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The Total Synthesis of Scytophycin C. Part 1: Stereocontrolled Synthesis of the C_1–C_{32} Protected Seco Acid.

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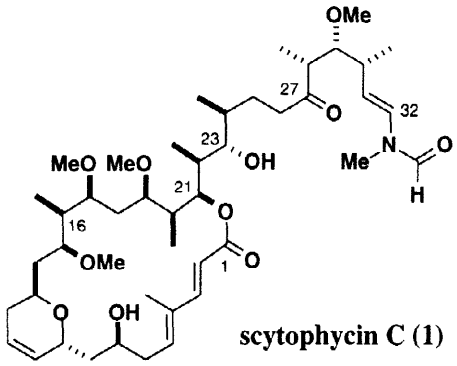
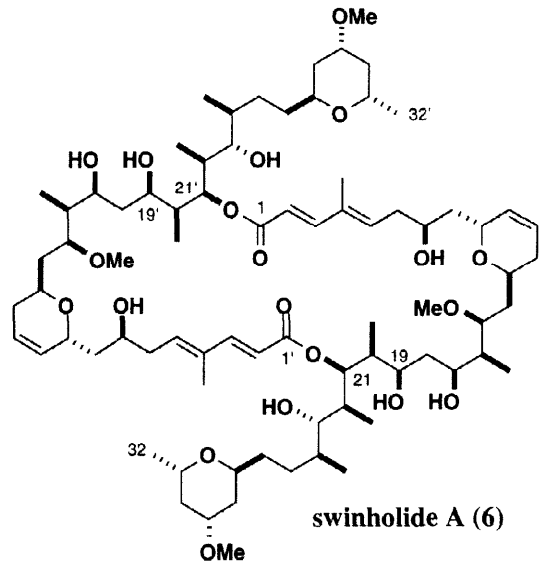
Abstract: A stereocontrolled synthesis of the C_1–C_{32} seco acid derivative **9** for scytophycin C (**1**) was completed in 14 steps (18.2% yield, 85% ds) from aldehyde (*S*)-**18**. Key steps include: (*i*) the asymmetric crotylboration of (*S*)-**18** to give homoallylic alcohol **15**; (*ii*) the boron-mediated aldol construction of aldehyde **14** from (*S*)-**17**; (*iii*) the $Ba(OH)_2$-promoted HWE reaction, **13** + **14** → **31**; (*iv*) the highly stereocontrolled Mukaiyama aldol coupling between silyl enol ether **33** and aldehyde **11** to give adduct **10**; (*v*) the chemoselective reduction at C_{17} of ketone **10** to produce 1,3-*syn*-diol **34**.



scytophycin C (1)

scytophycin	C_{16}	C_{27}
A (**2**)	O	OH
B (**3**)	O	O
D (**4**)	OH	O
E (**5**)	OH	O



swinholide A (6)

The scytophycins are a novel class of polyoxygenated, 22-membered, macrolides isolated from the cultured terrestrial blue-green alga *Scytonema pseudohofmanni* as part of the anti-tumour drug discovery effort conducted by Moore and Patterson.[1] Their structures were determined[1a] based on extensive spectroscopic analysis in combination with an X-ray crystallographic analysis performed on an acid degradation product of scytophycin C (**1**). All of the scytophycins (*cf.* **1–5**) have a characteristic C_{21} side chain terminating in an unusual *N*-methyl vinylformamide group, whereas scytophycins A to E differ from each other with regard to the substituents at C_{16} and C_{27}. Other analogues[2] of these five congeners featuring a different substitution pattern at C_6 have also been isolated from *Tolypothrix*, *Cylindrospermum* and other species of *Scytonema*. The scytophycin group of 22-membered macrolides exhibit potent cytotoxity against a variety of human cancer cell lines, as well as broad spectrum antifungal activity.[1b,c,2] Recently, it has been found that the scytophycins

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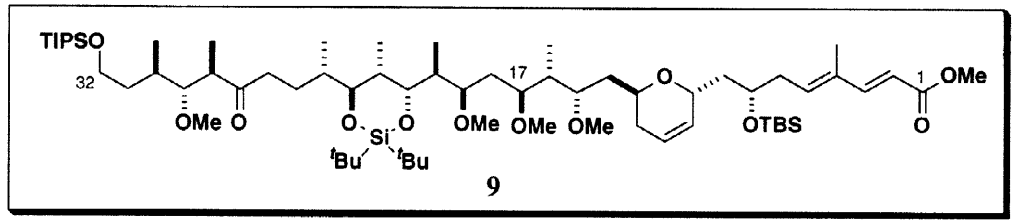
inhibit cytokinesis in cultured mammalian cells, along with inhibiting actin polymerization and inducing the depolymerization of F-actin *in vitro*.[3a] Furthermore, the scytophycins have also been shown to circumvent P-glycoprotein mediated multi-drug resistance in tumour cells and maintain their antiproliferative effects.[3b] Thus, this class of macrolides may have useful therapeutic value for the treatment of drug-resistant cancers.



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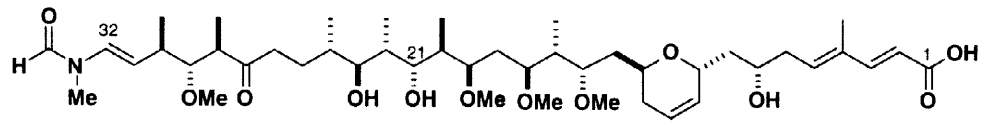

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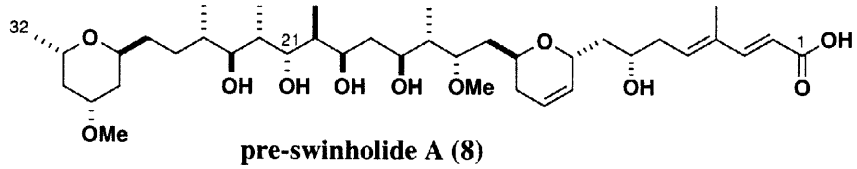


pre-swinholide A (8)

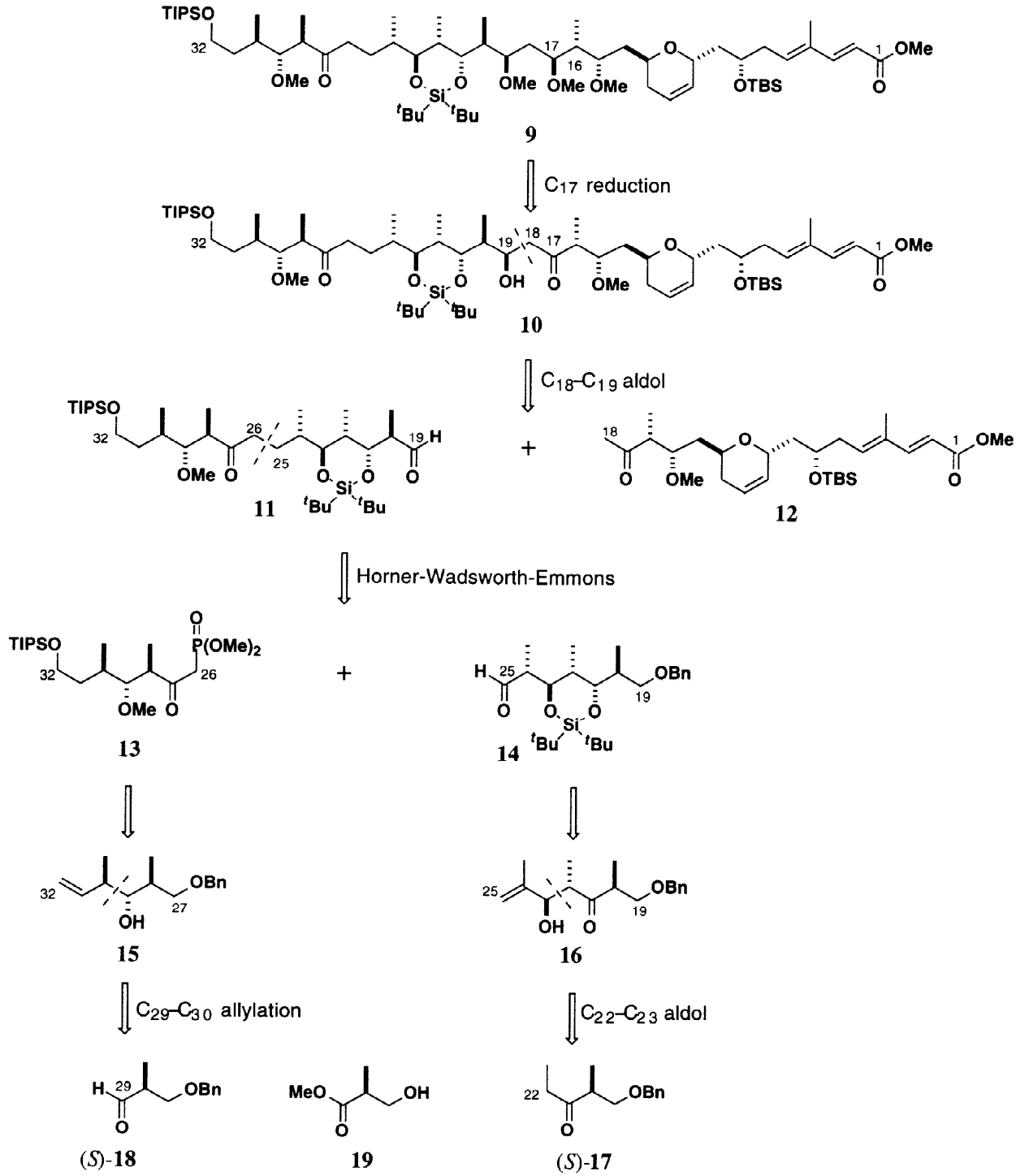
Interestingly, the stereostructure of scytophycin C (**1**) spanning from C_1 to C_{32} is remarkably similar to that present in swinholide A (**6**), a C_2-symmetric, 44-membered, macrodiolide isolated from the marine sponge *Theonella swinhoei*.[4] This structural homology is evident by comparing the seco acid (**7**) of scytophycin C with the monomeric seco acid (**8**) of swinholide A. Notably, swinholide A also exerts its cytotoxic effect by disrupting the actin cytoskeleton.[5] It has been demonstrated *in vitro* that swinholide A severs F-actin and sequesters G-actin dimers where one molecule of swinholide A binds to an actin dimer.

The complex molecular structure with multiple stereogenic centres, combined with the unique mechanism of anti-tumour action, make the scytophycins desirable targets for synthesis. Moreover, a total synthesis should enable access to novel analogues for further developing the structure activity relationship, for detailed studies of the mechanism of action, and for the elucidation of the cellular functions of actin binding proteins. In this and the accompanying paper,[6] we give full details of the first total synthesis of scytophycin C.[7-9] Here, we outline our synthetic strategy and describe the stereocontrolled synthesis of the C_1–C_{32} seco acid derivative **9**.

Synthetic Strategy for Constructing the Fully Protected Seco Acid of Scytophycin C

Our synthetic strategy for the scytophycins is summarised in **Scheme 1**. The known acid sensitivity[1a] of scytophycin C (**1**) dictated that the final stages of the synthesis should be performed with the utmost caution. In particular, the introduction of the *N*-methyl vinylformamide group, which leads to two slowly interconverting conformers around the C_{32}–N bond,[1a] would necessarily be delayed until the final stages. The C_1–C_{32}, fully protected, seco acid derivative **9** proved to be an appropriate pivotal intermediate for our synthesis. As with our earlier synthesis[10,11] of swinholide A, we chose to tie up the C_{21}–C_{23} *anti*-diol with a cyclic silicon protecting group, thus foregoing the opportunity for differential protection at these two hydroxyl groups which are apparently in similar steric environments.

The complete carbon skeleton of scytophycin C in **10** was anticipated to arise from an aldol coupling between the C_1–C_{18} methyl ketone **12** and the C_{19}–C_{32} aldehyde **11**. In our preliminary work,[8a,b] we envisaged the main aldol coupling step would be at the C_{16}–C_{17} bond. However, the precedent set by our total synthesis[10] of swinholide A gave us confidence that a C_{18}–C_{19} aldol coupling would be a safer option, which should proceed with high stereoselectivity under Felkin-Anh control.[10b,f] Finally, a challenging chemo- and stereoselective reduction of the C_{17} ketone group in the aldol product **10** would be required to complete the construction of **9** with installation of all 15 stereogenic centres of scytophycin C.

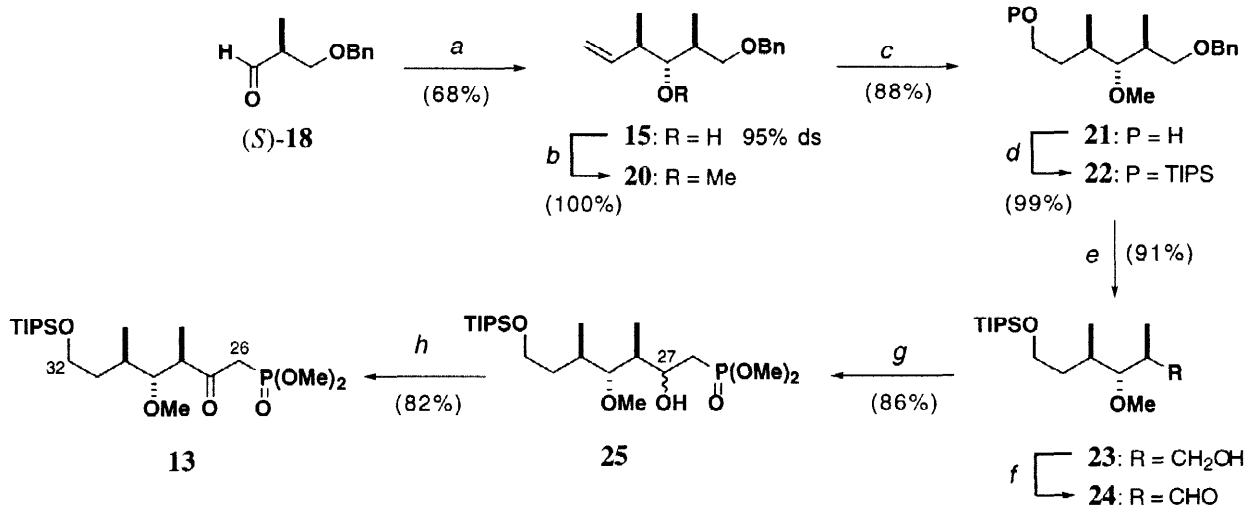


Scheme 1

Full details of the stereoselective synthesis of the C_1–C_{18} methyl ketone **12**, which is a common intermediate in our swinholide A synthesis, have already been reported[10b,c] such that this segment is not discussed further here. We envisaged that the corresponding aldehyde segment **11** could be contructed from the aldehyde **14** and the ketophosphonate **13** by a Horner-Wadsworth-Emmons (HWE) reaction to install the C_{25}–C_{26} bond. The C_{19}–C_{25} stereopentad **14**, in turn, should be readily accessible using our general synthetic approach[12a-c] to such polypropionate systems. In this case, the precursor would be the adduct **16** derived from an *anti* aldol reaction[12d] of the dipropionate reagent (*S*)-**17** with methacrolein. The three contiguous stereocentres in the ketophosphonate **13** could be secured by a suitable asymmetric crotylation[13] of the aldehyde (*S*)-**18**. Notably, both the chiral building blocks, **17** and **18**, can be prepared[14] from the commercially available, methyl (*S*)-(+)-2-methyl-3-hydroxypropionate (**19**). The foregoing strategy was designed to provide a flexible, highly convergent, synthetic route to scytophycin C (**1**).

Synthesis of C_{26}–C_{32} Ketophosphonate (13)

The *anti-anti* stereotriad spanning C_{27}–C_{31} could be set up efficiently by using Brown's asymmetric crotylboration reaction (**Scheme 2**). Thus, the homoallylic alcohol **15**[15a] was synthesised in 68% yield with 95% ds by *anti* crotylboration of the aldehyde (*S*)-**18** (prepared[16] in 3 steps from **19**) with the (*E*)-crotyl diisopinocampheylborane[15b,c] obtained from (+)-Ipc$_2$BOMe. This represents an improved yield over that reported in our earlier communication,[8a] which now compares favourably with that of Brown *et al.*[15a] The optimum reaction conditions required prior drying of the boron reagent under high vacuum (to remove some volatile decomposition product), maintaining the internal reaction temperature by efficient cooling and controlled addition of the reagents, and conducting the oxidative work-up at room temperature.



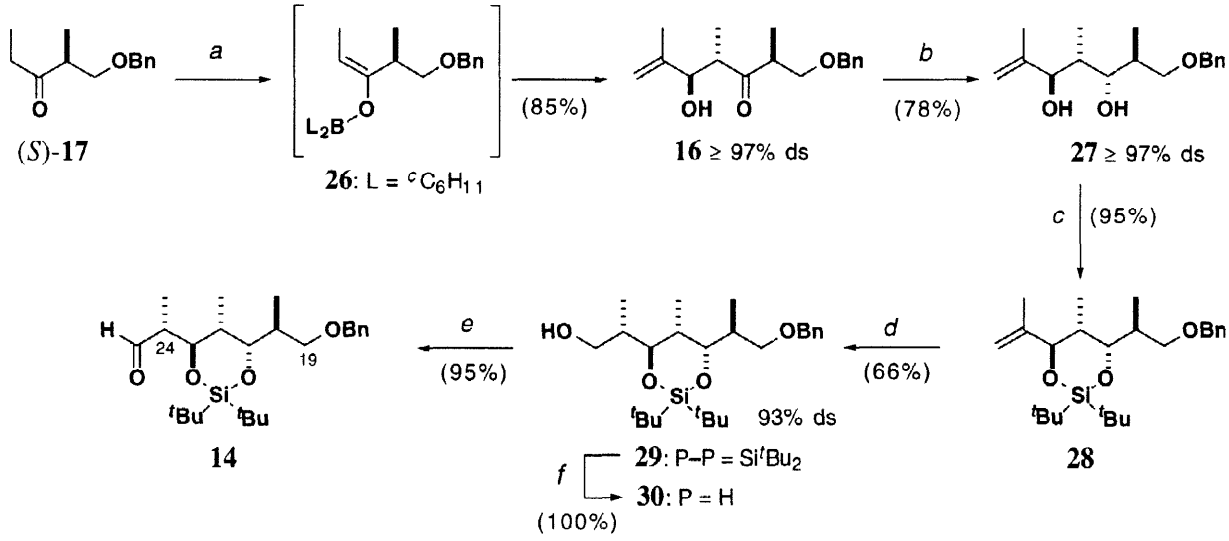
Scheme 2: (*a*) (*E*)-2-butene, KO^{t}Bu, ^{n}BuLi, THF, –78 → –50 °C, 1.5 h; (+)-Ipc$_2$BOMe, 30 min; BF_3•OEt_2, 30 min; (*S*)-**18**, –78 °C, 4 h; NaOH, 30% H_2O_2, 20 °C, 16 h; (*b*) MeI, NaH, THF, 20 °C, 17 h; (*c*) 9-BBN, THF, 20 °C, 5 h; H_2O_2/NaOH, 3 h; (*d*) TIPSCl, imidazole, CH_2Cl_2, 20 °C, 90 min; (*e*) H_2, 10% Pd/C, EtOH, 20 °C, 6 h; (*f*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 6 h; (*g*) $(MeO)_2P(O)Me$, ^{n}BuLi, THF, –78 °C, 15 min; (*h*) PDC, DMF, 30 °C, 1 h.

Conversion of the alcohol **15** into the ketophosphonate **13** was achieved uneventfully *via* a series of functional group manipulations. Accordingly, the hydroxyl group in **15** was methylated using NaH / MeI to give the methyl ether **20** (100%). The terminal alkene in **20** was then hydroborated using 9-BBN, followed by oxidative work-up, to give the primary alcohol **21** in 88% yield. Protection of the hydroxyl group in **21** as its

triisopropylsilyl (TIPS) ether was performed under standard conditions (TIPSCl, imidazole, CH_2Cl_2), followed by debenzylation (H_2, Pd / C, EtOH), to provide the alcohol **23** (90%). After oxidation of **23** using Dess-Martin periodinane,[17] the crude aldehyde **24** was reacted with lithiated $(MeO)_2P(O)Me$ in THF at –78 °C to give the β-hydroxyphosphonates **25**, which were isolated as a 2 : 1 diastereomeric mixture in 86% overall yield. Oxidation of the alcohols **25** with PDC at 30 °C then gave the required β-ketophosphonate **13** in 82% yield. Under these conditions, the major epimer was found to be oxidised slower than the minor isomer.

Synthesis of C_{19}-C_{25} Aldehyde (14)

The ethyl ketones (*R*)- and (*S*)-**17** have already been demonstrated to be versatile dipropionate reagents for polyketide synthesis and have seen extensive use in our laboratory.[14,18] The key step in the synthesis of the C_{19}–C_{25} stereopentad of scytophycin C is the *anti*-aldol reaction between (*S*)-**17** (prepared[16] in 3 steps from **19**) and methacrolein (**Scheme 3**). This serves to introduce the C_{20} stereocentre and sets up the C_{22} and C_{23} centres in a highly stereoselective manner. Thus, the aldol addition of the (*E*)-enol dicyclohexylborinate **26**, obtained by controlled enolisation of (*S*)-**17**, to methacrolein at 0 °C gave the *anti-anti* aldol product **16**[12b-d] in 85% yield with ≥97% ds. Next, the C_{21} stereocentre was installed *via* hydroxyl-directed ketone reduction employing $Me_4NBH(OAc)_3$ (1 : 1 MeCN / AcOH).[19] This reduction served to convert the aldol product **16** into the 1,3-*anti* diol **27** in 78% yield with >97% ds. The diol **27** was then protected as its di-*tert*-butylsilylene[18a,g,20] derivative **28** in 95% yield on extended reaction with $^tBu_2Si(OTf)_2$ / 2,6-lutidine (20 °C, 15 h).



Scheme 3: (*a*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; $H_2C{=}C(Me)CHO$, 0 °C. 3.5 h; H_2O_2, MeOH-pH7 buffer; (*b*) $Me_4NBH(OAc)_3$, 1:1 MeCN-AcOH, –30 °C, 2 h; (*c*) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 15 h; (*d*) 9-BBN, THF, 20 °C, 18 h; H_2O_2/NaOH, 3 h; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, –78 → –25 °C, 3 h; (*f*) HF•py, py, THF, 20 °C.

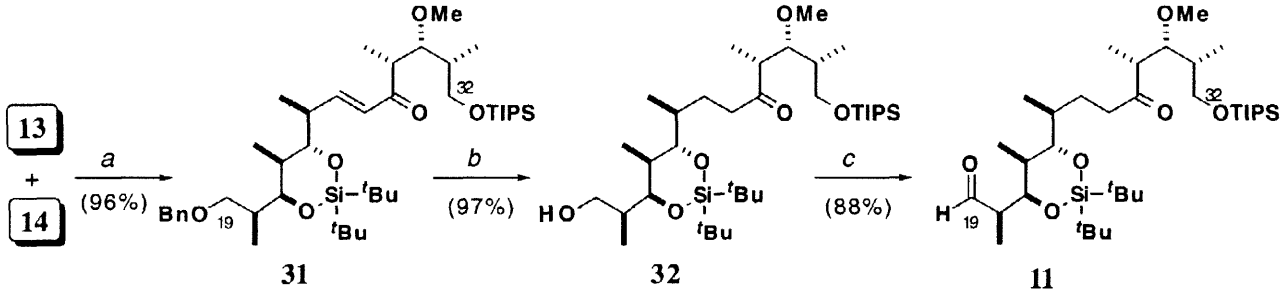
The remaining stereocentre at C_{24} was installed by controlled hydroboration[12a,21] of alkene **28** with 9-BBN to give, after oxidative work-up, the primary alcohol **29** in 66% yield with 93% ds. The desired isomer **29** could be chromatographically separated from the minor C_{24}-epimer. In an earlier study, the unprotected triol **30** had already been prepared[12a] with lower diastereoselectivity (85 : 15) by hydroboration of diol **27** using (+)-Ipc_2BH. Cleavage of the di-*tert*-butylsilylene group in **29** using HF•pyridine/pyridine[20] gave the same triol **30**, which exhibited ^1H NMR spectroscopic data and optical rotation, $[\alpha]_D^{20}$ +35.1 (*c* 0.2, $CHCl_3$), in agreement with that previously recorded,[12a] thus confirming the stereostructure. Swern oxidation of alcohol **29**

(quenching at –25 °C) then gave the aldehyde **14** in 95% yield. Hence, the required stereopentad **14** was readily prepared from (*S*)-**17**, using substrate-based stereocontrol, in only 5 steps.

Barium Hydroxide Induced HWE Reaction to Generate Aldehyde (11)

A key factor in achieving a successful total synthesis of scytophycin C was realising an efficient HWE coupling[22] (**Scheme 4**) between the sterically hindered aldehyde **14** and the ketophosphonate **13** to provide sufficient quantities of the key C_{18}–C_{19} segment **11** for late stage transformations. Model studies were initially carried out using aldehyde **14** and $(MeO)_2P(O)CH_2CO^iPr$ to establish the optimum reaction conditions. Using conventional conditions with NaH as the base (THF, 20 °C), this coupling reaction gave a 1 : 1 mixture of the (*E*)-enone and its β-eliminated product. Moreover, the (*E*)-enone was obtained as a mixture of epimers at C_{24}. In comparison, under Masamune-Roush conditions (LiCl, $^iPr_2NEt$, MeCN, 3Å mol. sieves, 20 °C),[23] no reaction was initially observed by TLC and a complex product mixture was obtained on prolonged stirring. Changing the base to the less hindered Et_3N[23b] led only to β-elimination in the aldehyde **14**.

Gratifyingly, we found that the real HWE coupling between aldehyde **14** and ketophosphonate **13** could be promoted efficiently by using barium hydroxide[24a] in wet THF to produce the desired (*E*)-enone **31** exclusively. Significantly, use of equimolar amounts of the aldehyde and ketophosphonate reactants gave rise to an excellent yield (96%) of **31**. We have found barium hydroxide to be generally useful in promoting efficient HWE couplings of β-ketophosphonates with structurally complex, base-sensitive aldehydes.[24b] The mild conditions employed are compatible with a wide variety of substrate functionalities, as demonstrated by their application in several demanding situations in macrolide and polyether fragment assembly.[24b-d,25] The (*E*)-enone **31** could be transformed efficiently into the ketoaldehyde **11** in two further steps. Thus, **31** was first converted into the alcohol **32** in 97% yield by alkene hydrogenation with concomitant debenzylation using palladium on charcoal as catalyst. Dess-Martin oxidation then gave the required aldehyde **11** in 88% yield.



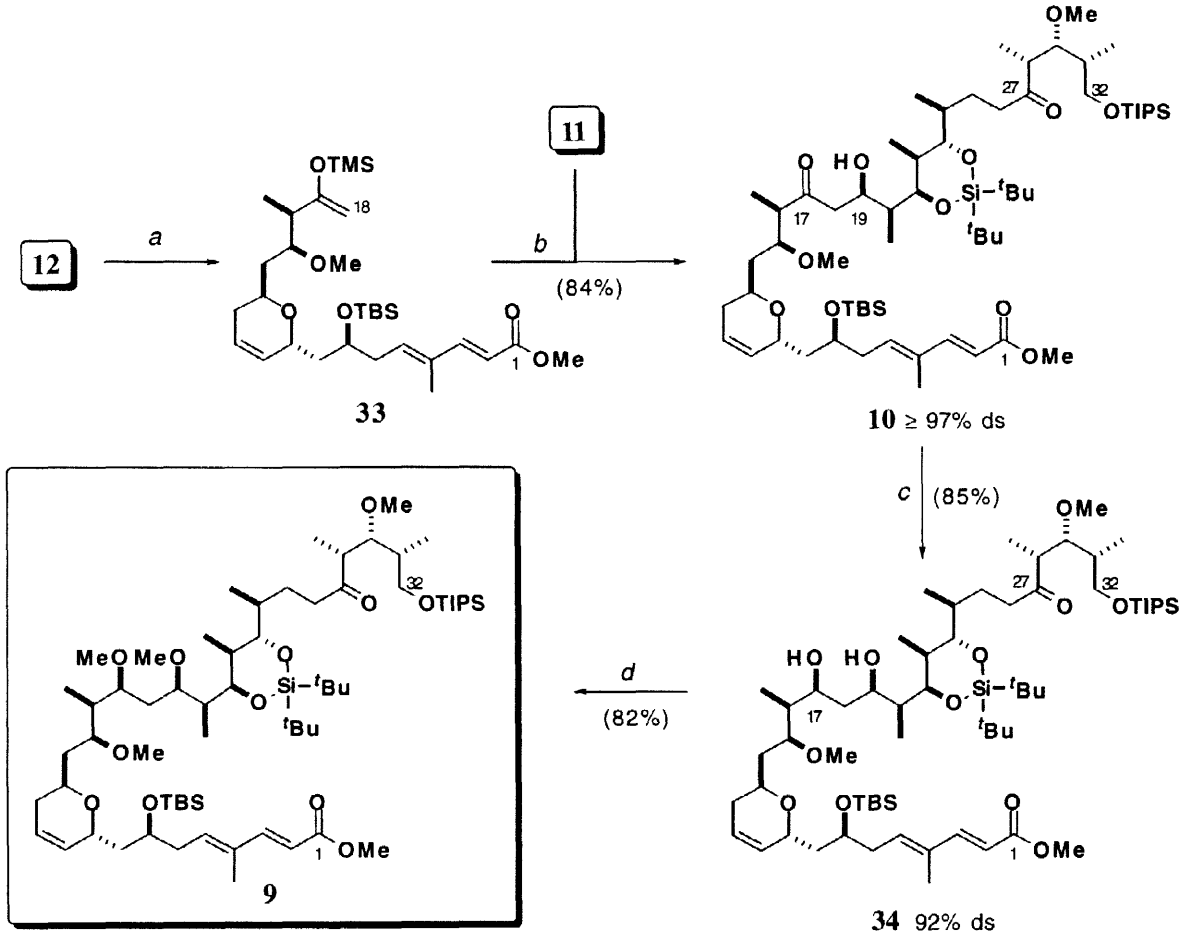
Scheme 4: (*a*) $Ba(OH)_2 \cdot 8H_2O$, 40:1 THF/H_2O, 20 °C, 6.5 h; (*b*) H_2, Pd/C, EtOH, 20 °C, 2.5 h; (*c*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 35 min.

C_{18}-C_{19} Aldol Coupling and Formation of the C_1-C_{32} Fully Protected Seco Acid (9)

As with our swinholide synthesis, a Mukaiyama aldol coupling was employed to unite the C_1–C_{18} and C_{19}–C_{32} segments and set up the C_{19} stereocentre under substrate control (**Scheme 5**).[10b] Thus, the silyl enol ether **33** was prepared from methyl ketone **12**[10c] by kinetic enolisation with lithium hexamethyldisilazide (THF, –78 °C) and *in situ* trapping with Me_3SiCl. After isolation using a pH 7 buffer/pentane workup, the enol derivative **33** was used immediately without purification. Addition of $F_3B \cdot OEt_2$ to a mixture of **33** and aldehyde **11** in CH_2Cl_2 at –78 °C promoted a rapid aldol addition and gave the β-hydroxy ketone **10** cleanly in

84% yield with ≥97% diastereoselectivity. The remarkably high degree of selectivity in the coupling of these two complex segments is presumably the result of a synergistic effect from the α- and β- stereocentres in aldehyde **11**, *i.e.* Felkin-Anh stereocontrol (1,2-induction) reinforced by a favourable dipole-dipole interaction (1,3-induction).[26]

In aldol adduct **10**, all the 15 stereocentres of scytophycin C have been installed except that at C_{17}. Two steps now remained to complete the synthesis of the C_1–C_{32} fully protected seco acid **9**. Notably, a challenging stereoselective reduction of the C_{17} ketone group in the presence of the C_{27} ketone was now required. Such a chemo- and stereoselective reduction was achieved by chelate-mediated, 1,3-*syn* reduction. Using a modification[27,12c] of the Narasaka-Prasad protocol,[28] adduct **10** was first treated with Bu_2BOMe in THF/MeOH to activate the C_{17} carbonyl group *via* boron aldolate formation, followed by the addition of $LiBH_4$. At –78 °C, the reduction was found to be slow, leading after 3.5 h to the isolation of a 1:1 mixture of the desired *syn*-isomer and recovered starting material. Carrying out the reaction at a higher temperature (–45 °C), gave a triol as a minor side product, presumably due to competing reduction at C_{27}. The optimum temperature was found to be –60 °C, which led to the isolation (after 2 h) of the desired *syn*-diol **34** in 57% yield with 92% ds and avoiding any triol formation. The use of catecholborane,[29] which has a dual role of activation *via* aldolate formation and reduction *via* hydride donation, also proved to be effective in realising this transformation, giving the *syn*-diol **34** in an improved yield (85%) with the same level of diastereoselectivity.



Scheme 5: (*a*) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, –78 °C, 40 min; (*b*) $F_3B{\bullet}OEt_2$, CH_2Cl_2, –78 °C, 30 min; (*c*) catecholborane, THF, –78 → –20 °C, 18 h; (*d*) MeOTf, 2,6-di-*tert*-butylpyridine, 20 °C, 24 h.

In the *syn*-diol **34**, the C_{17} and C_{19} hydroxyl groups are sterically hindered and, together with the presence of sensitive functional groups, make *bis-O*-methylation a demanding task. After several experiments, we found that the etherification of diol **34** was best achieved at room temperature[30] by using methyl triflate in the presence of the mild and non-nucleophilic base, 2,6-di-*tert*-butylpyridine. Initially, the reaction could not be driven to completion even in the presence of a large excess of reagents. The starting diol and two monomethylated compounds were always found to be present in the reaction mixture – these could conveniently be isolated and resubmitted to the same methylation conditions. Finally, under high concentration conditions, the reaction was driven to completion and the C_1–C_{32} fully protected seco acid **9** was obtained in 82% yield.

Conclusions

The C_1–C_{32} fully protected seco acid **9**, as required for the total synthesis of scytophycin C, has been prepared in 14 steps from the aldehyde (*S*)-**18** in 18.2% overall yield. The C_{20} and C_{28} stereogenic centres originate from (*S*)-**17** and (*S*)-**18** respectively, while the remaining 13 stereocentres were introduced in a highly controlled manner (85% overall ds). Notably, this approximates to the introduction of one stereocentre per step.[31] The synthesis of seco acid derivative **9** relied on only a single reagent-controlled reaction, the Brown asymmetric crotylboration, (*S*)-**18** → **15**, combined with a series of highly selective, substrate-controlled reactions, (*i*) the *anti*-selective boron aldol reaction, (*S*)-**17** → **16**, (*ii*) the 1,3-*anti*-reduction, **16** → **27**, (*iii*) the hydroboration, **28** → **29**, (*iv*) the Mukaiyama aldol coupling, **11** + **12** → **10** and (*v*) the 1,3-*syn*-reduction, **10** → **34**. The $Ba(OH)_2$-induced HWE coupling, as in **13** + **14** → **31**, also proved to be an important step, enabling the generation of ample quantities of the scytophycin skeleton. The synthesis of the C_1–C_{32} fully protected seco acid **9** sets the stage for the completion of the total synthesis of scytophycin C (**1**), as detailed in the following paper.[6,31]

Experimental Section

For general experimental details, see ref 10d.

(*S*)-3-(Benzyloxy)-2-methylpropanal (18)[14a, 16a-c] To a stirred solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**19**) (10.4 ml, 10.0 g, 84.66 mmol) in dry Et_2O (150 ml) under an Ar atmosphere was added benzyl-2,2,2-trichloroacetimidate (18.96 ml, 25.66 g, 101.6 mmol). The solution was cooled to 0 °C and triflic acid (1.0 ml, 9.8 mmol) was added dropwise, whereupon a white solid (trichloroacetamide) precipitated which redissolved on warming to room temperature over 2 h. The reaction mixture was poured into $NaHCO_3$ solution (200 ml; sat. aqueous), extracted with Et_2O (3 x 100 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting semi-solid (trichloroacetamide) was triturated from cold hexanes and removed by filtration. The filtrate was concentrated *in vacuo* and purified by flash chromatography (5 → 10% EtOAc in hexanes) to give the corresponding benzyl ether[14a] as a colourless oil (18.52 g, 94%); R_f (20% EtOAc/hexane) 0.51; $[\alpha]_D^{20}$ +12.1 (*c* 10.0, $CHCl_3$; ~99% ee); IR (liquid film) 1730 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.34–7.25 (5H, m, Ph), 4.52 (2H, s, C$\underline{H}_2$Ph), 3.69 (3H, s, O$\underline{Me}$), 3.65 (1H, dd, *J* = 8.9, 7.2 Hz, C$\underline{H}_X$H$_Y$OBn), 3.51 (1H, dd, *J* = 8.9, 5.9 Hz, CH$_X$$\underline{H}_Y$OBn), 2.79 (1H, dqd, *J* = 7.2, 7.1, 5.9 Hz, C$\underline{H}$Me), 1.18 (3H, d, *J* = 7.1 Hz, CH$\underline{Me}$); ^{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 (CI, NH_3) 226 ($[M+NH_4]^+$, 100), 209 ($[M+H]^+$, 11), 108 (4), 91 (3%); HRMS (CI, NH_3) $[M+NH_4]^+$ found 226.1450, $C_{12}H_{20}O_3N$ requires 226.1443.

The Weinreb amide was prepared by adaptation of the Merck procedure (which avoids the use of Me_3Al).[16d,e] The benzyl ether (30.05 g, 144.3 mmol), prepared as above, was mixed with *N,O*-dimethylhydroxylamine hydrochloride (21.82 g, 223.7 mmol, 1.55 eq.) and dry THF (100 ml). The resulting slurry was cooled to –20 °C and *iso*-propylmagnesium chloride (158.7 ml, 317.5 mmol, 2.2 eq.; 2 *M* solution in THF) was added dropwise, maintaining the solution temperature between –20 and –5 °C. The reaction mixture was stirred at –5 °C for 1 h, then poured into NH_4Cl solution (500 ml, sat. aqueous) and extracted with Et_2O (3 x 250 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (20 → 50% EtOAc in hexanes) gave the corresponding amide[14a] as a pale yellow oil (32.78 g, 96%); R_f (50% EtOAc/hexane) 0.35; $[\alpha]_D^{20}$ +5.8 (*c* 4.2, $CHCl_3$; ~99% ee); IR (liquid film) 1650 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.33–7.25 (5H, m, Ph), 4.55 (1H, d, *J* = 12.1 Hz, $C\underline{H}_AH_BPh$), 4.46 (1H, d, *J* = 12.1 Hz, $CH_A\underline{H}_BPh$), 3.70 (1H, dd, *J* = 8.7, 8.7 Hz, $C\underline{H}_XH_YOBn$), 3.68 (3H, s, O<u>Me</u>), 3.42 (1H, dd, *J* = 8.7, 5.7 Hz, $CH_X\underline{H}_YOBn$), 3.23 (1H, m, C<u>H</u>Me), 3.20 (3H, s, N<u>Me</u>), 1.10 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>); ^{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 (CI, NH_3) 238 ($[M+H]^+$, 100), 208 (15), 148 (11), 118 (4); HRMS (CI, NH_3) $[M+H]^+$ found 238.1443, $C_{12}H_{20}O_3N$ requires 238.1448.

To a stirred solution of the Weinreb amide (11.95 g, 57.4 mmol), prepared as above, in dry THF at –78 °C was slowly added DIBAL (63.1 ml, 63.1 mmol; 1 *M* in hexanes) over 20 min. The reaction mixture was stirred at –78 °C for 1 h, then MeOH (20 ml) was added cautiously. The resulting solution was poured into aqueous sodium potassium tartate solution (300 ml) and EtOAc (300 ml) and stirred vigorously for 1 h. The organic layer was decanted and the aqueous layer extracted with further EtOAc (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on florisil (10% EtOAc/hexanes) gave the sensitive aldehyde (*S*)-**18**[16a-c] as a colourless oil (10.13 g, 98%), which (after azeotroping from PhH) was used directly for the crotylboration step; IR (liquid film) 1725 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.70 (1H, d, *J* = 1.5 Hz, C<u>H</u>O), 7.34-7.26 (5H, m, Ph), 4.50 (2H, s, $C\underline{H}_2Ph$), 3.68-3.60 (2H, m, $C\underline{H}_2OBn$), 2.69-2.59 (1H, m, C<u>H</u>Me), 1.10 (3H, d, *J* = 7.2 Hz, <u>Me</u>).

(2*S*,3*S*,4*S*)-1-(Benzyloxy)-2,4-dimethylhex-5-en-3-ol (15)[15a] *Trans*-2-butene (*ca* 9.0 ml, 110 mmol) was condensed into a suspension of potassium *tert*-butoxide (7.23 g, 64.0 mmol; dried at 80 °C under high vacuum for 4 h before use) in THF (75 ml) at –78 °C. *n*-Butyllithium (40.2 ml, 64.4 mmol, ca 15% solution in hexane) was added slowly to the mixture, maintaining the solution temperature at –78 °C. The greenish-yellow reaction mixture was then warmed to –50 °C and stirred for 30 min. The resulting suspension was recooled to –78 °C and a solution of (+)-methoxydiisopinocampheylborane (20.38 g, 64.4 mmol, derived from (–)-α-pinene and dried under high vacuum before use) in THF (50 ml) was added *via* dropping funnel. The mixture was stirred at –78 °C for 30 min after which time the viscous yellow mixture dissolved to give a clear solution. Boron trifluoride etherate (12.25 g, 10.6 ml, 86.3 mmol) was then added slowly and the solution stirred at –78 °C until a white suspension formed (*ca* 30 min). A solution of the aldehyde (*S*)-**18** (8.59 g, 48.3 mmol) in THF (20 ml) was added *via* dropping funnel and the reaction mixture stirred at –78 °C for 4 h. The reaction was quenched by the addition of sodium hydroxide solution (32 ml, 3 M), followed by hydrogen peroxide solution (40 ml, 30% aq.) and then warmed to room temperature with stirring for 16 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 250 ml). The combined organic layers were washed, in turn, with $Na_2S_2O_3$ solution (250 ml) and brine (250 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (hexanes and EtOAc, 100% to 5% gradient) to give the alcohol **15** as a colourless oil[15] (7.62 g, 68%); R_f (5% Et_2O/CH_2Cl_2) 0.50; $[\alpha]_D^{20}$ –12.2 (*c* 1.6, MeOH); ^1H NMR δ (400 MHz, $CDCl_3$) 7.37-7.28 (5H, m, Ph), 5.89 (1H, ddd, *J* = 16.4, 10.8, 8.5 Hz, $CH_2=C\underline{H}$), 5.06 (1H, dd, *J* = 11.2, 1.9 Hz, $C\underline{H}_XH_y=CH$), 5.05 (1H, dd, *J* = 16.5, 1.9 Hz, $CH_x\underline{H}_y=CH$), 4.51 (2H, s, $C\underline{H}_2Ph$), 3.58 (1H, dd, *J* = 9.2, 4.5 Hz, $C\underline{H}_xH_yOBn$), 3.51 (1H, dd, *J* = 9.1, 8.4

Hz, CH_xH_yOBn), 3.41 (1H, br d, J = 3.9 Hz, OH), 3.36 (1H, ddd, J = 7.6, 3.6, 3.3 Hz, CHOH), 2.39-2.31 (1H, m, CHMe), 1.96-1.89 (1H, m, CHMe), 1.09 (3H, d, J = 6.8 Hz, CH_3), 0.88 (3H, d, J = 7.0 Hz, CH_3); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 139.7, 137.8, 128.4, 127.7, 127.6, 115.2, 79.6, 75.4, 73.4, 41.0, 36.2, 17.7, 13.8.

(2*S*,3*S*,4*S*)-1-(Benzyloxy)-3-methoxy-2,4-dimethyl-5-hexene (20) To a mixture of sodium hydride (2.16 g, 54.0 mmol, 60% dispersion in oil) in THF (95 ml) at room temperature was added, *via* cannula, a solution of homoallylic alcohol **15** (2.20 g, 9.39 mmol) in THF (30 ml). The mixture was stirred for 15 min before addition of methyl iodide (2.85 ml, 45.9 mmol, freshly distilled). After 17 h, the reaction mixture was quenched by the addition of ammonium chloride solution (60 ml, sat. aq.) and stirred until a clear solution formed. After dilution with ether (100 ml), the organic layer was separated, washed with brine (70 ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification of the crude product by flash chromatography (20% Et_2O/hexane) gave **20** as a colourless oil (2.32 g, 100%); R_f (20% Et_2O/hexane) 0.53; $[\alpha]_D^{20}$ –25.1 (*c* 1.3, $CHCl_3$); IR (liquid film) 1641, 1495, 1453, 1364, 1094 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.37-7.21 (5H, m, Ph), 5.83 (1H, ddd, J = 18.0, 9.6, 8.2 Hz, CH_2=CH), 5.01 (2H, overlapping dd's, J = 18.7, 12.1, 2.0 Hz, CH_2=), 4.50 (2H, s, CH_2Ph), 3.51 (2H, d, J = 4.9 Hz, CH_2OBn), 3.41 (3H, s, OMe), 2.79 (1H, dd, J = 8.3, 3.5 Hz, CHOMe), 2.42 (1H, dqd, J = 7.5, 7.1, 3.5 Hz, =CHCHMe), 1.90-1.84 (1H, m, CHMe), 1.09 (3H, d, J = 6.9 Hz, Me), 0.98 (3H, d, J = 6.9 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 140.1, 138.8, 128.3, 127.5, 127.4, 114.6, 87.0, 73.0, 72.4, 61.2, 40.4, 37.1, 17.9, 14.8; m/z (CI, NH_3) 249 (100, $[M+H]^+$), 217 (30), 193 (21), 108 (22), 91 (48%); HRMS (EI) $[M]^+$ found 248.1783, $C_{16}H_{24}O_2$ requires 248.1776.

(2*S*,3*R*,4*R*)-1-(Benzyloxy)-3-methoxy-2,4-dimethyl-5-hexanol (21) 9-BBN (0.6 ml, 0.3 mmol, 0.5 *M* solution in THF) was added dropwise with stirring to a solution of the alkene **20** (33.8 mg, 0.136 mmol) in THF (1.2 ml) at 0 °C. After 5 h at room temperature, the reaction mixture was recooled to 0 °C and treated, in turn, with a mixture of THF/EtOH (1 ml, 1:1), sodium hydroxide solution (1 ml, 10% aq.), followed by hydrogen peroxide solution (0.3 ml, 30% aq.). The resulting mixture was stirred at room temperature for 2 h, diluted with water (3 ml) and stirred for 1 h. The organic solution was washed with brine (2 x 2 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. After purification by flash chromatography (40% Et_2O/CH_2Cl_2), alcohol **21** was obtained as a colourless oil (31.9 mg, 88%); R_f (40% Et_2O/CH_2Cl_2) 0.37; $[\alpha]_D^{20}$ –21.5 (*c* 1.9, $CHCl_3$); IR (liquid film) 3600-3250 (br), 1460, 1375, 1100 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.33-7.25 (5H, m, Ph), 4.49 (2H, s, CH_2Ph), 3.73-3.48 (2H, m, CH_2OH), 3.56-3.50 (2H, m, CH_2OBn), 4.43 (3H, s, OMe), 2.99 (1H, dd, J = 8.3, 3.8 Hz, CHOMe), 2.92 (1H, br s, OH), 2.06-1.96 (1H, m, CHMe), 1.96-1.88 (1H, m, CHMe), 1.62-1.57 (2H, m, CH_2CH_2OH), 1.01 (3H, d, J = 7.0 Hz, Me), 0.98 (3H, d, J = 6.8 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.6, 128.3, 127.5, 127.4, 87.4, 73.0, 72.3, 61.4, 59.4, 36.7, 33.1, 32.3, 17.1, 15.0; m/z (CI, NH_3) 267 (100, $[M+H]^+$), 235 (53), 91 (38%); HRMS (EI) $[M]^+$ found 266.1870, $C_{16}H_{26}O_3$ requires 266.1882.

(2*S*,3*R*,4*R*)-1-(Benzyloxy)-6-triisopropylsilyloxy-3-methoxy-2,4-dimethylhexane (22) To a stirred mixture of alcohol **21** (2.05 g, 7.7 mmol) and imidazole (1.91 g, 28.1 mmol) in CH_2Cl_2 (27 ml) at room temperature was added triisopropylsilyl chloride (3.0 ml, 14.0 mmol). After 90 min, the reaction mixture was diluted with CH_2Cl_2 (55 ml) and then washed with sodium bicarbonate solution (2 x 35 ml, sat. aq.) and brine (35 ml). The organic solution was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Flash chromatography (20% Et_2O/hexane) of the crude product provided **22** as a colourless oil (3.23 g, 99%); R_f (20% Et_2O/hexane) 0.55; $[\alpha]_D^{20}$ –4.2 (*c* 1.9, $CHCl_3$); IR (liquid film) 1460, 1370, 1255, 1100 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.35-7.55 (5H, m, Ph), 4.50 (2H, s, CH_2Ph), 3.79-3.64 (2H, m, CH_2OSi), 3.55 (1H, dd, J = 8.8, 3.8 Hz, CH_xH_yOBn), 3.47 (1H, dd, J = 8.8, 6.3 Hz, CH_xH_yOBn), 3.41 (3H, s, OMe), 2.94 (1H, dd, J = 8.0, 3.7 Hz, CHOMe), 2.00-1.85 (2H, m, CH_2CH_2OSi), 1.79-1.71 (1H, m, CHMe), 1.33-1.25 (1H, m,

CHMe), 1.06-1.03 (3H, buried m, Me_2CHSi), 1.04 (18H, br d, J = 4.1 Hz, Me_2CHSi), 1.00 (3H, d, J = 4.3 Hz, Me), 0.98 (3H, d, J = 4.2 Hz, Me); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.8, 128.3, 127.5, 127.4, 88.2, 73.0, 72.7, 61.5, 61.3, 36.6, 33.5, 31.4, 18.0, 17.3, 15.1, 12.0; m/z (CI, NH_3) 423 (27, $[M+H]^+$), 249 (82), 141 (90), 109 (60), 91 (100%); HRMS (CI, NH_3) $[M+H]^+$ found 423.3294, $C_{25}H_{47}O_3Si$ requires 423.3294.

(2*S*,3*R*,4*R*)-6-Triisopropylsilyloxy-2,4-dimethyl-1-hexanol (23) A mixture of benzyl ether **22** (61.4 mg, 0.145 mmol) and 10% palladium on charcoal (0.12 g) in dry ethanol (2 ml) was stirred under a hydrogen atmosphere at room temperature for 6 h. The reaction mixture was filtered through celite and the solvent evaporated *in vacuo* to give the crude product, which was purified by flash chromatography (30% Et_2O/CH_2Cl_2) to give **23** as a colourless oil (44.0 mg, 91%); R_f (30% Et_2O/CH_2Cl_2) 0.43; $[\alpha]_D^{20}$ –1.9 (*c* 2.1, $CHCl_3$); IR (liquid film) 3600-3100 (br), 1470, 1390, 1255, 1105 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 3.79-3.56 (2H, m, CH_2OSi), 3.79-3.56 (2H, m, CH_2OH), 3.46 (3H, s, OMe), 2.95 (1H, dd, J = 7.1, 4.1 Hz, CHOMe), 2.00-1.91 (1H, m, $CH_xH_yCH_2OSi$), 1.91-1.83 (1H, m, $CH_xH_yCH_2OSi$), 1.81-1.73 (1H, m, CHMe), 1.35-1.27 (1H, m, CHMe), 1.06-1.01 (3H, buried m, Me_2CHSi), 1.04 (18H, br d, J = 4.2 Hz, Me_2CHSi), 0.97 (3H, d, J = 7.0 Hz, CHMe) 0.93 (3H, d, J = 7.0 Hz, CHMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 92.3, 66.7, 61.5, 60.9, 37.0, 34.4, 32.0, 18.0, 16.9, 15.3, 11.9; m/z (CI, NH_3) 333 (30, $[M+H]^+$), 257 (25), 159 (100), 141 (50), 109 (37%); HRMS (CI, NH_3) $[M+H]^+$ found 333.2825, $C_{18}H_{41}O_3Si$ requires 333.2825.

(2*S*,3*R*,4*R*)-3-Methoxy-6-triisopropylsilyloxy-2,4-dimethyl-1-hexanal (24) To a solution of Dess-Martin periodinane (3.30 g, 7.96 mmol) in CH_2Cl_2 (5 ml) at room temperature was added a solution of the alcohol **23** (0.51 g, 1.53 mmol) in CH_2Cl_2 (5 ml + 5 ml washings) *via* cannula. The reaction mixture was stirred for 6 h before dilution with Et_2O (10 ml) and treatment with $NaHCO_3/Na_2S_2O_3$ mixture (24 ml, 1 : 7, sat. aq.). The organic phase was washed in turn with $NaHCO_3$ solution (8 ml, sat. aq.) and brine (8 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to give the crude aldehyde **24** (0.55 g) – which was used immediately in the next step without any further purification. A pure sample was obtained by flash chromatography (20% Et_2O/hexane) using a short column of silica gel; R_f (20% Et_2O/hexane) 0.38; $[\alpha]_D^{20}$ –22.9 (*c* 1.7, $CHCl_3$); IR (liquid film) 1730, 1465, 1390, 1200, 1090 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.76 (1H, d, J = 2.4 Hz, CHO), 3.77 (1H, ddd, J = 10.0, 6.8, 4.8 Hz, CH_xH_yOSi), 3.69 (1H, ddd, J = 9.9, 8.3, 5.7 Hz, CH_xH_yOSi), 3.39 (3H, s, OMe), 3.22 (1H, dd, J = 6.1, 4.8 Hz, CHOMe), 2.62 (1H, dqd, J = 7.0, 6.2, 2.4 Hz, MeCHCHO), 2.04-1.93 (1H, m, $CH_xH_yCH_2OSi$), 1.80-1.70 (1H, m, $CH_xH_yCH_2OSi$), 1.40-1.30 (1H, m, CHMe), 1.07 (3H, d, J = 7.1 Hz, CHMe), 1.06-1.01 (3H, buried m, Me_2CHSiO), 1.04 (18H, br d, J = 4.3 Hz, Me_2CHSi), 0.94 (3H, d, J = 6.9 Hz, CHMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 204.9, 87.6, 61.3, 59.9, 48.6, 34.7, 31.7, 18.0, 16.2, 12.0, 11.5; m/z (CI, NH_3) 348 (8, $[M+NH_4]^+$), 347 (30), 173 (100%).

(3*S*,4*R*,5*R*)-7-Triisopropylsilyloxy-1-dimethoxyphosphinyl-4-methoxy-3,5-dimethyl-2-heptanol (25) *n*-Butyllithium (3.6 ml, 5.38 mmol, 15% solution in hexane) was added dropwise to a stirred solution of dimethyl methanephosphonate (0.65 ml, 5.90 mmol, freshly distilled) in THF (14 ml) at –78 °C. After 1 h, a solution of the crude aldehyde **24** (0.55 g, prepared by Dess-Martin oxidation) in THF (5 ml + 2 ml washings) was added *via* cannula. After 15 min, the reaction mixture was poured into brine (160 ml) and extracted with ether (4 x 100 ml). The ethereal solution was dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc) of the crude product gave recovered **23** (49.4 mg, 10%) and a 2:1 mixture of β-hydroxyphosphonates **25** as a colourless oil (0.54 g, 86% (based on **24**)); R_f (EtOAc) 0.20; IR (liquid film) 3570-3100, 1730 (br), 1465, 1390, 1240 (br), 1100, 1070, 1045 cm^{-1}; ^1H NMR (major isomer) δ (400 MHz, $CDCl_3$) 3.74 (6H, d, J = 10.9 Hz, POMe), 3.80-3.62 (2H, m, CH_2OTIPS), 3.80-3.62 (1H, buried m, CHOH), 3.48 (3H, s, CHOMe), 3.03 (1H, dd, J = 5.7, 5.7 Hz, CHOMe), 2.17-1.70 (2H, m, CH_2PO), 2.17-1.70 (2H, m, CHMe), 1.37-1.23 (2H, m, CH_2CH_2OTIPS), 1.05-1.01 (3H, buried m, Me_2CH), 1.03 (18H,

br d, J = 2.9 Hz, $\underline{Me}_2$CHSi), 0.94 (6H, d, J = 7.0 Hz, CH$\underline{Me}$); ^{13}C NMR (major isomer) δ (100.6 MHz, $CDCl_3$) 90.3, 65.8, 61.6, 39.7, 39.5, 34.5, 31.9, 31.4, 30.0, 18.0, 16.7, 12.0, 10.8; m/z (CI, NH_3) 455 (100, $[M+H]^+$), 281 (28), 155 (38), 123 (42), 99 (32%); HRMS (CI, NH_3) $[M+H]^+$ found 455.2960, $C_{21}H_{48}O_6PSi$ requires 455.2958.

(3*S*,4*R*,5*R*)-7-Triisopropylsilyloxy-1-dimethoxyphosphinyl-4-methoxy-3,5-dimethyl-2-heptanone (13) Pyridinium dichromate (0.16 g, 0.42 mmol) was added to a stirred mixture of β-hydroxyphosphonate **25** (23.5 mg, 52 μmol) and powered 3Å molecular sieves (a spatula end) in dry DMF (0.6 ml) at 30 °C. After 1 h, the dark brown mixture was poured into brine (15 ml) and extracted with Et_2O (4 x 8 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification by flash chromatography (9:1 EtOAc/CH_2Cl_2) gave **13** as a colourless oil (19.3 mg, 82%); R_f (9:1 EtOAc/CH_2Cl_2) 0.35; $[\alpha]_D^{20}$ –59.5 (*c* 1.9, $CHCl_3$); IR (liquid film) 1714, 1463, 1382, 1259, 1185, 1032 cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.80-3.73 (1H, buried m, C$\underline{H}_x$H$_y$OTIPS), 3.77 (3H, d, J = 11.1 Hz, PO$\underline{Me}$), 3.76 (3H, d, J = 11.2 Hz, PO$\underline{Me}$), 3.68-3.62 (1H, m, CH$_x\underline{H}_y$OTIPS), 3.33 (1H, dd, J = 22.0, 14.3 Hz, C$\underline{H}_x$H$_y$PO), 3.27 (3H, s, CHO$\underline{Me}$), 3.19 (1H, dd, J = 9.3, 2.6 Hz, C$\underline{H}$OMe), 3.10 (1H, dd, J = 21.8, 14.3 Hz, CH$_x\underline{H}_y$PO), 3.07-3.01 (1H, m, C$\underline{H}$C=O), 1.97-1.86 (1H, m, C$\underline{H}_x$H$_y$CH$_2$OTIPS), 1.76-1.63 (1H, m, C$\underline{H}$Me), 1.37-1.26 (1H, m, CH$_x\underline{H}_y$CH$_2$OTIPS), 1.12-1.02 (3H, buried m, Me$_2$C$\underline{H}$), 1.03 (18H, br d, J = 4.4 Hz, ($\underline{CH}_3$)$_2$CHSi), 0.99 (6H, d, J = 6.8 Hz, CH$\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 206.5, 89.5, 61.1, 60.6, 53.0, 52.9, 52.87, 52.8, 49.0, 43.3, 42.0, 33.4, 31.2, 18.0, 16.8, 13.5, 11.9; m/z (CI, NH_3) 453 (86, $[M+H]^+$), 409 (52), 279 (100%); HRMS (CI, NH_3) $[M+H]^+$ found 453.2800, $C_{21}H_{46}O_6PSi$ requires 453.2801.

(2*S*,4*S*,5*R*)-1-Benzyloxy-5-hydroxy-2,4,6-trimethylhept-6-en-3-one (16)[12a,b,d] To a stirred solution of triethylamine (2.1 ml, 15.1 mmol) and dicyclohexylboron chloride (3.9 g, 18.4 mmol) in ether (30 ml) at 0 °C was added ketone (*S*)-**17**[16] (1.9 g, 9.22 mmol) dropwise. After a further 2 h, methacrolein (1.4 ml, 16.9 mmol, freshly distilled over $CaCl_2$) was added and the resulting mixture was stirred for 3.5 h. The reaction mixture was kept at –20 °C in a freezer for 18 h. On work-up, pH 7 buffer (75 ml) was added and the layers separated. The aqueous layer was extracted with ether (3 x 360 ml) and the combined organic extracts were evaporated *in vacuo*. The crude mixture was dissolved in methanol (58 ml) and pH 7 buffer (58 ml) to give a white suspension which was cooled to 0 °C and hydrogen peroxide solution (35 ml, 30% aq.) added. This mixture was stirred for 1 h before the addition of distilled water (100 ml) and extracting with CH_2Cl_2 (3 x 200 ml). Each extract was washed with sodium bicarbonate solution (50 ml, sat. aq) and brine (50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow oil which was purified by flash chromatography (10% Et_2O/CH_2Cl_2) to give **16** as a colourless oil (2.17 g, 85%); R_f (10% Et_2O/CH_2Cl_2) 0.46; $[\alpha]_D^{20}$ +12.3 (*c* 1.6, $CHCl_3$); IR (liquid film) 3450, 1700 cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.32–7.25 (5H, m, Ph), 4.94 (1H, br s, olefinic), 4.91 (1H, br s, olefinic), 4.49 & 4.47 (2H, AB, J_{AB} = 12.2 Hz, OC$\underline{H}_2$Ph), 4.18 (1H, dd, J = 8.6, 4.3 Hz, C$\underline{H}$OH), 3.64 (1H, t, J = 8.6 Hz, C$\underline{H}_x$H$_y$OBn), 3.43 (1H, dd, J = 8.6, 5.1 Hz, CH$_x\underline{H}_y$OBn), 3.07 (1H, dqd, J = 8.6, 7.0, 5.1 Hz, C$\underline{H}$CH$_2$OBn), 2.92 (1H, dq, J = 8.6, 7.0 Hz, HOCHC$\underline{H}$(Me)C=O), 2.72 (1H, d, J = 4.3, O$\underline{H}$), 1.65 (3H, s, allylic $\underline{Me}$), 1.03 (3H, d, J = 7.0 Hz, $\underline{Me}$), 0.97 (3H, d, J = 7.0 Hz, $\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.3, 144.5, 137.8, 128.4 (2C), 127.7, 127.6 (2C), 114.0, 78.3, 73.3, 72.2, 49.1, 46.0, 16.8, 13.7, 13.5; m/z (CI, NH_3) 294 (50, $[M+NH_4]^+$), 259 (90), 224 (50), 207 (100), 108 (54), 91 (15%); HRMS (CI, NH_3) $[M+NH_4]^+$ found 294.2069; $C_{17}H_{28}O_3N$ requires 294.2069.

(2*S*,3*R*,4*R*,5*R*)-1-Benzyloxy-3,5-dihydroxy-2,4,6-trimethyl-6-heptene (27)[12a,b] A solution of tetramethylammonium triacetoxyborohydride (11.7 g, 37.1 mmol) in acetonitrile (30 ml) and anhydrous acetic acid (30 ml) was stirred at room temperature for 1 h. This mixture was cooled to –30 °C and a solution of ketone **16** (1.53 g, 5.53 mmol) in anhydrous acetic acid (15 ml) was added *via* cannula. The reaction mixture

was stirred at –30 °C for 2 h then quenched by addition of sodium potassium tartrate solution (120 ml, 0.5 *N* aq.) with vigorous stirring for 1 h, followed by extraction with CH_2Cl_2 (2 x 150 ml). The organic extracts were washed with sodium bicarbonate solution (225 ml, sat. aq.), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% Et_2O/CH_2Cl_2) to give recovered ketone **16** (0.17 g, 11%) and diol **27** as a colourless oil (1.06 g, 69%; 78% based on recovered **16**); R_f (10% Et_2O/CH_2Cl_2) 0.24; $[\alpha]_D^{20}$ +39.1 (*c* 0.5, $CHCl_3$); IR (liquid film) 3360 (br), 1640 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.38–7.28 (5H, m, Ph), 5.10 (1H, br s, olefinic), 4.94 (1H, br s, olefinic), 4.55 & 4.49 (2H, AB, J_{AB} = 11.8 Hz, $OC\underline{H}_2Ph$), 4.05 (1H, d, *J* = 9.5 Hz, C<u>H</u>OH), 4.05 (1H, buried, O<u>H</u>), 3.78 (1H, d, *J* = 9.5, C<u>H</u>OH), 3.58 (1H, dd, *J* = 8.9, 4.1 Hz, $C\underline{H}_xH_yOBn$), 3.48 (1H, t, *J* = 8.9 Hz, $CH_x\underline{H}_yOBn$), 3.35 (1H, d, *J* = 6.8 Hz, O<u>H</u>), 2.04–1.94 (1H, m, C<u>H</u>Me), 1.83–1.77 (1H, m, C<u>H</u>Me), 1.68 (3H, s, allylic <u>Me</u>), 1.02 (3H, d, *J* = 7.0 Hz, <u>Me</u>), 0.94 (3H, d, *J* = 7.0 Hz, <u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 146.2, 137.5, 128.4 (2C), 127.7, 127.6 (2C), 111.5, 79.1, 76.4, 75.7, 73.4, 35.7, 35.6, 16.6, 12.9, 9.9; m/z (CI, NH_3) 279 (60, $[M+H]^+$), 261 (100%); HRMS (CI, NH_3) $[M+H]^+$ found 279.1960; $C_{17}H_{27}O_3$ requires 279.1960.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-3,5-(di-*tert*-butylsilylene)dioxy-2,4,6-trimethyl-6-heptene (28) To a solution of the 1,3-diol **27** (1.04 g, 3.74 mmol) dissolved in CH_2Cl_2 (2.3 ml) at room temperature was added 2,6-lutidine (1.40 ml, 11.98 mmol) followed by di-*tert*-butylsilyl ditriflate (2.10 ml, 6.49 mmol). The reaction mixture was then stirred for 15 h at room temperature before diluting with CH_2Cl_2 (40 ml) and washing with sodium bicarbonate solution (40 ml, sat. aq.) and brine (40 ml). The organic solution was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. After purification by flash chromatography (10% Et_2O/CH_2Cl_2), **28** was obtained as a colourless oil (1.48 g, 95%); R_f (10% Et_2O/CH_2Cl_2) 0.87; $[\alpha]_D^{20}$ –24.8 (*c* 0.8, $CHCl_3$); IR (liquid film) 1650, 1450, 1365, 1260, 1215 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.34-7.25 (5H, m, Ph), 4.93 (1H, s, $C\underline{H}_xH_y$=), 4.75 (1H, s, $CH_x\underline{H}_y$=), 4.42 (2H, ABq, $C\underline{H}_2Ph$), 4.22 (1H, d, *J* = 4.2 Hz, C<u>H</u>OSi), 4.02 (1H, dd, *J* = 9.1, 3.6 Hz, C<u>H</u>OSi), 3.71 (1H, dd, *J* = 8.6, 3.3 Hz, $C\underline{H}_xH_yOBn$), 3.50 (1H, dd, *J* = 8.6, 6.8 Hz, $CH_x\underline{H}_yOBn$), 1.99-1.84 (1H, m, C<u>H</u>Me), 1.84-1.82 (1H, m, C<u>H</u>Me), 1.76, (3H, s, CH_2=C$C\underline{H}_3$), 1.05 (9H, s, $\underline{Me}_3CSi$), 1.05 (3H, d, *J* = 6.6 Hz, CH<u>Me</u>),1.04 (9H, s, $\underline{Me}_3CSi$), 0.95 (3H, d, *J* = 6.8 Hz, CH<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 147.6, 138.8, 128.2, 127.6, 127.3, 109.8, 82.2, 73.7, 73.1, 72.4, 37.7, 37.0, 28.1, 27.7, 22.1, 21.8, 17.8, 14.1, 13.7; m/z (CI, NH_3) 419 (100, $[M+H]^+$), 229 (18), 108 (32), 91 (78%); HRMS (CI, NH_3) $[M+H]^+$ found 419.2981, $C_{25}H_{43}O_3Si$ requires 419.2981.

(2*S*,3*S*,4*S*,5*S*,6*S*)-7-Benzyloxy-3,5-(di-*tert*-butylsilylene)dioxy-2,4,6-trimethyl-1-heptanol (29) To a solution of the alkene **28** (1.90 g, 4.56 mmol) in THF (37 ml) at 0 °C was added slowly 9-BBN (43.0 ml, 21.5 mmol, 0.5 *M* solution in THF). After 18 h at room temperature, the reaction mixture was cooled to 0 °C and treated, in turn, with a mixture of THF/EtOH (105 ml, 1:1), sodium hydroxide solution (105 ml, 10% aq.) and hydrogen peroxide solution (27 ml, 30% aq.). After stirring at room temperature for 3 h, water (290 ml) was added and the mixture was stirred for another 2 h. The mixture was extracted with ether (3 x 400 ml) and the ether solution washed with brine (400 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (hexanes and EtOAc, 100% to 15% gradient) gave the desired isomer **29** as a colourless oil (1.31 g, 66%); R_f (10% Et_2O/CH_2Cl_2) 0.56, (30% EtOAc/hexane) 0.49; $[\alpha]_D^{20}$ –21.3 (*c* 0.56, $CHCl_3$); IR (liquid film) 3441 (br), 1470, 1454, 1386, 1361, 1096 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 4.54-4.44 (2H, ABq, $C\underline{H}_2Ph$), 4.03 (1H, dd, *J* = 9.9, 3.0 Hz, C<u>H</u>OSi), 3.75-3.69 (2H, m, $HOC\underline{H}_2$), 3.67-3.62 (2H, m, $C\underline{H}_2OBn$), 3.35 (1H, dd, *J* = 7.0, 4.5 Hz, C<u>H</u>OSi), 1.93-1.85 (1H, m, $HOCH_2C\underline{H}$), 1.93-1.85 (1H, m, C<u>H</u>CH_2OBn), 1.84-1.79 (1H, m, C<u>H</u>Me), 1.05 (9H, s, $\underline{Me}_3CSi$), 1.03 (3H, d, *J* = 7.5 Hz, CH<u>Me</u>), 1.01 (9H, s, $\underline{Me}_3CSi$), 0.91 (3H, d, *J* = 11.7 Hz, CH<u>Me</u>), 0.86 (3H, d, *J* = 10.4 Hz, CH<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.7, 128.2, 127.6, 127.4, 85.6, 73.1, 72.9, 72.3, 67.7, 41.4, 37.3, 36.9, 28.4, 28.2, 27.6, 21.9, 21.7, 13.8, 13.7; m/z (CI, NH_3) 437 (100, $[M+H]^+$), 261 (22), 189 (22), 108 (50), 99 (27), 91 (96%); HRMS (CI, NH_3) $[M+H]^+$ found 437.3090, $C_{25}H_{45}O_4Si$ requires 437.3087.

(2*S*,3*S*,4*S*,5*S*,6*S*)-7-Benzyloxy-3,5-(di-*tert*-butylsilylene)dioxy-2,4,6-trimethyl-1-heptanal (14) To a solution of oxalyl chloride (0.40 ml, 4.59 mmol) in CH_2Cl_2 (20 ml) at –78 °C was added DMSO (0.68 ml, 9.58 mmol) dropwise. After 15 min, a solution of alcohol **29** (0.41 g, 0.94 mmol) in CH_2Cl_2 (6 ml + 6 ml washing + 3 ml washing) was added *via* cannula and the resulting mixture stirred for 1 h before the addition of triethylamine (1.80 ml, 12.91 mmol). The reaction mixture was stirred for another 3 h at –78 °C, then allowed to warm to –25 °C over 45 min and immediately quenched with ammonium chloride solution (30 ml, sat. aq.). The mixture was allowed to warm to room temperature, the organic layer separated and the aqueous layer extracted with hexane (3 x 30 ml). The combined organic extracts were washed with sodium bicarbonate solution (30 ml, sat. aq.) then brine (30 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (20% EtOAc/hexane) to give **14** as a colourless oil (0.39 g, 95%); R_f (20% EtOAc/hexane) 0.52; $[\alpha]_D^{20}$ –56.9 (*c* 0.4, $CHCl_3$); IR (liquid film) 1730, 1476, 1388, 1363, 1260, 1140, 1100, 1008 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.74 (1H, d, *J* = 3.4 Hz, C<u>H</u>O), 7.33-7.26 (5H, m, Ph), 4.54-4.43 (2H, ABq, C<u>H</u>$_2$Ph), 4.04-4.01 (2H, m, C<u>H</u>$_2$OBn), 3.64 (1H, dd, *J* = 8.5, 3.1 Hz, C<u>H</u>OSi), 3.55 (1H, dd, *J* = 8.5, 6.0 Hz, C<u>H</u>OSi), 2.57-2.52 (1H, m, CHOC<u>H</u>Me), 1.69-1.64 (2H, m, C<u>H</u>Me), 1.10 (3H, d, *J* = 7.3 Hz, CHOCH<u>Me</u>), 1.06 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>), 1.02 (9H, s, <u>Me</u>$_3$CSi) 0.98 (9H, s, <u>Me</u>$_3$CSi), 0.91 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 204.7, 138.7, 128.2, 127.6, 127.4, 81.1, 73.1, 72.5, 72.2, 52.6, 37.1, 35.6, 28.2, 27.6, 22.1, 21.6, 13.7, 13.6, 10.9; m/z (CI, NH_3) 435 (36, $[M+H]^+$), 229 (55), 91 (100%); HRMS (CI, NH_3) $[M+H]^+$ found 435.2903, $C_{25}H_{43}O_3Si$ requires 435.2903.

(2*S*,3*S*,4*R*,5*R*,6*R*,10*R*,11*R*,12*R*)-1-Benzyloxy-3,5-(di-*tert*-butylsilylene)dioxy-14-triisopropylsilyloxy-11-methoxy-2,4,6,10,12-pentamethyltetradec-7-en-9-one (31) A mixture of ketophosphonate **13** (0.35 g, 0.78 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (0.20 g, 0.62 mmol; activated by heating to 100-140 °C for 1-2 h before use) in THF (2 ml) was stirred at room temperature for 30 min. A solution of aldehyde **14** (0.34 g, 0.78 mmol) in wet THF (2 ml + 2 x 1 ml washings, 40:1 THF/H_2O) was then added and stirring was maintained at room temperature for 6.5 h. The reaction mixture was diluted with CH_2Cl_2 (60 ml) and washed with sodium bicarbonate solution (30 ml, sat. aq.) and brine (30 ml). The organic solution was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification by flash chromatography (20% Et_2O/hexane) gave **31** as a colourless oil (0.57 g, 96%); R_f (20% Et_2O/hexane) 0.40; $[\alpha]_D^{20}$ –38.7 (*c* 0.7, $CHCl_3$); IR (liquid film) 1695, 1671, 1627, 1462, 1374, 1142, 1095, 1006 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$, assigned by COSY) 7.34-7.26 (5H, m, Ph), 7.00 (1H, dd, *J* = 15.9, 8.2 Hz, 25-C<u>H</u>), 6.17 (1H, d, *J* = 15.9 Hz, 26-C<u>H</u>), 4.52-4.43 (2H, ABq, C<u>H</u>$_2$Ph), 3.87 (1H, dd, *J* = 9.6, 3.2 Hz, 21-C<u>H</u>), 3.79-3.62 (4H, m, 19-C<u>H</u>$_A$, 23-C<u>H</u>, 32-C<u>H</u>$_2$), 3.45 (1H, dd, *J* = 8.5, 6.9 Hz, 19-C<u>H</u>$_B$), 3.36 (1H, dd, *J* = 9.3, 2.0 Hz, 29-C<u>H</u>), 3.25 (3H, s, O<u>Me</u>), 3.10 (1H, dq, *J* = 9.3, 7.0 Hz, 28-C<u>H</u>), 2.50-2.42 (1H, m, 24-C<u>H</u>), 1.96-1.82 (3H, m, 20-C<u>H</u>, 22-C<u>H</u>, 30-C<u>H</u>), 1.73-1.65 (1H, m, 31-C<u>H</u>$_A$), 1.36-1.27 (1H, m, 31-C<u>H</u>$_B$), 1.11 (3H, d, *J* = 6.7 Hz, 24-C<u>Me</u>), 1.15-0.85 (3H, m, (Me$_2$C<u>H</u>)$_3$Si), 1.07-0.97 (6H, buried d's, 28-C<u>Me</u>, 30-C<u>Me</u>), 1.04 (18H, d, *J* = 4.3 Hz, (<u>Me</u>$_2$CH)$_3$Si), 1.02 (9H, s, ^{t}BuSi), 0.99 (9H, s, ^{t}BuSi), 0.94 (3H, d, *J* = 7.0 Hz, 20-C<u>Me</u> or 22-C<u>Me</u>), 0.89 (3H, d, *J* = 6.8 Hz, 20-C<u>Me</u> or 22-C<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 204.0, 149.1, 138.8, 130.8, 128.2, 127.6, 127.3, 88.0, 82.1, 73.4, 73.1, 72.5, 61.3, 60.7, 45.5, 43.8, 36.9, 36.5, 33.1, 30.9, 28.2, 27.7, 22.1, 21.8, 18.0, 17.0, 16.2, 14.1, 13.8, 13.5, 11.9; m/z (CI, NH_3) 761 (6, $[M+H]^+$), 729 (12), 377 (32), 229 (69), 99 (100%); HRMS (CI, NH_3) $[M+H]^+$ found 761.5570, $C_{44}H_{81}O_6Si_2$ requires 761.5571.

(2*S*,3*S*,4*R*,5*R*,6*R*,10*R*,11*R*,12*R*)-3,5-(Di-*tert*-butylsilylene)dioxy-1-hydroxy-14-triisopropylsilyloxy-11-methoxy-2,4,6,10,12-pentamethyltetradecan-9-one (32) A mixture of the *E*-enone **31** (76.8 mg, 0.101 mmol) and 10% palladium on charcoal (0.232 g) in dry ethanol (7 ml) was stirred under a hydrogen atmosphere at room temperature for 2.5 h. The reaction mixture was filtered through celite and the solvent evaporated *in vacuo*. Flash chromatography (50% Et_2O/hexane) gave **32** as a colourless oil (65.9 mg, 97%); R_f (50% Et_2O/hexane) 0.50; $[\alpha]_D^{20}$ –24.7 (*c* 1.2, $CHCl_3$); IR (liquid film) 3600-3200 (br),

1714, 1470, 1454, 1384, 1092 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.06 (1H, dd, C<u>H</u>OMe), 3.80-3.63 (4H, overlapping m's, C<u>H</u>$_2$OH and C<u>H</u>$_2$OSi), 3.62 (1H, dd, J = 5.8, 3.3 Hz, C<u>H</u>OSi), 3.58 (1H, dd, J = 10.1, 3.1 Hz, C<u>H</u>OSi), 3.28 (3H, s, O<u>Me</u>), 2.83 (1H, qd, J = 9.4, 7.0 Hz, C<u>H</u>C=O), 2.60 (1H, ddd, J = 17.1, 9.6, 5.3 Hz, C<u>H</u>$_x$H$_y$C=O), 2.46 (1H, ddd, J = 17.2, 9.2, 6.3 Hz, CH$_x$<u>H</u>$_y$C=O), 2.03-1.81 (4H, overlapping m's, C<u>H</u>$_x$H$_y$CH$_2$OSi and CH$_3$C<u>H</u>), 1.73-1.66 (1H, m, MeC<u>H</u>), 1.64-1.56 (1H, m, CH$_x$C<u>H</u>$_y$CH$_2$OSi), 1.56-1.42 (1H, m, C<u>H</u>$_x$H$_y$CH$_2$C=O), 1.39-1.21 (1H, m, CH$_x$<u>H</u>$_y$CH$_2$C=O), 1.08-1.02 (6H, 3 buried m's and 1 buried d, Me$_2$C<u>H</u>Si and <u>Me</u>CH), 1.06 (18H, d, J = 5.2 Hz, <u>Me</u>$_2$CHSi), 1.04 (18H, br s, <u>Me</u>$_3$CSi), 1.00 (3H, d, J = 7.0 Hz, <u>Me</u>CH), 0.95 (3H, d, J = 7.0 Hz, <u>Me</u>CH), 0.91 (3H, d, J = 6.6 Hz, <u>Me</u>CH) 0.75 (3H, d, J = 6.9 Hz, <u>Me</u>CH); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.7, 88.4, 82.8, 80.2, 69.5, 61.2, 60.8, 48.3, 41.5, 39.4, 37.3, 36.0, 33.3, 30.9, 28.2, 27.8, 24.9, 22.2, 21.9, 18.0, 17.1, 15.4, 14.2, 13.7, 13.2, 11.9; m/z (CI, NH_3) 371 (8), 273 (9), 229 (19), 195 (9), 99 (100), 58 (11%); HRMS (CI, NH_3) $[M+H]^+$ found 673.5260, $C_{37}H_{77}O_6Si_2$ requires 673.5258.

(2*S*,3*S*,4*R*,5*R*,6*R*,10*R*,11*R*,12*R*)-3,5-(Di-*tert*-butylsilylene)dioxy-14-triisopropylsilyloxy-9-keto-11-methoxy-2,4,6,10,12-pentamethyltetradecanal (11) A mixture of Dess-Martin periodinane (63 mg, 150 μmol) in CH_2Cl_2 (0.8 ml) was stirred at room temperature for 15 min. A solution of alcohol **32** (20.3 mg, 30.2 μmol) in CH_2Cl_2 (0.5 ml) was then added dropwise. After a further 35 min, the reaction mixture was diluted with ether (2.5 ml) and the resulting white suspension treated with a 1:7 mixture of $NaHCO_3/Na_2S_2O_3$ (2 ml, sat. aq.). After 10 min, the organic solution was separated, washed with sodium bicarbonate solution (2 ml, sat. aq.) and brine (2 ml), and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography (20% Et_2O/hexane) to give **11** as a colourless oil (17.9 mg, 88%); R_f (20% Et_2O/hexane) 0.35; $[\alpha]_D^{20}$ –58.3 (*c* 0.96, $CHCl_3$); IR (liquid film) 1740, 1470, 1480, 1400, 1375, 1100 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.89 (1H, d, J = 3.0 Hz, CO<u>H</u>), 4.29 (1H, dd, J = 9.3, 3.6 Hz, C<u>H</u>OMe), 3.80-3.74 (1H, m, C<u>H</u>$_x$CH$_y$OSi), 3.69-3.63 (1H, m, CH$_x$C<u>H</u>$_y$OSi), 3.65 (1H, dd, J = 4.5, 4.5 Hz, C<u>H</u>OSi), 3.29 (1H, dd, J = 9.6, 2.5 Hz, C<u>H</u>OSi), 3.28 (3H, s, O<u>Me</u>), 2.83 (1H, qd, J = 9.4, 7.0 Hz, C<u>H</u>C=O), 2.64-2.56 (2H, 1 ddd overlapped with 1 dqd, C<u>H</u>$_x$H$_y$C=O and C<u>H</u>COH), 2.46 (1H, ddd, J = 17.3, 9.0, 6.6 Hz, CH$_x$<u>H</u>$_y$C=O), 2.03-1.96 (1H, m, MeC<u>H</u>), 1.92-1.85 (1H, m, MeC<u>H</u>), 1.85-1.79 (1H, m, C<u>H</u>$_x$H$_y$CH$_2$OSi), 1.73-1.65 (1H, m, CH$_x$<u>H</u>$_y$CH$_2$OSi), 1.63-1.58 (1H, m, MeC<u>H</u>), 1.52-1.42 (1H, m, C<u>H</u>$_x$H$_y$CH$_2$C=O), 1.36-1.28 (1H, m, CH$_x$<u>H</u>$_y$CH$_2$C=O), 1.08-0.97 (6H, 3 buried m's and 1 buried d, Me$_2$C<u>H</u>Si and <u>Me</u>CH), 1.06 (3H, d, J = 3.8 Hz, <u>Me</u>CH), 1.05 (18H, br s, <u>Me</u>$_2$CHSi), 1.02 (9H, s, <u>Me</u>$_3$CSi), 1.00 (9H, s, <u>Me</u>$_3$CSi), 0.99 (3H, d, J = 3.4 Hz, <u>Me</u>CH), 0.94 (3H, d, J = 5.5 Hz, <u>Me</u>CH), 0.92 (3H, d, J = 5.2 Hz, <u>Me</u>CH); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.7, 205.3, 88.4, 81.9, 74.8, 61.2, 60.8, 49.2, 48.3, 41.4, 38.6, 36.2, 33.3, 30.9, 28.0, 27.7, 24.4, 22.1, 21.8, 18.0, 17.1, 15.6, 13.9, 13.7, 12.0, 10.8.

Mukaiyama Aldol Adduct (10) To a solution of the methyl ketone **12** (21.7 mg, 42.7 μmol) in THF (1.5 ml) at –78 °C was added a mixture of TMSCl/Et_3N (200 μl, 427 μmol, 1:1 v/v) followed by LiN(TMS)$_2$ (80 μl, 80 μmol, 1 *M* solution in THF). After 20 min, most of the ketone had reacted, as judged by TLC analysis. Further portions of LiN(TMS)$_2$ (150 μl, 150 μmol, 1 *M* solution in THF) and TMSCl/Et_3N (100 μl, 214 μmol, 1:1 v/v) were added to drive the reaction to completion. After a further 40 min, the reaction mixture was quenched with pH 7 buffer (2.5 ml), diluted with pentane (6 ml), and warmed to room temperature. The organic layer was separated and the aqueous layer re-extracted with pentane (3 x 2.5 ml). The combined organic extracts were washed with pH 7 buffer (4.5 ml) and brine (4.5 ml). The solution was dried ($MgSO_4$) and the solvent evaporated *in vacuo.* The residual solvent was removed under high vacuum (0.5 – 1.0 mmHg, *ca* 1 h) and the crude silyl enol ether **33** was used immediately in the next step.

To a stirred solution of the crude silyl enol ether **33** (prepared as above) in CH_2Cl_2 (1.5 ml) at –78 °C was added a solution of the aldehyde **11** (32.0 mg, 47.8 μmol) in CH_2Cl_2 (1.0 + 0.5 ml washings) *via* cannula, followed by the dropwise addition of $F_3B{\bullet}OEt_2$ (22.0 μl, 163 μmol). After a further 0.5 h, the reaction mixture was quenched with $NaHCO_3$ solution (6.0 ml, sat. aq.), then warmed to room temperature and diluted with

Et_2O (18 ml). The organic layer was separated and the aqueous layer re-extracted with Et_2O (3 x 5 ml). The combined organic extracts were washed with $NaHCO_3$ solution (10 ml, sat. aq.) and brine (10 ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification by flash chromatography (30% – 50% Et_2O/hexane) gave **10** as a colourless oil (42.2 mg, 84%); R_f (50% Et_2O/hexane) 0.50; $[\alpha]_D^{20}$ –56.7 (*c* 1.3, $CHCl_3$); IR (liquid film) 3529 (br), 1716, 1623, 1462, 1385, 1309, 1256, 1169, 1104, 1091, 983, 826 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$, assigned by COSY) 7.31 (1H, d, *J* = 15.7 Hz, 3-CH), 5.96 (1H, br t, *J* = 7.2 Hz, 5-CH), 5.79-5.73 (1H, m, 11-CH), 5.78 (1H, d, *J* = 15.7 Hz, 2-CH), 5.63 (1H, br d, *J* = 10.4 Hz, 10-CH), 4.57 (1H, br d, *J* = 9.7 Hz, 19-CH), 4.32 (1H, br d, *J* = 10.2 Hz, 9-CH), 4.15-3.99 (1H, m, 7-CH), 4.13 (1H, dd, *J* = 9.7, 2.6 Hz, 21-CH), 3.79-3.72 (1H, m, 32-CH_A), 3.73 (3H, s, CO_2Me), 3.71-3.63 (2H, m, 15-CH, 32-CH_B), 3.60-3.54 (1H, m, 13-CH), 3.57 (1H, dd, *J* = 6.3, 2.7 Hz, 23-CH), 3.32-3.26 (1H, dd, 29-CH), 3.31 (3H, s, CHOMe), 3.28 (3H, s, CHOMe), 3.23 (1H, d, *J* = 3.6 Hz, OH), 2.83 (1H, dq, *J* = 9.4, 7.0 Hz, 28-CH), 2.81-2.74 (2H, m, 18-CH_2), 2.72 (1H, qd, *J* = 7.1, 3.8 Hz, 16-CH), 2.63-2.43 (2H, m, 26-CH_2), 2.40 (2H, br dd, 6-CH_2), 1.98-1.58 (10H, m, 8-CH_A, 12-CH_2, 14-CH_2, 22-CH, 24-CH, 25-CH_A, 30-CH, 31-CH_A), 1.76 (3H, s, 4-Me), 1.58-1.45 (2H, m, 20-CH, 25-CH_B), 1.41-1.35 (1H, m, 8-CH_B), 1.34-1.27 (1H, m, 31-CH_B), 1.12 (3H, d, *J* = 7.1 Hz, 16-CHMe), 1.10-0.85 (3H, m, $(Me_2CH)_3Si$), 1.06-1.01 (3H, d, MeCH) 1.04 (18H, br d, *J* = 4.7 Hz, $(Me_2CH)_3Si$), 1.01, (18H, br s, $^tBu_2Si$), 0.99 (3H, d, *J* = 7.0 Hz, MeCH), 0.93 (3H, d, *J* = 7.0 Hz, 28-CHMe) 0.89-0.87 (3H, d, MeCH) 0.88 (9H, br s, 7-CHOSi^{t}Bu), 0.79 (3H, d, *J* = 7.0 Hz, 20-CHMe), 0.10 (3H, s, SiMe), 0.09 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.9, 214.8, 168.0, 149.6, 137.8, 134.2, 130.3, 123.6, 115.3, 88.3, 83.1, 78.7, 77.2, 73.2, 69.2, 67.9, 66.3, 63.8, 61.2, 60.8, 57.2, 51.5, 49.6, 48.3, 46.9, 41.4, 40.7, 40.4, 39.1, 37.6, 36.6, 35.4, 33.2, 30.84, 30.77, 28.4, 27.7, 25.9, 25.3, 22.1, 21.7, 18.0, 17.0, 15.4, 14.0, 13.7, 12.5, 11.9, 10.8, 9.5, –4.3, –4.7; m/z (+ve FAB) 1162 (55), 832 (100), 736 (70), 672 (60), 614 (50), 459 (50), 435 (65%); HRMS (+ve FAB, NOBA matrix) $[M+H]^+$ found 1179.8222, $C_{65}H_{123}O_{12}Si_3$ requires 1179.8322.

***Syn*-diol (34)** To a cooled (–78 °C) solution of ketone **10** (249 mg, 0.20 mmol) in THF (20 ml) was added catecholborane (268 μl, 2.53 mmol) in one portion. The reaction mixture was warmed gradually to –20 °C over 4 h. After a further 18 h, the reaction mixture was quenched by the addition of potassium sodium tartrate (20 ml, sat. aq.) and stirred at room temperature for 4 h. The layers were separated and the aqueous layer was diluted with water (20 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (2 → 20% Et_2O/CH_2Cl_2) gave **34** as a colourless oil (213 mg, 85%); R_f (10% Et_2O/CH_2Cl_2) 0.40; $[\alpha]_D^{20}$ –58.4 (*c* 1.1, $CHCl_3$); IR (liquid film) 3464, 1716, 1622, 1462, 1382, 1310, 1256, 1168, 1091, 1008, 984, 826 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$, assigned by COSY) 7.33 (1H, d, *J* = 15.7 Hz, 3-CH), 5.99 (1H, br t, *J* = 7.3 Hz, 5-CH), 5.80-5.73 (1H, m, 11-CH), 5.79 (1H, d, *J* = 15.7 Hz, 2-CH), 5.64 (1H, br d, *J* = 10.1 Hz, 10-CH), 4.35 (1H, br s, OH), 4.33 (1H, br d, 19-CH), 4.28 (1H, br d, *J* = 9.1 Hz, 9-CH), 4.17 (1H, dd, *J* = 9.4, 2.1 Hz, 21-CH), 4.12-4.05 (1H, m, 7-CH), 3.96 (1H, d, *J* = 3.8 Hz, OH), 3.87 (1H, br td, 17-CH), 3.80-3.72 (1H, m, 32-CH_A), 3.74 (3H, s, CO_2Me), 3.71-3.63 (2H, m, 15-CH, 32-CH_B), 3.63-3.55 (1H, m, 13-CH), 3.58 (1H, dd, *J* = 6.2, 2.1 Hz, 23-CH), 3.30-3.25 (1H, dd, 29-CH), 3.37 (3H, s, CHOMe), 3.29 (3H, s, CHOMe), 2.84 (1H, qd, *J* = 7.0, 7.0 Hz, 28-CH), 2.60 (1H, ddd, *J* = 16.6, 10.4, 5.6 Hz, 26-CH_A), 2.47 (1H, ddd, *J* = 16.6, 9.9, 6.4 Hz, 26-CH_B), 2.40 (2H, br dd, 6-CH_2), 2.00-1.96 (2H, m, 20-CH, 22-CH), 1.96-1.84 (4H, m, 8-CH_A, 12-CH_2, 25-CH_A), 1.76 (3H, s, 4-Me), 1.75-1.60 (7H, m, 14-CH_2, 16-CH, 18-CH_A, 24-CH, 30-CH, 31-CH_A), 1.54-1.43 (1H, m, 18-CH_B), 1.43-1.28 (3H, m, 8-CH_B, 25-CH_B, 31-CH_B), 1.11-1.03 (6H, buried d and m, MeCH, $(Me_2CH)_3Si$), 1.07 (18H, br d, *J* = 6.9 Hz, $(Me_2CH)_3Si$), 1.04, (18H, br s, $^tBu_2Si$), 1.01 (3H, d, *J* = 7.0 Hz, MeCH), 0.95 (3H, d, *J* = 6.9 Hz, MeCH) 0.91-0.87 (6H, d, MeCH, 28-CHMe) 0.89 (9H, br s, 7-CHOSi^{t}Bu), 0.82 (3H, d, *J* = 6.9 Hz, MeCH), 0.11 (3H, s, SiMe), 0.08 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.8, 168.0, 149.7, 137.9, 134.2, 130.4, 123.6, 115.3, 88.4, 83.2, 79.5, 77.2, 75.9, 74.1, 72.7, 69.1, 67.8, 64.1, 61.2, 60.8, 56.9, 51.4, 48.3, 41.4, 41.3, 40.43, 40.41, 39.0, 38.4, 37.5, 36.1, 35.6, 33.3, 30.9, 29.7, 28.5, 27.7, 25.9, 25.3, 22.1, 21.7, 18.0,

17.1, 15.5, 14.2, 13.7, 12.5, 12.0, 10.8, 10.6, –4.3, –4.7; ^{13}C NMR δ (100.6 MHz, C_6D_6) 212.7, 167.6, 149.6, 137.8, 134.5, 130.8, 124.0, 116.3, 88.5, 83.9, 79.8, 76.1, 74.1, 71.5, 69.4, 68.4, 64.3, 61.7, 60.7, 56.5, 51.1, 48.5, 42.4, 41.5, 40.8, 40.1, 39.6, 38.2, 36.2, 33.8, 31.5, 31.3, 28.9, 28.2, 26.16, 26.15, 26.1, 25.6, 22.5, 22.0, 18.3, 17.3, 15.8, 14.3, 13.9, 12.4, 12.3, 11.3, 9.9, –4.1, –4.5; m/z (+ve FAB) 1182 (100), 653 (20), 614 (40), 436 (65%); HRMS (+ve FAB, NOBA matrix) $[M+H]^+$ found 1181.8459, $C_{65}H_{125}O_{12}Si_3$ requires 1181.8478.

Fully Protected Seco Acid (9) To a solution of diol **34** (452 mg, 0.38 mmol) in 2,6-di-*tert*-butylpyridine (6 ml, 27 mmol) was added methyl triflate (1.5 ml, 13 mmol). The reaction mixture was stirred at room temperature for 18 h then quenched with water (10 ml, sat. aq.) and diluted with $NaHCO_3$ (50 ml, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 70 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10 → 50% Et_2O/hexane) gave **9** as a colourless oil (379 mg, 82%); R_f (30% Et_2O/hexane) 0.32; $[\alpha]_D^{20}$ –55.4 (*c* 0.7, $CHCl_3$); IR (liquid film) 1718, 1623, 1463, 1386, 1257, 1167, 1090, 982, 826 cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* = 15.6 Hz, 3-CH), 6.03 (1H, br t, *J* = 6.8 Hz, 5-CH), 5.84-5.67 (1H, m, 11-CH), 5.78 (1H, d, *J* = 15.6 Hz, 2-CH), 5.63 (1H, br d, *J* = 10.4 Hz, 10-CH), 4.32 (1H, br d, *J* = 9.6 Hz, 9-CH), 4.20-4.11 (1H, m, 7-CH), 4.15 (1H, dd, *J* = 9.8, 2.2 Hz, 21-CH), 4.04 (1H, dd, *J* = 10.0, 3.6 Hz, C<u>H</u>OMe), 3.80-3.72 (1H, m, 32-CH_A), 3.73 (3H, s, CO_2Me), 3.72-3.63 (2H, m, 15-CH, 32-CH_B), 3.60-3.50 (1H, m, 13-CH), 3.56 (1H, dd, *J* = 5.2, 2.0 Hz, 23-CH), 3.43 (3H, s, CHO<u>Me</u>), 3.33 (3H, s, CHO<u>Me</u>), 3.30-3.25 (1H, dd, *J* = 2.4 Hz, 29-CH), 3.28 (6H, s, CHO<u>Me</u>), 3.06 (1H, br ddd, *J* = 7.4, 9.4, 9.4, C<u>H</u>OMe), 2.84 (1H, qd, *J* = 9.2, 7.0 Hz, 28-CH), 2.60 (1H, ddd, *J* = 16.2, 10.0, 4.8 Hz, 26-CH_A), 2.36 (1H, ddd, *J* = 16.2, 7.9, 4.0 Hz, 26-CH_B), 2.50-2.41 (2H, m, 6-CH_2), 2.02-1.82, 1.79-1.46, 1.45-1.22 (17H, m, 8-CH_2, 12-CH_2, 14-CH_2, 16-CH, 18-CH_2, 20-CH, 22-CH, 24-CH, 25-CH_2, 30-CH, 31-CH_2), 1.74 (3H, s, 4-Me), 1.10-0.98 (3H, m, $(Me_2C\underline{H})_3Si$), 1.05 (18H, br s, $(\underline{Me_2}CH)_3Si$), 1.04, (9H, br s, ^{t}BuSi), 1.01, (9H, br s, ^{t}BuSi), 1.01-0.99 (3H, d, <u>Me</u>CH), 0.94 (3H, d, *J* = 7.2 Hz, <u>Me</u>CH) 0.89-0.87 (6H, d, 2 x <u>Me</u>CH) 0.88 (9H, br s, 7-CHOSi^t<u>Bu</u>), 0.85 (3H, d, *J* = 7.2 Hz, <u>Me</u>CH), 0.74 (3H, d, *J* = 6.8 Hz, <u>Me</u>CH), 0.11 (3H, s, Si<u>Me</u>), 0.07 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.9, 167.9, 149.6, 137.9, 134.0, 130.4, 123.8, 115.2, 88.5, 83.6, 80.3, 75.7, 72.6, 69.2, 67.4, 64.0, 61.3, 60.7, 59.2, 56.5, 56.1, 51.4, 48.3, 41.4, 40.9, 40.4, 39.1, 38.7, 37.3, 36.4, 35.2, 33.4, 32.8, 31.4, 31.0, 30.1, 29.7, 28.5, 27.6, 25.9, 25.6, 22.2, 21.7, 18.0, 17.1, 15.5, 14.2, 13.7, 12.4, 12.0, 9.4, 8.4, –4.4, –4.8; m/z (+ve FAB) 1178 (75), 1115 (50), 752 (46), 712 (70), 686 (92), 614 (48), 438 (50), 341 (66), 283 (100), 229 (98%); HRMS (+ve FAB, NOBA matrix) $[M+H]^+$ found 1209.8767, $C_{67}H_{129}O_{12}Si_3$ requires 1209.8791.

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