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The Total Synthesis of Swinholide A. Part 3: A Stereocontrolled Synthesis of (–)-Pre-Swinholide A.

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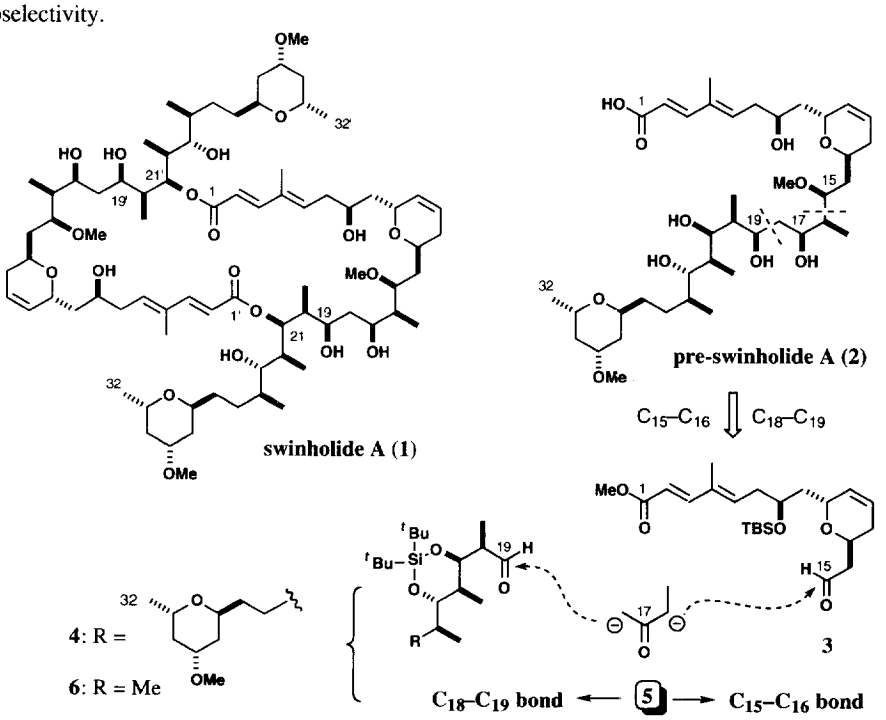
Abstract: Two coupling strategies for (–)-pre-swinholide A were devised based on the analysis in **Scheme 1**. In the first route, a boron-mediated aldol reaction between the ethyl ketone **19** and the aldehyde **3** was used to construct the C_{15}–C_{16} bond with moderate diastereoselectivity. In the second route, a Mukaiyama aldol reaction between the methyl ketone **54** and the aldehyde **4** introduced the C_{18}–C_{19} bond with complete stereocontrol.

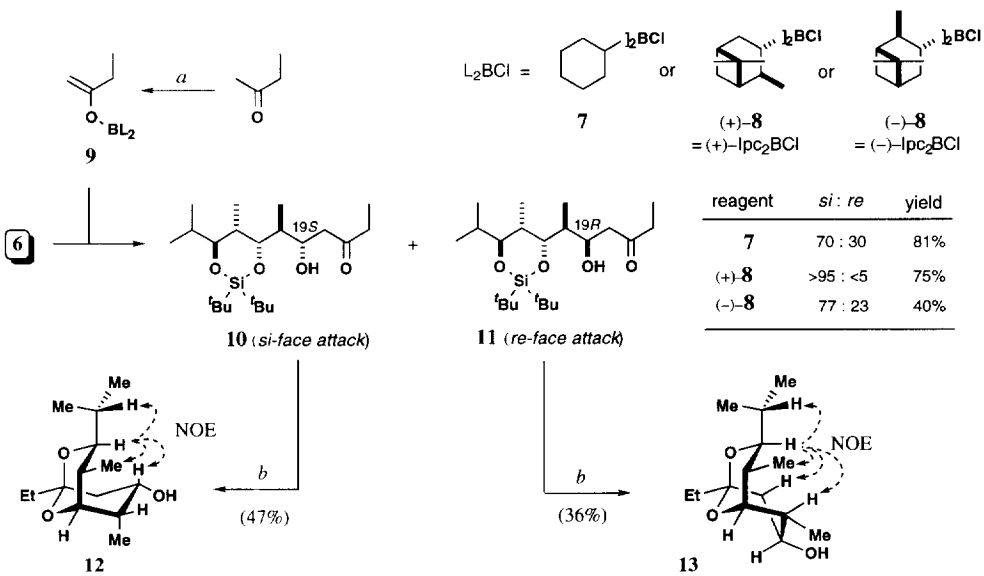
In the preceding two papers, we described our strategy[1a] for the total synthesis of swinholide A (**1**) *via* pre-swinholide A (**2**) and reported the preparation of the aldehydes **3**[1a] and **4**[1b] as C_1–C_{15} and C_{19}–C_{32} subunits. As shown in **Scheme 1**, we now required control in the sequential aldol coupling of these two chiral aldehydes with a suitable butanone synthon **5**, correctly incorporating the four stereocentres at C_{15}, C_{16}, C_{17}, and C_{19}, leading to a protected form of the monomeric unit **2**. In this third paper of the series,[1] we describe two syntheses of pre-swinholide A based on varying the order of construction of the C_{18}–C_{19} and C_{15}–C_{16} bonds.[2] The use of substrate- and reagent-based control in these aldol-type additions[3] was explored to optimise the stereoselectivity.



Scheme 1

First Synthesis of Pre-Swinholide A
Formation of the C_{18}–C_{19} Bond

Following the analysis outlined in **Scheme 1**, we initially considered the formation of the C_{18}–C_{19} bond of pre-swinholide A by aldol addition of the kinetic boron enolate of butanone to the C_{19}–C_{32} segment **4**. In order to conserve stocks of **4**, we first investigated this bond construction for the model aldehyde **6**[4] and the results are shown in **Scheme 2**. Regioselective enolisation of butanone at the methyl position has previously been reported to be difficult to achieve.[5] Fortunately, a timely report from Brown *et al.*[6] showed that dialkylboron chlorides, such as **7**, and Et_3N could achieve this conversion with complete regiocontrol, provided bulky ligands on boron were employed. We have previously introduced the use of the α-pinene-derived reagents (+)-**8** and (–)-**8** (together with the corresponding triflate derivatives) for promoting the asymmetric aldol additions of methyl ketones with aldehydes.[5a,7] In the case of aldehyde **6**, we now had an opportunity to explore the use of these chiral boron reagents for achieving reagent control[8] in the butanone aldol addition.

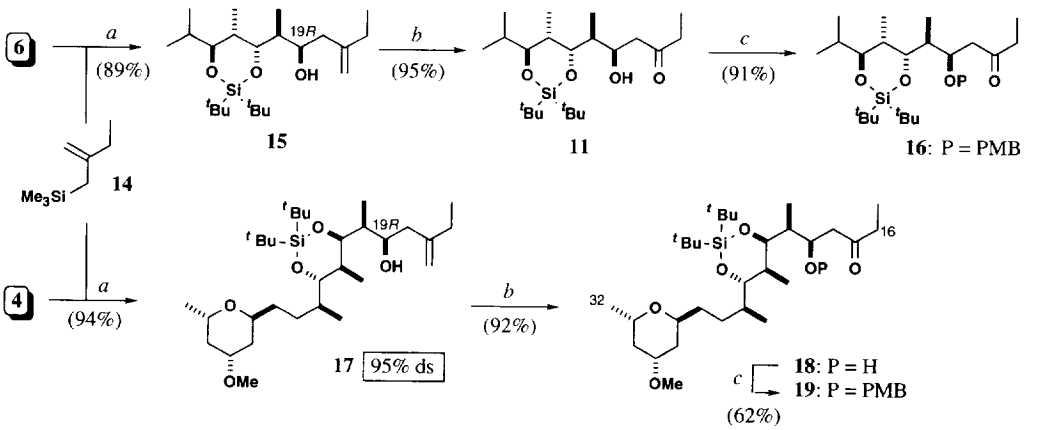


Scheme 2: (a) L_2BCl, Et_3N, Et_2O, 0 °C, 30 min (→ 9); **6**, –78 → –25 °C, 18 h; H_2O_2, MeOH-pH7 buffer; (b) HF•pyridine, pyridine, THF, 20 °C, 2 h.

Enolisation of butanone (Et_3N, Et_2O, 0 °C) by the three boron reagents (**7**, (+)-**8**, and (–)-**8**) generated the unsubstituted enol borinates **9** with essentially complete regioselectivity. In separate runs, these kinetically generated enolates were then added to aldehyde **6** to give a mixture of the aldol products **10** and **11** (following standard oxidative work-up). With achiral ligands on boron (*i.e.* using reagent **7**), a 70 : 30 ratio of the two C_{19} epimers was obtained in favour of **10**, resulting from undesired *si*-face attack on **6**. The Ipc reagent (+)-**8** gave a high level of *si*-face selectivity (>95% ds) in favour of **10**, as expected[8] for a matched combination of the substrate face selectivity with that of the influence[5a,7a] from the ligand chirality. Unexpectedly, the enantiomeric reagent (–)-**8** also favoured **10** with slightly improved selectivity (77 : 23) over the achiral enolate, albeit in

reduced yield (40%). Proof of the stereochemical outcome of these aldol additions was obtained by removal of the silylene protecting group in **10** and **11**. Treatment with HF•pyridine complex led to deprotection and concomitant cyclisation to give the bicyclic acetals **12** and **13**. Subsequent ^{1}H NMR NOE studies gave results that were in good agreement with the conformations predicted by computer modelling (MM2) of **12** and **13**.

The Ipc-mediated additions to aldehyde **6** are anomalous, since the substrate-induced *si*-face selectivity is enhanced for both enantiomers of the reagent **8**. There is clearly a significant contribution to the reaction diastereoselectivity from the aldehyde structure (including the β-stereocentre), together with the steric demands and chirality of the ligands on boron in the enolate component. Simple models for predicting asymmetric induction in methyl ketone boron aldol reactions with chiral aldehydes containing multiple stereocentres are unlikely to be reliable, particularly due to the accessibility of chair and boat cyclic transition structures.[5a,9]



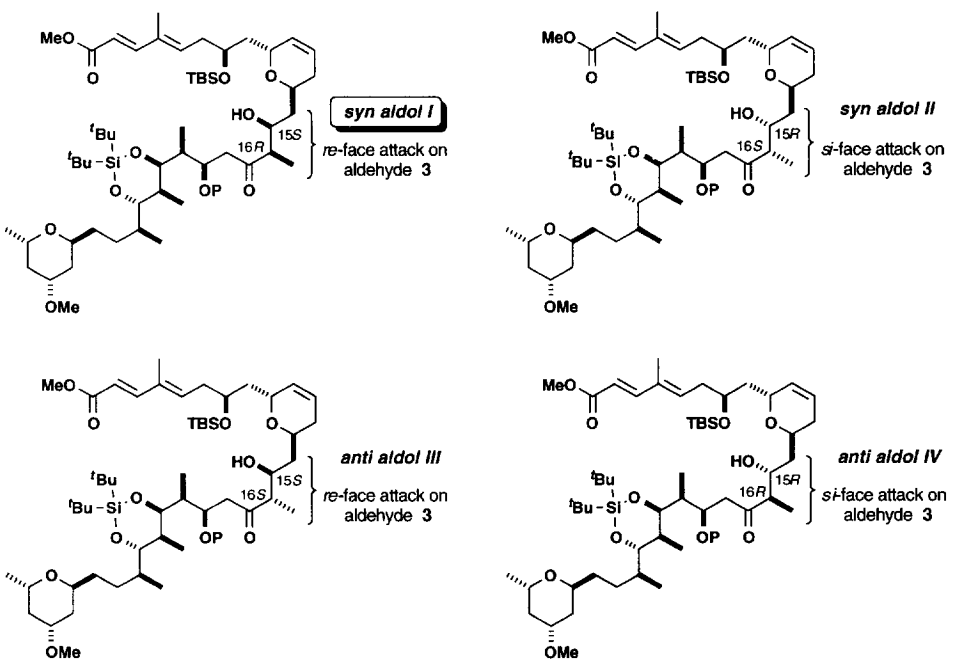
Scheme 3: (a) $TiCl_4$, CH_2Cl_2, –90 °C, 30 min; (b) O_3, CH_2Cl_2/MeOH, –78 °C, 15 min; Me_2S, –78 → 20 °C, 3 h; (c) PMBOC(CCl$_3$)=NH, TfOH (0.5 mol %), Et_2O, 20 °C, 1 h.

As boron enolates had failed to produce the desired isomer **11** selectively, a complementary approach to formation of the C_{18}–C_{19} bond relying on an open transition state was explored next. We turned to the use of the allylsilane **14**[10] (**Scheme 3**) as a masked butanone equivalent, requiring Felkin-Anh selectivity on its addition to aldehyde **6**. Using $TiCl_4$ as the Lewis acid (CH_2Cl_2, –90 °C), this addition gave the *desired* (19*R*)-adduct **15** in 89% yield with 95% diastereoselectivity. The correct stereochemistry was confirmed by ozonolysis, which gave the aldol product **11** in 95% yield. Protection of the β-hydroxyl as its *p*-methoxybenzyl (PMB) ether gave the ethyl ketone **16** in 91% yield, which could be used as a model for the C_{15}–C_{16} aldol bond construction.

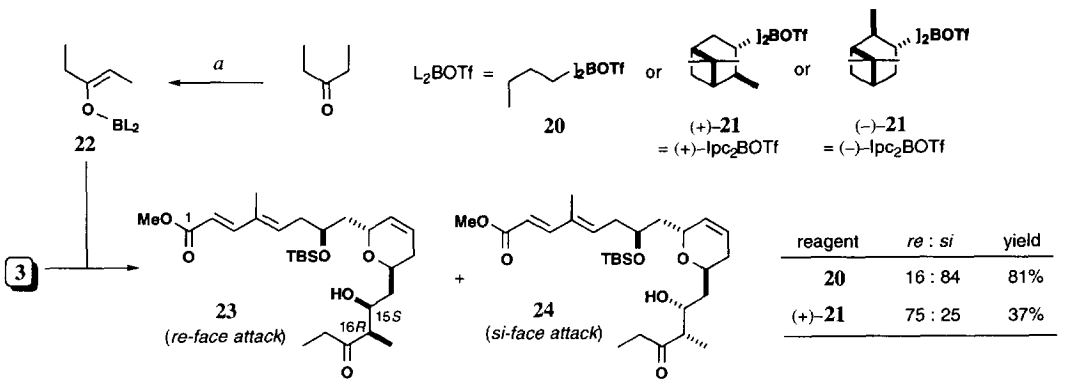
Applying this optimised allylsilane addition to the complete C_{19}–C_{32} aldehyde **4** now led to the formation of (19*R*)-adduct **17** in 94% yield with 95% diastereoselectivity. Ozonolysis of alkene **17** to give the β-hydroxy ketone **18**, followed by PMB protection, then gave the C_{16}–C_{32} segment **19** in 54% overall yield from **4**.

Formation of the C_{15}–C_{16} Bond

With the desired C_{16}–C_{32} segment **19** in hand, the stereocontrolled formation of the C_{15}–C_{16} bond by a suitable aldol reaction was addressed. Note that this would require control of the regioselectivity of enolisation in ethyl ketone **19** and selective formation of one of the four possible diastereomeric aldol adducts with aldehyde **3**: *i.e.* syn adducts **I** and **II**, anti adducts **III** and **IV**. For swinholide A, the syn aldol product **I** was required, which necessitated formation of the appropriate *Z*-enol borinate or an equivalent metal enolate. At the outset, we assumed that there would be minimal substrate bias from the ketone and aldehyde components and thus reagent control, using *Z*-enol diisopinocampheyl borinates,[7] might accomplish this ambitious task. This would then correspond to a rare case of triple asymmetric induction in the aldol reaction.[11]

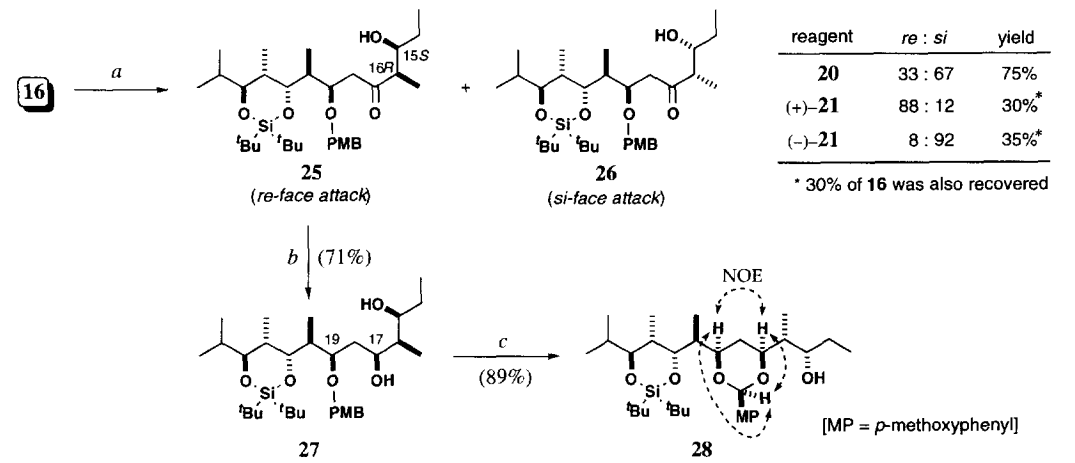


Initially, we investigated the inherent diastereoselectivity of the two coupling partners **3** and **19**. As summarised in **Scheme 4**, the π-facial selectivity of the aldehyde **3** with *Z*-enol borinates was explored to set up the correct syn aldol relationship at C_{15}–C_{16}. The boron triflate reagents **20** and (+)-**21**[7a] were first used to enolise diethyl ketone and the resulting enol borinates **22** were then added to aldehyde **3** resulting in a mixture of **23** and **24**. With achiral ligands on boron (L = ^{n}Bu), the undesired *si*-face attack predominated to give **24** with an unexpectedly high level of selectivity (**23** : **24** = 16 : 84). Nevertheless, this substrate bias could be overturned using reagent control employing (+)-**21** to give **23**, the product of *re*-face attack on **3**, with moderate selectivity (75% ds). The configuration of the newly formed alcohol stereocentre was determined by the advanced Mosher method through formation of the (*R*)- and (*S*)-MTPA esters and comparison of the ^{1}H NMR chemical shifts of the two epimers.[12]



Scheme 4: (a) L_2BOTf, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 2 h; **3**, −78 → −25 °C, 18 h; H_2O_2, MeOH–pH7 buffer.

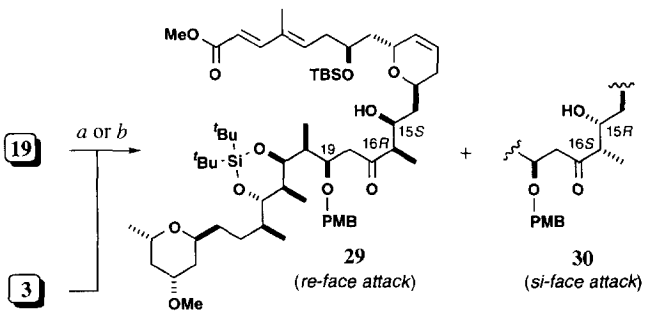
We next investigated the π-facial bias arising from the enolate component, making use of the model ketone **16** already prepared (**Scheme 5**). Enolisation of **16** using[13] the achiral triflate reagent **20**, followed by addition of propionaldehyde, gave a mixture of the syn aldol isomers **25** and **26**. Unfortunately, again the major isomer was that formed from undesired *si*-face attack on the aldehyde (no products arising from enolisation on the other side of ketone **16** were isolated). This undesired selectivity could be overturned by use[7a] of the chiral reagent (+)-**21** to give the desired isomer **25** with good selectivity (88% ds), albeit in poor conversion. The matched reagent (−)-**21**[7a] gave an enhancement of the intrinsic substrate selectivity but again the conversion was poor, suggesting that enolisation was incomplete. The configuration of the aldol product **25** was determined by selective anti-reduction[14] to give the diol **27** ($Me_4NBH(OAc)_3$), followed by oxidative cyclisation with DDQ of the PMB group[15] onto the neighbouring alcohol to give the acetal **28**. By performing NOE studies on the resulting acetal, it was established that a 1,3-syn relationship existed between the C_{17} and C_{19} positions.



Scheme 5: (a) L_2BOTf, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 2 h; EtCHO, −78 → −25 °C, 18 h; H_2O_2, MeOH–pH7 buffer; (b) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 °C, 48 h; (c) DDQ, CH_2Cl_2, 20 °C, 30 min.

The C_{15}–C_{16} Syn Aldol Coupling

At this stage, we realised from the results recorded in **Schemes 4** and **5** that the boron-mediated syn aldol coupling between segments **3** and **19** was likely to be a matched situation – unfortunately, favouring the wrong syn isomer by *si*-face attack. For access to swinholide A, we required addition of the *Z*-enol borinate from **19** to the *re*-face of the aldehyde in **3** (**Scheme 6**). In this real coupling situation, enolisation of the ketone **19** with $^{n}Bu_2BOTf/^{i}Pr_2NEt$,[13] followed by addition of aldehyde **3**, gave a mixture of syn aldol products **29** and **30** in 82% yield. The undesired syn (15*R*,16*S*) isomer **30** was formed preferentially with 77% ds, arising from *si*-face attack on aldehyde **3**. An attempt to overturn this selectivity using the chiral reagent (+)-**21** afforded now a 1 : 1 mixture of **29** and **30** in low yield (16%), after prolonged reaction at room temperature. Clearly, this mismatched situation was unsatisfactory. In one final attempt to selectively generate the desired aldol product **29**, the Sn(II) enolate[16] from ketone **19** was formed giving a 40 : 60 mixture of **29** and **30** on addition to **3**, but in only moderate yield (60%). In addition, significant amounts of anti aldol isomers were formed, which complicated product purification. Rather than accept a low yield of the desired syn isomer **29**, we decided to look at alternative options.



reagent	*re* : *si*	yield
20	23 : 77	82%
(+)-**21**	50 : 50	16%
$Sn(OTf)_2$	40 : 60	60%

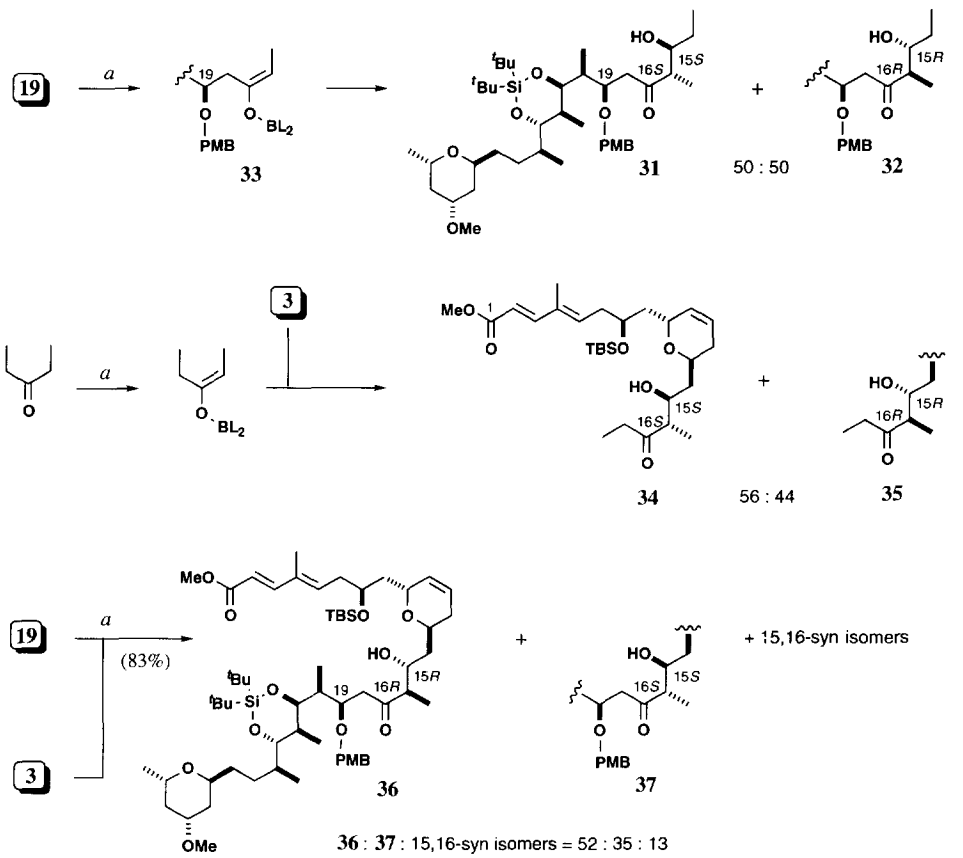
Scheme 6: (a) L_2BOTf, $^{i}Pr_2NEt$, CH_2Cl_2, –78 °C, 2 h; **3**, –78 → –25 °C, 18 h; H_2O_2, MeOH–pH7 buffer; (b) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, –78 °C, 2 h; **3**, –78 °C, 2 h.

The C_{15}–C_{16} Anti Aldol Coupling

As the aldehyde **3** had demonstrated an unforeseen propensity to undergo *si*-face addition of *Z*-enol borinates, which could not be overcome by use of reagent control, we investigated addition of the *E*-enol borinate derived from the ketone **19**. In this situation, *si*-face attack should then give an anti-aldol adduct with the correct stereochemistry at the C_{16} methyl-bearing stereocentre, while being epimeric to that required for swinholide at the C_{15} hydroxyl stereocentre. Once again, some model reactions were investigated (**Scheme 7**) in order to assess the aldehyde and enolate π-face selectivities in this new coupling situation.

Enolisation of the ketone **19** with the chloroborane **7**,[6] followed by addition of propionaldehyde, gave a 50 : 50 mixture of the two anti aldol isomers **31** and **32** (along with traces of the corresponding syn aldol products), thus demonstrating that the *E*-enol borinate **33** derived from ketone **19** showed little or no intrinsic π-facial selectivity. Similarly, enolisation of diethyl ketone with **7**, followed by addition of the aldehyde **3**, gave a 56 : 44 mixture of the two anti aldol isomers **34** and **35**. The stereochemistry of the major anti isomer **34** was determined by assigning the absolute configuraton of the alcohol stereocentre using the advanced Mosher

method.[12] The low level of diastereoselection observed here was unexpected, since the *si*-face selectivity of the aldehyde **3** appears to be much lower than in the corresponding *Z*-enol borinate reactions (cf. **Scheme 4**). This may be due in part to the difference in size of the ligands attached to boron.[17a]



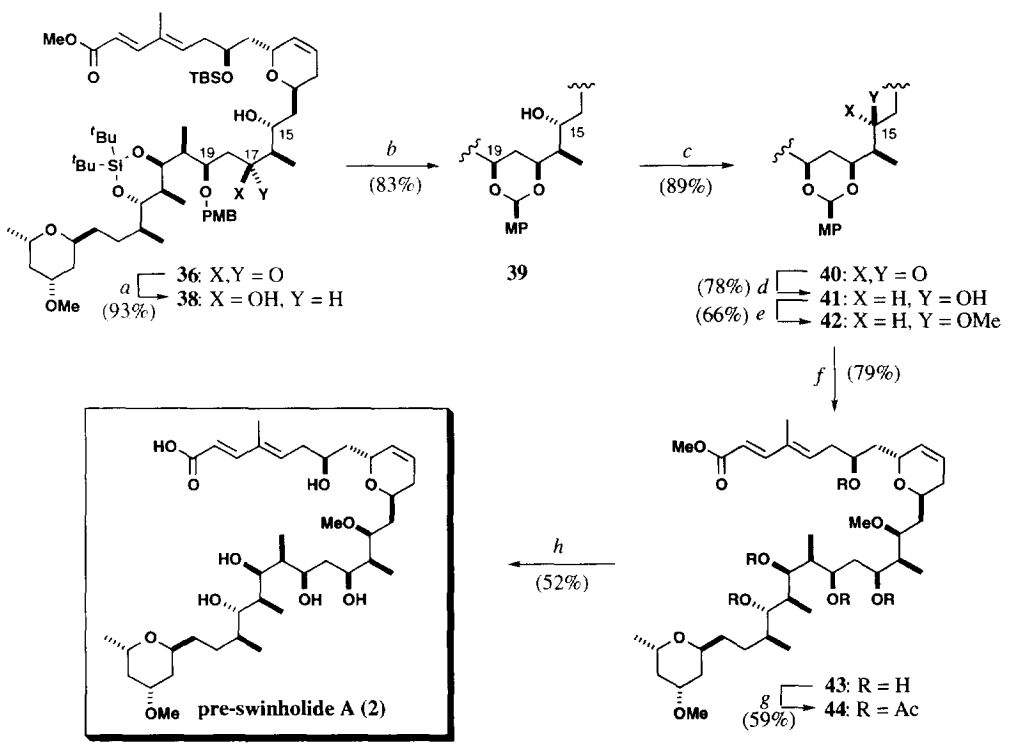
Scheme 7: (a) $(c\text{-}C_6H_{11})_2BCl$ (7), Et_3N, Et_2O, −78 → 0 °C, 2 h; then RCHO, −78 → 0 °C, 2 h; H_2O_2, MeOH–pH7 buffer.

When the anti aldol coupling between ketone **19** and aldehyde **3** was carried out, an 83% yield of isomeric aldol products was obtained (**36** : **37** : 15,16-syn isomers = 52 : 35 : 13).[17a] The desired anti aldol isomer **36** was isolated in 40% yield after HPLC separation of the product mixture. This should have the correct stereochemistry at C_{16} but requires inversion at C_{15}. We also investigated the use of Gennari's (+)-menthene-derived chloroborane[17b] to confer reagent control and enhance the reaction selectivity. However, this reagent gave inferior yields of aldol products and, more importantly, had *no effect* on the ratio of **36** and **37** obtained.

Completion of the First Synthesis of (–)-Pre-Swinholide A

With the anti aldol product **36** in hand, selective reduction of the C_{17} ketone was now required. In practice, this was achieved using catecholborane[18] in THF, which gave the desired 1,3-syn diol isomer **38** in 93% yield and

≥95% ds (**Scheme 8**). Treatment of **38** with DDQ, then oxidatively cyclised[15] the strategically positioned C_{19} PMB ether onto the C_{17} hydroxyl to give the *p*-methoxybenzylidene acetal **39** in 83% yield as a single isomer. The relative stereochemistry at the acetal centre was assigned by ^{1}H NMR NOE analysis later in the synthesis. Oxidation of **39** with the Dess-Martin periodinane[19] gave ketone **40** in 89% yield. Interestingly, the ^{1}H NMR data for the protons at C_3 and C_5 in ketone **40** were shifted downfield by 0.18 and 0.29 ppm respectively, compared to the starting alcohol **39**. That such a dramatic perturbation in magnetic environment should occur at a position apparently remote from the reacting centre suggests that the axially disposed C_1–C_8 sidechain is able to fold underneath the dihydropyran ring and orient itself relatively close in space to the other sidechain connected through C_{13}. This is supported by the X-ray crystal structure determined for a swinholide A derivative by Kitagawa *et al.*,[20a] which shows the two substituents attached to the dihydropyran ring to be relatively close in space. The consequence of such a conformational effect is to gain an element of unanticipated stereocontrol from remote stereocentres, as well as to assist macrocyclisation. This may contribute to the syn and anti aldol coupling selectivities obtained previously.



Scheme 8: (a) catecholborane, THF, –78 → 20 °C, 23 h; (b) DDQ, 4 Å mol. sieve powder, CH_2Cl_2, 20 °C, 0.5 h; (c) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 0.5 h; (d) LiAlH(O*t*-Bu)$_3$, Et_2O, THF, 0 °C, 0.5 h then –20 °C, 18 h; (e) MeOTf, 2,6-di-*tert*-butylpyridine, 50 °C, 4.25 h; (f) 40% aq. HF, MeCN, 0 → 20 °C, 2 h; (g) Ac_2O, pyridine, DMAP, 20 °C, 18 h; (h) NaOH, MeOH, H_2O, 20 °C, 5 h.

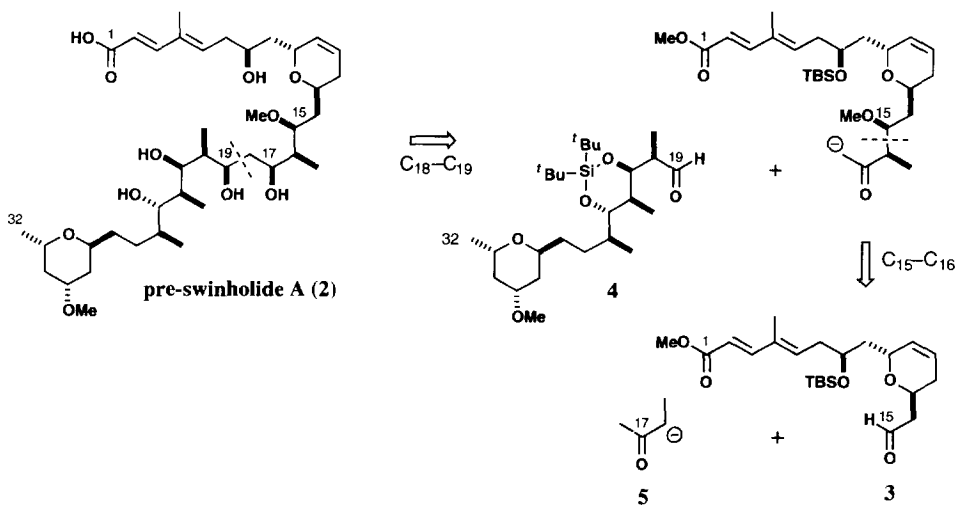
Reduction of ketone **40** with the bulky reagent $LiAlH(O^tBu)_3$ gave the two alcohols **41** and **39** in 94% yield. The diastereoselectivity in this reaction was somewhat variable, but up to 83% ds in favour of **41** could be obtained. The minor product, alcohol **39** can be recycled using this oxidation/reduction sequence.

With all of the stereocentres of pre-swinholide A now correctly installed, the C_{15} hydroxyl group required methylation. While strongly basic conditions (*e.g.* NaH, MeI, THF) led to unclean reactions, the use of methyl triflate[21] in neat 2,6-di-*tert*-butylpyridine at 50 °C gave the methyl ether **42** in 66% isolated yield, along with 12% recovered starting material. Final removal of all the hydroxyl protecting groups was accomplished in a single step using aqueous HF in acetonitrile to give (–)-pre-swinholide A methyl ester (**43**) in 79% yield. The ^1H NMR data for this compound ($CDCl_3$, C_6D_6) were in accord with the published values (see **Table 1** in the experimental section),[20b,c] and copies of the ^1H NMR spectra provided by Professor Kitagawa. Moreover, the ^1H NMR data (recorded in $CDCl_3$) obtained for synthetic **43** was identical to that obtained for an authentic sample, again kindly provided by Professor Kitagawa. In addition, **43** was converted into its known pentaacetate **44** which has also been prepared from natural material. All NMR data (^1H, ^{13}C, COSY and HETCOR) were in total agreement with the literature values (**Table 2**, experimental section).[20b,c] Finally, **43** was hydrolysed to give pre-swinholide A (**2**) in 52% yield following reverse-phase HPLC. Again, the data for this compound were consistent with that reported in the literature (**Table 3**, experimental section).[20d,e]

Second Synthesis of Pre-Swinholide A

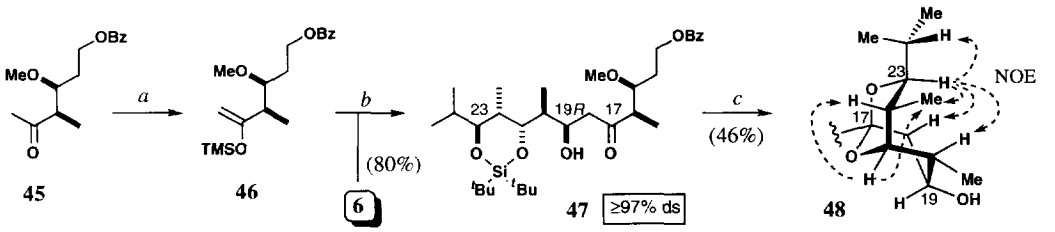
Formation of the C_{18}–C_{19} Bond by Aldol Coupling: Model Reactions

While the above route achieved the total synthesis of (–)-pre-swinholide A, it was difficult to generate large quantities of intermediate **42** required for swinholide A itself. Therefore, an alternative approach was investigated. As outlined in **Scheme 9**, this involved first attaching the butanone unit **5** to aldehyde **3** to form the C_{15}–C_{16} bond, followed by a methyl ketone aldol coupling with aldehyde **4** to form the C_{18}–C_{19} bond.



Scheme 9

In order to investigate this C_{18}–C_{19} coupling reaction, we first prepared[22] the model methyl ketone **45** (**Scheme 10**). Ketone **45** was converted into the silyl enol ether **46** (*via* the corresponding Sn(II) enolate[16]), which underwent a Mukaiyama aldol addition to the model aldehyde **6**, in the presence of BF_3•OEt_2, to generate the desired Felkin product **47** as a single isomer in 80% yield. The aldol stereochemistry was confirmed by extensive NOE studies performed on the bicyclic acetal **48**, which was obtained after removal of the silylene protecting group in **47** with HF•pyridine.



45 46 47 ≥97% ds 48

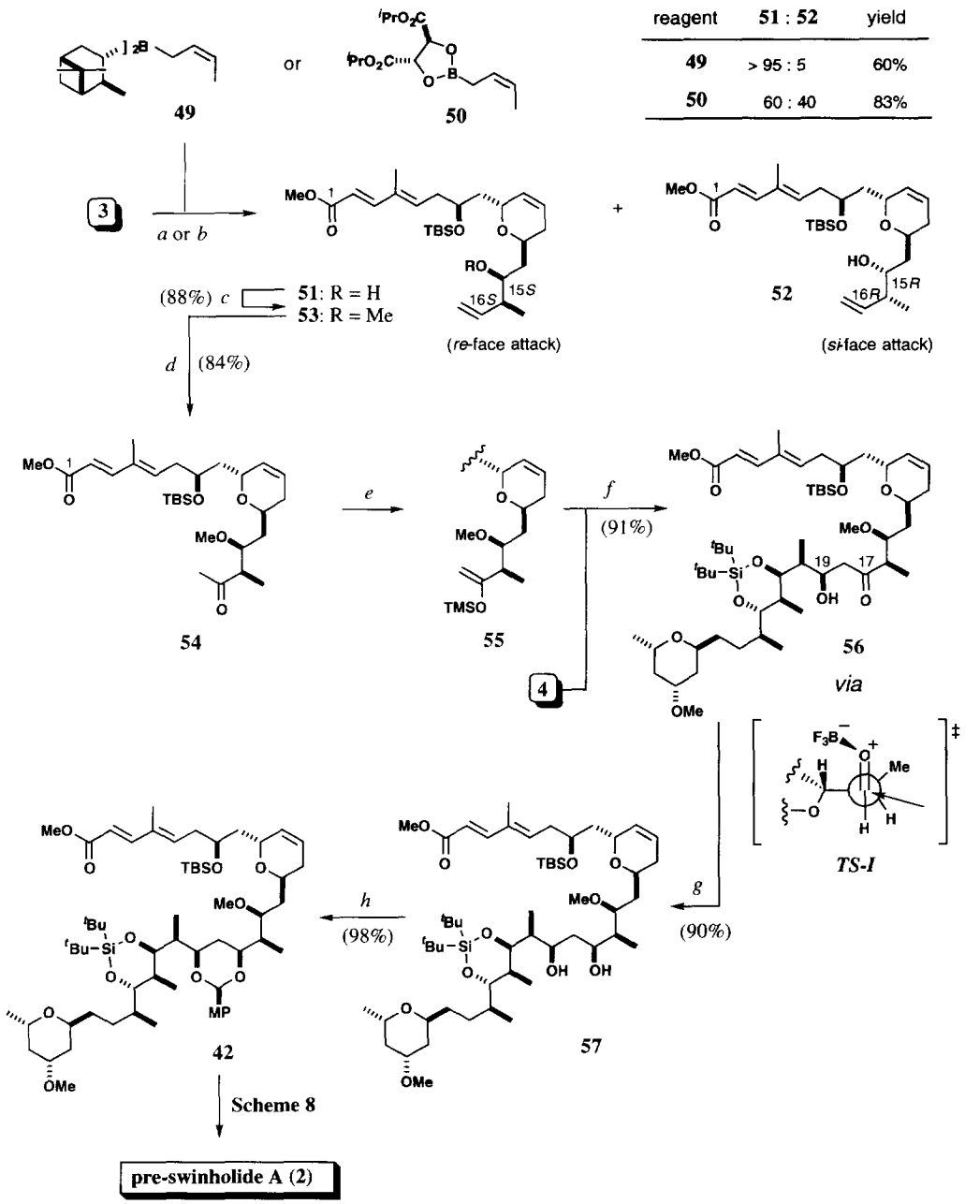
Scheme 10: (a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, –78 °C, 1 h; TMSCl; (b) **6**, BF_3•OEt_2, CH_2Cl_2, –78 °C, 30 min; (c) HF•pyridine, pyridine, THF, 20 °C, 15 min.

The Mukaiyama Aldol Route to Pre-Swinholide A

With confidence in the stereoselectivity of the C_{18}–C_{19} coupling reaction gained, we next addressed the attachment of the butanone unit **5** to the C_1–C_{15} segment **3**. We required access to a *Z* enolate equivalent of **5** in order to establish the correct syn C_{15}–C_{16} bond connection. Moreover, this would need to be a chiral reagent to overturn the unexpected substrate-based *si*-face of aldehyde **3**, which caused problems with our earlier route. In principle, an asymmetric syn crotylboration of the aldehyde **3** followed by Wacker oxidation of the terminal double bond should lead to the aldol product from reaction on the ethyl side of butanone.

The syn-crotylboration of aldehyde **3** was best achieved using Brown's (–)-α-pinene-derived reagent **49**,[23] which gave the desired alcohol **51** as a single isomer in 60% yield (**Scheme 11**). The corresponding tartrate-based reagent **50** of Roush[24] proved less selective in this (presumably) mismatched situation, giving a 60 : 40 mixture of the two syn isomers **51** and **52** in a combined yield of 83%. The (15*S*)-configuration at the newly formed hydroxyl stereocentre in **51** was confirmed by analysis of the ^1H NMR spectra of the diastereomeric (*R*)- and (*S*)-Mosher's esters.[12] Methylation of the C_{15} hydroxyl group in **51** was then accomplished as before, using methyl triflate in 2,6-di-*tert*-butylpyridine, to give an 88% yield of the methyl ether **53**.

Under optimum conditions, the Wacker oxidation proved highly selective for the terminal double bond in **53**. Pre-treatment of a mixture of palladium dichloride (20 mol %) and copper (I) chloride (2 equiv.) in aqueous DMF with oxygen for 2 h, was followed by addition of **53**. Stirring was then maintained under an oxygen atmosphere at room temperature for 3 days. On work-up, this gave a 66% yield of **54** and 21% recovered **53** (84% yield based on recovered starting material). This reaction could be driven to completion by use of stoichiometric $PdCl_2$, which indicated that catalyst turnover was impeded by the presence of the other double bonds in **54** which can also coordinate with the palladium. In this way, methyl ketone **54**, which corresponds to a C_1–C_{18} subunit for swinholide A, was obtained in just three steps from **3** with an excellent level of control over the two new stereocentres.



Scheme 11: (*a*) **49** (4 equiv.), THF, –78 °C, 2 h; H_2O_2, pH7 buffer/MeOH; (*b*) **50** (4 equiv.), PhMe, 4Å mol. sieves, –90 → –25 °C, 18 h; (*c*) MeOTf (30 equiv.), 2,6-di-*tert*-butylpyridine, 65 °C, 2.5 h; (*d*) $PdCl_2$ (20 mol %), CuCl, O_2 (1 atm), 7:1 DMF/H_2O, 20 °C, 72 h; (*e*) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, –78 °C, 30 min; (*f*) **4**, $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2, –78 °C, 30 min; (*g*) $^nBu_2BOMe$, 5:1 THF/MeOH, –78 °C, 15 min; $LiBH_4$, –78 → –40 °C, 2 h; H_2O_2, pH7 buffer/MeOH; (*h*) *p*-MeO(C_6H_4)CH($OMe)_2$, CSA (5 mol %), CH_2Cl_2, 20 °C, 1 h.

A stereocontrolled Mukaiyama coupling was now required to connect the C_1–C_{18} ketone **54** with the C_{19}–C_{32} aldehyde **4**. The silyl enol ether **55** was formed from **54** by kinetic enolisation using lithium hexamethyldisilazide with *in situ* quenching by trimethylsilyl chloride.[25] After isolation using a pH 7 buffer/pentane work-up, **55** was used immediately without purification. Addition of BF_3•OEt_2 to a mixture of **4** and **55** (CH_2Cl_2, –78 °C) led to a rapid and clean aldol addition, providing the desired (19*R*)-adduct **56** as the only product in 91% yield. The stereocontrol in this reaction is remarkably high (≥97% ds), which may be due to a cooperative effect from both the α and β stereocentres in the aldehyde as recently discussed by Evans *et al.*,[26] *i.e.* a combination of Felkin-Anh selectivity and opposed dipoles giving a transition state such as ***TS-I***.

The final stereocentre at C_{17} was introduced by a chelate-mediated 1,3-syn reduction using a modification of the conditions of Narasaka.[27] Thus treatment of **56** with di-*n*-butylmethoxyborane in THF/MeOH at –78 °C to generate the boron aldolate[28] was followed by the addition of $LiBH_4$ in THF. Slow warming to –40 °C gave complete conversion, leading to the 1,3-syn diol **57** in 90% yield with ≥97% ds. This diol was then protected as its *p*-methoxybenzylidene acetal, under standard conditions, giving **42** in 98% yield. This material was identical to that prepared earlier (**Scheme 8**) using our less efficient C_{15}–C_{16} anti aldol coupling approach. Since **42** has already been deprotected to give pre-swinholide A, all of the stereochemistry is secure.

Conclusions

In summary, the total synthesis of the monomeric secoacid (–)-pre-swinholide A (**2**) has been achieved. Two different bond construction strategies were examined for the union of the two complex aldehydes **3** and **4** with a butanone unit **5**. In the first instance, the C_{15}–C_{16} aldol bond coupling of **3** with **19** afforded sufficient amounts of **36** to convert through into (–)-pre-swinholide A, therefore, confirming the stereochemical integrity of the synthetic material. To allow the preparation of larger amounts of advanced intermediate **42** for elaboration into swinholide A, an efficient C_{18}–C_{19} coupling process was developed. This allowed the synthesis of (–)-pre-swinholide A in 8 steps from the two aldehydes **3** and **4** (15% overall yield). This latter coupling approach provides the fully protected coupled material **42** in 36% overall yield for the 6 steps from the two aldehydes **3** and **4**, with essentially complete stereocontrol. Key steps include (*i*) the syn crotylboration, **3** → **51**, (*ii*) the Wacker oxidation, **53** → **54**, (*iii*) the Mukaiyama aldol coupling, **4** + **55** → **56**, and (*iv*) the syn reduction, **56** → **57**. This route allowed us to prepare gram quantities of the advanced swinholide precursor **42**, thus setting the stage for completion of the total synthesis of swinholide A itself.[1c]

Experimental Section

For general experimental details, see the first paper in this series.[1a]

(5*R*,6*S*,7*S*,8*S*,9*S*,10*S*)-7,9-(Di-*tert*-butylsilylenedioxy)-5-hydroxy-3-methylene-6,8,10-trimethyl-12-((2S',4R',6S')-2-methyl-4-methoxytetrahydropyran-6-yl)-dodecane (17)

To a stirred solution of aldehyde **4** (600 mg, 1.27 mmol) and allylsilane **14** (557 mg, 0.75 ml, 3.81 mmol) in dry CH_2Cl_2 (15 ml) at –90 °C was added titanium tetrachloride (1.40 ml of a 1.0 M solution in CH_2Cl_2, 1.4 mmol). The reaction mixture was stirred at this temperature for a further 20 min before quenching with saturated $NaHCO_3$ solution (20 ml). The mixture was then extracted with CH_2Cl_2 (3 x 15 ml), washed with brine (25 ml), dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography (30% Et_2O/hexane) gave the desired

product **17** (646 mg, 94%) as a colourless oil with 95% ds: R_f = 0.24 (25% Et_2O/hexane); $[\alpha]_D^{20}$ = –37.0° (*c* 2.0, $CHCl_3$); IR (thin film) 3450 (s, br), 1227 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.84 (1H, br s, =C$\underline{H}_a$), 4.80 (1H, br s, =C$\underline{H}_b$), 4.18 (1H, dm, *J* = 9.2 Hz, 19-C$\underline{H}$), 4.12 (1H, dd, *J* = 9.6, 2.7 Hz, 21-C$\underline{H}$), 3.99 (1H, m, 27-C$\underline{H}$), 3.70 (1H, m, 31-C$\underline{H}$), 3.55 (1H, dd, *J* = 7.1, 2.5 Hz, 23-C$\underline{H}$), 3.51 (1H, m, 29-CH), 3.33 (3H, s, O$\underline{Me}$), 2.35 (1H, br s, CO$\underline{H}$), 2.27 (1H, dd, *J* = 14.0, 9.5 Hz, 18-C$\underline{H}_a$), 2.16 (1H, dd, *J* = 14.0, 4.0 Hz, 18-C$\underline{H}_b$), 2.08 (2H, m, 16-C$\underline{H}_2$), 1.96 (1H, m), 1.90-1.50 (6H, m), 1.18 (3H, d, *J* = 6.2 Hz, 31-C$\underline{Me}$), 1.03 (24H, s, 2 x *t*Bu, 2 x Me), 0.89 (3H, d, *J* = 6.6 Hz, C$\underline{Me}$), 0.78 (3H, d, *J* = 7.0 Hz, C$\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 148.8, 110.3, 83.4, 74.2, 73.3, 72.5, 69.0, 64.5, 55.2, 41.5, 40.0, 39.0, 38.7, 35.7, 34.8, 29.7, 28.6, 28.5, 28.4, 28.0, 27.7, 22.2, 21.9, 21.7, 15.8, 14.2, 14.1, 12.3, 10.2; m/z (FAB, NOBA) 541 (85, $[M+H]^+$), 539 (70), 524 (50), 472 (25), 341 (80), 297 (85), 269 (85), 199 (100); HRMS (FAB, NOBA) Calcd for $C_{31}H_{61}SiO_5$ ($[M+H]^+$): 541.4288, found 541.4261.

(5*R*,6*S*,7*S*,8*S*,9*S*,10*S*)-7,9-(Di-*tert*-butylsilylenedioxy)-5-hydroxy-6,8,10-trimethyl-12-((2S',4R',6S')-2-methyl-4-methoxytetrahydropyran-6-yl)-3-oxododecane (18)

Ozone gas (in a stream of O_2) was bubbled through a solution of the alkene **17** (640 mg, 1.2 mmol) in CH_2Cl_2/MeOH (3:1, 150 ml) at –78 °C for 15 min until a permanent blue colour appeared. Argon gas was then bubbled through to remove excess ozone, followed by addition of dimethyl sulphide (5ml, excess). The mixture was allowed to warm to room temperature and stirred overnight before evaporating. Flash chromatography (30% EtOAc/hexane) then gave the desired aldol product **18** as a colourless oil (591 mg, 92%): R_f = 0.29 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = –22.6° (*c* 1.9, $CHCl_3$); IR (thin film) 3420 (s, br), 1710 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.47 (1H, dm, *J* = 10.2 Hz, 19-C$\underline{H}$), 4.07 (1H, dd, *J* = 9.7, 2.4 Hz, 21-C$\underline{H}$), 3.92 (1H, m, 27-C$\underline{H}$), 3.63 (1H, m, 31-C$\underline{H}$), 3.51 (1H, dd, *J* = 7.0, 2.1 Hz, 23-C$\underline{H}$), 3.46 (1H, m, 29-CH), 3.27 (3H, s, O$\underline{Me}$), 3.19 (1H, d, *J* = 4.4 Hz, CO$\underline{H}$), 2.65 (1H, dd, *J* = 16.7, 10.3 Hz, 18-C$\underline{H}_a$), 2.42 (3H, m, 18-C$\underline{H}_b$, 16-C$\underline{H}_2$), 1.91 (1H, br d, *J* = 12.5 Hz), 1.77 (3H, m), 1.70-1.00 (7H, m), 1.13 (3H, d, *J* = 6.3 Hz, 31-C$\underline{Me}$), 1.03 (24H, s, 2 x *t*Bu, 2 x Me), 0.82 (3H, d, *J* = 6.6 Hz, C$\underline{Me}$), 0.72 (3H, d, *J* = 6.9 Hz, C$\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 212.3, 83.2, 73.5, 73.1, 72.3, 67.1, 64.4, 55.1, 46.8, 40.3, 39.0, 38.8, 36.6, 35.5, 34.7, 28.4, 28.3, 27.8, 27.7, 22.0, 21.8, 21.6, 15.7, 15.1, 14.0, 13.95, 9.9, 7.4; m/z (FAB, NOBA) 543 (60, $[M+H]^+$), 299 (100), 255 (40), 227 (50), 215 (40), 206 (50), 187 (50), 136 (50); HRMS (FAB, NOBA) Calcd for $C_{30}H_{59}SiO_6$ ($[M+H]^+$): 541.4081, found 541.4077.

(5*R*,6*S*,7*S*,8*S*,9*S*,10*S*)-7,9-(Di-*tert*-butylsilylenedioxy)-6,8,10-trimethyl-5-(*para*-methoxybenzyloxy)-12-((2S',4R',6S')-2-methyl-4-methoxytetrahydropyran-6-yl)-3-oxo-5-dodecane (19)

Triflic acid (176 μl of a 0.01 M solution in Et_2O, 0.3 mol %) was added to a solution of the ketone **18** (319 mg, 0.59 mmol) and *para*-methoxybenzyl trichloroacetimidate[29] (199 mg, 146 μl, 0.71 mmol) in Et_2O (5 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 min. MeOH (1 ml) was added and the mixture stirred for a further 1 h. Evaporation, followed by flash chromatography (20% EtOAc/hexane), gave the crude product. This was further purified by HPLC to give **19** as a colourless oil, which slowly crystallised to give a waxy solid (240 mg, 62%, m.p. 62-64 °C): R_f = 0.32 (20% EtOAc/hexane); t_R *ca* 25.3 min (19% EtOAc/hexane); $[\alpha]_D^{20}$ = –10.7° (*c* 3.4, $CHCl_3$); IR (thin film) 1715 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.19 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 6.83 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 4.56 (1H, td, *J* = 6.4, 1.9 Hz, 19-C$\underline{H}$), 4.42 (2H, s, ArC$\underline{H}_2$O), 4.09 (1H, dd, *J* = 9.9, 2.6 Hz, 21-C$\underline{H}$), 3.97 (1H, m, 27-C$\underline{H}$), 3.78 (3H, s, O$\underline{Me}$), 3.69 (1H, m, 31-C$\underline{H}$), 3.53 (1H, dd, *J* = 7.6, 2.2 Hz, 23-C$\underline{H}$), 3.48 (1H, m, 29-CH), 3.32 (3H, s, O$\underline{Me}$), 2.84 (1H, dd, *J* = 15.5, 5.9 Hz, 18-C$\underline{H}_a$), 2.56 (1H, dd, *J* = 15.5, 6.7 Hz, 18-C$\underline{H}_b$), 2.41 (2H, q, 16-C$\underline{H}_2$), 1.96 (1H, br d, *J* = 12.4 Hz), 1.84 (3H, m), 1.70-1.20 (7H, m), 1.17 (3H, d, *J* = 6.2 Hz, 31-C$\underline{Me}$), 1.02 (24H, s, 2 x *t*Bu, 2 x Me), 0.88 (3H, d, *J* = 6.6 Hz, C$\underline{Me}$), 0.83 (3H, d, *J* = 6.9 Hz, C$\underline{Me}$); ^{13}C NMR δ

(100.6 MHz, $CDCl_3$) 209.9, 158.8, 131.2, 128.4, 113.5, 83.5, 73.6, 72.9, 72.5, 70.9, 64.4, 55.2, 55.1, 46.7, 41.4, 38.9, 38.7, 36.1, 35.1, 34.7, 28.4, 28.1, 27.1, 22.1, 21.8, 21.6, 15.8, 14.0, 9.2, 7.6; m/z (FAB, NOBA) 661 (75, $[M+H]^+$), 525 (60), 339 (80), 299 (80), 283 (50), 269 (65), 241 (75), 227 (85), 137 (100); HRMS (FAB, NOBA) Calcd for $C_{38}H_{67}SiO_7$ ($[M+H]^+$): 661.4499, found 661.4552.

(*E*,*E*,7*S*)-Methyl-8-[(2*S*,6*S*)-6-{2*S*,3*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-hydroxy-6-(*para*-methoxybenzyloxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-4-one-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (29) and its isomer 30. A dry, tared, 5.0 ml volumetric flask fitted with a septum was flushed with argon, charged with neat $^nBu_2BOTf$ (0.889 g, 3.24 mmol) and diluted with Et_2O (2 ml), followed by addition of $^iPr_2NEt$ (0.68 ml, 3.9 mmol) and further dilution by Et_2O to give 5.0 ml volume. The resulting solution was therefore 0.65 *M* in boron triflate and 0.78 *M* in amine base. To a cooled (–78 °C) solution of the ketone **19** (67.0 mg, 0.101 mmol) in Et_2O (1 ml) was added a solution of *n*-Bu_2BOTf and $^iPr_2NEt$ in Et_2O (0.170 ml of the solution prepared above, 0.11 mmol of $^nBu_2BOTf$ and 0.13 mmol of $^iPr_2NEt$) dropwise. The resulting suspension was stirred at –78 °C for 10 min and was then warmed to 0 °C, whereupon more $^iPr_2NEt$•HCl was precipitated. After 1.5 h, the enolate mixture was warmed to room temperature for 30 min and then cooled to –78 °C. A solution of the aldehyde **3** (18.0 mg, 0.043 mmol) in Et_2O (0.2 ml + 2 x 0.2 ml rinses) was then added *via* cannula and the resulting suspension was strirred at –78 °C for 3.75 h, then the reaction flask was sealed and placed in a freezer at –20 °C for 18 h. The reaction mixture was then warmed to 0 °C and quenched by the addition of MeOH (1 ml). The resulting clear solution was treated with H_2O_2 solution (0.1 ml, 30% aq.) and stirred at 0 °C for 0.5 h. The reaction mixture was then poured into sodium metabisulphite solution (10 ml, 10% aq.) and extracted with Et_2O (3 x 15 ml). The organic layers were washed with brine (10 ml, sat. aq.), then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (gradient elution with 20→30% EtOAc/petroleum ether bp 40-60) gave a mixture of syn-aldol products, **29** and **30**, and minor amounts of anti-aldol products (37.9 mg, 82%), together with recovered **19**. The aldol product mixture was separated by preparative normal phase HPLC (30% EtOAc/hexane) to give the less polar, minor syn isomer **29** (7.4 mg, 16%) and the more polar, major syn isomer **30** (25.1 mg, 54%), together with minor amounts of anti-aldol products (1.2 mg combined, 2.5%). The syn : anti ratio in this reaction was therefore 96 : 4 and the aldehyde *si : re* face selectivity was 77 : 23.

Desired Syn-Aldol Isomer 29: R_f = 0.14 (20% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –64.3° (*c* 0.70, $CHCl_3$); IR (thin film) 3482 (m, br), 1718 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.34 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.18 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.82 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 5.96 (1H, br dd, *J* = 7.2, 7.2 Hz, 5-C<u>H</u>), 5.82 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.74 (1H, m, 11-C<u>H</u>), 5.61 (1H, br d, *J* = 10.2 Hz, 10-C<u>H</u>), 4.54 (1H, ddd, *J* = 5.9, 5.9, 2.4 Hz, 19-C<u>H</u>), 4.46 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>O), 4.42 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>O), 4.36 (1H, br d, *J* = 9.6 Hz, 9-C<u>H</u>), 4.11 (1H, dd, *J* = 9.8, 2.1 Hz, 21-C<u>H</u>), 3.98 (1H, m, 7-C<u>H</u>), 3.96 (1H, m, 27-C<u>H</u>), 3.93 (1H, br dd, *J* = 8.3, 5.8 Hz, 15-C<u>H</u>), 3.78 (3H, s, O<u>Me</u>), 3.74 (1H, m, 13-C<u>H</u>), 3.73 (3H, s, O<u>Me</u>), 3.70 (2H, m, 15-CO<u>H</u>, 31-C<u>H</u>), 3.55 (1H, dd, *J* = 7.2, 2.2 Hz, 23-C<u>H</u>), 3.51 (1H, dddd, J = 10.0, 10.0, 5.0, 5.0 Hz, 29-C<u>H</u>), 3.33 (3H, s, O<u>Me</u>), 3.00 (1H, dd, *J* = 16.7, 6.1 Hz, 18-C<u>H</u>$_a$), 2.77 (1H, dd, *J* = 16.7, 5.8 Hz, 18-C<u>H</u>$_b$), 2.67 (1H, dq, *J* = 6.6, 6.6 Hz, 16-C<u>H</u>), 2.39 (2H, m, 6-C<u>H</u>$_2$), 1.96 (1H, br d, *J* = 13.2 Hz, 30-C<u>H</u>$_a$), 1.90 (1H, m, 12-C<u>H</u>$_a$), 1.87 (3H, m, 12-C<u>H</u>$_b$, 22-C<u>H</u>, 26-C<u>H</u>$_a$), 1.83 (1H, m, 28-C<u>H</u>$_a$), 1.78 (3H, s, 4-C<u>Me</u>); 1.72 (1H, m, 8-C<u>H</u>$_a$), 1.66 (1H, m, 24-C<u>H</u>), 1.61 (1H, m, 20-C<u>H</u>), 1.59 (2H, m, 25-C<u>H</u>$_a$, 28-C<u>H</u>$_b$), 1.57 (1H, m, 14-C<u>H</u>$_a$), 1.52 (1H, m, 14-C<u>H</u>$_b$), 1.45 (1H, m, 8-C<u>H</u>$_b$), 1.37 (1H, m, 25-C<u>H</u>$_b$), 1.30 (1H, m, 26-C<u>H</u>$_b$), 1.18 (1H, m, 30-C<u>H</u>$_b$), 1.18 (3H, d, *J* = 6.3 Hz, 31-C<u>Me</u>), 1.14 (3H, d, *J* = 7.2 Hz, 16-C<u>Me</u>), 1.05 (9H, s, *t*-Bu), 1.02 (3H, d, *J* = 7.2 Hz, 22-C<u>Me</u>), 1.01 (9H, s, *t*-Bu), 0.89 (3H, s, 24-C<u>Me</u>), 0.87 (9H, s, *t*-Bu), 0.86 (3H, d, *J* = 7.2 Hz, 20-C<u>Me</u>), 0.06 (6H, s, 2x Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 212.7, 167.9, 158.8, 149.5, 137.4, 134.5, 131.4, 129.7, 128.5,

123.6, 115.6, 113.5, 83.5, 73.3 (3C), 72.6, 72.4, 71.1, 69.8, 69.1, 68.3, 68.1, 64.5, 55.3 (2C), 51.8, 51.5, 47.3, 41.5, 40.7, 39.2, 39.0, 37.6, 35.3, 34.8, 30.9, 29.7, 28.5, 28.2, 27.8, 25.8, 22.2, 21.9, 21.7, 18.0, 15.9, 14.2, 12.5, 12.1, 9.6, -4.2, -4.8; m/z (+FAB, NOBA + NaOAc) 1107 (0.3, $[M+Na]^+$), 121 (100).

Undesired Syn-Aldol Isomer 30: R_f = 0.11 (20% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –59.3° (*c* 1.1, $CHCl_3$); IR (thin film) 3508 (m, br), 1718 (s) cm^1; ^1H NMR δ (400 MHz, $CDCl_3$) 7.34 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.18 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.83 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 5.96 (1H, br dd, *J* = 7.3, 7.3 Hz, 5-C<u>H</u>), 5.81 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.77 (1H, m, 11-C<u>H</u>), 5.63 (1H, br d, *J* = 10.2 Hz, 10-C<u>H</u>), 4.60 (1H, ddd, *J* = 6.3, 6.0, 1.9 Hz, 19-C<u>H</u>), 4.43 (2H, s, Ar<u>CH</u>$_2$O), 4.34 (1H, br d, *J* = 10.4 Hz, 9-C<u>H</u>), 4.21 (1H, br d, *J* = 9.2 Hz, 15-C<u>H</u>), 4.12 (1H, dd, *J* = 10.0, 2.4 Hz, 21-C<u>H</u>), 4.04 (1H, m, 7-C<u>H</u>), 3.98 (1H, m, 27-C<u>H</u>), 3.85 (2H, m, 13-C<u>H</u>, 31-C<u>H</u>), 3.79 (3H, s, O<u>Me</u>), 3.73 (3H, s, O<u>Me</u>), 3.54 (1H, dd, *J* = 7.2, 2.1 Hz, 23-C<u>H</u>), 3.51 (1H, dddd, *J* = 10.2, 10.2, 4.6, 4.6 Hz, 29-C<u>H</u>), 3.33 (3H, s, O<u>Me</u>), 3.07 (1H, m, 15-CO<u>H</u>), 3.01 (1H, dd, *J* = 16.1, 6.0 Hz, 18-C<u>H</u>$_a$), 2.66 (1H, dd, *J* = 16.1, 6.3 Hz, 18-C<u>H</u>$_b$), 2.62 (1H, qd, *J* = 7.1, 3.9 Hz, 16-C<u>H</u>), 2.40 (2H, br dd, *J* = 6.5, 6.5 Hz, 6-C<u>H</u>$_2$), 2.07 (1H, m, 12-C<u>H</u>$_a$), 1.97 (1H, br d, *J* = 13.2 Hz, 30-C<u>H</u>$_a$), 1.86 (3H, m, 22-C<u>H</u>, 25-C<u>H</u>$_a$, 28-C<u>H</u>$_a$), 1.84 (1H, m, 12-C<u>H</u>$_b$), 1.78 (3H, s, 4-C<u>Me</u>); 1.72 (1H, m, 8-C<u>H</u>$_a$), 1.66 (1H, m, 24-C<u>H</u>), 1.65 (1H, m, 14-C<u>H</u>$_a$), 1.59 (2H, m, 26-C<u>H</u>$_a$, 28-C<u>H</u>$_b$), 1.57 (1H, m, 20-C<u>H</u>), 1.46 (1H, m, 14-C<u>H</u>$_b$), 1.41 (1H, m, 8-C<u>H</u>$_b$), 1.38 (1H, m, 25-C<u>H</u>$_b$), 1.36 (1H, m, 26-C<u>H</u>$_b$), 1.18 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 1.15 (1H, m, 30-C<u>H</u>$_b$), 1.12 (3H, d, *J* = 7.1 Hz, 16-C<u>Me</u>), 1.05 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 1.01 (3H, d, *J* = 7.2 Hz, 22-C<u>Me</u>),0.89 (3H, d, *J* = 6.9 Hz, 24-C<u>Me</u>), 0.88 (9H, s, *t*-Bu), 0.85 (3H, d, *J* = 6.9 Hz, 20-C<u>Me</u>), 0.054 (3H, s, Si<u>Me</u>), 0.049 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.7, 168.0, 158.6, 149.6, 137.6, 134.3, 131.2, 130.1, 128.5, 124.0, 115.5, 113.6, 83.5, 73.4, 73.3, 73.2, 72.6, 71.2, 69.6, 68.0 (2C), 64.6, 64.1, 55.3 (2C), 51.5, 51.2, 46.8, 41.5, 40.4, 39.1, 39.0 (2C), 37.6, 35.3, 34.8, 30.4, 28.5 (2C), 28.2, 27.8, 25.9, 22.2, 21.9, 21.7, 18.1, 15.9, 14.1, 12.5, 10.7, 9.5, -4.3, -4.7; m/z (+FAB, NOBA + NaOAc) 1107 (100, $[M+Na]^+$), 948 (15), 667 (20), 649 (15), 423 (20), 341 (65), 283 (80), 269 (30), 227 (50); HRMS Calcd for $C_{61}H_{104}NaO_{12}Si_2$ ($[M+Na]^+$): 1107.6964, found 1107.6966.

(*E*,*E*,7*S*)-Methyl-8-[(2*S*,6*S*)-6-{2*R*,3*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-hydroxy-6-(*para*-methoxybenzyloxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-4-one-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (36) and its isomer 37.

A tared, dry, 5.0 ml volumetric flask equipped with a septum was flushed with argon, and charged with neat (*c*-$C_6H_{11})_2BCl$ (0.497 g, 2.34 mmol). After diluting with Et_2O (3 ml), Et_3N (0.39 ml, 2.8 mmol) was added, and the resulting clear solution was made up to 5.0 ml with Et_2O. The concentration of this reagent solution was therefore 0.46 *M* in boron chloride and 0.56 *M* in Et_3N. To a cooled (–42 °C) solution of the ketone **19** (132 mg, 0.199 mmol) in Et_2O (2 ml) was added a solution of (*c*-$C_6H_{11})_2BCl$ and Et_3N in Et_2O (0.39 ml of the solution prepared above, 0.179 mmol of (*c*-$C_6H_{11})_2BCl$ with 0.22 mmol of Et_3N) and the resulting suspension was stirred at –42 °C for 0.5 h and then was allowed to warm to 0 °C over 0.5 h, whereupon more Et_3N•HCl precipitated. After 2 h, the enolate mixture was cooled to –78 °C and a solution of the aldehyde **3** (35.2 mg, 83.4 μmol) in Et_2O (0.2 ml + 2 x 0.2 ml rinses) was added *via* cannula. The suspension was stirred at –78 °C for 4.5 h, after which time the reaction flask was sealed and placed in a freezer at –20 °C for 18 h. The reaction mixture was then warmed to 0 °C and quenched with MeOH (2 ml), and H_2O_2 solution (0.18 ml, 30% aq.) was added. The resulting clear solution was stirred at 0 °C for 0.5 h, then poured into sodium metabisulphite solution (15 ml, 10% aqueous). The mixture was extracted with Et_2O (3 x 10 ml) and the organic layers were washed with brine (10 ml, sat. aq.), combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (gradient elution with 20→30% EtOAc/petroleum ether bp 40-60) afforded the aldol product mixture (75.4 mg, 83%), together with recovered starting ketone (8.9 mg) which was repurified by flash

chromatography (5→10% Et_2O/CH_2Cl_2). The aldol adducts were separated by preparative normal phase HPLC (30% EtOAc/hexane) to give the desired anti-aldol isomer **36** (33.1 mg) and the undesired anti-aldol isomer **37** (21.7 mg), together with minor amounts of *syn* isomers (8.0 mg combined).

Desired Anti-Aldol Isomer 36: R_f = 0.11 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = –60.6° (*c* 1.80, $CHCl_3$); IR (thin film) 3498 (m, br), 1718 (s) cm^{-1}; ^1H NMR δ (500 MHz, C_6D_6) 7.68 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.44 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.84 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 5.99 (1H, br d, *J* = 7.4, 7.4 Hz, 5-C<u>H</u>), 5.98 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.64 (1H, m, 11-C<u>H</u>), 5.54 (1H, dm, *J* = 10.1 Hz, 10-C<u>H</u>), 4.94 (1H, ddd, *J* = 6.4, 5.8, 1.7 Hz, 19-C<u>H</u>), 4.62 (2H, s, ArC<u>H</u>$_2$O), 4.57 (1H, br d, *J* = 11.4 Hz, 9-C<u>H</u>), 4.42 (1H, dd, *J* = 9.9, 2.6, 21-C<u>H</u>), 4.22 (1H, m, 7-C<u>H</u>), 4.16 (1H, m, 15-C<u>H</u>), 4.02 (1H, m, 27-C<u>H</u>), 3.86 (1H, br dd, *J* = 9.7, 9.7 Hz, 13-C<u>H</u>), 3.68 (1H, dd, *J* = 6.9, 2.4 Hz, 23-C<u>H</u>), 3.59 (1H, dqd, *J* = 9.1, 6.2, 2.9 Hz, 31-C<u>H</u>), 3.47 (3H, s, O<u>Me</u>), 3.35 (1H, dddd, *J* = 9.9, 9.9, 4.6, 4.6 Hz, 29-C<u>H</u>), 3.33 (3H, s, O<u>Me</u>), 3.15 (3H, s, O<u>Me</u>), 2.96 (1H, d, *J* = 3.1, 15-CO<u>H</u>), 2.92 (1H, dd, *J* = 16.8, 5.8 Hz, 18-C<u>H</u>$_a$), 2.66 (1H, dd, *J* = 16.8, 6.4 Hz, 18-C<u>H</u>$_b$), 2.47 (1H, dq, *J* = 7.2, 7.2 Hz, 16-C<u>H</u>), 2.42 (1H, m, 6-C<u>H</u>$_a$), 2.33 (1H, br ddd, *J* = 15.0, 7.4, 7.4 Hz, 6-<u>H</u>$_b$), 1.99 (1H, m, 22-C<u>H</u>), 1.93 (1H, m, 12-C<u>H</u>$_a$), 1.82 (2H, m, 20-C<u>H</u>, 26-C<u>H</u>$_a$), 1.80 (2H, m, 8-C<u>H</u>$_a$, 30-C<u>H</u>$_a$), 1.76 (1H, m, 28-C<u>H</u>$_a$), 1.73 (1H, m, 25-C<u>H</u>$_a$), 1.68 (2H, m, 24-C<u>H</u>, 28-C<u>H</u>$_b$), 1.64 (3H, s, 4-C<u>Me</u>), 1.58 (1H, m, 14-C<u>H</u>$_a$), 1.57 (1H, m, 12-C<u>H</u>$_b$), 1.50 (1H, m, 25-C<u>H</u>$_b$), 1.45 (1H, m, 14-C<u>H</u>$_b$), 1.39 (1H, m, 8-C<u>H</u>$_b$), 1.24 (9H, s, *t*-Bu), 1.23 (9H, s, *t*-Bu), 1.21 (1H, m, 30-C<u>H</u>$_b$), 1.20 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 1.14 (3H, d, *J* = 7.3 Hz, 22-C<u>Me</u>), 1.13 (1H, m, 26-C<u>H</u>$_b$), 1.00 (6H, d, *J* = 7.2 Hz, 16-C<u>Me</u>, 20-C<u>Me</u>), 0.99 (9H, s, *t*-Bu), 0.90 (3H, d, *J* = 6.6 Hz, 24-C<u>Me</u>), 0.24 (3H, s, Si<u>Me</u>), 0.19 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, C_6D_6) 212.9, 167.4, 159.5, 149.6, 137.7, 134.7, 131.8, 130.6, 128.7, 124.3, 116.3, 114.0, 84.1, 73.7, 73.6, 73.3, 71.7, 71.3, 70.3, 69.7, 68.6, 64.7, 63.8, 55.0, 54.7, 52.6, 51.0, 46.3, 42.0, 40.6, 40.3, 39.4, 39.2, 38.1, 35.9, 35.5, 31.3, 29.1, 28.8, 28.3, 28.2, 26.1, 22.5, 22.1, 22.0, 18.3, 16.2, 14.4, 14.0, 12.3, 9.6, -4.1, -4.4; m/z (+FAB, NOBA) 1108 (80, $[M+Na]^+$), 1027 (20), 667 (30), 649 (25), 341 (100), 283 (65), 129 (90), 117 (85); HRMS (+FAB, NOBA + NaOAc) Calcd for $C_{61}H_{104}NaO_{12}Si_2$ ($[M+Na]^+$): 1107.6964, found 1107.6953.

Undesired Anti-Aldol Isomer 37: R_f = 0.14 (20% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –60.6° (*c* 1.0, $CHCl_3$); IR (thin film) 3484 (m, br), 1718 (s) cm^{-1}; ^1H NMR δ ($CDCl_3$, 400 MHz) 7.35 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.19 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.83 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 5.95 (1H, br dd, *J* = 7.3, 7.3 Hz, 5-C<u>H</u>), 5.84 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.77 (1H, m, 11-C<u>H</u>), 5.62 (1H, br d, *J* = 10.2 Hz, 10-C<u>H</u>), 4.63 (1H, br dd, *J* = 6.0, 6.0 Hz, 19-C<u>H</u>), 4.47 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_a$O), 4.42 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_b$O), 4.38 (1H, br d, *J* = 10.1 Hz, 9-C<u>H</u>), 4.13 (1H, dd, *J* = 9.9, 2.3 Hz, 21-C<u>H</u>), 3.98 (2H, m, 7-C<u>H</u>, 27-C<u>H</u>), 3.84 (1H, m, 15-C<u>H</u>), 3.83 (1H, bs s, 15-CO<u>H</u>), 3.79 (3H, s, O<u>Me</u>), 3.78 (1H, m, 13-C<u>H</u>), 3.74 (3H, s, O<u>Me</u>), 3.71 (1H, m, 31-C<u>H</u>), 3.54 (1H, dd, *J* = 7.4, 2.3 Hz, 23-C<u>H</u>), 3.51 (1H, m, 29-C<u>H</u>), 3.32 (3H, s, O<u>Me</u>), 3.06 (1H, dd, *J* = 16.0, 5.4 Hz, 18-C<u>H</u>$_a$), 2.71 (1H, m, 18-C<u>H</u>$_b$), 2.71 (1H, m, 16-C<u>H</u>), 2.40 (2H, m, 6-C<u>H</u>$_2$), 2.00 (1H, m, 12-C<u>H</u>$_a$), 1.98 (1H, m, 30-C<u>H</u>$_a$), 1.94 (1H, m, 12-C<u>H</u>$_b$), 1.87 (1H, m, 22-C<u>H</u>), 1.85 (1H, m, 28-C<u>H</u>$_a$), 1.82 (1H, m, 26-C<u>H</u>$_a$), 1.78 (3H, s, 4-C<u>Me</u>); 1.71 (2H, m, 8-C<u>H</u>$_a$, 14-C<u>H</u>), 1.66 (1H, m, 24-C<u>H</u>), 1.58 (1H, m, 25-C<u>H</u>$_a$), 1.57 (2H, m, 20-C<u>H</u>, 28-C<u>H</u>$_b$),1.56 (1H, m, 14-C<u>H</u>$_b$), 1.44 (1H, ddd, *J* = 14.2, 10.1, 2.3 Hz, 8-C<u>H</u>$_b$), 1.38 (1H, m, 25-C<u>H</u>$_b$), 1.29 (1H, br ddd, *J* = 13, 6, 6 Hz, 26-C<u>H</u>$_b$), 1.18 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 1.14 (1H, m, 30-C<u>H</u>$_b$), 1.05 (3H, d, *J* = 7.2 Hz, 16-C<u>Me</u>), 1.05 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu), 1.01 (3H, d, *J* = 7.2 Hz, 22-C<u>Me</u>), 0.87 (9H, s, *t*-Bu), 0.88 (3H, d, *J* = 6.7 Hz, 24-C<u>Me</u>), 0.84 (3H, d, *J* = 6.9 Hz, 20-C<u>Me</u>), 0.06 (3H, s, Si<u>Me</u>), 0.05 (3H, s, Si<u>Me</u>); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 212.9, 168.0, 158.8, 149.5, 137.1, 134.6, 131.4, 129.7, 128.5, 123.4, 115.7, 113.5, 83.5, 74.0, 73.3, 73.0, 72.6, 70.6, 69.8, 68.4, 68.0, 64.5, 55.3, 55.2, 51.6 (2C), 47.7, 41.3, 40.5, 39.2, 39.0 (2C), 37.5, 35.2, 34.7, 31.1, 28.5, 28.4, 28.2, 27.8, 25.8, 22.2, 21.9, 21.7, 18.0, 15.9, 14.1, 12.8, 12.4, 9.2, -4.2, -4.9; m/z (+FAB, NOBA) 1108 (100, $[M+Na]^+$], 948 (25), 667 (25), 341 (60), 283 (75), 269

(35), 255 (30), 241 (40), 227 (55); HRMS Calcd for $C_{61}H_{104}NaO_{12}Si_2$ ([M+Na]$^+$): 1107.6964, found 1107.7013.

(*E*,*E*,7*S*)-Methyl-8-[(2*S*,6*S*)-6-{2*R*,3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2,4-dihydroxy-6-(*para*-methoxybenzyloxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (38)

A tared, argon flushed, 5.0 ml volumetric flask equipped with a septum was charged with freshly distilled catecholborane (0.604 g, 5.0 mmol) and the solution was diluted to 5.0 ml with THF to give a 1.0 *M* solution. To a cooled (–78 °C) solution of ketone **36** (45.8 mg, 0.0423 mmol) in THF (3 ml) was added a solution of catecholborane in THF (0.210 ml of a 1.0*M* solution, 0.21 mmol) and the resulting mixture was stirred at –78 °C for 2.5 h. The reaction flask was then sealed and placed in a freezer at –20 °C for 18 h, then warmed to 0 °C. More catecholborane in THF (0.210 ml of a 1.0*M* solution, 0.21 mmol) was then added and stirring at 0 °C was continued for 1 h, before the reaction mixture was warmed to room temperature for a further 4 h to take it to completion. The excess catecholborane was quenched by the addition of MeOH (1 ml) and sodium potassium tartrate solution (1 ml, sat. aqueous). The two-phase mixture was stirred for 1.5 h, then diluted with Et_2O (20 ml) and washed successively with NaOH solution (2 x 10 ml, 10% aq.), H_2O (10 ml), and brine (10 ml, sat. aq.). The aqueous layers were back-extracted with Et_2O (2 x 10 ml) and the combined ethereal phases were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (gradient elution with 25 →30% EtOAc/petroleum ether bp 40-60) gave diol **38** as a colourless glass (42.7 mg, 93%): R_f = 0.24 (30% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –74.2° (*c* 1.1, $CHCl_3$); IR (thin film) 3450 (m, br), 1720 (m) cm^{-1}; ^{1}H NMR δ (C_6D_6, 400 MHz) 7.74 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.39 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.85 (2H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.11 (1H, br d, *J* = 7.4, 7.4 Hz, 5-C<u>H</u>), 5.95 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.66 (1H, dm, *J* = 10.3 Hz, 11-C<u>H</u>), 5.53 (1H, m, 10-C<u>H</u>), 4.80 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_a$O), 4.64 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_b$O), 4.61 (1H, m, 9-C<u>H</u>), 4.55 (1H, m, 19-C<u>H</u>), 4.43 (1H, dd, *J* = 10.0, 2.4 Hz, 21-C<u>H</u>), 4.33 (1H, m, 7-C<u>H</u>), 4.07 (1H, m, 17-C<u>H</u>), 4.00 (2H, m, 15-C<u>H</u>, 27-C<u>H</u>), 3.96 (1H, m, 13-C<u>H</u>), 3.68 (1H, dd, *J* = 6.7, 2.1 Hz, 23-C<u>H</u>), 3.60 (1H, m, 31-C<u>H</u>), 3.45 (3H, s, O<u>Me</u>), 3.35 (1H, dddd, *J* = 10.0, 10.0, 5.0, 5.0 Hz, 29-C<u>H</u>), 3.31 (3H, s, O<u>Me</u>), 3.15 (3H, s, O<u>Me</u>), 2.44 (1H, m, 6-C<u>H</u>$_a$), 2.39 (1H, m, 6-C<u>H</u>$_b$), 2.10 (1H, m, 20-C<u>H</u>), 2.08 (1H, m, 18-C<u>H</u>$_a$), 2.04 (1H, m, 22-C<u>H</u>), 1.97 (1H, m, 18-C<u>H</u>$_b$), 1.94 (1H, m, 12-C<u>H</u>$_a$), 1.86 (1H, m, 8-C<u>H</u>$_a$), 1.82 (1H, m, 26-C<u>H</u>$_a$), 1.78 (1H, m, 30-C<u>H</u>$_a$), 1.75 (2H, m, 14-C<u>H</u>$_a$, 25-C<u>H</u>$_a$), 1.74 (2H, m, 16-C<u>H</u>, 28-C<u>H</u>$_a$), 1.71 (1H, m, 28-C<u>H</u>$_b$), 1.69 (1H, m, 24-C<u>H</u>), 1.59 (3H, s, 4-C<u>Me</u>), 1.54 (1H, m, 12-C<u>H</u>$_b$), 1.49 (1H, m, 25-C<u>H</u>$_b$), 1.43 (1H, m, 14-C<u>H</u>$_b$), 1.40 (1H, m, 8-C<u>H</u>$_b$), 1.25 (1H, m, 30-C<u>H</u>$_b$), 1.24 (9H, s, *t*-Bu), 1.23 (9H, s, *t*-Bu), 1.23 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 1.17 (3H, d, *J* = 7.3 Hz, 22-C<u>Me</u>), 1.16 (1H, m, 26-C<u>H</u>$_b$), 1.08 (3H, d, *J* = 6.9 Hz, 20-C<u>Me</u>), 1.00 (9H, s, *t*-Bu), 0.90 (3H, d, *J* = 6.5 Hz, 24-C<u>Me</u>), 0.81 (3H, d, *J* = 6.8 Hz, 16-C<u>Me</u>), 0.25 (3H, s, Si<u>Me</u>), 0.20 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (C_6D_6, 100.6 MHz) 167.6, 159.5, 149.7, 138.0, 134.6, 131.9, 130.4, 128.9, 124.4, 116.2, 114.1, 84.1, 76.7, 74.7, 74.1, 73.6, 73.1, 71.7, 71.1, 69.9, 68.6, 64.8, 64.3, 55.0, 54.7, 51.0, 44.7, 40.7, 40.4, 40.1, 39.3, 39.2, 38.3, 36.7, 36.2, 35.5, 31.3, 29.1, 28.8, 28.2 (2C), 26.1, 22.5, 22.1, 22.0, 18.3, 16.2, 14.4, 12.9, 13.4, 9.9, –4.1, –4.4; m/z (+FAB, NOBA + NaOAc) 1110 (1, [M+Na]$^+$, ion too weak for high resolution mass determination), 1088 (0.6, [M+H]$^+$), 832 (0.8), 121 (100).

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2*R*,3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-hydroxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (39)

A solution of DDQ (20 mg, 0.088 mmol, freshly recrystallised from $CHCl_3$) in CH_2Cl_2 was prepared and made up to 5.0 ml in a dry, argon flushed, volumetric flask equipped with a septum. The concentration was therefore 0.018*M*. To a stirred suspension of the syn-1,3-diol **38** (19.6 mg, 0.0181 mmol) and dry 4Å molecular sieve powder (70 mg) in CH_2Cl_2 (1 ml) was added a solution of DDQ in CH_2Cl_2 (1.5 ml of a 0.018*M* solution, 0.027 mmol) and the resulting brown mixture was stirred at room temperature for 0.5 h. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was passed through a short column of flash silica (10% Et_2O/CH_2Cl_2) to give a yellow oil, which was purified by the same technique but eluting instead with 30% EtOAc/petroleum ether (bp 40-60) to give, after removal of the solvent *in vacuo*, the acetal **39** as a colourless glass (16.3 mg, 83%): R_f = 0.21 (25% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –85.2° (*c* 0.92, $CHCl_3$); IR (thin film) 3508 (m, br), 1719 (m) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.63 (2H, d, *J* = 8.7 Hz, ArH), 7.60 (1H, d, *J* = 15.7 Hz, 3-CH), 6.85 (2H, d, *J* = 8.7 Hz, ArH), 5.92 (1H, d, *J* = 15.7 Hz, 2-CH), 5.91 (1H, m, 5-CH), 5.77 (1H, s, $ArCHO_2$), 5.65 (1H, m, 11-CH), 5.54 (1H, dm, *J* = 10.2 Hz, 10-CH), 4.71 (1H, br d, *J* = 11.2 Hz 19-CH), 4.60 (1H, dm, *J* = 11.2 Hz, 9-CH), 4.41 (1H, dd, *J* = 10.1, 2.5Hz, 21-CH), 4.29 (1H, m, 7-CH), 4.12 (1H, br dd, *J* = 8.6, 8.6 Hz, 15-CH), 4.05 (1H, br ddd, *J* = 8.3, 8.3, 1.5 Hz, 17-CH), 3.98 (1H, m, 13-CH), 3.96 (1H, m, 27-CH), 3.68 (1H, dd, *J* = 6.7, 2.5 Hz, 23-CH), 3.55 (1H, dqd, *J* = 9.0, 6.0, 3.0 Hz, 31-CH), 3.46 (3H, s, OMe), 3.33 (1H, dddd, *J* = 10.0, 10.0, 5.0, 5.0 Hz, 29-CH), 3.26 (3H, s, OMe), 3.14 (3H, s, OMe), 2.32 (2H, br dd, J = 6.7, 6.7 Hz, 6-CH_a, 6-CH_b), 1.98 (1H, m, 12-CH_a), 1.97 (1H, m, 22-CH), 1.89 (1H, m, 16-CH), 1.82 (1H, m, 8-CH_a), 1.79 (1H, m, 30-CH_a), 1.77 (2H, m, 26-CH_a, 18-CH_a), 1.75 (1H, m, 28-CH_a), 1.70 (2H, m, 20-CH, 14-CH_a), 1.69 (1H, m, 25-CH_a), 1.63 (1H, m, 28-CH_b), 1.60 (1H, m, 24-CH), 1.59 (1H, m, 12-CH_b), 1.52 (3H, s, 4-CMe), 1.48 (1H, m, 14-CH_b), 1.47 (1H, m, 25-CH_b), 1.39 (1H, m, 8-CH_b), 1.28 (1H, m, 18-CH_b), 1.25 (9H, s, *t*-Bu), 1.23 (9H, s, *t*-Bu), 1.22 (1H, m, 30-CH_b), 1.20 (3H, d, *J* = 6.2 Hz, 31-CMe), 1.14 (3H, d, *J* = 7.2 Hz, 22-CMe), 1.09 (1H, m, 26-CH_b), 1.01 (9H, s, *t*-Bu), 0.97 (3H, d, *J* = 6.9 Hz, 20-CMe), 0.87 (3H, d, *J* = 6.5 Hz, 24-CMe), 0.77 (3H, d, *J* = 7.0 Hz, 16-CMe), 0.26 (3H, s, SiMe), 0.21 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, C_6D_6) 167.4, 160.5, 149.6, 137.7, 134.4, 132.0, 130.5, 128.4 (partly obscured by solvent), 124.5, 116.1, 113.9, 102.0, 84.1, 81.4, 74.9, 73.6, 72.6, 71.6, 70.7, 69.6, 68.5, 64.7, 63.9, 55.0, 54.7, 50.9, 44.2, 41.5, 40.5, 40.0, 39.6, 39.2, 38.1, 36.0, 35.4, 31.8, 31.4, 29.1, 28.8, 28.3, 28.2, 26.1, 22.5, 22.1, 22.0, 18.3, 16.1, 14.0, 12.3, 11.9, 9.6, –4.1, –4.3; m/z (+FAB, NOBA + NaOAc) 1108 (1.3, $[M+Na]^+$, ion too weak for high resolution mass determination), 341 (20), 283 (10), 121 (100).

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2*R*3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-2-oxo-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (40)

To a solution of the alcohol **39** (19.7 mg, 0.0182 mmol) in CH_2Cl_2 (2 ml) was added solid Dess-Martin periodinane (30.0 mg, 0.071 mmol) and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was then poured into a vigorously stirred mixture containing sodium thiosulphate (0.5 g), $NaHCO_3$ solution (10 ml, sat. aq.) and Et_2O (20 ml) and stirring was continued until all of the solid had dissolved (*ca* 10 min). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 10 ml). The organic extracts were then washed successively with $NaHCO_3$ (10 ml, sat. aq.) and brine (10 ml, sat. aq.) and then combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/petroleum ether bp 40-60) to give the ketone **40** as a colourless glass (17.6 mg, 89%): R_f = 0.25 (20% EtOAc/petoleum ether bp 40-60); $[\alpha]_D^{20}$ = –53.3° (*c* 0.95, $CHCl_3$); IR (thin film) 1719 (s) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.78 (1H, d, *J* = 15.7 Hz, 3-CH), 7.55 (2H, d, *J* = 8.7 Hz, ArH), 6.79 (2H, d, *J* = 8.7 Hz, ArH), 6.20 (1H, br dd, *J* = 7.3, 7.3 Hz, 5-CH), 5.96 (1H, d, *J* = 15.7 Hz, 2-CH), 5.64 (1H, s, $ArCHO_2$), 5.54 (1H, m, 11-CH), 5.51 (1H, m, 10-CH), 4.62 (1H, br d, *J* = 11.2 Hz 19-CH),

4.53 (1H, br d, J = 9.3 Hz, 9-CH), 4.41 (1H, dd, J = 10.1, 2.4 Hz, 21-CH), 4.32 (1H, m, 7-CH), 4.16 (1H, m, 13-CH), 4.10 (1H, m, 17-CH), 3.97 (1H, m, 27-CH), 3.69 (1H, dd, J = 6.5, 2.5 Hz, 23-CH), 3.56 (1H, m, 31-CH), 3.47 (3H, s, OMe), 3.33 (1H, dddd, J = 10.0, 10.0, 5.0, 5.0 Hz, 29-CH), 3.22 (3H, s, OMe), 3.14 (3H, s, OMe), 2.62 (1H, m, 16-CH), 2.62 (1H, dd, J = 17.6, 8.6 Hz, 14-CH_a), 2.45 (2H, m, 6-CH_a, 6-CH_b), 2.34 (1H, dd, J = 17.6, 3.2 Hz, 14-CH_b), 1.97 (1H, m, 22-CH), 1.88 (1H, m, 8-CH_a), 1.79 (1H, m, 26-CH_a), 1.76 (1H, m, 30-CH_a), 1.74 (1H, m, 28-CH_a), 1.72 (1H, m, 12-CH_a), 1.71 (1H, m, 25-CH_a), 1.69 (1H, m, 28-CH_b), 1.65 (1H, m, 20-CH), 1.62 (1H, m, 24-CH), 1.60 (3H, s, 4-CMe), 1.57 (1H, m, 18-CH_a), 1.50 (1H, m, 12-CH_b), 1.48 (1H, m, 25-CH_b), 1.42 (1H, m, 8-CH_b), 1.22 (9H, s, t-Bu), 1.22 (1H, m, 30-CH_b), 1.20 (3H, d, J = 6.4 Hz, 31-CMe), 1.19 (9H, s, t-Bu), 1.15 (3H, d, J = 7.2 Hz, 22-CMe), 1.13 (1H, m, 18-CH_b), 1.12 (1H, m, 26-CH_b), 1.00 (9H, s, t-Bu), 0.97 (3H, d, J = 6.9 Hz, 20-CMe), 0.92 (3H, d, J = 7.1 Hz, 16-CMe), 0.89 (3H, d, J = 6.6 Hz, 24-CMe), 0.20 (3H, s, SiMe), 0.16 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, C_6D_6) 209.8, 167.4, 160.4, 149.8, 138.3, 134.4, 132.0, 130.7, 128.4, 124.0, 116.1, 113.7, 101.5, 84.0, 79.2, 74.4, 73.6, 72.6, 71.7, 69.7, 68.3, 64.7, 62.6, 55.0, 54.7, 51.8, 51.0, 50.1, 41.4, 40.7, 39.6, 39.2, 38.2, 36.1, 35.5, 32.0, 30.4, 29.0, 28.8, 28.2, 28.1, 26.1, 22.5, 22.2, 22.0, 18.3, 16.1, 14.0, 12.4, 11.9, 9.6, –4.1, –4.4; m/z (+FAB, NOBA) 1084 (4, $[M+H]^+$), 1027 (5), 786 (10), 341 (70), 283 (100); HRMS Calcd for $C_{61}H_{103}O_{12}Si_2$ ($[M+H]^+$): 1083.6988, found 1083.7035.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2*S*,3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-hydroxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (41)

To a cooled (0 °C) solution of the ketone **40** (34.7 mg, 0.0321 mmol) in Et_2O (4 ml) was added a solution of $LiAlH(O^tBu)_3$ in THF (0.43 ml of a 0.74*M* solution, 0.32 mmol) and the resulting solution was stirred at 0 °C for 0.5 h, then the reaction flask was sealed and placed in a freezer at –20 °C for 18 h. The excess hydride was then quenched by the addition of NH_4Cl solution (2 ml, sat. aq.) and the mixture was poured into brine (15 ml, sat. aq.) and extracted with Et_2O (3 x 10 ml). The combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by passing it down a short column of flash silica (30% EtOAc/hexane) to give a mixture of alcohols **41** and **39** (32.6 mg, 94%). These diastereomers were separated by preparative normal phase HPLC (20% EtOAc/petroleum ether bp 40-60) to give the less polar, major epimer **41** (20.0 mg) and the more polar, minor epimer **39** (4.2 mg), both as colourless glasses. The ketone *re : si* face selectivity was therefore 83 : 17: R_f = 0.24 (25% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –74.6° (*c* 1.1, $CHCl_3$); IR (thin film) 3517 (m, br), 1720 cm^{-1}; ^{1}H NMR δ (400 MHz, C_6D_6) 7.69 (2H, d, J = 8.7 Hz, ArH), 7.60 (1H, d, J = 15.7 Hz, 3-CH), 6.86 (2H, d, J = 8.7 Hz, ArH), 5.95 (1H, d, J = 15.7 Hz, 2-CH), 5.80 (1H, m, 5-CH), 5.79 (1H, s, $ArCHO_2$), 5.56 (1H, m, 11-CH), 5.46 (1H, dm, J = 10.3 Hz, 10-CH), 4.71 (1H, br d, J = 11.4 Hz 19-CH), 4.58 (1H, dm, J = 10.2 Hz, 9-CH), 4.43 (1H, dd, J = 10.1, 2.1Hz, 21-CH), 4.33 (1H, br d, J = 10.2 Hz, 15-CH), 4.17 (1H, m, 7-CH), 4.14 (1H, m, 17-CH), 3.97 (1H, m, 27-CH), 3.68 (1H, dd, J = 6.6, 2.3 Hz, 23-CH), 3.55 (2H, m, 13-CH, 31-CH), 3.47 (3H, s, OMe), 3.32 (1H, dddd, J = 10.0, 10.0, 5.0, 5.0 Hz, 29-CH), 3.26 (3H, s, OMe), 3.14 (3H, s, OMe), 2.25 (2H, br dd, J = 6.7, 6.7 Hz, 6-CH_a, 6-CH_b), 1.97 (1H, m, 22-CH), 1.82 (1H, m, 12-CH_a), 1.79 (2H, m, 26-CH_a, 30-CH_a), 1.78 (2H, m, 18-CH_a, 14-CH_a), 1.74 (1H, m, 28-CH_a), 1.68 (3H, m, 8-CH_a, 16-CH, 25-CH_a), 1.67 (1H, m, 28-CH_b), 1.61 (1H, m, 20-CH), 1.60 (1H, m, 24-CH), 1.58 (3H, s, 4-CMe), 1.55 (1H, m, 12-CH_b), 1.46 (1H, m, 25-CH_b), 1.37 (1H, m, 8-CH_b), 1.35 (1H, m, 18-CH_b), 1.25 (1H, m, 14-CH_b), 1.24 (9H, s, t-Bu), 1.23 (9H, s, t-Bu), 1.22 (1H, m, 30-CH_b), 1.20 (3H, d, J = 6.2 Hz, 31-CMe), 1.14 (3H, d, J = 6.9 Hz, 22-CMe), 1.11 (1H, m, 26-CH_b), 0.99 (3H, d, J = 7.1 Hz, 20-CMe), 0.96 (9H, s, t-Bu), 0.95 (3H, d, J = 7.0 Hz, 16-CMe), 0.87 (3H, d, J = 6.5 Hz, 24-CMe), 0.24 (3H, s, SiMe), 0.14 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, C_6D_6) 167.4, 160.4, 149.6, 137.5, 134.6, 132.7, 130.1, 128.3, 124.0, 116.3, 113.8, 102.0, 84.1, 79.2, 74.8,

73.6, 72.6, 71.7, 69.79, 69.75, 68.27, 68.22, 64.7, 55.0, 54.7, 51.0, 44.3, 41.6, 40.8, 40.6, 39.6, 39.3, 38.0, 36.0, 35.4, 32.8, 31.3, 29.0, 28.8, 28.3, 28.2, 26.1, 22.5, 22.2, 22.0, 18.3, 16.1, 14.0, 12.3, 9.7, 9.1, –4.1, –4.6; m/z (+FAB, NOBA) 1086 (1.5, $[M+H]^+$), 633 (6), 453 (8), 341 (100), 283 (60); HRMS Calcd for $C_{61}H_{105}O_{12}Si_2$ ($[M+H]^+$): 1085.7144, found 1085.7187.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2*S*,3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-methoxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (42)

Method A – methylation of **41**: To a warm (50 °C) solution of the alcohol **41** (29.8 mg, 0.0275 mmol) in 2,6-di-*tert*-butyl-pyridine (0.60 ml, dried over 4Å molecular sieves) was added MeOTf (0.079 ml, 0.7 mmol). After 4.5 h, more MeOTf (0.080 ml, 0.7 mmol) was added and the reaction mixture was maintained at 50 °C for 2 h, then cooled to 0 °C and treated with NH_3 solution (2 ml, 33% aq.). The mixture was stirred vigorously at room temperature for 0.5 h to ensure complete destruction of the excess MeOTf, and was then poured into H_2O (15 ml) and extracted with Et_2O (3 x 10 ml). The organic extracts were then washed with brine (10 ml, sat. aq.) and combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (gradiant elution with 15→20% EtOAc/petroleum ether bp 40-60) to give the methyl ether **42** as a colourless glass (20.0 mg, 66%), together with some recovered **41** (3.7 mg, 12%).

Method B – protection of diol **57**: To a solution of diol **57** (36.3 mg, 0.0370 mmol) in dry CH_2Cl_2 (0.5 ml) at room temperature was added anisaldehyde dimethyl acetal (19 µl, 20 mg, 0.111 mmol) followed by camphor-sulphonic acid (0.05 M solution in CH_2Cl_2, 37 µl, 0.0018 mmol). After 1h, solid $NaHCO_3$ (50 mg) was added, the mixture was stirred for 2 min, then diluted with CH_2Cl_2 and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (10% Et_2O/CH_2Cl_2) to yield **42** as a colourless glass (38.1 mg, 0.0346 mmol, 94%): R_f = 0.21 (20% EtOAc/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –84.3° (*c* 1.6, $CHCl_3$); IR (thin film) 1720 (m) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.68 (2H, d, *J* = 8.7 Hz, ArH), 7.68 (1H, d, *J* = 15.7 Hz, 3-CH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.98 (1H, m, 5-CH), 5.93 (1H, d, *J* = 15.7 Hz, 2-CH), 5.80 (1H, s, $ArCHO_2$), 5.63 (1H, m, 11-CH), 5.54 (1H, dm, *J* = 10.2 Hz, 10-CH), 4.74 (1H, br d, *J* = 11.2 Hz 19-CH), 4.56 (1H, dm, *J* = 9.8 Hz, 9-CH), 4.48 (1H, dd, *J* = 10.1, 2.4 Hz, 21-CH), 4.14 (1H, m, 7-CH), 4.08 (1H, m, 17-CH), 4.03 (1H, m, 15-CH), 3.98 (1H, m, 27-CH), 3.70 (1H, dd, *J* = 6.5, 2.5 Hz, 23-CH), 3.57 (1H, m, 31-CH), 3.53 (1H, m, 13-CH), 3.50 (3H, s, OMe), 3.36 (3H, s, OMe), 3.34 (1H, m, 29-CH), 3.31 (3H, s, OMe), 3.15 (3H, s, OMe), 2.25 (2H, m, 6-CH_a, 6-CH_b), 2.05 (1H, m, 14-CH_a), 2.01 (1H, m, 22-CH), 1.90 (1H, m, 12-CH_a), 1.79 (4H, m, 16-CH, 18-CH_a, 26-CH_a, 30-CH_a), 1.77 (1H, m, 20-CH), 1.74 (1H, m, 28-CH_a), 1.71 (1H, m, 25-CH_a), 1.65 (3H, m, 8-CH_a, 12-CH_b, 28-CH_b), 1.62 (1H, m, 24-CH), 1.57 (1H, m, 14-CH_b), 1.56 (3H, s, 4-CMe), 1.50 (1H, m, 25-CH_b), 1.46 (1H, m, 18-CH_b), 1.39 (1H, m, 8-CH_b), 1.22 (9H, s, *t*-Bu), 1.22 (1H, m, 30-CH_b), 1.21 (9H, s, *t*-Bu), 1.21 (3H, d, *J* = 6.2 Hz, 31-CMe), 1.16 (3H, d, *J* = 7.2 Hz, 22-CMe), 1.12 (1H, m, 26-CH_b), 1,04 (3H, d, *J* = 7.1 Hz, 20-CMe), 0.97 (9H, s, *t*-Bu), 0.92 (3H, d, *J* = 7.0 Hz, 16-CMe), 0.91 (3H, d, *J* = 6.5 Hz, 24-CMe), 0.18 (3H, s, SiMe), 0.02 (3H, s, SiMe); The stereochemistry at the *para*-methoxy-benzylidene acetal centre was established by NOE analysis. Irradiation of ArCH (δ_H 5.80) gave nuclear Overhauser enhancements to 17-CH (δ_H 4.08), 19-CH (δ_H 4.74) and ArH (δ_H 7.68). Irradiation of 19-CH gave nuclear Overhauser enhancements to ArCH (δ_H 5.80), 21-CH (δ_H 4.48), 17-CH (δ_H 4.08), 20-CH (δ_H 1.77) and 18-CH_AH_B (δ_H 1.46). Clean irradiation of 17-CH was not possible because of poor signal dispersion in that area of the spectrum; ^{13}C NMR δ (100.6 MHz, C_6D_6) 167.4, 160.3, 149.7, 138.3, 134.3, 132.5, 130.7, 128.7, 124.2, 116.1, 113.8, 101.8, 84.1, 79.3, 76.0, 74.9, 73.6, 72.7, 71.7, 69.5, 68.4, 64.7, 64.4, 57.6, 55.0, 54.7, 51.0, 42.0, 41.6, 41.0, 39.7, 39.3, 38.0, 37.6, 36.0, 35.5, 33.0, 31.7, 29.1, 28.8, 28.2 (2C), 26.1, 22.5, 22.2, 22.0, 18.3, 16.1, 14.1, 12.4, 9.8, 8.6, –4.0, –4.5; m/z (+FAB, NOBA) 1100 (2, $[M+H]^+$), 453 (10), 283 (100); HRMS Calcd

for $C_{62}H_{119}O_{12}Si_2$ ([M+H]$^+$): 1099.7301, found: 1099.7350; Anal calc. for $C_{62}H_{118}O_{12}Si_2$: C 67.72, H 9.72; found C 67.54, H 9.73.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*S*)-2-hydroxy-3-methylpent-4-en-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (51)

The crotylboronate **50** was prepared according to the procedure of Roush *et al.*[24] To a solution of (*S*,*S*)-diisopropyl-(*Z*)-crotylboronate **50** (≈ 0.7 M in toluene, 2.61 ml, 1.83 mmol), diluted with dry toluene (2 ml) at room temperature, was added powdered activated 4Å sieves (50 mg). The resulting mixture was cooled to –110 °C (liq. N_2/MeOH bath) and aldehyde **3** (prepared by Dess-Martin oxidation of the precursor alcohol, 0.1929 g, 0.455 mmol) in PhMe (1 ml + 1 ml washings) was then added dropwise *via* cannula. The resulting mixture was was then allowed to warmed to –90 °C and stirred for 0.5 h, before stirring at –78 °C for 3 h. After a further 12 h –20 °C, the reaction mixture was warmed to room temperature and the solvent evaporated *in vacuo*. The crude mixture was separated by flash chromatography (10 → 30% Et_2O/hexane) to give the desired isomer **51** (107.1 mg, 49%) and the minor isomer **52** (73.5 mg, 34%), both as colourless oils. Alternatively, use of Brown's[23] isopinocampheyl-based reagent **49** gave a 95 : 5 mixture of **51** and **52** in 60% yield.

51: R_f = 0.30 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = –80.7° (*c* 2.2, $CHCl_3$); IR (liquid film) 1720 (s), 1640 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.93 (1H, dd, *J* = 7.5, 7.5 Hz, 5-C<u>H</u>), 5.81 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.81 (1H, m, 17-C<u>H</u>), 5.76 (1H, m, 11-C<u>H</u>), 5.60 (1H, m, 10-C<u>H</u>), 5.03 (2H, m, 18-C<u>H</u>), 4.37 (1H, d, *J* = 10.3 Hz, 9-C<u>H</u>), 3.97 (1H, m, 7-C<u>H</u>), 3.73 (3H, s, O<u>Me</u>), 3.70 (1H, m, 15-C<u>H</u>), 3.53 (2H, m, 13-C<u>H</u>, CO<u>H</u>), 2.42 (2H, m, 6-C<u>H</u>), 2.35 (1H, m, 16-C<u>H</u>), 1.98 (1H, m, 12-C<u>H</u>$_a$), 1.91 (1H, m, 12-C<u>H</u>$_b$), 1.78 (3H, s, 4-C<u>Me</u>), 1.71 (2H, m, 14-C<u>H</u>), 1.49 (1H, m, 8-C<u>H</u>$_a$), 1.39 (1H, ddd, *J* = 14.7, 10.0, 2.3 Hz, 8-C<u>H</u>$_b$), 1.02 (3H, d, *J* = 6.9 Hz, 16-C<u>Me</u>), 0.86 (9H, s, ^{t}Bu), 0.07 (6H, s, 2 x Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.9, 149.5, 141.0, 137.4, 134.6, 129.7, 123.7, 115.7, 114.7, 75.3, 69.9, 68.7, 68.3, 51.5, 43.7, 40.6, 39.1, 37.7, 31.2, 25.8, 18.0, 15.2, 12.4, –4.2, –4.8; m/z (CI, NH_3) 479 (60, [M+H]$^+$), 439 (30), 251 (60), 233 (40), 181 (100), 132 (30), 111 (45), 81 (70%); HRMS (CI, NH_3) calc for $C_{27}H_{47}O_5Si$ ([M+H]$^+$) 479.3193, found 479.3193.

52: R_f = 0.19 (33% Et_2O/hexane); ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.94 (1H, dd, *J* = 7.3, 7.3 Hz, 5-C<u>H</u>), 5.80 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.75 (2H, m, 11-C<u>H</u>, 17-C<u>H</u>), 5.62 (1H, m, 10-C<u>H</u>), 5.05 (2H, m, 18-C<u>H</u>), 4.35 (1H, d, *J* = 10.7 Hz, 9-C<u>H</u>), 4.03 (1H, m, 7-C<u>H</u>), 3.87 (1H, m, 13-C<u>H</u>), 3.74 (3H, s, O<u>Me</u>), 3.73 (1H, m, 15-C<u>H</u>), 2.42 (2H, m, 6-C<u>H</u>), 2.26 (1H, m, 16-C<u>H</u>), 2.06 (1H, m, 12-C<u>H</u>$_a$), 1.84 (1H, m, 12-C<u>H</u>$_b$), 1.77 (3H, s, 4-C<u>Me</u>), 1.68 (2H, m, 14-C<u>H</u>), 1.58 (1H, m, 8-C<u>H</u>$_a$), 1.39 (1H, ddd, *J* = 14.3, 9.9, 2.2 Hz, 8-C<u>H</u>$_b$), 1.06 (3H, d, *J* = 6.8 Hz, 16-C<u>Me</u>), 0.88 (9H, s, ^{t}Bu), 0.09 (3H, s, Si<u>Me</u>), 0.08 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 168.0, 149.6, 140.9, 137.7, 134.3, 130.0, 124.1, 115.5, 115.2, 71.8, 69.5, 68.1, 64.5, 51.5, 44.0, 40.4, 38.9, 37.7, 30.7, 25.9, 18.1, 15.5, 12.5, –4.2, –4.7.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*S*)-2-methoxy-3-methylpent-4-en-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (53)

Alcohol **51** (173.7 mg, 0.363 mmol) was dissolved in dry $CHCl_3$ (5.5 ml) in a flask fitted with a reflux condenser. 2,6-Di-*tert*-butylpyridine (3.4 ml, 2.86 g, 15.0 mmol) was added and the resulting mixture was heated to 55 °C. Methyl triflate (0.85 ml, 1.23 g, 7.48 mmol) was added and the mixture stirred at 55 °C for 5.7 h. Concentrated ammonia solution (5 ml, aq.) was added dropwise with cooling in an ice bath, and the resulting mixture was stirred vigorously at room temperature for 30 min. The reaction mixture was partitioned between water (30 ml) and Et_2O (30 ml) and the aqueous layer extracted with Et_2O (2 x 30 ml). The combined organic extracts were washed with aqueous hydrochloric acid (2 x 30 ml, 1 M), $NaHCO_3$ (25 ml) and brine (25 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (20%→30%

Et_2O/hexane) to give methyl ether **53**, as a pale yellow oil (134.7 mg, 0.273 mmol, 75%), and recovered starting alcohol **51** (20 mg, 0.042 mmol, 12%): $R_f = 0.28$ (20% Et_2O/hexane); $[\alpha]_D^{20} = -91.2°$ (*c* 1.7, $CHCl_3$); IR (liquid film) 1721 (s), 1624 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.94 (1H, dd, *J* = 7.3, 7.3 Hz, 5-C<u>H</u>), 5.84 (1H, m, 17-C<u>H</u>), 5.79 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.77 (1H, m, 11-C<u>H</u>), 5.62 (1H, m, 10-C<u>H</u>), 5.03 (2H, m, 18-C<u>H</u>), 4.30 (1H, m, 9-C<u>H</u>), 4.02 (1H, m, 7-C<u>H</u>), 3.73 (3H, s, O<u>Me</u>), 3.63 (1H, m, 15-C<u>H</u>), 3.32 (3H, s, O<u>Me</u>), 3.22 (1H, m, 13-C<u>H</u>), 2.40 (3H, m, 16-C<u>H</u>, 6-C<u>H</u>), 1.95 (2H, m, 12-C<u>H</u>), 1.76 (3H, s, 4-C<u>Me</u>), 1.73 (1H, dd, *J* = 14.0, 7.1 Hz, 14-C<u>H</u>$_a$), 1.62 (1H, m, 14-C<u>H</u>$_b$), 1.57 (1H, m, 8-C<u>H</u>$_a$), 1.38 (1H, ddd, *J* = 14.3, 9.8, 2.6 Hz, 8-C<u>H</u>$_b$), 0.99 (3H, d, *J* = 6.8 Hz, 16-C<u>Me</u>), 0.87 (9H, s, ^{t}Bu), 0.08 (3H, s, Si<u>Me</u>), 0.06 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.9, 149.6, 141.0, 137.8, 134.2, 130.4, 123.8, 115.4, 114.5, 81.2, 69.2, 68.1, 64.3, 57.0, 51.4, 40.6, 40.1, 37.7, 36.7, 30.7, 25.9, 18.1, 14.6, 12.5, –4.3, –4.6; m/z (CI, NH_3) 231 (100%); HRMS (CI, NH_3) calc for $C_{28}H_{49}O_5Si$ ($[M+H]^+$) 493.3349, found 493.3349.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*R*)-2-methoxy-3-methylpentan-4-one-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (54)

To a 7:1 v/v mixture of DMF and water (0.5 ml), under an oxygen atmosphere (balloon), was added copper (I) chloride (20 mg, 0.205 mmol), which dissolved on stirring to give a green solution. Palladium (II) chloride (4.0 mg, 0.023 mmol) was then added and the resulting mixture stirred vigorously under O_2 for 2 h, during which time it turned muddy brown in colour. Methyl ether **53** (50.6 mg, 0.103 mmol) was added in solution in 7:1 DMF/H_2O (0.5 ml + 2 x 0.1 ml washing) *via* cannula under O_2 pressure. The resulting green-coloured mixture was stirred vigorously under O_2 (balloon). After 70 h, NH_4Cl solution (10 ml) was added and the resulting mixture was extracted with Et_2O (4 x 10 ml). The combined organic extracts were washed with water (10 ml), $NaHCO_3$ solution (10 ml, sat. aq.) and brine (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (30% Et_2O/hexane) gave recovered starting material **53** (10.7 mg, 21%) and methyl ketone **54** (34.3 mg, 0.0674 mmol, 66%) as a colourless oil: $R_f = 0.27$ (33% Et_2O/hexane); $[\alpha]_D^{20} = -73.2°$ (*c* 2.5, $CHCl_3$); IR (liquid film) 1714 (s), 1621 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.29 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.94 (1H, dd, *J* = 7.4, 7.4 Hz, 5-C<u>H</u>), 5.78 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.76 (1H, m, 11-C<u>H</u>), 5.62 (1H, m, 10-C<u>H</u>), 4.32 (1H, m, 9-C<u>H</u>), 4.05 (1H, m, 7-C<u>H</u>), 4.73 (3H, s, O<u>Me</u>), 3.69 (1H, m, 15-C<u>H</u>), 3.56 (1H, m, 13-C<u>H</u>), 3.30 (3H, s, O<u>Me</u>), 2.65 (1H, qd, *J* = 7.1, 4.4 Hz, 16-C<u>H</u>), 2.39 (2H, m, 6-C<u>H</u>), 2.18 (3H, s, 18-C<u>Me</u>), 1.95 (2H, m, 12-C<u>H</u>), 1.75 (3H, s, 4-C<u>Me</u>), 1.73 (1H, m, 14-C<u>H</u>$_a$), 1.64 (1H, ddd, *J* = 14.3, 10.6, 2.7 Hz, 8-C<u>H</u>$_a$), 1.57 (1H, ddd, *J* = 14.5, 7.1, 4.9 Hz, 14-C<u>H</u>$_b$), 1.38 (1H, ddd, *J* = 14.3, 9.9, 2.6 Hz, 8-C<u>H</u>$_b$), 1.09 (3H, d, *J* = 7.1 Hz, 16-C<u>Me</u>), 0.87 (9H, s, ^{t}Bu), 0.10 (3H, s, Si<u>Me</u>), 0.08 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 211.2, 167.9, 149.6, 137.8, 134.2, 130.2, 123.7, 115.4, 78.7, 69.3, 68.1, 63.9, 57.2, 51.4, 49.6, 40.6, 37.7, 36.8, 30.9, 29.5, 25.9, 18.1, 12.5, 11.0, –4.3, –4.7; m/z (CI, NH_3) 509 (10, $[M+H]^+$), 477 (20), 459 (70), 345 (40), 211 (80), 179 (100), 109 (30), 81 (30%); HRMS (CI, NH_3) calc for $C_{28}H_{49}O_6Si$ ($[M+H]^+$) 509.3298, found 509.3299.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*R*)-2-methoxy-3-methyl-4-trimethylsilyloxypent-4-en-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (55)

Chlorotrimethylsilane (1 ml) and triethylamine (1 ml) were separately mixed in a centrifuge tube fitted with a septum. The white precipitate was centrifuged down and 127 μl of the supernatant solution (≈ 0.50 mmol of chlorotrimethylsilane) was added to a –78 °C solution of ketone **54** (85.1 mg, 0.167 mmol) in dry THF (2 ml). Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 176 μl, 176 mmol) was then added dropwise. The resulting solution was stirred at –78 °C for 5 min, before the addition of a further 90 μl of lithium bis(trimethylsilyl)amide solution. After a further 10 min, 20 μl of lithium bis(trimethylsilyl)amide solution was

added. The resulting mixture was stirred for 15 min, before quenching with pH 7 buffer solution (3 ml) and diluting with pentane (10 ml). The layers were separated and the aqueous layer extracted with pentane (3 x 10 ml). The combined organic phases were washed with pH 7 buffer solution (10 ml) and brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude silyl enol ether **55** was used immediately in the next reaction.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-2-methoxy-3,7,9,11-tetramethyl-6-hydroxy-8,10-di-*tert*-butylsilylenedioxy-13-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-tridecan-4-one-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (56)

To a solution of silyl enol ether **55** (0.167 mmol) in dry CH_2Cl_2 (1 ml) at –78 °C was added a solution of aldehyde **4** (81.8 mg, 0.174 mmol) in CH_2Cl_2 (1 ml + 0.2 ml washing) *via* cannula. Then freshly distilled boron trifluoride etherate (25 µl, 28 mg, 0.20 mmol) was added. The reaction mixture was stirred at –78 °C for 40 min, then quenched with $NaHCO_3$ solution (5 ml, sat. aq.) and diluted with Et_2O (10 ml). The aqueous layer was extracted with Et_2O (3 x 10 ml), the combined organic extracts were washed with $NaHCO_3$ solution (10 ml, sat. aq.) and brine (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (25→ 30% EtOAc/hexane) to give **56**, as a colourless oil (134 mg, 0.137 mmol, 82%), and 26 mg of an inseparable mixture of starting aldehyde **4** and methyl ketone **54**: R_f = 0.22 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = –65.3° (*c* 3.8, $CHCl_3$); IR (liquid film) 3521 (br, OH), 1716 (s), 1622 (s) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.69 (1H, d, *J* = 15.5 Hz, 3-C<u>H</u>), 6.00 (1H, dd, *J* = 6.5, 6.5 Hz, 5-C<u>H</u>), 5.99 (1H, d, *J* = 15.5 Hz, 2-C<u>H</u>), 5.66 (1H, m, 11-C<u>H</u>), 5.57 (1H, m, 10-C<u>H</u>), 5.05 (1H, dd, *J* = 10.3, 1.8 Hz, 19-C<u>H</u>), 4.62 (1H, m, 9-C<u>H</u>), 4.53 (1H, dd, *J* = 9.7, 2.5 Hz, 21-C<u>H</u>), 4.25 (1H, m, 7-C<u>H</u>), 4.04 (1H, m, 27-C<u>H</u>), 3.83 (1H, ddd, *J* = 7.5, 4.8, 4.5 Hz, 15-C<u>H</u>), 3.74 (1H, dd, *J* = 6.3, 2.6 Hz, 23-C<u>H</u>), 3.63 (1H, m, 31-C<u>H</u>), 3.52 (3H, s, O<u>Me</u>), 3.51 (1H, m, 13-C<u>H</u>), 3.40 (1H, m, 29-C<u>H</u>), 3.20 (6H, s, 2 x O<u>Me</u>), 2.90 (1H, dd, *J* = 17.4, 10.3 Hz, 18-C<u>H</u>$_a$), 2.56 (1H, qd, *J* = 7.1, 4.3 Hz, 16-C<u>H</u>), 2.48 (1H, dd, *J* = 17.4, 1.8 Hz, 18-C<u>H</u>$_b$), 2.46 (1H, m, 6-C<u>H</u>$_a$), 2.36 (1H, m, 6-C<u>H</u>$_b$), 2.03 (1H, m, 22-C<u>H</u>), 1.91 (2H, m, 25-C<u>H</u>$_a$, 12-C<u>H</u>$_a$), 1.86 (3H, m, 14-C<u>H</u>$_a$, 26-C<u>H</u>$_a$, 30-C<u>H</u>$_a$), 1.75 (4H, m, 8-C<u>H</u>$_a$, 24-C<u>H</u>, 28-C<u>H</u>), 1.70 (1H, m, 20-C<u>H</u>), 1.66 (1H, 12-C<u>H</u>$_b$), 1.63 (1H, m, 25-C<u>H</u>$_b$), 1.62 (3H, s, 4-C<u>Me</u>), 1.56 (1H, m, 14-C<u>H</u>$_b$), 1.41 (1H, m, 8-C<u>H</u>$_b$), 1.34 (9H, s, ^{t}Bu), 1.27 (1H, m, 30-C<u>H</u>$_b$), 1.26 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 1.23 (9H, s, ^{t}Bu), 1.22 (1H, m, 26-C<u>H</u>$_b$), 1.18 (3H, d, *J* = 7.2 Hz, 22-C<u>Me</u>), 1.11 (3H, d, *J* = 7.1 Hz, 16-C<u>Me</u>), 1.04 (9H, s, ^{t}Bu), 0.99 (3H, d, *J* = 7.2 Hz, 20-C<u>Me</u>), 0.97 (3H, d, *J* = 7.1 Hz, 24-C<u>Me</u>), 0.75 (3H, s, Si<u>Me</u>), 0.68 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.7, 167.9, 149.6, 137.8, 134.2, 130.3, 123.7, 115.4, 83.4, 78.8, 73.3, 73.2, 72.5, 69.3, 68.1, 66.3, 64.6, 63.9, 57.2, 55.3, 51.4, 49.7, 47.0, 40.8, 40.6, 39.2, 39.0, 37.7, 36.8, 35.5, 34.8, 30.8, 28.7, 28.5, 28.1, 27.8, 25.9, 22.1, 21.9, 21.7, 18.1, 15.8, 14.0, 12.5, 10.9, 9.6, –4.3, –4.6; m/z (FAB) 471 (15), 341 (45), 283 (100), 229 (40), 151 (45), 115 (60%); HRMS (FAB) calc for $C_{54}H_{98}O_{11}Si_2Na$ ([M+Na]$^+$) 1001.6545, found 1001.6578.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*S*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-2-methoxy-3,7,9,11-tetramethyl-8,10-di-*tert*-butylsilylenedioxy-4,6-dihydroxy-13-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-tridecan-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (57)

To a cooled (–78 °C) solution of ketone **56** (96.9 mg, 0.0989 mmol) in dry THF (1.0 ml) and dry MeOH (0.2 ml) was added di-*n*-butylmethoxyborane (40 µl, 31 mg, 0.198 mmol). The resulting solution was stirred for 15 min, before addition of lithium borohydride solution (2.0 M in THF, 0.40 ml, 0.80 mmol) The reaction mixture was allowed to warm gradually to –40 °C over 45 min and stirred at this temperature for a further 1.5 h. The reaction was quenched by the addition of pH 7 buffer solution (1.5 ml), MeOH (1.5 ml) and H_2O_2 solution (0.5 ml, 30% aq.) The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h, followed

by dilution with water (10 ml) and extraction with Et_2O (4 x 20 ml). The combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (15% Et_2O/CH_2Cl_2) to give diol **57**, as a colourless glass (80.6 mg, 0.0821 mmol, 83%): R_f = 0.23 (15% Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = -65°$ (*c* 0.4, $CHCl_3$); IR (liquid film) 3452 (br), 1712 (s), 1622 (s), 1462 (s) cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.72 (1H, d, *J* = 15.6 Hz, 3-C<u>H</u>), 6.03 (1H, dd, *J* = 7.3, 7.3 Hz, 5-C<u>H</u>), 6.00 (1H, d, *J* = 15.6 Hz, 2-C<u>H</u>), 5.70 (1H, m, 11-C<u>H</u>), 5.60 (1H, m, 10-C<u>H</u>), 4.81 (1H, d, *J* = 9.8 Hz, 19-C<u>H</u>), 4.64 (1H, d, *J* = 11.0 Hz, 9-C<u>H</u>), 4.58 (1H, dd, *J* = 9.6, 2.5 Hz, 21-C<u>H</u>), 4.49 (1H, br s, CO<u>H</u>), 4.34 (1H, br s, CO<u>H</u>), 4.24 (1H, m, 7-C<u>H</u>), 4.05 (2H, m, 17-C<u>H</u>, 27-C<u>H</u>), 3.75 (1H, dd, *J* = 6.4, 2.5 Hz, 23-C<u>H</u>), 3.70 (1H, m, 15-C<u>H</u>), 3.64 (1H, m, 31-C<u>H</u>), 3.53 (1H, m, 13-C<u>H</u>), 3.51 (3H, s, O<u>Me</u>), 3.42 (1H, m, 29-C<u>H</u>), 3.18 (3H, s, O<u>Me</u>), 3.15 (3H, s, O<u>Me</u>), 2.42 (2H, m, 6-C<u>H</u>), 2.05 (1H, m, 22-C<u>H</u>), 1.96 (1H, m, 14-C<u>H</u>$_a$), 1.91 (1H, m, 30-C<u>H</u>$_a$), 1.90 (1H, m, 18-C<u>H</u>$_a$), 1.88 (3H, m, 12-C<u>H</u>$_a$, 20-C<u>H</u>, 26-C<u>H</u>$_a$), 1.81 (2H, m, 25-C<u>H</u>), 1.80 (1H, m, 24-C<u>H</u>), 1.79 (2H, 28-C<u>H</u>), 1.78 (1H, m, 8-C<u>H</u>$_a$), 1.69 (2H, m, 12-C<u>H</u>$_b$, 16-C<u>H</u>), 1.66 (3H, s, 4-C<u>Me</u>), 1.64 (1H, m, 18-C<u>H</u>$_b$), 1.56 (1H, m, 14-C<u>H</u>$_b$), 1.46 (1H, m, 8-C<u>H</u>$_b$), 1.37 (9H, s, ^{t}Bu), 1.31 (1H, m, 30-C<u>H</u>$_b$), 1.30 (3H, d, *J* = 6.3 Hz, 31-C<u>Me</u>), 1.25 (1H, m, 26-C<u>H</u>$_b$), 1.25 (9H, s, ^{t}Bu), 1.21 (3H, d, *J* = 7.2 Hz, 22-C<u>Me</u>), 1.07 (3H, d, *J* = 6.9 Hz, 20-C<u>Me</u>), 1.04 (9H, s, ^{t}Bu), 0.98 (3H, d, *J* = 6.5 Hz, 24-C<u>Me</u>), 0.79 (3H, d, *J* = 7.0 Hz, 16-C<u>Me</u>), 0.29 (3H, s, Si<u>Me</u>), 0.22 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, C_6D_6) 167.6, 149.6, 137.8, 134.5, 130.7, 124.0, 116.3, 84.0, 79.8, 76.1, 73.9, 73.6, 71.6, 71.4, 69.4, 68.4, 64.8, 64.3, 56.5, 55.0, 51.0, 42.4, 40.8, 40.7, 40.1, 39.5, 39.2, 38.2, 36.2, 36.2, 35.5, 31.3, 29.2, 28.8, 28.2, 28.2, 26.1, 22.5, 22.1, 22.0, 18.3, 16.1, 14.3, 12.4, 11.3, 9.9, –4.1, –4.5; m/z (FAB) 1004 (14, $[M+Na]^+$), 982 (10, $[M+H]^+$), 341 (40), 283 (100), 227 (40), 151 (45), 117 (80%); HRMS (FAB) calc for $C_{54}H_{101}O_{11}Si_2$ ($[M+H]^+$) 981.6882, found 981.6887; Anal calc. for $C_{54}H_{100}O_{11}Si_2$: C 66.08, H 10.27; found C 65.82, H 10.25.

Pre-swinholide A, methyl ester (43)

To a cooled (0 °C) solution of **42** (12.9 mg, 0.0117 mmol) in MeCN (2 ml) was added HF solution (0.2 ml, 40% aq.) and the resulting mixture was stirred at 0 °C for 0.5 h, then at room temperature for for 1.75 h. The excess HF was then quenched by pouring the reaction mixture into $NaHCO_3$ solution (10 ml, sat. aq.) and the product was extracted with EtOAc (3 x 15 ml). The organic extracts were washed successively with $NaHCO_3$ solution (10 ml, sat. aq.) and brine (10 ml, sat. aq.) and were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC (85% MeOH in H_2O) to give the monomeric methyl ester **43** as a colourless glass (6.7 mg, 79%): R_f = 0.29 (10% $MeOH/CH_2Cl_2$); t_R 20.5 min (85% $MeOH/H_2O$); $[\alpha]_D^{20} = -42°$ (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3415 (m, br), 1703 (s), cm^{-1} (m); ^1H NMR δ (400 MHz, $CDCl_3$) – see **Table 1**; ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 168.1, 149.5, 137.9, 134.6, 129.5, 123.6, 115.6, 80.6, 80.3, 77.1, 76.1, 73.3, 73.0, 71.9, 68.3, 67.8, 66.0, 64.9, 57.3, 55.3, 51.5, 39.9, 39.6, 39.3, 38.5, 37.0, 35.7, 35.3, 35.0, 34.8, 34.3, 29.9, 29.1, 28.5, 21.7, 16.6, 12.8, 12.4, 11.7, 10.7; m/z (+FAB, NOBA) 750 (20, $[M+Na]^+$), 728 (100, $[M+H]^+$), 223 (50); HRMS Calcd for $C_{40}H_{71}O_{16}$ ($[M+H]^+$): 727.4996, found: 727.5008.

Pre-swinholide A, methyl ester, pentaacetate (44)

To a solution of methyl ester **43** (6.7 mg, 0.0092 mmol) in dry pyridine (0.3 ml) was added Ac_2O (0.3 ml) and the resulting mixture was stirred at room temperature for 25 h. The reaction mixture was diluted with EtOAc (15 ml) and washed successively with $CuSO_4$ solution (2 x 10 ml, sat. aqueous) and brine (10 ml, sat. aqueous). The aqueous phases were back-extracted with EtOAc (2 x 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC (90% $MeOH/H_2O$) to give some of the pentaacetate **44** (0.5 mg, 6%) together with partially acetylated material (*ca* 8.0 mg). To a solution of the partially acetylated material in dry pyridine (0.5 ml) was added Ac_2O (0.5 ml)

followed by DMAP (*ca* 10 mg). The resulting orange solution was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc (15 ml) and washed successively with $CuSO_4$ solution (2 x 10 ml, sat. aq.), H_2O (10 ml), and brine (10 ml, sat. aq.). The aqueous phases were back-extracted with EtOAc (2 x 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC (90% MeOH/H_2O) to give more of the pentaacetate **44** (4.6 mg, 53%). The total yield of **44** was therefore 59%: t_R 25.8 min (90% MeOH/H_2O); $[\alpha]_D^{20} = -26°$ (*c* 0.23, $CHCl_3$); IR (CCl_4) 1739 (s) cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) – see **Table 2**; ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 170.9, 170.6 (2C), 170.3, 170.2, 167.9, 149.4, 135.9, 135.3, 129.3, 124.4, 116.0, 78.2, 77.3, 73.4, 72.8, 71.8, 71.2, 70.0, 69.7, 69.2, 64.8, 64.6, 57.0, 55.4, 51.6, 40.0, 38.6, 37.4, 36.5, 35.6, 35.1, 34.9, 33.8, 33.7, 33.1, 31.0, 29.1, 26.7, 21.9, 21.3, 21.2, 21.14, 21.07, 21.0, 16.9, 12.4, 10.1, 10.0, 8.8; m/z (+FAB, Glycerol) 938 (v. weak, $[M+H]^+$), 301 (10), 275 (10), 186 (35), 167 (15), 153 (10), 133 (100); (+FAB, NOBA) 960 (100, $[M+Na]^+$), 938 (60, $[M+H]^+$), 878 (100), 666 (50), 560 (50); HRMS Calcd for $C_{50}H_{81}O_{16}$ ($[M+H]^+$): 937.5524, found: 937.5603.

Pre-swinholide A (2)

To a solution of methyl ester **43** (5.2 mg, 0.0072 mmol) in a mixture of MeOH (0.5 ml) and H_2O (0.4 ml) was added NaOH solution (0.1 ml of a 2.5*M* solution, 0.25 mmol) and the resulting light brown mixture was stirred at room temperature for 5 h. The reaction mixture was then diluted with H_2O (10 ml) and washed with EtOAc (5 ml). The organic phase was back-extracted with H_2O and the combined aqueous phases were acidified with HCl (3*M*, aqueous), saturated with NaCl, and extracted with EtOAc (3 x 15 ml). The organic extracts were washed with brine (10 ml, sat. aq.), then combined, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as a glass (*ca* 6 mg). The residue was purified by preparative reverse phase HPLC (80% MeOH/H_2O) to give (–)-pre-swinholide A (**2**), as a colourless glass (2.7 mg, 52%). It was conceivable that the compound so prepared was isolated partly as a metal salt because the ^1H NMR spectra acquired in $CDCl_3$ showed very broad resonances for 2-CH, 3-CH, and 5-CH. In order to obtain a sample that provided sharp resonances in its ^1H NMR spectrum ($CDCl_3$), it was necessary to dissolve the secoacid in EtOAc (5 ml) and wash with brine (5 ml, sat. aq.) that had been acidified with hydrochloric acid. The aqueous phase was back-extracted with EtOAc (5 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give fully protonated pre-swinholide A (**2**): $R_f = 0.23$ (15% MeOH/CH_2Cl_2); t_R *ca* 13.5 min (broad peak) (80% MeOH/H_2O); $[\alpha]_D^{20} = -24°$ (*c* 0.25, MeOH); IR ($CDCl_3$) 3400 (s, br), 1718 (m) cm^{-1}; ^1H NMR δ (C_5D_5N, 500 MHz) – see **Table 3**; ^{13}C NMR δ (C_5D_5N, 125 MHz) 138.4, 131.3, 124.0, 79.7, 77.2, 74.6, 73.4, 72.8, 72.1, 71.8, 70.0, 67.0, 64.6, 64.5, 57.0, 54.9, 43.3, 42.1, 41.4, 39.3, 38.6, 38.4, 37.3, 36.0, 35.8, 35.5, 31.6, 29.7, 28.8, 22.0, 16.9, 12.5, 10.9, 10.7, 9.7. NB: the ^{13}C chemical shift data was obtained from a HETCOR spectrum acquired on this compound, hence all the quaternary carbons are not observed; m/z (+FAB, NOBA) 735 (60, $[M+Na]^+$), 713 (80, $[M+H]^+$), 391 (40), 307 (100), 289 (95); HRMS Calcd for $C_{39}H_{69}O_{11}$ ($[M+H]^+$): 713.4840, found: 713.4829.

Table 1: ^{1}H NMR Data in $CDCl_3$ for Pre-Swinholide A, Methyl Ester (**43**)

Position	δ_H[a]	Mult	*J* Hz	δ_H (lit[b])	Mult (lit)	*J* Hz (lit)
1	-	-	-	-	-	-
2	5.82	d	15.6	5.82	d	15.6
3	7.34	d	15.6	7.34	d	15.6
4	-	-	-	-	-	-
4-Me	1.80	s	-	1.80	s	-
5	5.99	dd	7.4, 7.4	5.99	dd	7.3, 7.3
6	2.48	ddd	15.0, 7.4, 7.4	2.47	ddd	15.0, 7.3, 7.3
	2.40	ddd	15.0, 7.4, 6.9	2.40	ddd	15.0, 6.7, 6.7
7	4.03	m	-	4.03	m	-
8	1.77	m	-	1.76	m	-
	1.56	m	-	1.57	m	-
9	4.53	br d	9.0	4.52	br d	9.0
10	5.65	dm	10.4	5.65	d	10.4
11	5.83	m	-	5.83	m	-
12	2.19	dm	17.2	2.19	br d	17.4
	1.93	m	-	1.92	m	-
13	3.88	m	-	3.87	m	-
14	2.05	ddd	14.4, 7.2, 7.2	2.05	ddd	14.3, 7.3, 7.3
	1.59	m	-	1.58	m	-
15	3.66	m	-	3.66	m	-
15-OMe	3.41	s	-	3.41	s	-
16	1.93	m	-	1.92	m	-
16-Me	0.86	d	7.3	0.86	d	7.0
17	3.88	m	-	3.87	m	-
18	1.62	m	-	1.61	m	-
	1.62	m	-	1.61	m	-
19	4.05	m	-	4.03	m	-
20	1.98	m	-	1.98	m	-
20-Me	0.77	d	7.0	0.77	d	7.0
21	4.04	m	-	4.03	m	-
22	1.76	m	-	1.75	m	-
22-Me	0.88	d	7.1	0.89	d	6.7
23	3.33	m	-	3.31	m	-
24	1.76	m	-	1.75	m	-
24-Me	1.03	d	7.0	1.04	d	7.0
25	1.71	m	-	1.70	m	-
	1.30	m	-	1.30	m	-
26	1.84	m	-	1.85	m	-
	1.32	m	-	1.35	m	-
27	4.02	m	-	4.03	m	-
28	1.85	m	-	1.84	m	-
	1.62	m	-	1.61	m	-
29	3.55	dddd	10, 10, 4.5, 4.5	3.55	dddd	10, 10, 4.5, 4.5
29-OMe	3.34	s	-	3.35	s	-
30	1.98	m	-	2.00	m	-
	1.21	m	-	1.22	m	-
31	3.74	m	-	3.75	m	-
31-Me	1.21	d	6.2	1.22	d	6.1
Ester Me	3.75	s	-	-[c]		

[a]Measured at 400 MHz in $CDCl_3$. Assignments were determined by COSY experiments.

[b]Measured at 500 MHz in $CDCl_3$ and taken from ref 20a.

[c]Not reported.

Table 2: ^{1}H NMR Data in $CDCl_3$ for Pre-Swinholide A Methyl Ester, Pentaacetate (**44**)

Position	δ_H[a]	Mult	*J* Hz	δ_H (lit[b])	Mult. (lit)	*J* Hz
1	-	-	-	-	-	-
2	5.82	d	15.7	5.82	d	15.7
3	7.33	d	15.7	7.33	d	15.7
4	-	-	-	-	-	-
4-Me	1.78	s	-	1.78	s	-
5	5.93	br dd	7.3, 7.3	5.93	dd	7.0, 7.0
6	2.62	ddd	14.8, 7.3, 5.3	2.61	ddd	14, 7, 7
	2.54	ddd	14.8, 7.3, 6.2	2.55	ddd	14, 7, 7
7	5.23	m	-	5.22	m	-
8	1.78	m	-	1.78	m	-
	1.67	m	-	1.67	m	-
9	4.22	br d	8.4	4.22	br d	8.5
10	5.62	br d	10.4	5.63	br d	10.4
11	5.81	m	-	5.81	m	-
12	1.95	m	-	1.96	m	-
	1.95	m	-	1.96	m	-
13	3.54	m	-	3.54	m	-
14	1.86	m	-	1.85	m	-
	1.53	m	-	1.52	m	-
15	3.43	m	-	3.43	m	-
15-OMe	3.26	s	-	3.26	s	-
16	1.81	m	-	1.81	m	-
16-Me	0.888	d	7.0	0.89	d	6.0
17	4.94	m	-	4.95	m	-
18	1.92	m	-	1.91	m	-
	1.92	m	-	1.91	m	-
19	4.74	br dd	7.0, 7.0	4.73	br dd	7.0, 7.0
20	2.04	m	-	2.04	m	-
20-Me	0.96	d	6.9	0.96	d	7.0
21	4.99	d	10.4	4.99	d	10.1
22	2.09	m	-	2.10	m	-
22-Me	0.92	d	6.9	0.92	d	6.7
23	4.67	dd	8.1, 4.6	4.67	dd	8.2, 4.6
24	1.92	m	-	1.93	m	-
24-Me	0.890	d	6.6	0.89	d	6.0
25	1.40	m	-	1.40	m	-
	1.16	m	-	1.15	m	-
26	1.84	m	-	1.84	m	-
	1.19	m	-	1.20	m	-
27	3.96	m	-	3.97	m	-
28	1.80	m	-	1.80	m	-
	1.58	m	-	1.58	m	-
29	3.52	dddd	10, 10, 4.5, 4.5	3.52	dddd	10, 10, 4.5, 4.5
29-OMe	3.34	s	-	3.34	s	-
30	1.96	m	-	1.97	m	-
	1.18	m	-	1.18	m	-
31	3.67	dqd	9.3, 6.3, 2.8	3.67	dqd	9.5, 6.5, 3.0
31-Me	1.20	d	6.3	1.20	d	6.5
Ester Me	3.75	s	-	3.75	s	-
Acetate Me	2.11, 2.02, 2.00, 1.98, 1.96	s	-	-[c]	-	-

[a]Measured at 500 MHz in $CDCl_3$. Assignments were determined by COSY experiments.

[b]Measured at 500 MHz and taken from ref. 20b.

[c]Not reported.

Table 3: ^{1}H NMR Data in D_5-Pyridine for Pre-Swinholide A (**2**)

Position	δ_H[a]	Mult	*J* Hz	δ_H (lit)[b]	Mult (lit)	*J* Hz (lit)	lit assignment
1	-	-	-	-	-	-	-
2	6.16	br d	14	6.15	d	15.6	2
3	7.73	br d	14	7.73	d	15.6	3
4	-	-	-	-	-	-	-
4-Me	1.78	s	-	1.78	s	-	4-Me
5	6.36	br m	-	6.38	dt	8, 8, 2	5
6	2.61	m	-	2.60	br t	6	6
	2.61	m	-	2.60	br t	6	
7	4.50	m	-	4.53	m	-	7
8	1.94	m	-	1.61	m	-	8
	1.64	m	-	1.61	m	-	
9	4.91	d	10.1	4.92	m	-	19
10	5.78	m	-	5.76	br s	-	10
11	5.78	m	-	5.76	br s	-	11
12	1.91	m	-	1.90	m	-	12
	1.91	m	-	1.90	m	-	
13	3.78	m	-	3.76	m	-	21
14	2.02	m	-	2.03	m	-	18
	1.67	m	-	1.66	m	-	
15	4.13	m	-	4.17	m	-	9
15-OMe	3.30	s	-	3.29	s	-	15-OMe
16	1.82	m	-	1.86	m	-	16
16-Me	0.96	d	6.5	0.94	d	6.6	16-Me
17	4.12	m	-	4.09	m	-	15
18	1.99	m	-	1.90	m	-	14
	1.92	m	-	1.90	m		
19	4.85[c]	m	-	4.86	m	-	17
20	1.99	m	-	1.90	m	-	20
20-Me	0.97	d	7.0	0.98	d	6.9	20-Me
21	4.59	d	9.3	4.58	br d	10.2	13
22	2.05	m	-	2.03	m	-	22
22-Me	1.18	d	6.8	1.19	d	6.9	22-Me
23	3.64	m	-	3.63	m	-	23
24	1.86	m	-	1.80	m	-	24
24-Me	0.95	d	6.8	0.92	d	5.4	24-Me
25	1.86	m	-	1.90	m	-	25
	1.46	m	-	1.52	m	-	
26	1.90	m	-	1.90	m	-	26
	1.18	m	-	1.12	m	-	
27	3.98	m	-	3.96	br s	-	29
28	1.78	m	-	1.9	m	-	28
	1.57	m	-	1.52	m	-	
29	3.46	dddd	10, 10, 5, 5	3.43	m	-	27
29-OMe	3.22	s	-	3.12	s	-	29-OMe
30	1.87	m	-	1.86	m	-	30
	1.12	m	-	1.12	m	-	-
31	3.64	m	-	-[d]	-	-	-
31-Me	1.13	d	6.3	1.12	d	6.3	31-Me

[a]Measured at 500 MHz in C_5D_5N. The ^{1}H NMR spectrum for synthetic **2** was referenced to the literature value for 4-Me (δ = 1.78 ppm) so that the results could be compared directly.

[b]Taken from ref. 20c. Note our reassignment of some of these resonances.

[c]Obscured by H_2O peak but observed in COSY spectrum.

[d]Not reported.

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swinholide A, Dr J. M. Goodman (Cambridge) for assistance with molecular modelling, and Dr R. J. Butlin (Zeneca) for helpful discussions.

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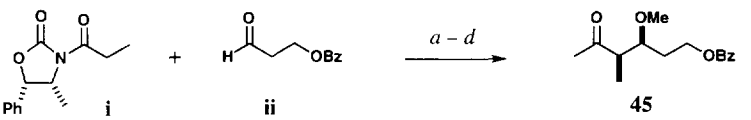

(a) **i**, *n*-Bu_2BOTf, $^iPr_2NEt$, CH_2Cl_2, -78 °C; aldehyde **ii**; (b) MeONHMe•HCl, Me_3Al, THF, 0 °C; (c) NaH, MeI, DMF, 20 °C; (d) MeMgCl, THF, -78 → 0 °C.

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