Development of a Synthesis of Lankacidins: Synthesis of the C(14)-C(6) Fragment and Introduction of the C(10)-C(13) Diene

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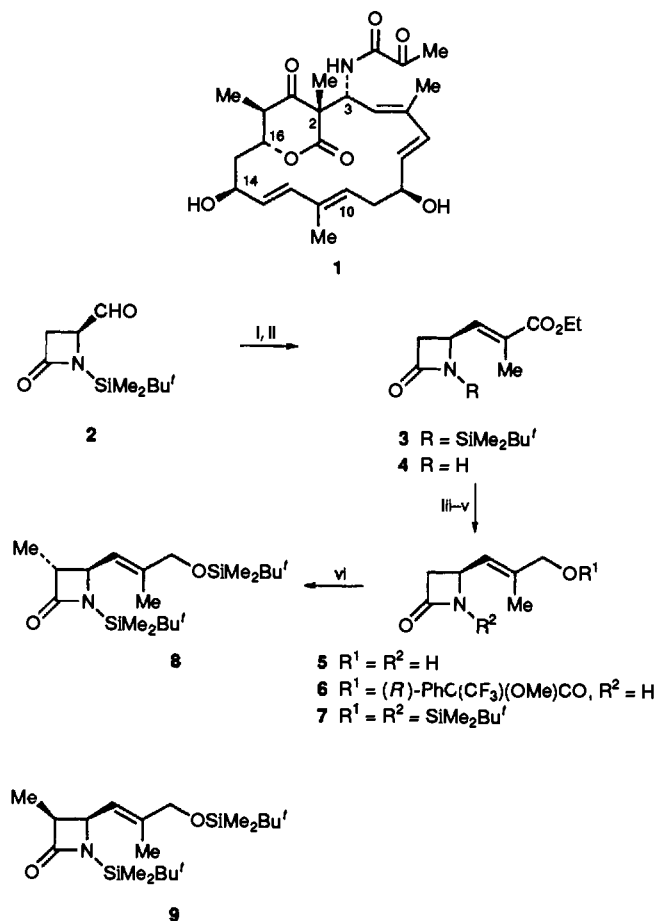
Acylation of the azetidinone **8** using the thioester **17**, prepared from dimethyl (*S*)-malate, gave the (3*S*,4*R*)-3-(3′,4′-bis-*tert*-butyldimethylsilyloxy-1′-oxobutyl)azetidinone **18** which was converted into the *N*-acylazetidinone **20**. Desilylation of this was selective for the primary *tert*-butyldimethylsilyl groups and gave mixtures of products in which the 7-membered lactone **25** was the major component rather than the 6-membered ring isomer required for a lankacidin synthesis. However, the (3*S*,4*R*)-3-(3′-*tert*-butyldimethylsilyloxy-2′-methyl-1′-oxohex-5-enyl)azetidinone **27** was similarly prepared and hydroxyl-induced azetidinone cleavage of the desilylated *N*-acyl derivative **30** gave the δ-lactone **31**. This lactone gave a complex mixture of products on attempted reduction of the ketone substituent, but the required hydroxy lactone **32** could be obtained directly from the azetidinone **30** using sodium borohydride in ethanol. Introduction of the C(10)-C(13) dienyl fragment into intermediates containing the δ-lactone was complicated by elimination. However, this diene could be introduced into azetidinone precursors of the δ-lactone using keto-phosphonate aldehyde condensations.

The lankacidins, *e.g.* lankacidin C **1**, are interesting targets for total synthesis because of their novel structures which incorporate a bridged 17-membered carbocyclic ring, and their potent antibacterial and antitumour activities.[1] We[2,3] and Kende[4] independently planned a synthetic approach to these compounds based on the introduction of the β-amino acid component by way of a stereoselective acylation of an azetidinone, and Kende has recently reported the first total synthesis of a lankacidin using this strategy.[5] We now describe details of our studies which have led to a synthesis of a δ-lactone corresponding to the C(14)-C(6) fragment, and a procedure for the introduction of the C(10)-C(13) diene unit.[6]
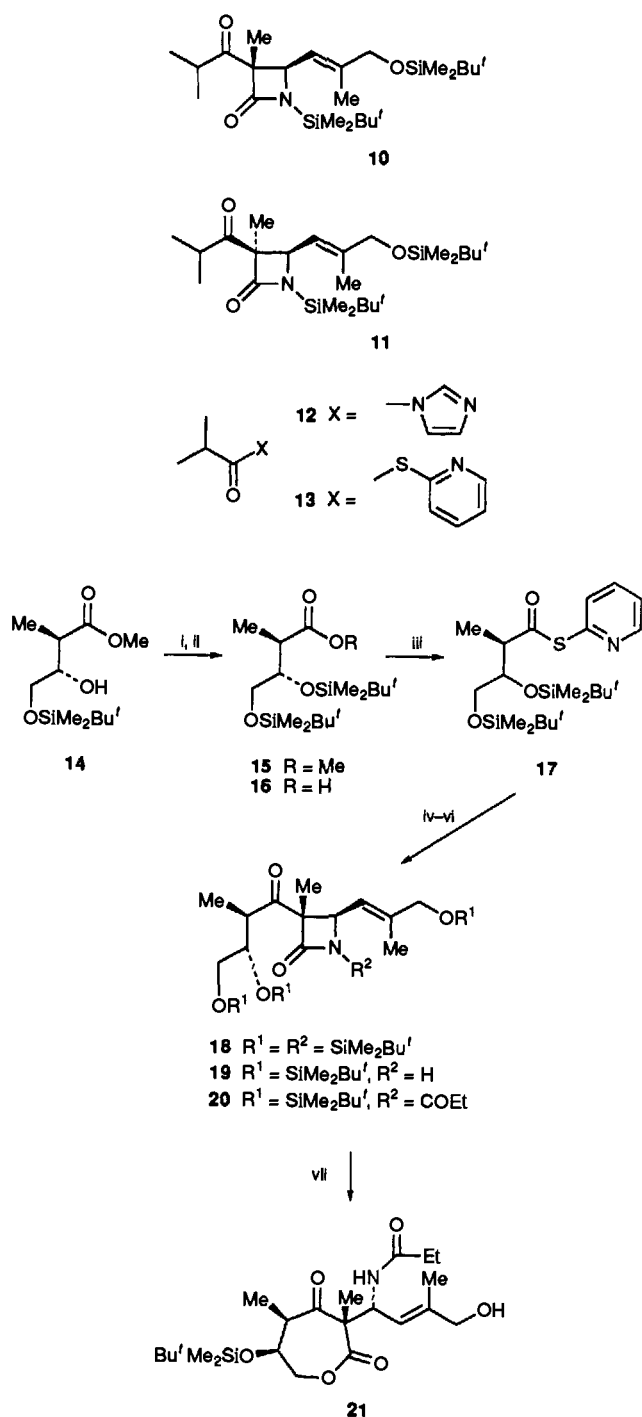
Results and Discussion

The (4*S*)-4-formylazetidinone **2** was prepared from aspartic acid,[7] and condensed with (1-ethoxycarbonylethylidene)triphenylphosphorane to give the αβ-unsaturated ester **3**. Reduction of this to the corresponding alcohol using diisobutylaluminium hydride was accompanied by ring-opening of the azetidinone, but this could be avoided by first removing the *N*-silyl substituent. Reduction then gave the 4-[(1′*E*)-3′-hydroxy-2′-methylprop-1′-enyl]azetidinone **5** (70%) (ee 74%; ^{19}F NMR of its Mosher's derivative **6**). Concomitant *O*- and *N*-silylation gave the fully protected 4-alkenylazetidinone **7** which was alkylated stereoselectively at C(3) to give the (3*R*,4*R*)-azetidinone **8** containing only traces of its (3*R*,4*S*)-diastereoisomer **9**.[8] Previously, the acylation of azetidinones at C(3) had been achieved by carrying out an aldol condensation followed by oxidation of the mixture of alcohols so obtained.[3] Following these procedures, the azetidinone **8** was converted into the (3*S*,4*R*)-3-(2′-methyl-1′-oxopropyl)azetidinone **10** (56%) and its (3*R*,4*R*)-diastereoisomer **11** (14%) by condensation with 2-methylpropanal and oxidation using pyridinium dichromate. However, on further investigation of the direct acylation of the azetidinone **8**, it was found that whereas the acyl imidazolide **12**[9] gave only a low of the ketones **10** and **11** (32%), the thioester **13** was more useful and gave the ketone **10** in a 70% yield.[10]

The 3,4-bis(*tert*-butyldimethylsiloxy)-2-methylbutanethioate **17** was prepared from the monosilylated (2*R*,2*S*)-dihydroxy

ester **14**[3] by silylation of the free hydroxyl group, saponification and condensation with 2-sulfanylpyridine using dicyclohexyl-

2

3 R = SiMe₂Bu^t
4 R = H

iii-v

8

5 R¹ = R² = H
6 R¹ = (*R*)-PhC(CF₃)(OMe)CO, R² = H
7 R¹ = R² = SiMe₂Bu^t

9

Scheme 1 *Reagents:* i, Ph₃P=CMeCO₂Et (85%); ii, DOWEX 50W-X8 (91%); iii, DIBAL-H, hexane, THF (70%); iv, (*R*)-PhC(CF₃)(OMe)COCl (70%); v, Me₂Bu^{t}SiCl (90%); vi, LDA, MeI (97%)

10

11

12 X =

13 X =

14

15 R = Me
16 R = H

17

18 R^1 = R^2 = SiMe$_2$Bu^t
19 R^1 = SiMe$_2$Bu^t, R^2 = H
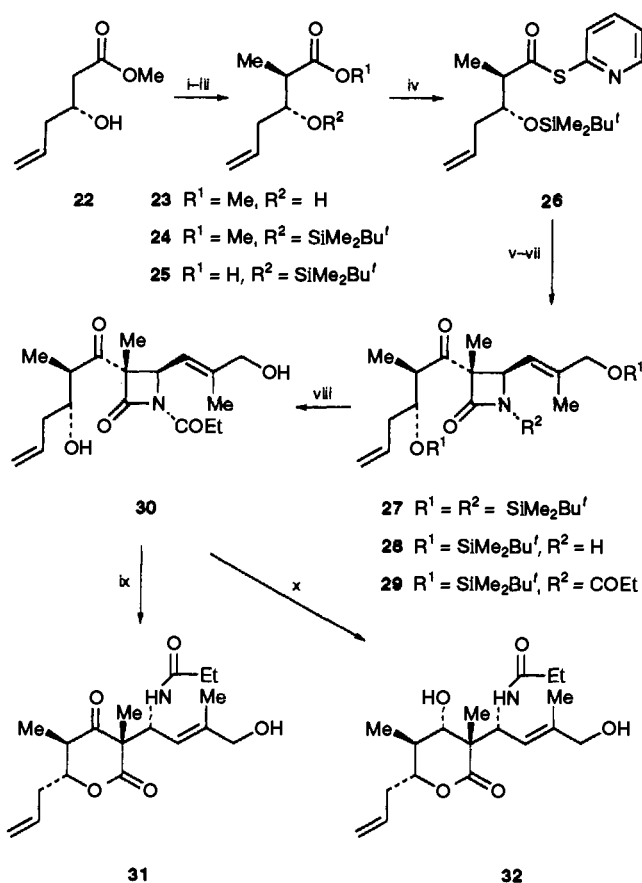**20** R^1 = SiMe$_2$Bu^t, R^2 = COEt

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Scheme 2 *Reagents:* i, Bu^{t}Me$_2$SiCl, imidazole (84%); ii, NaOH, aqueous ethanol (81%); iii, 2-sulfanylpyridine, dicyclohexylcarbodiimide (75%); iv, 8·Li (60%); v, KF, methanol (90%); vi, EtCOCl, 4-(dimethylamino)pyridine, triethylamine (96%); vii, toluene-*p*-sulfonic acid (35%)

carbodiimide. Acylation of the azetidinone **8** using the thioester **17** gave a 60% yield of the ketone **18**, the minor (3*R*)-diastereoisomer not being isolated. Selective *N*-desilylation and acylation gave the 1-propanoylazetidinone **20**. It was hoped that acid-catalysed deprotection of the hydroxyl groups would be followed by β-lactam cleavage to give a δ-lactone analogous to the C(16)–C(3) part of lankacidin C **1**. However, desilylation using toluene-*p*-sulfonic acid under conditions which had been useful for the formation of δ-lactones from acetidinones in

simpler systems,[3] gave rise to the formation of mixtures of products in which the 7-membered lactone **21** appeared to be the major component and was isolated in a 35% yield. This lactone was identified on the basis of spectroscopic data, in particular in its ^{1}H NMR spectrum, the 7-H$_2$ protons were at δ 4.2, *cf.* δ 3.63 in the azetidinone **20**. Other products were isolated which were not fully characterised, but which appeared to be αβ-unsaturated ketones formed by dehydration of the β-hydroxy ketone.

The protected monohydroxy thioester **26** was then used to acylate the azetidinone **8** in order to prepare intermediates in which the terminal double-bond could provide access, *e.g.* by oxidative cleavage, to functionality for further elaboration, without competing formation of 7-membered lactones. The thioester **26** was prepared from methyl (3*R*)-3-hydroxyhex-5-enoate **22**[11] by stereoselective methylation,[12] protection, saponification and condensation with 2-sulfanylpyridine. Acylation of the azetidinone **8** using the thioester **26** gave the (3S)-3-(1''-oxohexenyl)azetidinone **27** (50%) which was converted into the 1-(1-oxopropyl)azetidinone **29** by selective *N*-desilylation and acylation.[2,3] Treatment of this intermediate with boron trifluoride–diethyl ether gave the 3-(3''-hydroxyalkyl)-1-(1-oxopropyl)azetidinone **30** which was isolated and purified by flash chromatography. The stability of this 3-(3''-hydroxyalkyl-1-(1-oxopropyl)azetidinone contrasts with the spontaneous isomerisation to 3-(1'-amidoalkyl)-δ-lactones observed with simpler systems. However, rearrangement of the azetidinone **30** into the δ-lactone **31** was achieved on further
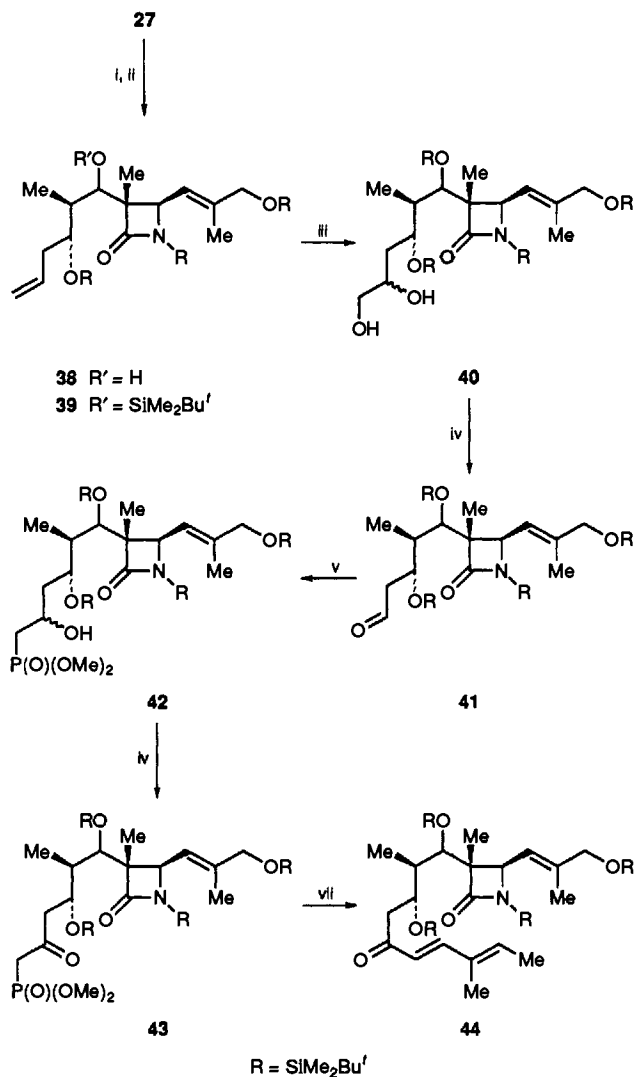
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23 R^1 = Me, R^2 = H
24 R^1 = Me, R^2 = SiMe$_2$Bu^t
25 R^1 = H, R^2 = SiMe$_2$Bu^t

26

30

27 R^1 = R^2 = SiMe$_2$Bu^t
28 R^1 = SiMe$_2$Bu^t, R^2 = H
29 R^1 = SiMe$_2$Bu^t, R^2 = COEt

31

32

Scheme 3 *Reagents:* i, lithium diisopropylamide, *N,N,N',N'*-tetramethylethylenediamine, methyl iodide (80%); ii, Me$_2$Bu^{t}SiCl, imidazole (95%); iii, NaOH, aqueous ethanol; iv, 2-sulfanylpyridine, dicyclohexylcarbodiimide (95% from **24**); v, 8-Li (50%); vi, KF, methanol (97%); vii, EtCOCl, 4-(dimethylamino)pyridine, triethylamine (86%); viii, boron trifluoride–diethyl ether (88%); ix, Merck silica gel 60 (40–63 μm), diethyl ether (75%); x, sodium borohydride, ethanol (70%)
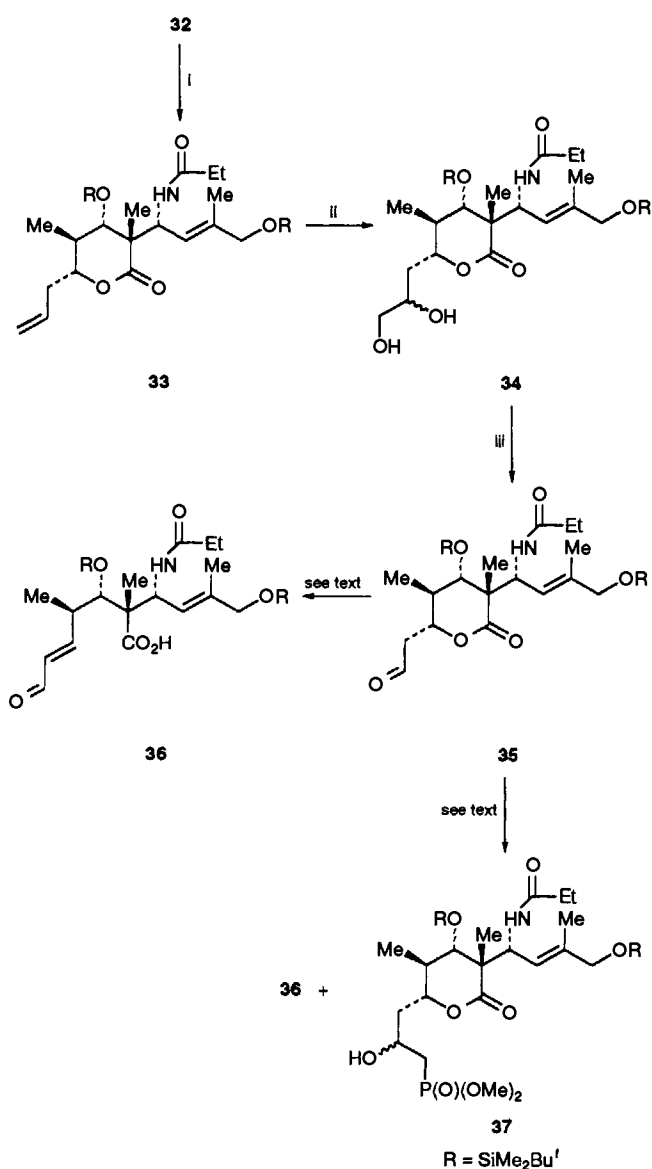
Scheme 4 *Reagents:* i, *tert*-butyldimethylsilyl trifluoromethanesulfonate, imidazole (70%); ii, osmium tetraoxide, pyridine (85%); iii, lead tetraacetate, sodium carbonate, dichloromethane (88%)

R = SiMe₂Buᵗ

Scheme 5 *Reagents:* i, sodium borohydride, lithium bromide, aq. THF (62%); ii, *tert*-butyldimethylsilyl trifluoromethanesulfonate (95%); iii, osmium tetraoxide, pyridine (70%); iv, lead tetraacetate, sodium carbonate (98%); v, LiCH₂P(OMe)₂ (87%); vi, pyridinium dichromate (75%); vii, lithium diisopropyl amide, (E)-2-methylbut-2-enal (75%)

treatment with Merck silica gel 60 (40–63 μm). This δ-lactone corresponds to the C(16)–C(6) fragment of lankacidin C 1,[1] and was the prime objective of this phase of our work, but it was found to be rather unstable, decomposing to give complex mixtures of products when stored at room temperature. Attempts to reduce it to the hydroxy lactone 32 were unsuccessful, mixtures of products again being obtained. However, reduction of the 3-(1″-oxoalkyl)azetidinone 30 using sodium borohydride in ethanol brought about both reduction and rearrangement, and gave the 4-hydroxy-δ-lactone 32 (70%) as a single diastereoisomer. The stereochemistry at C(4) was assigned on the basis of an 11 Hz coupling between 4-H and 5-H in its ¹H NMR spectrum.

Having prepared the δ-lactone 32, which has all the substituents required for a lankacidin synthesis, we decided to investigate the introduction of the C(10)–C(13) diene component. Protection of the hydroxy lactone 32 using *tert*-butyldimethylsilyl triflate gave the bis-silyl ether 33 which was converted into a mixture of the epimeric diols 34 on oxidation using osmium tetraoxide. Oxidative cleavage of this mixture of vicinal diols was carried out using lead tetraacetate and gave

the aldehyde 35, but attempts to purify this were thwarted by an elimination to give the αβ-unsaturated aldehyde 36. This elimination also complicated attempts to convert the aldehyde into the hydroxy phosphonate 37 by the addition of lithiated dimethyl methylphosphonate.

It would appear that the δ-lactone fragment is unstable in the presence of a carbonyl substituent at C(14) (lankacidin numbering), at least in the absence of the conformational limitations introduced by the presence of a macrocycle. It was decided, therefore, to study the introduction of the C(10)–C(13) dienyl fragment into the azetidinone precursors of the δ-lactone. Reduction of the silylated 3-(1″-oxohexenyl)azetidinone 27 gave the hydroxyalkylazetidinone 38 isolated as a single diastereoisomer, although the configuration at the newly introduced chiral centre was not established. Protection as its silyl ether 39 was followed by oxidative cleavage of the terminal double-bond to give the aldehyde 41. Addition of lithiated dimethyl methylphosphonate[13] to this aldehyde gave the hydroxy phosphonate 42 which on oxidation using pyridinium dichromate[14] was converted into the keto phosphonate 43. Condensation of this keto phosphonate with tiglic aldehyde was

achieved by deprotonation using lithium di-isopropylamide as the base followed by addition of the aldehyde. This procedure gave the dienyl ketone **44** in a 75% yield.

The work described in this and the preceding paper[3] provides a basis for a synthesis of the lankacidins. The use of an azetidinone as a template for the introduction of the required stereochemistry at C(3) and C(4), and the conditions required for the conversion of a 3-(3″-hydroxyalkyl)azetidinone into a 3-(1′-amidoalkyl)-δ-lactone have been established together with procedures for the introduction of the C(10)–C(13) dienyl component. Experience has been obtained into the selective manipulation of functional and protecting groups in these compounds, and of the stabilities of possible intermediates. A preliminary study concerned with the synthesis of the 17-membered ring of the lankacidins is now complete,[15] and present work is concerned with the completion of a synthesis of lankacidin C **1**.[16]

Experimental

For general experimental details, see the preceding paper. (4*S*)-1-(*tert*-Butyldimethylsilyl)-4-formylazetidin-2-one **2**, [α]$_D$ −30.2 (*c* 1 in CHCl$_3$), and methyl (3*R*)-3-hydroxyhex-5-enoate **22**, were prepared according to literature procedures.[7,11] A preparation of methyl (2*R*,3*S*)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-methylbutanoate **14** is reported in the preceding paper.[3]

(4S,1′E)-1-(tert-*Butyldimethylsilyl*)-4-(2′-*ethoxycarbonyl-prop*-1′-*enyl*)*azetidin-2-one* **3**.—(Ethoxycarbonylethylidene) triphenylphosphorane (7.25 g, 20.4 mmol) was added to a solution of the 4-formylazetidinone **2** (3.44 g, 16 mmol) in tetrahydrofuran (50 cm^3) and the mixture stirred for 3.5 h at room temperature. Upon concentration under reduced pressure it gave an oil which was purified by chromatography (ethyl acetate–light petroleum, 1:6) to give the *title compound* **3** (4 g, 85%) as an oil, [α]$_D^{20}$ −67 (*c* 0.56 in CHCl$_3$) (Found: M$^+$ − C$_4$H$_9$, 240.1060. C$_{11}$H$_{18}$NO$_3$Si requires *M*, 240.1056); *v*$_{max}$/cm^{-1} 1750, 1710 and 1650: δ$_H$ 0.17 and 0.22 (each 3 H, s, SiCH$_3$), 0.99 [9 H, s, SiC(CH$_3$)$_3$], 1.25 (3 H, t, *J* 7.5, CH$_2$C*H*$_3$), 1.90 (3 H, s, 2′-CH$_3$), 2.85 (1 H, dd, *J* 4, 16, 3-H), 3.40 (1 H, dd, *J* 6, 16, 3-H′), 4.20 (2 H, m, C*H*$_2$CH$_3$), 4.35 (1 H, ddd, *J* 4, 6, 9, 4-H) and 6.80 (1 H, d, *J* 9, 1′-H); *m/z* (EI) 240 (M$^+$ − 57, 70%). 166 (50), 112 (46) and 100 (100).

(4S,1′E)-4-(2′-*Ethoxycarbonylprop*-1′-*enyl*)*azetidin-2-one* **4**.—DOWEX 50W-X8 (0.5 g) was added to a solution of the azetidinone **3** (520 mg, 1.75 mmol) in methanol (10 cm^3) and the mixture stirred for 4.5 h at 20 °C. The DOWEX was filtered off and washed thoroughly with ethyl acetate, and the filtrate concentrated under reduced pressure. Chromatography of the residue (ethyl acetate–light petroleum, 3:1) gave the *title compound* **4** (292 mg, 91%) as a white solid, mp 53 °C (Found: C, 59.0; H, 7.4; N, 7.65. C$_9$H$_{13}$NO$_3$ requires C, 59.0; H, 7.1; N, 7.65%), [α]$_D^{20}$ −39 (*c* 0.67 in CHCl$_3$); *v*$_{max}$(CHCl$_3$)/cm^{-1} 3410, 1758, 1709 and 1652; δ$_H$ 1.28 (3 H, t, *J* 7.5, CH$_2$C*H*$_3$), 1.89 (3 H, s, 2′-CH$_3$), 2.80 (1 H, ddd, *J* 1, 3, 15, 3-H), 3.32 (1 H, ddd, *J* 1, 6, 15, 3-H′), 4.20 (2 H, q, *J* 7.5, C*H*$_2$CH$_3$), 4.46 (1 H, ddd, *J* 3, 6, 9, 4-H), 6.47 (1 H, br s, NH) and 6.72 (1 H, d, *J* 9, 1′-H); *m/z* (CI) 201 (M + 18, 100).

(4S,1′E)-4-(3′-*Hydroxy*-2′-*methylprop*-1′-*enyl*)*azetidin-2-one* **5**.—The ester **4** (6.95 g, 38 mmol) was dissolved in tetrahydrofuran (190 cm^3) and the solution cooled to −78 °C. DIBAL-H (1.0 mol dm^{-3} solution in hexane; 121 cm^3, 121 mmol) was added to the solution which was then allowed to warm to −50 °C, at which temperature it was stirred until TLC showed the complete absence of starting material. Water (35

cm^3) was added to the mixture which was then allowed to attain room temperature. The mixture was filtered and the solid residue was washed thoroughly with ethyl acetate. The filtrate was washed with water (1 × 100 cm^3), and the aqueous phase extracted with ethyl acetate (3 × 100 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel with ethyl acetate–methanol (19:1) as the eluent yielded the *title compound* **5** (3.75 g, 70%) as a white solid, mp 76 °C (Found: MH$^+$, 142.0859; C$_7$H$_{12}$NO$_2$ requires *M*, 142.0868); [α]$_D$ −3.7 (*c* 1.1 in CHCl$_3$); *v*$_{max}$(CHCl$_3$)/cm^{-1} 3282, 1742 and 1679; δ$_H$ 1.68 (3 H, s, 2′-CH$_3$), 2.70 (1 H, ddd, *J* 1, 2, 16, 3-H), 3.25 (1 H, ddd, *J* 1, 5, 16, 3-H′), 4.01 (2 H, s, 3′-H$_2$), 4.33 (1 H, ddd, *J* 2, 5, 9, 4-H), 5.55 (1 H, d, *J* 9, 1′-H) and 6.20 (1 H, br s, NH); *m/z* (CI) 159 (M + 18, 30%) and 142 (MH$^+$, 100).

(*R*)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (50 mm^3*, 0.3 mmol) was added to a solution of the alcohol **5** (30 mg, 0.2 mol) in dichloromethane (0.7 cm^3) and pyridine (0.2 cm^3, 2.5 mmol) and the resulting mixture was stirred overnight. After this, water (1 cm^3) was added to the mixture and the organic phase was separated from the aqueous phase and the latter was extracted with ether (3 × 1 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel gave the Mosher's derivative **6** (50 mg, 70%) as a colourless oil, [α]$_D$ −41.5 (*c* 1.3 in CHCl$_3$); δ$_H$(major isomer) 1.70 (3 H, s, 2′-CH$_3$), 2.69 (1 H, ddd, *J* 1, 2, 15, 3-H), 3.25 (1 H, ddd, *J* 1, 5, 15, 3-H′), 3.60 (3 H, s, OCH$_3$), 4.41 (1 H, ddd, *J* 2, 5, 9, 4-H), 4.64 (1 H, d, *J* 13, 3′-H), 4.79 (1 H, d, *J* 13, 3′-H′), 5.51 (1 H, d, *J* 9, 1′-H), 6.15 (1 H, br s, NH), 7.42 (3 H, m, ArH) and 7.52 (2 H, m, ArH); *m/z* (CI) 375 (M + 18, 100%).

(4S,1′E)-1-(tert-*Butyldimethylsilyl*)-4-(3′-tert-*butyldimethyl-silyloxy*-2′-*methylprop*-1′-*enyl*)*azetidin-2-one* **7**.—The alcohol **5** (3.6 g, 25.5 mmol) was dissolved in *N*,*N*-dimethylformamide (230 cm^3) and the solution was cooled to 0 °C. Triethylamine (8 cm^3, 57 mmol) was then added to it followed by *tert*-butyldimethylsilyl chloride (8.6 g, 57 mmol). The reaction mixture was stirred for 16 h at room temperature after which it was diluted with ether (200 cm^3) and washed with water (2 × 200 cm^3). The aqueous phase was extracted with ether (3 × 100 cm^3) and the combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1:6) as the eluent yielded the *title compound* **7** (8.4 g, 90%) as a white solid, mp 48 °C (Found: C, 61.8; H, 11.1; N, 3.75%; M$^+$ − C$_4$H$_9$, 312.1811. C$_{19}$H$_{39}$NO$_2$Si$_2$ requires C, 61.75; H, 10.65; N, 3.8%; C$_{15}$H$_{30}$NO$_2$Si requires *M*, 312.1815); [α]$_D$ −39 (*c* 0.3 in CHCl$_3$); *v*$_{max}$/cm^{-1} 1747 and 1679; δ$_H$ 0.05 (6 H, s, 2 × SiCH$_3$), 0.18 and 0.20 (each 3 H, s, SiCH$_3$), 0.90 and 0.95 [each 9 H, s, SiC(CH$_3$)$_3$], 1.66 (3 H, s, 2′-CH$_3$), 2.72 (1 H, dd, *J* 4, 16, 3-H), 3.30 (1 H, dd, *J* 5.5, 16, 3-H′), 4.00 (2 H, s, 3′-H$_2$), 4.32 (1 H, ddd, *J* 4, 5.5, 9, 4-H) and 5.52 (1 H, d, *J* 9, 1′-H); *m/z* (CI) 370 (MH$^+$, 100%).

(3R,4R,1′E)-1-(tert-*Butyldimethylsilyl*)-4-(3′-tert-*butyldi-methylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-*methylazetidin-2-one* **8**.—To a stirred solution of diisopropylamine (3.2 cm^3, 22.8 mmol) in THF (40 cm^3) at 0 °C was added butyllithium (1.55 mol dm^{-3} solution in hexane; 14.8 cm^3, 22.9 mmol); the solution was stirred at 0 °C for 15 min before being cooled to −78 °C. The azetidinone **7** (8.4 g, 22.8 mmol) in THF (23 cm^3) was added dropwise to the solution which was then stirred for a further 30 min at −78 °C. Methyl iodide (6.9 cm^3, 110 mmol) was added to the mixture which was then stirred for 2 h at

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* 1 mm^3 = 1 μl.

−78 °C before being allowed to warm to room temperature. Saturated aqueous ammonium chloride (100 cm^3) was added to the mixture after which the organic phase was separated from the aqueous phase and the latter was extracted with ether (3 × 100 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel with ether–light petroleum (1 : 6) as the eluent yielded the *title compound* **8** (8.5 g, 97%) as a white solid, mp 35 °C (Found: M$^+$ − C$_4$H$_9$, 326.1971. C$_{16}$H$_{32}$NO$_2$Si$_2$ requires *M*, 326.1972); [α]$_D$ −4.7 (*c* 1.7 in CHCl$_3$); ν$_{max}$/cm^{-1} 1735 and 1675; δ$_H$ 0.05 (6 H, s, 2 × SiCH$_3$), 0.15 and 0.20 (each 3 H, s, SiCH$_3$), 0.90 and 0.95 [each 9 H, s, SiC(CH$_3$)$_3$], 1.30 (3 H, d, *J* 7.5, 3-CH$_3$), 1.65 (3 H, s, 2′-CH$_3$), 2.88 (1 H, dq, *J* 2.5, 7.5, 3-H), 3.91 (1 H, dd, *J* 2.5, 9, 4-H), 4.02 (2 H, s, 3′-H$_2$) and 5.52 (1 H, d, *J* 9, 1′-H); *m/z* (EI) 368 (20%), 326 (M$^+$ − C$_4$H$_9$, 30) and 75 (100).

(3S,4R,1′E)-1-(tert-*Butyldimethylsilyl*)-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-*methyl*-3-(2″-*methyl*-1″-*oxopropyl*)*azetidine*-2-*one* **10** *and* (3R,4R,1′E)-1-(tert-*Butyldimethylsilyl*)-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-*methyl*-3-(2″-*methyl*-1″-*oxopropyl*)*azetidin*-2-*one* **11**.— *From* 2-*methylpropanal followed by oxidation.* To a solution of diethylamine (21 mm^3, 0.2 mmol) in THF (1 cm^3) at 0 °C was added butyllithium (1.6 mol dm^{-3} solution in hexane; 0.14 cm^3, 0.22 mmol). The solution was stirred at 0 °C for 15 min before being cooled to −78 °C; the azetidinone **8** (50 mg, 0.13 mmol) in THF (1 cm^3) was then added to it. The solution was stirred for a further 30 min at −78 °C before 2-methylpropanal (21 mm^3, 0.23 mmol) in THF (0.2 cm^3) was added to it and stirring continued for a further 4 h. The mixture was allowed to warm to room temperature after which saturated aqueous ammonium chloride (1 cm^3) was added to it. The organic phase was separated from the aqueous phase and the latter was extracted with ether (3 × 2 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. A solution of this crude aldol product in dichloromethane (2 cm^3) was added to a stirred suspension of pyridinium dichromate (147 mg, 0.4 mmol) and flame-dried, powdered 3 Å molecular sieves (150 mg) in dichloromethane (1 cm^3). The mixture was then stirred for 4 h at room temperature before dilution with ether (5 cm^3) and filtration. The solid residue was washed thoroughly with ether and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 15) as the eluent yielded the *ketone* **10** (33 mg, 56%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 396.2391. C$_{20}$H$_{38}$NO$_3$Si$_2$ requires *M*, 396.2390); [α]$_D$ −40.8 (*c* 1.25 in CHCl$_3$); ν$_{max}$/cm^{-1} 1745, 1707 and 1678; δ$_H$ 0.05 (6 H, s, 2 × SiCH$_3$), 0.15 and 0.22 (each 3 H, s, SiCH$_3$), 0.90 and 0.94 [each 9 H, s, SiC(CH$_3$)$_3$], 1.08 and 1.12 (each 3 H, d, *J* 6, C*H*$_3$CH), 1.30 (3 H, s, 3-CH$_3$), 1.68 (3 H, s, 2′-CH$_3$), 3.20 [1 H, hept, *J* 6, (CH$_3$)$_2$C*H*], 4.01 (2 H, s, 3′-H$_2$), 4.70 (1 H, d, *J* 10, 4-H) and 5.45 (1 H, d, *J* 10, 1′-H); *m/z* (EI) 396 (M$^+$ − 57, 30%); and *ketone* **11** (8 mg, 14%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 396.2382. C$_{20}$H$_{38}$NO$_3$Si$_2$ requires *M*, 396.2390); [α]$_D$ + 42.4 (*c* 0.16 in CHCl$_3$); ν$_{max}$/cm^{-1} 1745, 1710 and 1592; δ$_H$ −0.05 and 0.15 (each 6 H, s, 2 × SiCH$_3$), 0.91 and 0.98 [each 9 H, s, SiC(CH$_3$)$_3$], 1.13 and 1.20 (each 3 H, d, *J* 6.5, C*H*$_3$CH), 1.30 (3 H, s, 3-CH$_3$), 1.52 (3 H, s, 2′-CH$_3$), 3.11 [1 H, hept, *J* 6.5, (CH$_3$)$_2$C*H*], 3.71 (2 H, m, 3′-H$_2$), 3.97 (1 H, d, *J* 9.5, 4-H) and 5.59 (1 H, d, *J* 9.5, 1′-H); *m/z* (EI) 396 (M$^+$ − 57, 0.1%) and 277 (100).

From the thioester **13**. A solution of diethylamine (32 mm^3, 0.31 mmol) in tetrahydrofuran (THF) (0.5 cm^3) was cooled to 0 °C and butyllithium (1.6 mol dm^{-3} solution in hexane; 0.19 cm^3, 0.30 mmol) was added to it. The solution was then stirred for 15 min at 0 °C after which it was cooled to −78 °C. The β-lactam **8** (105 mg, 0.27 mmol) in THF (0.5 cm^3) was added to

the cooled solution which was then stirred for a further 30 min at −78 °C before addition of the thioester **13** (55 mg, 0.30 mmol) in THF (0.5 cm^3). The mixture was stirred for a further 5 min at −78 °C after which it was allowed to warm to room temperature when saturated ammonium chloride (1 cm^3) was added to it. The organic phase was separated from the aqueous phase and the latter was extracted with ether (3 × 2 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel with ether–light petroleum (1 : 15) as the eluent yielded the ketone **10** (85 mg, 70%).

2-*Pyridyl* 2-*Methylpropanethioate* **13**.—2-Sulfanylpyridine 0.5 g, 4.54 mmol) was added to 2-methylpropanoic acid (0.4 g, 4.54 mmol) and dicyclohexylcarbodiimide (1.2 g, 5.8 mmol) dissolved in ethyl acetate (15 cm^3) and the mixture was stirred overnight at room temperature. The solution was filtered and the filtrate washed with water (1 × 15 cm^3); the aqueous phase was then extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure to provide the thioester **13** as a yellow oil used without further purification; δ$_H$ 1.28 [6 H, d, *J* 6, (C*H*$_3$)$_2$CH], 2.90 (1 H, hept, *J* 6, (CH$_3$)$_2$C*H*), 7.29 (1 H, m, 5-H), 7.61 (1 H, d, *J* 8, 3-H), 7.75 (1 H, dt, *J* 1, 9, 4-H) and 8.62 (1 H, d, *J* 4, 6-H).

(2R,3S)-*Methyl* 3,4-*Di*(tert-*butyldimethylsilyloxy*)-2-*methylbutanoate* **15**.—The ester **14** (1.1 g, 4.4 mmol) was dissolved in *N,N*-dimethylformamide (11 cm^3) and the solution was cooled to 0 °C. Imidazole (0.77 g, 11.3 mmol) was then added to it followed by *tert*-butyldimethylsilyl chloride (0.9 g, 6 mmol). The solution was stirred overnight at room temperature after which it was diluted with ether (10 cm^3) and washed with water (1 × 10 cm^3). The aqueous phase was extracted with ether (3 × 10 cm^3) and the combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 20) as the eluent yielded the *title compound* **15** (1.4 g, 84%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 319.1761. C$_{14}$H$_{31}$O$_4$Si$_2$ requires *M*, 319.1756); [α]$_D$ −28.2 (*c* 1.1 in CHCl$_3$); ν$_{max}$/cm^{-1} 1730; δ$_H$ 0.05 (12 H, s, 4 × SiCH$_3$), 0.81 and 0.89 [each 9 H, s, SiC(CH$_3$)$_3$], 1.13 (3 H, d, *J* 7, 2-CH$_3$), 2.74 (1 H, quin, *J* 7, 2-H), 3.57 (2 H, m, 4-H$_2$), 3.68 (3 H, s, CO$_2$CH$_3$) and 3.92 (1 H, q, *J* 7, 3-H); *m/z* (EI) 319 (M$^+$ − 57, 45%).

(2R,3S)-2-*Pyridyl* 3,4-*Di*(tert-*butyldimethylsilyloxy*)-2-*methylbutanethioate* **17**.—The ester **15** (200 mg, 0.53 mmol) was dissolved in a solution of sodium hydroxide (100 mg, 2.75 mmol) in ethanol (3 cm^3) and water (0.4 cm^3) and the mixture was left overnight at room temperature. The solution was acidified with 3 mol dm^{-3} aqueous hydrochloric acid to pH 7 and extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure to provide the crude acid **16** (154 mg, 81%) as a yellow oil (Found: M$^+$ − C$_4$H$_9$, 305.1597. C$_{13}$H$_{29}$O$_4$Si$_2$ requires *M*, 305.1604); [α]$_D$ −10.8 (*c* 0.34 in CHCl$_3$); ν$_{max}$/cm^{-1} 3170 and 1712; δ$_H$ 0.05 and 0.10 (each 6 H, s, 2 × SiCH$_3$), 0.89 [18 H, s, 2 × SiC(CH$_3$)$_3$], 1.20 (3 H, d, *J* 7, 2-CH$_3$), 2.75 (1 H, m, 2-H), 3.61 (2 H, d, *J* 5, 4-H$_2$) and 3.92 (1 H, q, *J* 5, 3-H); *m/z* (CI) 363 (MH$^+$, 100%), 345 (M$^+$ − 17, 96) and 305 (M$^+$ − 57, 48).

The acid **16** (500 mg, 1.4 mmol) and dicyclohexylcarbodiimide (360 mg, 1.7 mmol) were dissolved in ethyl acetate (3 cm^3) and 2-sulfanylpyridine (325 mg, 2.9 mmol) was added to the mixture which was then stirred overnight. After this the mixture was filtered and the filtrate washed with water (1 × 3 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 2 cm^3) and the combined organic extracts were dried (MgSO$_4$) and

concentrated under reduced pressure. Chromatography of the residue on silica gel using ether–light petroleum (1 : 10) as the eluent yielded the *title compound* **17** (470 mg, 75%) as a yellow oil (Found: M^+ − C_4H_9, 398.1646. $C_{18}H_{32}NO_3SSi_2$ requires M, 398.1641); $[\alpha]_D$ − 57.8 (*c* 0.8 in $CHCl_3$); ν_{max}/cm^{-1} 1702, 1650, 1576 and 1565; δ_H 0.05 (12 H, s, 4 × $SiCH_3$), 0.88 [18 H, s, 2 × $SiC(CH_3)_3$], 1.25 (3 H, d, *J* 7, 2-CH_3), 3.09 (1 H, quin, *J* 7, 2-H), 3.64 (2 H, m, 4-H_2), 4.00 (1 H, q, *J* 7, 3-H), 7.25 (1 H, t, *J* 6, 5'-H), 7.63 (1 H, d, *J* 6, 3'-H), 7.75 (1 H, t, *J* 6, 4'-H) and 8.61 (1 H, d, *J* 6, 6'-H); *m/z* (EI) 398 (M^+ − 57, 21%) and 73 (100).

(3S,4R,1'E,2''R,3''S)-1-(tert-*Butyldimethylsilyl*)-4-(3'-tert-*butyldimethylsilyloxy*-2'-*methylprop*-1'-*enyl*)-3-[3'',4''-*di*(tert-*butyldimethylsilyloxy*)-2''-*methyl*-1''-*oxobutyl*]-3-*methylazeti-din*-2-*one* **18**.—A solution of diethylamine (31 mm³, 0.3 mmol) in THF (0.5 cm³) was cooled to 0 °C and butyllithium (1.6 mol dm⁻³ solution in hexane; 0.19 cm³, 0.3 mmol) was added to the solution. The mixture was stirred for 15 min at 0 °C after which it was cooled to −78 °C and the β-lactam **8** (100 mg, 0.29 mmol) in THF (0.5 cm³) added to it. The solution was stirred for a further 30 min at −78 °C after which the thioester **17** (122 mg, 0.27 mmol) in THF (0.5 cm³) was added to it and stirring continued for a further 2 h at −78 °C. The mixture was allowed to warm to room temperature when saturated aqueous ammonium chloride (1 cm³) was added to it. The organic phase was separated from the aqueous phase and the latter was extracted with ether (3 × 2 cm³). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 15) as the eluent yielded the *title compound* **18** (115 mg, 60%) as a colourless oil (Found: M^+ − C_4H_9, 670.4175. $C_{33}H_{68}NO_5Si_4$ requires M, 670.4183); $[\alpha]_D$ − 56.9 (*c* 0.65 in $CHCl_3$); ν_{max}/cm^{-1} 1735 and 1703; δ_H −0.09 (3 H, s, $SiCH_3$), 0.05 (15 H, s, 5 × $SiCH_3$), 0.10 and 0.21 (each 3 H, s, $SiCH_3$), 0.80 [9 H, s, $SiC(CH_3)_3$], 0.90 [27 H, br s, 3 × $SiC(CH_3)_3$], 0.99 (3 H, d, *J* 7, 2''-CH_3), 1.36 (3 H, s, 3-CH_3), 1.69 (3 H, s, 2'-CH_3), 3.44 (1 H, quin, *J* 7, 2''-H), 3.75 (2 H, m, 4''-H_2), 3.90 (1 H, td, *J* 4, 7, 3''-H), 4.01 (2 H, s, 3'-H_2), 4.90 (1 H, d, *J* 10, 4-H) and 5.43 (1 H, d, *J* 10, 1'-H); *m/z* (EI), 712 (35%), 670 (M^+ − 57, 14%) and 73 (100).

(3S,4R,1'E,2''R,3''S)-4-(3'-tert-*Butyldimethylsilyloxy*-2'-*methylprop*-1'-*enyl*)-3-[3'',4''-*di*(tert-*butyldimethylsilyloxy*)-2''-*methyl*-1''-*oxobutyl*]-3-*methylazetidin*-2-*one* **19**.—The β-lactam **18** (45 mg, 0.062 mmol) was dissolved in methanol (0.3 cm³) and the solution was cooled to 0 °C. Anhydrous potassium fluoride (4.3 mg, 0.074 mmol) in methanol (0.1 cm³) was added to the solution which was then stirred at 0 °C for 45 min. After this, saturated aqueous ammonium chloride (1 cm³) was added to the reaction mixture and the organic phase was separated from the aqueous phase; the latter was then extracted with ether (3 × 2 cm³). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel with ether–light petroleum (1 : 3) as the eluent gave the *title compound* **19** (34 mg, 90%) as a colourless oil (Found: M^+, 613.4002; $C_{31}H_{63}NO_5Si_3$ requires M, 613.4014); $[\alpha]_D$ − 19.1 (*c* 0.2 in $CHCl_3$); ν_{max}/cm^{-1} 3259, 1762 and 1707; δ_H 0.05 (18 H, s, 6 × $SiCH_3$) 0.81 [9 H, s, $SiC(CH_3)_3$], 0.88 [18 H, s, 2 × $SiC(CH_3)_3$], 1.01 (3 H, d, *J* 7.5, 2''-CH_3), 1.34 (3 H, s, 3-CH_3), 1.71 (3 H, s, 2'-CH_3), 3.44 (1 H, quin, *J* 7.5, 2''-H), 3.65 (2 H, m, 4''-H_2), 3.92 (1 H, td, *J* 4, 7.5, 3''-H), 4.02 (2 H, s, 3'-H_2), 4.90 (1 H, d, *J* 9, 4-H), 5.45 (1 H, d, *J* 9, 1'-H) and 5.88 (1 H, br s, NH); *m/z* (EI) 613 (M^+, 10%) and 513 (100).

(3S,4R,1'E,2''R,3''S)-4-(3'-*Butyldimethylsilyloxy*-2'-*methylprop*-1'-*enyl*)-3-[3'',4''-*di*(tert-*butyldimethylsilyloxy*)-2''-*methyl*-1''-*oxobutyl*]-3-*methyl*-1-*propanoylazetidin*-2-*one* **20**.—

The β-lactam **19** (160 mg, 0.26 mmol) was dissolved in dichloromethane (2.5 cm³) and the solution was cooled to 0 °C. Triethylamine (73 mm³, 0.52 mmol), 4-dimethylaminopyridine (40 mg, 0.33 mmol) and propionyl chloride (40 mm³, 0.46 mmol) were added to the mixture which was then stirred at room temperature overnight. After this the mixture was diluted with water (5 cm³) and the aqueous phase was separated from the organic phase; the former was extracted with ether (3 × 5 cm³). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 10) as the eluent yielded the *title compound* **20** (168 mg, 96%) as a colourless oil (Found: M^+ − C_4H_9, 612.3580. $C_{30}H_{58}NO_6Si_3$ requires M, 612.3572); $[\alpha]_D$ − 73.3 (*c* 0.3 in $CHCl_3$); ν_{max}/cm^{-1} 1783 and 1716; δ_H −0.10 (3 H, s, $SiCH_3$), 0.05 (15 H, s, 5 × $SiCH_3$), 0.80 [9 H, s, $SiC(CH_3)_3$], 0.88 [18 H, s, 2 × $SiC(CH_3)_3$], 1.00 (3 H, d, *J* 7.5, 2''-CH_3), 1.11 (3 H, t, *J* 7.5, CH_3CH_2), 1.42 (3 H, s, 3-CH_3), 1.78 (3 H, s, 2'-CH_3), 2.65 (2 H, q, *J* 7.5, CH_3CH_2), 3.40 (1 H, quin, *J* 7.5, 2''-H), 3.63 (2 H, m, 4''-H_2), 3.91 (1 H, td, *J* 2, 7.5, 3''-H), 4.05 (2 H, s, 3'-H_2), 5.21 (1 H, d, *J* 9, 4-H) and 5.38 (1 H, d, *J* 9, 1'-H); *m/z* (EI) 612 (M^+ − 57, 30%), 513 (61) and 73 (100).

(3S,5R,6S,1'R,2'E)-6-(tert-*Butyldimethylsilyloxy*)-3,5-*di-methyl*-3-(1'-*ethylcarbonylamino*-4'-*hydroxy*-3'-*methylbut*-2'-*enyl*)-4-*oxohexan*-6-*olide* **21**.—To a solution of the imide **20** (20 mg, 0.03 mmol) in aqueous THF (0.25 cm³ of THF–water, 20 : 1) was added toluene-*p*-sulfonic acid (2 mg, 0.011 mmol) and the reaction mixture was stirred for 48 h. After this, calcium hydroxide (6 mg, 0.08 mmol) was added to the reaction mixture and the suspension was stirred for a further hour. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica gel with ether as the eluent yielded the *title compound* **21** (4.5 mg, 35%) (Found: M^+, 441.2548. $C_{22}H_{39}NO_6Si$ requires M, 441.2546); ν_{max}/cm^{-1} 3430, 1748, 1712 and 1675; δ_H 0.03 and 0.09 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.10 (6 H, m, CH_3CH_2 and 5-CH_3), 1.41 (3 H, s, 3-CH_3), 1.79 (3 H, s, 3'-CH_3), 2.15 (2 H, m, CH_3CH_2), 3.03 (1 H, quin, *J* 7, 5-H), 3.81 (1 H, m, 6-H), 4.01 (2 H, s, 4'-H_2), 4.10–4.35 (2 H, m, 7-H_2), 5.28 (1 H, d, *J* 10, 2'-H), 5.38 (1 H, t, *J* 10, 1'-H) and 5.86 (1 H, d, *J* 10, NH); *m/z* (CI) 442 (MH⁺, 7%) and 304 (100).

(2R,3R)-*Methyl* 3-*Hydroxy*-2-*methylhex*-5-*enoate* **23**.— Butyllithium (1.6 mol dm⁻³ solution in hexane; 128 cm³, 0.2 mol) was added to a stirred solution of diisopropylamine (30 cm³, 0.214 mol) in THF (220 cm³) and the solution stirred for 15 min at 0 °C. The mixture was then cooled to −50 °C, and the hydroxy ester **22** (12.5 g, 86.9 mmol) in THF (30 cm³) was added to it. The mixture was allowed to warm to −10 °C and was then cooled to −60 °C when *N,N,N',N'*-tetramethylethyl-enediamine (14.5 cm³, 96 mmol) was added to it; after the solution had been stirred for 10 min methyl iodide (8 cm³, 107 mmol) was also added to it. After being stirred for 4 h at −70 °C, the mixture was allowed to warm to room temperature when saturated aqueous ammonium chloride was added to it. The mixture was then extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure and chromatography of the residue on silica gel with diethyl ether–light petroleum as the eluent yielded the *title compound* **23** (11 g, 80%) as a colourless oil (Found: MH⁺, 159.1015. $C_8H_{15}O_3$ requires M, 159.1021); $[\alpha]_D$ − 7.4 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 3459, 1737 and 1642; δ_H 1.15 (3 H, d, *J* 7.5, 2-CH_3), 2.08–2.39 (2 H, m, 4-H_2), 2.55 (1 H, quin., *J* 7.5, 2-H), 3.64 (3 H, s, CO_2CH_3), 3.72 (1 H, m, 3-H), 5.08–5.15 (2 H, m, 6-H_2) and 5.81 (1 H, m, 5-H); *m/z* (CI) 159 (MH⁺, 100%).

(2R,3R)-*Methyl* 3-tert-*Butyldimethylsilyloxy*-2-*methylhex*-5-

enoate **24**.—Following the procedure outlined above for the preparation of silyl ether **15** using *tert*-butyldimethylsilyl chloride, the alcohol **23** 0.41 g, 2.6 mmol) gave the *title compound* **24** (0.67 g, 95%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 215.1105. C$_{10}$H$_{19}$O$_3$Si requires *M*, 215.3438); [α]$_D$ −25 (*c* 0.55 in CHCl$_3$); ν_{max}/cm^{-1} 1747 and 1642; δ_H 0.02 and 0.06 (each 3 H, s, SiCH$_3$), 0.85 [9 H, s, SiC(CH$_3$)$_3$], 1.09 (3 H, d, *J* 7.5, 2-CH$_3$), 2.25 (2 H, m, 4-H$_2$), 2.62 (1 H, quin, *J* 7.5, 2-H), 3.66 (3 H. s, CO$_2$CH$_3$), 3.95 (1 H, m, 3-H), 5.05–5.12 (2 H, m, 6-H$_2$) and 5.85 (1 H, m, 5-H); *m/z* (EI), 231 (M$^+$ − 41, 14%) and 215 (M$^+$ − 57, 44).

(2R,3R)-2-*Pyridyl* 3-tert-*Butyldimethylsilyloxy-2-methylhex-5-enethioate* **26**.—Following the procedure outlined above for the preparation of the acid **16**, the ester **24** (5.48 g, 20.2 mmol) gave the crude acid **25** (5.22 g, 100%) as a yellow oil, ν_{max}/cm^{-1} 3078, 1695 and 1624; δ_H 0.02 and 0.05 (each 3 H, s, SiCH$_3$), 0.88 [12 H, s, SiC(CH$_3$)$_3$ and 2-CH$_3$], 2.12–2.32 (2 H, m, 4-H$_2$), 2.62 (1 H, m, 2-H), 4.00 (1 H, m, 3-H), 4.96–5.12 (2 H, m, 6-H$_2$) and 5.70–5.88 (1 H, m, 5-H); *m/z* (EI) 224 (10%) and 201 (M$^+$ − 57, 16).

Following the procedure outlined above for the preparation of the thioester **17**, the acid **25** (1.98 g, 7.67 mmol) gave the title *compound* **26** (2.57 g, 95%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 294.0979. C$_{14}$H$_{20}$NO$_2$SSi requires *M*, 294.0984); [α]$_D$ −60.5 (*c* 0.55 in CHCl$_3$); ν_{max}/cm^{-1} 1704 and 1573; δ_H 0.05 (6 H, s, 2 × SiCH$_3$), 0.88 [9 H, s, SiC(CH$_3$)$_3$], 1.17 (3 H, d, *J* 7.5, 2-CH$_3$), 2.19–2.40 (2 H, m, 4-H$_2$), 2.95 (1 H, quin., *J* 7.5, 2-H), 4.10 (1 H, m, 3-H) 5.03–5.12 (2 H, m, 6-H$_2$), 5.87 (1 H, m, 5-H), 7.25 (1 H, m, 5'-H), 7.64 (1 H, m, 3'-H), 7.75 (1 H, m, 4'-H) and 8.60 (1 H, m, 6'-H); *m/z* (EI) 294 (M$^+$ − 57, 66%).

(3S,4R,2'R,3'R,1''E)-1-tert-*Butyldimethylsilyl-3-(3'-tert-butyldimethylsilyloxy-2'-methyl-1'-oxohex-5'-enyl)-4-(3''-tert-butyldimethylsilyloxy-2''-methylprop-1''-enyl)-3-methylazetidin-2-one* **27**.—Following the procedure outlined above for the preparation of the 3-(1'-oxoalkyl)azetidinone **18**, the thioester **26** (0.98 g, 2.8 mmol) gave, after chromatography using ether–light petroleum (1 : 12) as eluent, the *title compound* **27** (0.85 g, 50%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 566.3527. C$_{29}$H$_{56}$NO$_4$Si$_3$ requires *M*, 566.3517); [α]$_D$ −90 (*c* 0.9 in CHCl$_3$); ν_{max}/cm^{-1} 1745 and 1706; δ_H −0.10 (3 H, s, SiCH$_3$), 0.05 (9 H, s, 3 × SiCH$_3$), 0.13 and 0.20 (each 3 H, s, SiCH$_3$), 0.82 [9 H, s, SiC(CH$_3$)$_3$], 0.92 [21 H, 2 × SiC(CH$_3$)$_3$ and 2'-CH$_3$], 1.33 (3 H, s, 3-CH$_3$), 1.69 (3 H, s, 2''-CH$_3$), 2.15–2.43 (2 H, m, 4'-H$_2$), 3.30 (1 H, m, 2'-H), 4.00 (3 H, m, 3'-H and 3''-H$_2$), 4.88 (1 H, d, *J* 9, 4-H), 5.05–5.13 (2 H, m, 6'-H$_2$), 5.42 (1 H, d, *J* 9, 1''-H) and 5.92 (1 H, m, 5'-H); *m/z* (EI) 566 (M$^+$ − 57, 33%), 469 (32), 468 (44), 467 (100), 466 (49) and 409 (86).

(3S,4R,2'R,3'R,1''E)-3-(3'-tert-*Butyldimethylsilyloxy-2'-methyl-1'-oxohex-5'-enyl)-4-(3''-tert-butyldimethylsilyloxy-2''-methylprop-1''-enyl)-3-methylazetidin-2-one* **28**.—Following the procedure outlined above for the synthesis of the azetidinone **19**, the azetidinone **27** (196 mg, 0.3 mmol), after chromatography on silica gel using ether–light petroleum (1 : 2) as the eluent gave the *title compound* **28** (145 mg, 97%) as a colourless oil (Found: M$^+$, 509.3362. C$_{27}$H$_{51}$NO$_4$Si$_2$ requires *M*, 509.3356); [α]$_D$ −87 (*c* 0.4 in CHCl$_3$); ν_{max}/cm^{-1} 3272, 1762 and 1707; δ_H −0.08 (3 H, s, SiCH$_3$), 0.05 (9 H, s, 3 × SiCH$_3$), 0.82 and 0.92 [each 9 H, s, SiC(CH$_3$)$_3$], 0.96 (3 H. d, *J* 7.5, 2'-CH$_3$), 1.35 (3 H, s, 3-CH$_3$), 1.68 (3 H, s, 2''-CH$_3$), 2.20–2.41 (2 H, m, 4'-H$_2$), 3.28 (1 H, m, 2'-H), 4.00 (3 H, m, 3'-H and 3''-H$_2$), 4.90 (1 H, d, *J* 9, 4-H), 5.05–5.15 (2 H, m, 6'-H$_2$), 5.43 (1 H, d, *J* 9, 1''-H), 5.75 (1 H, s, NH) and 5.91 (1 H, m, 5'-H); *m/z* (EI), 509 (M$^+$, 0.8%), 452 (M$^+$ − 57, 20), 411 (34), 410 (36) and 409 (100).

(3S,4R,2'R,3'R,1''E)-3-(3'-tert-*Butyldimethylsilyloxy-2'-methyl-1'-oxohex-5'-enyl)-4-(3''-tert-butyldimethyl-2''-methylprop-1''-enyl)-3-methyl-1-oxopropylazetidin-2-one* **29**.—Following the procedure outlined above for the synthesis of the *N*-acylazetidinone **20**, the azetidinone **28** (146 mg, 0.29 mmol), after chromatography on silica gel with ether–light petroleum (1 : 6) as the eluent gave the *title compound* **29** (141 mg, 86%) as a colourless oil (Found: M$^+$ − C$_4$H$_9$, 508.2908. C$_{26}$H$_{46}$NO$_5$Si$_2$ requires *M*, 508.2914); [α]$_D$ −98 (*c* 0.37 in CHCl$_3$); ν_{max}/cm^{-1} 1782, 1720 and 1641; δ_H −0.10 (3 H, s, SiCH$_3$), 0.05 (9 H, s, 3 × SiCH$_3$), 0.82 and 0.90 [each 9 H, s, SiC(CH$_3$)$_3$], 0.92 (3 H. d, *J* 7.5, 2'-CH$_3$), 1.15 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.42 (3 H, s, 3-CH$_3$), 1.80 (3 H, s, 2''-CH$_3$), 2.23–2.45 (2 H, m, 4'-H$_2$), 2.67 (2 H, q, *J* 7.5, CH$_3$C*H*$_2$), 3.20 (1 H, m, 2'-H), 4.02 (3 H, m, 3'-H and 3''-H$_2$), 5.05–5.18 (2 H, m, 6'-H$_2$), 5.20 (1 H, d, *J* 9, 4-H), 5.35 (1 H, d, *J* 9, 1''-H) and 5.92 (1 H, m, 5'-H); *m/z* (EI), 5.08 (M$^+$ − 57, 29%) and 409 (56).

(3S,4R,2'R,3'R,1''E)-3-(3'-*Hydroxy-2'-methyl-1'-oxohex-5'-enyl)-4-(3''-hydroxy-2''-methylprop-1''-enyl)-3-methyl-1-oxopropylazetidin-2-one* **30**.—The imide **29** (138 mg, 0.24 mmol) was dissolved in acetonitrile (2.5 cm^3) and the solution was cooled to 0 °C. Boron trifluoride–diethyl ether (60 mm^3, 0.49 mmol) was added to the solution which was then stirred for 1 h at 0 °C. After this, water (3 cm^3) was added to it and the organic phase was separated from the aqueous phase; the latter was extracted with ether (3 × 3 cm^3). The combined organic extracts were dried (MgSO$_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel using ether as the eluent gave the *title compound* **30** (70 mg, 88%) as a colourless oil (Found: M$^+$, 337.1866. C$_{18}$H$_{27}$NO$_5$ requires *M*, 337.1889); [α]$_D$ −76 (*c* 0.55 in CHCl$_3$); ν_{max}/cm^{-1} 3396, 1784, 1710 and 1641; δ_H 1.03 (3 H, d, *J* 7.5, 2'-CH$_3$), 1.10 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.40 (3 H, s, 3-CH$_3$), 1.78 (3 H, s, 2''-CH$_3$), 2.10 (1 H, m, 4'-H), 2.25–2.48 (2 H, m, 4'-H and OH), 2.69 (2 H, q, *J* 7.5, CH$_3$C*H*$_2$), 3.10 (1 H, quin., *J* 7.5, 2'-H), 3.85 (1 H, m, 3'-H), 4.03 (2 H, s, 3''-H$_2$), 5.10–5.20 (3 H, m, 4-H and 6'-H$_2$), 5.35 (1 H, d, *J* 9, 1''-H) and 5.82 (1 H, m, 5'-H); *m/z* (EI), 337 (M$^+$, 0.4%).

(3S,5R,6R,1'R,2'E)-3-(4'-*Hydroxy-3'-methyl-1'-propanoylaminobut-2'-enyl)-3,5-dimethyl-6-prop-2''-enyltetrahydropyran-2,4-dione* **31**.—Chromatography of the diol **30** (40 mg, 0.2 mmol) on Merck silica gel 60 (40–63 mm^3) with ether as the eluent gave the title compound **31** (30 mg, 75%) as an unstable colourless oil, δ_H 1.15 (6 H, m, 5-CH$_3$ and C*H*$_3$CH$_2$), 1.35 (3 H, s, 3-CH$_3$), 1.81 (3 H, s, 3'-CH$_3$), 2.20 (2 H, m, CH$_3$C*H*$_2$), 2.30–2.50 (2 H, m, 5-H and 1''-H), 2.60–2.75 (1 H, m, 1''-H'), 3.99 (2 H, s, 4'-H$_2$), 4.30 (1 H, m, 6-H), 5.15–5.30 (3 H, m. 2'-H and 3''-H$_2$), 5.50 (1 H, t, *J* 10, 1'-H), 5.90 (1 H, m, 2''-H) and 6.32 (1 H, d, *J* 10, NH).

(3S,4S,5S,6R,1'R,2'E)-3-(4'-*Hydroxy-3'-methyl-1'-propanoylaminobut-2'-enyl)-4-hydroxy-3,5-dimethyl-6-prop-2''-enyltetrahydropyran-2-one* **32**.—To the ketone **30** (30 mg, 0.09 mmol) in ethanol (1.5 cm^3) at 0 °C was added sodium borohydride (6 mg, 0.15 mmol) and the mixture was stirred at 0 °C for 1 h. After this, saturated aqueous ammonium chloride (2 cm^3) was added to the mixture which was then extracted with ethyl acetate (3 × 2 cm^3). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ethyl acetate–methanol (20 : 1) as the eluent yielded the *title compound* **32** (21 mg, 70%) as a colourless oil (Found: MH$^+$, 340.2123. C$_{18}$H$_{30}$NO$_5$ requires *M*, 340.2124); [α]$_D$ −11.3 (*c* 0.3 in CHCl$_3$); ν_{max}/cm^{-1} 3338, 1710, 1643 and 1515; δ_H 1.00 (3 H, d, *J* 7.5, 5-CH$_3$), 1.11 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.28 (3 H, s, 3-CH$_3$), 1.65 (4 H, m, 3'-CH$_3$ and 5-H), 2.15 (2 H, m, CH$_3$C*H*$_2$), 2.35 and 2.60 (each 1 H, m,

1″-H), 3.39 (1 H, d, *J* 11, 4-H), 3.95 (1 H, m, 6-H), 4.05 and 4.12 (each 1 H, d, *J* 15, 4′-H), 5.10–5.25 (3 H, m, 3″-H₂ and 1′-H), 5.80 (1 H, m, 2″-H), 6.00 (1 H, d, *J* 8, 2′-H) and 6.05 (1 H, d, *J* 7.5, NH); *m/z* (CI) 340 (MH⁺, 100%).

(3S,4S,5R,6R,1′R,2′E)-4-tert-*Butyldimethylsilyloxy*-3-(4′-tert-*butyldimethylsilyloxy*-1′-*ethylcarbonylamino*-3′-*methylbut*-2′-*enyl*)-3,5-*dimethyl*-6-*prop*-2″-*enyltetrahydropyran*-2-*one* **33**.—2,6-Dimethylpyridine (0.29 cm³, 2.4 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.29 cm³, 1.2 mmol) were added to a solution of the diol **32** (162 mg, 0.48 mmol) in dichloromethane at 0 °C and the mixture was stirred at room temperature for 2 h. After this, water (2.5 cm³) was added to the mixture and the aqueous phase was extracted into dichloromethane. The organic extracts were combined, dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum as the eluent gave the *title compound* **33** (194 mg, 70%) as a white solid, mp 125 °C (Found: MH⁺, 568.3867. C₃₀H₅₈NO₅Si₂ requires *M*, 568.3853); [α]_D −26.2 (*c* 1.75 in CHCl₃); *v*_max(CHCl₃)/cm⁻¹ 1725 and 1683; *δ*_H 0.01 (6 H, s, 2 × SiCH₃), 0.15 and 0.18 (each 3 H, s, SiCH₃), 0.90 [9 H, s, SiC(CH₃)₃], 0.94 (3 H, d, *J* 7.5, 5-CH₃), 1.03 [9 H, s, SiC(CH₃)₃], 1.12 (3 H, t, *J* 7.5, C*H*₃CH₂), 1.36 (3 H, s, 3-CH₃), 1.65 (3 H, s, 3′-CH₃), 2.11 (2 H, m, CH₃C*H*₂), 2.30 (1 H, m, 1″-H), 2.40 (1 H, m, 5-H), 2.55 (1 H, m, 1″-H), 3.55 (1 H, d, *J* 11, 4-H), 3.89 (1 H, m, 6-H), 3.95 (2 H, s, 4′-H₂), 5.11 (2 H, m, 3″-H₂), 5.56 (2 H, m, 1′-H and NH) and 5.80 (2 H, m, 2″-H and 2′-H); *m/z* (CI) 568 (MH⁺, 100%).

(3S,4S,5R,6R,1′R,2′E,2″RS)-4-tert-*Butyldimethylsilyloxy*-3-(4′-tert-*butyldimethylsilyloxy*-3′-*methyl*-1′-*propanoylaminobut*-2′-*enyl*)-6-(2″,3″-*dihydroxypropyl*)-3,5-*dimethyltetrahydropyran*-2-*one* **34**.—The lactone **33** (48 mg, 0.08 mmol) was dissolved in pyridine (1.3 cm³) and the solution was cooled to −40 °C. Osmium tetroxide (22 mg, 0.08 mmol) in pyridine (0.5 cm³) was added to the solution which was then stirred at −40 °C for 1 h before being allowed to warm to room temperature. Sodium metabisulfite (20% w/v aqueous solution; 1.3 cm³) was added to the mixture and stirring was continued for a further 1 h. After this, the mixture was diluted with chloroform (5 cm³) and the aqueous phase was separated from the organic phase; the former was then extracted with chloroform (3 × 4 cm³). The combined organic extracts were washed with water (1 × 10 cm³) and then saturated brine (1 × 10 cm³), dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as the eluent yielded the *title compound* **34** (40 mg, 85%) as a colourless oil, a mixture of 2″-diastereoisomers (Found: MH⁺, 602.3887. C₃₀H₆₀NO₇Si₂ requires *M*, 602.3908); *v*_max/cm⁻¹ 3337, 1711 and 1657; *δ*_H 0.05 and 0.07 (each 3 H, s, SiCH₃), 0.15, 0.17, 0.19 and 0.21 (each 1.5 H, s, SiCH₃), 0.90 [9 H, s, SiC(CH₃)], 1.01 [12 H, s, SiC(CH₃)₃ and 5-CH₃], 1.10 and 1.12 (each 1.5 H, t, *J* 7.5, C*H*₃CH₂), 1.38 and 1.43 (each 1.5 H, s, 3-CH₃), 1.63 (3 H, s, 3′-CH₃), 2.15 (4 H, m, CH₃C*H*₂ and 1′-H₂), 2.37 and 2.85 (each 0.5 H, m, 5-H), 3.35–3.90 (5 H, m, 2″-H, 3″-H₂, 6-H and 4-H), 3.95–4.15 (2 H, m, 4′-H₂), 5.40–5.65 (2 H, m, 1′-H and NH) and 5.88 and 6.18 (each 0.5 H, d, *J* 9, 2′-H); *m/z* (CI) 602 (MH⁺, 75%).

(3S,4S,5R,6R,1′R,2′E)-4-tert-*Butyldimethylsilyloxy*-3-(4′-tert-*butyldimethylsilyloxy*-1′-*propanoylamino*-3′-*methylbut*-2′-*enyl*)-6-(*formylmethyl*)-3,5-*dimethyltetrahydropyran*-2-*one* **35**. —The diol **34** (37 mg, 0.06 mmol) was dissolved in dichloromethane (1.5 cm³) and sodium carbonate (62 mg, 0.6 mmol) was added to the solution. The mixture was cooled to 0 °C and, after the addition to it of lead tetraacetate (30 mg, 0.067 mmol), was stirred for 45 min at 0 °C. It was then filtered

through a Celite and sodium sulfate mixture. The filtrate was concentrated under reduced pressure to provide the *aldehyde* **35** (30 mg, 88%) as a colourless oil (Found: M⁺ − C₄H₉, 512.2857. C₂₅H₄₆NO₆Si₂ requires *M*, 512.2863); *v*_max/cm⁻¹ 1727 and 1676; *δ*_H 0.05 (6 H, s, 2 × SiCH₃), 0.15 and 0.20 (each 3 H, s, SiCH₃), 0.90 [9 H, s, SiC(CH₃)₃], 0.95 (3 H, d, *J* 7, 5-CH₃), 1.00 [9 H, s, SiC(CH₃)₃], 1.12 (3 H, t, *J* 7, C*H*₃CH₂), 1.40 (3 H, s, 3-CH₃), 1.65 (3 H, s, 3′-CH₃), 2.15 (2 H, m, CH₃C*H*₂), 2.50 (1 H, m, 5-H), 2.70 (2 H, m, C*H*₂CHO), 3.60 (1 H, d, *J* 10, 4-H), 4.01 (2 H, s, 4′-H₂), 4.37 (1 H, m, 6-H), 5.52 (1 H, t, *J* 8, 1′-H), 5.59 (1 H, d, *J* 8, NH), 5.83 (1 H, d, *J* 8, 2′-H) and 9.78 (1 H, s, CHO); *m/z* (EI) 512 (M⁺ − 57, 0.25%).

(3S,4R,2′S,3′R,1″E)-1-tert-*Butyldimethylsilyl*-3-(3′-tert-*butyldimethylsilyloxy*-1′-*hydroxy*-2′-*methylhex*-5′-*enyl*)-4-(3″-tert-*butyldimethylsilyloxy*-2″-*methylprop*-1″-*enyl*)-3-*methylazetidin*-2-*one* **38**.—To a solution of the ketone **27** (50 mg, 0.08 mmol) in THF (0.5 cm³) was added a solution of sodium borohydride (10 mg, 0.26 mmol) and lithium bromide (23 mg, 0.26 mmol) in THF (0.4 cm³) and water (0.1 cm³). The mixture was stirred for 7 h after which it was poured into a mixture of saturated aqueous ammonium chloride (2 cm³) and ethyl acetate (2 cm³). The organic phase was separated from the aqueous phase and the latter extracted with ethyl acetate (3 × 2 cm³). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 7) as the eluent yielded one isomer of the *title compound* **38** (31 mg, 62%), as a white solid, mp 70 °C (Found: M⁺, 625.4375. C₃₃H₆₇NO₄Si₃ requires *M*, 625.4378); [α]_D −57.5 (*c* 0.21 in CHCl₃); *v*_max(CHCl₃)/cm⁻¹ 3427 and 1724; *δ*_H 0.00 (6 H, s, 2 × SiCH₃), 0.05, 0.07, 0.10 and 0.18 (each 3 H, s, SiMe), 0.88 [18 H, s, 2 × SiC(CH₃)₂], 0.92 [12 H, s, SiC(CH₃) and 2′-CH₃], 1.10 (3 H, s, 3-CH₃), 1.61 (3 H, s, 2″-CH₃), 1.80 (1 H, m, 2′-H), 2.20–2.40 (2 H, m, 4′-H₂), 3.30 (1 H, br s, OH), 3.65 (1 H, d, *J* 7.5, 1′-H), 3.80 (1 H, q, *J* 7.5, 3′-H), 3.95 (2 H, s, 3″-H₂), 4.35 (1 H, d, *J* 10, 4-H), 4.95–5.05 (2 H, m, 6′-H₂), 5.45 (1 H, d, *J* 10 1″-H), and 5.78 (1 H, m, 5′-H); *m/z* (EI) 625 (M⁺, 1%) and 568 (M⁺ − 57, 15).

(3S,4R,1′E,2″R,3″R)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*(tert-*butyldimethylsilyloxy*)-2″-*methylhex*-5″-*enyl*]-3-*methylazetidin*-2-*one* **39**.—The alcohol **38** (140 mg, 0.2 mmol) was dissolved in dichloromethane (1 cm³) and the solution was cooled to 0 °C. 2,6-Dimethylpyridine (120 mm³, 1 mmol) and tert-butyl-dimethylsilyl trifluoromethanesulfonate (120 mm³, 0.5 mmol) were added to it and stirring at room temperature was continued for 2 h. Water (1 cm³) was then added to the mixture after which the organic phase was separated and extracted with dichloromethane (3 × 1 cm³). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1 : 14) as the eluent yielded the *title compound* **39** (140 mg, 95%) as a white solid, mp 76 °C (Found: M⁺, 739.5221. C₃₉H₈₁NO₄Si₄ requires *M*, 739.5242); [α]_D −25.8 (*c* 0.24 in CHCl₃); *v*_max(CHCl₃)/cm⁻¹ 1733 and 1602; *δ*_H 0.01 (6 H, s, 2 × SiCH₃), 0.09 (9 H, s, 3 × SiCH₃), 0.12 (6 H, s, 2 × SiCH₃), 0.28 (3 H, s, SiCH₃), 0.73 (3 H, d, *J* 7.5, 2″-Me), 0.89[9 H, s, SiC(CH₃)₃], 0.95[27 H, s, 3 × SiC(CH₃)₃], 1.20 (3 H, s, 3-CH₃), 1.65 (3 H, s, 2′-CH₃), 1.85 (1 H, m, 2″-H), 2.10–2.40 (2 H, m, 4″-H₂), 3.65 (1 H, m, 3″-H), 4.00 (2 H, s, 3′-H₂), 4.38 (1 H, s, 1″-H), 4.77 (1 H, d, *J* 11, 4-H), 4.95–5.10 (2 H, m, 6″-H₂), 5.64 (1 H, d, *J* 11, 1′-H) and 5.85 (1 H, m, 5″-H); *m/z* (EI) 739 (M⁺, 0.3%) and 682 (M⁺ − 57, 12).

(3S,4R,1′E,2″R,3″R,5″RS)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*-

(tert-*butyldimethylsilyloxy*)-5″,6″-*dihydroxy*-2″*methylhexyl*]-3-*methylazetidin*-2-*one* **40**.—Following the procedure using osmium tetraoxide outlined above, oxidation of the alkene **39** (136 mg, 0.184 mmol) gave, after chromatography with ether–light petroleum (1:1) as the eluent, the *title compound* **40** (100 mg, 70%) as a colourless oil (Found: MH⁺, 774.5366. $C_{39}H_{84}NO_6Si_4$ requires M, 774.5376); v_{max}/cm^{-1} 3394, 1744, 1722 and 1677; δ_H −0.05–0.30 (24 H, overlapping peaks, 8 × SiCH₃), 0.80 (1 H, d, J 7.5, 2″-CH₃), 0.88 (2 H, d, J 7.5, 2″-CH₃), 0.90 and 0.95 [each 18 H, s, 2 × SiC(CH₃)₃], 1.21 (1 H, s, 3-CH₃), 1.22 (2 H, s, 3-CH₃), 1.68 (3 H, s, 2′-CH₃), 1.60–1.90 (2 H, m, 4″-H₂), 2.10 (1 H, m, 2″-H), 3.35–3.60 (2 H, m, 6″-H₂), 3.78 (0.3 H, m, 5″-H), 3.88 (0.7 H, m, 5″-H), 4.00 (2 H, s, 3′-H₂), 4.01 (1 H, m, 3″-H), 4.35 (1 H, s, 1″-H), 4.61 (0.3 H, d, J 9, 4-H), 4.81 (0.7 H, d, J 9, 4-H), 5.62 (0.7 H, d, J 9, 1′-H) and 5.78 (0.3 H, d, J 9, 1′-H); m/z (FAB) 774 (MH⁺, 8%).

(3S,4R,1′E,2″R,3″R)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*but-yldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*(tert-*butyl-dimethylsilyloxy*-4″-*formyl*-2″-*methylbutyl*]-3-*methylazetidin*-2-*one* **41**.—Following the procedure using lead tetraacetate outlined above, the diol **40** (46 mg, 0.06 mmol) gave the *aldehyde* **41** (44 mg, 98%) as a colourless oil (Found: MH⁺, 742.5141. $C_{38}H_{80}NO_5Si_4$ requires M, 742.5113); v_{max}/cm^{-1} 1744 and 1670; δ_H 0.00 and 0.01 (each 3 H, s, SiCH₃), 0.05 and 0.10 (each 6 H, s, 2 × SiCH₃), 0.14 and 0.30 (each 3 H, s, SiCH₃), 0.85 [9 H, s, SiC(CH₃)₃], 0.91 [30 H, overlapping peaks, 3 × SiC(CH₃)₃ and 2″-CH₃], 1.28 (3 H, s, 3-CH₃), 1.65 (3 H, s, 2′-CH₃), 1.90 (1 H, m, 2″-H), 2.55 (1 H, ddd, J 3, 7, 17, 4″-H), 2.65 (1 H, ddd, J 1, 4, 17, 4″-H′), 4.00 (2 H, s, 3′-H₂), 4.09 (1 H, m, 3″-H), 4.14 (1 H, d, J 2.5, 1″-H), 4.70 (1 H, d, J 9, 4-H), 5.75 (1 H, d, J 9, 1′-H) and 9.75 (1 H, m, CHO); m/z (FAB) 742 (MH⁺, 2%).

(3S,4R,1′E,2″R,3″R,5″RS)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*-(tert-*butyldimethylsilyloxy*)-6″-*dimethoxyphosphinoyl*-5″-*hydr-oxy*-2″-*methylhexyl*]-3-*methylazetidin*-2-*one* **42**.—To a stirred solution of dimethyl methylphosphonate (2.2 mm³, 0.02 mmol) in THF (0.6 cm³) at −78 °C was added butyllithium (1.6 mol dm⁻³ solution in hexane; 0.02 cm³, 0.03 mmol). The mixture was stirred for 1 h at −78 °C, after which the aldehyde **41** (15 mg, 0.02 mmol) in THF (0.2 cm³) was added to it. After the solution had been stirred for a further 45 min at −78 °C, water (0.5 cm³) was added to it and the mixture allowed to warm to room temperature. After an aqueous work-up, chromatography with ethyl acetate–light petroleum–methanol (1.5:6:0.5) as the eluent yielded the *title compound* **42** (15 mg, 87%) as a colourless oil (Found: MH⁺, 866.5411. $C_{41}H_{89}NO_8PSi_4$ requires M, 866.5402); v_{max}/cm^{-1} 3378, 1743, 1252 and 1069; δ_H −0.05–0.30 (24 H, overlapping peaks, 8 × SiCH₃), 0.90 (39 H, m, 4 × SiC(CH₃) and 2″-CH₃), 1.20 (1.5 H, s, 3-CH₃), 1.25 (1.5 H, s, 3-CH₃), 1.70 (3 H, s, 2′-CH₃), 1.70–2.00 (5 H, m, 4″-H₂, 6″-H₂ and 2″-H), 3.74 and 3.76 [each 3 H, d, J 11, P(OCH₃)₂], 3.95 (1 H, m, 5″-H), 3.99 (1 H, s, 3′-H₂), 4.01 (1 H, s, 3′-H₂), 4.18 (0.5 H, d, J 2, 1″-H), 4.20 (1 H, m, 3″-H), 4.30 (0.5 H, d, J 2, 1″-H), 4.65 and 4.77 (each 0.5 H, d, J 9, 4-H) and 5.66 (1 H, m, 1′-H); m/z (FAB) 866 (MH⁺, 4%).

(3S,4R,1′E,2″R,3″R)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*but-yldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*(tert-*butyl-dimethylsilyloxy*)-6″-*dimethoxyphosphinoyl*-2″-*methyl*-5″-*oxo-hexyl*]-3-*methylazetidin*-2-*one* **43**.—A solution of the alcohol **42** (11 mg, 12.7 μmol) in dichloromethane (0.2 cm³) was added to a stirred suspension of PDC (10 mg, 0.03 mmol) and powdered molecular sieves (10 mg) in dichloromethane (0.2 cm³). After being stirred for 16 h, the mixture was diluted with

ether (5 cm³), filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel using ethyl acetate–light petroleum–methanol (1.5:6:0.5) as the eluent yielded the *title compound* **43** (8 mg, 75%) as a colourless oil (Found: MH⁺, 864.5206. $C_{41}H_{87}NO_8PSi_4$ requires M, 864.5246); [α]$_D$ −5.7 (c 0.3 in CHCl₃); v_{max}/cm^{-1} 1744, 1254, 1192 and 1031; δ_H −0.01 and 0.00 (each 3 H, s, SiCH₃), 0.05 and 0.08 (each 6 H, s, 2 × SiCH₃), 0.10 and 0.30 (each 3 H, s, SiCH₃), 0.83 [9 H, s, SiC(CH₃)₃], 0.90 [30 H, s, 3 × SiC(CH₃)₃ and 2″CH₃], 1.25 (3 H, s, 3-CH₃), 1.62 (3 H, s, 2′-CH₃), 1.82 (1 H, m, 2″-H), 2.82 (2 H, d, J 6, 4″-H₂), 3.05 (2 H, m, 6″-H₂), 3.79 [6 H, d, J 11, P(OCH₃)₂], 3.95–4.18 (4 H, m, 3′-H₂, 1″-H and 3″-H), 4.69 (1 H, d, J 9, 4-H) and 5.70 (1 H, d, J 9, 1′-H); m/z (FAB) 864 (MH⁺, 3%).

(3S,4R,1′E,2″R,3″R,6″E,8″E)-1-tert-*Butyldimethylsilyl*-4-(3′-tert-*butyldimethylsilyloxy*-2′-*methylprop*-1′-*enyl*)-3-[1″,3″-*di*-(tert-*butyldimethylsilyloxy*)-2″,8″-*dimethyl*-5″-*oxodeca*-6″,8″-*di-enyl*]-3-*methylazetidin*-2-*one* **44**.—To a solution of diisoprop-ylamine (2 mm³, 14 μmol) in THF (0.1 cm³) at 0 °C was added butyllithium (1.6 mol dm⁻³ solution in hexane; 9 mm³, 14 μmol) and the solution was stirred at 0 °C for 15 min. The phosphonate **43** (8 mg, 9 μmol) in THF (0.1 cm³) was then added to the mixture after which it was stirred for a further 15 min at 0 °C. (E)-2-Methylbut-2-enal (1 mm³, 9 μmol) in THF (0.1 cm³) was added to the mixture which was stirred for 15 min at 0 °C and then at room temperature overnight. After this it was concentrated under reduced pressure. Chromatography of the residue on silica gel with ether–light petroleum (1:12) as the eluent yielded the *title compound* **44** (5.5 mg, 75%), as a colourless oil (Found: MH⁺, 822.5783. $C_{44}H_{88}NO_5Si_4$ requires M, 822.5739); [α]$_D$ −21.6 (c 0.5 in CHCl₃); v_{max}/cm^{-1} 1744 and 1672; δ_H −0.01 (6 H, s, 2 × SiCH₃), 0.04, 0.05, 0.09, 0.12, 0.15 and 0.29 (each 3 H, s, SiCH₃), 0.85 [9 H, s, SiC(CH₃)₃], 0.90 [21 H, s, 2 × SiC(CH₃)₃ and 2″-CH₃], 0.92 [9 H, s, SiC(CH₃)₃], 1.30 (3 H, s, 3-CH₃), 1.62 (3 H, s, 2′-CH₃), 1.79 (3 H, s, 8″-CH₃), 1.85 (1 H, m, 2″-H), 1.88 (3 H, d, J 7.5, 10″-H₃), 2.80 (2 H, d, J 6, 4″-H₂), 3.99 and 4.09 (each 1 H, d, J 15, 3′-H), 4.18 (1 H, m, 3″-H), 4.20 (1 H, d, J 1, 1″-H), 4.71 (1 H, d, J 9, 4-H), 5.68 (1 H, d, J 9, 1′-H), 6.03 (1 H, q, J 7.5, 9″-H), 6.05 (1 H, d, J 16, 6″-H) and 7.12 (1 H, d, J 16, 7″-H); m/z (FAB) 822 (MH⁺, 0.3%).

References

1 M. Uramoto, N. Otake, L. Carey and M. Tanabe, *J. Am. Chem. Soc.*, 1978, **100**, 3616; K. Kakinuma, J. Uzawa and M. Uramoto, *Tetrahedron Lett.*, 1982, **23**, 5303; S. Harada, J. Okada, M. Takeda and T. Yamazi, *J. Antibiotics*, 1985, **38**, 877.

2 E. J. Thomas and A. C. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 992.

3 E. J. Thomas and A. C. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1995, preceding paper.

4 A. S. Kende, M. J. Luzzio and K. Koch, in *Chemistry and Biotechnology of Biologically Active Natural Products. Proceedings of the Fourth International Conference*, C. Szantay, ed., Budapest, Hungary, 1987 (*Chem. Abstr.*, 1989, **111**, 214771m).

5 A. S. Kende, K. Koch, G. Dorey, I. Kaldor and K. Liu, *J. Am. Chem. Soc.*, 1993, **115**, 9842.

6 Preliminary communication: J. M. Roe and E. J. Thomas, *Synlett*, 1990, 727.

7 R. Labia and C. Morin, *Chem. Lett.*, 1984, 1007; T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161.

8 K. Okano, T. Izawa and M. Ohno, *Tetrahedron Lett.*, 1983, **24**, 217; I. Ojima and Y. Pei, *Tetrahedron Lett.*, 1990, **31**, 977; S. Hanessian, K. Sumi and B. Vanassa, *Synlett*, 1992, 33.
9 H. A. Stab, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 351.
10 L. E. Overman and R. J. McCready, *Tetrahedron Lett.*, 1982, **23**, 2355.
11 F. Bennett, D. W. Knight and G. Fenton, *Tetrahedron Lett.*, 1988, **29**, 4865.
12 G. Frater, *Helv. Chim. Acta*, 1979, **62**, 2825, 2829; D. Seebach and D. Wasmuth, *Helv. Chim. Acta*, 1980, **63**, 197.

13 K. C. Nicolaou, M. R. Pavia and S. P. Seitz, *J. Am. Chem. Soc.*, 1981, **103**, 1224.
14 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
15 E. Mata and E. J. Thomas, unpublished observations.
16 A. Chen and E. J. Thomas, unpublished observations.