–2.05 (1 H, m, C*H*CONH), 1.45 (1 H, quintet, *J* 8, C*H*SiMe$_2$Ph), 1.13 (3 H, d, *J* 6, *Me*CHOH), 1.00 (3 H, d, *J* 8, *Me*CHSi), 0.36 (3 H, s, Si*Me*$_A$Me$_B$) and 0.33 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 356 (6%, M − Me), 326 (10, M − C_2H_5O) and 135 (100, PhMe$_2$Si) (Found: C, 67.58; H, 7.91; N, 3.48; M − Me, 356.1690. $C_{21}H_{29}NO_3Si$ requires C, 67.88; H, 7.87; N, 3.77%; *M* − Me, 356.1682).

N-Benzyloxy-(3*RS*,4*RS*)-4-methyl-3-[(*SR*)-1-dimethyl(phenyl)-silylethyl]azetidin-2-one 26

Using the method of Miller,[19] the hydroxy hydroxamate **25** (260 mg, 0.67 mmol) was added to triphenylphosphine (67 mmol) in THF (15 cm^3) and the mixture stirred under nitrogen. Diethyl azodicarboxylate (0.126 cm^3, 0.8 mmol) in THF (5 cm^3) was added dropwise to the mixture and stirring was continued for 30 min. The solvent was removed under reduced pressure and flash column chromatography (SiO_2, hexane–EtOAc) gave the β-*lactam* **26** (190 mg, 77%) as an oil; R_f (hexane–EtOAc, 1:1) 0.61; ν_{max}(neat)/cm^{-1} 1765 (C=O) and 1500 (Ph); δ_H($CDCl_3$) 7.57–7.25 (10 H, m, Ph), 4.90 (2 H, s, CH_2Ph), 3.18 (1 H, dq, *J* 2 and 6, C*H*NOBn), 2.46 (1 H, dd, *J* 2 and 4, CHCO), 1.40 (1 H, dq, *J* 4 and 7, C*H*SiMe$_2$Ph), 1.03 (3 H, d, *J* 6, *Me*CHNOBn), 0.87 (3 H, d, *J* 7, *Me*CHSi), 0.27 (3 H, s, Si*Me*$_A$Me$_B$) and 0.25 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 338 (1%, M − Me), 135 (81, PhMe$_2$Si) and 91 (100, C_7H_7) (Found: M − Me, 338.1594. $C_{21}H_{27}NO_2Si$ requires *M* − Me, 338.1576).

N-Benzyloxy-(3*RS*,4*SR*)-4-methyl-3-[(*SR*)-1-dimethyl(phenyl)-silylethyl]azetidin-2-one 29

This was prepared in the same way from the hydroxamate **26** to give the β-*lactam* **29** (64%), as an oil; R_f (hexane–EtOAc, 1:1) 0.67; ν_{max}(neat)/cm^{-1} 1765 (C=O); δ_H($CDCl_3$) 7.65–7.28 (10 H, m, Ph), 4.92 (2 H, s, CH_2Ph), 3.67 (1 H, dq, *J* 5 and 6, C*H*NOBn), 2.69 (1 H, dd, *J* 5 and 11, CHCO), 1.56 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 1.08 (3 H, d, *J* 6, *Me*CHNOBn), 0.78 (3 H, d, *J* 7, *Me*CHSi), 0.44 (3 H, s, Si*Me*$_A$Me$_B$) and 0.39 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 338 (2%, M − Me), 135 (100, PhMe$_2$Si) and 91 (69, C_7H_7) (Found: M − Me, 338.1556. $C_{21}H_{27}NO_2Si$ requires *M* − Me, 338.1576).

N-Hydroxy-(3*RS*,4*SR*)-4-methyl-3-[(*RS*)-1-dimethyl(phenyl)-silylethyl]azetidin-2-one

The lactam **29** (700 mg, 1.98 mmol) in methanol (50 cm^3), was stirred with palladium on charcoal (10%, 150 mg) under a hydrogen atmosphere until the uptake of hydrogen was completed. The mixture was filtered through Celite and evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) gave the N-*hydroxylactam* (570 mg, 97%) as an oil; R_f (hexane–EtOAc, 1:1) 0.50; ν_{max}(neat)/cm^{-1} 3100 (OH) and 1740 (C=O); δ_H($CDCl_3$) 7.60–7.53 (5 H, m, Ph), 3.94 (1 H, dq, *J* 5 and 6, C*H*NOH), 2.75 (1 H, dd, *J* 5 and 11, CHCO), 1.31 (3 H, d, *J* 6, *Me*CHNOH), 1.19 (1 H, dq, *J* 11 and 7, C*H*SiMe$_2$Ph), 0.84 (3 H, d, *J* 7, *Me*CHSi), 0.44 (3 H, s, Si*Me*$_A$Me$_B$) and 0.39 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 246 (3%, M − OH) and 135 (100, PhMe$_2$Si) (Found: M − OH, 246.1307. $C_{14}H_{21}O_2Si$ requires *M* − OH, 246.1314).

(3*RS*,4*SR*)-4-Methyl-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-azetidin-2-one 30

Following Miller,[19] titanium trichloride (30% in H_2O, 0.5 cm^3) was added dropwise to a stirred solution of the *N*-hydroxy-lactam (40 mg, 0.15 mmol) in methanol (0.5 cm^3) and water (4 cm^3) under nitrogen and the solution maintained at pH 7 using aqueous sodium hydroxide (3 mol dm^{-3}). After stirring for 2 h, the mixture was adjusted to pH 8 and then extracted with ethyl acetate (5 × 10 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography (hexane–EtOAc) gave the β-*lactam* **30** (22 mg, 58%), as needles, mp 98–99 °C (from hexane–EtOAc); ν_{max}(CH_2Cl_2)/cm^{-1} 3400 (NH) and 1750 (C=O); δ_H($CDCl_3$) 7.62–7.34 (5 H, m, Ph), 5.73 (1 H, br s, NH), 3.79 (1 H, dq, *J* 5 and 6, C*H*NH), 3.04 (1 H, ddd, *J* 0.5, 5 and 12, CHCO), 1.31 (1 H, dq, *J* 12 and 7, C*H*SiMe$_2$Ph), 1.27 (3 H, d, *J* 6, *Me*CHNH), 0.83 (3 H, d, *J* 7, *Me*CHSi), 0.47 (3 H, s, Si*Me*$_A$Me$_B$) and 0.42 (3 H, s, SiMe$_A$-*Me*$_B$); *m*/*z* 247 (1%, M$^+$), 232 (33, M − Me) and 135 (100, PhMe$_2$Si) (Found: M$^+$, 247.1402. $C_{14}H_{21}SiNO$ requires *M*, 247.1392).

3-Dimethyl(phenyl)silylpropan-1-ol

Following Baum,[27] dimethyl(phenyl)silane[28] (16 g, 118 mmol) and tris-triphenylphosphinerhodium(I) chloride (Wilkinson's catalyst) (50 mg) were stirred at 130 °C and allyloxytrimethyl-silane (22.8 cm^3, 135 mmol) added dropwise over 4 h. The mixture was stirred at 130 °C for a further 45 min, and then added dropwise to a stirred mixture of methanol (200 cm^3) and hydrochloric acid (1 mol dm^{-3}, 50 cm^3) at room temperature. The mixture was stirred for 18 h and an equal volume of water was added. The product was extracted with dichloromethane and the organic extracts washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Distillation gave the alcohol (84%), bp 105–107 °C/0.3 mmHg (lit.,[29] 98–99 °C/0.2 mmHg).

3-Dimethyl(phenyl)silylpropanal

This was prepared from the alcohol using pyridinium dichromate to give the aldehyde (86%), bp 79 °C/3 mmHg; δ_H($CDCl_3$) 9.61 (1 H, s, CHO), 7.61–7.12 (5 H, m, Ph), 2.53–2.18 (2 H, m, CH_2CHO), 1.16–0.80 (2 H, m, CH_2SiMe$_2$Ph) and 0.29 (6 H, s, SiMe$_2$).

Benzyl (2*RS*,3*SR*)-3-hydroxy-5-dimethyl(phenyl)silyl-2-[(*SR*)-1-dimethyl(phenyl)silylethyl]pentanoate 32

This was prepared, following our earlier recipe,[30] from benzyl 3-dimethyl(phenyl)silylbutanoate **31**[30] and the β-silylpropion-aldehyde to give the *hydroxyester* **32** (71%) as an oil; R_f (hexane–EtOAc, 2:1) 0.42; ν_{max}(neat)/cm^{-1} 3500 (OH) and 1730 (C=O); δ_H($CDCl_3$) 7.55–7.26 (15 H, m, Ph), 4.92 (2 H, s, CH_2Ph), 3.67 (1 H, ddd, *J* 2, 8 and 9, CHOH), 2.63 (1 H, dd, *J* 6 and 8, C*H*CO$_2$Bn), 1.63–1.45 (2 H, m, CH_AH_BCHOH and MeC*H*Si), 1.24 (1 H, m, CH$_A$$H_B$CHOH), 1.00 (3 H, d, *J* 8, *Me*CH), 0.91 (1 H, m, CH_AH_BSiMe$_2$Ph), 0.56 (1 H, ddd, *J*, 5, 12 and 14, CH$_A$$H_B$SiMe$_2$Ph), 0.31, 0.29, 0.21 and 0.20 (3 H each, s, 2 × SiMe$_2$); *m*/*z* 427 (2%, M − C_6H_5), 311 (4, M − $C_{11}H_{17}OSi$) and 135 (100, PhMe$_2$Si) (Found: M − Ph, 427.2138. $C_{30}H_{40}O_3Si$ requires *M* − Ph, 427.2125).

Benzyl (2*RS*,3*RS*)-3-hydroxy-5-dimethyl(phenyl)silyl-2-[(*SR*)-1-dimethyl(phenyl)silylethyl]pentanoate

This was prepared, following our earlier recipe[30] from benzyl crotonate, the silylcuprate reagent and the β-silylpropion-aldehyde to give a mixture of the (2*RS*,3*RS*,1′*SR*)-hydroxy ester and the (2*RS*,3*SR*,1′*SR*)-ester **32** (overall 85%, 3*RS*:3*SR* 70:30) as an oil; R_f (hexane–EtOAc, 2:1) 0.42; ν_{max}(neat)/cm^{-1} 3450 (OH) and 1730 (C=O); δ_H($CDCl_3$) for the (2*RS*,3*RS*,1′*SR*) isomer 7.53–7.21 (15 H, m, Ph), 4.78 (1 H, d, *J* 12, CH_AH_BPh), 4.56 (1 H, d, *J* 12, CH$_A$$H_B$Ph), 3.72–3.56 (1 H, m, CHOH), 2.43 (1 H, dd, *J* 3 and 10, C*H*CO$_2$Bn), 1.72–1.42 (2 H, m, MeC*H*Si and CH_AH_BCHOH), 1.41–1.14 (1 H, m, CH$_A$$H_B$CHOH), 1.02 (3 H, d, *J* 7, MeC), 0.93–0.77 (1 H, m, CH_AH_BSiMe$_2$Ph), 0.68–0.51 (1 H, m, CH$_A$$H_B$SiMe$_2$Ph), 0.29, 0.25, 0.17 and 0.16 (3 H each, s, 2 × SiMe$_2$).

(2*RS*,3*SR*)-3-Hydroxy-5-dimethyl(phenyl)silyl-2-[(*SR*)-1-dimethyl(phenyl)silylethyl]pentanoic acid

The β-hydroxy ester **32** (5 g) and 10% palladium on charcoal (500 mg) in methanol (200 cm^3) was stirred under a hydrogen

atmosphere until the uptake of hydrogen was complete. The mixture was filtered through Celite and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) gave the *acid* (3.78 g, 92%), as an oil; R_f (hexane–EtOAc, 2:1) 0.19; ν_{max}(neat)/cm^{-1} 3600–2600 (OH) and 1705 (C=O); δ_H($CDCl_3$) 7.55–7.29 (10 H, m, Ph), 3.67 (1 H, dt, *J* 2 and 8, C*H*OH), 2.59 (1 H, dd, *J* 6 and 8, C*H*CO_2H), 1.62 (1 H, m, C$H_A$$H_B$CHOH), 1.50 (1 H, dq, *J* 6 and 8, MeC*H*Si), 1.31 (1 H, m, $CH_A$$H_B$CHOH), 1.00 (3 H, d, *J* 8, MeC), 0.91 (1 H, ddd, *J* 4, 12 and 14, C$H_A$$H_B$$SiMe_2$Ph), 0.59 (1 H, ddd, *J* 5, 12 and 14, $CH_A$$H_B$$SiMe_2$Ph) 0.32, 0.30, 0.24 and 0.23 (3 H each, s, 2 × $SiMe_2$); *m*/*z* 396 (1%, M − H_2O) and 135 (100, $PhMe_2Si$) (Found: M − H_2O, 396.1938. $C_{23}H_{34}O_3Si_2$ requires *M* − H_2O, 396.1941).

O-Benzyl (2*RS*,3*SR*)-3-hydroxy-5-dimethyl(phenyl)silyl-2-[(*SR*)-1-dimethyl(phenyl)silylethyl]pentanohydroxamate 33

This was prepared in the same way as the hydroxamate **25** to give the hydroxamate **33** (71%) as prisms, mp 93–95 °C (from hexane–EtOAc); ν_{max}(CCl_4)/cm^{-1} 3400 (OH) and 1660 (C=O); δ_H($CDCl_3$) 7.92 (1 H, br s, NH), 7.53–7.27 (15 H, m, Ph), 4.78 (2 H, s, CH_2Ph), 3.61 (1 H, ddd, *J* 2, 7 and 9, C*H*OH), 2.02 (1 H, ddd, *J* 1, 6 and 7, C*H*CONH), 1.65–1.40 (2 H, m, CH_A-H_BCHOH and MeC*H*), 1.55 (1 H, br s, OH), 1.21 (1 H, m, $CH_A$$H_B$CHOH), 0.90 (3 H, d, *J* 7, *Me*CH), 0.89–0.77 (1 H, m, C$H_A$$H_B$$SiMe_2$Ph), 0.53 (1 H, ddd, *J* 5, 12 and 14, $CH_A$$H_B$-$SiMe_2$Ph) 0.31, 0.28, 0.24 and 0.23 (3 H each, s, 2 × $SiMe_2$); *m*/*z* 504 (27%, M − Me), 486 (3, M − CH_5O), 442 (13, M − C_6H_5) and 326 (100, M − $C_{11}H_{17}OSi$) (Found: C, 68.8; H, 7.85; N, 2.48; M − Me, 504.2402. $C_{30}H_{41}NO_3Si_2$ requires C, 69.1; H, 7.95; N, 2.69%; *M* − Me, 504.2391).

N-Benzyloxy-(3*RS*,4*RS*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-[2-dimethyl(phenyl)silylethyl]azetidin-2-one 34

This was prepared in the same way as the azetidinone **26** to give the trans-N-*benzyloxyazetidinone* **34** (94%) as an oil; R_f (hexane–EtOAc, 2:1) 0.33; ν_{max}(neat)/cm^{-1} 1770 (C=O); δ_H($CDCl_3$) 7.46–7.25 (15 H, m, Ph), 4.85 (2 H, s, CH_2Ph), 3.15 (1 H, dt, *J* 2 and 5, C*H*NOCH_2Ph), 2.53 (1 H, dd, *J* 2 and 5, CHCO), 1.38 (3 H, m, C$H_2$$CH_2$Si and MeC*H*Si), 0.86 (3 H, d, *J* 8, *Me*CH), 0.53 (2 H, dd, *J* 7 and 8, C$H_2$$SiMe_2$Ph), 0.24 (3 H, s, Si$Me_A$$Me_B$), 0.22 (3 H, s, $SiMe_A$$Me_B$) and 0.21 (6 H, s, $SiMe_2$); *m*/*z* 501 (10%, M$^+$), 486 (12, M − Me) and 338 (100, M − $C_{10}H_{15}Si$) (Found: M$^+$, 501.2499. $C_{30}H_{39}NO_2Si_2$ requires *M*, 501.2519).

N-Hydroxy-(3*RS*,4*RS*)-3-[(*SR*)-1-dimethyl(phenyl)silylethyl]-4-(2-dimethyl(phenyl)silylethyl)azetidin-2-one

This was prepared from the *N*-benzyloxyazetidinone **34** in the same way as the hydroxyazetidinone derived from the lactam **29** to give the N-*hydroxyazetidinone* (97%) as an oil; R_f (hexane–EtOAc, 2:1) 0.16; ν_{max}(neat)/cm^{-1} 3400 (OH) and 1750 (C=O); δ_H($CDCl_3$) 10.18 (1 H, br s, OH), 7.49–7.29 (10 H, m, Ph), 3.49 (1 H, dt, *J* 1 and 5, C*H*NOH), 2.52 (1 H, dd, *J* 1 and 5, CHCO), 1.66–1.40 (2 H, m, C$H_2$$CH_2$Si), 1.35 (1 H, dq, *J* 5 and 7, MeC*H*), 0.93 (3 H, d, *J* 7, *Me*CH), 0.71–0.63 (2 H, m, C$H_2$$SiMe_2$Ph), 0.27 (3 H, s, Si$Me_A$$Me_B$) and 0.25 (3 H, s, $SiMe_A$$Me_B$) and 0.24 (6 H, s, $SiMe_2$); *m*/*z* 396 (6%, M − Me), 394 (7, M − OH) and 135 (100, $PhMe_2Si$) (Found: M − Me, 396.1812. $C_{23}H_{33}NO_2Si_2$ requires *M* − Me, 396.1815).

(3*RS*,4*RS*)-3-[(*SR*)-1-Dimethyl(phenyl)silylethyl]-4-[2-dimethyl-(phenyl)silylethyl]azetidin-2-one 35

This was prepared in the same way as the azetidinone **30** to give the *azetidinone* **35** (55%) as prisms, mp 86–88 °C (from hexane); ν_{max}(CCl_4)/cm^{-1} 3400 (NH) and 1745 (C=O); δ_H($CDCl_3$) 7.47–7.27 (10 H, m, Ph), 5.97 (1 H, s, NH), 3.17 (1 H, ddd, *J* 2, 4 and 6, C*H*NH), 2.73 (1 H, ddd, *J* 1, 2 and 5, CHCO), 1.53–1.23 (2 H, m, C$H_2$$CH_2$Si), 1.44 (1 H, dq, *J* 5 and 7, MeC*H*), 1.00 (3 H, d, *J* 7, *Me*CH), 0.68–0.46 (2 H, m, CH_2CH_2Si), 0.29 (3 H, s, Si$Me_A$$Me_B$), 0.27 (3 H, s, $SiMe_A$$Me_B$) and 0.24 (6 H, s, $SiMe_2$); *m*/*z* 395 (3%, M$^+$), 380 (30, M − Me) and 135 (100, $PhMe_2Si$) (Found: C, 69.4; H, 8.48; N, 3.75; M$^+$, 395.2119. $C_{23}H_{33}NOSi_2$ requires C, 69.8; H, 8.41; N, 3.53%; *M*, 395.2100).

(6*RS*,7*SR*)-7-[(*SR*)-1-Hydroxyethyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one 36 from the disilylazetidinone 35

Boron trifluoride acetic acid complex (0.12 cm^3, 3.5 equiv.) was added dropwise to a stirred solution of the disilylazetidinone **35** (100 mg, 0.25 mmol) in dichloromethane (5 cm^3) under nitrogen at room temperature. After 2 h, aqueous sodium hydrogen carbonate (saturated, 5 cm^3) was added and stirring continued for 10 min. The mixture was extracted with ether (3 × 10 cm^3) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the *fluorosilane*, which was taken up in methanol and THF (1:1, 3 cm^3). Peracetic acid (40% in AcOH, 0.2 cm^3) was added, followed by triethylamine (56 mg, 0.55 mmol) and the mixture stirred under nitrogen at room temperature for 6 h. All solvent was removed by evaporation under reduced pressure and the crude residue was taken up in dichloromethane (5 cm^3). 2,2-Dimethoxypropane (80 mg, 0.77 mmol) and toluene-*p*-sulfonic acid (45 mg, 0.26 mmol) were added and the mixture was stirred for 12 h. Solvent was evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc), gave the bicyclooctane[3] **36** (11 mg, 22%) as an oil; R_f (EtOAc) 0.20; ν_{max}(CH_2Cl_2) 3400 (OH) and 1735 (C=O), δ_H([$^2H_6$]Me2CO) 4.05 (1 H, dq, *J* 5 and 6, C*H*OH), 3.87 (1 H, dt, *J* 2 and 12, C$H_A$$H_B$O), 3.76 (1 H, ddd, *J* 2, 5 and 12, CH_A-H_BO), 3.61 (1 H, ddd, *J* 2, 5 and 11, CHN), 2.86 (1 H, dd, *J* 2 and 5, CHCO), 2.85 (1 H, s, OH), 1.88 (1 H, ddt, *J* 5, 13 and 2, C$H_A$$H_B$$CH_2$O), 1.61 (3 H, s, C$Me_A$$Me_B$), 1.37 (3 H, s, C$Me_A$-$Me_B$), 1.60 (1 H, m, $CH_A$$H_B$$CH_2$O), 1.23 (3 H, d, *J* 6, *Me*CH); *m*/*z* 199 (1%, M$^+$) 184 (29, M − Me), 141 (52, M − C_3H_6O), 98 (63, C_5H_8NO) and 84 (100, C_4H_6NO) (Found: M$^+$, 199.1212. $C_{10}H_{17}NO_3$ requires *M*, 199.1208).

(6*RS*,7*SR*)-7-[(*RS*)-1-Hydroxyethyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one 2

Formic acid (140 mg, 3 mmol) and diethyl azodicarboxylate (290 mg, 1.65 mmol) were successively added to a solution of the azetidinone **36** (30 mg, 1.5 mmol) and triphenylphosphine (430 mg, 1.65 mmol) in THF (20 cm^3). After stirring for 3 h the solution was diluted with ethyl acetate and washed with aqueous sodium hydrogen carbonate, and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc) to give (6RS,7SR)-7-[(RS)-1-*formyloxyethyl*]-2,2-*dimethyl*-3-*oxa*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (contaminated with diethyl azodicarboxylate) (320 mg) as an oil; R_f (EtOAc) 0.52; ν_{max}(CH_2Cl_2)/cm^{-1} 3400 (CHO), 1745 and 1720 (C=O); δ_H($CDCl_3$) 8.03 (1 H, s, HCO_2), 5.28 (1 H, dq, *J* 8 and 6, C*H*OCHO), 3.85–3.80 (2 H, m, CH_2CH_2O), 3.51 (1 H, ddd, *J* 2, 5 and 11, CHN), 2.95 (1 H, dd, *J* 2 and 8, CHCO), 1.89 (1 H, ddt, *J* 5, 13 and 2, C$H_A$$H_B$$CH_2$O), 1.73 (3 H, s, C$Me_A$$Me_B$), 1.40 (3 H, s, C$Me_A$$Me_B$), 1.66 (1 H, m, $CH_A$$H_B$$CH_2$O) and 1.40 (3 H, d, *J* 6, *Me*CH); *m*/*z* 227 (5%, M$^+$), 212 (54, M − Me) and 98 (100, C_5H_8NO) (Found: M$^+$, 227.1167. $C_{11}H_{17}NO_4$ requires *M*, 227.1157). The formate was dissolved in 1,4-dioxan (20% in H_2O, 50 cm^3) at 0 °C and aqueous sodium hydroxide (1 mol dm^{-3}, 10 cm^3) was added. The mixture was stirred for 3 h and extracted with ethyl acetate (3 × 25 cm^3). The combined organic extracts were washed with water, with brine, dried ($MgSO_4$) and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, EtOAc) gave the azetidinone[3] (195 mg, 65%) as an oil; R_f (EtOAc) 0.21; ν_{max}(neat)/cm^{-1} 3350 (OH) and 1740 (C=O); δ_H($CDCl_3$) 3.93 (1 H, dq, *J* 7 and 6, C*H*OH), 3.84 (1 H, dt, *J* 2 and 12, C$H_A$$H_B$O), 3.74 (1 H, ddd, *J* 2, 5 and 12, $CH_A$$H_B$O), 3.63 (1 H, ddd, *J* 2, 5 and 11, CHN), 3.04 (1 H, s, OH), 2.69 (1 H, dd, *J* 2 and 7, CHCO), 1.88 (1 H, ddt, *J* 5, 13 and 2, C$H_A$$H_B$$CH_2$O), 1.62 (3 H, s, C$Me_A$$Me_B$), 1.35 (3 H, s,

CMe_AMe_B), 1.60 (1 H, m, $CH_AH_BCH_2O$) and 1.22 (3 H, d, *J* 6, *Me*CH); *m*/*z* 199 (2%, M^+), 184 (39, M − Me) and 84 (100, C_4H_6NO) (Found: M^+, 199.1221. $C_{10}H_{17}NO_3$ requires *M*, 199.1208).

(6*RS*,7*SR*)-7-{(*RS*)-1-[(*p*-Nitrobenzyloxy)carbonyloxy]ethyl}-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one

Toluene-*p*-sulfonic acid (170 mg, 1 mmol) was added to a solution of the *p*-nitrobenzyl carbonate **37** (5 g, 14.9 mmol) and dimethoxypropane (1.7 g, 16.4 mmol) in dichloromethane at room temperature and the mixture stirred for 3 h. Solvent was evaporated under reduced pressure and flash column chromatography of the residue (SiO_2, hexane–EtOAc) gave the bicyclocarbonate as prisms, mp 99–100 °C (from hexane–EtOAc) (lit.,[3] 101 °C); $\delta_H(CDCl_3)$ 8.2 (2 H, d, *J* 9, ArH *o* to NO_2), 7.52 (2 H, d, *J* 9, ArH *m* to NO_2), 5.20 (2 H, s, CH_2Ar), 5.00 (1 H, dq, *J* 8 and 6, MeC*H*), 3.78 (2 H, dd, *J* 3 and 8, CH_2CH_2O), 3.51 (1 H, ddd, *J* 2, 5 and 11, CHN), 2.91 (1 H, dd, *J* 2 and 8, CHCO), 1.93–1.63 (2 H, m, CH_2CH_2O), 1.65 (3 H, s, CMe_AMe_B), 1.34 (3 H, s, CMe_AMe_B) and 1.36 (3 H, d, *J* 6, *Me*CH).

Hydrogenolysis of the *p*-nitrobenzyl carbonate

The *p*-nitrobenzyl carbonate (3.5 g, 9.3 mmol) and palladium on charcoal (10%, 300 mg) in methanol were stirred under a hydrogen atmosphere until uptake of hydrogen was complete. The solution was filtered through Celite and evaporated under reduced pressure. Flash column chromatography on (SiO_2, eluting with hexane–EtOAc) gave the (6*RS*,7*SR*,1′*RS*)-hydroxyethylazetidinone identical to that prepared from the azetidinone **36** by inversion of configuration at C-1′.

(6*RS*,7*SR*)-7-[(*SR*)-1-Hydroxyethyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one 36 (from the azetidinone 2)

The (6*RS*,7*SR*,1′*RS*)-hydroxyethylazetidinone was formylated in the same way as the formylation of the azetidinone **36** to give (6RS,7SR)-7-[(SR)-*formyloxyethyl*]-2,2-*dimethyl*-3-*oxa*-1-*azabicyclo*[4.2.0]*octan*-8-*one* as an oil; R_f (EtOAc) 0.54; ν_{max}(neat)/cm^{-1} 3350 (CHO), 1745 and 1720 (C=O); $\delta_H(CDCl_3)$ 8.03 (1 H, s, HCO_2C), 5.33 (1 H, dq, *J* 5 and 6, C*H*OCHO), 3.84–3.78 (2 H, m, CH_2CH_2O), 3.41 (1 H, m, CHN), 3.03 (1 H, dd, *J* 2 and 5, CHCO), 1.86 (1 H, ddt, *J* 5, 13 and 2, $CH_AH_BCH_2O$), 1.71 (3 H, s, CMe_AMe_B) and 1.37 (3 H, s, CMe_AMe_B), 1.65 (1 H, m, $CH_AH_BCH_2O$) and 1.37 (3 H, d, *J* 6, *Me*CH); *m*/*z* 227 (3%, M^+), 212 (58, M − Me) and 98 (100, C_5H_8NO) (Found: M^+, 227.1176. $C_{11}H_{17}NO_4$ requires *M*, 227.1157). The formyloxyethylazetidinone was hydrolysed in the same way as the hydrolysis of its diastereoisomer to give the azetidinone **36** (68% over three steps) identical to the sample prepared from the disilylazetidinone.

Acknowledgements

We thank the SERC (now EPSRC) and Beecham Pharmaceuticals (now SmithKline Beecham) for a CASE award (J. D. K.), for the sample of the β-lactam **37**, and Drs R. Southgate and D. F. Corbett in particular for their interest in this work.

References

1 G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 6491.
2 Reviews: T. Kametani, *Heterocycles*, 1982, **17**, 463; M. Shibuya, *J. Synth. Org. Chem., Jpn.*, 1983, **41**, 62; R. Labia and C. Moris, *J. Antibiot.*, 1984, **37**, 103; G. I. Georg, in *Studies in Natural Product Chemistry*, ed. A.-ur Rahman, Elsevier, Amsterdam, 1989, vol. 4, p. 431. More recent syntheses: S. Hanessian, D. Desilet and Y. Bennani, *J. Org. Chem.*, 1990, **55**, 3098; J. Montgomery, G. M. Wieber and L. Hegedus, *J. Am. Chem. Soc.*, 1990, **112**, 6255; N. Ikota, O. Yoshino and K. Koga, *Chem. Pharm. Bull.*, 1991, **39**, 2201; J. H. Bateson, S. C. M. Fell, R. Southgate, D. S. Eggleston and P. W. Baures, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1305; Y. Yamamoto, N. Asao and T. Uyehara, *J. Am. Chem. Soc.*, 1992, **114**, 5427; Y. Kitagi, N. Shibata, T. Miki, Y. Takemura and O. Tamura, *Chem. Pharm. Bull.*, 1992, **40**, 12; G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1994, 379; H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato and M. Ikeda, *J. Org. Chem.*, 1995, **60**, 1276; P. A. Jacobi, S. Murphee, F. Ruprecht and W. Zheng, *J. Org. Chem.*, 1996, **61**, 2413; S. G. Davies, C. J. R. Hedgecock and J. M. McKenna, *Tetrahedron: Asymmetry*, 1996, **6**, 2507; L. Banfi, G. Guanti and M. T. Zannetti, *Tetrahedron Lett.*, 1996, **37**, 521; S. G. Davies and D. R. Fenwick, *Chem. Commun.*, 1997, 565.
3 F. A. Bouffard, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1130; S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135; S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1142.
4 I. Fleming and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3295.
5 I. Fleming, *Chemtracts: Org. Chem.*, 1996, **9**, 1; G. R. Jones and Y. Landais, *Tetrahedron*, 1996, **37**, 7599; K. Tamao, *Adv. Silicon Chem.*, JAI Press, Greenwich, CT, 1996, **3**, 1.
6 I. Fleming and J. D. Kilburn, *J. Chem. Soc., Chem. Commun.*, 1986, 1198.
7 S. Danishefsky, A. Guingant and M. Prisbylla, *Tetrahedron Lett.*, 1980, **21**, 2033.
8 I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 317.
9 D. J. Hart and D. C. Ha, *Chem. Rev.*, 1989, **89**, 1447.
10 C. Palomo, J. M. Aizpurua, R. Urchegui and M. Iturburu, *J. Org. Chem.*, 1992, **57**, 1571.
11 D.-C. Ha, D. J. Hart and T.-K. Yang, *J. Am. Chem. Soc.*, 1984, **106**, 4819.
12 G. Zweifel and S. J. Backlund, *J. Am. Chem. Soc.*, 1977, **99**, 3184; G. Zweifel and H. Arzoumanian, *J. Am. Chem. Soc.*, 1967, **89**, 291.
13 G. Stork and E. Colvin, *J. Am. Chem. Soc.*, 1971, **93**, 2080.
14 P. F. Hudrlik, A. M. Hudrlik and A. K. Kulkarni, *J. Am. Chem. Soc.*, 1985, **107**, 4260.
15 P. F. Hudrlik, J. P. Arcoleo, R. H. Schwartz, R. N. Misra and R. J. Rona, *Tetrahedron Lett.*, 1977, 591.
16 I. Fleming and N. K. Terrett, *J. Organomet. Chem.*, 1984, **264**, 99; W. Bernhard and I. Fleming, *J. Organomet. Chem.*, 1984, **271**, 281.
17 A. G. Brown, D. F. Corbett, A. J. Eglington and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 523; D. F. Corbett, A. J. Eglington and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 953; A. G. Brown, D. F. Corbett, A. J. Eglington and T. T. Howarth, *J. Antibiotics*, 1979, **32**, 961.
18 W. F. Huffman, K. G. Holden, T. F. Buckley, III, J. G. Gleason and L. Wu, *J. Am. Chem. Soc.*, 1977, **99**, 2352; R. Zamboni and G. Just, *Can. J. Chem.*, 1979. **57**, 1945; D. R. Kronenthal, C. Y. Han and M. K. Taylor, *J. Org. Chem.*, 1982, **47**, 2765; B. Ernest and D. Bellus, German Patent, DE 3 620 467, 1987 (*Chem. Abstr.*, 1987, **106**, 176 045); C. Palomo, F. P. Cossio, J. M. Odriozola, M. Oiarbide and J. M. Ontoria, *Tetrahedron Lett.*, 1989, **30**, 4577; C. Palomo, J. M. Ontoria, J. M. Odriozola, J. M. Aizpurua and I. Ganboa, *J. Chem. Soc., Chem. Commun.*, 1990, 248.
19 P. G. Mattingly and M. J. Miller, *J. Org. Chem.*, 1980, **45**, 410; M. J. Miller, P. G. Mattingly, M. A. Morrison and J. F. Kerwin, Jr., *J. Am. Chem. Soc.*, 1980, **102**, 7026.
20 K. Baum, D. A. Lerdal and J. S. Horn, *J. Org. Chem.*, 1978, **43**, 203.
21 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
22 D. F. Corbett, S. Coulton and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1982, 3011.
23 J. Graymore, *J. Chem. Soc.*, 1931, 1490.
24 H. Kritzler, K. Wagner and H. Holtschmidt, Belg P 621 378 (*Chem. Abstr.*, 1963, **59**, 9816f).
25 S. E. Denmark and T. K. Jones, *J. Org. Chem.*, 1982, **47**, 4595.
26 M. J. Carter, I. Fleming and A. Percival, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2415.
27 K. Baum, D. A. Lerdal and J. S. Horn, *J. Org. Chem.*, 1978, **43**, 203.
28 R. A. Benkeser and D. J. Foster, *J. Am. Chem. Soc.*, 1952, **74**, 5314.
29 J. W. Wilt, W. K. Chwang, C. F. Dockus and N. M. Tomiuk, *J. Am. Chem. Soc.*, 1978, **100**, 5534.
30 I. Fleming, S. Gil, A. K. Sarkar and T. Schmidlin, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3351.

Paper 8/04271C
Received 5th *June* 1998
Accepted 23rd *June* 1998