Stereoselective synthesis of allylic amines by rearrangement of allylic trifluoroacetimidates: stereoselective synthesis of polyoxamic acid and derivatives of other α-amino acids

Ian Savage,[a] Eric J. Thomas *[b] and Peter D. Wilson [b]

[a] *The Dyson Perrins Laboratory, South Parks Road, Oxford, UK OX1 3QY*
[b] *The Department of Chemistry, The University of Manchester, Manchester, UK M13 9PL*

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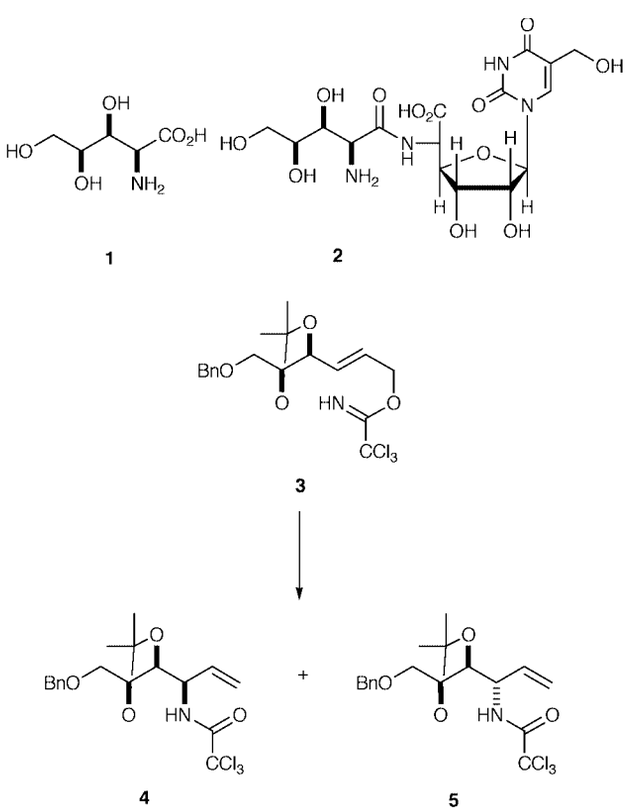
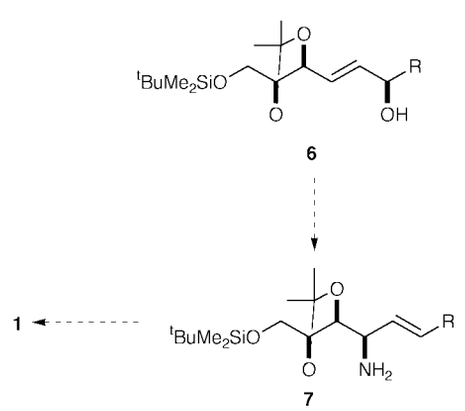
On heating in xylene under reflux, allylic *trifluoro*acetimidates undergo [3,3] sigmatropic rearrangement to regioisomeric allylic trifluoroacetamides. Examples include the rearrangements of the trifluoroacetimidates **16** and **73** to the trifluoroacetamides **17** and **74**, which were incorporated into stereoselective syntheses of polyoxamic acid **1**, and the rearrangement of the trifluoroacetimidate **26**. The rearrangement was the key step in asymmetric syntheses of the (*S*)- and (*R*)-valine derivatives **37** and **48**. Other examples include rearrangements of the trifluoroacetimidates **52**, **54** and **56** prepared from geraniol, cinnamyl alcohol and sorbyl alcohol, respectively, and the more complex trifluoroacetimidates **62** and **69**. The stereoselectivity of these rearrangements, which are somewhat faster than rearrangements of analogous allylic *trichloro*acetimidates, is consistent with the participation of chair-like, six-membered, transition structures.

The [3,3] sigmatropic rearrangement of allylic *trichloro*acetimidates introduced and developed by Overman, is widely used for the stereoselective synthesis of amines.[1] Polyoxamic acid **1** a



component of the polyoxins, a group of nucleoside antibiotics exemplified by polyoxin B **2**,[2] has been the subject of many synthetic studies[3] including an early non-stereoselective synthesis based on the Overman rearrangement of the trichloroacetimidate **3**.[4] This rearrangement gave a mixture of the trichloroacetamides **4** and **5** which were separated and taken through to polyoxamic acid **1** and its 2-epimer. Since the Overman rearrangement is known to proceed with effective 1,3-transfer of chirality,[1] it was decided to investigate the rearrangement of trichloroacetimidates derived from the chiral alcohols **6** as a stereoselective route *via* amines **7** to polyoxamic acid **1**.

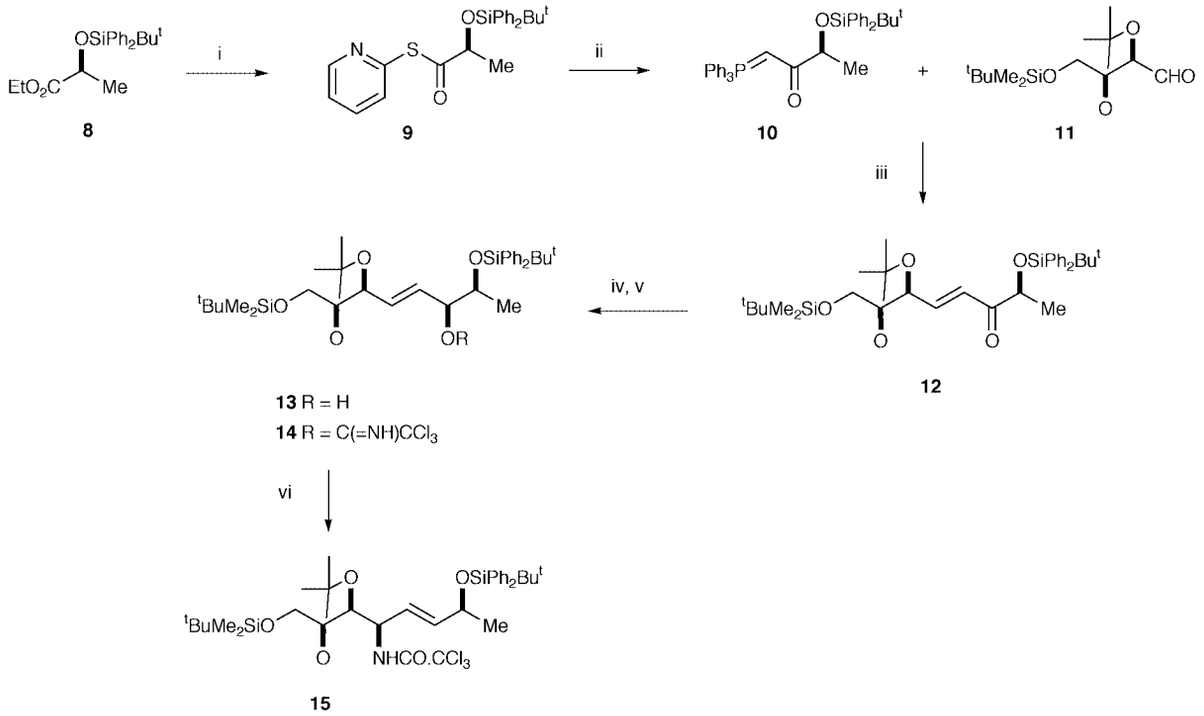


During the course of this work, the [3,3] sigmatropic rearrangements of *trifluoro*acetimidates were investigated. We here report full details of these investigations including stereoselective syntheses of polyoxamic acid and derivatives of other α-amino acids using trifluoroacetimidates.[5,6]

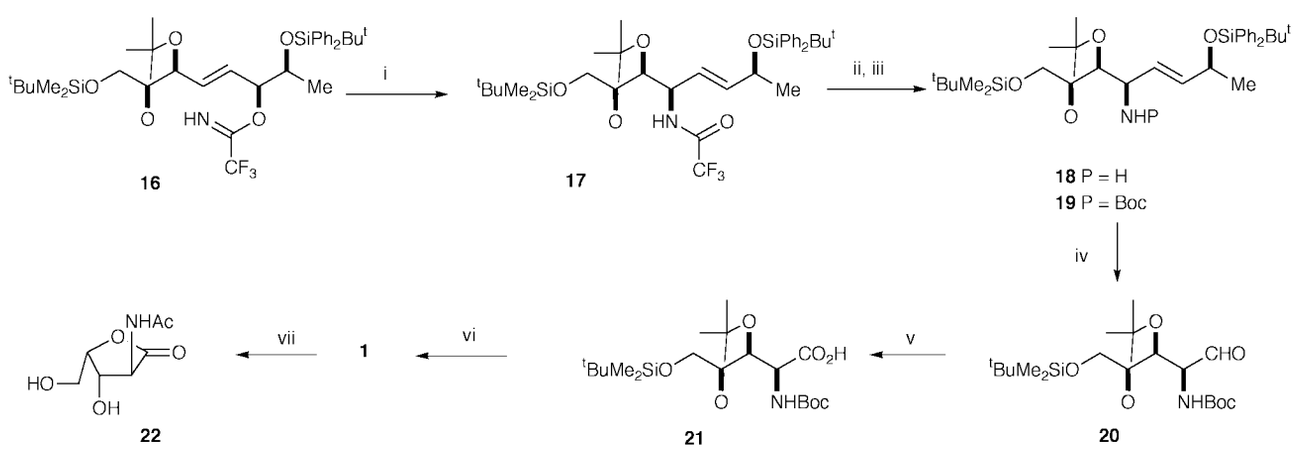
Results and discussion

Stereoselective synthesis of polyoxamic acid

The trichloroacetimidate **14** was prepared as outlined in Scheme 1. The ylide **10** was prepared from the thioester **9** and an excess of methylenetriphenylphosphorane, and on heating with the L-threose derivative **11**[7] in benzene under reflux gave a good yield of the enone **12**. Reduction of this enone using L-Selectride at −78 °C was highly stereoselective and gave the alcohol **13**, the all-*syn* configuration initially being assigned to the alcohol on the basis of Felkin–Anh control of the reduction,[8] and was later confirmed by the conversion of the alcohol



Scheme 1 *Reagents and conditions*: i, KOH, MeOH then dicyclohexylcarbodiimide, 2-mercaptopyridine (70%); ii, Ph_3PMeBr, butyllithium (75%); iii, benzene, reflux, 5 h (85%); iv, L-Selectride, tetrahydrofuran, −78 °C, 40 min (90%); v, butyllithium, trichloroacetonitrile (85%); vi, xylene, heat, 48 h (40%).

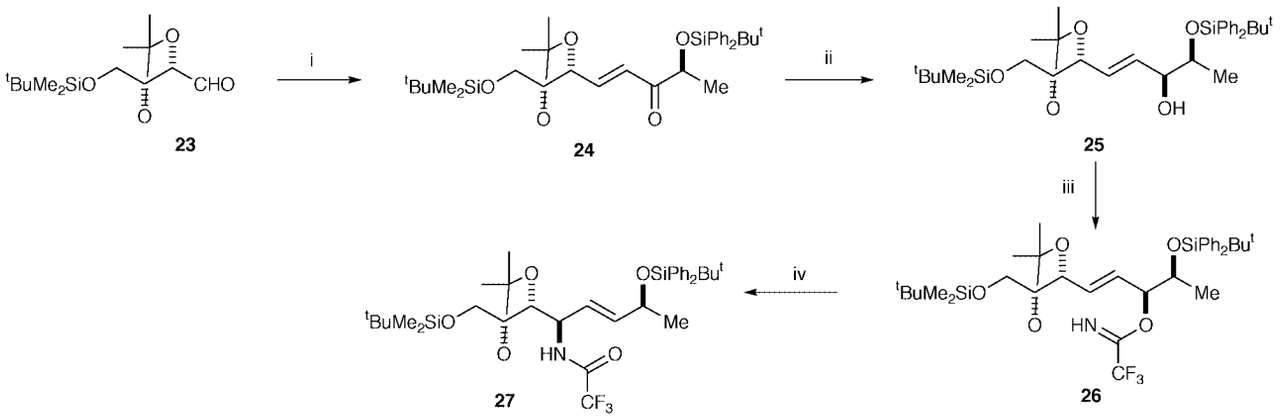


Scheme 2 *Reagents and conditions*: i, xylene, heat, 20 h (80%); ii, $NaBH_4$, ethanol (75%); iii, $(Boc)_2O$, Et_3N (>95%); iv, ozone, methanol, dimethyl sulfide; v, $RuCl_3$, $NaIO_4$, MeCN (69%); vi, trifluoroacetic acid, methanol (72%); vii, Ac_2O, methanol (60%).

13 into polyoxamic acid **1**. It was important to quench this reduction by the addition of glacial acetic acid at a low temperature. If the reaction mixture was allowed to warm to room temperature before acidification, a mixture of the alcohol **13** and its regioisomer in which the *tert*-butyldiphenylsilyl group had migrated from the 4-OH to the 3-OH was obtained. Conversion of the alcohol **13** into the trichloroacetimidate **14** was carried out by deprotonation of the alcohol using butyllithium and addition of the solution of the alkoxide to a solution of trichloroacetonitrile (85%).[9]

The rearrangement of the trichloroacetimidate **14** into the trichloroacetamide **15** was carried out by heating under reflux in xylene and was highly stereoselective, the *syn*-configuration of the product being assigned on the basis of participation of a chair-like transition structure in the [3,3] sigmatropic rearrangement.[1] However, the reaction required heating for a long period of time for completion (*ca*. 48 h) and only a modest yield (40%) of the trichloroacetamide was isolated because of competing decomposition under the prolonged reaction conditions. The slowness of the reaction was attributed to the presence of several oxygen-containing, electron-withdrawing groups in the allyl component of the trichloroacetimidate.[10] It was decided to investigate the rearrangement of the corresponding *trifluoro*-acetimidate since it was felt that the presence of three, very electron-withdrawing, fluorine substituents in the acetimidate component would allow the sigmatropic rearrangement to proceed under milder conditions.[1]

The trifluoroacetimidate **16** was prepared by adding a solution of the lithium alkoxide of the alcohol **13** to a solution of trifluoroacetonitrile in tetrahydrofuran at −78 °C,[11] see Scheme 2. The rearrangement of the trifluoroacetimidate into the trifluoroacetamide **17** in xylene under reflux was found to be highly stereoselective and was complete after 20 h. A good yield (85%) of the trifluoroacetamide **17** was obtained with no other stereoisomer being isolated or detected (≤4%). To complete a stereoselective synthesis of polyoxamic acid, the trifluoroacetamide **17** was converted into the amine **18** by reduction using sodium borohydride in ethanol[12] and the amine converted into the carbamate **19** under standard conditions. Ozonolysis of the carbamate gave the aldehyde **20** which was



Scheme 3 *Reagents and conditions*: i, **10**, benzene, heat (65%); ii, L-Selectride, tetrahydrofuran, −78 °C, then add acetic acid (82%); iii, butyllithium, trifluoroacetonitrile, −78 °C (70%); iv, xylene, heat, 20 h (76%).

immediately converted into the acid **21** using ruthenium trichloride and sodium periodate.[13] Deprotection using trifluoroacetic acid then gave polyoxamic acid **1** the structure of which was confirmed by conversion into the lactone **22** on treatment with acetic anhydride, and direct comparison of the lactone with an authentic sample.[4]

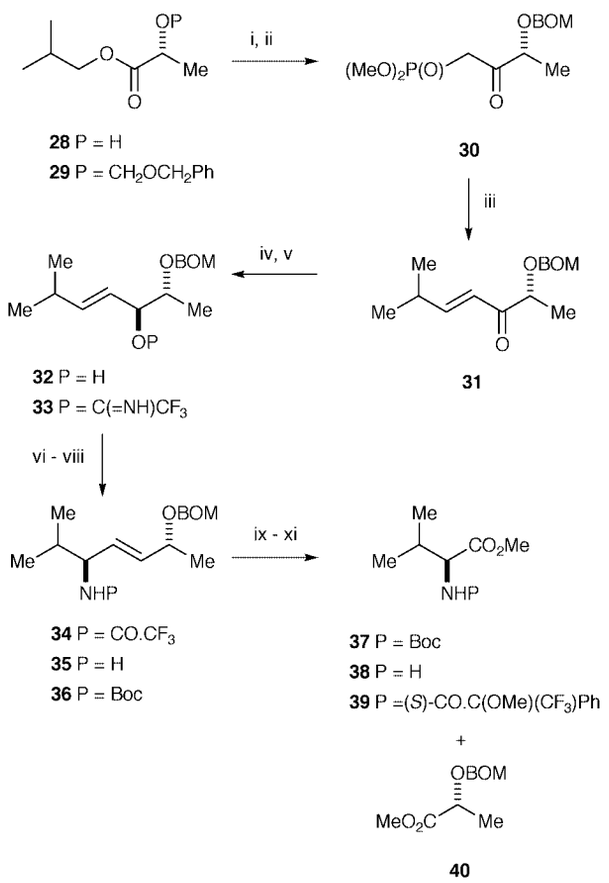
To check that the stereoselectivity of the trifluoroacetimidate rearrangement was not being influenced significantly by the presence of remote chiral centres in the substrate, rearrangement of the isomeric trifluoroacetimidate **26** was examined, see Scheme 3. This was prepared from the threose derivative **23** and was found to rearrange stereoselectively to the trifluoroacetamide **27** (76%) on heating in xylene under reflux; no other isomeric rearrangement product was isolated or detected (≤4%).

It would appear that the [3,3] sigmatropic rearrangement of allylic trifluoroacetimidates to allylic trifluoroacetamides is an efficient process. It was decided to investigate this reaction further to evaluate its use for stereoselective synthesis.

Further evaluation of the allylic trifluoroacetimidate to trifluoroacetamide rearrangement

The trifluoroacetimidate rearrangement was applied to complete asymmetric syntheses of derivatives of (*S*)- and (*R*)-valine, see Schemes 4 and 5. In this work it was decided to use chelation control to direct the reduction of the intermediate enone to avoid the problems associated with migration of the *O*-silyl protecting group encountered during the synthesis of polyoxamic acid.

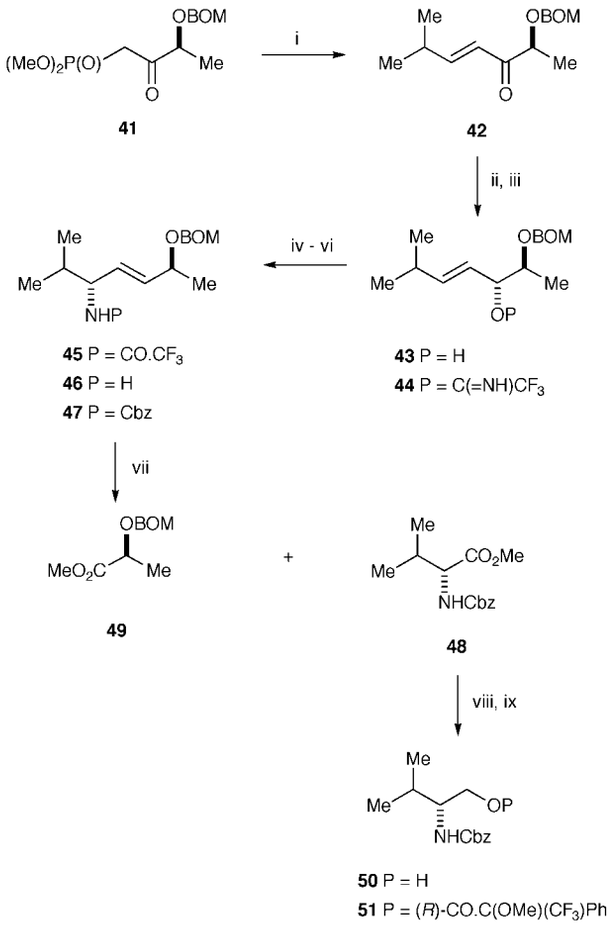
Isobutyl (*R*)-lactate **28** was protected as its benzyloxymethyl ether **29** which was converted into the ketophosphonate **30** by treatment with lithiated dimethyl methylphosphonate. Condensation of this ketophosphonate with 2-methylpropanal gave the enone **31** (77%) which was reduced to the *anti*-alcohol **32** using zinc borohydride,[14] *ca*. 99 : 1 *anti* : *syn* stereoselectivity,† the *anti*-configuration being assigned to the major product on the basis of chelation control of the reduction.[8] The alcohol **32** was converted into the trifluoroacetimidate **33** by treatment with butyllithium and trifluoroacetonitrile at −78 °C, the optimum conditions requiring only a catalytic amount of base. The [3,3] rearrangement of the trifluoroacetimidate proceeded cleanly in xylene heated under reflux to give the trifluoroacetamide **34** (89%) which appeared to be a single diastereoisomer by ^{1}H NMR. The trifluoroacetamide was converted into the *tert*-butoxycarbonyl derivative **36** which was cleaved by ozonolysis



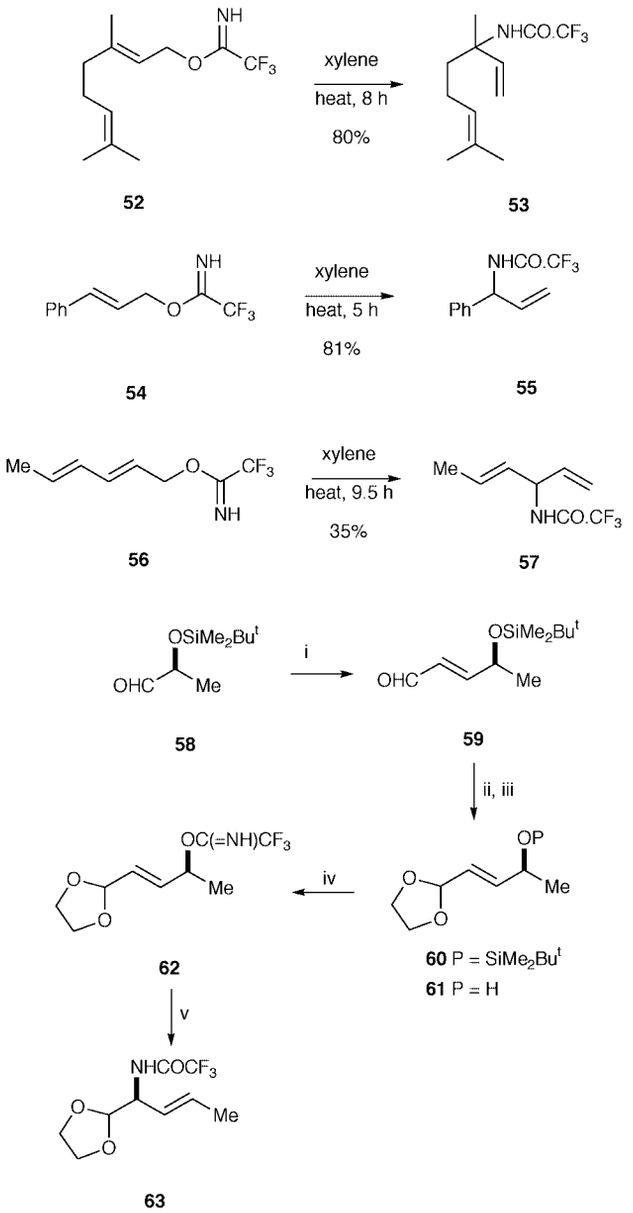
Scheme 4 *Reagents and conditions*: i, benzyl chloromethyl ether, *N*,*N*-diisopropylethylamine (83%); ii, $(MeO)_2P(O)CH_2Li$, tetrahydrofuran (92%); iii, lithium chloride, DBU, 2-methylpropanal (77%); iv, $Zn(BH_4)_2$, ether, −35 °C (97%); v, butyllithium (0.2 eq.), trifluoroacetonitrile, −78 °C (90%); vi, xylene, reflux, 4 h (89%); vii, $Ba(OH)_2$, methanol; viii, Boc_2O, Et_3N, ether (79% from **34**); ix, ozone, methanol, −78 °C, then dimethyl sulfide followed by bromine in methanol (65%); x, trifluoroacetic acid, methanol; xi, (*S*)-methoxytrifluoromethylphenylacetyl chloride, pyridine (73% from **37**).

with immediate oxidation of the intermediate aldehyde using bromine in methanol[15] to give the (*S*)-valine derivative **37**. This procedure was found to minimize racemisation during the ozonolysis and oxidation steps but gave a mixture of the methyl ester **37** and methyl (*R*)-2-benzyloxymethoxypropanoate **40**. The isolation of ester **40** corresponds, at least formally, to a recovery of the chiral auxiliary used in this synthesis since the isobutyl ester **29** was the original source of chirality. However, the two methyl esters **37** and **40** were difficult to separate and the (*S*)-valine derivative **37** was only obtained pure using

† In all cases, the product mixture from reduction of the enones using zinc borohydride was compared by HPLC with a mixture of *syn* and *anti*-diastereoisomeric alcohols prepared by non-stereoselective reduction using sodium borohydride. The chelation controlled reduction was invariably ≥98 : 2 stereoselective.



Scheme 5 *Reagents and conditions*: i, lithium chloride, DBU, 2-methylpropanal (75%); ii, $Zn(BH_4)_2$, ether, −35 °C (95%); iii, butyllithium (0.2 eq.), trifluoroacetonitrile, −78 °C (92%); iv, xylene, reflux, 4 h (91%); v, $Ba(OH)_2$, methanol; vi, benzyl chloroformate, $KHCO_3$ (86% from **45**); vii, ozone, methanol, −78 °C, then dimethyl sulfide followed by bromine in methanol (84%); viii, $NaBH_4$, lithium chloride (95%); ix, (*R*)-methoxytrifluoromethylphenylacetyl chloride, pyridine (>95%).



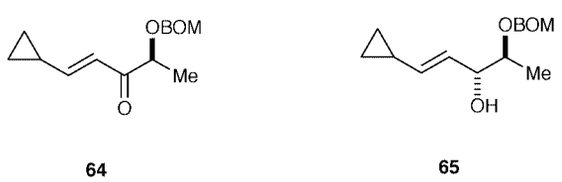
Scheme 6 *Reagents and conditions*: i, $Ph_3PCH{\cdot}CHO$ (87%); ii, ethane-1,2-diol, toluene-*p*-sulfonic acid (cat.), benzene (76%); iii, NBu_4F, tetrahydrofuran (94%); iv, butyllithium, trifluoroacetonitrile (79%); v, xylene, heat (93%).

HPLC. Its optical purity was estimated to correspond to an ee of *ca*. 80% using the ^{19}F NMR spectrum of its (*S*)-Mosher's derivative **39**.

When this sequence was repeated in the enantiomeric series starting with the (*S*)-phosphonate **41**, prepared from ethyl (*S*)-lactate, the rearrangement product **45** was converted into its benzyloxycarbonyl derivative **47** before the oxidative cleavage steps. This gave the methyl ester of Cbz-protected (*R*)-valine **48** which was more easily separated from the recovered auxiliary **49**. Reduction of the ester **48** using sodium borohydride–lithium chloride gave the alcohol **50** which was estimated to have an ee of 85% from the ^{19}F NMR spectrum of its (*R*)-Mosher's derivative **51**.

To evaluate further the scope of the trifluoroacetimidate rearrangement, the trifluoroacetimidates **52**, **54** and **56** were prepared from geraniol, cinnamyl alcohol and sorbyl alcohol, respectively. The sigmatropic rearrangements were carried out in xylene heated under reflux and gave the corresponding trifluoroacetamides **53**, **55** and **57** in reasonable yields (*ca*. 80%, not optimised) except for the hexadienyl trifluoroacetamide **57** which was only obtained in a yield of 35%. The reasons for this low yield were not investigated. As a preliminary study for a proposed synthesis of an unsaturated amino-acid, (*S*)-2-*tert*-butyldimethylsilylpropanal **58**[16] was converted into the unsaturated acetal **60** *via* the enal **59** (Scheme 6). Desilylation of the enal gave the alcohol **61** which was converted into the trifluoroacetimidate **62**. Rearrangement of this under the standard conditions gave the trifluoroacetamide **63** in excellent yield.

Except for the formation of **57**, in all cases investigated, the rearrangement of allylic trifluoroacetimidates was efficient and appeared to be highly stereoselective, but in some cases difficulties were experienced in preparing the allylic trifluoroacetimidates efficiently from the alcohol and trifluoroacetonitrile. In particular, the hydroxyalkenylcyclopropane **65**, prepared by



chelation controlled reduction of the enone **64**, gave a complex mixture of products perhaps formed by participation of an allylic carbocation. Similarly only a modest yield of the trifluoroacetimidate **69** was obtained from the alcohol **68** (Scheme 7) although the rearrangement of **69** into the trifluoroacetamide **70** was both efficient and stereoselective (^1H NMR).

In this case it may be that the Boc-protected amine is interfering with the conversion of the alcohol into its trifluoroacetimidate.

Finally, an improved synthesis of polyoxamic acid was developed as outlined in Scheme 8. Condensation of the phosphonate **30** with the aldehyde **11** gave the enone **71**. Chelation controlled reduction gave the alcohol **72** which was converted into the trifluoroacetimidate **73**. Rearrangement of the trifluoroacetimidate in xylene heated under reflux gave the trifluoroacetamide **74** with excellent stereoselectivity (≥96 : 4, ^{1}H NMR). Oxidative cleavage of the carbamate **76**, available in two steps from the trifluoroacetamide, by ozonolysis followed by treatment of the ozonide with bromine in methanol, gave the methyl ester **77** together with BOM-protected methyl lactate **40**. Saponification of this mixture gave the acid **21** which was taken through to polyoxamic acid **1** and the lactone **22** as before.

Conclusions

The [3,3] sigmatropic rearrangement of allylic trifluoroacetimidates would appear to be an efficient process with effective 1,3-transfer of chirality consistent with the participation of a chair-like transition structure, *cf.* Fig. 1. This

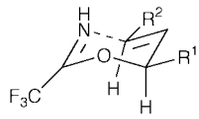


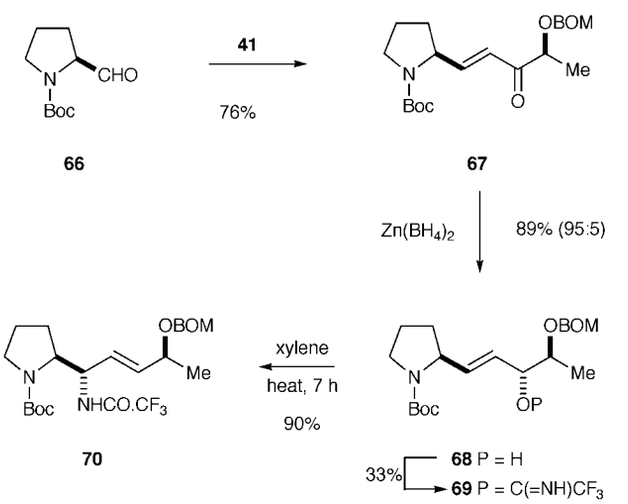
Fig. 1 Chair-like transition state for the trifluoroacetimidate rearrangement.

rearrangement would appear to be faster than rearrangement of the corresponding trichloroacetimidates, *e.g.* for the rearrangement of the *trifluoro*acetimidate **16** in xylene under reflux, $t_{1/2}$ is about 10 h, whereas for the *trichloro*acetimidate **14**, it is about 20 h. This increase in reactivity can lead to improved yields in some cases. The use of this reaction in synthesis may be limited by the precautions necessary when handling trifluoroacetonitrile, which is a highly toxic gas, and the difficulties encountered in some cases in preparing the trifluoroacetimidates. Nevertheless, this rearrangement has been used to complete asymmetric syntheses of α-amino-acids including polyoxamic acid **1**. The accompanying paper reports a total synthesis of thymine polyoxin C using this chemistry.[17]

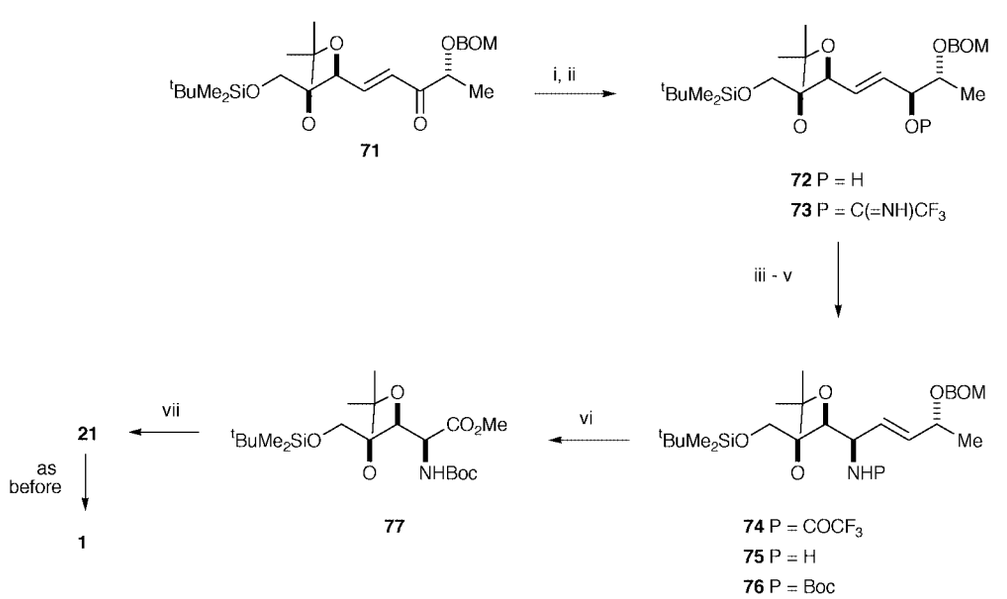
Experimental

^{1}H NMR spectra were recorded on Varian Unity 500, Bruker AC 300, Varian XL 300 and Varian Gemini 200 spectrometers in chloroform-d_1 unless otherwise stated. ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 75 MHz. IR spectra were recorded on a Perkin-Elmer 1710FT spectrometer as liquid films unless otherwise stated. Mass spectra were recorded on a Kratos MS25 mass spectrometer using electron impact (El), chemical ionisation (CI) and fast atom bombardment (FAB) ionisation. Melting points were determined on a Kofler Block apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity AA100 polarimeter. Chromatography refers to flash column chromatography using Merck silica gel 60H (40–63 μm, 230–300 mesh) or May and Baker Sorbsil C60 (40–60 μm) silica gel as the stationary phase. Light petroleum refers to the fraction boiling between 40 and 60 °C and was distilled before use. All reagents and solvents were purified and dried by standard procedures.

Trifluoroacetonitrile was used as a gas or in solution in



Scheme 7



Scheme 8 *Reagents and conditions*: i, zinc borohydride, ether, −35 °C (99%); ii, butyllithium, trifluoroacetonitrile, −78 °C (86%); iii, xylene, heat under reflux, 9.5 h (91%); iv, barium hydroxide, methanol; v, $(Boc)_2O$, Et_3N (84% from **74**); vi, ozone, methanol, −78 °C then bromine, methanol, $NaHCO_3$ (91%); vii, LiOH, aqueous tetrahydrofuran (96%).

tetrahydrofuran and was either purchased‡ or prepared as follows.[18] An intimate mixture of powdered trifluoroacetamide (10 g, 88 mmol) and phosphorus pentoxide (24 g, 148 mmol) was prepared in a 500 cm^3 round bottomed flask fitted with a nitrogen inlet and water cooled condenser. From the top of the condenser a PTFE tube led first to a trap cooled in an ice–salt mixture, then to a trap cooled to ~−100 °C (ether–liq. N_2) and finally, *via* a tube packed with calcium chloride, to a bath containing aqueous sodium hydroxide. The reaction mixture was heated gradually to 150 °C and held at this temperature for 3 h under a gentle stream of dry nitrogen. The trifluoroacetonitrile distilled out and was collected as a colourless liquid (~6 cm^3) in the low temperature trap. Previously cooled tetrahydrofuran (20 cm^3) was then added to the condensed trifluoroacetonitrile to provide a stock solution.

(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-oxobutylenetriphenylphosphorane 10

A solution of the ethyl ester **8**[19] (0.39 g, 1.09 mmol) and potassium hydroxide (0.31 g, 4.4 mmol) was stirred at ambient temperature in methanol (5 cm^3) for 10 h. After acidification with aqueous hydrogen chloride (1 M; 10 cm^3), the mixture was extracted with ether and the organic extract dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 cm^3), 2-mercaptopyridine (0.11 g, 1 mmol) and dicyclohexylcarbodiimide (0.24 g, 1.17 mmol) were added and the mixture stirred at ambient temperature for 9 h. The mixture was filtered, and the filtrate washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (9:1) as eluent afforded *S*-(2-pyridyl) (*S*)-2-(*tert*-butyldiphenylsilyloxy)thiopropanoate **9** (0.31 g, 70%) as a yellow oil: $[\alpha]_D^{23}$ −70.7 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1705, 1585, 1450, 1430, 1420, 1155, 1115 and 1105; δ_H 1.25 [12 H, m, CH_3 and $C(CH_3)_3$], 4.5 (1 H, q, *J* 6.5, 2-H), 7.2–7.9 (13 H, m, ArH) and 8.7 (1 H, m, ArH); *m*/*z* (CI) 422 (M^+ + 1, 60%) and 112 (100).

Butyllithium (1.6 M in hexane; 0.21 cm^3, 0.34 mmol) was added to a suspension of methyltriphenylphosphonium bromide (0.125 g, 0.35 mmol) in tetrahydrofuran (2 cm^3) at ambient temperature. After 5 min, a solution of the thioester **9** (67 mg, 0.16 mmol) in tetrahydrofuran (2 cm^3) was added and the resulting suspension was stirred for 30 min then filtered through Celite. Ether and aqueous potassium carbonate were added and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum as eluent (3:1) gave the *title compound* **10** (70 mg, 75%) as a yellow foam (Found: C, 77.95; H, 7.05; P, 5.0. $C_{38}H_{39}O_2PSi$ requires C, 77.8; H, 6.7; P, 5.3%); $[\alpha]_D^{23}$ −18.6 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3060, 1620, 1590, 1520, 1440, 1140 and 1110; δ_H 1.15 [9 H, s, $C(CH_3)_3$], 1.35 (3 H, d, *J* 5, 4-H_3), 4.2 (1 H, q, *J* 5, 3-H), 4.5 (1 H, d, *J* 25, 1-H), 7.2–7.8 (25 H, m, ArH); *m*/*z* (CI) 586 (M^+, 30%), 508 (20) and 303 (100).

(4*S*,5*S*) and (4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(4*S*,1*E*)-4-*tert*-butyldiphenylsilyloxy-3-oxopentenyl]-2,2-dimethyl-1,3-dioxolanes 12 and 24

A solution of the phosphorane **10** (5.6 g, 9.45 mmol) and aldehyde **11**[7] (2.6 g, 9.45 mmol) in benzene (120 cm^3) was heated under reflux for 5 h then concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (19:1) as eluent gave the (4*S*,5*S*)-isomer of the *title compound* **12** (4.65 g, 85%) (Found: C, 67.75; H, 8.95. $C_{33}H_{50}O_5Si_2$ requires C, 68.0; H, 8.65%); $[\alpha]_D^{23}$ −38 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1700, 1630, 1470, 1460, 1430, 1380, 1370, 1250 and 1112; δ_H 0.09 and 0.1 (each 3 H, s, $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.22 (3 H, d, *J* 6, 5″-CH_3), 1.41 and 1.46 (each 3 H, s, CH_3), 3.8 (3 H, m, 4-H and 1′-H_2), 4.3 (1 H, q, *J* 6, 4″-H), 4.55 (1 H, dd, *J* 6, 2, 5-H), 6.95 (2 H, m, 1″-H and 2″-H) and 7.35–7.8 (10 H, m, ArH); *m*/*z* (EI) 526 (M^+ − 57, 20%), 507 (50) and 135 (100).

Following this procedure, the aldehyde **23**[7] (0.26 g, 0.94 mmol) gave the (4*R*,5*R*)-isomer of the *title compound* **24** (0.36 g, 65%), $[\alpha]_D^{23}$ −32 (*c* 1.1, $CHCl_3$) (Found: C, 68.1; H, 8.35. $C_{33}H_{50}O_5Si_2$ requires C, 68.0; H, 8.65%); ν_{max}/cm^{-1} ($CHCl_3$) 1700, 1630, 1470, 1430, 1380 and 1250; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.3 (3 H, d, *J* 7, 5″-H_3), 1.4 and 1.45 (each 3 H, s, CH_3), 3.85 (3 H, m, 4-H and 1′-H_2), 4.3 (1 H, q, *J* 7, 4″-H), 4.55 (1 H, m, 5-H), 6.95 (1 H, dd, *J* 16, 4, 1″-H), 7.0 (1 H, dd, *J* 16,1, 2″-H) and 7.35–7.8 (10 H, m, ArH).

(4*S*,5*S*)- and (4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*S*,1*E*)-4-*tert*-butyldiphenylsilyloxy-3-hydroxypentenyl]-2,2-dimethyl-1,3-dioxolane 13 and 25

Lithium tri-*sec*-butylborohydride in tetrahydrofuran (1 M; 2.05 cm^3, 2.05 mmol) was added to a solution of the enone **12** (1 g, 1.71 mmol) in tetrahydrofuran (5 cm^3) at −78 °C and the reaction mixture stirred at this temperature for 40 min. Glacial acetic acid (0.3 cm^3) was added and the mixture allowed to warm to ambient temperature. Water was added and the mixture extracted into ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ether (4:1) as eluent gave the (4*S*,5*S*)-isomer of the *title compound* **13** (0.9 g, 90%) (Found: C, 68.00; H, 9.15. $C_{33}H_{52}O_5Si_2$ requires C, 67.75; H, 8.95%. Found M − OH, 567.3320. $C_{33}H_{51}O_4Si_2$ requires *M*, 567.3326); $[\alpha]_D^{23}$ −19.4 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3560, 1470, 1460, 1430, 1380, 1255 and 1110; δ_H (C_6D_6) 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (3 H, d, *J* 6, 5″-H_3), 1.1 [9 H, s, $SiC(CH_3)_3$], 1.4 and 1.46 (each 3 H, s, CH_3), 2.1 (1 H, d, *J* 5, OH), 3.6 (1 H, dd, *J* 11, 5, 1′-H), 3.7 (1 H, dd, *J* 11, 4, 1′-H′), 3.8 (2 H, m, 4-H and 4″-H), 4.0 (1 H, m, 3″-H), 4.5 (1 H, dd, *J* 7, 8, 5-H), 5.9 (1 H dd, *J* 16, 3, 2″-H), 6.0 (1 H, dd, *J* 16, 6, 1″-H) and 7.2–7.8 (10 H, m, ArH); *m*/*z* (CI) 527 (M^+ − 57, 50%) and 311 (100).

Following this procedure, the enone **24** (30 mg, 0.05 mmol) in tetrahydrofuran (1 cm^3) gave the (4*R*,5*R*)-isomer of the *title compound* **25** (25 mg, 82%); $[\alpha]_D^{23}$ −5.1 (*c* 1, $CHCl_3$), ν_{max}/cm^{-1} ($CHCl_3$) 3560, 1470, 1430, 1380 and 1255; δ_H 0.1 (6 H, s, 2 × $SiCH_3$) 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (3 H, d, *J* 6, 5″-H_3), 1.1 [9 H, s, $SiC(CH_3)_3$], 1.4 (6 H, s, 2 × CH_3), 2.5 (1 H, d, *J* 4, OH), 3.9 (4 H, m), 4.0 (1 H, m, 3″-H), 4.3 (1 H, m, 5-H), 5.9 (2 H, m, 1″-H and 2″-H) and 7.2–7.8 (10 H, m, ArH).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*S*,1*E*)-4-*tert*-butyldiphenylsilyloxy-3-(2,2,2-trichloroacetimidoyloxy)-pentenyl]-2,2-dimethyl-1,3-dioxolane 14

Butyllithium (1.6 M in hexane; 1.5 cm^3, 2.4 mmol) was added to a solution of the alcohol **13** (1.4 g, 2.4 mmol) in tetrahydrofuran (20 cm^3) at −78 °C and the solution stirred at this temperature for 1 h before being transferred to a solution of trichloroacetonitrile (0.42 g, 2.88 mmol) in tetrahydrofuran (10 cm^3) at −78 °C. The mixture was allowed to warm to ambient temperature. and was stirred for 2 h. Saturated aqueous ammonium chloride (0.5 g, 8.8 mmol) was added and the mixture extracted into ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ether (19:1) gave the *title compound* **14** (1.48 g, 85%) as a yellow oil (Found: C, 57.65; H, 7.45; N, 1.75. $C_{35}H_{52}C1_3NO_5Si_2$ requires C, 57.65; H, 7.2; N, 1.9%); $[\alpha]_D^{23}$ −13 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3340, 1665, 1470, 1430, 1380, 1255, 1112 and 840; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (3 H, d, *J* 6, 5″-H_3), 1.1 [9 H, s, $SiC(CH_3)_3$], 1.5 (6 H, s, 2 × CH_3), 3.7 (3 H, m, 4-H and 1′-H_2), 4.1 (1 H, quintet, *J* 6, 4″-H), 4.4 (1 H, br t, *J* 5, 5-H), 5.5 (1 H, t, *J* 6, 3″-H), 5.85

‡ Supplied by Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire, UK SK13 9RY.

(1 H, dd, *J* 16, 6, 2″-H), 5.9 (1 H, dd, *J* 16, 5, 1″-H), 7.3–7.8 (10 H, m, ArH) and 8.2 (1 H, s, NH); *m*/*z* (EI) 670 ($M^+ - 57$, 25%), 612, 614 (50) and 311 (100).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(1*R*,4*S*,2*E*)-*tert*-butyldiphenylsilyloxy-1-(2,2,2-trichloroacetylamino)pent-2-enyl]-2,2-dimethyl-1,3-dioxolane 15

A solution of the trichloroacetimidate **14** (70 mg, 0.096 mmol) in xylene was thoroughly degassed using a stream of argon then heated under reflux for 48 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (19 : 1) gave the *title compound* **15** (28 mg, 40%), $[\alpha]_D^{23}$ −40.6 (*c* 1, $CHCl_3$) (Found: $M^+ - C_4H_9$, 670.1723. $C_{31}H_{43}Cl_3NO_5Si_2$ requires *M*, 670.1745); ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1720, 1500, 1480, 1430, 1380, 1370, 1255, 1120 and 1085; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.2 (3 H, d, *J* 6, 5″-H_3), 1.39 and 1.41 (each 3 H, s, CH_3), 3.7–3.9 (3 H, m, 4-H and 1′-H_2), 4.05 (1 H, d, *J* 7.5, 5-H), 4.3 (1 H, quintet, *J* 6, 4″-H), 4.55 (1 H, dd, *J* 7.5, 7, 1″-H), 5.6 (1H, dd, *J* 16, 7.5, 2″-H), 5.9 (1 H, dd, *J* 16, 6, 3″-H), 7.1 (1 H, d, *J* 8, NH) and 7.3–7.8 (10 H, m, ArH); *m*/*z* (EI) 670 ($M^+ - 57$, 10%).

Preparation of trifluoroacetimidates using gaseous trifluoroacetonitrile

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*S*,1*E*)-4-*tert*-butyldiphenylsilyloxy-3-(2,2,2-trifluoroacetimidoyloxy)-pentenyl]-2,2-dimethyl-1,3-dioxolane 16. Butyllithium (1.6 M in hexane; 0.29 cm^3, 0.46 mmol) was added to a solution of the alcohol **13** (0.25 g, 0.43 mmol) in tetrahydrofuran (6 cm^3) at −78 °C and the solution stirred for 1 h. A stream of trifluoroacetonitrile was bubbled through the solution for 5 min then the solution was allowed to warm to ambient temperature over a period of 1 h. Ammonium chloride (0.2 g, 3.6 mmol) was added and the mixture concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (9 : 1) gave the *title compound* **16** (0.24 g, 81%), $[\alpha]_D^{23}$ −5.7 (*c* 0.5, $CHCl_3$) (Found: C, 61.7; H, 7.4. $C_{35}H_{52}F_3NO_5Si_2$ requires C, 61.8; H, 7.7%; Found: $M^+ - C_4H_9$, 622.2630. $C_{31}H_{43}F_3NO_5Si_2$ requires *M*, 622.2632); ν_{max}/cm^{-1} ($CHCl_3$) 3360, 1680, 1470, 1430, 1380, 1200, 1170, 1112 and 840; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (3 H, d, *J* 7, 5″-H_3), 1.1 [9 H, s, $SiC(CH_3)_3$], 1.45 (6 H, s, 2 × CH_3), 3.74 (3 H, 1′-H_2 and 4-H), 4.2 (1 H, quintet, *J* 6, 4″-H), 4.44 (1 H, m, 5-H), 5.5 (1 h, t, *J* 6, 3″-H), 5.85 (1 H, dd, *J* 5, 6, 2″-H), 5.9 (1 H, dd, *J* 16, 5, 1″-H), 7.3–7.8 (10 H, m, ArH) and 8.2 (1 H, s, NH); *m*/*z* (EI) 622 ($M^+ - 57$, 4%).

The following trifluoroacetimidate was prepared using this procedure.

(4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*S*,1*E*)-4-*tert*-butyldiphenylsilyloxy-3-(2,2,2-trifluoroacetimidoyloxy)-pentenyl]-2,2-dimethyl-1,3-dioxolane 26. (47 mg, 70% from the alcohol **25** (60 mg, 0.1 mmol), $[\alpha]_D^{23}$ −15.2 (*c* 1.2, $CHCl_3$) (Found: C, 61.65; H, 7.4. $C_{33}H_{52}F_3NO_5Si_2$ requires C, 61.8; H, 7.7%); ν_{max}/cm^{-1} ($CHCl_3$) 3360, 1680, 1470, 1430 and 1380; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (3 H, d, *J* 6, 5″-H_3), 1.1 [9 H, s, $SiC(CH_3)_3$], 1.4 (6 H, s, 2 × CH_3), 3.8 (3 H, m, 4-H and 1′-H_2), 4.1 (1 H, quintet, *J* 6, 4″-H), 4.4 (1 H, dd, *J* 7.5, 5, 5-H), 5.5 (1 H, t, *J* 6, 3″-H), 5.85 (1 H, dd, *J* 16, 5, 1″-H), 5.95 (1 H, dd, *J* 16, 6, 2″-H), 7.3–7.8 (10 H, m, ArH) and 8.2 (1 H, s, NH).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(1*R*,4*S*,2*E*)-4-*tert*-butyldiphenylsilyloxy-1-(2,2,2-trifluoroacetylamino)pent-2-enyl]-2,2-dimethyl-1,3-dioxolane 17

A solution of the trifluoroacetimidate **16** (90 mg, 0.13 mmol) in xylene (2 cm^3) was thoroughly degassed with argon and heated under reflux for 20 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (15 : 1) gave the *title compound* **17** (74 mg, 82%), $[\alpha]_D^{23}$ −50.6 (*c* 1.1, $CHCl_3$) (Found: C, 61.5; H, 8.05. $C_{35}H_{52}F_3NO_5Si_2$ requires C, 61.8; H, 7.7%; Found: $M^+ - C_4H_9$, 622.6225. $C_{31}H_{43}F_3NO_5Si_2$ requires *M*, 622.2632); ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1730, 1530, 1480, 1470, 1430, 1370, 1170, 1110, 1080 and 840; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.2 (3 H, d, *J* 6, 5″-H_3), 1.4 (6 H, s, 2 × CH_3), 3.7 (2 H, m, 1′-H_2), 3.85 (1 H, m, 4-H), 4.0 (1 H, dd, *J* 8, 2, 5-H), 4.3 (1 H, quintet, *J* 6, 4″-H), 4.67 (1 H, t, *J* 7.5, 1″-H), 5.5 (1 H, dd, *J* 16, 7, 2″-H), 5.75 (1H, dd, *J* 16, 6, 3″-H), 6.85 (1 H, d, *J* 9, NH) and 7.3–7.8 (10 H, m, ArH); *m*/*z* (EI) 664 ($M^+ - 15$, 60%) and 662 (60).

The following trifluoroacetamide was prepared using this procedure.

(4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(1*R*,4*S*,2*E*)-4-*tert*-butyldiphenylsilyloxy-1-(2,2,2-trifluoroacetylamino)pent-2-enyl]-2,2-dimethyl-1,3-dioxolane 27. (38 mg, 76% from the trifluoroacetimidate **26**, 50 mg, 0.074 mmol), $[\alpha]_D^{23}$ −36 (*c* 0.8, $CHCl_3$) (Found: C, 61.75; H, 7.4. $C_{35}H_{52}F_3NO_5Si_2$ requires C, 61.8; H, 7.7%); ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1730, 1530, 1480, 1430 and 1370; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.15 (3 H, d, *J* 6, 5″-H_3), 1.32 and 1.38 (each 3 H, s, CH_3), 3.8 (3 H, m, 4-H and 1′-H_2), 4.0 (1 H, dd, *J* 7, 4, 5-H), 4.4 (1 H, quintet, *J* 6, 4″-H), 4.65 (1 H, dt, *J* 4, 8, 1″-H), 5.7 (1 H, dd, *J* 15, 8, 2″-H), 5.9 (1 H, dd, *J* 15, 6, 3″-H), 6.7 (1 H, d, *J* 8, NH) and 7.3–7.8 (10 H, m, ArH).

(4*S*,5*S*)-5-[(1*R*,4*S*,2*E*)-1-Amino-4-*tert*-butyldiphenylsilyloxy-pent-2-enyl]-4-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolane 18

Sodium borohydride (32 mg, 0.8 mmol) was added to a solution of the trifluoroacetamide **17** (70 mg, 0.1 mmol) in ethanol (0.75 cm^3) at 0 °C. The reaction mixture was allowed to warm to 23 °C and was stirred for 5 h. Saturated aqueous ammonium chloride (2 cm^3) was added and the mixture extracted into ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (3 : 1) as eluent gave the *title compound* **18** (44 mg, 75%), $[\alpha]_D^{23}$ −29.9 (*c* 1.1, $CHCl_3$) (Found: C, 68.05; H, 9.45. $C_{33}H_{53}NO_4Si_2$ requires C, 67.85; H, 9.15%; Found: $M^+ - C_4H_9$, 526.2808. $C_{29}H_{44}NO_4Si_2$ requires *M*, 526.2809); ν_{max}/cm^{-1} ($CHCl_3$) 3300br, 1590, 1470, 1460, 1430, 1380, 1370, 1250, 1140, 1110, 1080, 970 and 840; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $C(CH_3)_3$], 1.2 (3 H, d, *J* 6, 5″-H_3), 1.39 and 1.42 (each 3 H, s, CH_3), 1.5 (2 H, br s, NH_2), 3.3 (1 H, t, *J* 7, 1″-H), 3.7 (2 H, m, 1′-H_2), 3.75 (1 H, dd, *J* 7, 6, 5-H), 3.9 (1 H, m, 4-H), 4.3 (1 H, quintet, *J* 6, 4″-H), 5.3 (1 H, dd, *J* 16, 8, 2″-H), 5.7 (1 H, dd, *J* 16, 6, 3″-H) and 7.3–7.8 (10 H, m, ArH); *m*/*z* (EI) 584 ($M^+ + 1$, 13%), 526 (60) and 199 (100).

(4*S*,5*S*)-5-[(1*R*,4*S*,2*E*)-1-*tert*-Butoxycarbonylamino-4-*tert*-butyldiphenylsilyloxypent-2-enyl]-4-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolane 19

Di-*tert*-butyl dicarbonate (65 mg, 0.29 mmol) was added to a solution of the amine **18** (0.16 g, 0.27 mmol) and triethylamine (0.04 cm^3, 0.29 mmol) in ether (3.5 cm^3) at 23 °C and the solution stirred for 20 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (13 : 1) gave the *title compound* **19** (0.18 g, 100%) as a colourless oil, $[\alpha]_D^{23}$ −31 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3450, 1710, 1500, 1470, 1430 and 1370; δ_H 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 and 1.1 [each 9 H, s, $SiC(CH_3)_3$], 1.15 (3 H, d, *J* 5, 5″-H_3), 1.4 (6 H, s, 2 × CH_3), 1.45 [9 H, s, $OC(CH_3)_3$], 3.6–4.0 (4 H, m, $SiOCH_2CHCH$), 4.3 (2 H, m, 1″-H and 4″-H), 5.1 (1 H, d, *J* 8, NH), 5.5 (1 H, dd, *J* 15, 5, 2″-H), 5.7 (1 H, dd, *J* 15, 5, 3″-H) and 7.3–7.8 (10 H, m, ArH).

(4*S*,5*S*)-5-[(1*S*)-(*tert*-Butoxycarbonylamino)(carboxy)methyl]-4-(*tert*-butyldimethylsilyloxymethyl)-1,3-dioxolane 21

A solution of the alkene **19** (40 mg, 0.059 mmol) in methanol (2 cm^3) was cooled to −78 °C whilst oxygen was bubbled through. After 10 min, ozone was passed through the solution until starting material had been consumed (TLC using 3:1 light petroleum–ether). The reaction mixture was purged with oxygen for a further 10 min, then dimethyl sulfide (0.05 cm^3, 0.7 mmol) was added and the reaction mixture allowed to warm to ambient temperature over 1 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (3:1) as eluent gave the aldehyde **20** (21 mg). This was dissolved in a mixture of carbon tetrachloride (0.2 cm^3), acetonitrile (0.2 cm^3) and water (0.3 cm^3) and sodium periodate (40 mg, 0.18 mmol) was added. The mixture was stirred at ambient temperature for 15 min then ruthenium trichloride (1 mg) was added. The mixture was stirred for 1 h at ambient temperature then partitioned between ether and water. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum–acetic acid (24:75:1) as eluent gave the *title compound* **21** (16.5 mg, 69%) as a white powder, mp 131–133 °C, $[\alpha]_D^{26}$ −4.2 (*c* 1.32, $CHCl_3$) (Found: C, 54.6; H, 9.1; N, 3.3. $C_{19}H_{37}NO_7Si$ requires C, 54.4; H, 8.9; N, 3.3%; Found: $M^+ + H$, 420.2408. $C_{19}H_{38}NO_7Si$ requires *M*, 420.2418); ν_{max}/cm^{-1} ($CHCl_3$) 3600–2200, 1713, 1502, 1370, 1253, 1165, 1090 and 840; δ_H (C_6D_6) 0.1 (6 H, s, 2 × $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.33 and 1.39 (each 3 H, s, CH_3), 1.45 [9 H, s, $C(CH_3)_3$], 3.7 and 3.8 (each 1 H, dd, *J* 10, 3, 1′-H), 4.1 (1 H, m, 5-H), 4.71 (1 H, d, *J* 8, 4-H), 4.9 (1 H, d, *J* 10, 1″-H) and 5.6 (1 H, d, *J* 10, NH); *m*/*z* (CI) 437 ($M^+ + 18$, 2%), 420 ($M^+ + 1$, 47) and 320 (100).

Polyoxamic acid 1

A mixture of trifluoroacetic acid (0.27 cm^3, 3.54 mmol) and methanol (0.03 cm^3) cooled to 0 °C was added to the dioxolane **21** (28 mg, 0.067 mmol) and the solution stirred at ambient temperature for 30 min. After concentration under reduced presure, the residue was dissolved in aqueous ammonium hydroxide (0.6 M; 2 cm^3) and chromatographed through a column of Dowex 50W X8 (H^+) to give polyoxamic acid **1** (8 mg, 72%): mp 149–162 °C decomp. (lit.,[4] 171–173 °C decomp.), $[\alpha]_D^{23}$ 6.38 (*c* 0.4, H_2O) (lit.,[4] 2.8 (*c* 1, H_2O)); δ_H (D_2O) 3.5–3.6 (2 H, m, 5-H_2), 3.75 (1 H, m, 2-H), 3.78 (1 H, m, 4-H) and 4.09 (1 H, t, *J* 2.5, 3-H); *m*/*z* (FAB) 166 ($M^+ + 1$, 100%).

Acetic anhydride (0.1 cm^3, 1 mmol) was added to a solution of synthetic polyoxamic acid **1** (10 mg, 0.06 mmol) in methanol (0.75 cm^3) at ambient temperature and the mixture stirred for 20 h. Water (0.2 cm^3) was added and the mixture concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–methanol (19:1) gave the lactone **22** (6.7 mg, 60%) as a white solid, mp 150 °C decomp. (lit.[4], mp 150–152 °C); δ_H (acetone-d_6) 1.9 (3 H, s, $COCH_3$), 3.9 and 4.0 (each 1 H, m, 5-H), 4.1 (1 H, t, *J* 6, OH), 4.55 (2 H, m, 2-H and 4-H), 4.7 (1H, dt, *J* 7.5, 5, 3-H), 5.1 (1 H, d, *J* 5, OH) and 7.8 (1 H, br s, NH); *m*/*z* (CI) 207 ($M^+ + 18$, 34%), 190 ($M^+ + 1$, 84) and 172 (100).

2-Methylpropyl (*R*)-2-(benzyloxymethoxy)propanoate 29

Benzyl chloromethyl ether (7.5 cm^3, 54 mmol) was added to a solution of 2-methylpropyl (*R*)-lactate **28** (6.56 g, 45 mmol) and *N*,*N*-diisopropylethylamine (15.5 cm^3, 89 mmol) in dichloromethane (50 cm^3) and the mixture was stirred at ambient temperature for 15 h. Dichloromethane (100 cm^3) was added and the mixture washed with saturated aqueous ammonium chloride (3 × 50 cm^3), back extracting the combined washings with dichloromethane (2 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum (1:15) as eluent gave the *title compound* **29** (4.93 g, 41%) as a colourless oil, $[\alpha]_D^{23}$ +67.7 (*c* 3 in $CHCl_3$) (Found: M^+, 267.1603. $C_{15}H_{22}O_4$ requires *M*, 267.1518); ν_{max}/cm^{-1} 1750, 1176, 1123 and 1051; δ_H 0.93 (3 H, d, *J* 6.5, 3-H_3), 1.45 (6 H, d, *J* 7, 2 × CH_3), 1.94 (1 H, septet, *J* 6.5, CH), 3.91 (2 H, m, OCH_2), 4.33 (1 H, q, *J* 6.5, 2-H), 4.65 (2 H, s, $PhCH_2$), 4.85 (2 H, s, OCH_2O) and 7.33 (5 H, m, ArH); *m*/*z* (EI) 267 ($M^+ + 1$, 100%) and 237 (46).

Dimethyl [(3*R*)-3-benzyloxymethoxy-2-oxobutyl]phosphonate 30

Butyllithium (1.6 M in hexane, 21 cm^3, 33.6 mmol) was added to a solution of dimethyl methylphosphonate (4.1 g, 33 mmol) in tetrahydrofuran (20 cm^3) at −78 °C. After 1 h, a solution of the ester **29** (4 g, 15 mmol) in tetrahydrofuran (10 cm^3) was added and the mixture stirred for a further 2 h. Water (30 cm^3) was added and the mixture allowed to warm to ambient temperature. Ether (200 cm^3) was added and the aqueous layer acidified with aqueous hydrogen chloride (2 M) to ~pH 2. The aqueous layer was extracted with ether (2 × 100 cm^3), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate–methanol (6:2:1) as eluent gave the *title compound* **30** (4.35 g, 92%) as a colourless oil, $[\alpha]_D$ +27.7 (*c* 7.8 in $CHCl_3$) (Found: $M^+ + NH_4$, 334.1426. $C_{14}H_{25}NO_6P$ requires *M*, 334.1420); ν_{max}/cm^{-1} 1722, 1455, 1259, 1182, 1037 and 812; δ_H 1.37 (3 H, d, *J* 7, 4-H_3), 3.27 (2 H, m, 1-H_2), 3.77 (6 H, d, *J* 11, 2 × CH_3O), 4.3 (1 H, q, *J* 7, 3-H), 4.61 and 4.67 (each 1 H, d, *J* 12, PhC*H*H), 4.82 and 4.87 (each 1 H, d, *J* 7, OC*H*HO) and 7.33 (5 H, m, ArH); *m*/*z* (CI) 334 ($M^+ + 18$, 69%), 317 (92) and 287 (100).

Following this procedure, the (*S*)-enantiomer of the title compound **41** (2.38 g, 90%) was prepared as a colourless oil from ethyl (*S*)-2-benzyloxymethoxypropanoate[20] (2 g, 8.4 mmol), $[\alpha]_D^{26}$ −26.2 (c 0.9 in $CHCl_3$) (Found: $M^+ + 1$, 317.1165. $C_{14}H_{22}O_6P$ requires *M*, 317.1154).

Synthesis of enones using phosphonates 30 and 41

(2*R*,4*E*)- and (2*S*,4*E*)-2-(Benzyloxymethoxy)-6-methylhept-4-en-3-one 31 and 42. A solution of the phosphonate **30** (3.89 g, 12.3 mmol) in acetonitrile (10 cm^3) was added to a suspension of lithium chloride (0.53 g, 12.4 mmol) in acetonitrile (40 cm^3). 1,8-Diazabicyclo[5.7.0]undec-7-ene (1.6 cm^3, 10.7 mmol) was added after 15 min and, after a further 30 min, 2-methylpropanal (0.95 cm^3, 10.5 mmol) was added. The resulting solution was stirred for 20 h, then saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane (3 × 150 cm^3). The organic extracts were washed with water (30 cm^3), brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ether (10:1) as eluent gave the (2*R*,4*E*)-enantiomer of the *title compound* **31** (2.11 g, 77%) as a colourless oil (Found: $M^+ + NH_4$, 280.1907. $C_{16}H_{26}NO_3$ requires *M*, 280.1913), $[\alpha]_D$ +54.9 (*c* 3.7 in $CHCl_3$); ν_{max}/cm^{-1} 1697, 1627, 1455, 1108, 1041, 989, 738 and 699; δ_H 1.06 (6 H, d, *J* 6.5, 2 × CH_3), 1.37 (3 H, d, *J* 7, 1-H_3), 2.47 (1 H, m, 6-H), 4.38 (1 H, q, *J* 7, 2-H), 4.63 (2 H, s, $PhCH_2$), 4.78 and 4.81 (each 1 H, d, *J* 8, O*H*CHO), 6.36 (1 H, dd, *J* 16, 1.5, 4-H), 6.99 (1 H, dd, *J* 16, 6.5, 5-H) and 7.31 (5 H, m, ArH); *m*/*z* (CI) 280 ($M^+ + 18$, 10%), 263 (15), 233 (40) and 199 (100%).

This procedure using the (*S*)-phosphonate **41** gave the (2*S*,4*E*)-enantiomer of the *title compound* **42** (Found: $M^+ + H$, 263.1641. $C_{16}H_{23}O_3$ requires *M*, 263.1647), $[\alpha]_D^{26}$ −55.8 (*c* 0.98 in $CHCl_3$).

The following enones were synthesised using this procedure.

[(4*S*,1*E*)-4-Benzyloxymethoxy-3-oxopent-1-enyl]cyclopropane 64. (0.26 g, 79%) From cyclopropanecarbaldehyde (0.12 g, 1.71 mmol) as a colourless oil after chromatography

using light petroleum–ether (8:1) as eluent, $[\alpha]_D^{22}$ −39.2 (*c* 1.22, $CHCl_3$) (Found: $M^+ + H$, 261.1481. $C_{16}H_{21}O_3$ requires *M*, 261.1490); ν_{max}/cm^{-1} 1691, 1615, 1498, 1454, 1380, 1269, 1179, 1107, 1040 and 936; δ_H 0.68 and 0.98 (each 2 H, m, CH_2), 1.36 (3 H, d, *J* 7, 5′-H_3), 1.60 (1 H, m, 1-H), 4.33 (1 H, q, *J* 7, 4′-H), 4.64 (2 H, s, $PhCH_2$), 4.77 and 4.85 (each 1 H, d, *J* 7, OC*H*HO), 6.51 (2 H, m, 1′-H and 2′-H) and 7.25–7.38 (5 H, m, ArH); δ_C 9.38, 15.33, 18.17, 69.97, 77.36, 93.83, 121.80, 127.61, 127.70, 128.29, 137.48, 154.53 and 198.81; *m*/*z* (CI) 278 ($M^+ + 18$, 22%), 261 ($M^+ + 1$, 69) and 153 (100).

(2*S*)-[(4*S*,1*E*)-4-Benzyloxymethoxy-3-oxopent-1-enyl]-*N*-(*tert*-butoxycarbonyl)pyrrolidine 67. (1.56 g, 76%) From the formylpyrrolidine **66**[21] (1.05 g, 5.27 mmol) as a pale yellow gum after chromatography using light petroleum–ether (4:3) as eluent, $[\alpha]_D^{20}$ +110.8 (*c* 0.6, $CHCl_3$) (Found: $M^+ + H$, 390.2270. $C_{22}H_{32}NO_5$ requires *M*, 390.2280); ν_{max}/cm^{-1} 1695, 1630, 1479, 1454, 1168, 1110 and 1040; δ_H 1.33 (3 H, d, *J* 7, 5-H_3), 1.39 [9 H, s, $C(CH_3)_3$], 1.65–1.85 (3 H, m, 3-H and 4-H_2), 2.05 (1 H, m, 3-H′), 3.40 (2 H, m, 5-H_2), 4.33 (1 H, q, *J* 7, 4′-H), 4.47 (1 H, m, 2-H), 4.58 (2 H, s, $PhCH_2$), 4.72 and 4.81 (each 1 H, d, *J* 8, O*H*CHO), 6.39 (1 H, d, *J* 16, 2′-H), 6.83 (1 H, dd, *J* 16, 6, 1′-H) and 7.22–7.32 (5 H, m, ArH); *m*/*z* (CI) 390 ($M^+ + 1$, 3%), 290 (16), 198 (84) and 134 (100).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(4*R*,1*E*)-4-benzyloxymethoxy-3-oxopent-1-enyl]-2,2-dimethyl-1,3-dioxolane 71. (2.1 g, 90%) From the aldehyde **11** (1.37 g, 5 mmol) as a colourless oil after chromatography using light petroleum–ether (7:1) as eluent, $[\alpha]_D^{27}$ +31.1 (*c* 0.88, $CHCl_3$); ν_{max}/cm^{-1} 1702, 1634, 1380, 1255, 1168, 1098, 1040 and 838; δ_H 0.07 (6 H, s, 2 × $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.37 (3 H, d, *J* 7, 5″-H_3), 1.42 and 1.44 (each 3 H, s, CH_3), 3.77 (3 H, m, 4-H and 1′-H_2), 4.37 (1 H, q, *J* 7, 4″-H), 4.57 (1 H, m, 5-H), 4.64 (2 H, s, $PhCH_2$), 4.77 and 4.85 (each 1 H, d, *J* 7, O*H*CHO), 6.74 (1 H, dd, *J* 16, 1.5, 2″-H), 6.98 (1 H, dd, *J* 16, 5, 1″-H) and 7.30 (5 H, m, ArH); δ_C −5.25, −5.19, 17.93, 18.49, 26.06, 26.99, 27.12, 62.90, 70.21, 77.62, 78.12, 81.02, 94.11, 110.10, 124.723, 127.95, 128.61, 137.60, 144.37 and 199.66; *m*/*z* (FAB) 465 ($M^+ + 1$).

Reduction of enones using zinc borohydride

(2*R*,3*S*,4*E*)- and (2*S*,3*R*,4*E*)-2-(Benzyloxymethoxy)-6-methylhept-4-en-3-ol 32 and 43. Zinc borohydride (0.15 M in ether; 75 cm^3, 11 mmol) was added dropwise to a solution of the ketone **31** (1.64 g, 6.25 mmol) in ether (50 cm^3) at −35 °C. After 2.5 h, water (25 cm^3) was added and the mixture allowed to warm to ambient temperature before the addition of acetic acid (6 cm^3, 105 mmol) in water (25 cm^3). The mixture was extracted with ether (3 × 75 cm^3) and the organic extracts were washed with saturated aqueous sodium bicarbonate (2 × 50 cm^3) and back extracted with ether (2 × 50 cm^3). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3:1) as eluent gave the (2*R*,3*S*,4*E*)-isomer of the *title compound* **32** (1.61 g, 97%), as a colourless oil, $[\alpha]_D$ −15.8 (*c* 2.09 in $CHCl_3$) (Found: $M^+ + NH_4$, 282.2049. $C_{16}H_{28}NO_3$ requires *M*, 282.2069); ν_{max}/cm^{-1} 3459, 1455, 1382, 1169, 1103, 1042, 975 and 737; δ_H 1.05 (6 H, d, *J* 6.5, 2 × CH_3), 1.16 (3 H, d, *J* 6.5, 1-H_3), 2.33 (1 H, m, 6-H), 3.83 (1 H, dq, *J* 6.5, 3, 2-H), 4.09 (1 H, dd, *J* 7, 3, 3-H), 4.63 and 4.7 (each 1 H, d, *J* 11.5, Ph*H*H), 4.83 and 4.86 (each 1 H, d, *J* 7, OC*H*HO), 5.44 (1 H, ddd, *J* 15.5, 7, 1, 4-H), 5.7 (1 H, ddd, *J* 15.5, 6.5, 1, 5-H) and 7.33 (5 H, m, ArH); *m*/*z* (CI) 282 ($M^+ + 18$, 10%), 264 (M^+, 0.4%) and 217 (100%).

Reduction of the (2*S*)-ketone **42** gave the (2*S*,3*R*,4*E*)-isomer of the *title compound* **43** (Found: $M^+ + NH_4$, 282.2084. $C_{16}H_{28}NO_3$ requires *M*, 282.2069), $[\alpha]_D^{26}$ +14.3 (*c* 1.3 in $CHCl_3$).

The following alcohols were prepared using this procedure.

[(3*R*,4*S*,1*E*)-4-Benzyloxymethoxy-3-hydroxypent-1-enyl]-cyclopropane 65. (1.5 g, 97%) From the enone **64** (1.54 g, 5.91 mmol) as a colourless oil after chromatography using light petroleum–ether (2:1) as eluent, $[\alpha]_D^{18}$ +11.5 (*c* 1, $CHCl_3$) (Found: $M^+ - OH$, 245.1555. $C_{16}H_{21}O_2$ requires *M*, 245.1541); ν_{max}/cm^{-1} 3451, 3082, 1667, 1498, 1454, 1381, 1166, 1102, 1041 and 966; δ_H 0.39 and 0.72 (each 2 H, m, CH_2), 1.17 (3 H, d, *J* 7, 5′-H_3), 1.42 (1 H, m, 1-H), 2.55 (1 H, br s, OH), 3.82 (1 H, dq, *J* 7, 3, 4′-H), 4.07 (1 H, m, 3′-H), 4.61 and 4.7 (each 1 H, d, *J* 12, PhC*H*H), 4.82 and 4.86 (each 1 H, d, *J* 7, OC*H*HO), 5.25 (1 H, ddd, *J* 15.5, 9, 4, 1′-H), 5.57 (1 H, dd, *J* 15.5, 7, 2′-H) and 7.35 (5 H, ArH); δ_C 6.89, 6.92, 13.72, 15.47, 69.77, 74.98, 77.63, 93.77, 125.27, 127.66, 127.72, 128.33, 137.42 and 137.71; *m*/*z* (CI) 262 (M^+, 3%) and 245 (100); HPLC (column: Spheresorb 5 μm ODS PP/3634; eluent: 78:22 methanol–water) ratio of epimers ≥95:5.

(2*S*)-2-[(3*R*,4*S*,1*E*)-4-Benzyloxymethoxy-3-hydroxypent-1-enyl]-*N*-(*tert*-butoxycarbonyl)pyrrolidine 68. (0.19 g, 89%) From the ketone **67** (0.21 g, 0.54 mmol) as a colourless gum after chromatography using light petroleum–ether (4:5) as eluent, $[\alpha]_D^{25}$ −18.6 (*c* 0.7, $CHCl_3$) (Found: $M^+ + H$, 392.2438. $C_{22}H_{34}NO_5$ requires *M*, 392.2437); ν_{max}/cm^{-1} 3432, 1690, 1399, 1169, 1106 and 1041; δ_H 1.14 (3 H, d, *J* 6.5, 5′-H_3), 1.44 [9 H, s, $C(CH_3)_3$], 1.71 (1 H, m, 3-H), 1.83 (2 H, m, 4-H_2), 2.01 (1 H, m, 3-H′), 2.25 (1 H, br s, OH), 3.37 (2 H, m, 5-H_2), 3.83 (1 H, dq, *J* 6.5, 3, 4′-H), 4.16 (1 H, m, 3′-H), 4.32 (1 H, m, 2-H), 4.61 and 4.67 (each 1 H, d, *J* 11, PhC*H*H), 4.82 and 4.85 (each 1 H, d, *J* 7, OC*H*HO), 5.57 (2 H, m, 1′-H and 2′-H) and 7.35 (5 H, m, ArH); *m*/*z* (CI) 409 ($M^+ + 18$, 5%), 392 ($M^+ + 1$, 8.2) and 318 (49).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*R*,1*E*)-4-benzyloxymethoxy-3-hydroxypent-1-enyl]-2,2-dimethyl-1,3-dioxolane 72. (1.9 g, 99%) From the enone **71** (1.92 g, 4.131 mmol), as a colourless oil after chromatography using light petroleum–ethyl acetate (5:1) as eluent, HPLC (column: Spheresorb 5 silica NF0/262; eluent: 6:1 hexane–ethyl acetate) 3″*S*:3″*R* = 98:2, $[\alpha]_D^{27}$ −19.7 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 3452, 1461, 1380, 1254, 1040 and 838; δ_H 0.05 (6 H, s, 2 × $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.17 (3 H, d, *J* 6.5, 5″-H_3), 1.42 (6 H, s, 2 × CH_3), 2.35 (1 H, br s, OH), 3.74 (3 H, m, 4-H and 1′-H_2), 3.85 (1 H, dq, *J* 6.5, 3, 4″-H), 4.18 (1 H, m, 3″-H), 4.41 (1 H, m, 5-H), 4.61 and 4.69 (each 1 H, d, *J* 12, PhC*H*H), 4.82 and 4.85 (each 1 H, d, *J* 7, OC*H*HO), 5.83 (2 H, m, 1″-H and 2″-H) and 7.35 (5 H, m, ArH); δ_C −5.22, −5.12, 15.40, 18.55, 26.10, 27.14, 27.27, 62.60, 70.15, 74.33, 78.41, 81.73, 94.10, 109.28, 128.02, 128.08, 128.67, 130.13, 131.65 and 137.75; *m*/*z* (FAB) 489 ($M^+ + 23$).

(4*S*,2*E*)-4-*tert*-Butyldimethylsilyloxypent-2-enal 59

(*S*)-2-*tert*-Butyldimethylsilyloxypropanal **58** (3.77 g, 20 mmol) was added to a suspension of formylmethylene(triphenyl)-phosphorane (6.7 g, 22 mmol) in benzene (200 cm^3) and the mixture stirred for 3 d before being filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (10:1) as eluent gave the *title compound* **59** (3.73 g, 87%), as a colourless oil, $[\alpha]_D^{21}$ +15.7 (*c* 1.25, $CHCl_3$); ν_{max}/cm^{-1} 1696, 1257, 1159, 1125, 1091, 1051, 977, 920, 837 and 778; δ_H (C_6D_6) 0.00 and 0.03 (each, 3 H, s, $SiCH_3$), 0.97 [9 H, s, $SiC(CH_3)_3$], 1.02 (3 H, d, *J* 6.5, 5-H_3), 4.12 (1 H, m, 4-H), 6.16 (1 H, dd, *J* 16, 4, 3-H), 6.34 (1 H, ddd, *J* 15.5, 8, 1.5, 2-H) and 9.44 (1 H, d, *J* 8, 1-H): δ_C (C_6D_6) −4.92, −4.90, 18.21, 23.23, 25.84, 67.67, 130.21, 159.17 and 192.24; *m*/*z* (CI) 232 ($M^+ + 18$, 14%), 215 ($M^+ + 1$, 17) and 214 (M^+, 4).

2-[(3*S*,1*E*)-3-*tert*-Butyldimethylsilyloxybut-1-enyl]-1,3-dioxolane 60

A solution of the aldehyde **59** (1.49 g, 6.95 mmol), ethanediol

(0.65 g, 10.5 mmol) and toluene-*p*-sulfonic acid (50 mg, 0.26 mmol) in benzene was heated under reflux for 1.5 h in a Dean–Stark apparatus. The resulting solution was allowed to cool and potassium carbonate (2.5 g) was added. The resulting suspension was filtered and concentrated under reduced presure. Chromatography of the residue using light petroleum–ether (15:1) as eluent gave the *title compound* **60** (1.37 g, 76%), as a pale yellow oil, $[\alpha]_D^{21}$ +6.6 (*c* 1.65, $CHCl_3$) (Found: $M^+ + H$, 259.1726. $C_{13}H_{27}O_3Si$ requires *M*, 259.1729); ν_{max}/cm^{-1} 1696, 1473, 1394, 1255, 1149, 1087, 1053, 967, 836 and 778; δ_H (C_6D_6) 0.12 and 0.14 (each 3 H, s, $SiCH_3$), 1.04 [9 H, s, $SiC(CH_3)_3$], 1.19 (3 H, d, *J* 6.5, 4′-H_3), 3.47 and 3.63 (each 2 H, m, 2 × OCH_2), 4.26 (1 H, m, 3′-H), 5.34 (1 H, d, *J* 4.5, 2-H) and 5.97 (2 H, m, 1′-H and 2′-H); δ_C (C_6D_6) −4.70, −4.48, 18.37, 24.28, 26.04, 64.83, 68.60, 103.82, 125.89 and 140.09; *m*/*z* (CI) 259 ($M^+ + 1$, 100%) and 127 (50).

2-[(3*S*,1*E*)-3-Hydroxybut-1-enyl]-1,3-dioxolane 61

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 5 cm^3, 5 mmol) was added to a solution of the silyl ether **60** (1.14 g, 4.41 mmol) in tetrahydrofuran at 0 °C and the mixture stirred for 2 h at ambient temperature. Water (20 cm^3) was added and the resulting mixture extracted with dichloromethane (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (2:1) as eluent gave the *title compound* **61** (0.6 g, 94%), as a colourless oil, $[\alpha]_D^{20}$ +11.3 (*c* 1.2, $CHCl_3$) (Found: $M^+ - H$, 143.0709. $C_7H_{11}O_3$ requires *M*, 143.0708); ν_{max}/cm^{-1} 3419, 1400, 1294, 1146, 1060 and 968; δ_H (C_6D_6) 1.26 (3 H, d, *J* 6.5, 4′-H_3), 2.00 (1 H, br s, OH), 3.59 and 3.76 (each 2 H, m, OCH_2), 4.24 (1 H, m, 3′-H), 5.42 (1 H, d, *J* 5, 2-H) and 6.30 (2 H, m, 1′-H and 2′-H); δ_C (C_6D_6) 23.75, 65.53, 68.00, 104.15, 126.72 and 140.95; *m*/*z* (EI) 144 (M^+, 0.3%), 143 ($M^+ - 1$, 4), 127 (19) and 99 (100).

Synthesis of trifluoroacetimidates using a solution of trifluoroacetonitrile in tetrahydrofuran

(2*R*,3*S*,4*E*)- and (2*S*,3*R*,4*E*)-2-(Benzyloxymethoxy)-6-methyl-3-(2,2,2-trifluoroacetimidoyloxy)hept-4-ene 33 and 44. Butyllithium (1.6 M in hexane; 0.05 cm^3, 0.08 mmol) was added to a solution of the alcohol **32** (0.1 g, 0.39 mmol) in tetrahydrofuran (4 cm^3) at 0 °C and the mixture stirred for 15 min then cooled to −78 °C and stirred for a further 45 min. An excess of the standard trifluoroacetonitrile solution (2 cm^3) was added *via* a cannula and the mixture stirred for 1 h before being allowed to warm to ambient temperature. Ammonium chloride (50 mg) and light petroleum (6 cm^3) were added and the mixture was filtered and concentrated under reduced pressure. Chromatography on base washed silica using gradient elution (40:1→20:1→10:1→3:1 light petroleum–ether) gave the (2*R*,3*S*,4*E*)-isomer of the *title compound* **33** as a colourless oil (0.12 g, 91%), $[\alpha]_D^{26}$ +57.3 (*c* 1.34 in $CHCl_3$) (Found: M^+, 359.1697. $C_{18}H_{24}F_3NO_3$ requires *M*, 359.1708); ν_{max}/cm^{-1} 3353, 1685, 1498, 1382, 1201, 1167, 1081 and 1042; δ_H 1.01 (6 H, d, *J* 7, 2 × CH_3), 1.21 (3 H, d, *J* 6.5, 1-H_3), 2.35 (1 H, m, 6-H), 4.06 (1 H, dq, *J* 6.5, 3, 2-H), 4.63 (2 H, s, OCH_2O), 4.84 (2 H, s, $PhCH_2$), 5.66 (2 H, m, 3-H and 5-H), 5.81 (1 H, dd, *J* 14.5, 6.5, 4-H), 7.30 (5 H, m, ArH) and 8.10 (1 H, br s, NH); δ_F 3.80 and 3.93 (3:97); *m*/*z* (CI) 377 ($M^+ + 18$, 6%), 360 ($M^+ + 1$, 1) and 217 (100).

The alcohol **43** similarly gave the (2*S*,3*R*,4*E*)-isomer of the *title compound* **44** (Found: $M^+ + NH_4$, 377.2063. $C_{18}H_{28}F_3N_2O_3$ requires *M*, 377.2052).

The following were prepared using this procedure.

(2*E*)-1-(2,2,2-Trifluoroacetimidoyloxy)-3,7-dimethylocta-2,6-diene 52. (0.22 g, 88%) From geraniol (0.15 g, 0.98 mmol), as a colourless oil after chromatography on base washed silica using gradient elution (40:1→20:1 light petroleum–ether) (Found: M^+, 249.1136. $C_{12}H_{18}F_3NO$ requires *M*, 249.1340); ν_{max}/cm^{-1} 3355, 1685, 1449, 1380, 1202, 1165, 1076 and 842; δ_H (C_6D_6) 1.50 and 1.55 (each 3 H, s, 2 × CH_3), 1.7 (3 H, s, CH_3), 1.95 (2 H, m, 5-H_2), 2.05 (2 H, m, 4-H_2), 4.74 (2 H, d, *J* 7, 1-H_2), 5.15 (1 H, m, 6-H), 5.45 (1 H, m, 2-H) and 8.05 (1 H, br s, NH); δ_C (C_6D_6) 16.26, 17.60, 25.69, 26.48, 39.65, 64.61, 116.22, 117.99, 124.13, 131.60, 143.08 and 157.61; δ_F (C_6D_6) −75.85; *m*/*z* (CI) 267 ($M^+ + 18$, 11%), 250 ($M^+ + 1$, 2), 249 (M^+, 9) and 154 (99).

(*E*)-1-(2,2,2-Trifluoroacetimidoyloxy)-3-phenylprop-2-ene 54. (0.27 g, 83%) From cinnamyl alcohol (0.19, 1.44 mmol), as a colourless oil after chromatography on base washed silica using gradient elution (40:1→20:1 light petroleum–ether) (Found: M^+, 229.0721. $C_{11}H_{10}F_3NO$ requires *M*, 229.0714); ν_{max}/cm^{-1} 3349, 1686, 1356, 1202, 1166 and 1076; δ_H (C_6D_6) 4.68 (2 H, d, *J* 7, 1-H_2), 6.09 (1 H, dt, *J* 16, 6.5, 2-H), 6.42 (1 H, d, *J* 16, 3-H), 7.14 (5 H, m, ArH) and 8.10 (1 H, br s, NH); δ_C (C_6D_6) 68.27, 116.22, 122.15, 135.21, 136.42 and 157.42, remaining signals obscured by C_6D_6; δ_F (C_6D_6) −75.81; *m*/*z* (EI) 229 (M^+, 30%), 200 (23), 160 (12) and 115 (100).

(2*E*,4*E*)-1-(2,2,2-Trifluoroacetimidoyloxy)hexa-2,4-diene 56. (0.45 g, 77%) From sorbyl alcohol (0.3 g, 3.06 mmol), as a colourless oil after chromatography on base washed silica using gradient elution (40:1→20:1 light petroleum–ether) (Found: M^+, 193.0720. $C_8H_{10}F_3NO$ requires *M*, 193.0714); ν_{max}/cm^{-1} 3300, 1686, 1201 and 1165; δ_H (C_6D_6) 1.55 (3 H, d, *J* 6.5, 6-H_3), 4.62 (2 H, d, *J* 7, 1-H_2), 5.52 (2 H, m), 5.89 (1 H, m), 6.12 (1 H, m) and 8.10 (1 H, br s, NH); δ_C (C_6D_6) 17.91, 68.16, 116.21, 122.85, 130.85, 131.29, 135.90 and 157.44; δ_F (C_6D_6) −75.93; *m*/*z* (EI) 193 (M^+, 5%) and 164 (2).

2-[(3*S*,1*E*)-3-(2,2,2-Trifluoroacetimidoyloxy)but-1-enyl]-1,3-dioxolane 62. (0.2 g, 79%) From the alcohol **61** (0.15 g, 1.04 mmol), as a colourless oil after chromatography on base washed silica using gradient elution (light petroleum–ether 20:1→10:1), $[\alpha]_D^{20}$ −52.2 (*c* 1.18, PhH); ν_{max}/cm^{-1} 3304, 1684, 1400, 1204, 1161, 1082, 1038, 968 and 845; δ_H (C_6D_6) 1.12 (3 H, d, *J* 6.5, 4′-H_3), 3.48 (4 H, m, OCH_2CH_2O), 5.24 (1 H, m, 2-H), 5.52 (1 H, m, 3-H), 5.88 (2 H, m, 1′-H and 2′-H) and 8.05 (1 H, br s, NH); δ_C (C_6D_6) 19.07, 64.80, 73.14, 103.02, 116.13, 129.37, 133.30 and 156.66; δ_F (C_6D_6) −76.22; *m*/*z* (CI) 239 (M^+, 4%), 127 (20) and 116 (22).

(2*S*)-2-[(3*R*,4*S*,1*E*)-4-Benzyloxymethoxy-3-(2,2,2-trifluoroacetimidoyloxy)pent-1-enyl]-*N*-(*tert*-butoxycarbonyl)pyrrolidine 69. (65 mg, 45%) From the alcohol **68** (0.12 g, 0.3 mmol) as a colourless gum after chromatography on base washed silica using gradient elution (20:1→10:1→ 3:1→1:1 light petroleum–ether), $[\alpha]_D^{25}$ −53 (*c* 2, PhH); ν_{max}/cm^{-1} 3281, 1691, 1396, 1199, 1165 and 1041; *m*/*z* (EI) 486 (M^+, 1%), 386 (15), 318 (60) and 91 (100).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*R*,1*E*)-4-benzyloxymethoxy-3-(2,2,2-trifluoroacetimidoyloxy)pent-1-enyl]-2,2-dimethyl-1,3-dioxolane 73. (0.24 g, 86%) From alcohol **72** (0.23 g, 0.49 mmol), as a colourless oil after chromatography on base washed silica using gradient elution (40:1→20:1 light petroleum–ether), $[\alpha]_D^{25}$ +24.1 (*c* 1.00, PhH) (Found: $M^+ + NH_4$, 579.3072. $C_{27}H_{46}F_3N_2O_6Si$ requires *M*, 579.3077); ν_{max}/cm^{-1} 3301, 3250, 1688, 1381, 1202, 1167, 1086, 1041 and 878; δ_H (C_6D_6) 0.12 and 0.14 (each 3 H, s, $SiCH_3$), 1.03 [9 H, s, $SiC(CH_3)_3$], 1.13 (3 H, d, *J* 6.5, 5″-H_3), 1.45 and 1.49 (each 3 H, s, CH_3), 3.73 (2 H, m, 1′-H_2), 3.84 (1 H, m, 4-H), 4.02 (1 H, dq, *J* 6.5, 4, 4″-H), 4.51 (1 H, m, 5-H), 4.61 (2 H, s, $PhCH_2$), 4.68 and 4.77 (each 1 H, d, *J* 7.5 O*H*CHO), 5.67 (1 H, m, 3″-H), 6.06 (2 H, m, 1″-H and 2″-H), 7.13–7.42 (5 H, m, ArH) and 8.12 (1 H, br s, NH); δ_C (C_6D_6) −5.34, −5.29, 15.98, 18.47, 26.03, 27.09, 27.18, 63.07, 69.37, 73.36, 78.28, 79.76, 81.91, 93.27, 109.36, 116.21, 126.13, 128.52, 134.07, 138.55 and 156.94;

δ_F (C_6D_6) −76.04; *m/z* (CI) 580 (M^+ + 19, 10%), 579 (M^+ + 18, 8), 391 (50) and 361 (100).

Rearrangement of trifluoroacetimidates

(2*R*,5*S*,3*E*)-2-(Benzyloxymethoxy)-6-methyl-5-(2,2,2-trifluoroacetylamino)hept-3-ene 34. (60 mg, 89%) From the trifluoroacetimidate **33** (67 mg, 0.19 mmol), as a white wax, after heating under reflux in xylene (2 cm^3) ~4 h and chromatography using light petroleum–ether (6:1) as eluent, mp 49–51 °C, $[\alpha]_D^{22}$ +48.9 (*c* 1.12 $CHCl_3$) (Found: C, 60.5; H, 6.8; N, 3.8; F, 15.5. $C_{18}H_{24}F_3NO_3$ requires C, 60.2; H, 6.8; N, 3.9; F, 15.9%; Found: $M^+ + NH_4$, 377.2048. $C_{18}H_{28}F_3N_2O_3$ requires *M*, 377.2052); ν_{max}/cm^{-1} 3285, 3092, 3069, 3034, 1699, 1556, 1208, 1183, 1104 and 1038; δ_H 0.92 and 0.93 (each 3 H, d, *J* 6.5, 2 × CH_3), 1.28 (3 H, d, *J* 6.5, 1-H_3), 1.86 (1 H, m, 6-H), 4.30 (2 H, m, 2-H and 5-H), 4.55 and 4.67 (each 1 H, d, *J* 11.5, PhC*H*H), 4.73 and 4.76 (each 1 H, d, *J* 6.5, OC*H*HO), 5.58 (2 H, m, 3-H and 4-H), 6.35 (1 H, br d, *J* 7, NH) and 7.30 (5 H, m, ArH); δ_C 18.35, 18.80, 21.50, 32.25, 56.97, 69.68, 72.12, 92.14, 116.09, 127.91, 128.07, 128.35, 128.63, 135.04, 138.04 and 156.69; δ_F 2.90 and 3.07 (99:1); *m/z* (CI) 377 (M^+ + 18, 100%).

(2*S*,5*R*,3*E*)-2-(Benzyloxymethoxy)-6-methyl-5-(2,2,2-trifluoroacetylamino)hept-3-ene 45. (0.23, 91%) From the trifluoroacetimidate **44** (0.25 g, 0.7 mmol) in xylene (25 cm^3), as a white wax, after heaing under reflux in xylene for ~4 h and chromatography using light petroleum–ether (6:1) as eluent, mp 49–50 °C, $[\alpha]_D^{23}$ −55.2 (*c* 0.86 $CHCl_3$) (Found: C, 59.85; H, 7.0; N, 3.9. $C_{18}H_{24}F_3NO_3$ requires C, 60.2; H, 6.8; N, 3.9%; Found: $M^+ + NH_4$, 377.2055. $C_{18}H_{28}F_3N_2O_3$ requires *M*, 377.2052).

3-(2,2,2-Trifluoroacetylamino)-3,7-dimethylocta-1,6-diene 53. (0.16 g, 80%) From the trifluoroacetimidate **52** (0.19 g, 0.78 mmol), as a colourless oil, after heating under reflux in xylene (15 cm^3) for 8 h and chromatography using light petroleum–ether (40:1) as eluent (Found: M^+, 249.1329. $C_{12}H_{18}F_3NO$ requires *M*, 249.1340); ν_{max}/cm^{-1} 3326, 3089, 1712, 1547 and 1185; δ_H 1.53, 1.61 and 1.69 (each 3 H, s, CH_3), 1.81 (2 H, m, 4-H_2), 2.02 (2 H, m, 5-H_2), 5.15 (3 H, m, 1-H_2 and 6-H), 5.90 (1 H, dd, *J* 17, 10, 2-H) and 6.40 (1 H, br s, NH); δ_C 17.65, 22.56, 24.02, 25.59, 39.09, 58.81, 113.71, 115.65, 123.34, 133.33, 140.76 and 155.90; δ_F −77.75; *m/z* (EI) 249 (M^+, 2%), 234 (1.5), 166 (19) and 136 (44).

1-(2,2,2-Trifluoroacetylamino)-1-phenylprop-2-ene 55. (0.20 g, 81%) From the trifluoroacetimidate **54** (0.25 g, 1.09 mmol), as a colourless crystalline solid, after heating under reflux in xylene (15 cm^3) for 5 h and chromatography using light petroleum–ether (10:1) as eluent, mp 76–77 °C (needles from light petroleum) (Found: C, 58.1; H, 4.7; F, 25.1; N, 6.0. $C_{11}H_{10}F_3NO$ requires C, 57.6; H, 4.4; F, 24.9; N, 6.1%; Found: M^+, 229.0716. $C_{11}H_{10}F_3NO$ requires *M*, 229.0714); ν_{max}/cm^{-1} 3308, 1701, 1549, 1205 and 1176; δ_H 5.34 (2 H, m, 3-H_2), 5.64 (1 H, m, 1-H), 6.04 (1 H, m, 2-H), 6.5 (1 H, br s, NH) and 7.32 (5 H, m, ArH); δ_C 55.76, 115.83, 117.33, 127.20, 128.52, 129.14, 135.26, 138.42 and 156.27; δ_F −77.33; *m/z* (EI) 229 (M^+, 59%) and 160 (55).

(*E*)-3-(2,2,2-Trifluoroacetylamino)hexa-1,4-diene 57. (0.14 g, 35%) From the trifluoroacetimidate **56** (0.38 g, 1.98 mmol), as a colourless oil, after heating under reflux in xylene (25 cm^3) for 9.5 h and chromatography using gradient elution (40:1→20:1 light petroleum–ether) (Found: M^+, 193.0712. $C_8H_{10}F_3NO$ requires *M*, 193.0715); ν_{max}/cm^{-1} 3294, 1703, 1552 and 1185; δ_H 1.73 (3 H, m, 6-H_3), 4.99 (1 H, m, 3-H), 5.21 (1 H, m, 1-H), 5.26 (1 H, m, 1-H′), 5.45 (1 H, m, 4-H), 5.78 (2 H, m, 2-H and 5-H) and 6.45 (1 H, br s, NH); δ_C 17.72, 53.49, 115.85, 116.81, 127.48, 129.82, 135.34 and 156.19; δ_F −77.51; *m/z* (EI) 193 (M^+, 17%), 178 (15), 166 (9) and 152 (9).

2-[(1*S*,2*E*)-1-(2,2,2-Trifluoroacetylamino)but-2-enyl]-1,3-dioxolane 63. (0.16 g, 93%) From the trifluoroacetimidate **62** (0.17 g, 0.71 mmol), as colourless crystals, after heating under reflux in xylene (15 cm^3) for 16 h and chromatography using light petroleum–ether (4:1) as eluent, mp 53–54 °C, $[\alpha]_D^{20}$ −16.6 (*c* 1.10, PhH) (Found: C, 45.4; H, 5.1; N, 6.0; F, 24.1. $C_9H_{12}F_3NO_3$ requires C, 45.2; H, 5.1; N, 5.9; F, 23.8%; Found: $M^+ + NH_4$, 257.1115. $C_9H_{16}N_2F_3O_3$ requires *M*, 257.1113); ν_{max}/cm^{-1} 3280, 1706, 1561, 1211 and 1187; δ_H 1.75 (3 H, d, *J* 6.5 4′-H_3), 3.97 (4 H, m, OCH_2CH_2O), 4.72 (1 H, t, *J* 7, 1′-H), 4.94 (1 H, d, *J* 2, 2-H), 5.42 (1 H, m, 2′-H), 5.80 (1 H, m, 3′-H) and 6.53 (1 H, d, *J* 5.5, NH); δ_C 17.88, 53.30, 65.45, 65.67, 103.29, 115.89, 124.16, 131.44 and 156.73; δ_F −77.478; *m/z* (CI) 257 (M^+ + 18, 46%), 240 (M^+ + 1, 9%) and 35 (100).

(2*S*)-2-[(1*S*,4*S*,2*E*)-4-Benzyloxymethoxy-1-(2,2,2-trifluoroacetylamino)pent-2-enyl]-*N*-(*tert*-butoxycarbonyl)pyrrolidine 70. (18 mg, 90%) From the trifluoroacetimidate **69** (20 mg, 0.042 mmol) in xylene (5 cm^3), as a colourless gum, after heating under reflux in xylene for 7 h and chromatography using light petroleum–ether (4:1) as eluent, $[\alpha]_D^{22}$ −73.7 (*c* 0.63, $CHCl_3$) (Found: M^+ + H, 487.2419. $C_{24}H_{34}F_3N_2O_5$ requires *M*, 487.2420); ν_{max}/cm^{-1} 3250, 1724, 1669, 1547, 1400 and 1164; δ_H 1.27 (3 H, d, *J* 6.5, 5′-H_3), 1.47 [9 H, s, $C(CH_3)_3$], 1.76–1.94 (4 H, m, 3-H_2 and 4-H_2), 3.35 (2 H, m, 5-H_2), 3.98 (1 H, m, 2-H), 4.07 (1 H, m, 1′-H), 4.26 (1 H, m, 4′-H), 4.56 and 4.67 (each 1 H, d, *J* 12, OC*H*HO), 4.74 (2 H, s, $PhCH_2$), 5.45 (1 H, m, 2′-H), 5.73 (1 H, m, 3′-H), 7.35 (5 H, m, ArH) and 8.87 (1 H, br d, *J* 6, NH); δ_C 21.29, 23.45, 28.15, 28.23, 47.09, 57.96, 59.03, 69.51, 72.17, 81.05, 92.09, 115.88, 127.49, 127.69, 127.91, 128.43, 136.64, 137.94, 157.178 and 157.81; δ_F −77.68, −77.86 (95:5); *m/z* (CI) 504 (M^+ + 18), 487 (M^+ + 1), 387 (50) and 293 (55).

(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*R*,1*E*)-4-benzyloxymethoxy-3-(2,2,2-trifluoroacetylamino)pent-2-enyl]-2,2-dimethyl-1,3-dioxolane 74. (188 mg, 91%) From the trifluoroacetimidate **73** (208 mg, 0.37 mmol), as a colourless oil, after heating under reflux in xylene (20 cm^3) for 9.5 h and chromatography using light petroleum–ether (7:1) as eluent, $[\alpha]_D^{25}$ +27 (*c* 0.8, $CHCl_3$) (Found: $M^+ + NH_4$, 579.3083. $C_{27}H_{46}F_3N_2O_6Si$ requires *M*, 579.3077); ν_{max}/cm^{-1} 3319, 1730, 1526, 1255, 1212, 1169, 1093, 1039 and 838; δ_H 0.08 (6 H, s, 2 × $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.28 (3 H, d, *J* 6.5, 5″-H_3), 1.38 and 1.42 (each 3 H, s, CH_3), 3.69 (2 H, m, 1′-H_2), 3.86 (1 H, m, 4-H), 4.06 (1 H, dd, *J* 7, 2 5-H), 4.30 (1 H, m, 4″-H), 4.56 and 4.68 (each 1 H, d, *J* 11, Ph*H*CH), 4.76 (3 H, m, OCH_2O and 1″-H), 5.69 (2 H, m, 3″-H and 4″-H), 6.69 (1 H, br d, *J* 8, NH) and 7.35 (5 H, m, ArH); δ_C −5.51, −5.42, 18.41, 21.23, 25.90, 26.90, 50.37, 63.24, 69.53, 71.62, 80.22, 92.12, 109.60, 115.89, 127.12, 127.72, 127.90, 128.45, 135.17, 137.92 and 156.64; δ_F −77.34; *m/z* (CI) 579 (M^+ + 18, 60%) and 424 (100).

(2*R*,5*S*,3*E*)-2-(Benzyloxymethoxy)-6-methyl-5-(*tert*-butoxycarbonylamino)hept-3-ene 36

Barium hydroxide (0.19 g, 0.59 mmol) was added to a solution of the trifluoroacetamide **34** (27 mg, 0.074 mmol) in methanol (3 cm^3) at 0 °C and the mixture stirred at ambient temperature overnight. The mixture was then filtered through a pad of Celite and silica, eluting with methanol, and the filtrate concentrated under reduced pressure to give the amine **35** (Found: M^+ + H, 264.1963. $C_{16}H_{26}NO_2$ requires *M*, 264.1963); δ_H 0.87 and 0.91 (each 3 H, d, *J* 8, 2 × CH_3), 1.13 (2 H, br s, NH_2), 1.28 (3 H, d, *J* 8, 1-H_3), 1.62 (1 H, m, 6-H), 3.10 (1 H, m, 5-H), 4.27 (1 H, m, 2-H), 4.56 and 4.68 (each 1 H, d, *J* 12, PhC*H*H), 4.73 and 4.79 (each 1H, d, *J* 8, OC*H*HO), 5.47 and 5.61 (each 1 H, dd, *J* 15, 7, 3-H and 4-H) and 7.32 (5 H, m, ArH): *m/z* (CI) 264 (M^+ + 1, 100%).

The amine was dissolved in ether (1 cm^3) and the resulting solution cooled to 0 °C. Triethylamine (0.012 cm^3, 0.086 mmol) and a solution of di-*tert*-butyl dicarbonate (18 mg, 0.082 mmol) in ether (2 cm^3) were added and the solution stirred overnight at ambient temperature. The mixture was concentrated under reduced pressure and chromatography of the residue using light petroleum–ether (5:1) as eluent gave the *title compound* **36** (21 mg, 79%), as a white wax (Found: C, 69.1; H, 9.2 and N, 3.9. $C_{21}H_{33}NO_4$ requires C, 69.4; H, 9.2 and N, 3.9%; Found: $M^+ + H$, 364.2413. $C_{21}H_{34}NO_4$ requires *M*, 364.2487); δ_H 0.87 and 0.90 (each 3 H, d, *J* 7, 2 × CH_3), 1.27 (3 H, d, *J* 6.5, 1-H_3), 1.44 [9 H, s, $C(CH_3)_3$], 1.75 (1 H, m, 6-H), 3.99 (1 H, m, 5-H), 4.28 (1 H, m, 2-H), 4.48 (1 H, br d, *J* 7, NH), 4.55 and 4.68 (each 1 H, d, *J* 12, PhC*H*H), 4.72 and 4.77 (each 1 H, d, *J* 7, OC*H*HO), 5.51 (2 H, m, 3-H and 4-H) and 7.35 (5 H, m, ArH); *m*/*z* (CI) 381 ($M^+ + 18$, 46%), 364 ($M^+ + 1$, 4) and 91 (100).

N-*tert*-Butoxycarbonyl-L-valine methyl ester 37

A solution of the alkene **36** (0.14 g, 0.38 mmol) in methanol (8 cm^3) was cooled to −78 °C whilst oxygen was bubbled through the solution. After 10 min, ozone was bubbled into the solution for 20 min and then the mixture was purged with oxygen for a further 10 min. Dimethyl sulfide (0.3 cm^3, 4 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 1 h then concentrated under reduced pressure. The residue was dissolved in methanol (8 cm^3) and water (0.15 cm^3) and cooled to 0 °C. Sodium bicarbonate (0.64 g, 7.62 mmol) and bromine (0.3 g, 1.88 mmol) were added and the resulting suspension stirred overnight at ambient temperature. Sodium thiosulfate (0.3 g) and ether (100 cm^3) were added and the mixture washed with water (2 × 5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (10:1) as eluent gave a mixture of the methyl ester **37** and methyl (*R*)-2-benzyloxymethoxypropanoate **40** (0.11 g, 65%, ~1:1 mixture). Preparative HPLC (column: 5 μm ODS; eluent: 70:30 methanol–water) afforded the *title compound* **37** as a colourless oil, $[\alpha]_D^{18}$ −17.6 (*c* 3.23, MeOH) [lit.,[22] −22.7 (*c* 2, MeOH)]; ν_{max}/cm^{-1} 3372, 1744, 1717, 1438, 1368 and 1160; δ_H 0.88 and 0.95 (each 3 H, d, *J* 7, CH_3), 1.43 [9 H, s, $C(CH_3)_3$], 2.12 (1 H, m, 3-H), 3.73 (3 H, s, OCH_3), 4.22 (1 H, m, 2-H) and 5.01 (1 H, br d, *J* 7, NH); δ_C 17.63, 18.96, 28.32, 31.33, 51.99, 58.58, 79.78, 155.67 and 172.91. Methyl (*R*)-2-benzyloxymethoxypropanoate **40** was also isolated as a colourless oil, $[\alpha]_D^{24}$ +59.9 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 1752, 1454, 1209, 1174, 1122, 1083, 1049 and 1026; δ_H 1.43 (3 H, d, *J* 7, 3-H_3), 3.70 (3 H, s, OCH_3), 4.31 (1 H, q, *J* 7, 2-H), 4.61 and 4.67 (each 1 H, d, *J* 11, Ph*H*CH), 4.83 (2 H, s, OCH_2O) and 7.35 (5 H, m, ArH); *m*/*z* (CI) 242 ($M^+ + 18$, 2%) and 225 ($M^+ + 1$, 2).

A solution of trifluoroacetic acid (0.9 cm^3) in methanol (0.1 cm^3) was added at 0 °C to a 1:1 mixture of ester **37** and methyl (*R*)-2-benzyloxymethoxypropanoate **40** (85 mg) and the mixture stirred for 30 min at ambient temperature. Ethyl acetate (7 cm^3) was added and the mixture washed with saturated aqueous sodium bicarbonate (3 × 5 cm^3), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane–methanol (9:1) as eluent gave the amine **38**. This was dissolved in carbon tetrachloride (10 drops) and pyridine (10 drops) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (94 mg, 0.37 mmol) was added. The resulting suspension was stirred overnight at ambient temperature and then diluted with ether (50 cm^3), washed with saturated aqueous ammonium chloride (2 cm^3), sodium bicarbonate (2 cm^3) and water (2 cm^3) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3:1) as eluent gave the (*S*)-Mosher's derivative **39** (48 mg, 73%), as a colourless oil; δ_H (major diastereoisomer) 0.81 and 0.87 (each 3 H, d, *J* 7, CH_3), 2.21 (1 H, m, 3-H), 3.55 (3 H, s, OCH_3), 3.77 (3 H, s, CO_2CH_3), 4.62 (1 H, dd, *J* 9, 5, 2-H), 7.06 (1 H, br d, *J* 9, NH) and 7.35–7.65 (5 H, m, ArH); δ_F −70.39, −70.70 (90:10); δ_H (minor diastereoisomer) 0.95 and 1.0 (each 0.3 H, d, *J* 7, CH_3).

(2*S*,5*R*,3*E*)-2-(Benzyloxymethoxy)-6-methyl-5-(benzyloxycarbonylamino)hept-3-ene 47

Barium hydroxide (0.83 g, 2.63 mmol) was added to a solution of the trifluoroacetamide **45** (0.12 g, 0.33 mmol) in methanol (10 cm^3) at 0 °C and the mixture stirred overnight at ambient temperature then filtered through a pad of Celite and silica using methanol as eluent. The filtrate was concentrated under reduced pressure and the residue dissolved in water (2 cm^3) and ethyl acetate (3 cm^3). Benzyl chloroformate (68 mg, 0.4 mmol) and potassium bicarbonate (0.165 g, 1.64 mmol) were added and the mixture stirred overnight at ambient temperature. Ethyl acetate (100 cm^3) was added and the organic layer was washed with saturated aqueous ammonium chloride (2 × 5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (5:1) as eluent gave the *title compound* **47** (0.11 g, 86%) as a pale yellow gum, $[\alpha]_D^{20}$ −81.7 (*c* 0.86, $CHCl_3$) (Found: $M^+ + NH_4$, 415.2608. $C_{24}H_{35}N_2O_4$ requires *M*, 415.2597); ν_{max}/cm^{-1} 3328, 1705, 1455, 1238, 1100 and 1026; δ_H 0.88 and 0.92 (each 3 H, d, *J* 7, 2 × CH_3), 1.27 (3 H, d, *J* 6.5, 1-H_3), 1.78 (1 H, m, 6-H), 4.08 (1 H, m, 5-H), 4.27 (1 H, m, 2-H), 4.52–4.78 (5 H, m, OCH_2O, $PhCH_2$ and NH), 5.12 (2 H, s, $PhCH_2OCO$), 5.55 (2 H, m, 3-H and 4-H) and 7.36 (10 H, m, ArH); *m*/*z* (CI) 415 ($M^+ + 18$, 32%), 307 (23), 264 (57) and 260 (100).

N-Benzyloxycarbonyl-D-valine methyl ester 48

Following the general procedure for the ozonolysis–bromine in methanol oxidation, the alkene **47** (92 mg, 0.23 mmol) gave the *title compound* **48** (52 mg, 84%), as a colourless gum, after chromatography using gradient elution (10:1→5:1 light petroleum–ether), $[\alpha]_D^{23}$ +11.5 (*c* 0.9, MeOH) [lit. for the enantiomer[23] −18.9 (*c* 1, MeOH)] (Found: M^+, 265.1321. $C_{14}H_{19}NO_4$ requires *M*, 265.1314). Methyl (*S*)-2-benzyloxymethoxypropanoate **49** was also isolated as a colourless oil (38 mg, 73%), $[\alpha]_D^{20}$ −64.1 (*c* 1.67, $CHCl_3$).

The ester **48** (42 mg, 0.16 mmol), sodium borohydride (60 mg, 1.6 mmol) and lithium chloride (67 mg, 1.6 mmol) in ethanol (2.5 cm^3) and tetrahydrofuran (1.5 cm^3) were stirred for 2 h at ambient temeprature then acetic acid (0.25 cm^3) and water (3 cm^3) were added. After extraction into ethyl acetate and concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the alcohol **50** (36 mg, 95%), as a white wax, $[\alpha]_D^{22}$ +22.9 (*c* 0.45, $CHCl_3$) [lit. for the enantiomer[24] −16.9 (*c* 2, methanol)] (Found: $M^+ + H$, 238.1438. $C_{13}H_{20}NO_3$ requires *M*, 238.1443); *m*/*z* (CI) 255 ($M^+ + 18$, 13%), 238 ($M^+ + 1$, 100); ν_{max}/cm^{-1} 3400, 1697, 1533 and 1245.

Following the general procedure, the alcohol **50** (20 mg, 0.085 mmol) afforded the (*R*)-Mosher's derivative **51** (41 mg, 100%), as a colourless gum, after chromatography using light petroleum–ether (3:1) as eluent; ν_{max}/cm^{-1} 3318, 1747, 1696, 1538 and 1453; δ_H 0.85 and 0.90 (each 3 H, d, *J* 7, CH_3), 1.73 (1 H, m, 3-H), 3.47 (3 H, s, OCH_3), 3.76 (1 H, m, 2-H), 4.35 (2 H, m, CH_2O), 4.63 (1 H, d, *J* 9.5, NH), 5.05 (2 H, s, $PhCH_2$) and 7.28–7.49 (10 H, m, ArH), peaks due to a minor product were also present, ratio, 92.3:7.7; *m*/*z* (EI) 453 (M^+, 3%), 189 (26) and 91 (100).

(4*S*,5*S*)-4-[(1*R*,4*R*,2*E*)-1-(*tert*-Butoxycarbonylamino)-4-benzyloxymethoxypent-2-enyl]-5-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolane 76

Barium hydroxide (0.75 g, 2.4 mmol) was added to a solution of the trifluoroacetamide **74** (0.17 g, 0.30 mmol) in methanol (10 cm^3) at ambient temperature and the resulting suspension

stirred for 19 h before being filtered through a pad of Celite and silica and concentrated under reduced pressure. The residue (145 mg) was dissolved in ether (2 cm^3) cooled to 0 °C and triethylamine (0.05 cm^3, 0.36 mmol) and a solution of di-*tert*-butyl dicarbonate (70 mg, 0.32 mmol) in ether (2 cm^3) were added. The mixture was stirred at ambient temperature for 14 h then concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (7:1) as eluent afforded the *title compound* **76** (142 mg, 84%) as a colourless oil, $[\alpha]_D^{26}$ +61.2 (*c* 0.74, $CHCl_3$) (Found: $M^+ + H$, 566.3522. $C_{30}H_{52}NO_7Si$ requires *M*, 566.3513); ν_{max}/cm^{-1} 3354, 1720, 1368, 1253, 1169, 1085, 1038 and 838; δ_H 0.09 (6 H, s, 2 × $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.28 (3 H, d, *J* 6.5, 5″-H_3), 1.36 and 1.41 (each 3 H, s, CH_3), 1.44 [9 H, s, $C(CH_3)_3$], 3.70 (1 H, m, 4-H), 3.81 (2 H, m, 1′-H_2), 3.99 (1 H, m, 5-H), 4.29 (1 H, m, 4″-H), 4.41 (1 H, m, 1″-H), 4.54 and 4.68 (each 1 H, d, *J* 12, PhC*H*H), 4.72 and 4.78 (each 1 H, d, *J* 8, OC*H*HO), 5.26 (1 H, br d, *J* 7, NH), 5.65 (2 H, m, 2″-H and 3″-H) and 7.34 (5 H, m, ArH); δ_C −5.39, 18.44, 21.48, 25.99, 26.67, 27.01, 28.40, 50.96, 63.42, 69.43, 72.05, 79.49, 80.63, 91.88, 108.91, 127.64, 127.91, 128.41, 129.90, 132.93, 138.07 and 155.41; *m*/*z* (CI) 566 ($M^+ + 1$, 10%) and 372 (100).

(4*S*,5*S*)-4-[(*S*)-(*tert*-Butoxycarbonylamino)methoxycarbonylmethyl]-5-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolane 77

In accordance with the general procedure for ozonolysis–bromine in methanol oxidation the alkene **76** (0.44 g, 0.78 mmol) afforded a mixture of the *title compound* **77** and methyl (*R*)-2-benzyloxymethoxypropanoate **40** after chromatography using gradient elution (10:1→5:1→3:1 light petroleum–ether) as a colourless oil (0.47 g, ~90%): title compound **77**; δ_H 0.10 (6 H, s, 2 × $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.37 and 1.42 (each 3 H, s, CH_3), 1.45 [9 H, s, $C(CH_3)_3$], 3.78 (3 H, s, CO_2CH_3), 3.82 (2 H, m, 1′-H_2), 3.91 (1 H, m), 4.40 (1 H, m), 4.45 (1 H, m) and 5.35 (1 H, d, *J* 10, NH). Lithium hydroxide (50 mg, 1.19 mmol) was added to a solution of the mixture of the methyl ester **77** and methyl (*R*)-2-benzyloxymethoxypropanoate **40** (0.19 g) in tetrahydrofuran (3 cm^3) and water (1 cm^3) at 0 °C and the resulting solution stirred for 3 h at ambient temperature. Saturated aqueous ammonium chloride (30 cm^3) was added and the mixture extracted with ether (3 × 30 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the acid **21** (0.12 g, 96%) as a white solid with data identical to those obtained before. The aqueous layer was then acidified to pH 2, and re-extracted with ether (3 × 30 cm^3). After drying ($MgSO_4$), these extracts were concentrated under reduced pressure to give the BOM-protected lactic acid (48 mg, 79%).

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