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The Total Synthesis of Swinholide A. Part 1: A Stereocontrolled Synthesis of a C_{19}-C_{32} Segment.

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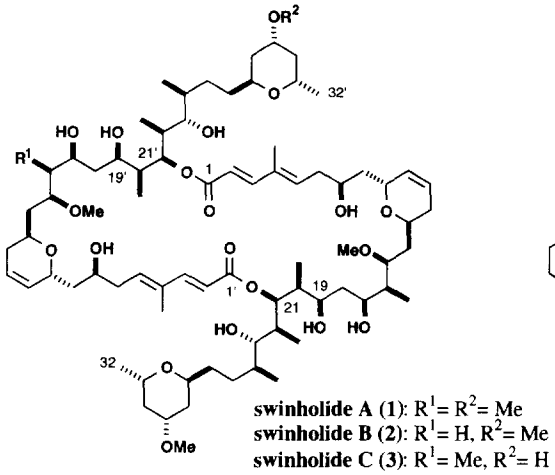
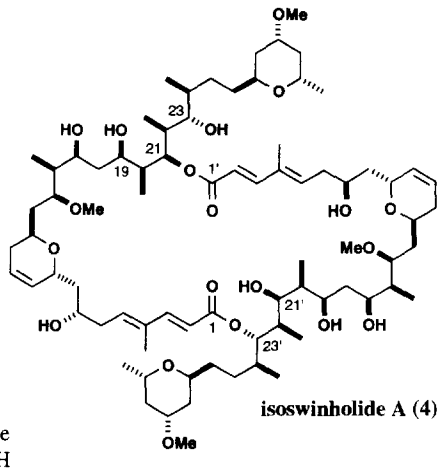
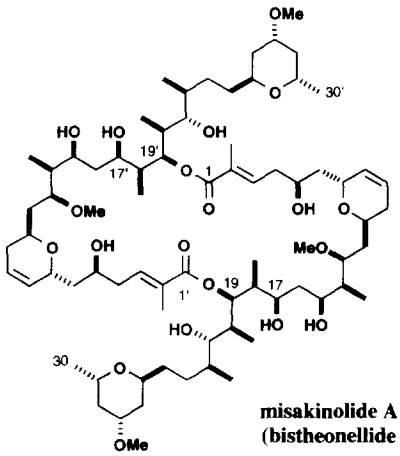
Abstract: The C_{19}-C_{32} segment **10** of swinholide A was prepared in 15 steps (8% yield, 82% ds) from (±)-**16**. Key steps include (*i*) the Sharpless epoxidation, **16** → **17**, (*ii*) the acetal allylation, **15** → **23**, (*iii*) the anti aldol addition, **13** + **14** → **12**, and (*iv*) the alkene hydroboration, **30** → **31**.



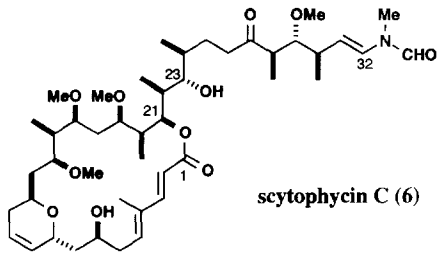
swinholide A (1): $R^1 = R^2 = Me$
swinholide B (2): $R^1 = H$, $R^2 = Me$
swinholide C (3): $R^1 = Me$, $R^2 = H$



isoswinholide A (4)



misakinolide A (5)
(bistheonellide A)



scytophycin C (6)

The swinholides are a series of complex polyketide macrodiolides, which display potent cytotoxicity against a variety of human tumour cell lines.[1,2] Swinholide A, isolated from the marine sponge *Theonella swinhoei*, was first reported as an antifungal agent by Carmely and Kashman in 1985.[1] Using NMR methods and chemical

derivatisation, the gross structure of swinholide A was initially misassigned as a monomeric, 22-membered macrolide. Subsequently, Kitagawa and co-workers[2a-d] re-isolated swinholide A and noted its potent cytotoxic activity. They then went on to elucidate its true dimeric nature by mass spectroscopy ($C_{78}H_{132}O_{20}$),[2a] as well as determining the full stereochemistry using a combination of Mosher ^1H NMR analysis performed on the *bis*-MTPA ester formed at $C_{23,23'}$ and X-ray crystallography. The C_2-symmetrical, highly oxygenated structure **1** of swinholide A, which is based on a 44-membered macrodiolide ring, is a striking feature. Moreover, this unusually large macrocyclic ring is apparently required for its cytotoxic activity.[2d]

A number of unsymmetrical congeners, *e.g.* swinholides B (**2**) and C (**3**),[2e] as well as isoswinholide A (**4**),[2e] which has a 46-membered ring, have also been isolated from *Theonella swinhoei*. The monomeric secoacid pre-swinholide A, believed to be the biosynthetic precursor of swinholide A, has also been reported,[2f,g] while its methyl ester derivative has been prepared by degradation of swinholide A.[2c] The 40-membered dilactone misakinolide A (**5**)[3a-c] (≡ bistheonellide A[3b,d]), together with two unsymmetrical desmethyl congeners, are closely related metabolites to the swinholides and are also isolated from marine sponges of the genus *Theonella*.

The stereostructures of the monomeric units of swinholide A and misakinolide A are remarkably similar to that of scytophycin C (**6**),[4] one of a class of antifungal and cytotoxic monomeric macrolides isolated from the terrestrial blue-green alga *Scytomena pseudohofmanni*. This structural homology implies a genetic link between the producing organisms, lending support to the assumption that the swinholides are actually polyketide metabolites of symbiotic microorganisms associated with *Theonella* sp. Indeed, the presence of a symbiotic blue-green alga in the marine sponge *Theonella swinhoei* has been detected using electron microscopy.[2c]

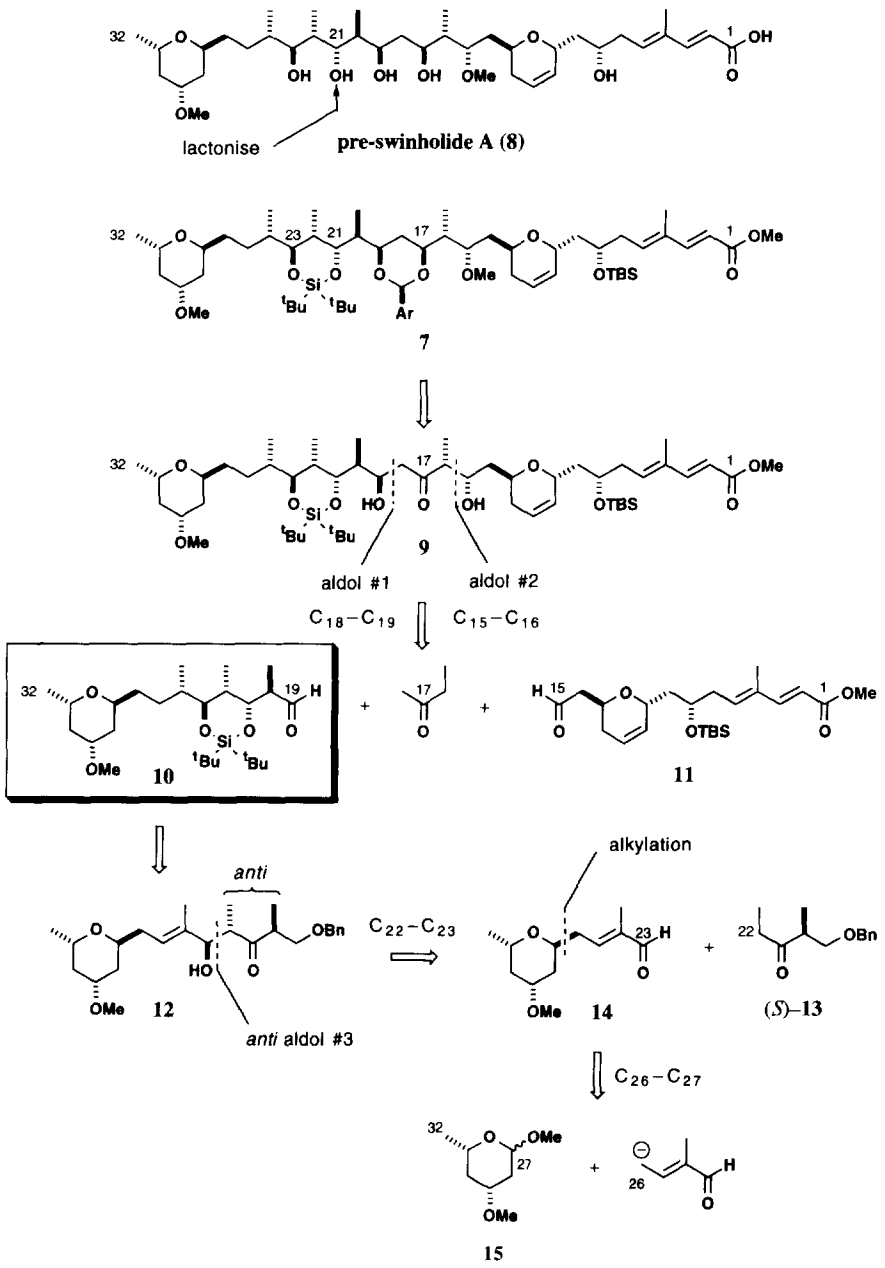
The swinholides are characterised by potent cytotoxicity, *e.g.* swinholide A has an IC_{50} value of 0.04 and 0.03 μg/ml against KB and L1210 tumour cells *in vitro*.[2b,d] The limited natural supply of the swinholides and their potential utility in anticancer studies makes synthesis an option to produce adequate quantities for full biological testing, as well as making available novel structural analogues. Moreover, the complex dimeric structures of this unique class of marine macrolide, comprising fifteen stereogenic centres with two isomerisable double bonds and five hydroxyl sites available for acylation in each monomeric unit, make them challenging targets for total synthesis.[5-8]

In this series of four papers, we report full details of our recently completed total synthesis[5,6] of swinholide A and the related compounds, iso-swinholide A and pre-swinholide A, together with that of some unnatural monomeric lactone analogues. In this first paper, we outline our synthetic strategy and describe the synthesis of a C_{19}–C_{32} segment for swinholide A.[5a] The following papers of this series[8] describe the synthesis of a corresponding C_1–C_{15} segment[8a] and coupling studies to give the monomeric seco acid,[8b] followed by an efficient dimerisation-macrolactonisation sequence to provide swinholide A.[8c]

Synthetic Strategy Adopted for Swinholide A and Pre-swinholide A

Scheme 1 summarises our strategy for the synthesis of **7**, a fully protected version of the monomeric secoacid pre-swinholide A (**8**). This advanced intermediate **7** was viewed as an appropriate subtarget for synthesis, which would enable us to confirm the stereochemistry by deprotection to give pre-swinholide A. An appropriate plan would then be needed to give the symmetrical 44-membered ring system of swinholide A from **7**, involving selective deprotection and controlled dimerisation through acylation of the C_{21} hydroxyl group. At the outset,

we chose to simplify the synthetic route by installing a cyclic silicon protecting group for the C_{21} and C_{23} hydroxyls in **7** and forego the opportunity for differential protection. In this bold strategy, we would thus need to discriminate between these hydroxyls (which are in similar steric environments) on dimerisation and macrolactonisation.[6,8c]

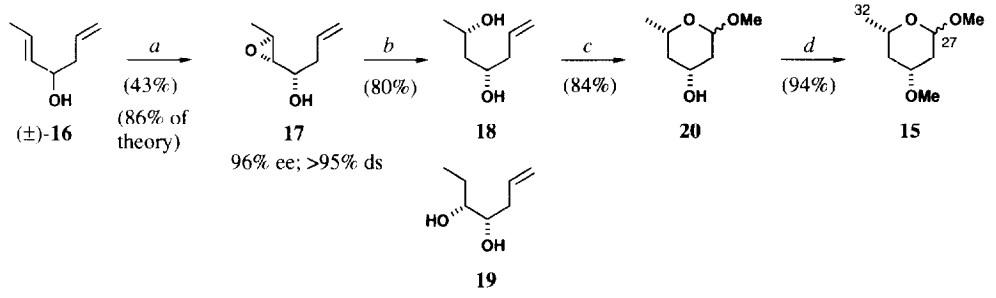


Scheme 1

We planned a highly convergent aldol-based route for the construction of the carbon and oxygen skeleton of the secoacid derivative **7**. This aldol approach was anticipated to rely heavily on the use of our chiral boron enolate methodology.[9] In this plan, disconnections at the C_{15}–C_{16} and C_{18}–C_{19} bonds in the corresponding C_{17} ketone **9** afford the key aldehyde segments **10** and **11**, and a suitable equivalent of butanone to serve as a linking unit (*i.e.* C_{16}–C_{18}). Suitable substrate- or reagent-based control in the introduction of all the stereocentres in **7**, especially those created in the fragment coupling process, would be a critically important issue in defining the eventual success or failure of the synthesis. Segment **10**, containing the C_{19}–C_{25} stereopentad and the trisubstituted tetrahydropyran ring, should then be attainable *via* the β-hydroxy ketone **12** using our general synthetic approach[9a,b] to such polypropionate systems. In this case, an anti-anti aldol reaction[9c] between our dipropionate reagent (*S*)-**13**[9] and the enal **14** was required to control the C_{22} and C_{23} stereocentres in **12**. The aldehyde component **14** required for this aldol reaction should be available, in turn, from the tetrahydropyran acetal **15** by a suitable alkylation reaction at C_{27}.

Synthesis of the C_{27}-C_{32} tetrahydropyran (15)

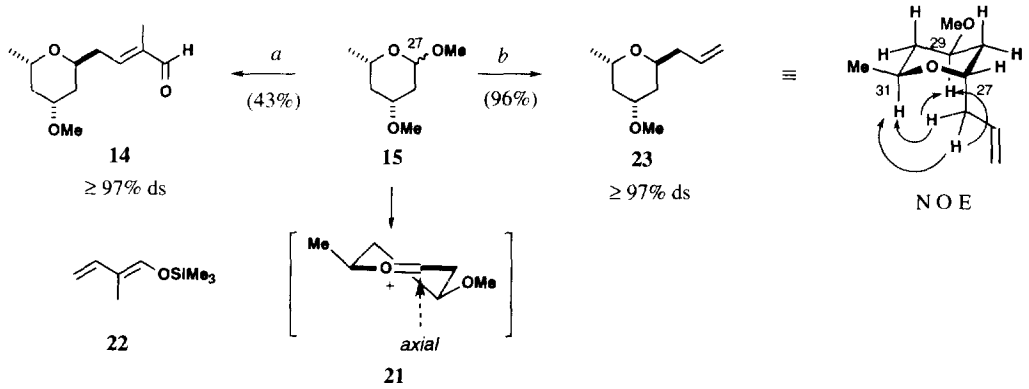
As shown in **Scheme 2**, the starting point for the synthesis of the C_{19}–C_{32} segment **10** was (*E*)-1,5-heptadien-4-ol (**16**), which was prepared by the method of Shono *et al.*[10] in 80% yield (1 mole scale) from crotonaldehyde and allyl bromide. Catalytic asymmetric epoxidation[11a] of (±)-**16** with kinetic resolution gave the (*S*,*S*,*S*) epoxide **17**[11b] in 43% yield (corresponding to 86% yield based on consumption of the fast-reacting enantiomer) with >95% ds. The enantiomeric purity of epoxide **17** was determined as 96% ee by ^{1}H NMR analysis of the Mosher ester formed from (*R*)-(+)-MTPA.[12] Hydroxyl-directed reductive opening of the epoxide **17** was achieved using Red-al®[13] giving the 1,3-anti diol **18** in 80% yield, together with 4% of a mixture of isomeric by-products which consisted mainly of the 1,2-diol **19**. Ozonolysis of diol **18** in methanol, followed by work-up with dimethyl sulphide and dilute acid, gave the tetrahydropyran acetal **20** in 84% yield as a mixture of anomers. *O*-Methylation under standard conditions then afforded the completed C_{27}–C_{32} tetrahydropyran unit **15** in 94% yield.



Scheme 2: (a) (+)-DIPT (15 mol %), $Ti(O^iPr)_4$ (10 mol %), ^{t}BuOOH (49 mol %), 4Å sieves, CH_2Cl_2, –20 °C, 20 h; Me_2S, 20 °C, 16 h; (b) Red-al®, THF, 20 °C, 18 h; (c) O_3, MeOH, –20 °C, 10 min; Me_2S, 20 °C, 16 h; 1 M HCl(aq), 3 h; (d) NaH, MeI, THF, 20 °C, 18 h.

Introduction of the Sidechain at C_{27}

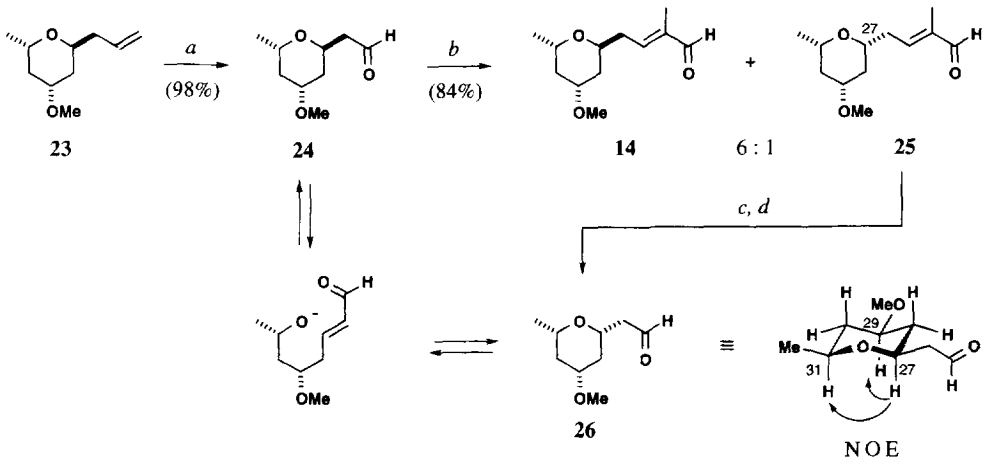
Having constructed the tetrahydropyran ring system, we next planned to elaborate the sidechain at C_{27} *via* a stereocontrolled alkylation of acetal **15** to give the C_{23}–C_{32} aldehyde **14** (**Scheme 1**). It was anticipated that the desired stereocontrol would arise from kinetically-controlled axial attack on the intermediate oxonium ion **21**, as shown in **Scheme 3**. The required transformation was first attempted in a single step by the Lewis acid-mediated addition of the 1-silyloxydiene **22**[14] to the acetal **15**.[15] Use of one equivalent of a variety of Lewis acids ($(^iPrO)_2TiCl_2$,[15] $TiCl_4$, $BF_3{\bullet}OEt_2$, Me_3SiI) in various solvents (CH_2Cl_2, EtCN, MeCN) gave none of the desired product. The desired conversion was finally achieved using trimethylsilyl triflate (10 mol %) in acetonitrile at –20 °C, giving aldehyde **14** as a single isomer in 43% yield (1 mmol scale), with 20% recovered starting material. Unfortunately, when the reaction was scaled up the yield deteriorated. As this reaction was not sufficiently clean or high yielding for our purposes, an alternative strategy was devised. This involved the Lewis acid-mediated addition of allyltrimethylsilane to acetal **15**, followed by an ozonolysis-Wittig sequence to provide the enal **14**. Use of allyltrimethylsilane with catalytic trimethylsilyl triflate (10 mol %) in acetonitrile[16] at –20 °C led to the rapid (< 2 min) and exclusive formation of the *trans*-substituted tetrahydropyran **23** in 96% yield. ^1H NMR coupling constants and NOE difference experiments performed on **23** served to confirm the relative stereochemistry at C_{27} and suggested a preferred chair conformation with the allyl group axially disposed.



Scheme 3: (a) **22**, Me_3SiOTf (10 mol %), MeCN, –20 °C, 30 min; (b) $H_2C{=}CHCH_2SiMe_3$, Me_3SiOTf (10 mol %), MeCN, –20 °C, 2 min.

Ozonolysis of the allylic sidechain in tetrahydropyran **23** proceeded well, giving **24** in 98% yield (**Scheme 4**). Aldehyde **24** then underwent a stereoselective Wittig reaction with 2-formylethylidenetriphenyl phosphorane[17] to give the desired aldehyde **14** as the major product. Initially, the reactions were performed using benzene as solvent under reflux, giving products **14** and **25** in approximately 6 : 1 ratio. Use of toluene as solvent gave a higher yield (84%), but with the same product ratio. The byproduct (which was initially misassigned as the *Z* isomer of **14**)[5a] was identified as the C_{27} epimer **25** by conversion into aldehyde **26**, which was spectroscopically different from aldehyde **24**. ^1H NMR NOE difference experiments on **26** indicated an all-equatorial ring substitution. When the reaction time was lengthened the proportion of epimer **25** increased. It was also found that when the reaction was stopped before completion a small amount of the epimeric starting aldehyde **26** was isolated. These results suggest that epimerisation is occurring in both the starting material and

the product, presumably, by β-elimination followed by ring-reclosure, to give the thermodynamically preferred all-equatorial tetrahydropyran. No traces of *Z* double bond isomers were detected.

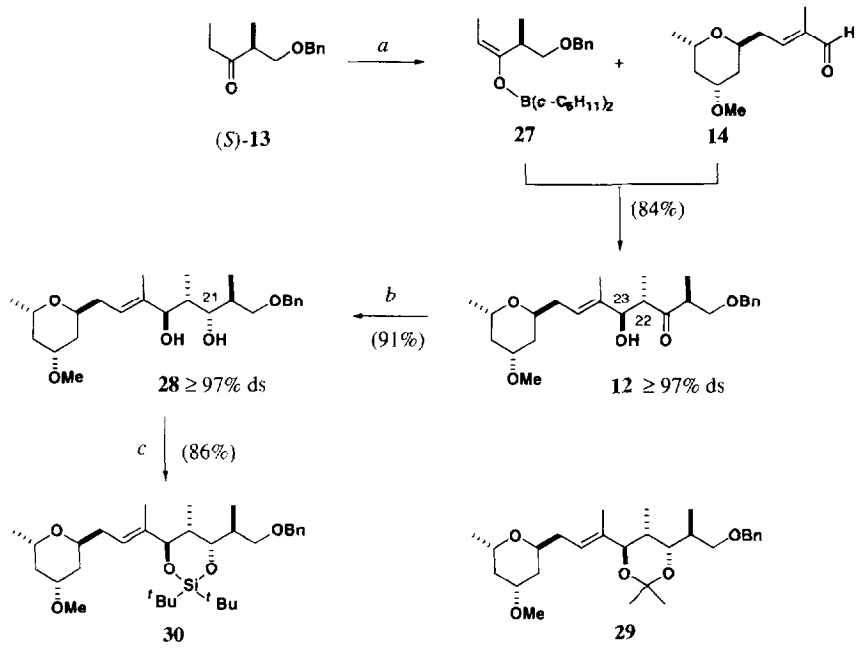


Scheme 4: (a) O_3, 3:1 CH_2Cl_2/MeOH, $NaHCO_3$(s), –78 °C, 10 min; Me_2S, 20 °C, 16 h; (b) $Ph_3P{=}C(Me)CHO$, PhMe, reflux, 3 h; (c) DIBAL, THF, 0 °C, 30 min; (d) O_3, 3:1 CH_2Cl_2/MeOH, $NaHCO_3$(s), –78 °C, 10 min; Ph_3P, 20 °C, 1 h.

Stereoselective Extension Using a Dipropionate Aldol Reaction

The key reaction in our synthesis of the C_{19}–C_{32} segment **10** of swinholide A is the anti-selective aldol coupling of aldehyde **14** with the dipropionate reagent (*S*)-**13**. This serves to introduce the C_{20} stereocentre, while also controlling the formation of the C_{22} and C_{23} stereocentres (**Scheme 5**). The (*E*)-enol dicyclohexylborinate **27**, derived from ketone **13** by enolisation with dicyclohexylchloroborane and triethylamine, is known to react in a highly stereoselective manner with aldehydes to give predominantly the 1,2-anti-2,4-anti aldol adduct.[9c] The selectivity arises purely from substrate-control and this reaction has been used extensively in our laboratory for the stereocontrolled synthesis of a variety of polypropionate-derived natural products.[18] Applying the usual conditions to the aldol reaction of ketone (*S*)-**13** with aldehyde **14** (equimolar amounts) cleanly gave product **12** in 84% yield with ≥97% ds (no other aldol isomers were detected). The product stereochemistry was assigned as shown on the basis of the well-precedented stereochemical outcome of the aldol reactions of **27**.[9c,18]

Next, the stereocentre at C_{21} was introduced by a hydroxyl-directed ketone reduction using the method of Evans *et al.*[19] Reaction of **12** with $Me_4NBH(OAc)_3$ afforded the 1,3-anti diol **28** in 91% yield with none of the corresponding syn isomer being detected. The stereochemistry of the reduction was confirmed by preparation of the acetonide derivative **29**. The ^{13}C NMR spectrum of **29** showed acetonide methyl resonances at δ 24.7 and 23.8 ppm, indicating a 1,3-anti relationship.[20] At this stage, we made the strategic decision not to introduce differential hydroxyl protection at C_{21} and C_{23}. The hydroxyl groups in diol **28** were thus protected as the di-*tert*-butylsilylene derivative **30** using di-*tert*-butylsilylbistriflate in 86% yield.[18a,b,21]

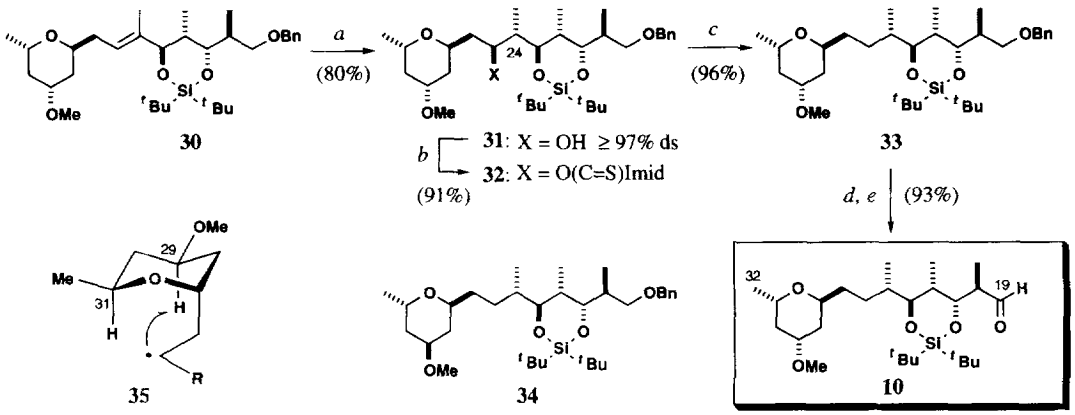


Scheme 5: (a) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; **14**, −78 → −20 °C, 14 h; H_2O_2, pH7 buffer, MeOH, 0 °C, 1 h; (b) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, −20 °C, 19 h; (c) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 16 h.

Stereoselective Hydroboration and Completion of the Synthesis of the C_{19}–C_{32} Segment

The remaining stereocentre at C_{24} was introduced by means of a substrate-controlled stereoselective hydroboration reaction (**Scheme 6**).[22] Model studies indicated that thexylborane gave the best balance between selectivity and reactivity for the trisubstituted alkene in **30**. Thus treatment of alkene **30** with thexylborane, followed by work-up with sodium hydroperoxide afforded alcohol **31** in 80% yield with no other isomers being detected. The stereochemical outcome was assumed to follow the precedent first detailed by Still *et al.*[22a]

The surplus hydroxyl group at C_{25} was then removed by a two-step radical deoxygenation procedure.[23] The thiocarbonylimidazolide derivative **32** was prepared from **31** and treated with 1.5 equivalents of tri-*n*-butylstannane in refluxing toluene giving the desired product **33** and a minor epimeric byproduct, tentatively assigned as structure **34**. These products showed considerable differences in their ^1H NMR spectra. This byproduct was presumed to arise from an intramolecular hydrogen abstraction at C_{29} (or C_{31}) by the intermediate carbon radical **35**, leading to epimerisation at this centre. By use of 10 equivalents of tri-*n*-butylstannane and more concentrated reaction conditions, this competing pathway was entirely suppressed and the desired product **33** was now isolated in high yield (87% over 2 steps). Finally, the synthesis of the C_{19}–C_{32} segment was completed by hydrogenolysis of the benzyl ether in **33** and subsequent Swern oxidation, giving the desired aldehyde **10** in 93% overall yield.



Scheme 6: (a) Thexylborane, THF, 20 °C, 3 h; H_2O_2/NaOH, 0 → 20 °C, 1 h; (b) $(Imid)_2C{=}S$, THF, 60 °C, 16 h; (c) $^n Bu_3SnH$, PhMe, reflux, 30 min; (d) H_2, 10% Pd/C, EtOH, 20 °C, 5 h; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h; Et_3N, −78 → −25 °C, 30 min.

Conclusions

In summary, the synthesis of a C_{19}-C_{32} segment **10** for swinholide A has been achieved. This route is very efficient (15 steps from (±)-**16**, in 8% overall yield and 84% diastereoselectivity), with each of the 7 stereogenic centres being introduced in a highly controlled manner (the remaining stereocentre at C_{20} comes from (*S*)-**13**). It relies on a single *reagent*-controlled reaction, the Sharpless epoxidation **16** → **17**, and a series of *substrate*-controlled reactions, (*i*) the acetal allylation, **15** → **23**, (*ii*) the boron-mediated aldol reaction, **13** + **14** → **12**, (*iii*) the ketone reduction, **12** → **28**, and (*iv*) the alkene hydroboration, **30** → **31**. Importantly, the synthesis is amenable to scale-up and this route has been used to prepare more than 10 g of intermediate **10**, enabling the completion of the total synthesis of swinholide A (see the following papers[8]).

Experimental Section

General. ^1H NMR spectra were recorded using internal deuterium lock for the indicated reference at ambient probe temperatures on the following Fourier transform instruments: Bruker AM500 (500 MHz), AM400 (400 MHz), AM250 (250 MHz), AC200 (200 MHz) or Varian VXR-400S (400 MHz). The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.25), C_6D_6 (δ_H 7.20), $(CD_3)_2CO$ (δ_H 2.05). Data are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and interpretation. Assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, decoupling / COSY experiments or by analogy to fully interpreted spectra for related compounds. ^{13}C NMR spectra were recorded by *J* modulated spin echo (APT) experiments using internal deuterium lock for the indicated reference at ambient probe temperatures on Bruker AM400 (100.6 MHz), AM250 (62.9 MHz), AC200 (50.3 MHz), or Varian VXR-400S (100.6 MHz) Fourier transform instruments, and are reported in ppm on the δ scale. The following internal references were used: $CDCl_3$ (δ_C 77.0), C_6D_6 (δ_C 128.0), $(CD_3)_2CO$ (δ_C 29.8). IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer or 1600

FTIR spectrophotometer calibrated relative to polystyrene, using 5 mm sodium chloride plates or 0.1 cm sodium chloride solution cell. Wavelengths of maximum absorbance (υmax) are quoted in cm^{-1}; the abbreviations s, m, w and br indicate strong, medium, weak and broad absorbances, respectively. Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Absorbance bands are reported in wavenumbers (cm^{-1}), and the following abbreviations are used to describe their appearance: w, weak; m, medium; s, strong; vs, very strong; br, broad. High and low resolution mass spectra were carried out, either by the EPSRC Mass Spectrometry Service Centre at Swansea or the departmental service at Cambridge, using chemical ionisation (CI) with ammonia gas or positive fast atom bombardment (FAB, matrix). For compounds of high molecular mass, where FAB measurements were not possible, low resolution mass spectra using positive fast ion bombardment (FIB, matrix) were recorded. Optical rotations were measured on a Perkin-Elmer 241 or a 1975-Optical Activity Ltd polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{20}$, concentration (*c* in g/100 ml) and solvent. Circular dichroism (CD) and ultra violet (UV) spectra were recorded on a Jasco J-720 spectropolarimeter at the Protein Engineering Unit, IRC, University of Cambridge, and reported as follows: CD max (in nm), solvent, $\Delta\varepsilon$, and concentration (in mM); UV max (in nm) and solvent. All optical measurements were carried out at a temperature of 20 °C. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected.

Flash column chromatography[24] was carried out on Merck Kieselgel 60 (230-400 mesh) under a positive pressure by means of a compressed-air line or a hand pump, using distilled solvents The procedure included the subsequent evaporation of solvents *in vacuo*. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualisation by ultraviolet and/or anisaldehyde dip.[25] Preparative normal phase high performance liquid chromatography (HPLC) was carried out using a Rainin Instrument Co. Inc. DYNAMAX 21.4 x 250 mm Macro-HPLC column prepacked with 8 micron irregular silica particles with a Gilson refractive index detector (model 131). Preparative reverse phase HPLC was carried out using a Rainin Instrument Co. Inc. DYNAMAX 21.4 x 250 mm HPLC column packed with 8 micron C_{18} bonded reverse phase silica particles, using UV_{270} detection with a Gilson model 111B detector. In both cases, a standard flow rate of 10 ml min^{-1} was used and retention times (t_R) were given in minutes from the point of injection. All solvents were vacuum-filtered and degassed prior to use. Chiral gas chromatography (GC) was performed on a HP 5790A series GC using a CYDEX-B column of 0.25 mm diameter and 25 m length with a flame ionization detector (FID) and helium as the carrier gas.

Reagents and solvents were purified by standard means. Dichloromethane (CH_2Cl_2), hexane, cyclohexane, acetonitrile (MeCN), toluene (PhMe) and methanol (MeOH) were distilled from calcium hydride (CaH_2) and stored under an argon atmosphere; tetrahydrofuran (THF) and diethyl ether (ether, Et_2O) were distilled from sodium wire/benzophenone and stored under an argon atmosphere; dimethyl sulphoxide (DMSO), triethylamine (Et_3N), diisopropylethylamine ($^iPr_2NEt$), 2,6-lutidine and pyridine (py) were distilled from and stored over calcium hydride. All other chemicals were used as received, except where otherwise noted in the experimental text. All extractive procedures were performed using distilled solvents. All experiments were performed under anhydrous conditions in an atmosphere of Ar, except where otherwise stated, using oven-dried apparatus under a stream of Ar, and employing standard techniques for handling air-sensitive materials.

(4*S*,5*S*,6*S*)-5,6-Epoxyhept-1-en-4-ol (17)[11b]

To a solution of the allylic alcohol **16**[10] (5.60 g, 50.0 mmol) and distilled L-(+)-diisopropyl tartrate (1.76 g, 7.5 mmol, 0.15 equiv) in dry CH_2Cl_2 (200 ml) at room temperature was added powdered, activated, 4Å molecular sieves (1.4 g). The solution was cooled to –20 °C and titanium (IV) isopropoxide (1.49 ml, 1.42 g, 5.0 mmol,

0.10 equiv) added. The mixture was stirred at –20 °C for 30 min, followed by the addition of *tert*-butyl hydroperoxide (4.45 ml of a 5.5 M solution in isooctane, 24.5 mmol, 0.49 equiv). The reaction mixture was maintained at –20 to –25 °C in the freezer for 20 h and the reaction was then quenched by addition of dimethylsulphide (3 ml), with stirring at room temperature overnight. The reaction mixture was then filtered through a sintered glass funnel and the filtrate concentrated *in vacuo*. The crude product mixture was separated by flash column chromatography (25% then 33% Et_2O/hexane) to give the resolved starting alcohol **16** (1.96 g, 35%) and the required epoxide (–)-**17** (2.76 g, 43%; 86% of theory), which was obtained in 96% ee as determined by ^1H NMR analysis of its derived (*R*)-MTPA ester; R_f = 0.26 (50% Et_2O/hexane); ^1H NMR δ (400 MHz, $CDCl_3$) 5.84 (1H, m, C<u>H</u>=CH_2), 5.13 (2H, m, CH=C<u>H</u>$_2$), 3.77 (1H, m, C<u>H</u>OH), 3.05 (1H, qd, *J* = 5.2, 2.3 Hz, MeC<u>H</u>(O)), 2.72 (1H, dd, *J* = 3.5, 2.3 Hz, CH(OH)C<u>H</u>(O)), 2.38 (1H, m, CH(OH)C<u>H</u>$_A$H$_B$), 2.27 (1H, m, CH(OH)CH$_A$<u>H</u>$_B$), 2.12 (1H, d, *J* = 2.5 Hz, O<u>H</u>), 1.30 (3H, d, *J* = 5.2 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 133.6, 118.1, 68.3, 61.3, 51.5, 38.1, 17.1.

(4*S*,6*S*)-1-Hepten-4,6-diol (18)

To a solution of epoxide (–)-**17** (2.46 g, 19.2 mmol) in dry THF (150 ml) at room temperature was added Red-al® (10.7 ml of a 70% solution in toluene, 38.4 mmol, 2 equiv) and the mixture stirred for 18 h at room temperature. The reaction mixture was poured into sodium potassium tartrate solution (50 ml, sat. aq.) and the layers separated, the aqueous layer extracted with Et_2O (3 x 50 ml) and the combined organic extracts washed with brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (50% Et_2O/CH_2Cl_2) to give **18** (2.00 g, 15.4 mmol, 80%) and byproduct **19** (77 mg, 4%).

18: R_f = 0.32 (50% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +20.7° (*c* 2.9, $CHCl_3$); IR (liquid film) 3353 (br m), 1641 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.81 (1H, m, C<u>H</u>=CH_2), 5.13 (2H, m, CH=C<u>H</u>$_2$), 4.15 (1H, m, MeC<u>H</u>(OH)), 3.99 (1H, m, C<u>H</u>(OH)CH_2CH=CH_2), 2.48 (2H, br s, 2 x O<u>H</u>), 2.25 (2H, m, C<u>H</u>$_2$CH=CH_2), 1.61 (2H, dd, *J* = 5.9, 5.7 Hz, CH(OH)C<u>H</u>$_2$CH(OH)), 1.23 (3H, d, *J* = 6.3 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 134.6, 118.3, 68.1, 65.4, 43.5, 41.9, 23.5; m/z (CI, NH_3) 148 (100, $[M+NH_4]^+$), 131 (35, MH^+), 95 (10%); HRMS (CI, NH_3) calc for $C_7H_{15}O_2$ (MH^+) 131.1072 found 131.1072.

19: R_f = 0.42 (50% Et_2O/CH_2Cl_2); ^1H NMR δ (250 MHz, $CDCl_3$) 5.52 (1H, m, C<u>H</u>=CH_2), 5.16 (2H, m, CH=C<u>H</u>$_2$), 3.57 (2H, m, 2 x C<u>H</u>OH), 2.31 (2H, m, C<u>H</u>$_2$CH=CH_2), 1.97 (2H, br s, 2 x OH), 1.49 (2H, m, MeC<u>H</u>$_2$), 0.99 (3H, t, *J* = 7.4 Hz, Me).

(2*S*,4*R*,6*R*)-2-Methyl-4-hydroxy-6-methoxytetrahydropyran (20A) and (2*S*,4*R*,6*S*)-2-Methyl-4-hydroxy-6-methoxytetrahydropyran (20B)

Diol **18** (414 mg, 3.18 mmol) was dissolved in MeOH (25 ml) and the solution cooled to –20 °C. Ozone in a stream of dry oxygen was bubbled through the solution for 10 min, followed by purging under a stream of argon. Dimethylsulphide (3 ml) was added and the mixture allowed to warm to room temperature and stirred for 16 h. The Me_2S and some of the MeOH was removed *in vacuo* and 1M HCl (3 drops) was added. The resulting mixture was stirred at room temperature for 3 h, after which time t.l.c. analysis indicated complete reaction. Solid $NaHCO_3$ was added to neutralise the acid, and the solvent removed *in vacuo*. The residue was extracted with CH_2Cl_2 (3 x 25 ml), and the extracts filtered through a pad of celite. Concentration of the filtrate *in vacuo* gave the crude product which contained DMSO. Elution through a short silica gel column (50% Et_2O/CH_2Cl_2) gave **20** (391 mg, 84%) as a mixture of anomers (1.7:1 by ^1H NMR). After standing overnight in the freezer, the product appeared as a white amorphous solid. For characterisation purposes, separation of the anomers was achieved by flash column chromatography (50% EtOAc/hexane).

20A: R_f = 0.23 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = –145.5° (*c* 2.8, $CHCl_3$); IR (liquid film) 3500 (br, m), 1720 cm^{-1}; ^1H NMR δ (400 MHz, $CHCl_3$) 4.78 (1H, d, *J* = 3.5 Hz, H_{27}), 4.01 (1H, m, H_{31}), 3.79 (1H, m, H_{29}), 3.27 (3H, s, OMe), 2.53 (1H, br s, OH), 2.00 (1H, m, H_{30eq}), 1.90 (1H, ddd, *J* = 12.4, 4.6, 2.3 Hz, H_{28eq}), 1.44 (1H, ddd, *J* = 12.4, 11.4, 3.5 Hz, H_{28ax}), 1.17 (4H, buried m + d, *J* = 6.4 Hz, H_{30ax}, Me_{32});

^{13}C NMR δ (100.6 MHz, $CDCl_3$) 99.1, 63.8, 63.6, 54.4, 42.4, 38.9, 21.3; m/z (CI, NH_3) 164 (10), 132 (20), 114 (25), 97 (100%); HRMS (CI, NH_3) calc for $C_7H_{18}NO_3$ ($[M+NH_4]^+$) 164.1287 found 164.1287.
20B: R_f = 0.15 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = –63.2° (*c* 0.4, $CHCl_3$) ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.27 (1H, dd, *J* = 9.7, 2.1 Hz, H_{27}), 3.79 (1H, m, H_{31}), 3.48 (3H, s, OMe), 3.45 (1H, m, H_{29}), 2.14 (1H, m, H_{28eq}), 1.90 (1H, m, H_{30eq}), 1.31 (1H, ddd, *J* = 11.9, 11.6, 9.7 Hz, H_{28ax}), 1.26 (3H, d, *J* = 6.2 Hz, Me_{32}), 1.16 (1H, ddd, *J* = 12.4, 11.2, 8.6 Hz, H_{30ax}); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 101.0, 68.0, 66.7, 56.3, 42.1, 40.5, 21.1.

(2*S*,4*R*,6*R*)-2-Methyl-4,6-dimethoxytetrahydropyran (15A) and (2*S*,4*R*,6*S*)-2-Methyl-4,6-dimethoxytetrahydropyran (15B)

Sodium hydride (1.34 g of 60% dispersion in oil, 33.4 mmol, 1.3 equiv) was washed under argon with dry hexane (2 x 10 ml) and suspended in dry THF (10 ml). Acetal **20** (3.90 g, 26.7 mmol, 1.0 equiv) was added dropwise *via* cannula in dry THF (7 ml + 2 x 2 ml washings) at room temperature. The mixture was stirred for 20 min before addition of methyl iodide (3.3 ml, 7.52 g, 53 mmol, 2.0 equiv). After 18 h, ethanol (0.5 ml) was added to quench excess sodium hydride, followed by dilution of the mixture with hexane. Solids were removed by filtration through a pad of celite and removal of the solvents *in vacuo* gave crude **15** (4.23 g, 99%). Kugelrohr distillation (b.p. 125 °C, 30 mm Hg) gave **15** (4.02 g, 25.1 mmol, 94%) as a mixture of anomers (1.5:1 by ^{1}H NMR). For characterisation purposes, separation of the anomers was achieved using flash column chromatography (25% EtOAc/hexane);
15A: R_f = 0.42 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –145.5° (*c* 2.8, $CHCl_3$); IR (liquid film) 1450, 1386, 1122, 1101 cm^{-1}; ^{1}H NMR δ (250 MHz, CD_2Cl_2) 4.79 (1H, d, *J* = 3.5 Hz, H_{27}), 3.78 (1H, dqd, *J* = 11.6, 6.3, 2.0 Hz, H_{31}), 3.57 (1H, dddd, *J* = 11.3, 11.2, 4.6, 4.6 Hz, H_{29}), 3.28 (3H, s, OMe), 3.27 (3H, s, OMe), 2.07 & 2.00 (1H + 1H, m, H_{28eq}/H_{30eq}), 1.35 (1H, ddd, *J* = 12.5, 11.3, 3.5 Hz, H_{28ax}), 1.16 (3H, d, *J* = 6.3 Hz, Me_{32}), 1.07 (1H, ddd, *J* = 11.8, 11.6, 11.2 Hz, H_{30ax}); ^{13}C NMR δ (62.9 MHz, CD_2Cl_2) 99.4, 72.6, 63.9, 55.2, 54.5, 39.5, 36.1, 21.5.
15B: R_f = 0.33 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –63.2° (*c* 0.4, $CHCl_3$); IR (liquid film) 1447, 1390, 1148, 1105 cm^{-1}; ^{1}H NMR δ (400 MHz, CD_2Cl_2) 4.24 (1H, dd, *J* = 9.7, 2.1 Hz, H_{27}), 3.43 (3H, s, OMe), 3.40 (1H, m), 3.34 (1H, m), 3.30 (3H, s, OMe), 2.15 (1H, dddd, *J* = 11.9, 4.2, 2.1, 1.8 Hz, H_{28eq}), 1.94 (1H, dddd, *J* = 12.3, 4.2, 2.1, 1.8 Hz, H_{30eq}), 1.23 (3H, d, *J* = 6.2 Hz, Me_{32}), 1.15 (1H, ddd, *J* = 11.9, 11.5, 9.7 Hz, H_{28ax}), 1.03 (1H, ddd, *J* = 12.3, 11.3, 11.2 Hz, H_{30ax}); ^{13}C NMR δ (100.6 MHz, CD_2Cl_2) 101.5, 75.6, 68.2, 56.2, 55.5, 39.1, 37.6, 21.3; m/z (CI, NH_3) 146 (35, $[M+NH_4–MeOH]^+$), 114 (100), 97 (80%); HRMS (CI, NH_3) calc for $C_8H_{18}NO_3$ ($[M+NH_4–H_2]^+$) 176.1287 found 176.1287.

(2*S*,4*R*,6*S*)-2-Methyl-4-methoxy-6-allyltetrahydropyran (23)

To a solution of acetal **15** (mixture of anomers) (130 mg, 0.813 mmol) in dry acetonitrile (8 ml) under argon at –20 °C was added allyltrimethylsilane (212 µl, 152 mg, 1.34 mmol, 1.6 equiv), followed by trimethylsilyltriflate (17 µl, 20 mg, 0.09 mmol, 0.1 equiv). The reaction mixture was stirred for 2 min and then poured into $NaHCO_3$ solution (2 ml, sat. aq.). The resulting solution was extracted with Et_2O (3 x 15 ml) and the combined organic extracts were washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (25% Et_2O/hexane) gave **23** (132 mg, 0.78 mmol, 96%); R_f = 0.48 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –62.3 (*c* 3.8, $CHCl_3$); IR (liquid film) 3076 (s), 1642 (m) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.75 (1H, dddd, *J* = 17.1, 10.0, 7.1, 7.0 Hz, C$\underline{H}$=CH_2), 5.05 (1H, d, *J* = 17.1 Hz, CH=C$\underline{H}_A$$H_B$), 5.03 (1H, d, *J* = 10.0 Hz, CH=C$H_A$$\underline{H}_B$), 4.05 (1H, m, H_{27}), 3.73 (1H, dqd, *J* = 9.4, 6.2, 2.9 Hz, H_{31}, NOE enhancements at δ 2.43, 2.19, 1.95), 3.50 (1H, m, H_{29}, NOE enhancements at δ 2.43, 2.19, 1.95, 1.84), 3.30 (3H, s, OMe), 2.43 (1H, m, C$\underline{H}_A$$H_B$CH=C, NOE enhancements at δ 5.75, 5.05, 5.03, 3.73, 3.50, 2.19), 2.19 (1H, m, C$H_A$$\underline{H}_B$CH=C, NOE enhancements at δ 5.75, 5.05, 5.03, 3.73, 3.50, 2.43), 1.95 (1H, m, H_{30eq}), 1.84 (1H, m, H_{28eq}), 1.52 (1H, ddd, *J* = 12.9, 10.2, 5.4 Hz, H_{28ax}), 1.19 (1H,

buried m, H_{30ax}), 1.18 (3H, d, J = 6.2 Hz, Me_{32}); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 135.0, 117.0, 72.9, 71.4, 65.1, 55.2, 38.4, 36.7, 33.7, 21.6; m/z (CI, NH_3) 171 (100, MH^+), 139 (20), 97 (20%); HRMS (CI, NH_3) calc for $C_{10}H_{19}O_2$ (MH^+) 171.1385 found 171.1385.

((2*S*,4*R*,6*R*)-2-Methyl-4-methoxytetrahydropyran-6-yl)-ethanal (24)

Allyl pyranoside **23** (327 mg, 1.92 mmol) was dissolved in 3:1 CH_2Cl_2:MeOH (20 ml) and the solution cooled to –78 °C. Solid $NaHCO_3$ (1 g) was added then ozone in a stream of oxygen was bubbled through until the solution turned blue (10 min). Argon was bubbled through for 2 min, then dimethylsulphide (1.5 ml) was added and the mixture allowed to warm to room temperature with stirring for 16 h. The solvent and excess Me_2S were removed *in vacuo* and the residue washed with CH_2Cl_2 (5 x 10 ml). The combined washings were filtered and concentrated *in vacuo*. Flash column chromatography (50% Et_2O/hexane) gave **24** as a colourless oil (324 mg, 1.88 mmol, 98%); R_f = 0.14 (50% Et_2O/hexane); $[\alpha]_D^{20}$ = –30.4° (*c* 9.3, $CHCl_3$); IR (liquid film) 1710 cm^{-1} (s); ^1H NMR δ (250 MHz, $CDCl_3$) 9.74 (1H, dd, J = 3.4, 1.6 Hz, C<u>H</u>O), 4.68 (1H, m, H_{27}), 3.76 (1H, dqd, J = 9.4, 6.3, 3.2 Hz, H_{31}), 3.49 (1H, m, H_{29}), 3.32 (3H, s, OMe), 2.80 (1H, ddd, J = 15.9, 9.2, 3.4 Hz, C<u>H</u>$_A$H$_B$CHO), 2.47 (1H, ddd, J = 15.9, 5.3, 1.6 Hz, CH$_A$<u>H</u>$_B$CHO), 1.97 (1H, m, H_{30eq}), 1.80 (1H, dddd, J = 13.2, 4.2, 4.1, 1.5 Hz, H_{28eq}), 1.68 (1H, ddd, J = 13.2, 9.2, 5.2 Hz, H_{28ax}), 1.25 (1H, m, H_{30ax}), 1.21 (3H, d, J = 6.3 Hz, Me_{32}); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 200.8, 72.8, 66.4, 65.9, 56.5, 46.5, 37.6, 34.5, 21.3; m/z (CI, NH_3) 190 (100, $[M+NH_4]^+$), 173 (100, MH^+), 141 (45), 114 (20), 97 (40%); HRMS (CI, NH_3) calc for $C_9H_{20}NO_3$ ($[M+NH_4]^+$) 190.1443 found 190.1443.

(*E*)-2-Methyl-5-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-but-2-enal (14)

α-Formylethylidenetriphenylphosphorane (280 mg, 0.87 mmol) and aldehyde **24** (100 mg, 0.58 mmol) were dissolved in dry toluene (2 ml). The resulting yellow mixture was heated under reflux for 3 h then allowed to cool. Hexane (20 ml) was added and the mixture cooled to 0 °C, then filtered and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O/hexane) gave 88.3 mg of **14** (72%) and 14.5 mg of **25** (12%).

14: R_f = 0.18 (66% Et_2O/hexane); $[\alpha]_D^{20}$ = –5.7° (*c* 1.0, $CHCl_3$); IR (liquid film) 2690, 1660 (s), 1630 cm^{-1} (s); ^1H NMR δ (250 MHz, $CDCl_3$) 9.42 (1H, s, H_{23}), 6.55 (1H, ddq, J = 7.1, 7.1, 1.0 Hz, H_{25}), 4.22 (1H, m, H_{27}), 3.78 (1H, dqd, J = 9.3, 6.2, 3.0 Hz, H_{31}), 3.56 (1H, m, H_{29}), 3.34 (3H, s, OMe), 2.75 (1H, m, H_{26A}), 2.47 (1H, m, H_{26B}), 1.99 (1H, m, H_{30eq}), 1.83 (1H, dddd, J = 13.1, 4.2, 4.2, 1.6 Hz, H_{28eq}), 1.76 (3H, d, J = 1.0 Hz, $C_{24}Me$), 1.66 (1H, ddd, J = 13.1, 9.5, 5.2 Hz, H_{28ax}), 1.26 (1H, m, H_{30ax}), 1.23 (3H, d, J = 6.2 Hz, Me_{32}); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 195.1, 150.5, 140.4, 72.9, 70.2, 65.7, 55.5, 37.7, 34.5, 32.1, 21.4, 9.4; m/z (CI, NH_3) 230 (32, $[M+NH_4]^+$), 213 (28, MH^+), 201 (100), 114 (25), 97 (50%); HRMS (CI, NH_3) calc for $C_{12}H_{24}NO_3$ ($[M+NH_4]^+$) 230.1756 found 230.1756.

25: R_f = 0.31 (50% Et_2O/hexane); IR (liquid film) 2680, 1665 (s), 1635 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 9.42 (1H, s, C<u>H</u>O, NOE enhancement at δ 6.59), 6.59 (1H, dd, J = 7.2, 7.1 Hz, C<u>H</u>=CMe, NOE enhancements at δ 9.42, 3.45), 3.52–3.29 (3H, m, H_{31}, H_{29}, H_{27}), 3.34 (3H, s, OMe), 2.56 (2H, m, H_{26}), 1.99 (2H, m, H_{30eq}, H_{28}), 1.74 (3H, s, C=C<u>Me</u>, NOE enhancement at δ 9.42), 1.23 (3H, d, J = 6.2 Hz, Me_{32}), 1.13 (1H, m, H_{30ax}); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 196.1, 150.2, 140.6, 76.3, 74.1, 71.9, 55.3, 39.2, 37.1, 35.6, 21.7, 10.7.

((2*S*,4*R*,6*S*)-2-Methyl-4-methoxytetrahydropyran-6-yl)-ethanal (26)

To a 0 °C solution of enal **25** (0.73 g, 3.44 mmol) in dry THF (25 ml) was added diisobutylaluminium hydride (8.6 ml, 1 M solution in hexane, 8.6 mmol) dropwise. The resulting solution was stirred at 0 °C for 30 min before quenching with MeOH (5 ml). Water (30 ml) and Et_2O (30 ml) were added and the mixture filtered through a pad of celite. The aqueous layer was extracted with Et_2O (30 ml) and the combined organic phases washed with brine (30 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (50% Et_2O/hexane) gave ((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-but-2-en-1-ol (0.39 g, 53%). The

foregoing alcohol (0.39 g, 1.82 mmol) was dissolved in 3:1 CH_2Cl_2/MeOH (40 ml) and solid $NaHCO_3$ (0.12 g) was added. The mixture was cooled to –78 °C and ozone in a stream of oxygen was bubbled through for 10 min. Triphenylphosphine (0.72 g) was added and the reaction mixture allowed to warm to room temperature and stirred for 1 h The mixture was then cooled to 0 °C, the $NaHCO_3$ was filtered off and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% Et_2O/hexane) to give aldehyde **26** as a colourless oil (157 mg, 50%); R_f = 0.25 (66% Et_2O/hexane); $[\alpha]_D^{20}$ = +12.6° (*c* 2.1, $CHCl_3$); IR (liquid film) 2690, 1660 (s), 1630 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.77 (1H, dd, *J* = 2.1, 1.9 Hz, C<u>H</u>O), 3.83 (1H, m, H_{27}, NOE enhancements at δ 3.47, 3.38, 2.65, 2.48), 3.47 (1H, m, H_{31}), 3.38 (1H, m, H_{29}), 3.32 (3H, s, OMe), 2.65 (1H, ddd, *J* = 16.6, 7.7, 2.4 Hz, C<u>H</u>$_A$H$_B$CHO), 2.48 (1H, ddd, *J* = 16.6, 4.8, 1.7 Hz, CH$_A$<u>H</u>$_B$CHO), 2.00 (2H, m, H_{28eq}, H_{30eq}), 1.18 (3H, d, *J* = 6.2 Hz, Me_{32}, NOE enhancement at δ 3.47), 1.10 (2H, m, H_{28ax}, H_{30ax}); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 200.8, 76.0, 71.8, 70.5, 55.1, 49.4, 38.9, 37.0, 21.5.

(*S*)-1-Benzyloxy-2-methylpentan-3-one (13)

To a stirred solution of (*S*)-methyl 3-hydroxy-2-methylpropanoate (Aldrich, 16.5 ml, 150 mmol) in CH_2Cl_2 (375 ml) was added a solution of benzyl-2,2,2-trichloroacetimidate (30.7 ml, 165 mmol) in cyclohexane (750 ml). Triflic acid (5.31 ml, 60.0 mmol) was added dropwise, whereupon a white solid (trichloroacetamide) precipitated out. The mixture was stirred at room temperature for 18 h during which time it became deep yellow in colour. The precipitate was allowed to settle and the supernatant liquor decanted into a separating funnel. The white crystalline residue was washed with hexane (2 x 150 ml) and the washings combined with the supernatant liquor. The combined organic extracts were washed with $NaHCO_3$ (300 ml, sat. aq.) and then brine (300 ml), before being dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was triturated with hexane (2 x 300 ml), whereupon the remaining trichloroacetamide precipitated out. The combined washings, which contained some dibenzyl ether, were then concentrated *in vacuo* and the crude product purified by flash chromatography (15% EtOAc/hexane) to give (*S*)-methyl-3-benzyloxy-2-methylpropanoate as a colourless oil, (26.4 g, 0.127 mol, 84%); R_f = 0.35 (15% EtOAc/hexane); $[\alpha]_D^{20}$ = +12.1° (*c* 10.0, $CHCl_3$); IR (liquid film) 1730 cm^{-1} (s); ^1H NMR δ (250 MHz, $CDCl_3$) 7.37–7.21 (5H, m, Ph), 4.51 (2H, s, C<u>H</u>$_2$Ph), 3.69 (3H, s, OMe), 3.65 (1H, dd, *J* = 9.0, 7.3 Hz, C<u>H</u>$_A$H$_B$OBn), 3.47 (1H, dd, *J* = 9.0, 5.9 Hz, CH$_A$<u>H</u>$_B$OBn), 2.78 (1H, dqd, *J* = 7.3, 7.1, 5.9 Hz, C<u>H</u>Me), 1.17 (3H, d, *J* = 7.1 Hz, CH<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 175.3, 138.1, 128.4, 127.6, 73.1, 71.9, 51.7, 40.2, 14.0; m/z 226 ($[M+NH_4]^+$ 100), 209 ($[M+H]^+$ 11), 108 (4), 91 (3%); HRMS (CI, NH_3) $[M+NH_4]^+$ found 226.1450, calc. for $C_{12}H_{20}NO_3$ requires 226.1443.

N,O-Dimethylhydroxylamine hydrochloride (6.82 g, 70.0 mmol) in dry toluene (60 ml) was cooled to 0 °C and trimethylaluminium (35.0 ml, 70.0 mmol, 2 M solution in hexane) added cautiously (**care**! gas evolution) with magnetic stirring. After completion of the addition (30 min), the reaction mixture was allowed to warm to room temperature for 15 min and then recooled to 0 °C. The mixture was diluted with more toluene (90 ml) and (*S*)-methyl-3-benzyloxy-2-methylpropanoate (7.27 g, 35.0 mmol) was added as a solution in toluene (130 ml total) *via* cannula. After heating at 70–80 °C for 2 h, the mixture was transferred *via* cannula into tartaric acid solution (200 ml, 1 M aqueous). This mixture was stirred vigorously for 1 h, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 150 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/CH_2Cl_2) to give (*S*)-3-benzyloxy-*N*-methoxy-*N*,2-dimethylpropanamide as a colourless oil, (5.83 g, 24.6 mmol, 70%); R_f = 0.33 (10% Et_2O/CH_2Cl_2); IR (liquid film) 1650 cm^{-1} (s); $[\alpha]_D^{20}$ = +5.0° (*c* 3.9, $CHCl_3$); ^1H NMR δ (250 MHz, $CDCl_3$) 7.36–7.25 (5H, m, Ph), 4.55 (1H, d, *J* = 12.1 Hz, OC<u>H</u>$_A$H$_B$Ph), 4.46 (1H, d, *J* = 12.1 Hz, OCH$_A$<u>H</u>$_B$Ph), 3.71 (1H, dd, *J* = 8.7, 8.7 Hz, C<u>H</u>$_A$H$_B$OBn), 3.69 (3H, s, OMe), 3.42 (1H, dd, *J* = 8.7, 5.8 Hz, CH$_A$<u>H</u>$_B$OBn), 3.23 (1H, m, C<u>H</u>Me), 3.20 (3H, s, NMe), 1.10 (3H, d, *J* =

6.9 Hz, CHMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 175.9, 138.4, 128.3, 127.5 (2C), 73.2, 72.6, 61.5, 35.6, 32.1, 14.2; m/z 238 ([M+H]$^+$ 100), 208 (15), 148 (11), 118 (4), 108 (4), 91 (2%); HRMS (CI, NH_3), calc. for $C_{13}H_{20}NO_3$ 238.1443 [M+H]$^+$, found 238.1448.

To a stirred solution of (*S*)-3-benzyloxy-*N*-methoxy-*N*,2-dimethylpropanamide (5.83 g, 24.6 mmol) in dry THF (400 ml) was added, dropwise, ethyl magnesium bromide (1 M solution in THF, 49.2 ml, 49.2 mmol) at 0 °C. The reaction was complete within 1.5 h and was quenched by careful addition of ammonium chloride solution (60 ml, sat. aq.). The layers were separated and the aqueous phase was extracted with ether (3 x 150 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (15% EtOAc/hexane) gave **13** as a colourless oil, (4.14 g, 82 %); R_f = 0.35 (15% EtOAc/hexane); $[\alpha]_D^{20}$ = +25.8° (*c* 8.2, $CHCl_3$); IR (liquid film) 1705 cm^{-1} (s); ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.37–7.23 (5H, m, Ph), 4.50 (1H, d, *J* = 12.3 Hz, OC$\underline{H}_A$H$_B$Ph), 4.45 (1H, d, *J* = 12.3 Hz, OCH$_A\underline{H}_B$Ph), 3.62 (1H, dd, *J* = 9.0, 7.9 Hz, C$\underline{H}_A$H$_B$OBn), 3.45 (1H, dd, *J* = 9.0, 5.5 Hz, CH$_A\underline{H}_B$OBn), 2.88 (1H, dqd, *J* = 7.9, 7.1, 5.5 Hz, C$\underline{H}$Me), 2.51 (2H, q, *J* = 7.3 Hz, C$\underline{H}_2$Me), 1.06 (3H, d, *J* = 7.1 Hz, CH$\underline{Me}$), 1.04 (3H, t, *J* = 7.3 Hz, CH$_2\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.8, 138.1, 128.4, 127.6, 127.5, 73.2, 72.4, 46.2, 35.3, 13.6, 7.5; m/z 224 ([M+NH_4]$^+$ 100), 207 (85 [M+H]$^+$), 129 (20), 91 (100), 57 (20%); HRMS (CI, NH_3) calc. for $C_{13}H_{22}NO_2$ 224.1651 [M+NH_4]$^+$, found 224.1659.

(*E*)-(2*S*,4*S*,5*R*)-1-Benzyloxy-5-hydroxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-oct-6-en-3-one (12)

To a stirred solution of triethylamine (0.11 ml, 0.80 mmol) and dicyclohexylboron chloride (0.162 ml, 0.75 mmol) in dry Et_2O (0.5 ml) at 0 °C was added ketone (*S*)-**13** (103 mg, 0.50 mmol) dropwise (neat, washing through with 0.2 ml Et_2O). The mixture was stirred at 0 °C for 2 h, before enal **14** (106 mg, 0.50 mmol) was added at –78 °C. After a further 2 h, the reaction mixture was left to stand at –20 °C under an argon atmosphere for 12 h. To work up, pH7 buffer (4 ml) was added and the layers separated. The aqueous layer was extracted with Et_2O (3 x 20 ml) and the combined organic extracts evaporated *in vacuo*. The crude mixture was dissolved in methanol (3 ml) and pH7 buffer (3 ml) was added to give a white suspension, which was cooled to 0 °C before adding hydrogen peroxide solution (1.5 ml, 30% aq.). This mixture was stirred for 1 h before diluting with distilled water (40 ml) and extracting with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with $NaHCO_3$ (40 ml, sat. aq.) and brine (20 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give **12** as a colourless oil, (175 mg, 84%); R_f = 0.27 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = –18.4° (*c* 2.0, $CHCl_3$); IR (liquid film) 3420 (br), 1735 (m), 1710 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ph), 5.45 (1H, dd, *J* = 6.8, 6.6 Hz, H_{25}), 4.52 (1H, d, *J* = 12.1 Hz, OC$\underline{H}_A$H$_B$Ph), 4.47 (1H, d, *J* = 12.1 Hz, OCH$_A\underline{H}_B$Ph), 4.18 (1H, dd, *J* = 9.3, 2.7 Hz, H_{23}), 4.05 (1H, m, H_{27}), 3.72 (1H, m, H_{31}), 3.68 (1H, dd, *J* = 8.9, 8.7 Hz, H_{19A}), 3.53 (1H, m, H_{29}), 3.45 (1H, dd, *J* = 8.9, 5.0 Hz, H_{19B}), 3.34 (3H, s, OMe), 3.10 (1H, dqd, *J* = 8.7, 7.0, 5.0 Hz, H_{20}), 2.88 (1H, dq, *J* = 9.3, 7.1 Hz, H_{22}), 2.62 (1H, s, OH), 2.45 (1H, m, H_{26A}), 2.21 (1H, m, H_{26B}), 1.99 (1H, m, H_{30eq}), 1.85 (1H, m, H_{28eq}), 1.63 (3H, s, C_{24}Me), 1.57 (1H, ddd, *J* = 12.9, 10.3, 5.5 Hz, H_{28ax}), 1.20 (1H, m, H_{30ax}), 1.19 (3H, d, *J* = 6.2 Hz, Me_{32}), 1.06 (3H, d, *J* = 7.0 Hz, C_{20}Me), 0.92 (3H, d, *J* = 7.1 Hz, C_{22}Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.2, 137.8, 136.1, 128.4, 127.7, 127.6, 125.6, 80.0, 73.3, 73.1, 72.3, 71.8, 65.2, 55.3, 49.5, 45.8, 38.6, 34.0, 30.5, 21.7, 13.7, 13.6, 11.0; m/z (CI, NH_3) 436 (15, [M+NH_4]$^+$), 401 (25), 369 (25), 207 (70), 181 (20), 129 (22), 114 (25), 97 (100%); HRMS (CI, NH_3) calc for $C_{25}H_{42}O_5N$ 436.3063 ([M+NH_4]$^+$), found 436.3063.

(*E*)-(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-oct-6-en-3,5-diol (28)

A solution of tetramethylammonium triacetoxyborohydride (1.52 g, 5.77 mmol) in anhydrous acetonitrile (4 ml) and anhydrous acetic acid (4 ml) under argon was stirred at room temperature for 1 h. This solution was cooled to –25 °C and a solution of aldol product **12** (201 mg, 0.48 mmol) in anhydrous acetonitrile (4 ml) was added *via* cannula. The reaction mixture was stirred at –25 °C for 1 h, before being left to stand at –20 °C for 18 h. The reaction was quenched by addition of sodium potassium tartrate solution (10 ml, 0.5 M, aq.) with vigorous stirring for 1 h, followed by extraction with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were washed with $NaHCO_3$ solution (20 ml, sat. aq.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (66% EtOAc/hexane) gave **28** as a colourless oil (185 mg, 91%); R_f = 0.36 (66% EtOAc/hexane); $[\alpha]_D^{20}$ = +1.7° (*c* 1.8, $CHCl_3$); IR (liquid film) 3600-3200 (br), 1740 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.35–7.27 (5H, m, Ph), 5.51 (1H, dd, *J* = 6.7, 6.7 Hz, H_{25}), 4.52 (1H, d, *J* = 11.8 Hz, $OC\underline{H}_AH_BPh$), 4.47 (1H, d, *J* = 11.8 Hz, $OCH_A\underline{H}_BPh$), 4.02 (3H, m), 3.76 (2H, m), 3.52 (3H, m), 3.31 (3H, s, OMe), 3.03 (1H, br s, OH), 2.39 (1H, m, H_{26A}), 2.29 (1H, m, H_{26B}), 1.97 (2H, m), 1.86 (1H, m), 1.74 (1H, m), 1.58 (3H, s, $C_{24}Me$), 1.52 (1H, m), 1.19 (4H, d, *J* = 6.1 Hz, Me_{32} + 1H, m), 0.89 (3H, d, *J* = 7.0 Hz), 0.74 (3H, d, *J* = 6.9 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 137.8, 137.5, 128.4, 127.8, 127.6, 122.7, 79.9, 76.7, 75.6, 73.4, 73.1, 72.0, 65.2, 55.2, 38.6, 36.4, 35.6, 33.7, 30.4, 21.7, 13.1, 12.4, 9.8; m/z (CI, NH_3) 403 (30, MH^+-H_2O), 225 (100), 196 (15), 97 (35%); HRMS (CI, NH_3) calc for $C_{25}H_{39}O_4$ ($M+H^+-H_2O$) 403.2848, found 403.2848.

(*E*)-(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,5-isopropylidenedioxyoct-6-ene (29)

Diol **28** (37 mg, 0.088 mmol) was dissolved in dry CH_2Cl_2 (1 ml) and dry 2,2-dimethoxypropane (1 ml) under argon. One crystal of pyridinium *p*-toluene sulphonate was added and the reaction mixture stirred at room temperature for 2 h. The reaction was quenched with sodium bicarbonate solution (1 ml, sat. aq.), the layers were separated, and the aqueous layer extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (25% EtOAc/hexane) gave **29** as a colourless oil (33 mg, 81%); R_f = 0.26 (25% EtOAc/hexane); ^1H NMR δ (400 MHz, C_6D_6) 7.36 (2H, d, *J* = 7.2 Hz, Ph, *ortho*), 7.22 (2H, m, Ph, *meta*), 7.14 (1H, m, Ph, *para*), 5.53 (1H, dd, *J* = 7.2, 6.7 Hz, H_{25}), 4.43 (1H, d, *J* = 12.0 Hz, $OC\underline{H}_AH_BPh$), 4.39 (1H, d, *J* = 12.0 Hz, $OCH_A\underline{H}_BPh$), 4.09 (1H, m, H_{27}), 3.94 (1H, dd, *J* = 10.8, 4.4 Hz, H_{21}), 3.85 (1H, d, *J* = 7.5 Hz, H_{23}), 3.61 (3H, m, H_{19}, H_{31}), 3.33 (1H, m, H_{29}), 3.14 (3H, s, OMe), 2.39 (1H, m, H_{26A}), 2.14 (1H, m, H_{26B}), 1.95 (2H, m, H_{20}, H_{22}), 1.79 (3H, s, $C_{23}Me$), 1.77 (2H, m, H_{30eq}, H_{28eq}), 1.64 (1H, ddd, *J* = 13.1, 9.8, 5.3 Hz, H_{28ax}), 1.44 (3H, s, $O_2C\underline{Me}_AMe_B$), 1.43 (3H, s, $O_2CMe_A\underline{Me}_B$), 1.25 (1H, m, H_{30ax}), 1.23 (3H, d, *J* = 6.3 Hz, Me_{32}), 1.02 (3H, d, *J* = 6.7 Hz), 0.96 (3H, d, *J* = 7.1 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.8, 135.6, 128.2, 127.5, 127.3, 123.7, 100.7, 81.4, 73.2, 73.1, 72.4, 71.8, 70.1, 65.1, 55.3, 38.5, 35.6, 34.0, 33.9, 30.4, 24.7, 23.8, 21.7, 13.5, 12.1, 11.4.

(*E*)-(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,5-di-*tert*-butylsilylenedioxyoct-6-ene (30)

To a solution of diol **28** (55.2 mg, 0.131 mmol) in dry CH_2Cl_2 (0.1 ml) at room temperature was added 2,6-lutidine (0.46 ml, 0.40 mmol) followed by di-*tert*-butylsilylbistriflate (0.72 ml, 0.20 mmol). The resulting mixture was stirred for 16 h, before being diluted with CH_2Cl_2 (2 ml) and quenched with $NaHCO_3$ solution (1 ml, sat. aq.). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 ml). The combined organic extracts were washed with brine (2 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc/hexane) to give **30** as a colourless oil (63.5 mg, 86%); R_f = 0.41 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = –36.9° (*c* 2.6, $CHCl_3$); IR (liquid film) 1450 (m) cm^{-1}; ^1H

NMR δ (400 MHz, $CDCl_3$) 7.33–7.22 (5H, m, Ph), 5.37 (1H, dd, J = 6.9, 6.9 Hz, H_{25}), 4.53 (1H, d, J = 11.9 Hz, $OC\underline{H}_AH_BPh$), 4.48 (1H, d, J = 11.9 Hz, $OCH_A\underline{H}_BPh$), 4.16 (1H, d, J = 4.8 Hz, H_{23}), 4.05 (1H, m, H_{27}), 4.00 (1H, m, H_{21}), 3.73 (1H, m, H_{31}), 3.71 (1H, m, H_{19A}), 3.54 (1H, m, H_{29}), 3.48 (1H, m, H_{19B}), 3.32 (3H, s, OMe), 2.39 (1H, m, H_{26A}), 2.22 (1H, m, H_{26B}), 1.97 (1H, m, H_{30eq}), 1.94 (1H, m, H_{22}), 1.90 (1H, m, H_{20}), 1.88 (1H, m, H_{28eq}), 1.65 (3H, s, $C_{24}Me$), 1.54 (1H, ddd, J = 12.8, 10.3, 5.5 Hz, H_{28ax}), 1.20 (1H, m, H_{30ax}), 1.18 (3H, d, J = 6.2 Hz, Me_{32}), 1.03 (9H, s, ^tBu_A), 1.02 (9H, s, ^tBu_B), 0.98 (3H, d, J = 7.3 Hz, $C_{22}Me$), 0.94 (3H, d, J = 6.8 Hz, $C_{20}Me$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 139.1, 138.8, 128.2, 127.6, 127.3, 120.8, 83.5, 74.2, 73.2, 73.1, 72.4, 71.9, 65.2, 55.3, 38.7, 38.1, 37.0, 33.8, 30.3, 28.1, 27.7, 22.1, 21.8, 21.7, 14.3, 13.6, 11.9; m/z (CI, NH_3) 561 (15), 337 (55), 225 (20), 204 (15), 129 (30), 108 (40), 97 (100%); HRMS (CI, NH_3) calc for $C_{33}H_{57}O_5Si$ ($[M+H]^+$) 561.3975 found 561.3975.

(2*S*,3*S*,4*R*,5*S*,6*S*,7*S*)-1-Benzyloxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxy-tetrahydropyran-6-yl)-3,5-di-*tert*-butylsilylenedioxyoctan-7-ol (31)

To a solution of alkene **30** (237 mg, 0.423 mmol) in dry THF (2 ml) at room temperature was added a solution of thexyl borane (1.7 ml, 0.5 M in THF, 0.85 mmol). After being stirred at 0 °C for 2 h, then at room temperature for 1 h, the mixture was recooled to 0 °C and hydrogen peroxide solution (2.5 ml, 30% aq.) was added dropwise, followed by sodium hydroxide solution (4 ml, 10% aq.). The mixture was allowed to warm to room temperature and stirred for 50 min, before being quenched with water (100 ml). The resulting mixture was extracted with EtOAc (3 x 50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc/hexane) to give **31** as a colourless oil (197 mg, 80%); R_f = 0.28 (40% EtOAc/Hexane); $[\alpha]_D^{20}$ = –45.3° (*c* 2.2, $CHCl_3$); IR (liquid film) 3600–3300 (br) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.34–7.27 (5H, m, Ph), 4.54 (1H, d, J = 11.9 Hz, $OC\underline{H}_AH_BPh$), 4.47 (1H, d, J = 11.9 Hz, $OCH_A\underline{H}_BPh$), 4.41 (1H, m), 4.08 (1H, m), 4.03 (1H, m), 3.75 (1H, m), 3.68 (2H, m), 3.55 (2H, m), 3.34 (3H, s, OMe), 3.12 (1H, br, OH), 2.00-1.85 (5H, m), 1.65 (2H, m), 1.33 (1H, m), 1.23 (1H, m), 1.20 (3H, d, J = 6.2 Hz), 1.08 (3H, d, J = 7.3 Hz, Me_{32}), 1.06 (9H, s, ^tBu_A), 1.03 (9H, s, ^tBu_B), 0.93 (3H, d, J = 6.8 Hz), 0.85 (3H, d, J = 6.7 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.8, 128.2, 127.6, 127.3, 83.6, 73.3, 73.1, 72.6, 72.4, 69.4, 68.6, 65.1, 55.3, 45.1, 38.7, 37.1, 36.4, 35.1, 33.5, 28.4, 27.8, 22.0, 21.9, 21.7, 13.9, 13.6, 11.2; m/z (CI, NH_3) 579 (50), 108 (57), 91 (100), 58 (56%); HRMS (CI, NH_3) calc for $C_{33}H_{59}O_6Si$ ($[M+H]^+$) 579.4081, found 579.4081.

(2*S*,3*S*,4*S*,5*S*,6*S*)-1-Benzyloxy-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxy-tetrahydropyran-6-yl)-3,5-di-*tert*-butylsilylenedioxyoctane (33)

Alcohol **31** (483 mg, 0.832 mmol) was dissolved in dry THF (2.5 ml) and solid thiocarbonyldiimidazole (330 mg, 1.66 mmol) was added. The resulting mixture was stirred at 60 °C for 16 h, allowed to cool, and the solvent removed *in vacuo*. Purification using a short silica gel column (50% EtOAc/hexane) gave the thiocarbonylimidazolide **32** as a white foam (524 mg, 91%); $[\alpha]_D^{20}$ = –5.7° (*c* 4.5, $CHCl_3$); IR ($CHCl_3$) 1470, 1395 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 8.33 (1H, s, imid), 7.62 (1H, s, imid), 7.30-7.20 (5H, m, Ph), 7.00 (1H, s, imid), 6.26 (1H, ddd, J = 9.0, 4.0, 4.0 Hz, H_{25}), 4.53 (1H, d, J = 11.8 Hz, $OC\underline{H}_AH_BPh$), 4.45 (1H, d, J = 11.8 Hz, $OCH_A\underline{H}_BPh$), 4.17 (1H, m, H_{27}), 4.01 (1H, dd, J = 10.0, 2.6 Hz, H_{21}), 3.72 (1H, m, H_{31}), 3.66 (1H, dd, J = 8.5, 3.0 Hz, H_{19A}), 3.61 (1H, dd, J = 10.0, 2.4 Hz, H_{23}), 3.50 (2H, m, H_{19B}, H_{29}), 3.31 (3H, s, OMe), 2.43 (1H, m), 2.27 (1H, m), 1.93 (1H, m), 1.85 (1H, m), 1.77 (1H, m), 1.63 (3H, m), 1.24 (1H, m), 1.13 (3H, d, J = 6.2 Hz, Me_{32}), 1.08 (9H, s, ^tBu_A), 1.07 (3H, buried d, Me), 1.05 (9H, s, ^tBu_B), 0.91 (3H, d, J = 6.9 Hz, Me), 0.90 (3H, d, J = 7.0 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 183.0, 138.6, 136.5, 130.5, 128.2, 127.6, 127.3, 81.9, 81.5, 73.0, 72.2, 72.1, 67.9, 65.0, 55.2, 41.2, 38.6, 37.0, 36.7, 34.6, 28.6, 28.3, 27.6, 22.2, 22.0, 21.8, 14.1, 13.5, 10.2; m/z (FAB) 689 (80, MH^+), 561 (100), 377 (80), 271 (75), 229 (100%); HRMS (FAB) calc for $C_{37}H_{61}O_6N_2SSi$ ($[M+H]^+$) 689.4019, found 689.3974.

To a refluxing solution of **32** (467 mg, 0.679 mmol) in dry toluene (10 ml) was added tri-*n*-butyltin hydride (1.98 g, 6.79 mmol). The resulting solution was refluxed for 30 min then allowed to cool. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (10% EtOAc/hexane) to give **33** as a colourless oil (367 mg, 96%); R_f = 0.29 (15% EtOAc/hexane); $[\alpha]_D^{20}$ = –45.8° (*c* 3.3, $CHCl_3$); IR (liquid film) 1510 cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.38 (2H, m, Ph), 7.23 (2H, m, Ph), 7.14 (1H, m, Ph), 4.50 (1H, d, *J* = 11.8 Hz, $OC\underline{H}_AH_BPh$), 4.39 (1H, d, *J* = 11.8 Hz, $OCH_A\underline{H}_BPh$), 4.25 (1H, dd, *J* = 9.7, 2.9 Hz, H_{21}), 4.04 (1H, m, H_{27}), 3.80 (1H, dd, *J* = 8.4, 5.5 Hz, H_{19A}), 3.73 (1H, dd, *J* = 6.3, 2.9 Hz, H_{23}), 3.68 (1H, dd, *J* = 8.4, 3.0 Hz, H_{19B}), 3.64 (1H, m, H_{31}), 3.39 (1H, m, H_{29}), 3.19 (3H, s, OMe), 1.98 (2H, m), 1.86 (2H, m), 1.77 (1H, m), 1.72 (3H, m), 1.54 (1H, m), 1.27 (1H, buried m), 1.26 (3H, buried m, Me_{32}), 1.25 (18H, s, 2 x $^tBu_2$), 1.18 (1H, m), 1.10 (3H, d, *J* = 7.3 Hz, Me), 1.05 (3H, d, *J* = 6.9 Hz, Me), 0.95 (3H, d, *J* = 6.5 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.9, 128.2, 127.7, 127.3, 83.1, 73.3, 73.1, 72.6, 72.5, 64.5, 55.3, 39.2, 39.0, 37.1, 35.6, 34.8, 28.6, 28.4, 27.8, 22.2, 21.9, 21.8, 15.8, 13.9, 13.8; m/z (CI, NH_3) 563 (15), 355 (30), 337 (10), 229 (10), 177 (10), 108 (32), 91 (100%); HRMS (CI, NH_3) calc for $C_{33}H_{59}O_5Si$ ($[M+H]^+$) 563.4132, found 563.4129.

(2*S*,3*S*,4*S*,5*S*,6*S*)-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,5-di-*tert*-butylsilylenedioxyoctanal (10)

To a stirred solution of benzyl ether **33** (16.0 mg, 0.0285 mmol) in dry ethanol (1 ml) was added 10% Pd on charcoal catalyst (18 mg). The argon atmosphere was replaced by hydrogen (double balloon) and the resulting mixture stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of celite, rinsing through with dry ethanol, and the filtrate concentrated *in vacuo*. Flash column chromatography (25% EtOAc/hexane) gave (2*S*,3*S*,4*S*,5*S*,6*S*)-2,4,6-trimethyl-8-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydro-pyran-6-yl)-3,5-di-*tert*-butylsilylenedioxyoctan-1-ol as a colourless oil (13.2 mg, 98%); R_f = 0.25 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –35.8° (*c* 2.1, $CHCl_3$); IR (liquid film) 3500 (br) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 4.15 (1H, dd, *J* = 9.8, 2.8 Hz, H_{21}), 4.02 (1H, m, H_{27}), 3.84 (1H, dd, *J* = 10.5, 7.3 Hz, H_{19A}), 3.76 (1H, m, H_{19B}), 3.69 (1H, dd, *J* = 5.8, 3.0 Hz, H_{23}), 3.63 (1H, m, H_{31}), 3.39 (1H, m, H_{29}), 3.19 (3H, s, OMe), 2.96 (1H, br m, OH), 1.97 (1H, m), 1.86 (3H, m), 1.74 (2H, m), 1.65 (2H, m), 1.51 (1H, m,), 1.29 (1H, m, H_{30ax}), 1.25 (3H, d, *J* = 6.3 Hz, Me_{32}), 1.23 (9H, s, ^tBu_A), 1.19 (1H, m, H_{26B}), 1.16 (9H, s, ^tBu_B), 1.05 (3H, d, *J* = 7.3 Hz, Me), 0.93 (3H, d, *J* = 6.6 Hz, Me), 0.63 (3H, d, *J* = 6.9 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 82.9, 80.0, 73.3, 72.2, 69.4, 64.5, 55.3, 39.4, 38.8, 37.3, 36.0, 34.9, 28.6, 28.2, 27.8, 27.6, 22.2, 21.9, 15.6, 14.2, 13.2; m/z (CI, NH_3) 473 (60), 455 (20), 383 (20), 297 (30), 265 (100), 247 (70), 229 (25), 189 (30), 129 (20), 97 (37%); HRMS (CI, NH_3) calc for $C_{26}H_{53}O_5Si$ ($[M+H]^+$) 473.3662, found 473.3663.

To a cooled (–78 °C) solution of oxalyl chloride (40 mg, 28 μl, 0.32 mmol) in dry CH_2Cl_2 (1 ml) was added dimethylsulphoxide (50 mg, 45 μl, 0.64 mmol) dropwise by syringe. After 15 min at –78 °C, the above alcohol (34.0 mg, 0.0719 mmol) was added as a solution in dry CH_2Cl_2, (0.8 ml + 0.2 ml washing) *via* cannula. The resulting mixture was stirred at –78 °C for 1 h before addition of triethylamine (96 mg, 133 μl, 0.952 mmol). After a further 10 min, the reaction mixture was allowed to warm to –25 °C over 20 min, before quenching with NH_4Cl solution (1 ml, sat. aq.) and diluting with Et_2O (3 ml). The layers were separated and the aqueous layer extracted with Et_2O (2 x 3 ml). The combined organic extracts were washed with $NaHCO_3$ solution (2 ml, sat. aq.) and brine (2 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was eluted through a short silica gel column (25% EtOAc/hexane) to give **10** as a colourless oil (32.3 mg, 95%); R_f = 0.35 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –75.9° (*c* 1.3, $CHCl_3$); IR (liquid film) 1735 cm^{-1} (s); ^1H NMR (assigned using COSY) δ (400 MHz, C_6D_6) 9.97 (1H, d, *J* = 2.6 Hz, CHO), 4.31 (1H, dd, *J* = 9.1, 3.6 Hz, H_{21}, NOE enhancements at δ 9.97, 1.89, 0.79), 4.02 (1H, m, H_{27}, NOE enhancement at δ 1.74), 3.70 (1H, dd, *J* = 4.8, 4.6 Hz, H_{23}), 3.60 (1H, m, H_{30}), 3.38 (1H, m, H_{29}, NOE enhancements at δ 1.84, 1.74), 3.19 (3H, s, OMe), 2.46 (1H,

dqd, J = 9.1, 7.0, 2.6 Hz, H_{20}, NOE enhancements at δ 9.97, 0.91, 0.79), 1.89 (1H, m, H_{22}), 1.86 (1H, m, H_{26A}), 1.84 (1H, m, H_{30eq}), 1.74 (2H, m, H_{28}), 1.61 (2H, m, H_{24}, H_{25A}), 1.51 (1H, m, H_{25B}), 1.30 (1H, m, H_{30ax}), 1.25 (3H, d, J = 6.4 Hz, Me_{32}), 1.16 (19H, s + buried m, $^tBu_2$, H_{26B}), 0.95 (3H, d, J = 6.7 Hz, $C_{24}Me$), 0.91 (3H, d, J = 7.3 Hz, $C_{22}Me$), 0.79 (3H, d, J = 7.0 Hz, $C_{20}Me$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 203.2, 82.3, 75.4, 73.6, 71.0, 64.8, 55.0, 49.3, 38.9, 38.5, 36.7, 35.6, 29.3, 28.3, 27.9, 26.9, 22.2, 22.0, 16.1, 13.9, 10.8; m/z (CI, NH_3) 471 (70), 453 (20), 439 (60), 421 (55), 381 (90), 341 (20), 295 (67), 245 (64), 205 (60), 155 (100), 123 (73), 97 (50%); HRMS (CI, NH_3) calc for $C_{26}H_{51}O_5Si$ ($[M+H]^+$) 471.3506, found 471.3501.

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