Enantioselective Synthesis of Indolizidine Alkaloids: Formal Synthesis of (−)-Swainsonine and of (+)-Pumiliotoxin 251D

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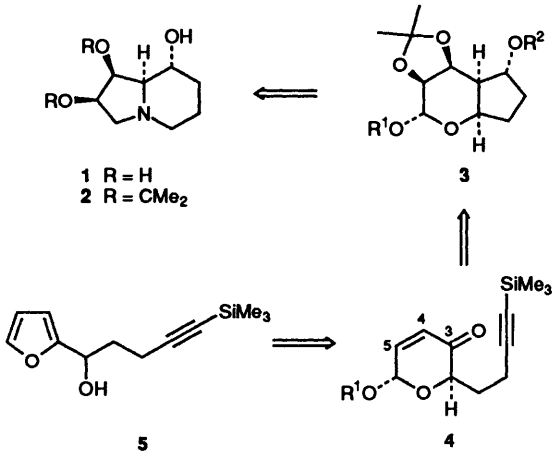
Oxidative treatment of optically active 2-furylmethanol (furfuryl alcohol) derivative (*R*)-**5**, obtained by Sharpless kinetic resolution of the racemate, afforded the pyranone **9**, which on successive reduction with lithium aluminium hydride in the presence of copper(I) iodide and with sodium boranuide ($NaBH_4$), followed by conversion into imidazolide **14**, was subjected to a radical cyclization reaction to provide the bicyclic compound **15**, stereoselectively. The cyclopentanone oxime (*E*)-**25**, derived from the ketone **23**, was subjected to Beckmann rearrangement to afford lactam **26**, which was further cyclized to give the indolizidine **30**, an intermediate for (+)-pumiliotoxin 251D **31**. Whereas dihydroxylation of lactol **32** gave triol **34**, which after protection as acetonide **35** was also converted into imidazolide **37**. Radical cyclization of compound **37** produced the bicyclic compound **38**, stereoselectively, whose Lemieux–Johnson oxidation followed by Birch reduction gave alcohol **40**. The cyclopentanone **45** was further formally transformed into swainsonine **1** by a similar synthetic route to that above.

Indolizidine alkaloids have been isolated, from plants and fungi, and also from animal sources, with a wide range of structural and stereochemical features.[1] Since this class of alkaloids has been known to exhibit interesting biological activities, intensive efforts have been devoted to their synthesis to date.[1–3] One of this class of compounds, which is of considerable interest, is swainsonine, isolated from the fungae *Rhizoctonia leguminicola*[4a] and *Metarhizium anisopliae* F-3522[4b] as well as from locoweed *Astragalus lentiginosus*[4c] and *Swainsona canescens*.[4d] This alkaloid is known to be a potent inhibitor of both lysosomal α-mannosidase and mannosidase II and to disrupt the processing of glycoproteins.[5] The total synthesis of this compound has been achieved by several groups.[6] We have also been interested in the stereoselective synthesis of swainsonine in optically active form and report here our successful results.[7]

Results and Discussion

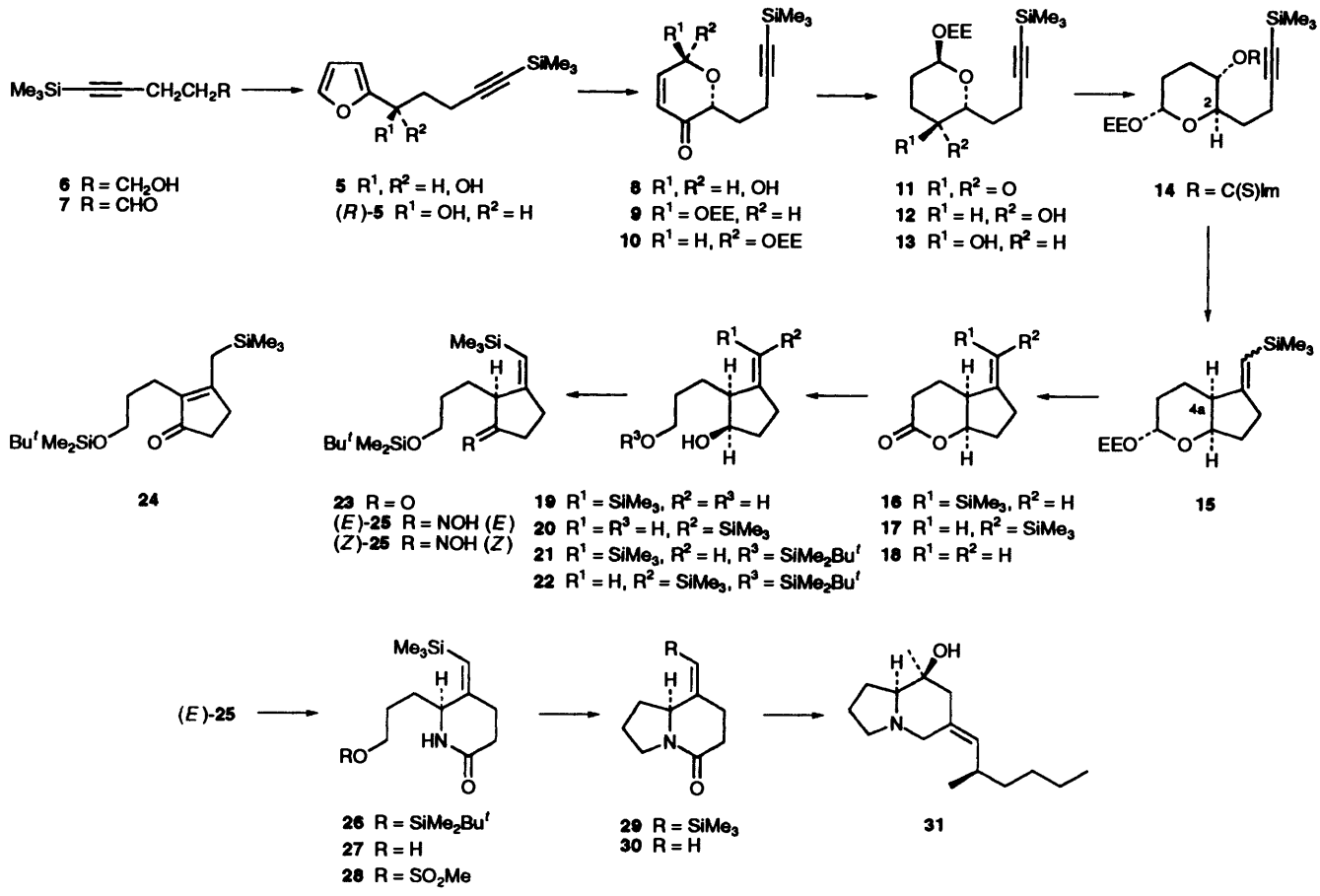
The key feature of our synthesis of swainsonine **1** is based on stereoselective conversion of the acetylenic pyranone **4**, readily prepared from the furyl alcohol **5**,[8] into the *cis*-fused oxabicyclononane **3** by dihydroxylation at the C-4 and -5 positions and hex-5-ynyl radical cyclization[9] between C-3 and the alkyne moiety (Scheme 1). Ring transformation of the pyran **3** into the indolizidine skeleton **2**, an intermediate for swainsonine **1**, could be achieved by Beckmann rearrangement[10] as a crucial step.

Our synthesis began with the preparation of an optically active furfuryl alcohol (*R*)-**5** (Scheme 2). Racemate **5**, obtained by Swern oxidation of alcohol **6**[6h] followed by addition of 2-lithiofuran to the aldehyde **7** in 78% overall yield, was subjected to Sharpless kinetic resolution[11,12] by employing 0.1 mol equiv. of titanium tetraisopropoxide, 0.15 mol equiv. of diisopropyl L-tartrate, and *tert*-butyl hydroperoxide to give optical isomer (*R*)-**5** in 48% yield with >95% ee. The absolute configuration of the resolved compound was assumed to be *R* based on previous results[12] and was unambiguously determined by its conversion into the known lactam **30**. Oxidative ring transformation of (*R*)-**5** with *N*-bromosuccinimide (NBS)[13] in aq. tetrahydrofuran (THF) gave lactol **8** quantitatively, which was protected as its 1-ethoxyethyl ether to afford pyranones **9** and **10** in 62 and 18% yield, respectively.



Scheme 1

We first demonstrated a method for conversion of the pyranone **9** into the indolizidine **30**, an intermediate for (+)-pumiliotoxin 251D **31**.[14] Sequential reduction of the enone moiety in **9** with lithium aluminium hydride (LAH)–copper(I) iodide[15] and then sodium boranuide furnished alcohols **12** and **13**, *via* ketone **11**, in 81 and 13% overall yields. The major alcohol **12** reacted with thiocarbonyldiimidazole to give radical precursor **14** (83%). Treatment of imidazolide **14** with tributyltin hydride and a catalytic amount of azoisobutyronitrile (AIBN) in benzene under reflux produced oxabicyclononane **15** as an inseparable mixture of geometrical isomers, in 87% yield, which on hydrolysis and then oxidation afforded lactones **16** and **17** in 40 and 25% yield, respectively. The stereochemistry at 4a-H in acetal **15** was expected to be the α-orientation, since cyclization of silane **14** would proceed in the *syn* sense with respect to the adjacent ether group at C-2,[9] and deduced by ^1H NMR analyses, including difference nuclear Overhauser enhancement (NOE) between 4a-H and 7a-H in the lactones. The olefin geometry was also assigned by NOE experiments between the vinylic hydrogen and 4a-H. Desilylation of compounds **16** and **17** with aq. hydrogen fluoride afforded olefin **18** as the sole product. *Z*-Vinylsilane **16** was converted into the

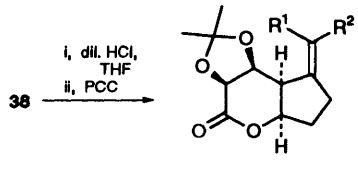


Scheme 2 OEE = 1-ethoxyethoxy, Im = imidazol-1-yl

cyclopentanone **23** by sequential reduction (LAH), selective silylation of primary alcohol **19**, and oxidation [with pyridinium chlorochromate (PCC)] of compound **21** in 55% overall yield, whereas the same treatments of *E*-isomer **17** resulted in olefinic isomerization to give enone **24**, *via* intermediates **20** and **22**, in 50% overall yield. Ketone **23** reacted with hydroxylamine to produce the *E* and *Z* oximes **25** in 65 and 16% yield, respectively. Major compound (*E*)-**25** was subjected to Beckmann rearrangement[10] with thionyl dichloride to give δ-lactam **26** in 41% yield. Deprotection of the silyl ether group in compound **26**, mesylation of primary alcohol **27**, and then intramolecular cyclization of mesyl ester **28** furnished the desired indolizidine skeleton **29** in 65% overall yield. The vinylsilane **29** was desilylated with toluene-*p*-sulfinic acid[6h] to give the known olefin **30** (70%), whose physicochemical properties, including spectroscopic data, are identical with those reported.[14] Since compound **30** has been converted into (+)-pumiliotoxin 251D **31**,[14] this constitutes a formal synthesis of the title compound **31**.

Having developed a method for the stereoselective construction of the indolizidine skeleton, we focused our attention on the synthesis of (−)-swainsonine **1** from ketone **9** (Scheme 3). Reduction of enone **9** with LAH gave mainly alcohol **32** (92%) together with isomer **33** (4%). Dihydroxylation[16] of compound **32** with osmium tetraoxide proceeded diastereoselectively to afford triol **34** (70%), which on protection as an acetonide furnished regioisomers **35** and **36** in 74 and 15% yield, respectively. Acylation of compound **35** with thiocarbonyldiimidazole followed by radical cyclization of intermediate **37** produced an inseparable mixture of geometrical isomers **38** in 63% overall yield. The stereochemical course of the cyclization was identical with the previous result (**14** ⟶ **15**).* Although ozonolysis of the vinylsilane **38** followed by reductive treatment yielded complex mixtures,[17] Lemieux–Johnson oxidation[18] of compound **38** afforded ketone **39** in 86% yield. Birch reduction[19] of ketone **39** with sodium in liquid ammonia and ethanol produced alcohols **40** and **41** in 55 and 30% yield, whereas sodium boranuide reduction of ketone **39** gave the β-ol **41** as the sole product. The stereochemistry at C-5 in alcohols **40** and **41** was deduced based on the expectation that sodium boranuide reduction of ketone **39** would occur from the less hindered, convex side to form *endo*-alcohol **41**. Alcohol **41** could be recycled by Swern oxidation. Conversion of the oxabicyclononane **40** into the cyclopentanol **44** was carried out by sequential benzylation, hydrolysis of acetal **42**, reduction of the lactol, and selective silylation of primary alcohol **43** in 95% overall yield. Perruthenate oxidation[20] of the alcohol **44** followed by reaction of the ketone **45** with hydroxylamine gave (*E*)-oxime **46** (86%) as a single isomer, which was subjected to

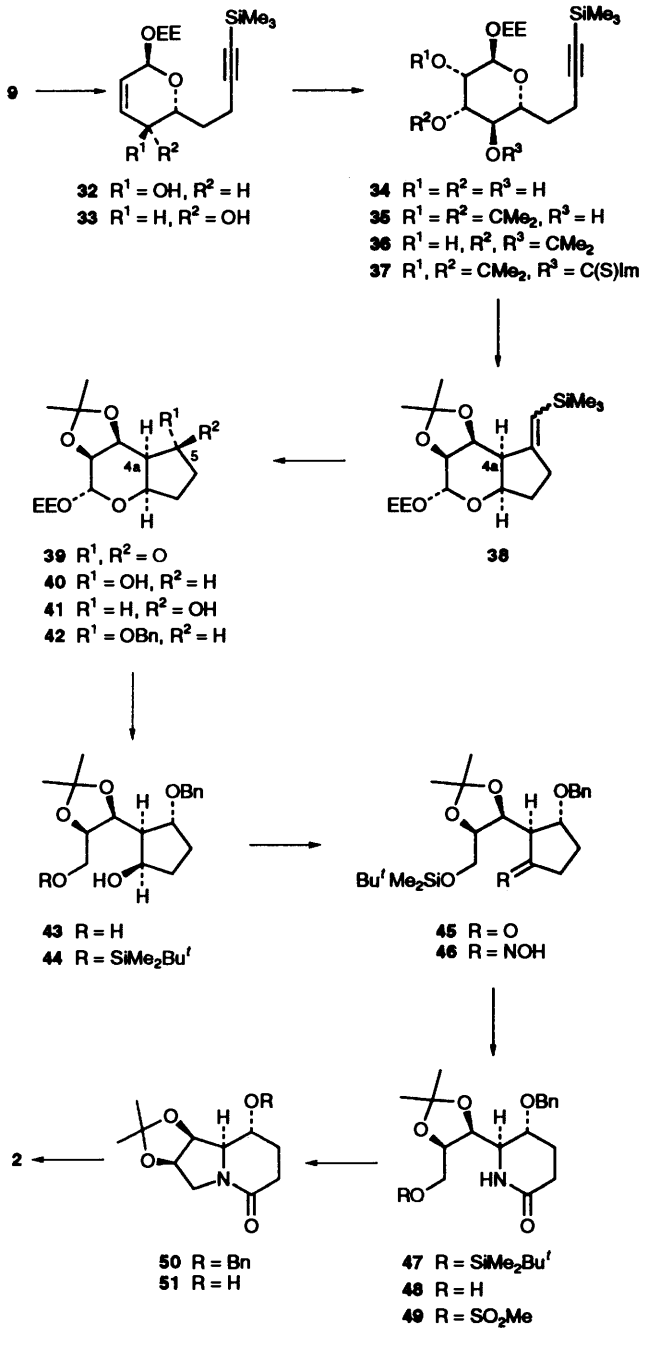
* The stereochemistry at C-4a in compound **38** was assigned by ^{1}H NMR analyses including NOE experiments on the corresponding lactones **i** and **ii** prepared as follows:



i R1 = SiMe3, R2 = H (26% yield from **38**)
ii R1 = H, R2 = SiMe3 (23% yield from **38**)

Beckmann rearrangement to furnish δ-lactam **47** in 83% yield. Conversion of silyl ether **47** into the indolizidine skeleton **50** was achieved, *via* intermediates **48** and **49**, in 96% overall yield by the same sequences as above. Hydrogenolysis of benzyl ether **50** with Pearlman's catalyst[21] afforded lactam **51**, whose reduction with borane–dimethyl sulfide complex followed by hydrolysis with potassium carbonate provided the indolizidine **2** quantitatively. The physicochemical properties, including spectroscopic data, are identical with those reported.[6c,6f,6i,6k,22] Conversion of compound **2** to (−)-swainsonine **1** has been accomplished by several groups,[6c,6f,6i,6k] and this synthesis therefore constitutes its formal synthesis.

Thus, we have developed an enantiocontrolled synthesis of (−)-swainsonine by ring transformation of a pyranone and this strategy could be applied to the synthesis of polyhydroxylated indolizidine alkaloids such as castanospermine.



Scheme 3 Bn = benzyl

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL GSX-270 instrument; chemical shifts are reported on the δ-scale from internal $SiMe_4$, and *J*-values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter, and are reported in units of 10^{-1} deg cm^2 g^{-1}.

5-(Trimethylsilyl)pent-4-ynal **7**.—To a stirred solution of oxalyl dichloride (8.4 cm^3, 96.2 mmol) in CH_2Cl_2 (200 cm^3) was added a solution of dimethyl sulfoxide (DMSO) (9.2 cm^3, 128 mmol) in CH_2Cl_2 (100 cm^3) at −50 °C under argon. After stirring of this mixture for 30 min at the same temperature, a solution of the alcohol **6** (10 g, 64.1 mmol) in CH_2Cl_2 (100 cm^3) was added and the reaction mixture was stirred for 1 h. Triethylamine (44.6 cm^3, 320 mmol) was added, and the mixture was stirred for a further 15 min at the same temperature. After addition of saturated aq. NH_4Cl the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aq. NH_4Cl and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent to afford the aldehyde **7** (9.1 g, 92%) as an oil; ν_{max}/cm^{-1} 2200 and 1730; δ_H 0.22 (9 H, s, $SiMe_3$), 2.49–2.81 (4 H, m, 2- and 3-H_2) and 9.87 (1 H, s, CHO).

1-(2'-Furyl)-5-(trimethylsilyl)pent-4-yn-1-ol **5**.—To a stirred solution of 2-lithiofuran, prepared from furan (4.5 cm^3, 62.3 mmol) and butyllithium (42.5 cm^3 of a 1.58 mol dm^{-3} hexane solution, 67.5 mmol) in THF (50 cm^3), was added a solution of aldehyde **7** (8.0 g, 51.9 mmol) in THF (50 cm^3) at −78 °C under argon. The reaction mixture was warmed to room temperature, and saturated aq. NH_4Cl was added. Concentration of the mixture afforded an oil, which was extracted with AcOEt. The organic layer was washed with saturated aq. NH_4Cl and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (9:1, v/v) as eluent to afford the alcohol **5** (9.7 g, 85%) as an oil; ν_{max}/cm^{-1} 3520 and 2190; δ_H 0.15 (9 H, s, $SiMe_3$), 2.06 (2 H, dd, *J* 6.7 and 12.9, 2-H_2), 2.21 (1 H, br s, OH), 2.26–2.49 (2 H, m, 3-H_2), 4.85 (1 H, t, *J* 6.7, 1-H), 6.26 (1 H, d, *J* 3.1, 3'-H), 6.34 (1 H, dd, *J* 1.8 and 3.1, 4'-H) and 7.38 (1 H, d, *J* 1.8, 5'-H) (Found: C, 64.65; H, 8.35. Calc. for $C_{12}H_{18}O_2Si$: C, 64.80; H, 8.15%).

(1R)-1-(2'-Furyl)-5-(trimethylsilyl)pent-4-yn-1-ol (R)-**5**.—To a solution of the 2-furyl alcohol **5** (15.0 g, 67.6 mmol) and diisopropyl L-tartrate (2.37 g, 10.1 mmol) in CH_2Cl_2 (230 cm^3) were added activated molecular sieves 3 Å (4.5 g) at room temperature. The mixture was cooled to −25 °C, treated with titanium tetraisopropoxide (2.01 cm^3, 6.67 mmol) and stirred for a further 30 min at the same temperature. The reaction mixture was treated with *tert*-butyl hydroperoxide (8.7 cm^3 of 5.08 mol dm^{-3} toluene solution, 43.9 mmol) and stirred for 15 h. A freshly prepared solution of iron(II) sulfate heptahydrate (3.76 g, 13.5 mmol) and tartaric acid (12.17 g, 81.1 mmol) in deionized water (200 cm^3) was added to the reaction mixture at −25 °C and the resulting mixture was stirred vigorously, without cooling, for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluent. The first fraction gave alcohol (*R*)-**5**

(7.1 g, 48%) as an oil; $[\alpha]_D^{25}$ −10.7 (*c* 1.1, $CHCl_3$). The optical purity of compound (*R*)-**5** was >95% ee by ^1H NMR analysis of the corresponding 'α-methoxy-α-(trifluoromethyl)phenylacetate' (MTPA) ester. The second fraction gave (2*S*)-6-hydroxy-2-[4'-(trimethylsilyl)but-3'-ynyl]-3,6-dihydropyran-3(2*H*)-one (8.2 g, 51%) as an oil; ν_{max}/cm^{-1} 3350, 2200, 1700 and 1640; δ_H 0.14 (9 H, s, $SiMe_3$), 1.78–2.01 (1 H, m, 1'-H), 2.12–2.28 (1 H, m, 1'-H), 2.32–2.50 (2 H, m, 2'-H_2), 3.08 (0.7 H, br s, OH), 3.40 (0.3 H, br s, OH), 4.26 (0.3 H, ddd, *J* 1.2, 3.7 and 9.2, 2-H), 4.74 (0.7 H, dd, *J* 3.7 and 9.2, 2-H), 5.62–5.71 (1 H, m, 6-H), 6.12 (0.7 H, d, *J* 10.4, 4-H), 6.17 (0.3 H, dd, *J* 1.2 and 10.4, 4-H), 6.91 (0.7 H, dd, *J* 3.7 and 10.4, 5-H) and 6.95 (0.3 H, dd, *J* 1.8 and 10.4, 5-H) (Found: M^+, 238.1033. Calc. for $C_{12}H_{18}O_3Si$: M, 238.1025).

(2R)-6-*Hydroxy*-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]-3,6-*dihydropyran*-3(2H)-*one* **8**.—To a stirred solution of alcohol (*R*)-**5** (4.55 g, 20.5 mmol) and anhydrous sodium acetate (1.85 g, 22.5 mmol) in aq. THF (50 cm^3; THF–water 4:1) was added portionwise NBS (4.01 g, 22.5 mmol) at 0 °C, and the mixture was stirred for 30 min at the same temperature. After addition of 10% aq. KI and then saturated aq. sodium thiosulfate, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (7:3, v/v) as eluent to afford the pyranone **8** (4.8 g, 98%) as an oil (Found: C, 60.4; H, 7.75. Calc. for $C_{12}H_{18}O_3Si$: C, 60.45; H, 7.60%). The spectroscopic data of (*R*)-**8** were identical with those of the corresponding (*S*)-lactol.

(2R,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]-3,6-*dihydropyran*-3(2H)-*one* **9** *and* (2R,6S)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]-3,6-*dihydropyran*-3(2H)-*one* **10**.—To a stirred solution of lactol **8** (20.0 g, 84.0 mmol) in CH_2Cl_2 (500 cm^3) were added ethyl vinyl ether (160 cm^3, 1.68 mol) and a catalytic amount of pyridinium toluene-*p*-sulfonate (PPTS) at 0 °C, and the mixture was stirred for a further 5 h at room temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent. The first fraction gave the β-ethoxyethyl ether **9** (16.1 g, 62%) as an oil; ν_{max}/cm^{-1} 2190, 1700 and 1640; δ_H 0.13 (9 H, s, $SiMe_3$), 1.24 and 1.25 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.41 and 1.46 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.71–1.88 and 2.15–2.30 (each 1 H, each m, 1'-H), 2.34–2.46 (2 H, m, 2'-H_2), 3.47–3.86 (2 H, m, CH_2Me), 4.59 and 4.65 (each 0.5 H, each dd, *J* 3.6 and 9.2, 2-H), 4.96 and 5.07 (each 0.5 H, each q, *J* 5.5, C*H*Me), 5.53 and 5.56 (each 0.5 H, each d, *J* 3.7, 6-H), 6.09 and 6.12 (each 0.5 H, each d, *J* 10.4, 4-H) and 6.79 and 6.87 (each 0.5 H, each dd, *J* 3.7 and 10.4, 5-H) [Found: (M^+ − 15), 295.1360. Calc. for $C_{15}H_{23}O_4Si$: (M − 15), 295.1365]. The second fraction gave the α-ethoxyethyl ether **10** (4.67 g, 18%) as an oil; ν_{max}/cm^{-1} 2190, 1700 and 1640; δ_H 0.14 (9 H, s, $SiMe_3$), 1.21 and 1.24 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.31 and 1.41 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.72–2.02 and 2.11–2.31 (each 1 H, each m, 1'-H), 2.34–2.47 (2 H, m, 2'-H_2), 3.41–3.86 (2 H, m, CH_2Me), 4.25 and 4.73 (each 0.5 H, each dd, *J* 3.7 and 9.2, 2-H), 5.06 and 5.12 (each 0.5 H, each q, *J* 5.5, C*H*Me), 5.53 and 5.65 (each 0.5 H, each d, *J* 3.7, 6-H), 6.11 and 6.12 (each 0.5 H, each d, *J* 10.4, 4-H) and 6.86 and 6.90 (each 0.5 H, each dd, *J* 3.7 and 10.4, 5-H) [Found: (M^+ − 15), 295.1359].

(2R,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsily*)*but*-3'-*ynyl*]*tetrahydropyran*-3-*one* **11**.—To a stirred suspension of LAH (0.37 g, 9.7 mmol) in THF (60 cm^3) was added a suspension of copper(I) iodide (1.84 g, 9.7 mmol) in THF–hexamethylphosphoric triamide (HMPA) (60 cm^3; 1:1) at −78 °C under argon, and the mixture was stirred for a further 30 min at the same temperature. Then, a solution of enone **9** (3.0 g, 9.7 mmol) in THF (30 cm^3) was added dropwise to the mixture at −78 °C, and the mixture was stirred for 1 h at the same temperature. After addition of saturated aq. NH_4Cl to the reaction mixture, the insoluble material was filtered off and washed with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (93:7, v/v) as eluent to afford ketone **11** (2.87 g, 95%) as an oil; ν_{max}/cm^{-1} 2190 and 1730; δ_H 0.13 (9 H, s, $SiMe_3$), 1.22 and 1.23 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.39 and 1.41 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.61–2.65 (8 H, m, 4-, 5-, 1'- and 2'-H_2), 3.43–3.87 (2 H, m, CH_2Me), 4.30 and 4.38 (each 0.5 H, each dd, *J* 3.7 and 8.5, 2-H), 4.92 and 5.02 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.32 (1 H, dd, *J* 4.3 and 8.5, 6-H) (Found: C, 61.55; H, 9.25. Calc. for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.05%).

(2R,3R,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]*tetrahydropyran*-3-*ol* **12** *and* (2R,3S,6R)-6-(1-*Ethoxyethoxy*)-2-(4'-*trimethylsilylbut*-3'-*ynyl*)*tetrahydropyran*-3-*ol* **13**.—To a stirred solution of ketone **11** (5.0 g, 16.0 mmol) in THF (50 cm^3) was added portionwise $NaBH_4$ (0.61 g, 16.0 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at the same temperature. After addition of saturated aq. NH_4Cl, the reaction mixture was concentrated to leave an oil, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (85:15, v/v) as eluent. The first fraction gave the α-alcohol **12** (4.27 g, 85%) as an oil; ν_{max}/cm^{-1} 3500 and 2190; δ_H 0.14 (9 H, s, $SiMe_3$), 1.20 and 1.22 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.35 and 1.36 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.55–2.14 (7 H, m, 4-, 5- and 1'-H_2, and OH), 2.20–2.51 (2 H, m, 2'-H_2), 3.39–3.87 (4 H, m, 2- and 3-H, and CH_2Me), 4.83 and 4.91 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.02 and 5.05 (each 0.5 H, each br s, 6-H) (Found: C, 61.2; H, 9.85. Calc. for $C_{16}H_{30}O_4Si$: C, 61.10; H, 9.60%). The second fraction gave the β-alcohol **13** (0.7 g, 14%), as an oil; ν_{max}/cm^{-1} 3400 and 2170; δ_H 0.14 (9 H, s, $SiMe_3$), 1.21 and 1.24 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.37 (3 H, d, *J* 5.5, CH*Me*), 1.47–2.14 (7 H, m, 4-, 5- and 1'-H_2, and OH), 2.24–2.46 (2 H, m, 2'-H_2), 3.42–3.85 (3 H, m, 2-H and CH_2Me), 3.88–4.08 (1 H, m, 3-H), 4.85 and 4.93 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.19 (1 H, br s, 6-H) [Found: (M^+ − 15), 299.1670. Calc. for $C_{16}H_{30}O_4Si$: (M − 15), 299.1677].

O-{2R,3S,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]*tetrahydropyranimidazole*-1-*thiocarboxylate* **14**.—To a stirred solution of alcohol **12** (4.2 g, 13.4 mmol) in 1,2-dichloroethane (230 cm^3) were added 1,1'-thiocarbonyldiimidazole (7.9 g, 40.1 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) at room temperature under argon, and the resulting mixture was heated at reflux for 14 h. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (85:15, v/v) as eluent to afford thiocarbonylimidazolide **14** (4.72 g, 83%) as an oil; ν_{max}/cm^{-1} 2190; δ_H 0.15 (9 H, s, $SiMe_3$), 1.23 and 1.24 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.40 and 1.42 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.56–2.48 (8 H, m, 4-, 5-, 1'- and 2'-H_2), 3.44–3.87 (2 H, m, CH_2Me), 4.11 and 4.20 (each 0.5 H, each dt, *J* 2.4 and 9.8, 2-H), 4.88 and 4.96 (each 0.5 H, each q, *J* 5.5, C*H*Me), 5.09–5.19 (1 H, br s, 6-H), 5.26 and 5.28 (each 0.5 H, each dt, *J* 2.4 and 9.8, 3-H), 7.05 (1 H, s, CH=NC*H*=CH), 7.63 (1 H, s, CH=NCH=C*H*) and 8.43 (1 H,

s, CH=N) (Found: C, 56.45; H, 7.7; N, 6.45. Calc. for $C_{20}H_{32}N_2O_4SSi$: C, 56.55; H, 7.60; N, 6.60%).

(2R,4aS,7aR)-2-(1-*Ethoxyethoxy*)-5-(*trimethylsilylmethylene*)*octahydrocyclopenta*[b]*pyran* **15**.—To a stirred, refluxing solution of thiocarbonylimidazolide **14** (2.1 g, 4.95 mmol) in benzene (1200 cm^3) was added dropwise a solution of Bu_3SnH (1.87 cm^3, 6.93 mmol) and AIBN (81.0 mg, 0.5 mmol) in benzene (100 cm^3) under argon, and the mixture was stirred for a further 30 min. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (98:2, v/v) as eluent to afford the bicyclic compound **15** (1.29 g, 87%) as an oil; ν_{max}/cm^{-1} 1630; δ_H 0.10 (9 H, s, $SiMe_3$), 1.20 and 1.21 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.34 and 1.38 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.42–2.80 (9 H, m, 3-, 4-, 6-, 7-H_2 and 4a-H), 3.39–3.90 (2 H, m, CH_2Me), 4.18–4.46 (1 H, m, 7a-H), 4.85 and 4.94 (each 0.5 H, each q, *J* 5.5, C*H*Me), 4.80–5.12 (1 H, m, 2-H), 5.36 (3/7 H, q, *J* 1.8, C=CH) and 5.42 (4/7 H, br s, C=CH) (Found: M^+, 298.1963. Calc. for $C_{16}H_{30}O_3Si$: M, 298.1963).

(4aS,7aR)-5-[(Z)-*Trimethylsilylmethylene*]*octahydrocyclopenta*[b]*pyran*-2-*one* **16** *and* (4aS,7aR)-5-[(E)-*Trimethylsilylmethylene*]*octahydrocyclopenta*[b]*pyran*-2-*one* **17**.—To a stirred solution of ethoxyethyl ether **15** (2.67 g, 8.94 mmol) in THF (50 cm^{-3}) was added dropwise 2 mol dm^{-3} HCl (10 cm^3, 20 mmol) at 0 °C, and the mixture was stirred for another 15 h at the same temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (85:15, v/v) as eluent to afford (4a*S*,7a*R*)-5-(trimethylsilylmethylene)octahydrocyclopenta[*b*]pyran-2-ol (1.5 g, 74%) as an oil; ν_{max}/cm^{-1} 3400 and 1630; δ_H 0.11 (9 H, s, $SiMe_3$), 1.16–3.21 (10 H, m, 3-, 4-, 6-, 7-H_2 and 4a-H, and OH), 4.12–4.23 (3/7 H, m, 2-H), 4.31–4.42 (4/7 H, m, 2-H), 4.61–4.72 (3/14 H, m, 7a-H), 4.78–4.87 (3/14 H, m, 7a-H), 5.16–5.27 (4/7 H, m, 7a-H) and 5.29–5.50 (1 H, m, C=CH) (Found: C, 63.7; H, 10.05. Calc. for $C_{12}H_{22}O_2Si$: C, 63.65; H, 9.80%).

To a stirred suspension of PCC (4.55 g, 20.6 mmol), Celite (4.5 g) and anhydrous sodium acetate (1.69 g, 20.6 mmol) in CH_2Cl_2 (15 cm^3) was added a solution of the above lactol (1.55 g, 6.9 mmol) in CH_2Cl_2 (10 cm^3) at room temperature under argon, and the mixture was stirred for a further 30 min. After addition of Et_2O (150 cm^3) to the reaction mixture, vigorous stirring was continued for 10 min. Insoluble material was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (9:1, v/v) as eluent. The first fraction gave the (*Z*)-olefin **16** (830 mg, 54%) as an oil: $[\alpha]_D^{25}$ −94.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1730 and 1620; δ_H 0.12 (9 H, s, $SiMe_3$), 1.68–2.74 (8 H, m, 3-, 4-, 6- and 7-H_2), 2.87–2.99 (1 H, m, 4a-H), 4.90 (1 H, q, *J* 6.1, 7a-H) and 5.50 (1 H, q, *J* 1.8, C=CH) (Found: C, 64.2; H, 9.2. Calc. for $C_{12}H_{20}O_2Si$: C, 64.25; H, 9.00%). The second fraction gave the (*E*)-olefin **17** (505 mg, 33%) as an oil: $[\alpha]_D^{25}$ −64.9 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 1730 and 1630; δ_H 0.10 (9 H, s, $SiMe_3$), 1.83–2.56 (8 H, m, 3-, 4-, 6- and 7-H_2), 2.74–2.85 (1 H, m, 4a-H), 4.85 (1 H, dt, *J* 1.8 and 4.9, 7a-H) and 5.43 (1 H, q, *J* 2.4, C=CH) (Found: C, 64.15; H, 9.25%).

(4aS,7aR)-5-*Methyleneoctahydrocyclopenta*[b]*pyran*-2-*one* **18** *from Silyl Ether* **17**.—To a stirred solution of the vinylsilane **17** (563 mg, 2.5 mmol) in MeCN (15 cm^3) was added dropwise 50% aq. HF (0.75 cm^3) at room temperature, and the resulting mixture was stirred for 30 min. Saturated aq. $NaHCO_3$ was added to the reaction mixture at 0 °C and concentration of the mixture afforded an oil, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (6:4, v/v) as eluent to afford olefin **18** (343 mg, 90%) as an oil; $[\alpha]_D^{25}$ −93.8 (*c* 0.44, $CHCl_3$); ν_{max}/cm^{-1} 1720 and 1600; δ_H 1.84–2.64 (8 H, m, 3-, 4-, 6- and 7-H_2), 2.78–2.89 (1 H, m, 4a-H), 4.85 (1 H, dt, *J* 1.8 and 4.9, 7a-H) and 4.92 and 5.09 (each 1 H, each q, *J* 2.4, C=CH_2) (Found: M^+, 152.0830. Calc. for $C_9H_{12}O_2$: M, 152.0835).

(4aS,7aR)-5-*Methyleneoctahydrocyclopenta*[b]*pyran*-2-*one* **18** *from Silyl Ether* **16**.—To a stirred solution of the vinylsilane **16** (20 mg, 0.09 mmol) in MeCN (0.5 cm^3) was added dropwise 50% aq. HF solution (30 mm^3) at room temperature, and the resulting mixture was stirred for 30 min. Saturated aq. $NaHCO_3$ was added to the reaction mixture at 0 °C, and concentration of the mixture afforded an oil, which was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (6:4, v/v) as eluent to afford olefin **18** (8.4 mg, 62%) as an oil.

(1R,2S)-2-(3′-*Hydroxypropyl*)-3-[(Z)-*trimethylsilylmethylene*]*cyclopentanol* **19**.—To a stirred suspension of LAH (272 mg, 7.14 mmol) in Et_2O (30 cm^3) was added dropwise a solution of lactone **16** (800 mg, 3.57 mmol) in Et_2O (10 cm^3) at 0 °C under argon. The reaction mixture was warmed to room temperature, and water was added slowly. The precipitate was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (4:6, v/v) as eluent to afford diol **19** (795 mg, 98%) as a glass: $[\alpha]_D^{25}$ −60.3 (*c* 0.92, $CHCl_3$); ν_{max}/cm^{-1} 3420 and 1630; δ_H 0.10 (9 H, s, $SiMe_3$), 1.40–1.52 (1 H, m, 2-H), 1.63–1.96 (4 H, m, 1′- and 2′-H_2), 2.05–2.69 (4 H, m, 4- and 5-H_2), 3.57–3.77 (2 H, m, 3′-H_2), 4.32 (1 H, q, *J* 6.1, 1-H) and 5.33 (1 H, q, *J* 1.8, C=CH) (Found: C, 62.85; H, 10.9. Calc. for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.60%).

(1R,2S)-2-[3′-(tert-*Butyldimethylsiloxy*)*propyl*]-3-[(Z)-*trimethylsilylmethylene*]*cyclopentanol* **21**.—To a stirred solution of diol **19** (748 mg, 3.28 mmol) in CH_2Cl_2 (25 cm^3) were added a catalytic amount of DMAP, triethylamine (0.55 cm^3, 3.94 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (247 mg, 3.61 mmol) at room temperature under argon. After stirring of the mixture for 1 h, triethylamine (0.55 cm^3, 3.94 mmol) and TBDMSCl (247 mg, 3.61 mmol) were added again to the reaction mixture. The mixture was stirred for a further 1 h. After addition of saturated aq. NH_4Cl the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent to afford silyl ether **21** (1.05 g, 93%) as an oil; $[\alpha]_D^{25}$ −48.1 (*c* 0.97, $CHCl_3$); ν_{max}/cm^{-1} 3430 and 1620; δ_H 0.07 (6 H, s, $SiMe_2$), 0.10 (9 H, s, $SiMe_3$), 0.90 (9 H, s, Bu^t), 1.41–1.94 (6 H, m, 5-, 1′- and 2′-H_2), 2.12–2.28 (1 H, m, 2-H), 2.34 (1 H, br s, OH), 2.50–2.70 (2 H, m, 4-H_2), 3.59–3.74 (2 H, m, 3′-H_2), 4.31 (1 H, q, *J* 6.1, 1-H) and 5.32 (1 H, q, *J* 1.8, C=CH) (Found: C, 63.4; H, 11.6. Calc. for $C_{18}H_{38}O_2Si_2$: C, 63.10; H, 11.20%).

(2S)-2-[3′-(tert-*Butyldimethylsiloxy*)*propyl*]-3-[(Z)-*trimethylsilylmethylene*]*cyclopentanone* **23**.—To a stirred suspension of PCC (945 mg, 4.39 mmol), Celite (950 mg) and anhydrous sodium acetate (360 mg, 4.39 mmol) in CH_2Cl_2 (4 cm^3) was added a solution of the alcohol **21** (500 mg, 1.46 mmol) in CH_2Cl_2 (3 cm^3) at 0 °C under argon, and the mixture was

stirred for a further 30 min at room temperature. After addition of Et_2O (40 cm^3), the reaction mixture was vigorously stirred for 10 min. Insoluble material was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (97:3, v/v) as eluent to afford ketone **23** (298 mg, 60%) as an oil; $[\alpha]_D^{25}$ −178.6 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1750 and 1640; δ_H 0.03 (6 H, s, $SiMe_2$), 0.11 (9 H, s, $SiMe_3$), 0.87 (9 H, s, Bu^t), 1.41–1.82 (4 H, m, 1'- and 2'-H_2), 2.22–2.68 (3 H, m, 2-H and 4-H_2), 2.73–2.92 (2 H, m, 5-H_2), 3.50–3.67 (2 H, m, 3'-H_2) and 5.53 (1 H, m, C=CH) (Found: C, 63.4; H, 10.95. Calc. for $C_{18}H_{36}O_2Si_2$: C, 63.45; H, 10.65%).

(1R,2S)-2-(3'-*Hydroxypropyl*)-3-[(E)-*trimethylsilylmethylene*]*cyclopentanol* **20**.—To a stirred suspension of LAH (10.2 mg, 0.27 mmol) in Et_2O (1 cm^3) was added dropwise a solution of lactone **17** (30 mg, 0.13 mmol) in Et_2O (0.5 cm^3) at 0 °C under argon. The reaction mixture was warmed to room temperature, and water was added slowly. The precipitate was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (4:6, v/v) as eluent to afford diol **20** (27 mg, 88%) as a glass; ν_{max}/cm^{-1} 3420 and 1630; δ_H 0.09 (9 H, s, $SiMe_3$), 1.37–1.92 (7 H, m, 2-H, and 4-, 1'- and 2'-H_2), 2.28–2.64 (4 H, m, 1- and 3'-OH, and 5-H_2), 3.58–3.80 (2 H, m, 3'-H_2), 4.25–4.33 (1 H, m, 1-H) and 5.33 (1 H, q, *J* 2.4, C=CH) (Found: M^+, 228.1537. Calc. for $C_{12}H_{24}O_2Si$: M, 228.1544).

(1R,2S)-2-[3'-(tert-*Butyldimethylsiloxy*)*propyl*]-3-[(E)-*trimethylsilylmethylene*]*cyclopentanol* **22**.—To a stirred solution of diol **20** (50 mg, 0.22 mmol) in CH_2Cl_2 (1 cm^3) were added a catalytic amount of DMAP, triethylamine (37 mm^3, 0.26 mmol) and TBDMSCl (36 mg, 0.24 mmol) at room temperature under argon. After stirring of the mixture for 1 h, further triethylamine (37 mm^3, 0.26 mmol) and TBDMSCl (36 mg, 0.24 mmol) were added to the reaction mixture, which was then stirred for a further 1 h. After addition of saturated aq. NH_4Cl, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent to afford silyl ether **22** (63 mg, 91%) as an oil; ν_{max}/cm^{-1} 3450 and 1620; δ_H 0.07 (6 H, s, $SiMe_2$), 0.09 (9 H, s, $SiMe_3$), 0.91 (9 H, s, Bu^t), 1.34–1.93 (7 H, m, 2-H, and 4-, 1'- and 2'-H_2), 2.26 (1 H, br s, OH), 2.35–2.64 (2 H, m, 5-H_2), 3.59–3.76 (2 H, m, 3'-H_2), 4.25–4.35 (1 H, m, 1-H) and 5.32 (1 H, q, *J* 2.4, C=CH).

2-[3'-(tert-*Butyldimethylsiloxy*)*propyl*]-3-(*trimethylsilylmethyl*)*cyclopent*-2-*enone* **24**.—To a stirred suspension of PCC (119 mg, 0.55 mmol), Celite (120 mg) and anhydrous sodium acetate (45 mg, 0.55 mmol) in CH_2Cl_2 (0.5 cm^3) was added a solution of alcohol **22** (63 mg, 0.18 mmol) in CH_2Cl_2 (0.5 cm^3) at 0 °C under argon, and the mixture was stirred for another 30 min at room temperature. After addition of Et_2O (10 cm^3), the reaction mixture was vigorously stirred for 10 min. Insoluble material was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (9:1, v/v) as eluent to afford enone **24** (38.8 mg, 62%) as an oil; δ_H 0.06 (6 H, s, $SiMe_2$), 0.09 (9 H, s, $SiMe_3$), 0.90 (9 H, s, Bu^t), 1.52–1.69 (2 H, m, 2'-H_2), 2.05 (2 H, s, CH_2SiMe_3), 2.20 (2 H, t, *J* 7.9, 5-H_2), 2.29–2.39 (2 H, m, 1'-H_2), 2.41–2.52 (2 H, m, 4-H_2) and 3.58 (2 H, t, *J* 6.1, 3'-H_2).

(2S)-2-[3'-(tert-*Butyldimethylsiloxy*)*propyl*]-3-[(Z)-*trimethylsilylmethylene*]*cyclopentanone* (E)-*Oxime* (E)-**25** *and* (2S)-2-[3'-(tert-*Butyldimethylsiloxy*)*propyl*]-3-[(Z)-*trimethylsilylmethylene*]*cyclopentanone* (Z)-*Oxime* (Z)-**25**.—To a stirred solution of ketone **23** (590 mg, 1.74 mmol) in MeOH (15 cm^3) were added pyridine (0.21 cm^3, 2.6 mmol) and NH_2OH·HCl (144 mg, 2.1 mmol) at room temperature under argon, and the resulting mixture was stirred for 3 h. After addition of water, the reaction mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent. The first fraction gave the (*E*)-oxime (*E*)-**25** (402 mg, 65%) as a glass; $[\alpha]_D^{25}$ −48.5 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3350 and 1640; δ_H 0.03 (6 H, s, $SiMe_2$), 0.11 (9 H, s, $SiMe_3$), 0.88 (9 H, s, Bu^t), 1.39–1.81 (4 H, m, 1'- and 2'-H_2), 2.34–2.47 (1 H, m, 5-H), 2.56–2.66 (2 H, m, 4-H_2), 2.66–2.78 (1 H, m, 5-H), 3.08–3.16 (1 H, m, 2-H), 3.52–3.69 (2 H, m, 3'-H_2), 5.35 (1 H, m, C=CH) and 7.18 (1 H, br s, OH) (Found: C, 60.9; H, 10.7; N, 3.75. Calc. for $C_{18}H_{37}NO_2Si_2$: C, 60.80; H, 10.50; N, 3.95%).

The second fraction gave the (*Z*)-oxime (*Z*)-**25** (99 mg, 16%) as a glass; $[\alpha]_D^{25}$ −50.7 (*c* 0.94, $CHCl_3$); ν_{max}/cm^{-1} 3350 and 1630; δ_H 0.03 (6 H, s, $SiMe_2$), 0.11 (9 H, s, $SiMe_3$), 0.88 (9 H, s, Bu^t), 1.42–1.75 (4 H, m, 1'- and 2'-H_2), 2.31–2.84 (4 H, m, 4- and 5-H_2), 3.16–3.25 (1 H, m, 2-H), 3.51–3.71 (2 H, m, 3'-H_2), 5.41 (1 H, s, C=CH) and 7.67 (1 H, br s, OH) (Found: M^+, 355.2368. Calc. for $C_{18}H_{37}NO_2Si_2$: M, 355.2363).

(6S)-6-[3'-(tert-*Butyldimethylsiloxy*)*propyl*]-5-[(Z)-*trimethylsilylmethylene*]*piperidin*-2-*one* **26**.—To a stirred solution of oxime (*E*)-**25** (84 mg, 0.24 mmol) in THF (2.5 cm^3) was added dropwise thionyl dichloride (29 mm^3, 0.35 mmol) at 0 °C under argon, and the resulting mixture was stirred for 20 min at the same temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was stirred for a further 1 h. Removal of the solvent gave an oil, which was extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (1:1, v/v) as eluent to afford lactam **26** (34 mg, 41%) as an oil; $[\alpha]_D^{25}$ −129.5 (*c* 0.65, $CHCl_3$); ν_{max}/cm^{-1} 1660 and 1470; δ_H 0.05 and 0.06 (each 3 H, each s, $SiMe_2$), 0.12 (9 H, s, $SiMe_3$), 0.89 (9 H, s, Bu^t), 1.58–1.80 (4 H, m, 1'- and 2'-H_2), 2.20–2.43 (2 H, m, 4-H_2), 2.43–2.57 and 2.61–2.79 (each 1 H, each m, 3-H_2), 3.55–3.76 (2 H, m, 3'-H_2), 4.03–4.13 (1 H, m, 6-H), 5.42 (1 H, s, C=CH) and 6.57 (1 H, br s, NH) (Found: C, 60.6; H, 10.7; N, 3.8. Calc. for $C_{18}H_{37}NO_2Si_2$: C, 60.75; H, 10.50; N, 3.95%).

(6S)-6-(3'-*Hydroxypropyl*)-5-[(Z)-*trimethylsilylmethylene*]-*piperidin*-2-*one* **27**.—To a stirred solution of silyl ether **26** (69 mg, 0.19 mmol) in THF (1.5 cm^3) was added dropwise 2 mol dm^{-3} HCl (0.2 cm^3; 0.4 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at the same temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (95:5, v/v) as eluent to afford the alcohol **27** (45 mg, 96%) as an oil; $[\alpha]_D^{25}$ −175.1 (*c* 0.57, $CHCl_3$); ν_{max}/cm^{-1} 3320, 1660 and 1460; δ_H 0.12 (9 H, s, $SiMe_3$), 1.50–1.83 (4 H, m, 1'- and 2'-H_2), 2.15–2.39 (2 H, m, 4-H_2), 2.39–2.53 and 2.60–2.78 (each 1 H, each m, 3-H_2), 3.03 (1 H, br s, OH), 3.55–3.76 (2 H, m, 3'-H_2), 4.02–4.28 (1 H, m, 6-H), 5.41 (1 H, s, C=CH) and 7.51 (1 H, br s, NH) (Found: M^+, 241.1489. Calc. for $C_{12}H_{23}NO_2Si$: M, 241.1496).

3'-{6-*Oxo*-3-[(Z)-*trimethylsilylmethylene*]*piperidin*-2-*yl*}-*propyl Methanesulfonate* **28**.—To a stirred solution of the alcohol **27** (32 mg, 0.13 mmol) in CH_2Cl_2 (1 cm^3) were added triethylamine (21 mm^3, 0.27 mmol) and methanesulfonyl chloride (MsCl) (37 mm^3, 0.27 mmol) at 0 °C under argon, and the mixture was stirred for another 30 min at the same temperature before being extracted with CH_2Cl_2. The extract

was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (95:5, v/v) as eluent to afford mesyl ester **28** (34 mg, 78%) as an oil; ν_{max}/cm^{-1} 1660 and 1360; δ_H 0.13 (9 H, s, $SiMe_3$), 1.52–1.99 (4 H, m, 3'- and 2'-H_2), 2.23–2.45 (2 H, m, 4-H_2), 2.45–2.58 and 2.62–2.78 (each 1 H, each m, 3-H_2), 3.01 (3 H, s, Ms), 4.04–4.14 (1 H, m, 6-H), 4.16–4.33 (2 H, m, 1'-H_2), 5.48 (1 H, d, *J* 1.2, C=CH) and 6.52 (1 H br s, NH).

(8a*S*)-8-[(*Z*)-*Trimethylsilylmethylene*]*octahydroindolizin*-5-*one* **29**.—A mixture of mesyl ester **28** (34 mg, 0.1 mmol) and potassium carbonate (14 mg, 0.1 mmol) in aq. 1,4-dioxane (1.5 cm^3; dioxane–water = 4:1) was stirred at 90 °C for 2 h. The mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (1:3, v/v) as eluent to afford the bicyclic lactam **29** (20 mg, 87%) as an oil; $[\alpha]_D^{25}$ −248.4 (*c* 0.42, $CHCl_3$); ν_{max}/cm^{-1} 1630 and 1460; δ_H 0.14 (9 H, s, $SiMe_3$), 1.48–2.14 (4 H, m, 2- and 6-H_2), 2.21–2.64 (4 H, m, 1- and 7-H_2), 3.26 (1 H, dt, *J* 3.7 and 12.2, 3-H), 3.86 (1 H, dt, *J* 8.6 and 12.2, 3-H), 4.11 (1 H, dd, *J* 5.5 and 11.6, 8a-H) and 5.49 (1 H, s, C=CH) (Found: M^+, 223.1390. Calc. for $C_{12}H_{21}NOSi$: M, 223.1391).

(8a*S*)-8-*Methyleneoctahydroindolizin*-5-*one* **30**.—To a stirred solution of the vinylsilane **29** (36 mg, 0.16 mmol) in aq. MeCN (3 cm^3; MeCN–water = 50:1) was added toluene-*p*-sulfinic acid (50.7 mg, 0.33 mmol) at room temperature, and the resulting mixture was heated at reflux for 3 h. Removal of the solvent gave an oil, which was dissolved in $CHCl_3$. The organic layer was washed with saturated aq. $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (1:9, v/v) as eluent to afford olefin **30** (17 mg, 70%) as an oil; $[\alpha]_D^{25}$ −95.0 (*c* 0.27, $CHCl_3$) {lit.,[14] $[\alpha]_D^{20}$ −98.3 (*c* 1.2, $CHCl_3$)}; ν_{max}/cm^{-1} 1630 and 1460; δ_H 1.60–2.26 (4 H, m, 2- and 6-H_2), 2.35–2.68 (4 H, m, 1- and 7-H_2), 3.49 (1 H, ddd, *J* 2.4, 9.2 and 12.2, 3-H), 3.63 (1 H, dt, *J* 8.6 and 12.2, 3-H), 4.00 (1 H, dd, *J* 4.9 and 10.4, 8a-H) and 4.92 and 4.98 (each 1 H, each s, C=CH_2) (Found: M^+, 151.0991. Calc. for $C_9H_{13}NO$: M, 151.0996).

(2R,3S,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]-3,6-*dihydro*-2H-*pyran*-3-*ol* **32** *and* (2R,3R,6R)-6-(1-*Ethoxyethoxy*)-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]-3,6-*dihydro*-2H-*pyran*-3-*ol* **33**.—To a stirred suspension of LAH (2.45 g, 64.5 mmol) in Et_2O (150 cm^3) was added dropwise a solution of enone **9** (10.0 g, 32.3 mmol) in Et_2O (50 cm^3) at 0 °C under argon. The reaction mixture was warmed to room temperature, and water was added slowly. The precipitate was filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent. The first fraction gave the β-alcohol **32** (9.3 g, 92%) as an oil; ν_{max}/cm^{-1} 3430, 2170 and 1660; δ_H 0.14 (9 H, s, $SiMe_3$), 1.21 and 1.22 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.37 and 1.39 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.54–1.80 and 2.02–2.18 (each 1 H, each m, 1'-H_2), 2.25–2.56 (2 H, m, 2'-H_2), 3.42–3.87 (4 H, m, 2-H, OH and CH_2Me), 3.88–4.00 (1 H, m, 3-H), 4.88 and 5.00 (each 0.5 H, each q, *J* 5.5, C*H*Me), 5.22 and 5.26 (each 0.5 H, each s, 6-H), 5.69 and 5.78 (each 0.5 H, each dt, *J* 2.4 and 10.4, 5-H) and 5.91–6.01 (1 H, m, 4-H) (Found: C, 61.75; H, 9.3. Calc. for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.05%). The second fraction gave the α-alcohol **33** (422 mg, 4%) as an oil; ν_{max}/cm^{-1} 3550, 2190 and 1610; δ_H 0.14 (9 H, s, $SiMe_3$), 1.22 and 1.23 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.37 and 1.40 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.76–2.01 (2 H, m, 1'-H_2), 2.25–2.50 (2 H, m, 2'-H_2), 3.43–3.87 (4 H, m, 2-H, OH and CH_2Me), 4.19–4.40 (1 H, m, 3-H), 4.90 and 5.01 (each 0.5 H, each q, *J* 5.5, C*H*Me), 5.26 and 5.30 (each 0.5 H, each d, *J* 3.1, 6-H), 5.83 and 5.92 (each 0.5 H, each dd, *J* 3.1 and 10.4, 5-H) and 6.13–6.24 (1 H, m, 4-H) [Found: (M^+ − 15), 297.1512. Calc. for $C_{15}H_{25}O_4Si$: (M − 15), 297.1520].

(2R,3S,4S,5S,6R)-2-(1-*Ethoxyethoxy*)-6-[4'-(*trimethylsilyl*)-*but*-3'-*ynyl*]*tetrahydropyran*-3,4,5-*triol* **34**.—To a stirred solution of olefin **32** (309 mg, 0.99 mmol) in Et_2O (6 cm^3) were added pyridine (0.3 cm^3) and osmium tetraoxide (327 mg, 1.29 mmol) at room temperature under argon, and the mixture was stirred for another 10 h. Removal of the solvent gave a residue, which was dissolved in aq. pyridine (36 cm^3; pyridine–water = 7:5). To the mixture was addded $NaHSO_3$ (1.34 g, 12.9 mmol) at room temperature, and the mixture was stirred for an additional 2 h. After addition of brine, the mixture was extracted with AcOEt. The extract was washed with saturated aq. $KHSO_4$ and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (95:5, v/v) as eluent to afford triol **34** (293 mg, 70%) as an oil: ν_{max}/cm^{-1} 3570 and 2180; δ_H 0.14 (9 H, s, $SiMe_3$), 1.21 (3 H, t, *J* 7.3, CH_2Me), 1.35 and 1.37 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.57–1.81 and 1.98–2.18 (each 1 H, each m, 1'-H_2), 2.20–2.54 (2 H, m, 2'-H_2), 3.40–3.99 (6 H, m, 3-, 4-, 5- and 6-H, and CH_2Me), 4.85 and 4.92 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.08 (1 H, s, 2-H) (Found: C, 55.45; H, 8.95. Calc. for $C_{16}H_{30}O_6Si$: C, 55.45; H, 8.75%).

(2R,3R,4S,5S,6R)-6-(1-*Ethoxyethoxy*)-4,5-*isopropylidenedioxy*-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]*tetrahydropyran*-3-*ol* **35** and (2R,3S,4R,5R,6R)-2-(1-*Ethoxyethoxy*)-4,5-*isopropylidenedioxy*-6-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]*tetrahydropyran*-3-*ol* **36**.—To a stirred solution of triol **34** (614 mg, 1.77 mmol) in *N*,*N*-dimethylformamide (DMF) (6 cm^3) were added acetone (1.5 cm^3), a catalytic amount of PPTS, and 2,2-dimethoxypropane (4.4 cm^3, 35.5 mmol) at 0 °C under argon, and the resulting mixture was stirred for 10 h at room temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluent. The first fraction gave the *syn*-acetonide **35** (504 mg, 74%) as an oil; ν_{max}/cm^{-1} 3510 and 2190; δ_H 0.14 (9 H, s, $SiMe_3$), 1.22 (3 H, t, *J* 7.3, CH_2Me), 1.35 and 1.39 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.36 and 1.52 (each 3 H, each s, CMe_2), 1.64–1.86 and 1.92–2.11 (each 1 H, each m, 1'-H_2), 2.22–2.53 (3 H, m, 2'-H_2 and OH), 3.40–3.84 (4 H, m, 2-and 3-H, and CH_2Me), 4.07–4.19 (2 H, m, 4- and 5-H), 4.87 and 4.95 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.25 and 5.30 (each 0.5 H, each s, 6-H) (Found: C, 58.9; H, 9.0. Calc. for $C_{19}H_{34}O_6Si$: C, 59.05; H, 8.85%).

The second fraction gave the *anti*-acetonide **36** (101 mg, 15%) as an oil; ν_{max}/cm^{-1} 3570 and 2190; δ_H 0.14 (9 H, s, $SiMe_3$), 1.22 and 1.23 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.36 and 1.38 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.44 and 1.45 (each 3 H, each s, CMe_2), 1.70–1.87 and 1.90–2.08 (each 1 H, each m, 1'-H_2), 2.19 (1 H, br s, OH), 2.26–2.51 (2 H, m, 2'-H_2), 3.43–3.83 (4 H, m, 3- and 6-H, and CH_2Me), 3.88–4.06 (1 H, m, 4-H), 4.20 and 4.30 (each 0.5 H, each s, 5-H), 4.85 and 4.93 (each 0.5 H, each q, *J* 5.5, C*H*Me) and 5.10–5.16 (1 H, m, 2-H) [Found: (M^+ − 15), 371.1895. Calc. for $C_{18}H_{31}O_6Si$: (M − 15), 371.1890].

O-{(2R,3R,4S,5S,6R)-6-(1-*Ethoxyethoxy*)-4,5-*isopropylidenedioxy*-2-[4'-(*trimethylsilyl*)*but*-3'-*ynyl*]*tetrahydropyran*-3-*yl*}*imidazole*-1-*thiocarboxylate* **37**.—To a solution of alcohol **35** (576 mg, 1.50 mmol) in 1,2-dichloroethane (30 cm^3) were added 1,1'-thiocarbonyldiimidazole (594 mg, 2.98 mmol) and a catalytic amount of DMAP at room temperature under argon,

and the resulting mixture was heated at reflux for 5 h. Removal of the solvent gave a residue, which was dissolved in CH_2Cl_2. The organic layer was washed successively with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (85:15, v/v) as eluent to afford thiocarbonylimidazolide **37** (509 mg, 68%) as an oil; ν_{max}/cm^{-1} 2190; δ_H 0.13 (9 H, s, $SiMe_3$), 1.25 (3 H, t, *J* 7.3, CH_2Me), 1.40 and 1.44 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.37 and 1.60 (each 3 H, each s, CMe_2), 1.68–1.87 (2 H, m, 1'-H_2), 2.23–2.49 (2 H, m, 2'-H_2), 3.46–3.86 (2 H, m, CH_2Me), 3.98–4.07 and 4.08–4.13 (each 0.5 H, each m, 2-H), 4.16 and 4.24 (each 0.5 H, each d, *J* 5.5, 5-H), 4.44 (1 H, dd, *J* 5.5 and 7.3, 4-H), 4.92 and 5.00 (each 0.5 H, each q, *J* 5.5, C*H* Me), 5.41 (1 H, br s, 6-H), 5.73 and 5.74 (each 0.5 H, each dd, *J* 7.3 and 9.8, 3-H), 7.15 (1 H, s, CH=NC*H*=CH), 7.69 (1 H, s, CH=NCH=C*H*) and 8.53 (1 H, s, CH=N) (Found: M^+, 496.2071. Calc. for $C_{23}H_{36}N_2O_6SSi$: M, 496.2064. Found: C, 55.2; H, 7.45; N, 5.5. Calc. for $C_{23}H_{36}N_2O_6SSi \cdot 1/10H_2O$: C, 55.40; H, 7.60; N, 5.60%).

(2R,3S,4S,4aS,7aR)-2-(1-*Ethoxyethoxy*)-3,4-*isopropylidenedioxy*-5-(*trimethylsilylmethylene*)*octahydrocyclopenta*[b]*pyran* **38**.—To a stirred refluxing solution of thiocarbonylimidazolide **37** (148 mg, 0.3 mmol) in benzene (150 cm^3) was added dropwise a solution of Bu_3SnH (96 mm^3, 0.36 mmol) and AIBN (5 mg, 0.03 mmol) in benzene (10 cm^3) under argon, and the mixture was stirred for another 30 min. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (95:5, v/v) as eluent to afford the bicyclic compound **38** (101 mg, 92%) as an oil; ν_{max}/cm^{-1} 1620; δ_H 0.11 (9 H, s, $SiMe_3$), 1.20 and 1.21 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.33 and 1.35 (each 0.75 H, each d, *J* 5.5, CH*Me*), 1.36 and 1.37 (each 0.75 H, each d, *J* 5.5, CH*Me*), 1.28 and 1.46 (each 1.5 H, each s, CMe_2), 1.32 and 1.50 (each 1.5 H, each s, CMe_2), 1.96–2.18 (2 H, m, 7-H_2), 2.18–2.72 (2 H, m, 6-H_2), 2.77–2.87 and 2.98–3.09 (each 0.5 H, each m, 4a-H), 3.41–3.87 (2 H, m, CH_2Me), 4.00 and 4.02 (each 0.25 H, each d, *J* 7.3, 3-H), 4.06 and 4.09 (each 0.25 H, each d, *J* 7.3, 3-H), 4.12–4.38 (1 H, m, 7a-H), 4.50 and 4.51 (each 0.25 H, each dd, *J* 3.7 and 7.3, 4-H), 4.56 and 4.57 (each 0.25 H, each dd, *J* 3.7 and 7.3, 4-H), 4.78–4.98 (1 H, m, C*H* Me), 4.87 and 4.92 (each 0.25 H, each s, 2-H), 4.90 and 4.95 (each 0.25 H, each s, 2-H) and 5.47 and 5.59 (each 0.5 H, each q, *J* 1.8, C=CH) [Found: (M^+ − 15), 355.1933. Calc. for $C_{18}H_{31}O_5Si$: (M − 15), 355.1939].

(2R,3S,4S,4aS,7aR)-2-(1-*Ethoxyethoxy*)-3,4-(*isopropylidenedioxy*)*octahydrocyclopenta*[b]*pyran*-5-*one* **39**.—To a stirred solution of the vinylsilane **38** (200 mg, 0.54 mmol) in Bu'OH (0.5 cm^3) were added pyridine (0.13 cm^3, 1.62 mmol), 0.5 mol dm^{-3} aq. $NaIO_4$ (3.2 cm^3, 1.62 mmol) and 19.7 mmol dm^{-3} osmium tetraoxide in Bu'OH (1.37 cm^3, 0.03 mmol) at room temperature, and the resulting mixture was stirred for 4.5 h. After addition of brine, the reaction mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (5:1, v/v) as eluent to afford ketone **39** (139 mg, 86%) as an oil; ν_{max}/cm^{-1} 1740; δ_H 1.21 and 1.22 (each 1.5 H, each t, *J* 7.3, CH_2Me), 1.28 and 1.48 (each 3 H, each s, CMe_2), 1.35 and 1.38 (each 3 H, each d, *J* 5.5, CH*Me*), 2.10–2.70 (5 H, m, 4a-H and 6- and 7-H_2), 3.50–3.80 (2 H, m, CH_2Me), 4.02 and 4.08 (each 0.5 H, each d, *J* 7.3, 3-H), 4.40 and 4.54 (each 0.5 H, each q, *J* 8.5, 7a-H), 4.75 (1 H, dd, *J* 4.3 and 7.3, 4-H), 4.84 and 4.94 (each 0.5 H, each q, *J* 5.5, C*H* Me) and 4.96 and 4.99 (each 0.5 H, each br s, 2-H) [Found: (M^+ − 15), 285.1334. Calc. for $C_{14}H_{21}O_6$: (M − 15), 285.1337. Found: C, 60.4; H, 8.3. Calc. for $C_{15}H_{24}O_6$: C, 60.00; H, 8.05%).

(2R,3S,4S,4aS,5R,7aR)-2-(1-*Ethoxyethoxy*)-3,4-(*isopropylidenedioxy*)*octahydrocyclopenta*[b]*pyran*-5-*ol* **40** *and* (2R,3S,4S,-4aS,5S,7aR)-2-(1-*Ethoxyethoxy*)-3,4-(*isopropylidenedioxy*)*octahydrocyclopenta*[b]*pyran*-5-*ol* **41**.—To a stirred mixture of ketone **39** (40 mg, 0.13 mmol), THF (1 cm^3), EtOH (1 cm^3) and liquid NH_3 (20 cm^3) was added sodium metal (15 mg, 0.65 mmol) at −78 °C, and the resulting mixture was stirred for 20 min at the same temperature. After stirring of the mixture for 1 h at room temperature, saturated aq. NH_4Cl was added and the reaction mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluent. The first fraction gave the *endo* alcohol **41** (21 mg, 30%) as an oil; ν_{max}/cm^{-1} 3520; δ_H 1.21 (3 H, t, *J* 7.3, CH_2Me), 1.34 and 1.36 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.35 and 1.50 (each 3 H, each s, CMe_2), 1.80–2.00 (4 H, m, 6- and 7-H_2), 2.47–2.57 (1 H, m, 4a-H), 2.50–2.92 (1 H, br s, OH), 3.42–3.84 (2 H, m, CH_2Me), 4.01 and 4.06 (each 0.5 H, each d, *J* 7.3, 3-H), 4.03–4.30 (1 H, m, 5-H), 4.35–4.45 (1 H, m, 7a-H), 4.65 and 4.66 (each 0.5 H, each dd, *J* 4.3 and 7.3, 4-H), 4.81 and 4.88 (each 0.5 H, each q, *J* 5.5, C*H* Me) and 4.92 and 4.96 (each 0.5 H, each br s, 2-H) [Found: (M^+ − 15), 287.1498. Calc. for $C_{14}H_{23}O_6$: (M − 15), 287.1495. Found: C, 59.5; H, 8.85. Calc. for $C_{15}H_{26}O_6$: C, 59.60; H, 8.65%]. The second fraction gave the *exo* alcohol **40** (22 mg, 55%) as an oil; ν_{max}/cm^{-1} 3550; δ_H 1.21 (3 H, t, *J* 6.7, CH_2Me), 1.34 and 1.36 (each 1.5 H, each d, *J* 5.5, CH*Me*), 1.35 and 1.52 (each 3 H, each s, CMe_2), 1.70–2.30 (5 H, m, 4a-H and 6- and 7-H_2), 2.25–2.41 (1 H, br s, OH), 3.43–3.81 (2 H, m, CH_2Me), 4.00 and 4.05 (each 0.5 H, each d, *J* 7.3, 3-H), 4.16–4.40 (1 H, m, 5-H), 4.44–4.52 (1 H, m, 7a-H), 4.66 (1 H, t, *J* 7.3, 4-H), 4.83 and 4.89 (each 0.5 H, each q, *J* 5.5, C*H* Me) and 5.05 and 5.12 (each 0.5 H, each br s, 2-H) [Found: (M^+ − 15), 287.1485. Found: C, 59.5; H, 8.85%].

$NaBH_4$ *Reduction of Ketone* **39**.—To a stirred solution of ketone **39** (300 mg, 1.0 mmol) in MeOH (3 cm^3) was added $NaBH_4$ (42 mg, 1.1 mmol) at 0 °C, and the mixture was stirred for a further 30 min at the same temperature. After addition of saturated aq. NH_4Cl to the reaction mixture, most of the solvent was removed to give an oil, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluent to afford the *endo* alcohol **41** (289 mg, 96%) as an oil.

Oxidation of Alcohol **41**.—To a stirred solution of oxalyl dichloride (0.12 cm^3, 1.40 mmol) in CH_2Cl_2 (1 cm^3) was added a solution of DMSO (0.13 cm^3, 1.86 mmol) in CH_2Cl_2 (1 cm^3) at −78 °C under argon. After the mixture had been stirred for 15 min at the same temperature, a solution of the alcohol **41** (281 mg, 0.93 mmol) in CH_2Cl_2 (4 cm^3) was added and the reaction mixture was stirred for 30 min. Triethylamine (0.65 cm^3, 4.65 mmol) was added, and the mixture was stirred for a further 15 min at the same temperature. After addition of saturated aq. NH_4Cl, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (4:1, v/v) as eluent to afford ketone **39** (271 mg, 97%) as an oil.

(2R,3S,4S,4aS,5R,7aR)-5-*Benzyloxy*-2-(1-*ethoxyethoxy*)-3,4-(*isopropylidenedioxy*)*octahydrocyclopenta*[b]*pyran* **42**.—To a stirred solution of alcohol **40** (115 mg, 0.38 mmol) in THF (2 cm^3) were added sodium hydride [(60% in mineral oil), 46 mg, 1.14 mmol], Bu_4NI (14 mg, 0.04 mmol) and benzyl bromide (0.11 cm^3, 0.95 mmol) at 0 °C under argon, and the resulting

mixture was stirred for 15 h at room temperature. After addition of saturated aq. NH_4Cl, the reaction mixture was concentrated to give an oil, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (8:1, v/v) as eluent to afford benzyl ether **42** (146 mg, 98%) as an oil; δ_H 1.20 and 1.21 (each 1.5 H, each t, *J* 6.7, CH_2Me), 1.34 and 1.36 (each 1.5 H, each d, *J* 5.5, $CHMe$), 1.31 and 1.45 (each 3 H, each s, CMe_2), 1.53–2.26 (4 H, m, 6- and 7-H_2), 2.38 (1 H, dt, *J* 4.3 and 9.2, 4a-H), 3.42–3.85 (2 H, m, CH_2Me), 3.96 and 4.01 (each 0.5 H, each d, *J* 7.3, 3-H), 4.17–4.43 (1 H, m, 7a-H), 4.30 (1 H, dt, *J* 4.3 and 6.7, 5-H), 4.52 and 4.53 (each 1 H, each br s, CH_2Ph), 4.50–4.60 (1 H, m, 4-H), 4.82 and 4.89 (each 0.5 H, each q, *J* 5.5, $CHMe$), 4.88 and 4.92 (each 0.5 H, each br s, 2-H) and 7.24–7.35 (5 H, m, Ph) [Found: (M^+ − 15), 377.1967. Calc. for $C_{21}H_{29}O_6$: (M − 15), 377.1964. Found: C, 67.8; H, 8.45. Calc. for $C_{22}H_{32}O_6$: C, 67.30; H, 8.20%].

(1R,2R,3R)-3-*Benzyloxy*-2-[(1′S,2′R)-3′-*hydroxy*-1′,2′-(*isopropylidenedioxy*)*propyl*]*cyclopentanol* **43**.—To a stirred solution of ethoxyethyl ether **42** (115 mg, 0.29 mmol) in THF (3 cm^3) was added dropwise 2 mol dm^{-3} HCl (0.26 cm^3, 0.52 mmol) at 0 °C, and the mixture was stirred for another 2 h at room temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluent to afford (3*S*,4*S*,4a*S*,5*R*,7a*R*)-5-benzyloxy-3,4-(isopropylidenedioxy)octahydrocyclopenta[*b*]pyran-2-ol (91.5 mg, 98%) as an oil; ν_{max}/cm^{-1} 3450; δ_H 1.31 and 1.44 (each 1.5 H, each s, ½ of CMe_2), 1.36 and 1.48 (each 1.5 H, each s, ½ of CMe_2), 1.52–2.26 (4 H, m, 6- and 7-H_2), 2.44 (1 H, dt, *J* 4.3 and 8.5, 4a-H), 2.87 (1 H, d, *J* 3.1, OH), 3.98 (1 H, d, *J* 7.3, 3-H), 4.30 (1 H, dt, *J* 4.3 and 6.7, 5-H), 4.37–4.43 (1 H, m, 7a-H), 4.46–4.63 (1 H, m, 4-H), 4.51 and 4.53 (each 1 H, each br s, CH_2Ph), 5.03 (1 H, d, *J* 3.1, 2-H) and 7.27–7.35 (5 H, m, Ph) (Found: M^+, 320.1623, C, 67.4; H, 7.65%. Calc. for $C_{18}H_{24}O_5$: M, 320.1623; C, 67.50; H, 7.55%).

To a stirred solution of the above lactol (173 mg, 0.54 mmol) in MeOH–CH_2Cl_2 (4 cm^3; 7:1) was added $NaBH_4$ (205 mg, 5.4 mmol) at 0 °C, and the mixture was stirred for another 1 h at room temperature. After addition of saturated aq. NH_4Cl to the reaction mixture, most of the solvent was removed to give an oil, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (3:2, v/v) as eluent to afford diol **43** (173.6 mg, 100%) as an oil; $[\alpha]_D^{22}$ −67.0 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3400; δ_H 1.35 and 1.42 (each 3 H, each s, CMe_2), 1.68–2.28 (5 H, m, 2-H and 4- and 5-H_2), 2.33 and 3.13 (each 1 H, each br s, 1- and 3′-OH), 3.51–3.58 and 3.73–3.81 (each 1 H, each m, 3′-H_2), 3.92–3.98 (1 H, m, 3-H), 4.16 (1 H, dt, *J* 3.7 and 5.5, 2′-H), 4.29 (1 H, dd, *J* 5.5 and 10.4, 1′-H), 4.38 and 4.59 (each 1 H, each d, *J* 11.6, CH_2Ph), 4.45 (1 H, t, *J* 4.3, 1-H) and 7.26–7.39 (5 H, m, Ph) [Found: (M^+ − 15), 307.1542. Calc. for $C_{17}H_{23}O_5$: (M − 15), 307.1544. Found: C, 67.15; H, 8.3. Calc. for $C_{18}H_{26}O_5$: C, 67.05; H, 8.15%).

(1R,2R,3R)-3-*Benzyloxy*-2-[(1′S,2′R)-3′-(tert-*butyldimethylsiloxy*)-1′,2′-(*isopropylidenedioxy*)*propyl*]*cyclopentanol* **44**.—To a stirred solution of diol **43** (70 mg, 0.22 mmol) in CH_2Cl_2 (1 cm^3) were added DMAP (10.6 mg, 0.09 mmol), triethylamine (0.24 cm^3, 1.74 mmol) and TBDMSCl (99 mg, 0.65 mmol) at 0 °C under argon, and the mixture was stirred for a further 10 h at room temperature. After addition of saturated aq. NH_4Cl, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (6:1, v/v) as eluent to afford silyl ether **44** (94.6 mg, 100%) as an oil; $[\alpha]_D^{22}$ −45.9 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3500; δ_H 0.04 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.33 and 1.46 (each 3 H, each s, CMe_2), 1.65–2.26 (5 H, m, 2-H and 4- and 5-H_2), 3.01 (1 H, br s, OH), 3.68 (1 H, dd, *J* 6.1 and 11.0, 3′-H), 3.88 (1 H, dd, *J* 5.5 and 11.0, 3′-H), 4.02 (1 H, dt, *J* 4.9 and 7.3, 3-H), 4.14 (1 H, dt, *J* 5.5 and 6.1, 2′-H), 4.40 (1 H, dd, *J* 6.1 and 7.3, 1′-H), 4.40 and 4.59 (each 1 H, each d, *J* 11.6, CH_2Ph), 4.46 (1 H, t, *J* 4.3, 1-H) and 7.25–7.36 (5 H, m, Ph) [Found: (M^+ − 15), 421.2401. Calc. for $C_{23}H_{37}O_5Si$: (M − 15), 421.2409. Found: C, 66.2; H, 9.45. Calc. for $C_{24}H_{40}O_5Si$: C, 66.00; H, 9.25%].

(2S,3R)-3-*Benzyloxy*-2-[(1′S,2′R)-3′-(tert-*butyldimethylsiloxy*)-1′,2′-(*isopropylidenedioxy*)*propyl*]*cyclopentanone* (E)-*Oxime* **46**.—To a stirred solution of the alcohol **44** (185 mg, 0.42 mmol), 4-methylmorpholine *N*-oxide (75 mg, 0.64 mmol) and molecular sieves 4 Å (185 mg) in CH_2Cl_2 (3 cm^3) was added portionwise tetrapropylammonium perruthenate (30 mg, 0.08 mmol) at room temperature under argon, and the mixture was stirred for another 30 min. Insoluble material was filtered off, and the filtrate was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave ketone **45**.

To a stirred solution of the crude ketone **45** in MeOH (1.5 cm^3) were added pyridine (0.1 cm^3, 1.27 mmol) and NH_2OH·HCl (74 mg, 1.06 mmol) at 0 °C under argon, and the resulting mixture was stirred for 30 min at the same temperature. After addition of brine, the reaction mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (6:1, v/v) as eluent to afford oxime **46** (176 mg, 86%) as an oil; $[\alpha]_D^{25}$ −18.9 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3350; δ_H 0.07 and 0.07 (each 3 H, each s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.31 and 1.39 (each 3 H, each s, CMe_2), 1.83–2.16 (2 H, m, 4-H_2), 2.39–2.50 (1 H, m, 5-H), 2.71 (1 H, dt, *J* 7.9 and 18.3, 5-H), 3.06 (1 H, br s, 2-H), 3.90 (1 H, dd, *J* 5.5 and 10.4, 3′-H), 3.98 (1 H, q, *J* 4.3, 3-H), 4.13 (1 H, dd, *J* 6.1 and 10.4, 3′-H), 4.20–4.29 (2 H, m, 1′- and 2′-H), 4.50 and 4.55 (each 1 H, each d, *J* 11.6, CH_2Ph), 7.26–7.36 (5 H, m, Ph) and 7.72 (1 H, br s, OH) [Found: (M^+ − 15), 434.2365. Calc. for $C_{23}H_{36}NO_5Si$: (M − 15), 434.2363. Found: C, 64.3; H, 8.95; N, 3.0. Calc. for $C_{24}H_{39}NO_5Si$: C, 64.10; H, 8.75; N, 3.10%].

(5R,6R)-5-*Benzyloxy*-6-[(1′S,2′R)-3′-(tert-*butyldimethylsiloxy*)-1′,2′-(*isopropylidenedioxy*)*propyl*]*piperidin*-2-*one* **47**.—To a stirred solution of oxime **46** (170 mg, 0.38 mmol) was added dropwise thionyl dichloride (83 mm^3, 1.14 mmol) at 0 °C under argon, and the resulting mixture was stirred for 1 h at room temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (5:4, v/v) as eluent to afford lactam **47** (140.5 mg, 83%) as a glass; $[\alpha]_D^{23}$ −52.6 (*c* 0.88, $CHCl_3$); ν_{max}/cm^{-1} 1650; δ_H 0.10 and 0.12 (each 3 H, each s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 1.34 and 1.46 (each 3 H, each s, CMe_2), 1.78–1.89 (1 H, m, 4-H), 2.14–2.21 (1 H, m, 4-H), 2.30 (1 H, dt, *J* 5.5 and 9.2, 3-H), 2.50 (1 H, dt, *J* 5.5 and 17.1, 3-H), 3.57 (1 H, br d, *J* 6.7, 6-H), 3.70 (1 H, ddd, *J* 3.7, 6.7 and 9.2, 5-H), 3.81 (1 H, dd, *J* 3.7 and 11.6, 3′-H), 3.90 (1 H, dd, *J* 6.7 and 11.6, 3′-H), 4.18 (1 H, dd, *J* 3.7 and 6.7, 1′-H), 4.22 (1 H, dt, *J* 3.7 and 6.7, 2′-H), 4.52 and 4.66 (each 1 H, each d, *J* 11.6, CH_2Ph), 6.25 (1 H, br s, NH) and 7.26–7.38 (5 H, m, Ph)

[Found: (M^+ − 15), 434.2359. Calc. for $C_{23}H_{36}NO_5Si$: (M − 15), 434.2361. Found: C, 64.25; H, 9.0; N, 3.05. Calc. for $C_{24}H_{39}NO_5Si$: C, 64.10; H, 8.75; N, 3.10%].

(5R,6R)-5-*Benzyloxy*-6-[(1'S,2'R)-3'-*hydroxy*-1',2'-(*isopropylidenedioxy*)*propyl*]*piperidin*-2-*one* **48**.—To a stirred solution of silyl ether **47** (159 mg, 0.35 mmol) in THF (1.5 cm^3) was added dropwise Bu_4NF (0.14 cm^3 of a 1.0 mol dm^{-3} THF solution, 0.53 mmol) at 0 °C, and the mixture was stirred for another 1 h at the same temperature. After addition of saturated aq. NH_4Cl to the reaction mixture, most of the solvent was removed to give an oil, which was extracted with $CHCl_3$–MeOH (9:1). The organic layer was dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (97:3, v/v) as eluent to afford alcohol **48** (118.5 mg, 100%) as an oil; $[\alpha]_D^{23}$ −50.0 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3380 and 1650; δ_H 1.34 and 1.46 (each 3 H, each s, CMe_2), 1.79–1.95 and 2.14–2.28 (each 1 H, each m, 4-H_2), 2.33 (1 H, dt, *J* 6.1 and 9.2, 3-H), 2.53 (1 H, dt, *J* 6.1 and 17.1, 3-H), 2.63 (1 H, br s, OH), 3.51 (1 H, m, 6-H), 3.61–3.68 (2 H, m, 3'- and 5-H), 3.87 (1 H, br d, *J* 11.6, 3'-H), 4.15–4.23 (2 H, m, 1'- and 2'-H), 4.51 and 4.68 (each 1 H, each d, *J* 11.6, CH_2Ph), 6.56 (1 H, br s, NH) and 7.26–7.65 (5 H, m, Ph) [Found: (M^+ − 15), 320.1504. Calc. for $C_{17}H_{22}NO_5$: (M − 15), 320.1498. Found: C, 62.85; H, 7.6; N, 3.9. Calc. for $C_{18}H_{25}NO_5 \cdot \frac{1}{2}H_2O$: C, 62.75; H, 7.50; N, 4.20%].

(1S,2R,8R,8aR)-8-*Benzyloxy*-1,2-(*isopropylidenedioxy*)*octahydroindolizin*-5-*one* **50**.—To a stirred solution of the alcohol **48** (105 mg, 0.31 mmol) in CH_2Cl_2 (1.5 cm^3) were added triethylamine (87 mm^3, 0.63 mmol), DMAP (4 mg, 0.03 mmol) and MsCl (36 mm^3, 0.47 mmol) at 0 °C under argon, and the mixture was stirred a further 1 h at the same temperature. After addition of saturated aq. NH_4Cl, the reaction mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. Evaporation of the solution gave mesyl ester **49**.

A mixture of the crude mesyl ester **49** and potassium carbonate (63 mg, 0.45 mmol) in aq. 1,4-dioxane (1.5 cm^3; dioxane–water = 4:1) was stirred at 90 °C for 1 h. After addition of saturated aq. NH_4Cl, the reaction mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. Evaporation of the solution gave a residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (98:2, v/v) as eluent to afford the bicyclic lactam **50** (95 mg, 96%) as needles; $[\alpha]_D^{23}$ −29.3 (*c* 0.42, $CHCl_3$); m.p. 96–98 °C (from hexane–AcOEt); ν_{max}/cm^{-1} 1630; δ_H 1.32 and 1.39 (each 3 H, each s, CMe_2), 1.78–1.93 and 2.11–2.21 (each 1 H, each m, 7-H_2), 2.33 (1 H, ddd, *J* 5.5, 11.0 and 17.1, 6-H), 2.50 (1 H, dt, *J* 4.9 and 17.1, 6-H), 3.06 (1 H, dd, *J* 4.9 and 13.4, 3-H), 3.39 (1 H, dd, *J* 3.7 and 7.3, 8a-H), 3.98 (1 H, ddd, *J* 3.7, 4.9 and 11.0, 8-H), 4.18 (1 H, d, *J* 13.4, 3-H), 4.62 and 4.69 (each 1 H, each d, *J* 11.6, CH_2Ph), 4.68–4.77 (2 H, m, 1- and 2-H) and 7.27–7.37 (5 H, m, Ph) (Found: M^+, 317.1622. Calc. for $C_{18}H_{23}NO_4$: M^+, 317.1625. Found: C, 67.5; H, 7.35; N, 4.25. Calc. for $C_{18}H_{23}NO_4 \cdot \frac{1}{5}H_2O$: C, 67.35; H, 7.35; N, 4.35%).

(1S,2R,8R,8aR)-8-*Hydroxy*-1,2-(*isopropylidenedioxy*)*octahydroindolizin*-5-*one* **51**.—A suspension of benzyl ether **50** (38 mg, 0.12 mmol) and 20% $Pd(OH)_2$ on carbon (19 mg) in EtOH (1 cm^3) was stirred for 1 h at room temperature under hydrogen (1 atm). The catalyst was filtered off, and the filtrate was evaporated to give a residue, which was purified by column chromatography on silica gel with AcOEt–MeOH (19:1) as eluent to afford the alcohol **51** (27 mg, 99%) as crystals; $[\alpha]_D^{22}$ +13.9 (*c* 0.54, MeOH); m.p. 132–133 °C (from hexane–AcOEt); ν_{max}/cm^{-1} 3400 and 1640; δ_H 1.34 and 1.43 (each 3 H, each s, CMe_2), 1.82–1.95 and 2.08–2.18 (each 1 H, each m, 7-H_2), 2.34 (1 H, d, *J* 4.9, OH), 2.37–2.58 (2 H, m, 6-H_2), 3.14 (1 H, dd, *J* 4.3 and 13.4, 3-H), 3.33 (1 H, dd, *J* 4.3 and 7.9, 8a-H), 4.10–4.21 (1 H, m, 8-H), 4.20 (1 H, d, *J* 13.4, 3-H) and 4.75 and 4.81 (each 1 H, each dd, *J* 4.3 and 6.1, 1- and 2-H) (Found: M^+, 227.1156. Calc. for $C_{11}H_{17}NO_4$: M, 227.1156). The ^1H NMR spectrum of compound **51** was identical with that reported.[6f]

(1S,2R,8R,8aR)-1,2-(*Isopropylidenedioxy*)*octahydroindolizin*-8-*ol* **2**.—To a stirred solution of lactam **51** (53 mg, 0.23 mmol) in THF (1 cm^3) was added dropwise borane–dimethyl sulfide complex (0.7 cm^3 of a 2.0 mol dm^{-3} THF solution, 1.40 mmol) at 0 °C under argon, and the mixture was stirred for a further 1 h at room temperature. Removal of the solvent gave an oil, which was dissolved in aq. 1,4-dioxane (1.2 cm^3; dioxane–water = 3:1). Potassium carbonate (323 mg, 2.33 mmol) was added to the mixture, and the mixture was stirred at 65 °C for 2 h. After addition of brine, the reaction mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (97:3, v/v) as eluent to afford swainsonine acetonide **2** (49.4 mg, 99%) as needles; $[\alpha]_D^{20}$ −81.6 (*c* 0.62, MeOH) {lit.,[22] $[\alpha]_D^{24}$ −75.1 (*c* 1.54, MeOH)}; m.p. 102–105 °C (from hexane–Et_2O) (lit.,[22] 105–107 °C,[6c] 100–103 °C,[6i] 103–106 °C); ν_{max}/cm^{-1} 3450; δ_H 1.16–1.70 (4 H, m, 6- and 7-H_2), 1.34 and 1.51 (each 3 H, each s, CMe_2), 1.81–1.91 (1 H, m, 5-H), 2.00–2.20 (2 H, m, 8a-H and OH), 2.13 (1 H, dd, *J* 4.3 and 10.4, 3-H), 2.99 (1 H, dt, *J* 3.1 and 10.4, 5-H), 3.16 (1 H, d, *J* 10.4, 3-H), 3.84 (1 H, ddd, *J* 4.3, 8.5 and 11.0, 8-H) and 4.61 and 4.71 (each 1 H, each dd, *J* 4.3 and 6.1, 1- and 2-H) (Found: M^+, 213.1358. Calc. for $C_{11}H_{19}NO_3$: M, 213.1363).

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