Development of a Synthesis of Lankacidins: Stereoselective Synthesis of the δ-Lactone Fragment

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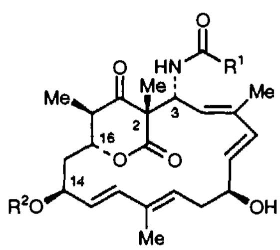
Electrophiles react at C(3) stereoselectively on the less hindered face of the enolate derived from the 4-substituted azetidinone **5** to give products in which the new substituent is *trans* to the (*tert*-butyldimethylsilyloxymethyl) group at C(4). Aldol addition with 3-(*tert*-butyldimethylsilyloxy)-propanal gave the alcohols **27** and **29**, ratio 80:20, which were separated as mixtures at C(1'). Oxidation, followed by exchange of protecting groups, gave the 3-(1'-oxopropyl)azetidinones **39** and **41** which, on selective monodesilylation, were converted into the δ-lactones **43** and **44**. The benzyloxymethyl protected 3-(hydroxyalkyl)azetidinones **40** and **42** were similarly prepared and gave the δ-lactones **43** and **44** on hydrogenolysis. The stereochemistry of the major δ-lactone **43** corresponds to that of the lankacidins at C(2) and C(3). The 3-(1'-oxopropyl)azetidinone **26**, which has additional substituents at C(16) and C(17) (lankacidin numbering), was similarly prepared.

The lankacidins[1] are a group of natural products of interest because they possess both antibiotic and antitumour activity.[2,3] Structurally they are characterised by the presence of a 17-membered carbocyclic ring which is bridged by a lactone, *e.g.* lankacidin C **1** and the lankacidinols **2** and **3**. The incorporation



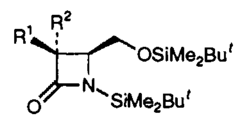
1 R¹ = Ac, R² = H
2 R¹ = CH(OH)Me, R² = H
3 R¹ = CH(OH)Me, R² = Ac

of labelled precursors has established that the lankacidins are derived biosynthetically from a linear polyketide initiated by glycine which has incorporated eight acetate units.[4] The four methyl groups are derived from *S*-adenosylmethionine. The formation of the macrocycle may involve a Favorskii type of ring contraction.[5]

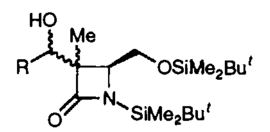
The novel structures and biological activities of the lankacidins makes them interesting targets for total synthesis, the control of stereochemistry at the quaternary centre, C(2), and at C(3) being of particular interest. We now report an approach to the synthesis of the C(14)–C(3) fragment. Our approach is based on the introduction of a β-amino acid derived unit corresponding to C(1)–C(3) by stereoselective acylation of an azetidinone at C(3).[6,7] A related strategy was independently conceived by Kende,[8] who recently used this approach to complete the first total synthesis of a lankacidin.[9]

Results and Discussion

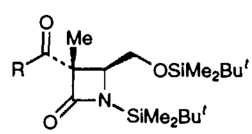
The protected (*S*)-4-(hydroxymethyl)azetidinone **4** was prepared from (*S*)-aspartic acid as described in the literature.[10] Methylation using lithium diisopropylamide (LDA) and methyl iodide was stereoselective and gave the (3*R*)-3-methylazetidinone **5** containing only *ca.* 10% of its (3*S*)-epimer.[7] Attempts to methylate the azetidinone **5** a second time at C(3) using LDA as base were unsuccessful since the starting material was recovered, but treatment with lithium diethylamide followed by the addition of an excess of methyl iodide gave the 3,3-dimethylazetidinone **6** (86%). Other alkyl halides gave the (3*R*)-3-alkyl-3-methylazetidinones **7–9** each containing *ca.* 10%



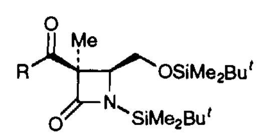
4 R¹ = R² = H
5 R¹ = H, R² = Me
6 R¹ = R² = Me
7 R¹ = Me, R² = Et
8 R¹ = Me, R² = Bu
9 R¹ = Me, R² = Bn



10 R = Prⁱ
11 R = Ph



12 R = Prⁱ
13 R = Ph



14 R = Prⁱ
15 R = Ph

of the (3*S*)-epimer. The configurations of the major products were assigned on the basis of nuclear Overhauser enhancement (NOE) difference spectra, the 4-CH_2 group showing a significant NOE effect with the *cis*-substituent at C(3).[7]

Aldol condensations of the (3*R*)-3-methylazetidinone **5** were carried out by addition of 2-methylpropanal and benzaldehyde to a solution of the enolate of the azetidinone generated using lithium diethylamide at −78 °C. Mixtures of aldol products **10** and **11** were obtained which were partially separated by flash chromatography. Oxidation of these alcohols gave the (3*S*)- and (3*R*)-3-(2'-methyl-1'-oxopropyl)azetidinones **12** and **14** and the (3*S*)- and (3*R*)-3-benzoylazetidinones **13** and **15**, respectively, each product containing *ca.* 20% of the (3*R*)-diastereoisomer. The configurations of the major products were assigned on the basis of NOE difference spectra.

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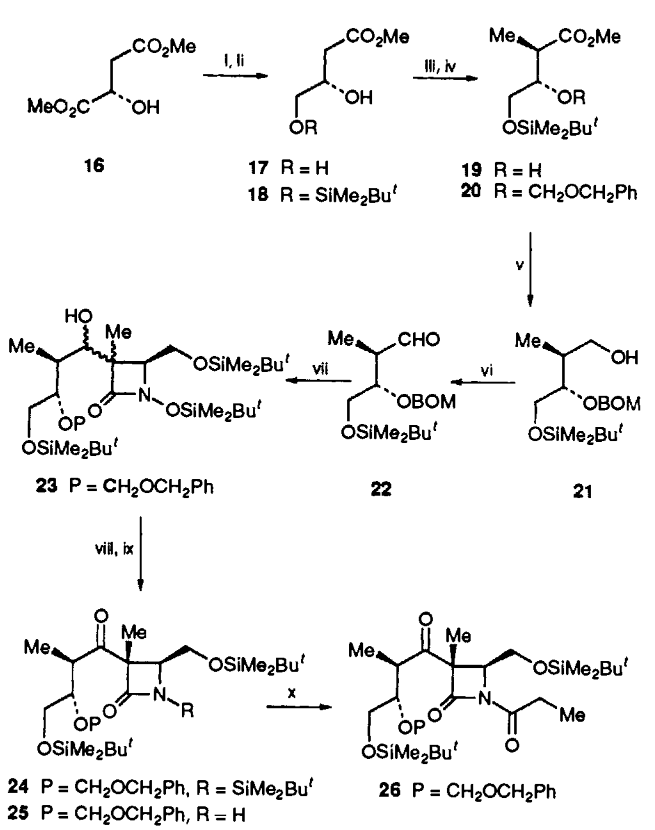
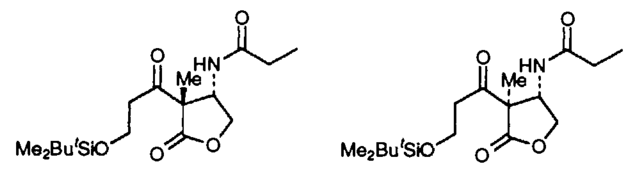


Scheme 1 *Reagents and conditions:* i, $NaBH_4$, BH_3, tetrahydrofuran; ii, Me_2Bu^tSiCl, Et_3N, 4-(dimethylamino)pyridine (73%); iii, lithium diisopropylamide, −10 to −60 °C, TMEDA, MeI (86%); iv, $BnOCH_2Cl$, Pr^i_2NEt, 4-(dimethylamino)pyridine (92%); v, diisobutylaluminium hydride (94%); vi, dimethyl sulfoxide, oxalyl chloride (97%); vii, 5·Li (98%); viii, dimethyl sulfoxide, oxalyl chloride (96%); ix, potassium fluoride, MeOH (85%); x, propanoyl chloride, triethylamine, 4-(dimethylamino)pyridine (90%)

To prepare intermediates with more of the functionality of the lankacidins, the aldehyde **22** was prepared from (2*S*)-dimethyl malate **16** (Scheme 1). Selective reduction of (2*S*)-dimethyl malate according to the literature procedure[11] gave the dihydroxy ester **17** which was monoprotected as its *tert*-butyldimethylsilyl ether **18**. Stereoselective methylation[12] of this 3-hydroxy ester gave the *anti*-product **19** which was protected as its benzyloxymethoxy derivative **20** and taken through to the aldehyde **22** by reduction followed by oxidation. The aldol condensation between the azetidinone **5** and aldehyde **22** gave a mixture of diastereoisomeric products. The major diastereoisomer was isolated by flash chromatography and accounted for 70% of the product mixture. By analogy with earlier results, it was identified as one of the 1′-epimers with the *S*-configuration at C(3), and was oxidised to the (3*S*)-3-(1′-oxoalkyl)azetidinone **24** using Swern[13] conditions. Selective deprotection on nitrogen and *N*-acylation using propanoyl chloride gave the 1-(1″-oxobutyl)azetidinone **26**. This has functionality and configurations at its four chiral centres corresponding to those at C(2), C(3), C(16) and C(17) of the lankacidins, and would appear to be a useful intermediate for a lankacidin synthesis. It was necessary now to investigate the ring-opening of the azetidinone and formation of the δ-lactone to establish a strategy for the synthesis of the C(14)–C(4) fragment of the lankacidins.

To develop conditions for the formation of the δ-lactone by an intramolecular, hydroxyl-induced, ring-opening of an azetidinone, the azetidinone **5** and 3-(*tert*-butyldimethylsilyloxy)propanal were condensed to give the adducts **27** and **29** which were separated as mixtures of epimers at C(1′), ratio **27**:**29** = 80:20, combined yield 96%. Oxidation of these alcohols gave the 3-(1′-oxopropyl)azetidinones **31** and **35**, the configurations of which were established by NOE difference spectra. Selective *N*-desilylation was achieved using potassium fluoride and *N*-acylation using propanoyl chloride gave the 1-(1′-oxopropyl)azetidinones **39** and **41**. Attempts to remove the 3′-silyl group in order to release the free 3′-hydroxyl group using tetrabutylammonium fluoride were unsuccessful as mixtures of products were obtained. However, treatment with toluene-*p*-sulfonic acid in aqueous tetrahydrofuran effected selective monodesilylation and concomitant transacylation to give the δ-lactones **43** and **44** (Scheme 2). The structures of these products were established on the basis of spectroscopic data. In particular the ring-opening of the azetidinone was apparent from IR spectra which no longer had absorptions corresponding to the C=O stretch of the azetidinone carbonyl group.

To check that the δ-lactones **43** and **44** had been formed rather than the isomeric γ-lactones **45** and **46**, this reaction



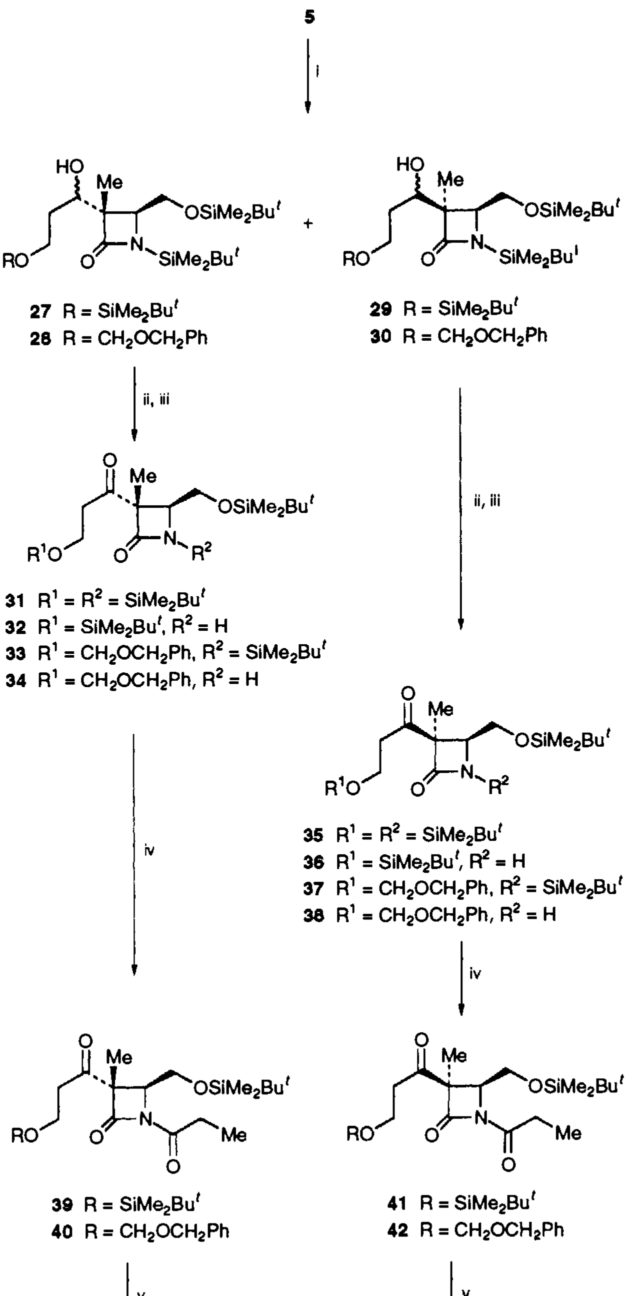
45 **46**

sequence was repeated using 3-(benzyloxymethoxy)propanal. The aldol reaction with azetidinone **5** gave the alcohols **28** and **30**, again as mixtures of epimers at C(1′). In this case, three of the stereoisomers were separated by flash chromatography and isolated pure. Oxidation of the separated diastereoisomers gave the ketones **33** and **37**, and selective *N*-desilylation and acylation gave the 1-(1″-oxopropyl)azetidinones **40** and **42**. These on hydrogenolysis gave the δ-lactones **43** and **44** identical with samples prepared by selective monodesilylation of the bis-silyl ethers **39** and **41**. Overall the δ-lactone **43** was obtained from the azetidinone **5** in five steps in yields of 46% using 3-(*tert*-butyldimethylsilyloxy)propanal and 55% using the 3-(benzyloxy)propanal. The isomeric δ-lactone **44** was obtained by way of the minor azetidinone aldol products in overall yields of *ca.* 11% (both routes).

These syntheses of the δ-lactone **43** by the stereoselective acylation of the azetidinone **5** and the intramolecular transacylation of the azetidinones **39** and **40** help to establish an approach to the synthesis of the δ-lactone component of the lankacidins. However, preliminary attempts to hydrogenolyse the benzyloxymethoxy group in the more heavily functionalised azetidinone **26** and so effect opening of the azetidinone and formation of the δ-lactone, were not successful. Since hydrogenolysis would be incompatible with the presence of a conjugated diene component of the lankacidins, a modification of this approach was investigated, and is described in the following paper.[14]

Experimental

All non-aqueous reactions were carried out under an atmosphere of dry nitrogen or argon. ^1H NMR spectra were recorded on Bruker WH 300, Bruker AC 300 or Varian XL 300 spectrometers in [^2H]chloroform, unless otherwise stated. *J* Values are given in Hz. IR spectra were measured on Perkin-Elmer 257 and 297 spectrometers as evaporated films unless otherwise stated. Mass spectra were recorded on a VG Micromass 16 F or Kratos MS 20 or MS 25 spectrometers using electron impact (EI) or chemical ionisation (CI) modes. Mps were determined on a Köfler block and are uncorrected. $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1}.



Scheme 2 *Reagents:* i, lithium diethylamide, $ROCH_2CH_2CHO$ (95–96%); ii, PDC, dichloromethane (91–96%); iii, potassium fluoride, MeOH; iv, propanoyl chloride, triethylamine, 4-(dimethylamino)pyridine (90–97%); v, toluene-*p*-sulfonic acid, aqueous tetrahydrofuran (R = $SiMe_2Bu^t$; 61–62%) or hydrogen, 10% palladium-on-charcoal (R = CH_2OCH_2Ph; 83–87%)

Solvents were dried by standard procedures and distilled. Light petroleum refers to the fraction which distils at 40–60 °C and ether to diethyl ether. Chromatography refers to flash chromatography on either Merck silica gel 60 (40–63 µm) or May and Baker Sorbsil C60 silica gel (40–60 µm). (*S*)-1-(*tert*-Butyldimethylsilyl)-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one **4** was prepared as described in the literature, $[\alpha]_D^{20}$ −26 (*c* 1.3 in $CHCl_3$) [lit.,[10] $[\alpha]_D^{20}$ −25.3 (*c* 0.95 in $CHCl_3$)]. 3-(*tert*-Butyldimethylsilyloxy)propanal was prepared as described in the literature.[15] 3-(Benzyloxymethoxy)propanal was prepared from propane-1,3-diol by selective monoprotection using benzyl chloromethyl ether, *N,N*-diisopropylethylamine and 4-(dimethylamino)pyridine in dichloromethane followed by oxidation using the Swern procedure;[13] $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ_H 2.78 (2 H, dt, *J* 2, 6, 2-H_2), 4.0 (2 H, t, *J* 6, 3-H_2), 4.67 (2 H, s, $PhCH_2$), 4.83 (2 H, s, OCH_2O), 7.3–7.4 (5 H, m, ArH) and 9.8 (1 H, t, *J* 2, 1-H); *m/z* (CI) 212 (M^+ + 18) and 193 (M^+ − 1, 100). Methyl (*S*)-3,4-dihydroxybutanoate **17** was prepared according to the literature procedure.[11]

(3R,4S)-1-(tert-*Butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*one* **5**.—Butyllithium (1.8 mol dm^{-3} in hexane; 28.5 cm^3, 51.3 mmol) was added to a solution of diisopropylamine (7.2 cm^3, 5.2 g, 51.4 mmol) in tetrahydrofuran (THF) (100 cm^3) at 0 °C. After being stirred for 15 min, the solution was cooled to −78 °C, and a solution of the azetidinone **4** (11.25 g, 34.2 mmol) in THF (50 cm^3) was added dropwise to it. After 30 min, iodomethane (10 cm^3, 22.8 g, 161 mmol) was added to the mixture which was then stirred for 2 h before being allowed to warm to room temperature. Saturated aqueous ammonium chloride (200 cm^3) was added to the reaction mixture and the phases were separated. 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 to afford an oil. This was chromatographed (ether–light petroleum) to give the *title compound* **5** (11.56 g, 98%) as an oil (Found: $M^+ - C_4H_9$, 286.1660. $C_{13}H_{28}NO_2Si$ requires *M*, 286.1659); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ_H(major isomer) 0.04 [6 H, s, $Si(CH_3)_2$], 0.2 and 0.25 (each 3 H, s, $SiCH_3$), 0.90 and 0.97 [each 9 H, s, $SiC(CH_3)_3$], 1.30 (3 H, d, *J* 7.5, 3-CH_3), 2.94 (1 H, dq, *J* 2.5, 7.5, 3-H), 3.21 (1 H, m, 4-H), 3.60 (1 H, dd, *J* 10.5, 6, *H*CH) and 3.78 (1 H, dd, *J* 10.5, 4.3, HC*H*); peaks due to the minor (3*S*,4*S*)-diastereoisomer were detected at δ_H 1.20 (0.3 H, d, *J* 7.5, 3-CH_3), 3.27 (0.1 H, m, 4-H) and 3.65 (0.2 H, m, 4-CH_2)]; *m/z* (EI) 286 ($M^+ - C_4H_9$, 25%) and 129 (100).

Alkylation of the Azetidinone **5**.—*General procedure.* A solution of the azetidinone **5** (typically 1 mmol) in THF (5 cm^3) was added to a solution of lithium diethylamide (1.2 mmol) in THF (2.5 cm^3) at −78 °C and the mixture was stirred for 30 min. An excess of the alkyl halide was added to the mixture which was then stirred for 4 h before being allowed to warm to room temperature. Saturated aqueous ammonium chloride was added to the mixture and the phases were separated. The aqueous phase was extracted with ether, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ether–light petroleum) followed by distillation gave the products as follows.

(4S)-1-(tert-*Butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3,3-*dimethylazetidin*-2-*one* **6** (329 mg, 86%), bp 152 °C/0.08 mmHg (Kugelrohr), $[\alpha]_D^{20}$ −16.6 (*c* 0.25 in $CHCl_3$) (Found: $M^+ - CH_3$, 342.2284. $C_{17}H_{36}NO_2Si_2$ requires *M*, 342.2284); $\nu_{max}(CHCl_3)/cm^{-1}$ 1755, 1262, 1100, 845 and 782; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.20 and 0.25 (each 3 H, s, $SiCH_3$), 0.90 and 0.96 [each 9 H, s, $SiC(CH_3)_3$], 1.19 and 1.31 (each 3 H, s, 3-CH_3), 3.28 (1 H, dd, *J* 8, 5, 4-H), 3.65 (1 H, dd, *J* 10.5, 8, *H*CH) and 3.77 (1 H, dd, *J* 10.5, 5, HC*H*); *m/z* (CI) 358 (M^+ + 1, 100).

(3R,4S)-1-(tert-*Butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*ethyl*-3-*methylazetidin*-2-*one* **7** (528 mg, 98%), bp 165 °C/0.08 mmHg (Kugelrohr), $[\alpha]_D^{20}$ −25.2 (*c* 1.45 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 314.1971. $C_{15}H_{32}NO_2Si_2$ requires *M*, 314.1971); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1470, 1460, 1255, 1090 and 840; δ_H 0.06 [6 H, s, $Si(CH_3)_2$], 0.20 and 0.23 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.95 [12 H, overlapping s and m, $SiC(CH_3)_3$ and CH_2CH_3], 1.17 (3 H, s, 3-CH_3), 1.63 (2 H, m, CH_2CH_3), 3.31 (1 H, dd, *J* 8, 5, 4-H), 3.62 (1 H, dd, *J* 10.5, 8, *H*CH) and 3.76 (1 H, dd, *J* 10.5, 5, HC*H*); *m/z* (CI) 372 (M^+ + 1, 100).

(3R,4S)-3-*Butyl*-1-(tert-*butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*one* **8** (552 mg, 95%), bp 180 °C/0.08 mmHg (Kugelrohr), $[\alpha]_D^{20}$ −27.4 (*c* 0.42 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 342.2289. $C_{17}H_{36}NO_2Si_2$ requires *M*, 342.2284); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1470, 1460, 1258, 1090 and 840; δ_H 0.06 [6 H, s, $Si(CH_3)_2$], 0.20 and 0.24 (each 3 H, s, $SiCH_3$), 0.90 [12 H, overlapping s and m, $SiC(CH_3)_3$ and CH_2CH_3], 0.95 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, s, 3-CH_3), 1.25–1.65 (6 H, m, 3 × CH_2), 3.32 (1 H, dd, *J* 8, 5, 4-H), 3.62 (1 H, dd, *J* 10.5, 8, *H*CH) and 3.76 (1 H, dd, *J* 10.5, 5, HC*H*); *m/z* (CI) 400 (M^+ + 1, 100).

(3R,4S)-3-*Benzyl*-1-(tert-*butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*one* **9** (495 mg, 87%), bp 200 °C/0.08 mmHg (Kugelrohr), $[\alpha]_D^{20}$ −23.5 (*c* 2.27 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 376.2127. $C_{16}H_{21}NO_2Si_2$ requires *M*, 376.2128); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1470, 1460, 1298, 1253, 1100, 1082 and 840; δ_H 0.01 and 0.02 (each 3 H, s, $SiCH_3$), 0.04 [6 H, s, $Si(CH_3)_2$], 0.82 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 1.26 (3 H, s, 3-CH_3), 2.72 and 3.02 (each 1 H, d, *J* 14, *H*CHPh), 3.40 (1 H, dd, *J* 8, 5.5, 4-H), 3.62 (1 H, dd, *J* 10.5, 8, *H*CH), 3.72 (1 H, dd, *J* 10.5, 5.5, HC*H*) and 7.16–7.35 (5 H, m, ArH); *m/z* (CI) 434 (M^+ + 1, 100).

(3S,4S)-1-(tert-*Butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methyl*-3-(2-*methyl*-1-*oxopropyl*)*azetidin*-2-*one* **12**.—2-Methylpropanal (150 mg, 2.08 mmol) in tetrahydrofuran (1.9 cm^3) was added to a solution of the azetidinone **5** (500 mg, 1.46 mmol) in tetrahydrofuran at −78 °C which had been deprotonated using lithium diethylamide as described above. After being stirred for 4 h, the solution was allowed to warm to room temperature, and saturated aqueous ammonium chloride (5 cm^3) was added to it. The phases were separated, and the aqueous layer was extracted with ether (2 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Short column chromatography of the residue gave two fractions. The less polar fraction (341 mg, 56%) contained a mixture of three diastereoisomers of the alcohol **10** ($M^+ - C_4H_9$, 358.2233. $C_{17}H_{36}NO_3Si_2$ requires *M*, 358.2234); $\nu_{max}(CHCl_3)/cm^{-1}$ 3510, 1720 and 1590. The more polar fraction (204 mg, 34%) comprised a single diastereoisomer of the alcohol **10** (Found: $M^+ - C_4H_9$, 358.2233. $C_{17}H_{36}NO_3Si_2$ requires *M*, 358.2234); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 1720, 1585, 1260, 1110 and 840; δ_H 0.06, 0.07, 0.22 and 0.25 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.93 (3 H, d, *J* 7, $CHCH_3$), 0.95 [9 H, s, $SiC(CH_3)_3$], 1.01 (3 H, d, *J* 7, $CHCH_3$), 1.17 (3 H, s, 3-CH_3), 1.85 [1 H, m, $CH(CH_3)_2$], 1.97 (1 H, br s, OH), 3.62 (1 H, m, C*H*OH) and 3.69–3.88 (3 H, m, 4-H and 4-CH_2); *m/z* (CI) 416 (M^+ + 1, 100%).

A solution of the more polar alcohol **10** (110 mg, 0.27 mmol) in dichloromethane was added to a suspension of PDC (0.81 mmol) and powdered 2A sieves in dichloromethane and the mixture stirred until no starting material remained (TLC). Ether was added to the mixture which was then stirred for 30 min before being filtered through a plug of Florisil and Celite and concentrated under reduced pressure. The residue was chromatographed to give the *title compound* **12** (110 mg, 86%), $[\alpha]_D^{20}$ −36 (*c* 3.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1735, 1700, 1470, 1460, 1255 and 840; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.21 and 0.27 (each 3 H, s, $SiCH_3$), 0.89 and 0.95 [each 9 H, s, $SiC(CH_3)_3$], 1.07 and 1.11 (each 3 H, d, *J* 7, $CHCH_3$), 1.48 (3 H, s, 3-CH_3), 3.17 (1 H, hept, *J* 7, 2′-H), 3.73 (1 H, dd, *J* 11, 7, *H*CH), 3.80 (1 H, dd, *J* 11, 5, HC*H*) and 3.95 (1 H, dd, *J* 7, 5, 4-H); *m/z* (CI) 430 (M^+ + 17, 25%), 414 (M^+ + 1, 50) and 257 (100).

Oxidation of the less polar mixture of the alcohols **10** (120 mg, 0.29 mmol) using PDC following the above procedure gave a mixture of ketones **12** and **14**, ratio *ca.* 2:1 (102 mg, 85%); δ_H(minor component) 0.05 [6 H, s, $Si(CH_3)_2$], 0.22 and 0.32 (each 3 H, s, $SiCH_3$), 0.89 and 0.98 [each 9 H, s, $SiC(CH_3)_3$], 1.04 and 1.22 (each 3 H, d, *J* 7, $CHCH_3$), 1.57 (3 H, s, 3-CH_3), 3.02 (1 H, hept, *J* 7, 2′-H), 3.41 (1 H, m, 4-H) and 3.75 (2 H, m, 4-CH_2).

(3S,4S)- *and* (3R,4S)-3-*Benzoyl*-1-(tert-*butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*one* **13** *and* **15**.—Following the procedure outlined above, the azetidinone **5** (500 mg, 1.46 mmol) was deprotonated using lithium diethylamide in tetrahydrofuran and condensed with benzaldehyde (220 mg, 2.08 mmol). Short column chromatography of the crude mixture of products gave three fractions. The least polar fraction was identified as a mixture of the 1′-epimers of the (3*R*,4*S*-)-3-(1′-hydroxy-1′-phenylmethyl)azetidinone **11** (126 mg, 19%), an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1735 and 1600; δ_H 0.12 and 0.14 [each 2.1 H, s, $Si(CH_3)_2$], 0.17 and 0.18 [each 0.9 H, s, $Si(CH_3)_2$], 0.22 (0.9 H, s, $SiCH_3$), 0.24 (2.1 H, s, $SiCH_3$), 0.26 (2.1 H, s, $SiCH_3$), 0.27 (0.9 H, s, $SiCH_3$), 0.94 [18 H, 2 × $SiC(CH_3)_3$], 1.20 (2.1 H, s, 3-CH_3), 1.30 (0.9 H, s, 3-CH_3), 3.14 (0.7 H, d, *J* 6, OH), 3.39 (0.7 H, dd, *J* 8, 5, 4-H), 3.45 (0.3 H, dd, *J* 7, 5, 4-H), 3.87 (1 H, dd, *J* 11, 5, *H*CH), 4.05 (1 H, dd, *J* 11, 8, HC*H*), 4.37 (0.3 H, d, *J* 1.6, OH), 4.92 (0.7 H, d, *J* 6, 1′-H), 5.29 (0.3 H, d, *J* 1.6, 1′-H) and 7.2–7.65 (5 H, m, ArH); *m/z* (CI) 450 (M^+ + 1, 100%). The second fraction was identified as one of the 1′-epimers of (3*S*,4*S*)-3-(1′-hydroxyl-1′-phenylmethyl)azetidinone **11** (246 mg, 38%), an oil, $[\alpha]_D^{20}$ −24.4 (*c* 0.86 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1735, 1600 and 1580; δ_H 0.04, 0.05, 0.07 and 0.14 (each 3 H, s, $SiCH_3$), 0.86 and 0.88 [each 9 H, s, $SiC(CH_3)_3$], 1.28 (3 H, s, 3-CH_3), 2.69 (1 H, d, *J* 3, OH), 3.57–3.75 (3 H, overlapping m, 4-H and 4-CH_2), 4.90 (1 H, d, *J* 3, 1′-H) and 7.16–7.45 (5 H, m, ArH); *m/z* (CI) 450 (M^+ + 1, 100%). The most polar fraction was identified as the other 1′-epimer of (3*S*,4*S*)-3-(1′-hydroxy-1′-phenylmethyl)azetidinone **11** (256 mg, 39%), an oil, $[\alpha]_D^{20}$ −56.2 (*c* 1 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1735, 1600 and 1580; δ_H −0.02 and 0.25 [each 6 H, s, $Si(CH_3)_2$], 0.83 and 0.96 [each 9 H, s, $SiC(CH_3)_3$], 1.13 (3 H, s, 3-CH_3), 2.64 (1 H, br s, OH), 3.54 (1 H, dd, *J* 11, 8, *H*CH), 3.71 (1 H, dd, *J* 11, 6, HC*H*), 3.96 (1 H, dd, *J* 8, 6, 4-H), 4.79 (1 H, s, 1′-H) and 7.24–7.41 (5 H, m, ArH); *m/z* (CI) 450 (M^+ + 1, 100%).

Oxidation of the second fraction containing one of the 1′-epimers of (3*S*,4*S*)-3-(1′-hydroxy-1′-phenylmethyl)azetidinone **11** (200 mg, 0.44 mmol) using PDC following the above procedure gave the (3*S*,4*S*)-diastereoisomer of the *title compound* **13** (172 mg, 86%) as an oil, $[\alpha]_D^{20}$ +26.9 (*c* 4.1 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 390.1927. $C_{20}H_{32}NO_3Si_2$ requires *M*, 390.1921); ν_{max}/cm^{-1} 3070, 1745, 1675, 1600, 1580, 1256, 1202, 1182, 1112, 840 and 780; δ_H 0.12 [6 H, s, $Si(CH_3)_2$], 0.22 and 0.29 (each 3 H, s, $SiCH_3$), 0.93 and 0.94 [each 9 H, s, $SiC(CH_3)_3$], 1.64 (3 H, s, 3-CH_3), 3.84 (1 H, dd, *J* 11, 7, *H*CH), 3.91 (1 H, dd, *J* 11, 5, HC*H*), 4.34 (1 H, dd, *J* 7, 5, 4-H), 7.43–7.55 (3 H, m, ArH) and 8.25–8.30 (2 H, m, ArH); *m/z* (CI) 448 (M^+ + 1, 60%) and 291 (100). Oxidation of the third fraction containing the other 1′-epimer of the (3*S*,4*S*)-alcohol **11** (207 mg, 0.46 mmol) also gave the (3*S*,4*S*)-ketone **13** (178 mg, 86%).

Oxidation of the least polar fraction containing both 1′-epimers of the (3*R*,4*S*)-alcohol **11** using PDC as outlined above, gave the (3*R*,4*S*)-diastereoisomer of the *title compound* **15** (85%), as an oil, $[\alpha]_D^{20}$ +25.7 (*c* 1.17 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 390.1924. $C_{20}H_{32}NO_3Si_2$ requires *M*, 390.1921);

ν_{max}/cm^{-1} 3070, 1740, 1665, 1600, 1580, 1255, 1198, 1185, 840 and 780; δ_H −0.14, −0.10, 0.22 and 0.33 (each 3 H, s, $SiCH_3$), 0.64 and 1.01 [each 9 H, s, $SiC(CH_3)_3$], 1.77 (3 H, s, 3-CH_3), 3.61 (1 H, t, *J* 3, 4-H), 3.78 and 4.05 (each 1 H, dd, *J* 11, 3, *H*CH), 7.38–7.57 (3 H, m, aromatic H) and 8.34 (2 H, m, ArH); *m/z* (CI) 448 (M^+ + 1) and 159 (100).

Methyl (S)-4-(tert-*Butyldimethylsilyloxy*)-3-*hydroxybutanoate* **18**.—Triethylamine (16 g, 0.158 mol), 4-(dimethylamino)-pyridine (0.6 g, 4.9 mmol) and *tert*-butyldimethylsilyl chloride (20 g, 0.133 mol) were added to a solution of the dihydroxy ester **17** (16.2 g, 0.121 mol) in dichloromethane (150 cm^3). The mixture was stirred overnight and poured into water. The two phases were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **18** (22 g, 73%), as an oil, $[\alpha]_D^{20}$ −10.25 (*c* 1.9 in $CHCl_3$) (Found: M^+ − CH_3O, 217.1260. $C_{10}H_{21}O_3$ requires *M*, 217.1260); $\nu_{max}(CHCl_3)$/cm^{-1} 3560, 1730, 1260, 1120 and 840; δ_H 0.08 [6 H, s, $Si(CH_3)_2$], 0.90 [9 H, s, $SiC(CH_3)_3$], 2.52 (2 H, m, 2-H_2), 2.87 (1 H, br s, OH), 3.57 (1 H, dd, *J* 10, 6, 4-H), 3.64 (1 H, dd, *J* 10, 5, 4-H′), 3.71 (3 H, s, OCH_3) and 4.05–4.11 (1 H, m, 3-H); *m/z* (CI) 249 (M^+ + 1, 100%).

Methyl (2R,3S)-4-(tert-*Butyldimethylsilyloxy*)-3-*hydroxy*-2-*methylbutanoate* **19**.—A solution of lithium diisopropylamide was prepared by adding butyllithium (1.35 mol dm^{-3} in hexane; 66 cm^3, 89.1 mmol) to diisopropylamine (10.11 g, 0.1 mol) in tetrahydrofuran (100 cm^3) at 0 °C. After 15 min, the solution was cooled to −50 °C, and the hydroxy ester **18** (9.9 g, 40 mmol) in tetrahydrofuran (50 cm^3) was added dropwise to it. The mixture was allowed to warm to −10 °C and then cooled to −60 °C. Tetramethylethylenediamine (5.1 g, 44 mmol) was added to the mixture followed, after 10 min, by iodomethane (8.66 g, 51 mmol). This gave white suspension which was stirred at −70 °C for 4 h before being allowed to warm to room temperature. Saturated aqueous ammonium chloride (200 cm^3) was added to the mixture and the aqueous layer was separated and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil which was chromatographed using light petroleum–ether (3:1) as eluent to give the *title compound* **19** (9 g, 86%), an oil, $[\alpha]_D^{20}$ −13.56 (*c* 2.1 in $CHCl_3$) (Found: M^+ − C_4H_9, 205.0897. $C_8H_{17}O_4Si$ requires *M*, 205.0896); $\nu_{max}(CHCl_3)$/cm^{-1} 3560, 1730, 1255, 1120, 1090 and 840; δ_H 0.08 [6 H, s, $Si(CH_3)_2$], 0.90 [9 H, s, $SiC(CH_3)_3$], 1.19 (3 H, d, *J* 7, 2-CH_3), 2.69 (1 H, m, 2-H), 2.88 (1 H, d, *J* 5, OH) and 3.56–3.8 (6 H, overlapping s and m, OCH_3, 3-H and 4-H_2); *m/z* (CI) 263 (M^+ + 1, 100%).

Methyl (2R,3S)-3-*Benzyloxymethoxy*-4-(tert-*butyldimethylsilyloxy*)-2-*methylbutanoate* **20**.—A solution containing the hydroxy ester **19** (7.86 g, 30 mmol), diisopropylethylamine (11.13 g, 86 mmol), 4-(dimethylamino)pyridine (0.5 g, 4.1 mmol) and benzyl chloromethyl ether (7.8 g, 50 mmol) in dichloromethane (125 cm^3) was stirred for 60 h at room temperature and then diluted with ether (300 cm^3) and poured into water (500 cm^3). The organic layer was separated, washed with water (150 cm^3) and saturated aqueous ammonium chloride (2 × 150 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was distilled to give the *title compound* **20** (10.54 g, 92%), bp 140–145 °C/0.04 mmHg, $[\alpha]_D^{20}$ −32 (*c* 1.9 in $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 3090, 3060, 3030, 3010, 1730, 1255, 1040, 1027 and 840; δ_H 0.06 [6 H, s, $Si(CH_3)_2$], 0.90 [9 H, s, $SiC(CH_3)_3$], 1.20 (3 H, d, *J* 7, 2-CH_3), 2.90 (1 H, m, 2-H), 3.69 (3 H, s, OCH_3), 3.74 (1 H, dd, *J* 11, 5, 4-H), 3.81 (1 H, dd, *J* 11, 4, 4-H′), 3.95 (1 H, m, 3-H), 4.59 and 4.64 (each 1 H, d, *J* 12, *H*CHPh), 4.80 and 4.87 (each 1 H, d, *J* 7, O*H*CHO) and 7.3–7.4 (5 H, m, ArH); *m/z* (CI) 275 (M^+ − 107, 100%).

(2R,3S)-3-*Benzyloxymethoxy*-4-(tert-*butyldimethylsilyloxy*)-2-*methylbutanal* **22**.—A solution of DIBAL-H (1 mol dm^{-3} in hexane; 55 cm^3) was added to a solution of the ester **20** (10.36 g, 27.1 mmol) in tetrahydrofuran (200 cm^3) at −78 °C, and the mixture stirred overnight at −25 °C. After the mixture had been cooled to −78 °C methanol (50 cm^3) was added to it and the whole was stirred for 15 min; it was then allowed to warm to room temperature before being poured into a stirred suspension of Celite (50 g) in water (250 cm^3). After being stirred for 30 min, the suspension was filtered, and the aqueous and organic layers were separated. The aqueous layer was extracted with ether (3 × 200 cm^3), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was chromatographed to give (2R,3S)-3-*benzyloxymethoxy*-4-(tert-*butyldimethylsilyloxy*)-2-*methylbutanol* **21** (9.03 g, 94%) as an oil, $[\alpha]_D^{20}$ −41.5 (*c* 1.6 in $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 3460, 3090, 3060, 3030, 3010, 1497, 1256, 1105, 1030, 840 and 700; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.91 [9 H, s, $SiC(CH_3)_3$], 1.03 (3 H, d, *J* 7, 2-CH_3), 1.92–2.04 (1 H, m, 2-H), 2.94 (1 H, br s, OH), 3.60 (1 H, m, 3-H), 3.70 and 3.79 (each 2 H, m), 4.61 and 4.72 (each 1 H, d, *J* 12, *H*CHPh), 4.82 and 4.93 (each 1 H, d, *J* 7, O*H*CHO) and 7.3–7.4 (5 H, m, ArH); *m/z* (CI) 247 (M^+ − 107, 100%).

A solution of dimethyl sulfoxide (330 mg, 4.2 mmol) in dichloromethane (5 cm^3) was added to a solution of oxalyl chloride (291 mg, 2.3 mmol) in dichloromethane (5 cm^3) at −78 °C. After 10 min, the alcohol **21** (425 mg, 1.2 mmol) in dichloromethane (5 cm^3) was added dropwise to the mixture which was then stirred for 5 min before being allowed to warm to room temperature. It was then diluted with water (25 cm^3) and the layers were separated. The aqueous layer was extracted with ether (2 × 10 cm^3) and the combined organic extracts were washed with brine (2 × 25 cm^3) and saturated aqueous ammonium chloride (2 × 25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was dissolved in light petroleum and the solution filtered through a plug of silica gel. Concentration of the filtrate under reduced pressure gave the title compound **22** as an oil (417 mg, 97%) which was used without further purification; $[\alpha]_D^{20}$ −13.7 (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} 3040, 3010, 2770 and 2730; δ_H 0.05 [6 H, s, $Si(CH_3)_2$], 0.88 [9 H, s, $SiC(CH_3)_3$], 1.15 (3 H, d, *J* 7, 2-CH_3), 2.72 (1 H, m, 2-H), 3.73 (2 H, m, 4-H_2), 4.05 (1 H, m, 3-H), 4.59 and 4.65 (each 1 H, d, *J* 12, *H*CHPh), 4.81 and 4.88 (each 1 H, d, *J* 7, O*H*CHO), 7.3–7.4 (5 H, m, ArH) and 9.74 (1 H, d, *J* 1.5, 1-H); *m/z* (CI) 370 (M^+ + 18, 100%).

(3S,4S)-3-[(2′R,3′S)-3′-*Benzyloxymethoxy*-4′-(tert-*butyldimethylsilyloxy*)-2′-*methyl*-1′-*oxobutyl*]-1-(tert-*butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*one* **24**.—Following the procedure outlined above, the azetidinone **5** (1.49 g, 4.3 mmol) was deprotonated using lithium diethylamide in tetrahydrofuran and condensed with the aldehyde **22** (1.68 g, 4.8 mol). Short column chromatography of the mixture of crude products gave two fractions. The less polar fraction was identified as one of the 1′-epimers of the (3*S*,4*S*)-3-(hydroxyalkyl)azetidinone **23** (2.07 g, 69%), an oil, $[\alpha]_D^{20}$ −19.2 (*c* 2.36 in $CHCl_3$); ν_{max}/cm^{-1} 3500, 3010, 1730, 1470, 1460, 1255, 1100, 1038 and 840; δ_H 0.01 and 0.03 [each 6 H, s, $Si(CH_3)_2$], 0.15 and 0.19 (each 3 H, s, $SiCH_3$), 0.85, 0.86 and 0.91 [each 9 H, s, $SiC(CH_3)_3$], 1.11 (3 H, d, *J* 7, 2′-CH_3), 1.15 (3 H, s, 3-CH_3), 1.98 (1 H, m, 2′-H), 3.12 (1 H, m), 3.55–3.80 (6 H, overlapping m), 3.93 (1 H, br s), 4.53 and 4.62 (each 1 H, d, *J* 12, *H*CHPh), 4.74 and 4.84 (each 1 H, d, *J* 7, O*H*CHO) and 7.21–7.29 (5 H, m, ArH); *m/z* (CI) 696 (M^+ + 1, 5%) and 588 (M^+ − 107, 80%). The more polar fraction (889 mg, 29%) was a mixture of compounds including the other three diastereoisomers of the 3-(hydroxyalkyl)azetidinone **23**.

A solution of dimethyl sulfoxide (165 mg, 2.12 mmol) in dichloromethane (2.5 cm^3) was added to a solution of oxalyl chloride (175 mg, 1.37 mmol) in dichloromethane (2.5 cm^3) at −78 °C followed by the less polar (3*S*,4*S*)-alcohol **23** (403 mg, 0.58 mmol) in dichloromethane (5 cm^3). The mixture was stirred at −78 °C for 30 min, after which diisopropylethylamine (816 mg, 6.31 mmol) was added to it. After being stirred for 30 min the mixture was allowed to warm to room temperature when saturated aqueous ammonium chloride (10 cm^3) was added to it. The two layers were separated, and the organic phase was washed with water (3 × 10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give an oil which was chromatographed to give the *title compound* **24** (387 mg, 96%) as an oil, $[\alpha]_D^{20}$ −43.2 (*c* 0.35 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 636.3573. $C_{32}H_{58}NO_6Si_3$ requires *M*, 636.3572); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 3010, 1740 and 1710; δ_H 0.06 [12 H, s, 2 × $Si(CH_3)_2$], 0.2 and 0.27 (each 3 H, s, $SiCH_3$), 0.87, 0.91 and 0.94 [each 9 H, s, $SiC(CH_3)_3$], 1.03 (3 H, d, *J* 7, 2′-CH_3), 1.54 (3 H, s, 3-CH_3), 3.57 (1 H, m), 3.68–3.93 (5 H, overlapping m), 4.13 (1 H, dd, *J* 7, 5, 4-H), 4.49 and 4.54 (each 1 H, d, *J* 12, *H*CHPh), 4.66 and 4.71 (each 1 H, d, *J* 7, OHCHO) and 7.28–7.36 (5 H, m, ArH); *m/z* (CI) 694 (M^+ + 1, 5%), 636 (M^+ − 57, 40) and 606 (M^+ − 87, 45).

(3S,4S)-3-[(2″R,3″S)-3″-*Benzyloxymethoxy*-4″-(tert-*butyldimethylsilyloxy*)-2″-*methyl*-1″-*oxobutyl*]-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methyl*-1-(1′-*oxopropyl*)*azetidin*-2-*one* **26**.—A solution of the *N*-silyl lactam **24** (361 mg, 0.52 mmol) and potassium fluoride (0.52 mmol) in methanol (1.5 cm^3) was stirred at 0 °C until the starting material could no longer be detected by TLC. Glacial acetic acid (0.52 mmol) was added to the solution which was then stirred for 10 min before being concentrated under reduced pressure to give an oil. This was suspended in ethyl acetate, and the mixture filtered. Concentration of the filtrate under reduced pressure gave the crude azetidinone **25** (256 mg, 85%) which was dissolved in dichloromethane and the solution cooled to 0 °C. Triethylamine (1.04 mmol), 4-(dimethylamino)pyridine (0.05 mmol) and propanoyl chloride (0.75 mmol) were added to the solution which was then stirred at room temperature until the azetidinone **25** could no longer be detected by TLC. The solution was poured into water, and the organic phase was separated, washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was chromatographed to give the *title compound* **26** (253 mg, 90%), $[\alpha]_D^{20}$ −69.8 (*c* 1.98 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 578.2971; $C_{29}H_{48}NO_7Si_2$ requires *M*, 578.2969); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 3010, 1785, 1710 and 1600; δ_H 0.03 (3 H, s, $SiCH_3$), 0.06 (9 H, s, 3 × $SiCH_3$), 0.86 and 0.92 [each 9 H, s, $SiC(CH_3)_3$], 1.04 (3 H, d, *J* 7, 2″-CH_3), 1.13 (3 H, t, *J* 7, 3′-H_3), 1.66 (3 H, s, 3-CH_3), 2.70 (2 H, q, *J* 7, 2′-H_2), 3.55 (1 H, m, 2″-H), 3.71 (1 H, m, 3″-H), 3.83–3.95 (3 H, m), 4.18 (1 H, dd, *J* 11, 5, 4‴-H), 4.43 and 4.55 (3 H, m), 4.65 and 4.76 (each 1 H, d, *J* 7, O*H*CHO) and 7.28–7.35 (5 H, m, ArH); *m/z* (CI) 528 (M^+ − 197, 60%).

(3R,4S)- *and* (3S,4S)-1-(tert-*Butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-[3′-(tert-*butyldimethylsilyloxy*)-1′-*oxopropyl*]-3-*methylazetidin*-2-*ones* **35** *and* **31**.—Following the procedure outlined above the azetidinone **5** (1.25 g, 3.64 mmol) was deprotonated using lithium diethylamide and condensed with 3-(*tert*-butyldimethylsilyloxy)propanal (850 mg, 4.52 mmol). Short column chromatography of the crude product gave two fractions, a less polar fraction (370 mg, 19%) and a more polar fraction (1.49 g, 77%). Oxidation of a sample (200 mg, 0.38 mmol) of the less polar fraction using PDC (1.14 mmol) in dichloromethane as outlined above gave the (3*R*,4*S*)-isomer of the *title compound* **35** (190 mg, 95%), $[\alpha]_D^{20}$ +44.7 (*c* 0.94 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 472.2739. $C_{22}H_{46}NO_4Si_3$ requires *M*, 472.2735); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740, 1710, 1255, 1102 and 840; δ_H 0.03 (3 H, s, $SiCH_3$), 0.04 (9 H, s, 3 × $SiCH_3$), 0.19 and 0.32 (each 3 H, s, $SiCH_3$), 0.86, 0.87 and 0.98 [each 9 H, s, $SiC(CH_3)_3$], 1.53 (3 H, s, 3-CH_3), 2.68 (1 H, dt, *J* 18, 6, 2′-H), 3.17 (1 H, dt, *J* 18, 7, 2′-H), 3.44 (1 H, t, *J* 3, 4-H) and 3.72–3.96 (4 H, overlapping m, 4-CH_2 and 3′-H_2); *m/z* (EI) 472 (M^+ − 57, 20%). Oxidation of a sample (200 mg, 0.38 mmol) of the more polar fraction using PDC (1.14 mmol) in dichloromethane as outlined above gave the (3*S*,4*S*)-isomer of the *title compound* **31** (188 mg, 94%), $[\alpha]_D^{20}$ −10.12 (*c* 6 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 472.2734. $C_{22}H_{46}NO_4Si_3$ requires *M*, 472.2735); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740, 1710, 1255, 1104 and 838; δ_H 0.04 and 0.07 [each 6 H, s, $Si(CH_3)_2$], 0.22 and 0.26 (each 3 H, s, $SiCH_3$), 0.86, 0.89 and 0.95 [each 9 H, s, $SiC(CH_3)_3$], 1.46 (3 H, s, 3-CH_3), 2.74–2.93 (2 H, m, 2′-H_2), 3.70 (1 H, dd, *J* 11, 7, *H*CH), 3.79 (1 H, dd, *J* 11, 5, HC*H*), 3.90 (2 H, t, *J* 6, 3′-H_2) and 3.99 (1 H, dd, *J* 7, 5, 4-H); *m/z* (EI) 472 (M^+ − 57, 20%).

(3S,4S)- *and* (3R,4S)-4-(tert-*Butyldimethylsilyloxymethyl*)-3-[3″-(tert-*butyldimethylsilyloxy*)-1″-*oxopropyl*]-1-(1′-*oxopropyl*)-3-*methylazetidinones* **39** *and* **41**.—A solution of potassium fluoride (1.26 mmol) in methanol (1 cm^3) was added to a solution of the azetidinone **31** (664 mg, 1.26 mmol) in methanol (5 cm^3) at 0 °C, and the solution stirred until no starting material could be detected by TLC. Glacial acetic acid (1.26 mmol) was added to the mixture which, after a further 10 min, was concentrated under reduced pressure. The residue was suspended in ethyl acetate, and the mixture filtered. The filtrate was concentrated under reduced pressure to give the azetidinone **32**. This was immediately dissolved in dichloromethane (5 cm^3) and triethylamine (2.52 mmol), 4-(dimethylamino)pyridine (0.1 mmol) and propanoyl chloride (1.9 mmol) were added to the solution. The mixture was stirred until the azetidinone **32** could no longer be detected by TLC, after which it was poured into water. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was chromatographed to give the (3*S*,4*S*)-diastereoisomer of the *title compound* **39** (579 mg, 95%), $[\alpha]_D^{20}$ −37.5 (*c* 7.2 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 414.2135. $C_{19}H_{36}NO_5Si_2$ requires *M*, 414.2132); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785, 1710, 1600, 1380, 1260, 1110 and 840; δ_H 0.03 (3 H, s, $SiCH_3$), 0.04 [6 H, s, $Si(CH_3)_2$], 0.07 (3 H, s, $SiCH_3$), 0.86 and 0.87 [each 9 H, s, $SiC(CH_3)_3$], 1.15 (3 H, t, *J* 7, 1′-H_3), 1.61 (3 H, s, 3-CH_3), 2.64–2.93 (4 H, m, 2′-H_2 and 2″-H_2), 3.88–4.00 (3 H, m, *H*CH and 3″-H_2), 4.15 (1 H, dd, *J* 11, 6, HC*H*) and 4.41 (1 H, dd, *J* 6, 2, 4-H); *m/z* (CI) 472 (M^+ + 1, 80%) and 414 (100).

Following the above procedure the azetidinone **35** (500 mg, 0.95 mmol) was deprotected and acylated to give the (3*R*,4*S*)-diastereoisomer of the *title compound* **41** (431 mg, 97%), $[\alpha]_D^{20}$ −5.3 (*c* 2.72 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785, 1710, 1600, 1380, 1315, 1260, 1105 and 840; δ_H −0.04 and −0.02 (each 3 H, s, $SiCH_3$), 0.05 [6 H, s, $Si(CH_3)_2$], 0.81 and 0.87 [9 H, s, $SiC(CH_3)_3$], 1.24 (3 H, t, *J* 7.5, 1′-H_3), 1.58 (3 H, s, 3-CH_3), 2.63–2.83 (3 H, m, 2′-H_2 and 2″-H), 3.15–3.3 (1 H, dt, *J* 17, 6, 2″-H), 3.86–4.05 (4 H, m, 4-H, *H*CH and 3″-H_2) and 4.23 (1 H, dd, *J* 11, 2.5, HC*H*); *m/z* (CI) 472 (M^+ + 1, 100) and 414 (M^+ − 57, 50).

(3S)-3-[(1′S)-2′-tert-*Butyldimethylsilyloxy*-1′-(*propanoylamino*)*ethyl*]-3-*methyltetrahydropyran*-2,4-*dione* **43**.—Toluene-*p*-sulfonic acid (8 mg, 42 μmol) was added to a solution of the ketone **39** (177 mg, 0.38 mmol) in aqueous tetrahydrofuran (tetrahydrofuran–water, 20:1; 2.5 cm^3), and the solution stirred at room temperature for 3 h. Calcium hydroxide (30 mg) was then added to it and the suspension stirred for 30 min. The mixture was filtered and the filtrate dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. This was chromatographed (light petroleum–ethyl acetate, 3:2) to give the *title compound* **43** (94 mg, 62%), $[\alpha]_D^{20}$ −32 (*c* 0.96 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 300.1270. $C_{13}H_{22}NO_5Si$ requires *M*, 300.1267); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1745, 1715, 1670, 1505, 1391, 1261, 1110 and 840; δ_H 0.01 [6 H, s, $Si(CH_3)_2$], 0.84 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, t, *J* 8, CH_2CH_3), 1.49 (3 H, s, 3-CH_3), 2.29 (2 H, m, CH_2CH_3), 2.73 (1 H, ddd, *J* 16, 7, 5, 5-H), 2.92 (1 H, ddd, *J* 16, 8, 5, 5-H), 3.56 (1 H, dd, *J* 11, 5, 2′-H), 3.80 (1 H, dd, *J* 11, 3, 2′-H), 4.45 (1 H, ddd, *J* 12, 9, 4, 6-H), 4.60 (1 H, ddd, *J* 12, 7, 5, 6-H), 4.82 (1 H, ddd, *J* 10, 5, 4, 1′-H) and 6.73 (1 H, d, *J* 10, NH); *m/z* (CI) 358 (M^+ + 1, 100).

(3R)-3-[(1′S)-2′-tert-*Butyldimethylsilyloxy*-1′-(*propanoylamino*)*ethyl*]-3-*methyltetrahydropyran*-2,4-*dione* **44**.—Following the above procedure, the ketone **41** (181 mg, 0.38 mmol) gave the *title compound* **44** (84 mg, 61%), $[\alpha]_D^{20}$ −44.7 (*c* 0.8 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 300.1270. $C_{13}H_{22}NO_5Si$ requires *M*, 300.1267); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1740, 1710, 1670, 1395, 1260 and 840; δ_H 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, t, *J* 8, CH_2CH_3), 1.43 (3 H, s, 3-CH_3), 2.28 (2 H, q, *J* 8, CH_2CH_3), 2.82 (2 H, m, 5-H_2), 3.53 (1 H, dd, *J* 11, 7, 2′-H), 3.68 (1 H, dd, *J* 11, 5, 2′-H), 4.54 (2 H, m, 6-H_2), 4.85 (1 H, ddd, *J* 10, 7, 5, 1′-H) and 6.74 (1 H, d, *J* 10, NH); *m/z* (CI) 358 (M^+ + 1, 100).

(3R,4S)- *and* (3S,4S)-3-[3′-(*Benzyloxymethoxy*)-1′-*oxopropyl*)-1-(tert-*butyldimethylsilyl*)-4-(tert-*butyldimethylsilyloxymethyl*)-3-*methylazetidin*-2-*ones* **37** *and* **33**.—Following the procedure outlined above, the azetidinone **5** (3.43 g, 10 mmol) and 3-(benzyloxymethoxy)propanal (2.45 g, 12.6 mmol) were condensed using lithium diethylamide as base. Short column chromatography gave four fractions **A**, **B**, **C** and **D** (401 mg, 7%; 404 mg, 7%; 425 mg, 8% and 3.92 g, 73%, respectively). Oxidation of samples of fractions **A** and **B** (214 mg, 0.4 mmol and 247 mg, 0.46 mmol) using PDC in dichloromethane as outlined above gave the (3*R*,4*S*)-diastereoisomer of the *title compound* **37** (207 mg, 97% and 224 mg, 91%), $[\alpha]_D^{20}$ +46.5 (*c* 3.55 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3010, 1740, 1710, 1255, 1053 and 840; δ_H 0.03, 0.04, 0.20 and 0.33 (each 3 H, s, $SiCH_3$), 0.87 and 0.99 [each 9 H, s, $SiC(CH_3)_3$], 1.56 (3 H, s, 3-CH_3), 2.81 (1 H, dt, *J* 18, 6, 2′-H), 3.24 (1 H, ddd, *J* 18, 7, 6, 2′-H), 3.46 (1 H, t, *J* 3, 4-H), 3.74–3.94 (4 H, m, 4-CH_2 and 3′-H_2), 4.59 (2 H, s, CH_2Ph), 4.73 (2 H, s, OCH_2O) and 7.28–7.45 (5 H, m, ArH); *m/z* (CI) 553 (M^+ + 18, 20%) and 536 (M^+ + 1, 100). Oxidation of samples of fractions **C** and **D** (245 mg, 0.46 mmol and 1.53 g, 2.85 mmol) using PDC in dichloromethane as outlined above gave the (3*S*,4*S*)-diastereoisomer of the *title compound* **33** (232 mg, 95% and 1.45 g, 95%), $[\alpha]_D^{20}$ −12.3 (*c* 1.6 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 3010, 1740, 1710, 1470, 1462, 1237, 1112, 1055 and 840; δ_H 0.08 [6 H, s, $Si(CH_3)_2$], 0.22 and 0.28 (each 3 H, s, $SiCH_3$), 0.90 and 0.85 [each 9 H, s, $SiC(CH_3)_3$], 1.49 (3 H, s, 3-CH_3), 2.80–3.05 (2 H, m, 2′-H_2), 3.73 (1 H, dd, *J* 11, 7, *H*CH), 3.81 (1 H, dd, *J* 11, 5, HC*H*), 3.88 (2 H, t, *J* 6, 3′-H_2), 4.05 (1 H, dd, *J* 7, 5, 4-H), 4.58 (2 H, s, CH_2Ph), 4.73 (2 H, s, OCH_2O) and 7.28–7.37 (5 H, m, aromatic H); *m/z* (CI) 553 (M^+ + 18, 2%), 536 (M^+ + 1, 4%) and 271 (100).

(3S,4S)-3-[3″-(*Benzyloxymethoxy*)-1″-*oxopropyl*]-4-(tert-*butyldimethylsilyloxymethyl*)-1-(1′-*oxopropyl*)-3-*methylazetidinone* **40**.—The azetidinone **33** (753 mg, 1.41 mmol) was selectively *N*-deprotected and *N*-acylated following the procedure outlined above to give the *title compound* **40** (618 mg, 92%), $[\alpha]_D^{20}$ −40.1 (*c* 1.1 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 420.1844. $C_{21}H_{30}NO_6Si$ requires *M*, 420.1842); $\nu_{max}(CHCl_3)$ 3030, 3010, 1780, 1710, 1378, 1114, 1050 and 840; δ_H 0.03 and 0.06 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.14 (3 H, t, *J* 7, CH_2CH_3), 1.62 (3 H, s, 3-CH_3), 2.70 (2 H, q, *J* 7, CH_2CH_3), 2.89 (2 H, m, 2″-H_2), 3.87 (2 H, t, *J* 6, 3″-H_2), 3.95 (1 H, dd, *J* 11, 2, *H*CH), 4.16 (1 H, dd, *J* 11, 6, HC*H*), 4.40 (1 H, dd, *J* 6, 2, 4-H), 4.57 (2 H, s, CH_2Ph), 4.71 (2 H, s, OCH_2O) and 7.30–7.38 (5 H, m, ArH); *m/z* (CI) 495 (M^+ + 18, 60%) and 478 (M^+ + 1, 100).

A solution of the azetidinone **40** (320 mg, 0.67 mmol) in ethanol (2.5 cm^3) was added to a suspension of palladium-on-charcoal (10% w/w; 75 mg) in ethanol (2.5 cm^3), and the suspension shaken under an atmosphere of hydrogen for 6 h. The mixture was filtered, and the filtrate concentrated under reduced pressure. Chromatography of the residue gave the tetrahydropyran-2,4-dione **43** (199 mg, 83%).

(3R,4S)-3-[3″-(*Benzyloxymethoxy*)-1″-*oxopropyl*]-4-(tert-*butyldimethylsilyloxymethyl*)-1-(1′-*oxopropyl*)-3-*methylazetidinone* **42**.—The azetidinone **37** (304 mg, 0.57 mmol) was selectively *N*-protected and *N*-acylated following the procedure outlined above to give the *title compound* **42** (244 mg, 90%), $[\alpha]_D^{20}$ +20 (*c* 1.92 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 420.1840. $C_{21}H_{30}NO_6Si$ requires *M*, 420.1842); $\nu_{max}(CHCl_3)/cm^{-1}$ 3030, 1780, 1710, 1380, 1315, 1255, 1110, 1052, 1025 and 840; δ_H −0.03 and −0.01 (each 3 H, s, $SiCH_3$), 0.81 [9 H, s, $SiC(CH_3)_3$], 1.18 (3 H, t, *J* 7, CH_2CH_3), 1.57 (3 H, s, 3-CH_3), 2.63–2.86 (3 H, m, CH_2CH_3 and 2″-H), 3.24 (1 H, m, 2″-H), 3.78 (1 H, m), 3.90–3.99 (3 H, m), 4.21 (1 H, dd, *J* 11, 2, HC*H*), 4.20 (2 H, s, CH_2Ph), 4.74 (2 H, s, OCH_2O) and 7.28–7.42 (5 H, m, ArH); *m/z* (CI) 478 (M^+ + 1, 20%) and 340 (100).

Hydrogenolysis of the azetidinone **42** (750 mg, 1.57 mmol) following the procedure outlined above gave the tetrahydropyran-2,4-dione **44** (488 mg, 87%).

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