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VIP

Total Synthesis of Rapamycin

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Abstract: For over 30 years, rapamycin has generated a sustained and intense interest from the scientific community as a result of its exceptional pharmacological properties and challenging structural features. In addition to its well known therapeutic value as a potent immunosuppressive agent, rapamycin and its derivatives have recently gained prominence for the treatment of a wide variety of other human malignancies. Herein we disclose full details of our extensive investigation into the synthesis of rapamycin that culminated in a new and convergent preparation featuring a macro-etherification/catechol-templating strategy for construction of the macrocyclic core of this natural product.

Keywords: anticancer agents · immunosuppressive agents · macrocyclization · natural products · total synthesis

Introduction

Rapa Nui (Easter Island) has long been a source of intrigue and wonder since the Dutch Admiral Jacob Roggeveen first landed on its shores onboard De Arend, part of a Dutch West India Company expedition, on Easter Sunday 1722. In search of Terra Australis, he instead came across one of the world's most isolated inhabited islands, situated in the vast expanse of the South Pacific Ocean, over 1250 miles from its nearest neighbour. It was from this remote location that a soil sample containing the fungus *Streptomyces hygroscopicus* was first collected in 1975 by Vézina and co-workers.[1] Isolation of the lypophilic macrolide contained within realised the discovery of rapamycin (**1**), whose structure was subsequently determined through a combination of X-ray crystallography[2] and extensive NMR studies (Figure 1).[3] Whilst its initial biological activity as an antifungal agent[4] attracted little attention, the disclosure of the immunosuppressive properties of the related macrolide FK506[5] some ten years later led to a dramatic reassessment. The obvious structural homology between these two molecules, combined with the importance of such immunomodulating effects, initiated massive research efforts across a broad spectrum of scientific disciplines. Subsequently, four distinct total syntheses of rapamycin (**1**) were reported in the 1990s by the organic synthesis community.[6]

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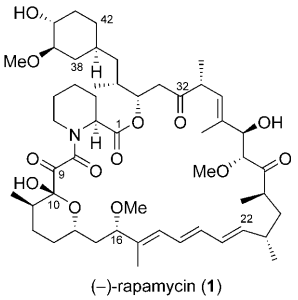

(–)-rapamycin (**1**)

Figure 1. Structure of (–)-rapamycin (**1**).

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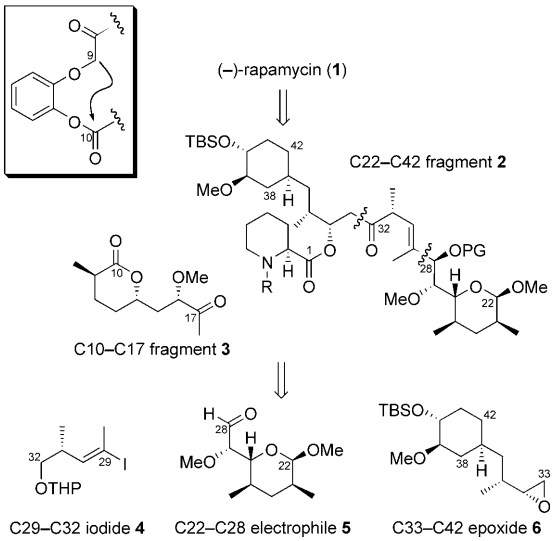
Concurrently, detailed investigation into the molecular targets and mode of action of **1** was slowly providing insight. Critical to the improved understanding in this regard was the parallel study of the related macrolides FK506,[7] L-685 818,[8] FR-900520,[9] meridamycin,[10] ascomycin[9a,11] and the antascomicins,[12] as well as of synthetic derivatives of rapamycin itself. The subsequent elucidation of distinctly novel biological signalling pathways of fundamental importance[13] from this study has had significant ramifications. In addition to rapamycin's (**1**) commercial launch by Wyeth in 1999 for the prevention of allograft rejection following liver transplantation, many other human ailments are now being targeted.[13b,14] Principle amongst these are applications related to cancer treatment,[15] whereby C40-derivatives of **1**, such as CCI-779, RAD001, and AP23573 are in various levels of clinical trials as antitumour agents.[16] Indeed, CCI-779 has recently been approved by the FDA for the first-line treatment of patients with advanced renal cell carcinoma.[17] It is now recognised that the diverse array of pharmacological applications for rapamycin (**1**) are directly linked to the importance of its principle biological target as a central enzyme in regulating anabolic and catabolic processes at the cellular level. This enzyme, known as the mammalian target of rapamycin (mTOR; also known as FRAP, RAFT, RAPT, or SEP)[18] is inhibited by a rapamycin-enzyme (FKBP12) complex.[18b,19] It is the ability to manipulate such fundamental processes as cell proliferation, growth, differentiation, migration, and survival through the use of rapamycin (**1**) and its derivatives that is currently providing great promise for the novel treatment of so many human disorders.

We embarked upon a rapamycin synthesis program of our own almost two decades ago. As a result of this, we published a series of fragment syntheses[20] and related synthetic studies[21] in the early 1990s, and finally a completed synthesis[22] of rapamycin (**1**) that coincided with a resurgence of interest in this natural product as a result of its expanding pharmacological application. Herein we present full synthetic details of the successful route, but also take time to discuss other strategies which were investigated en route to this fascinating natural product, along with many of the successes and disappointments that were experienced along the way.

Synthetic plan: Our initial retrosynthetic analysis was developed in 1990, two years before the first synthetic papers on rapamycin were published. The lack of precedent for any of the planned major bond constructions at that time placed extra importance on the choice of suitable target fragments with which to achieve the overall objective. From the outset we were intrigued by the possibility of using a catechol-template to achieve ring-closure through a rare carbon–carbon (C9–C10) macrocyclic bond forming event. Further disconnection across the triene via a Pd^0 cross-coupling process seemed the most obvious choice for additional simplification of the target structure. However, uncertainty about exactly which C–C bond formation (C18–C19, or C20–C21) would provide us with optimal results led us to seek intermediates that would allow all possibilities to be explored. Accordingly the C22–C42 and C10–C17 fragments (**2** and **3**, respectively), were revealed, in which either of the carbonyls at C17 or C22 might be manipulated (Scheme 1).



Scheme 1. Retrosynthetic analysis.

For the larger C22–C42 subunit (**2**) we envisioned the sequential carbanionic coupling of vinyl iodide **4** (wherein the C32–OTHP represents a precursor to a sulfone), aldehyde **5**, and epoxide **6**. The potential interchangeability order of these should provide additional flexibility. Given the notorious difficulty with stereocontrol in acetate aldols,[23] we chose to exploit a stereodefined epoxide electrophile for coupling with a nucleophilic C32 centre to achieve the correct configuration at C34. Additionally, the use of a sulfone acyl anion equivalent should avoid any undesired β-elimination, which has been documented to occur in the presence of the C32 ketone.[24] Lithiation of a trisubstituted olefin at C29 followed by its addition to a suitable electrophile at C28 was anticipated for the union of **4** and **5**. Although control of the resulting secondary carbinol stereochemistry was uncertain, we felt confident that the adjacent stereodefined C27-methyl ether might provide some advantage. Finally, for electrophile **5**, we speculated that the use of a cyclic acetal as a scaffold would offer several benefits over a linear system. In particular, both the C26 ketone and C22 aldehyde would be protected (the latter in the correct oxidation state) and the cyclic nature of the C22–C26 skeleton should afford opportunities for substrate-based stereocontrol in constructing the C27 and C28 chiral centres.

Results and Discussion

Degradation studies: With the initial strategy delineated, preliminary efforts were directed towards the synthesis of the key building blocks (**3**–**6**). Concurrent with this work, we sought to exploit an in-house supply of rapamycin (**1**) by

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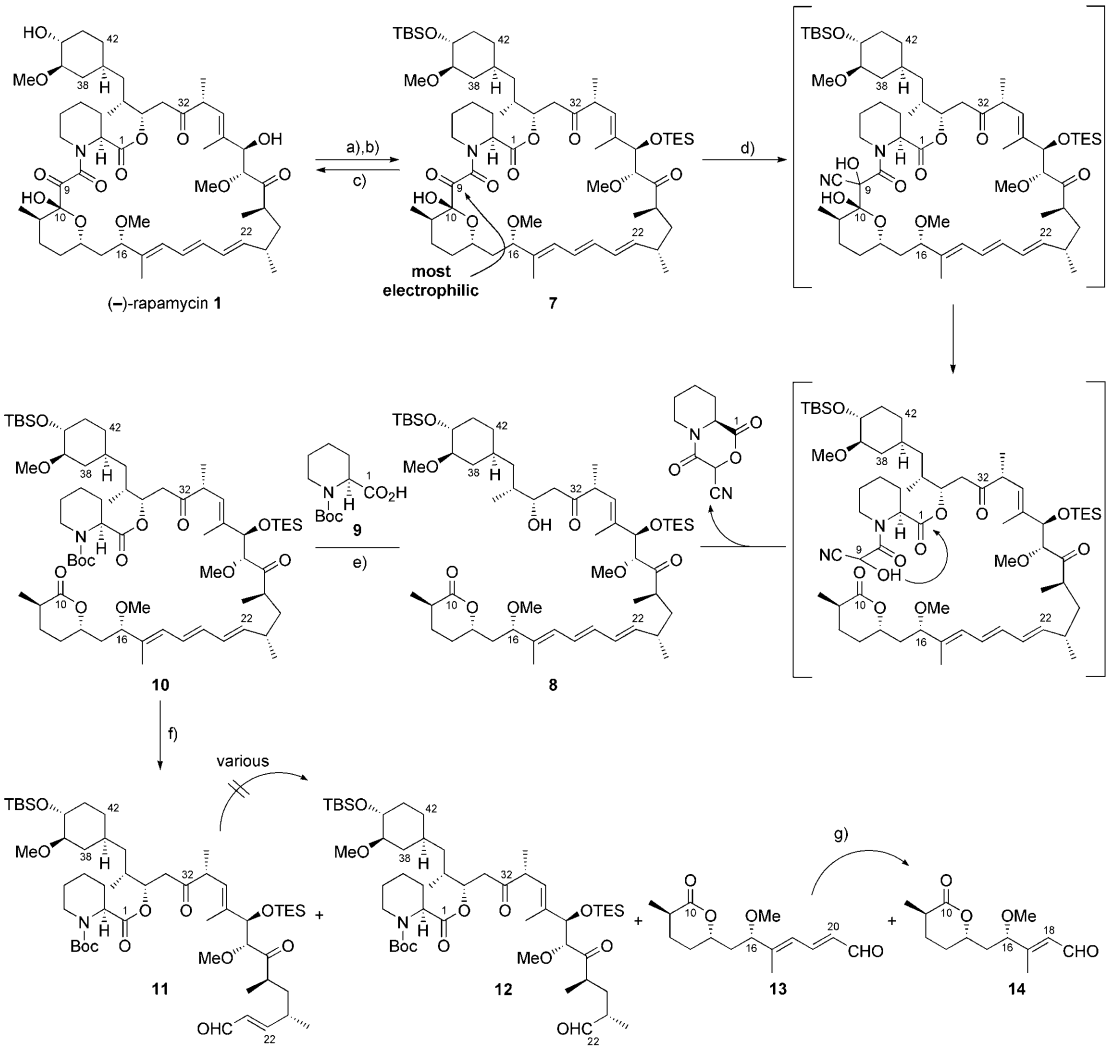
initiating extensive degradative studies upon the natural product. By analogy with the results reported by Danishefsky in his rapamycin endeavour,[6j,25] we felt that the manipulation of late stage intermediates would validate any final steps in the protecting group strategy, and potentially also afford large intact fragments which could be used to confirm configurations of advanced synthetic intermediates and, if necessary, supplement synthetic material.

To this end, preliminary protecting group studies suggested that differentiated silyl groups at C40 (TBS) and C28 (TES) were desired and conditions were optimised to install these selectively[26] and in high yield (see Scheme 2). Selective TBS protection at C40 was possible using TBSCl, while the TES group was introduced subsequently at C28 with TESOTf to afford **7**. Both silyl protecting groups could be removed under sufficiently mild conditions to regenerate the natural product **1** in a pleasing 82% yield. With this result in hand, excision of the pipecolinate and tricarbonyl regions from **7** utilizing conditions developed by Luengo[27] afforded the large intact secondary alcohol **8** with a minimal amount of enone by-product arising from β-elimination across the C32–C34 aldol linkage (cf. **15**, Scheme 3). Subsequent reinstallation of the pipecolinate moiety in its Boc-protected form (**10**) with DCC at −5 °C occurred in high yield and without racemisation at C1.

At this point two principle goals were identified. Firstly, as we expected to construct the C17–C22 triene portion of the molecule by a late-stage cross-coupling reaction, we felt it prudent to attempt the selective cleavage of this portion of the molecule to gain access to both a suitable C20–C42 (or C22–C42) fragment and, potentially, also to its lactone coupling partner. The other major objective centred about exploring the chemistry of the C32 ketone, as the known propensity for loss of various functionality at C34 through



Scheme 2. a) TBSCl, Im, DMF, RT, 97%; b) TESOTf, 2,6-lut., CH_2Cl_2, 0 °C, 99%; c) HF·Py, THF, 45 °C, 82%; d) nBu_4NCN, H_2O, THF, −5 °C, 64%; e) **9**, DCC, DMAP, CH_2Cl_2, −5 °C, 86–99%; f) O_2/O_3 (80 V, 50 L h^{-1}, ca. 1 min per 3 mg of **10**), CH_2Cl_2, −78 °C, then Me_2S, −78 °C→RT, 40% for **11**, 16% for **12**, 8:1 mixture of **13**/**14**; g) mixture of **13** and **14** resubjected to ozonolysis [see: e)] for 30 min, 65% **14** over 2 steps. TBS = *tert*-butyldimethylsilyl, Im = imidazole, DMF = *N*,*N*-dimethylformamide, TES = triethylsilyl, OTf = trifluoromethanesulfonate, 2,6-lut. = 2,6-lutidine, Py = pyridine, THF = tetrahydrofuran, Bu = butyl, Boc = *tert*-butyloxycarbonyl, DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.

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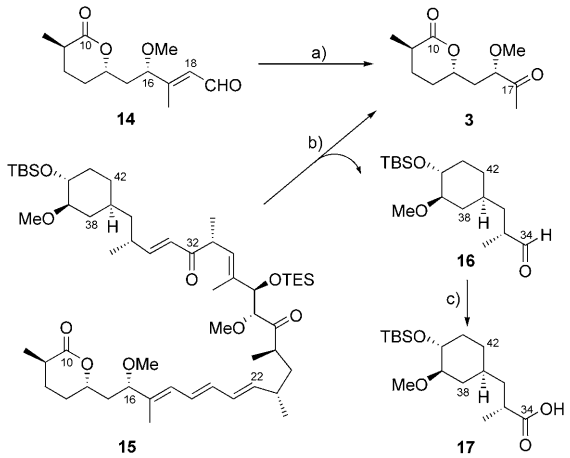
β-elimination[24] made its protection in some fashion seemingly unavoidable.

In addressing the first objective, previous experience with selective ozonolysis in our avermectin B_{1a} total synthesis project[28] influenced our efforts at cleaving this portion of the molecule. Gratifyingly, ozonolysis of **10** under carefully controlled conditions furnished both the C20–C42 enal (**11**) and the corresponding aldehyde (**12**). Separation of these by rapid column chromatography (necessary to suppress epimerisation of **12** at C21) completed access to reasonable amounts of two major intact degradation fragments. These were potentially very useful in the forward synthesis for the reasons mentioned previously. Unfortunately, under no circumstances were we able to convert enal **11** (or reduced derivatives) cleanly to **12**.

Of additional benefit, ozonolysis of **10** also yielded two lactone fragments (**13** and **14**, although as an inseparable mixture at this stage), that we similarly hoped to exploit. It was subsequently found that re-subjecting the isolated lactone mixture to the same ozonolysis conditions for an extended reaction time afforded only **14** in 65% overall yield (Scheme 2). More forcing conditions could then be used to afford simplified ketone **3**,[29] a primary target on the basis of our retrosynthetic analysis (Scheme 1), although only in modest yield (32%). Incidentally, this same fragment could also be derived in an improved yield by exhaustive ozonolysis of enone **15**, the previously obtained by-product of the cyanide-promoted excision of the pipecolinate moiety (Scheme 3). In addition, this degradation afforded aldehyde **16**,[30] a potentially useful C33–C42 epoxide check-point. Unfortunately, upon isolation this aldehyde underwent what appeared to be rapid autooxidation, most likely due to the presence of trace atmospheric oxygen. The corresponding C34-carboxylic acid (**17**) could not be used productively in any way.



Scheme 3. a) O_2/O_3 (160 V, 40 L h^{-1}), CH_2Cl_2, −78 °C, then Me_2S, −78 °C→RT, 32%; b) O_2/O_3 (160 V, 40 L h^{-1}), CH_2Cl_2, −78 °C, then Me_2S, −78 °C→RT, 51% for **3**, 34% for **16**; c) 0 °C overnight (neat), yield not determined.

We now focused our attention on investigation of the C32-carbonyl group. Treatment of **10** with a range of reducing reagents indicated that the C32 ketone was more reactive towards hydride reduction than the C26 ketone (Scheme 4). Similar results have also been noted by Danishefsky with a related substrate.[25a] In our system, treatment with $LiAlH(OtBu)_3$ gave solely the C32-reduction product (**18**). Interestingly on this silylated derivative, Luche conditions[31] gave near identical results, in contrast to those reported by Luengo[32] wherein competing C26 and C32 reduction was observed upon exposure of rapamycin (**1**) to $NaBH_4$ and $CeCl_3$ at low temperature. At this stage, although it was clear that only the C32 ketone of **10** had been reduced, rotameric effects in a highly complex NMR spectrum made it impossible to tell which diastereomer had been formed, let alone with what selectivity. To simplify the system, we relied on the known propensity of rapamycin derivatives to undergo retro-aldol cleavage across the C27–C28 linkage. Thus, selective desilylation at C28 of **18** with HF·Py, followed either by treatment of the resulting diol with LDA[24] or excess $ZnCl_2$[33] effected the desired bond scission yielding ketone **20** and aldehyde **21** in good yields. For the latter reagent, it was necessary to increase the reaction temperature from 0 to 60 °C to avoid extended reactions times which led to low yields. Subsequent cleavage of the pipecolinate unit from **21** was most easily achieved using DIBAL-H, with concomitant reduction at C28 to afford triol **22**, from which the C32–C34 acetonide was formed without incident. Analysis of the ^{13}C NMR spectrum of **23** indicated that the shifts of the acetonide methyl groups were at 19.79 and 30.19 ppm, while the ketal carbon resonated at 98.27 ppm. These results led us to conclude a *syn* relationship on the basis of observations by Rychnovsky[34] and Evans.[35] With the (*R*)-absolute stereochemistry established for the C32 alcohol it appears a six-membered chelate involving the C34 oxygen was operative in the reduction of **10**, overriding the inherent C31 Felkin–Anh bias (Scheme 4).

Finally, after much optimisation, it was found that the C32-alcohol of **18** could be efficiently protected as its Alloc derivative provided that a large excess of 4-pyrrolidinopyridine (PPy) was employed as the base. Deprotection of **19** upon treatment with $[Pd(PPh_4)_3]$ in the presence of dimedone returned **18** in good yield, demonstrating the compatibility of the Alloc group with the wealth of functional groups present within this advanced intermediate. These early degradative studies would ultimately prove highly valuable in our rapamycin synthesis program (Scheme 4).

Synthesis of epoxide 6: In the forward direction the approach to the first major subunit, C33–C42 epoxide **6**,[20b,21] was designed about the intramolecular trapping of oxonium ions by allyl silanes for construction of the cyclohexane core.[21] Model studies using α-alkoxy sulfones as oxonium ion precursors rapidly demonstrated the viability of the approach. Unfortunately, regardless of the nature of the Lewis acid or protecting group at the C40 secondary alcohol, the

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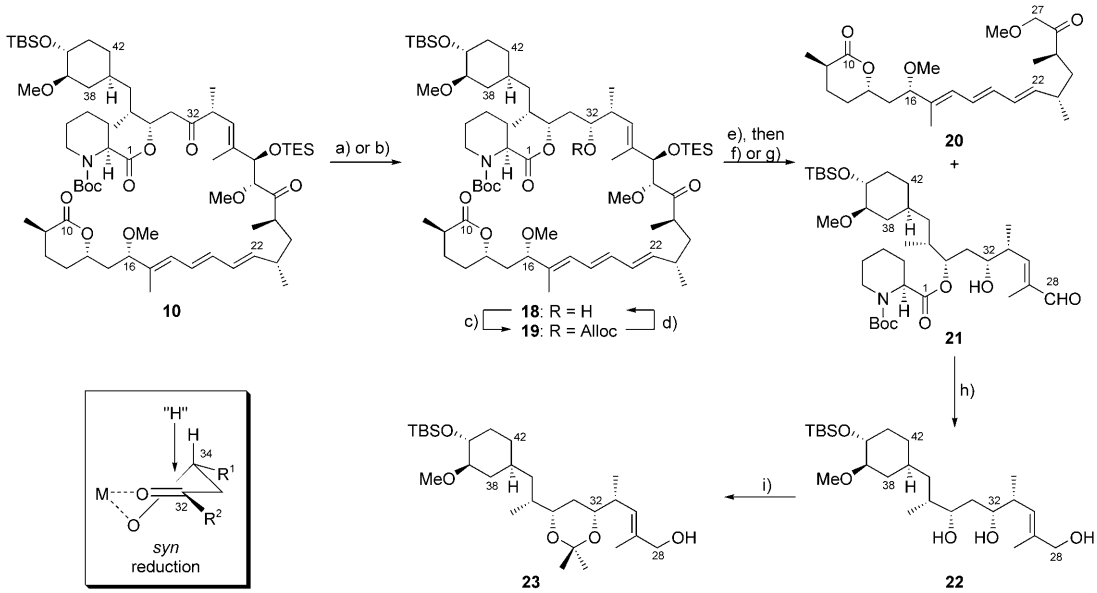
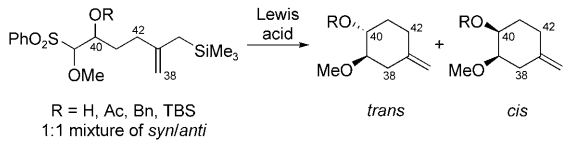


Scheme 4. a) $LiAlH(OtBu)_3$, THF, −10 °C, 5 h, 84 %; b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 3 h, 79 %; c) AllocCl, PPy, CH_2Cl_2, RT, 81 %; d) $[Pd(PPh_3)_4]$, dimedone, THF, RT, 87 %; e) HF·Py, Py, THF, RT, 78 %, f) LDA, THF, −78 °C, 5 h, 71 % for **20**, 64 % for **21**; g) $ZnCl_2$, Et_2O, THF, 60 °C, 1 h, 78 % for **20**, 94 % for **21**; h) DIBAL-H, $PhCH_3$, −78 °C, 67 %; i) 2,2-dimethoxypropane, PPTS, THF, DMF, RT, 59 %. AllocCl = allyloxycarbonyl chloride, PPy = 4-pyrrolidinopyridine, LDA = lithium diispropylamide, DIBAL-H = diisobutylaluminum hydride, Ph = phenyl, PPTS = pyridinium *para*-toluenesulfonate.

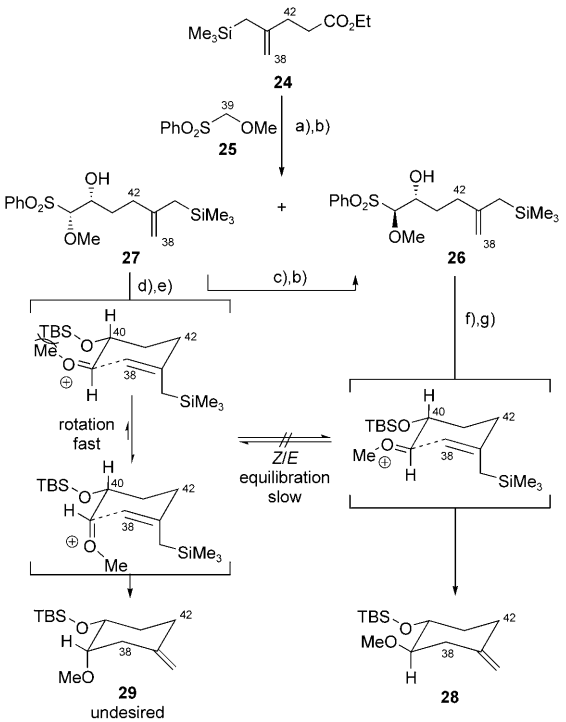
key cyclisation showed a general lack of stereoselectivity, giving rise to mixtures of *cis* and *trans* isomers. At best, after much optimisation only a 1.5:1 ratio of the desired *trans* isomer could be obtained (R = Bn, Lewis acid = $MgBr_2{\cdot}OEt_2$) (Scheme 5).



Scheme 5. Low observed levels of stereoselectivity in the cyclisation of α-alkoxy sulfones derivatives.

In an effort to better understand the factors governing selectivity in this transformation, the stereochemically pure acyclic precursors **26** and **27** were prepared. Thus, mono-addition of the lithio anion of sulfone **25** to the readily available ester **24**[36] afforded a racemic β-ketosulfone, which after asymmetric reduction using the CBS system[37] generated a separable mixture (**26**/**27** 1:2) of enantioenriched alcohols (Scheme 6).

Interestingly, although it had been expected that the same intermediate oxonium ion would form from either silylated (TBS) diastereomer **26** or **27** upon treatment with $SnCl_4$, intramolecular collapse of the pendent allyl silane from the *syn*-isomer (**27**) gave predominantly the *cis*-ring product (**29**) whereas the *anti*-isomer (**26**) resulted in a 5:1 mixture in favour of the *trans*-cyclohexane (**28**). With the underlying source of the originally poor selectivity discerned



Scheme 6. a) **25**, *t*BuLi, DME, −78 °C, then **24**, −78 °C→RT, 87 %; b) $BH_3{\cdot}$DMS, 10 % (*S*)-CBS, THF, 100 %, **26**/**27** 1:2, *ee*(**26**) = 80 %; c) PCC, CH_2Cl_2, 0 °C→RT, 50 %; d) TBSOTf, Py, DMAP, CH_2Cl_2, 0 °C, 70 %; e) $SnCl_4$, CH_2Cl_2, −78 °C, 90 %, *trans*-(**28**)/*cis*-(**29**) = 1:6; f) TBSOTf, Py, DMAP, CH_2Cl_2, 0 °C, 70 %; g) $SnCl_4$, CH_2Cl_2, −78 °C, 90 %, *trans*-(**28**)/*cis*-(**29**) = 5:1. DME = 1,2-dimethoxyethane, DMS = dimethylsulfide, CBS = Corey–Bakshi–Shibata oxazaborolidine; PCC = pyridinium chlorochromate.

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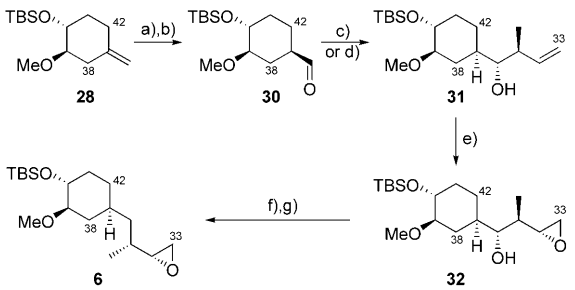
(Scheme 5), theoretical calculations (MM2 level) suggested that this unexpected stereo-outcome was a consequence of intramolecular capture by the pendant allylsilane at a sufficient rate that the initially formed oxonium ions (present as single geometric isomers) do not have time to equilibrate between *Z* and *E* forms.[38] Consequently, the *syn* starting material **27** generates the *Z*-oxonium ion which, by virtue of both $A_{1,3}$ allylic strain with the adjacent (C40) axial proton, and unfavourable steric interactions with the silyl ether, may prefer to adopt a pseudoaxial position and thus favour the *cis* product. On the other hand, the *anti*-substrate (**26**) producing the *E*-oxonium ion naturally achieves the favourable pseudoequatorial orientation giving rise preferentially to the desired *trans*-product **28** (Scheme 6).

Only **26** favoured the desired cyclisation product **28**, but unfortunately it was not possible to epimerise either **27** or its TBS-derivative to the desired *anti*-isomer. However, material could be salvaged from **27** to **26** through a two-step oxidation/reduction sequence which proceeds by way of epimerisation at C39 (Scheme 6).

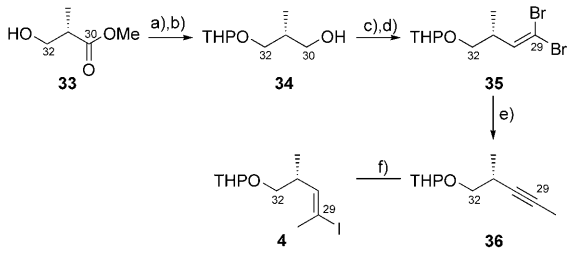
After regio- and stereoselective hydroboration of the exomethylene moiety of **28** with 9-BBN, the undesired minor *cis*-diastereomer from the cyclisation could be easily removed by chromatography. Oxidation of the primary alcohol in the desired diastereomer under Swern conditions afforded aldehyde **30**. Chain extension of this through Brown crotylation[39] installed the key C35 methyl group (**31**) in good yield, although on larger scales the use of Roush's diisopropyl tartrate modified (*E*)-crotylboronate[40] was found to proceed in more consistent—albeit slightly lower—yields. The resulting free hydroxyl group at C36 was then employed productively in a $VO(acac)_2$ directed homoallylic epoxidation[41] which proceeded with good selectivity for the desired isomer (**32**), affording only traces of the diastereoisomeric by-product. Its function completed, the superfluous C36–OH was then excised through a standard two-step Barton deoxygenation protocol[42] completing access to the desired epoxide (**6**) in 13 overall steps (Scheme 7). This material



Scheme 7. a) 9-BBN, THF, 0 °C→RT, then NaOH (aq), 30% H_2O_2, 76%; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→RT, 92%; c) (−)-(*E*)-crotylB(Ipc)$_2$, THF, Et_2O, −78 °C, then NaOH (aq), 30% H_2O_2, −78 °C→RT, 71%; d) (*E*)-2-butene, *t*BuOK, −78 °C, then *n*BuLi, $B(OiPr)_3$, then **30**, $PhCH_3$, 60%; e) $VO(acac)_2$, *t*BuOOH, CH_2Cl_2, RT, 71%; f) *n*BuLi, THF, −20 °C, then ClC(S)OPh, 85%; g) nBu_3SnH, AIBN, PhH, reflux, 86%. 9-BBN = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide, Ipc = isopinocampheyl, acac = acetylacetonate, AIBN = azobisisobutyronitrile.

proved exceptionally robust and could be stored (>3 g) for periods longer than three years with no noticeable decomposition.

Synthesis of iodide 4 and electrophile 5: The (*S*)-Roche ester (**33**) served as a convenient starting point for the construction of the C29–C32 iodide (**4**). THP protection followed by reduction yielded primary alcohol **34** which could be oxidised via the Swern protocol to the corresponding aldehyde. To avoid racemisation at C31, rigorous removal of Et_3N was required prior to concentration during work-up by washing the organic layer repeatedly with a saturated NH_4Cl solution. The sensitive aldehyde was then converted immediately to intermediate dibromoolefin **35**, and finally alkyne **36** through trapping of the in situ formed acetylide anion with methyl iodide. Regioselective hydrozirconation of the internal triple bond with an excess of freshly prepared Schwartz reagent[43] was possible by driving the initial kinetic 1:1 mixture to a single regioisomer through equilibration, presumably occurring via alkyldizirconium intermediates.[44] This could be accomplished either by heating at 60 °C in benzene for 24 h or stirring in THF for the same amount of time at room temperature. The latter protocol gave consistently higher yields of the desired vinyl iodide (**4**) after quenching with I_2, and thus was adopted as the standard reaction conditions for this transformation (Scheme 8).



Scheme 8. a) DHP, PPTS, THF, RT, 99%; b) $LiAlH_4$, Et_2O, RT, 95%; c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→RT; d) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 90% over 2 steps; e) *n*BuLi, THF, −78 °C, then CH_3I, −78 °C→RT, 99%; f) $Cp_2Zr(H)Cl$, THF, RT, then I_2, 85%. DHP = 3,4-dihydro-2*H*-pyran, Cp = cyclopentadienyl.

The key building block for the synthesis of the C22–C28 electrophile (**5**)[20a] was *meso*-anhydride **37**.[45] This was originally prepared by the standard recrystallisation of a mixture of *meso*- and D,L-isomers of **37**, but recent improvements via dynamic crystallisation of this normal mixture[46] have made access to **37** much more practical and it is readily available on multi-hundred gram scale. Reduction of the anhydride to the corresponding diol occurred quantitatively on treatment with lithium aluminium hydride. At this stage, enzymatic desymmetrisation of the *meso*-diol was routinely achieved using porcine pancreatic lipase (PPL) immobilised on Celite.[47] Unfortunately, this approach invariably provided material of only moderate enantiomeric excess (81–92%) and in addition was often somewhat capricious due to differences in batch production of the supported enzyme. Never-

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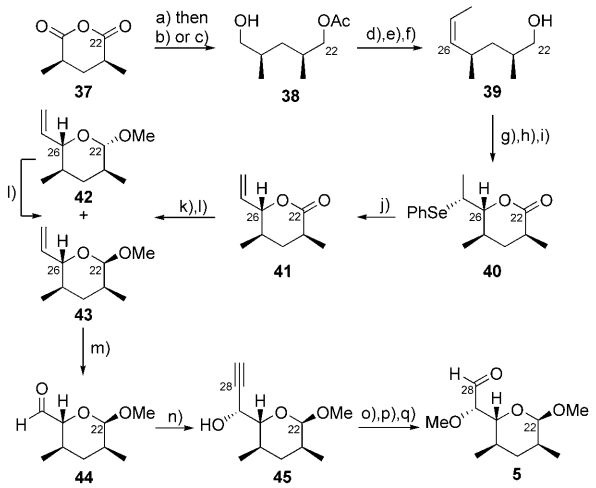
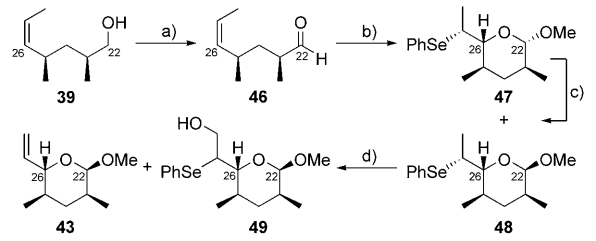
theless, this reagent was used productively for many years until relatively recently, when advances in enzymatic desymmetrisation led us to replace PPL with the commercially available and inexpensive Lipase PS-30.[48] Pleasingly, this gave the same desired product (**38**) with much improved results (*ee* 96–99%). A simple three step procedure accomplished conversion of **38** to hydroxy alkene **39** (10:1 *Z*/*E* selectivity for Wittig ethylenation) from which a two-step oxidation to the corresponding C22 carboxylic acid and selenocyclisation under known conditions[49] afforded lactone **40** in good yield. As expected for a presumed chair-like transition wherein both C23 and C25 methyl groups adopt an equatorial transition-state, this cyclisation occurred with good stereocontrol and only trace amounts of a minor diastereomer were noted. Removal of the phenylselenyl moiety was accomplished via oxidative elimination by exposure to hydrogen peroxide. With a C27–C28 olefin now in place, DIBAL-H reduction of the lactone (**41**) and treatment with MeOH under acidic conditions gave a mixture of lactol anomers **42** and **43**, which were separated at this stage for convenience. Incidentally, the minor (*S*)-C22 anomer (**42**) could be funnelled gradually to the desired (*R*)-isomer (**43**) by resubjecting the isolated material to the same reaction conditions. Ozonolysis of the pendant vinyl group established the C28 electrophilic centre (**44**), to which the addition of ethynylmagnesium bromide occurred with both excellent yield and selectivity (dr 10:1) in formation of the C27 stereocentre, consistent with a chelation controlled process (**45**). Interestingly, the same reaction was repeated with the (*S*)-C22 anomer (**42**) and displayed only mild stereoselectivity (dr 7:4), highlighting the unexpected importance of the convenient separation and interconversion of **42** and **43**. From this point, all that remained to complete the first viable route to a C22–C28 coupling partner **5** was the partial reduction of the alkyne with activated zinc ($LiAlH_4$ was also effective, but in a slightly lower yield), followed by *O*-methylation, and a final ozonolysis, which proceeded in high yield to afford the key electrophilic fragment (Scheme 9).



Scheme 9. a) $LiAlH_4$, THF, 0°C → RT; b) Lipase PS-30 (8 wt%), vinyl acetate, DME, RT, 72% over 2 steps, *ee* 96–99%; c) PPL on Celite, MeOAc, RT, 66%, *ee* 81–92%; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C→RT; e) Ph_3PEtBr, *n*BuLi, THF, 0°C; f) NaOH (aq), Bu_4NOH, THF, 60°C, 86% over 3 steps; g) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C→RT; h) NaO_2Cl, KH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, RT, 81% over 2 steps; i) *N*-phenylselenophthalimide, $SnCl_4$ (10 mol%), CH_2Cl_2, RT, 82%; j) H_2O_2, THF, 0°C, 75%; k) DIBAL-H, $PhCH_3$, −78°C; l) MeOH, Amberlyst 15, RT, 26% for **42** and 33% for **43**, over 2 steps, separable: **42** may be equilibrated to a mixture of **42** and **43** under the same conditions in quantitative yield and similar ratio; m) O_2/O_3, CH_2Cl_2, −78°C, then Ph_3P, −78°C→RT, 83%; n) ethynylmagnesium bromide, $PhCH_3$, THF, −78°C, 90%, 10:1 mixture of epimers at C27; o) Zn, MeOH, H_2O, RT, 88%; p) NaH, CH_3I, THF, 0°C→RT, 99%; q) O_2/O_3, CH_2Cl_2, −78°C, then Ph_3P, −78°C→RT, 94%.

Critical evaluation of this initial approach to the C22–C28 fragment (**5**) suggested that improvement could be made by avoiding repeated oxidation state adjustments. Thus, alcohol **39** was subjected to Swern conditions wherein the oxidation state of the product (**46**) at C22 is now the same as the acetal present in **43**. Based upon precedent established by Sharpless,[50] and after much optimisation, cyclisation to a near equimolar mixture of separable acetals **47** and **48** could be accomplished by treatment of **46** with *N*-phenylselenophthalimide in dichloromethane containing 10 molar equivalents of methanol (Scheme 10).



Scheme 10. a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C→RT; b) *N*-phenylselenophthalimide, MeOH, CH_2Cl_2, RT, 30% for **47**, 36% for **48**, over 2 steps, separable; c) MeOH, Amberlyst 15, RT, 98%; **47**/**48** 1:1.2; d) H_2O_2, DHP, THF, 0°C, 98% for **43** (only traces of **49** observed when DHP present).

At this stage, the undesired acetal anomer (**47**) could be partially recycled to **48** by subjection to acidic methanol. Finally, oxidative elimination of the phenylselenyl moiety afforded olefin **43**. However, the by-product of this reaction, phenylselenic acid, appeared to suppress yields of **43** by addition back into the double bond giving **49**. This phenomenon had not been seen earlier with the olefinic lactone (cf. **41**, Scheme 9), presumably because the olefin in this case is rendered less nucleophilic by the allylic oxycarbonyl substituent. Nevertheless, we were able to avoid this side-reaction by adding dihydropyran to the reaction mixture,[51] and consequently the intermediate olefin was obtained in near quantitative yield. This improved route featuring a selenoacetalisation reaction not only eliminated two steps from the overall sequence, but also offered the same desired acetal **43** in excess of double the yield previously obtained (Scheme 10). Further conversion to the C22–C28 electrophile (**5**) as before occurred without incident.

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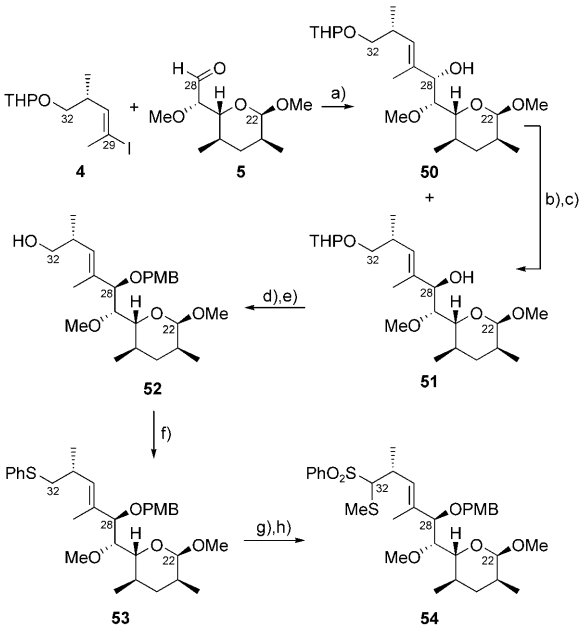
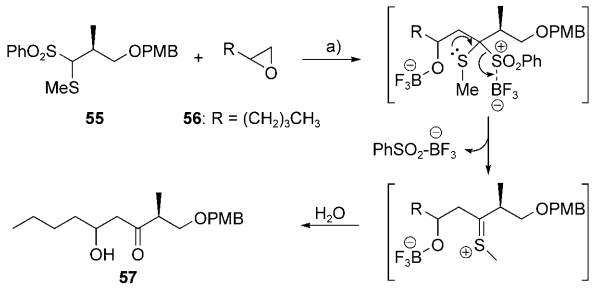
Union of fragments 4, 5 and 6: With all three fragments, **4**, **5**, and **6**, of the C22–C42 framework in hand, attention focused on their union. Coupling of vinyl iodide **4** with electrophile **5** was achieved without difficulty and in reasonable yield under Nozaki–Hiyama–Kishi[52] conditions, giving a 3:1 mixture of readily separable diastereomers **51**/**50** in favour of the desired *S* configuration. TPAP oxidation[53] of the minor secondary alcohol (**50**) followed by chelation controlled *anti*-1,2 reduction with zinc borohydride[54] simultaneously recycled the unwanted diastereomer and confirmed that the major addition product (**51**) had the desired C27–C28 1,2-*anti* configuration (the non-chelation controlled addition product) (Scheme 11).



Scheme 11. a) $CrCl_2$ (0.5% $NiCl_2$), DMSO, RT, 69%, **50**/**51** 1:3, separable; b) TPAP, NMO, 4 Å MS, CH_2Cl_2, RT, 99%; c) $Zn(BH_4)_2$, Et_2O, 0 °C, 81%; d) NaH, PMBCl, NaI, THF, 0 °C→RT, 76%; e) MeOH, Amberlyst 15, RT, 84%; f) Bu_3P, *N*-phenylthiosuccinimide, PhH, RT, 85%; g) Oxone, pH 4 buffer, THF, MeOH, RT, 93%; h) *t*BuLi, THF, −78 °C, then $(MeS)_2$, 81%. TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves, PMB = *para*-methoxybenzyl.

Although initial degradative studies had suggested that a TES group was eventually desired for the protection of the C28 hydroxyl function, we elected to install the more robust PMB ether at this point in preparation for hydrolysis of the C22–C28 acetal. Removal of the THP protecting group in acidic methanol then revealed the primary C32 hydroxyl group (**52**) ready for conversion to an acyl anion equivalent. Although the use of a C32 1,3-dithiane was considered, we feared substantial racemisation of the sensitive C31 stereocentre would occur as a consequence of its juxtaposition between the C29–C30 olefin and a necessary C32 aldehyde intermediate. Preliminary studies with a variety of oxidants indicated that this was indeed the case, leading us to consider a C32 sulfone to allow coupling to the remaining epoxide fragment (**6**). However, by this time we were aware of the difficulties Schreiber had encountered in the oxidative cleavage of a similar C32 sulfone in his approach to rapamycin,[6f] and thus we opted to investigate a possible oxidation of the sulfone prior to the coupling reaction. Of promise, Kotake had introduced the use of a sulfenyl–sulfone variant for the mild one-pot synthesis of ketones.[55] Accordingly, conversion of **52** to the sulfide (**53**) was readily achieved using Mitsunobu conditions, and following oxidation with Oxone the intermediate sulfone was isolated in good yield. Construction of the sulfenyl-sulfone moiety by deprotonation at C32 with *t*BuLi (*n*BuLi caused decomposition) and trapping with dimethyldisulfide gave the desired, but somewhat unstable coupling precursor **54** (purifiable by chromatography on Florisil only), in good yield (Scheme 11).

A model system was devised to simulate the eventual coupling of advanced intermediate **54** with the C33–C42 epoxide (**6**) and allow investigation without consumption of precious intermediates. Initially, deprotonation of a simplified Roche ester derived sulfenyl–sulfone **55** followed solely by addition of 1,2-epoxyhexane **56** gave only starting materials. However, adding 1 molar equivalent of $BF_3{\cdot}OEt_2$ resolved this reactivity issue and, to our surprise, gave directly the desired β-hydroxyketone (**57**) following standard aqueous work-up.[56] With further study, we soon found that complete consumption of the starting material could only be achieved by adding a second equivalent of $BF_3{\cdot}OEt_2$. These observations suggested the requirement of at least 2 equivalents of Lewis acid and the direct production of **57** according to the mechanistic proposal shown in Scheme 12.



Scheme 12. a) **55**, *n*BuLi, THF, −78 °C, then **56**, $BF_3{\cdot}OEt_2$ (2 equiv), −78 °C, 67%.

Application of these conditions (with slight modification) to the real system gave the desired coupling product (**58**) in an unoptimised yield of 46%. With the production of this advanced C22–C42 intermediate, further advancement towards the final union of fragments and exploration of the final steps of the synthesis of rapamycin (**1**) seemed imminent. Yet, to our great frustration, all efforts to convert the six-membered acetal present within **58** (or reduced and protected C32 derivatives of **58**) to an acyclic form to unmask the C22-aldehyde failed, affording only starting material or decomposition products under the necessary acidic condi-

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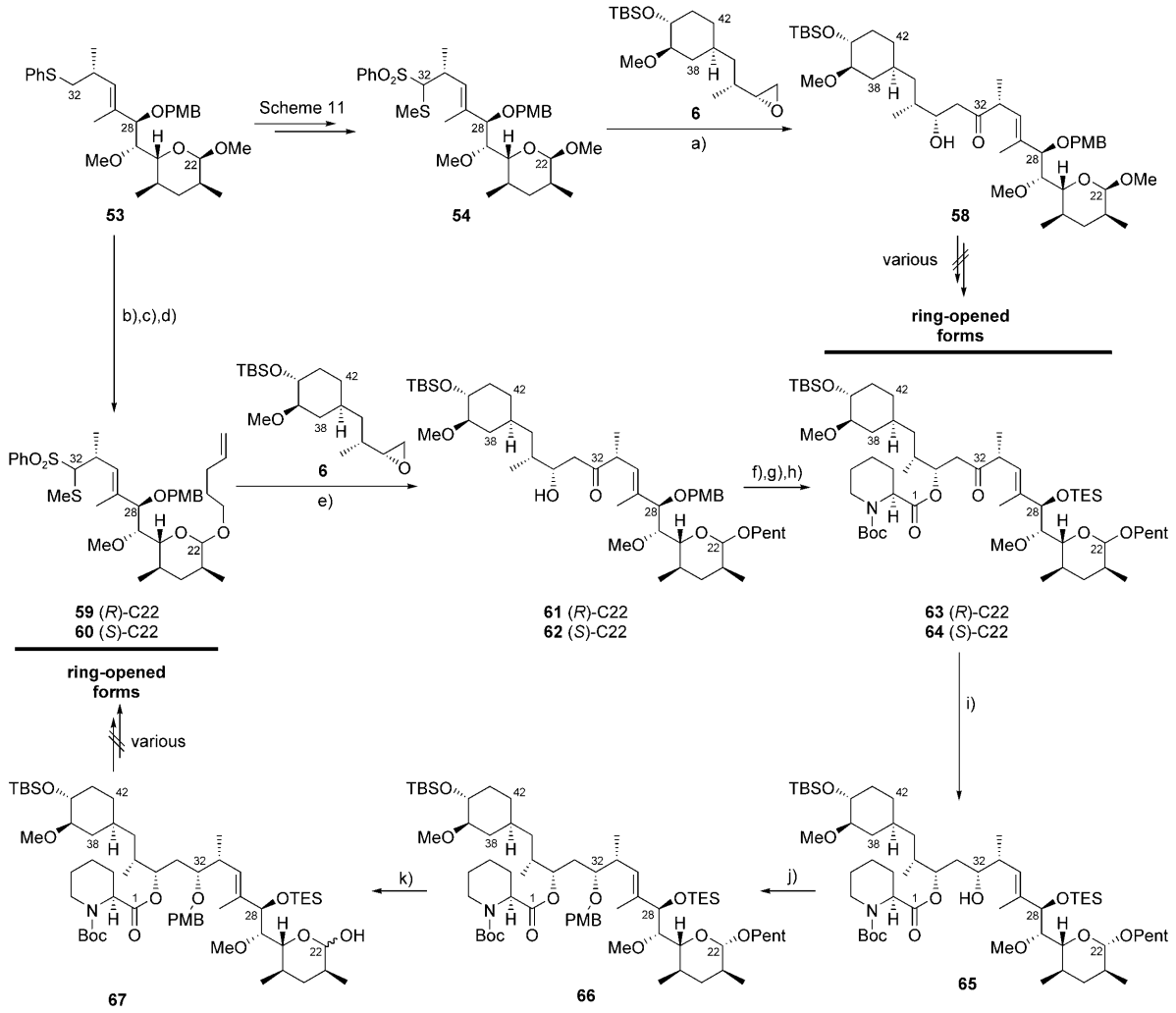
tions. This disappointing result forced us to re-evaluate the nature of the acetal moiety at C22, such that it might be deprotected under milder, or even neutral conditions. Reports by Fraser-Reid of the use of 4-pentenyl acetals[57] for this purpose inspired further investigation.

Returning to sulfide **53** allowed anomeric exchange of the methyl acetal to the pentenyl equivalent in good yield, albeit under rather forcing conditions. After separation of the anomers for convenience (both were used in further transformations), and subsequent functional group manipulations as employed previously, two additional sulfenyl–sulfones were obtained (**59** and **60**) for coupling to the C33–C42 epoxide (**6**). In the event, coupling of the two advanced fragments occurred smoothly, giving the desired β-hydroxyketones in 50 and 58% yield for the (*R*)-C22 and (*S*)-C22 anomers (**61** and **62**), respectively. Employing knowledge gained during the degradation studies, a sequence of esterification, protecting group manipulations to install the desired C28 TES ether, and reduction at C32 with $LiAlH(OtBu)_3$, furnished **65**. At this stage, orthogonal protection of the newly formed alcohol as its PMB ether under acidic conditions gave **66** (the final conclusion regarding the use of a C32-Alloc protecting group had not yet been reached by this time). Pleasingly, treatment of the acetal in **66** with NBS in wet acetonitrile successfully generated the desired lactol (**67**), from which productive elaboration appeared straightforward. Unfortunately, in the event, we were thwarted yet again by the stubborn stability of the cyclic form of **67**. In no instance were we able to homologate an open chain C22-aldehyde form of **67** through olefination processes, nor were any attempts to derivatise via external acetal or thioacetal formation successful (Scheme 13).



Scheme 13. a) **54**, *t*BuLi, THF, −78°C, then **6**, then $BF_3{\cdot}OEt_2$, −78°C→0°C, 28%; b) 4-penten-1-ol, PPTS, $ClCH_2CH_2Cl$, 90°C, 93%, ca. 1:1 mixture of C22 anomers, separable; c) Oxone, THF, MeOH, pH 4 buffer, 0°C, 89% for (*R*)-C22, 93% for (*S*)-C22; d) *t*BuLi, THF, −78°C, then $(MeS)_2$, 97% for **59**, 91% for **60**; e) **59** or **60**, *t*BuLi, THF, −78°C, then **6**, then $BF_3{\cdot}OEt_2$, −78°C→0°C, 50% for **61**, 58% for **62**; f) *N*-Boc-L-pipecolinic acid, DCC, DMAP, CH_2Cl_2, −5°C, 88% for (*R*)-C22, 81% for (*S*)-C22; g) DDQ, CH_2Cl_2, H_2O, 0°C, 91% for (*R*)-C22, 96% for (*S*)-C22; h) TESOTf, 2,6-lut., CH_2Cl_2, 0°C, 78% for **63**, 98% for **64**; i) $LiAlH(OtBu)_3$, THF, −10°C, 86%; j) PMBTCA, TfOH (0.12 mol%), Et_2O, −78°C, 49%; k) NBS, 1% H_2O-CH_3CN, RT, 56%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TCA = trichloroacetimidate, TfOH = triflic acid, NBS = *N*-bromosuccinimide.

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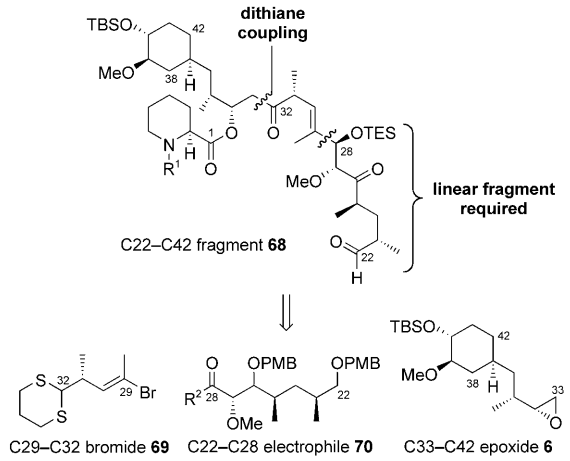
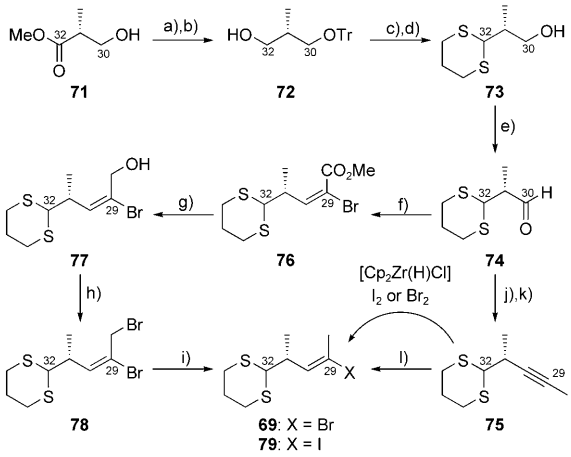
Revised approach to a C22–C42 fragment: It was apparent that the use of a cyclic acetal, although beneficial in generating the stereochemical array of the C22–C28 electrophile, proved a significant liability later in the synthesis as a consequence of its stability. Consequently, a number of other approaches based upon the ring-opening of this moiety prior to anionic coupling were investigated. However, all such attempts employing a sulfenyl–sulfone or a sulfone for the construction of the C32−C33 bond ultimately failed, now due either to poor reactivity in coupling with the epoxide **6** or to an inability to effect oxidative desulfonylation. Reversal of the order of couplings, so as to form the C32−C33 bond prior to union with the C22–C28 fragment, also met with little success. Difficulties were again encountered with the oxidative desulfonylation at C32, along with new problems in maintaining the stereochemical integrity of the C31-α-keto-methyl group. Thus, major revisions were made to our approach to the C22–C42 backbone of rapamycin (**1**) wherein a dithiane would now be employed for the central C29–C32 formal dianion equivalent in place of the compromised sulfone or sulfenyl-sulfone approach, and the C22–C28 electrophile would be pursued in a linear form (Scheme 14).



Scheme 14. Revised retrosynthetic analysis for the C22–C42 fragment (**68**).

Synthesis of vinyl bromide 69: For the synthesis of the revised C29–C32 fragment **69** (or the corresponding iodide **79**) the Roche ester once again served as a convenient starting point. From a strategic point of view, it was decided that introduction of the dithiane function must occur prior to formation of the double bond as previous experience had made clear that epimerisation of the C31 stereocentre was a serious concern for intermediates containing both a C32 carbonyl and a C29−C30 olefin. Accordingly, standard functional group manipulations upon commercially available chiral pool starting material **71** afforded dithiane alcohol **73** as a single enantiomer, confirmed by Mosher's ester analysis. Unfortunately, all attempts to install the desired halogenated olefin based upon the previous synthesis of the related fragment **4** (see above) via the Schwartz hydrozirconation of an alkyne (**75**) failed. Partial success was realised through palladium catalysed hydrostannylation of **75** followed by trapping with iodine. However, the observed 5:1 mixture of inseparable *E*/*Z* isomers (**79**) was deemed unsuitable for further elaboration. To resolve this selectivity issue, an interesting variant[58] of the Still–Gennari phosphonate[59] was employed whereby prior bromination of the reagent and reaction with freshly prepared aldehyde **74** gave the trisubstituted bromoalkene (**76**) as the only detectable olefin isomer. Subsequent excision of the superfluous methyl ester functionality was best accomplished by reduction of the corresponding allylic bromide (**78**) by reduction with Super Hydride to afford the revised C29–C32 dianion equivalent (**69**) in nine steps and about 85% overall yield (Scheme 15).



Scheme 15. a) TrCl, Py, CH_2Cl_2, 0 °C→RT; b) $LiAlH_4$, THF, 0 °C, 93% over 2 steps; c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then DIPEA, −78 °C→0 °C; d) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C→RT, 99% over 2 steps; e) $SO_3{\cdot}Py$, DIPEA, DMSO, CH_2Cl_2, RT, 99%; f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, THF, then Br_2, then 18-C-6, KHMDS, then **74**, THF, −45 °C, 96%; g) DIBAL-H, CH_2Cl_2, −78 °C, 96%; h) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, then LiBr, DMF, 72-99%; i) $LiEt_3BH$, THF, 0 °C, 99%; j) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 93%; k) *n*BuLi, THF, −78 °C, then CH_3I, −78 °C→RT, 99%; l) Bu_3SnH, $[(Ph_3P)_2PdCl_2]$, THF, −10 °C, then I_2, 57%, *E*/*Z* 5:1, inseparable. Tr = trityl, DIPEA = diisopropylethylamine, KHMDS = potassium bis-(trimethylsilyl)amide, Ms = methanesulfonyl.

Approaches to a linear C22–C28 electrophile: A number of strategies were pursued for the synthesis of a linear C22–C28 electrophile **70**, each of which began from the readily available enantioenriched *syn*-1,3-dimethylated alcohol (**38**) discussed previously. These strategies met with varying levels of success. One of the initial approaches was based around the homologation of a readily prepared benzyl derivative (**81**) to afford α,β-unsaturated Weinreb amide **82** directly. Although this reaction returned the desired compound as a single (*E*)-olefin isomer, this transformation was somewhat capricious giving isolated yields which varied from 40 to 70%. Nevertheless, subsequent dihydroxylation of the enamide (**82**) using a modified[60] Sharpless Asymmetric Dihydroxylation[61] procedure afforded *syn*-diol **83** exclu-

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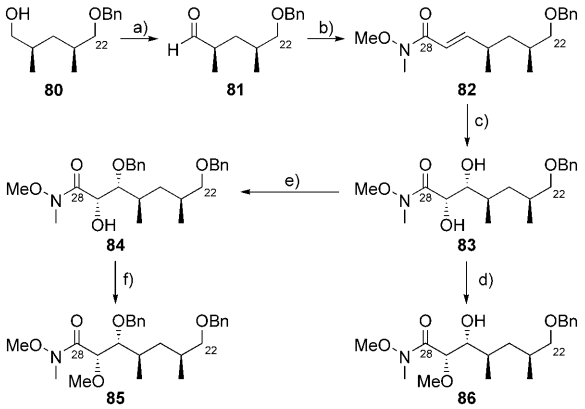
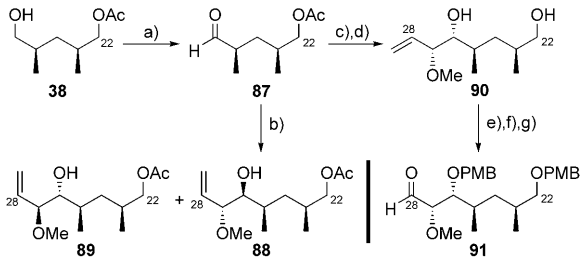
sively.[62] Key to the further elaboration of this was the ability to differentiate between the vicinal hydroxyl groups which, despite initial optimism, turned out to be non-trivial. Selective methyl ether formation of the C27 alcohol (**86**) based on decreased reactivity of the β-hydroxyl group through intramolecular hydrogen bonding was entirely unsuccessful despite literature precedent.[63] After much experimentation, the C26-benzyl ether (**84**) could instead be selectively formed via the intermediate dibutylstannylene acetal,[64] but only in 48% yield. Similarly, methylation of the remaining hydroxyl group was unexpectedly problematic and low yielding (**85**) and the combined loss of material during homologation and the sequential ether formation led us to abandon this synthetic sequence (Scheme 16).



Scheme 16. a) SO_3·Py, DMSO, DIPEA, CH_2Cl_2, 0°C→RT, 99%; b) *N*-methoxy-*N*-methyl(triphenylphosphoranylidene)acetamide, CH_2Cl_2, reflux, 40–70%; c) AD-mix-β, K_2OsO_4·$2H_2O$, $(DHQD)_2PHAL$, *t*BuOH/H_2O (1:1), then $MeSO_2NH_2$, 0°C → RT, 98%; d) Ag_2O, CH_3I (various equivalents), CH_2Cl_2 or DMF, no selectivity; e) Bu_2SnO, MeOH, reflux, then CsF, then BnI, DMF, 0°C → RT, 48%; f) Ag_2O, CH_3I, CH_3CN, 50°C, dark, 42%. $(DHQD)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether.

To avoid further difficulties associated with the selective protection of a vicinal diol, methodologies were selected that either directly installed the C27-methyl ether, or did so in a suitable masked form. Recognising that the stereochemical configuration of the C26 alcohol is ultimately of no consequence, reaction of acetate derived aldehyde **87** with a γ-methoxyallylzinc reagent[65] (derived from transmetallation of zinc onto the lithio anion of allyl methyl ether)[66] was explored. This transformation was high yielding but poorly selective, slightly favouring the undesired diastereomer (**89**). Although separable, isolating **88** by purification on silica gel was tedious and in the end impractical. Fortunately, reagent control via asymmetric Brown alkoxyallylation[67] of the same aldehyde, followed by removal of the acetate protecting group (necessary to facilitate purification), furnished **90** as a single diastereomer.[68] The yield over these two steps was somewhat disappointing. However, the reaction utilised the product of enzymatic desymmetrisation without the need for protecting group manipulation and could be performed on large-scale without difficulty. Moreover, by masking the C28 carbonyl as an olefin, protection of the C26 alcohol as its PMB ether was facile and upon application of standard conditions, the bis-PMB derivative was isolated in excellent yield. While direct ozonolysis of this substrate proved problematic, a two-step dihydroxylation/cleavage protocol afforded the desired electrophile (**91**) in good yield. Notably, cleavage of the intermediate diol resulting from dihydroxylation with $Pb(OAc)_4$ was clean and high yielding, hence purification of this sensitive coupling partner (**91**) could be avoided (Scheme 17).



Scheme 17. a) SO_3·Py, DIPEA, DMSO, CH_2Cl_2, RT, 99%; b) allyl methyl ether, *s*BuLi, $ZnCl_2$, −78°C→−45°C, then **87**, 95%, **88**/**89** 4:5, separable; c) allyl methyl ether, *s*BuLi, THF, −78°C, then (−)-MeOBIpc$_2$, then BF_3·OEt_2, then **87**, then NaOH (aq), 30% H_2O_2, −78°C→RT; d) K_2CO_3, MeOH, RT, 40% over 2 steps; e) NaH, PMBCl, TBAI, DMF, RT, 99%; f) OsO_4, NMO, acetone, H_2O, RT, 78%; g) $Pb(OAc)_4$, PhH, RT, 99%. TBAI = tetrabutylammonium iodide.

Although this approach allowed for the synthesis of multi-gram amounts of a suitable C22−C28 electrophile (**70**) we remained dissatisfied by the low yield in the alkoxyallylation of **87**. Accordingly, a second higher-yielding construction of the C26−C27 bond was pursued that involved the application of our recently developed butane-2,3-diacetal (BDA)[69] protected variant of glycolic acid (**93**) to effect a highly selective aldol condensation[70] with either **87** or **92**. The PMB protected derivative **95** proved more practical than **94** for advancement in later transformations although, as expected, protection of the secondary alcohol at C26 was extremely difficult as a result of the β-disposition of the ester carbonyl function and of the numerous acetal moieties present within **95**. Eventually, treatment with PMBTCA and a catalytic amount of $TrBF_4$[71] was identified as a suitable protocol for the production of **96**. Stubbornly, and despite prolonged investigation, this reaction would not go to completion although this was mitigated somewhat through the essentially quantitative recovery of unreacted starting material **95**. Further transformation of **96** to the desired electrophile (**99**) was straightforward, involving deprotection by transesterification (**97**), methylation of the released alcohol (**98**) and, finally formation of the Weinreb amide[72] to conclude a second viable route to the C22–C28 fragment (Scheme 18).

An alternative approach designed to alleviate difficulties associated with the frustrating C26 hydroxyl PMB protection began with exhaustive reduction of **95** to the corre-

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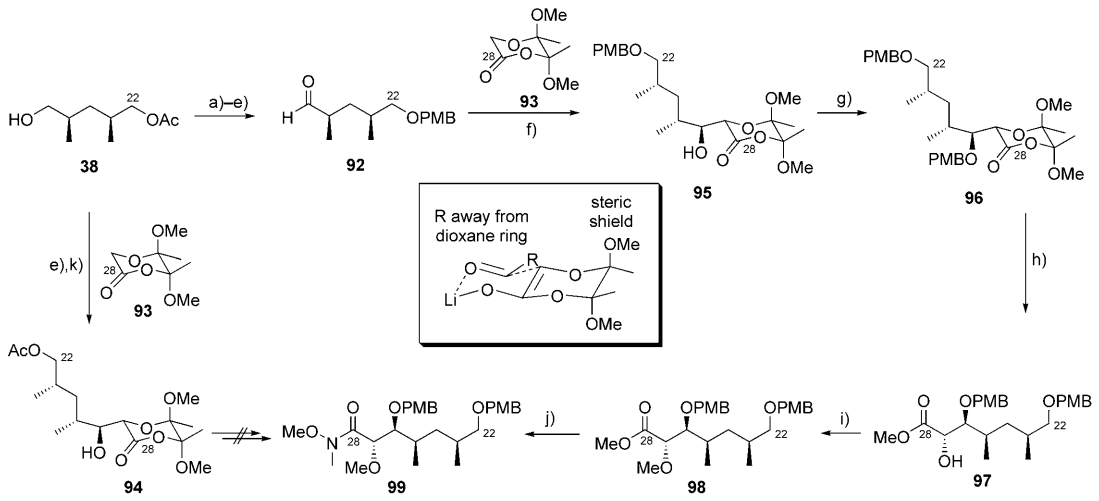
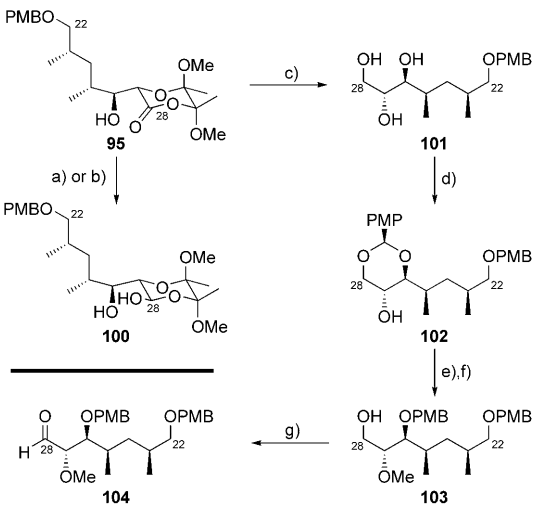


Scheme 18. a) TBSCl, Im, CH_2Cl_2, 0 °C→RT; b) K_2CO_3, MeOH, RT, 98% over 2 steps; c) NaH, PMBCl, TBAI, THF, 0 °C→RT, 99%; d) TBAF, THF, 0 °C, 93%; e) SO_3·Py, DIPEA, DMSO, CH_2Cl_2, RT, 99%; f) **93**, LiHMDS, THF, −78 °C, then **92**, then AcOH, −78 °C→RT, 92%; g) PMBTCA, $TrBF_4$ (5 mol%), THF, RT, 47%; h) (±)-CSA, MeOH, RT, 80%; i) Ag_2O, CH_3I, CH_2Cl_2, 50 °C, 74%; j) LiHMDS, MeO(Me)NH·HCl, THF, −20 °C, then **98**, −20 °C→−10 °C, 97%; k) **93**, LiHMDS, THF, −78 °C, then aldehyde derived from **38** (**87**), then AcOH, −78 °C→RT, 84%. TBAF = tetra-*n*-butylammonium fluoride, CSA = camphorsulfonic acid.

sponding triol **101**. Unexpectedly forcing conditions ($LiAlH_4$, THF, reflux) were required to effect this transformation as the intermediate lactol (**100**), isolated exclusively in its non-anomerically stabilised form, proved to be quite stable. Nevertheless, with **101** in hand selective formation of the six-membered *para*-methoxyphenyl (PMP) acetal was readily accomplished under standard conditions to furnish **102** as a single diastereomer. Methylation of the remaining hydroxyl group with sodium hydride and iodomethane in DMF, followed by treatment with DIBAL-H resulted in ring-opening of the 1,3-PMP acetal in the expected regiochemical sense, affording solely primary alcohol **103**. Now, with the desired PMB and methyl ethers correctly situated at C26 and C27, all that remained to complete the formation of a third viable C22–C28 coupling partner **104** was oxidation, which was readily accomplished under Swern conditions (Scheme 19).



Scheme 19. a) $LiAlH_4$, $ZnCl_2$, Et_2O, then **95**, 0 °C→RT, 99%; b) DIBAL-H, THF, −78 °C→RT, 92%; c) $LiAlH_4$, THF, 0 °C to reflux, 79%; d) anisaldehyde dimethyl acetal, (±)-CSA, CH_2Cl_2, RT, 88%; e) NaH, CH_3I, DMF, 0 °C→RT, 98%; f) DIBAL-H, CH_2Cl_2, −78 °C→RT, 88%; g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then DIPEA, −78 °C→RT, 73%.

Fragment coupling towards the C22–C42 portion of rapamycin (1): With the revised central dianion equivalent **69** and a variety of linear C22–C28 fragments in hand, that is, **91**, **99**, and **104**, attention was once again turned to their effective union. Trial lithiation of **69** with *t*BuLi in THF at −100 °C followed by quenching with D_2O established that the vinyl bromide could be cleanly metallated with no undesired abstraction of the C32 dithiane proton observed. Application of these conditions to the real coupling employing equimolar amounts of **69** and aldehyde **91** was initially disappointing, returning low yields of the desired coupled product. Fortunately, the use of an excess (2 equiv) of the lithio anion of **71** resolved this issue, returning a partially separable mixture of C28 diastereomers (**105**/**106** 3:1) in reasonable yield and in favour of the undesired *syn*-product. Efforts were not made to improve this ratio through the addition of salts or other modifications of the experimental conditions, since oxidation to the corresponding enone followed by *anti*-1,2-reduction with $Zn(BH_4)_2$[54] effectively returned the desired configuration of alcohol **106** as a single diastereomer. Interestingly, relative to other reports in the literature[6j] (and indeed other substrates explored in this synthesis program, see below) this latter reduction, although highly selective, was unexpectedly sluggish and required reaction times of three days to go to completion. Moreover, this transformation was further complicated by difficulty in removing zinc residues from the product mixture, which were initially mis-

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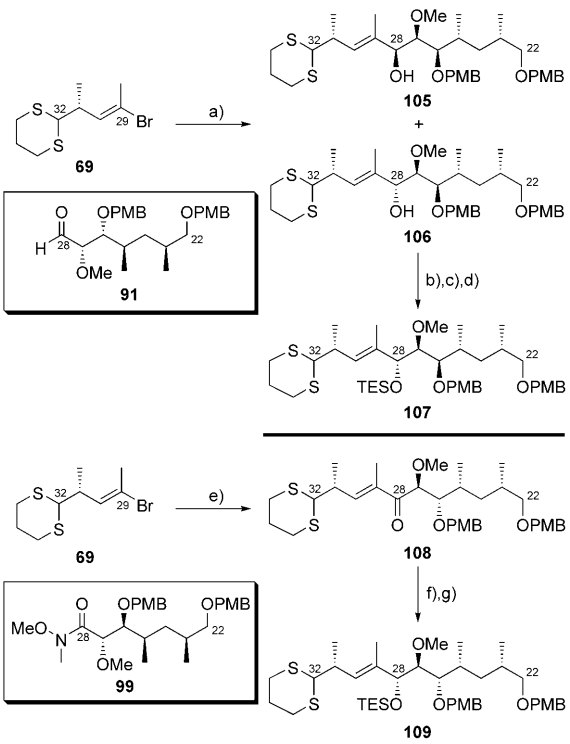
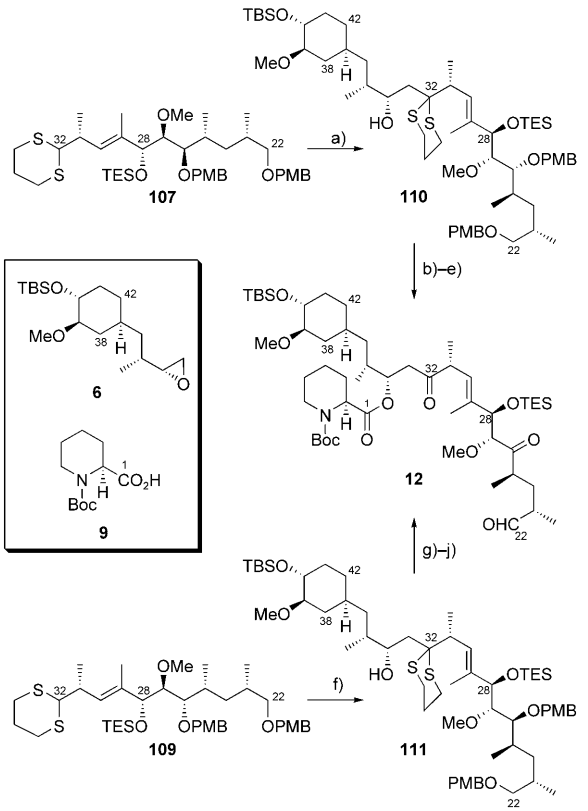
taken for poor facial selectivity in the reduction of the C28 enone (the chelated Zn product strongly resembles undesired **105** in the ^{1}H NMR spectra of crude reaction mixtures). Nevertheless, conditions were reliable and subsequent TES protection at low temperature afforded the completed C22–C32 fragment (**107**) ready for coupling to the C33–C42 epoxide (**6**) (Scheme 20).



Scheme 20. a) *t*BuLi, THF, −100 °C, then **91**, −100 °C, 66 % (**105**/**106** 3:1); b) SO_3·Py, DMSO, DIPEA, CH_2Cl_2, 0 °C, 97 %; c) $Zn(BH_4)$, Et_2O, −20 °C, 3 d, 80 %; d) TESOTf, 2,6-lut., CH_2Cl_2, −78 °C, 40 min, 99 %; e) *t*BuLi, THF, −100 °C, then **99**, −100 °C→−78 °C, 80 %; f) $Zn(BH_4)_2$, Et_2O, −20 °C, 2 h, 83 %; g) TESCl, Im, DMF, 50 °C, 93 %.

An identical set of fragment coupling conditions applied to Weinreb amide **99** directly afforded a significantly improved yield of enone analogue **108**, avoiding the problems associated with a diastereomeric mixture previously obtained with **91**. Subsequent *anti*-1,2-reduction of this substrate, in contrast to that observed previously, occurred rapidly and without the problems of zinc chelate purification, yet was still highly selective. This variation of reactivity, arising solely from the difference in the C26 configuration, was once again apparent during TES production of the resulting C28 alcohol which was unsuccessful with TESOTf even at room temperature. Switching to TESCl and imidazole in DMF, and heating the mixture resolved this issue and afforded a second completed C22–C32 fragment (**109**) ready for coupling to the epoxide **6** (Scheme 20). With two viable fragments now established, further investigation with electrophile **104** was not undertaken.

Lithiation of either **107** or **109** with *t*BuLi in the presence of epoxide **6** and with HMPA as an additive, followed by immediate warming resulted in smooth epoxide ring-opening and construction of the C22–C42 carbon framework affording **110** and **111**, respectively. This procedure, based upon work by Smith et al.,[73] was important to achieve good yields as α-methyl-1,3-dithianes of this type (e.g. **107** or **109**) are known to form lithio-anions almost instantaneously in a mixture of THF/HMPA but then rapidly lose their reactivity,[73,74] presumably through aggregation. Subsequent removal of the dithiane moiety in both series using the mild bis-(trifluoroacetoxy)iodobenzene protocol of Stork and Zhao[75] occurred smoothly, and was necessary to permit esterification of the C34 alcohol with *N*-Boc-L-pipecolinic acid (**9**). PMB deprotection with buffered DDQ revealed alcohols at C22 and C26 (the latter epimeric in the two series) which were subsequently both oxidised under Swern conditions in quantitative yield to the common intermediate **12**, identical in all respects to each other *and* to material obtained previously by degradation of the natural product (cf. Scheme 2). The particular use of the Swern oxidation in this



Scheme 21. a) **6**, *t*BuLi, THF/HMPA (5:1), −78 °C, 2 min, then −40 °C, 40 min, 51–77 %; b) $PhI(OCOCF_3)_2$, THF/MeOH/H_2O (10:9:1), RT, 84 %; c) **9**, DCC, DMAP, CH_2Cl_2, −5 °C, 84 %; d) DDQ, pH 7 buffer, CH_2Cl_2, RT, 93 %; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 99 %; f) **6**, *t*BuLi, THF/HMPA (9:1), −78 °C, 2 min, then −40 °C, 10 min, 81 %; g) $PhI(OCOCF_3)_2$, THF/MeOH/H_2O (10:9:1), RT, 83 %; h) **9**, DCC, DMAP, CH_2Cl_2, −5 °C, 99 %; d) DDQ, pH 7 buffer, CH_2Cl_2, RT, 90 %; i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 99 %. HMPA = hexamethylphosphoramide.

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instance was critical to avoid spontaneous formation of the undesired lactol/lactone arising from preferential oxidation at C22 followed by cyclisation of the C26 secondary alcohol (Scheme 21).

Further elaboration of 12 to a Stille coupling partner: By this stage we had chosen to pursue a Stille coupling reaction for the installation of the triene portion of rapamycin (**1**) through union of **12** to a suitable C10–C17 lactone (**3**). However, we were still undecided whether to use this strategy to target formation of the C18−C19 or the C20−C21 bond, leaving us with a choice of four possible sets of coupling partners (Figure 2).

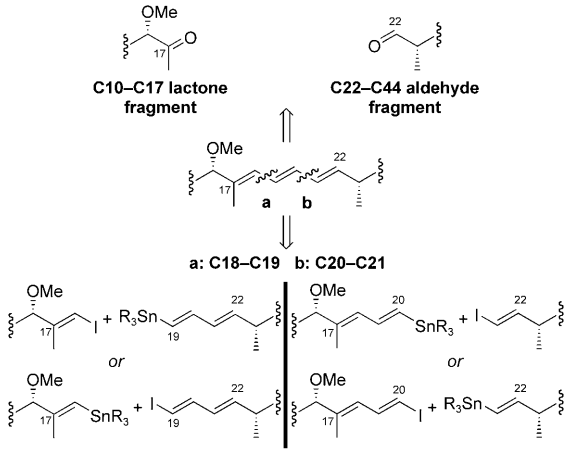
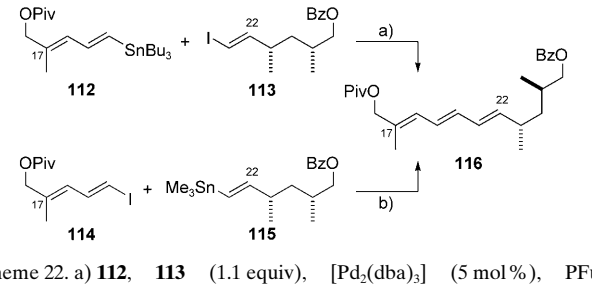


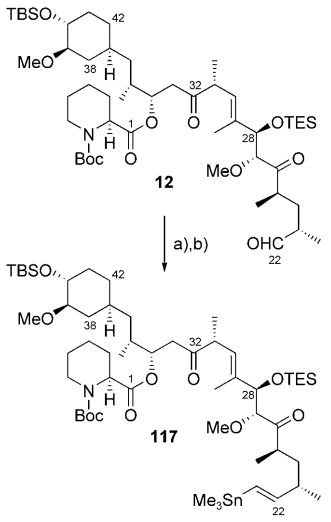
Figure 2. Coupling partner possiblilities for the introduction of the triene moiety.

Early explorations for construction of the C18−C19 bond did not prove encouraging. Furthermore, at this time we became aware of Smith's successful Stille coupling across C20−C21,[6k] and thus we examined this approach in more detail. Accordingly, model substrates were prepared using straightforward synthetic sequences (see Supporting Information) to test the influence of the nucleophilic and electrophilic partners in this cross-coupling reaction (Scheme 22).

Dienyl stannane **112** was found to be highly unstable, and despite immediate use after purification, underwent noticeable decomposition during its cross-coupling to vinyl iodide **113**. Although this latter reaction was successful to generate triene **116** as a single olefin isomer, the moderate yield observed as a result of the instability of **112** caused us concern. Fortunately, exchange of the reacting functional groups at the C20 and C21 termini led to much improved results in terms of the stability of the respective coupling partners **114** and **115**, as well as a slight improvement in the yield of triene **116** (once again, isolated solely as the *E*,*E*,*E*-conjugated system). With these results in mind, aldehyde **12** was elaborated to the corresponding C21-vinyl stannane (**117**) through Takai olefination[76] followed by palladium catalysed introduction of trimethylstannane. For this latter reaction the original conditions, whereby Farina's catalyst system of $[Pd(PFur_3)_n]$[77] was generated in situ, were completely ineffective. Recourse to freshly prepared $[Pd(PFur_3)_2Cl_2]$[78] resolved this issue to furnish **117** in 82% yield (Scheme 23).



Scheme 22. a) **112**, **113** (1.1 equiv), $[Pd_2(dba)_3]$ (5 mol%), $PFur_3$ (0.2 equiv), NMP, RT, 49%; b) **114** (1.3 equiv), **115**, $[Pd_2(dba)_3]$ (5 mol%), $PFur_3$ (0.2 equiv), NMP, RT, 77%. Fur = 2-furyl, NMP = *N*-methyl pyrrolidinone, dba = dibenzylidene acetone.



Scheme 23. a) $CrCl_2$, CHI_3, THF, 0°C→RT, 82%; b) $[Pd(PFur_3)_2Cl_2]$, $(Me_3Sn)_2$, NMP, dark, RT, 82%.

Construction of the C10–C20 lactone 142: The construction of the last remaining major fragment of rapamycin afforded us an opportunity to demonstrate the utility of iron carbonyl methodology developed within our group[79] for construction of the key δ-lactone moiety.[20c] Starting from *cis*-4-benzyloxy-2-buten-1-ol (**118**), application of the Sharpless asymmetric epoxidation reaction,[80] followed by Parikh–Doering oxidation and Horner–Wadsworth–Emmons olefination using the Masamune–Roush protocol[81] gave enoate **119**. Treatment of this with DIBAL-H accomplished the reduction of both the ester and oxirane functionalities, the latter in a regioselective fashion furnishing only the desired product **120** from hydride addition at the more electrophilic carbon centre (C15). Standard protecting group manipulations converted the resulting diol to methyl ether **121**. A second Sharpless asymmetric epoxidation, followed by oxidation of the primary alcohol and methylenation of the intermediate aldehyde gave vinyl epoxide **122** without inci-

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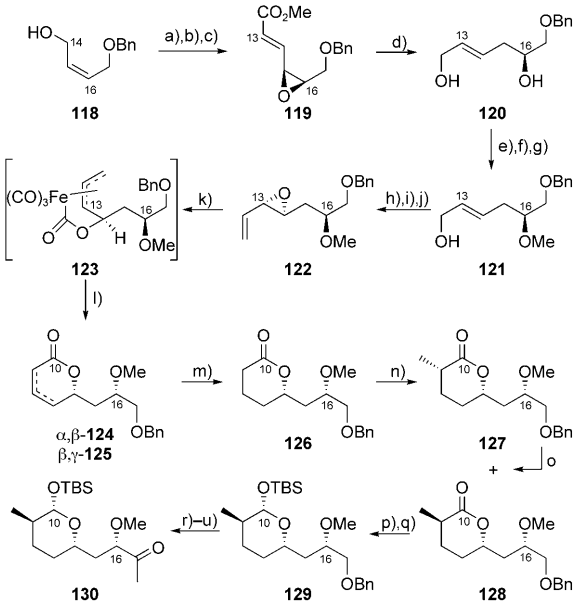
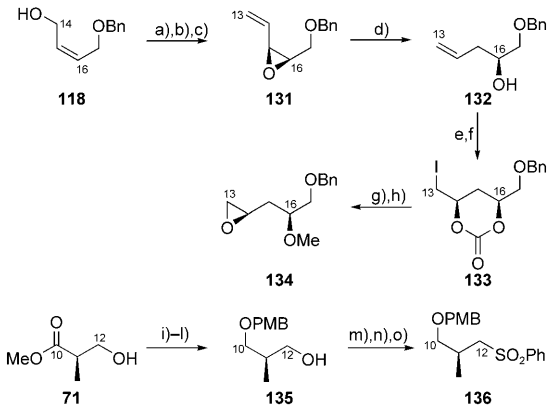
dent. The stage was now set for application of the key methodology. Thus, **122** was treated with $[Fe_2(CO)_9]$ to give the intermediate *endo*-η^3-π-allyltricarbonyliron lactone intermediate **123** as the predominant product. Subjecting this to carbon monoxide at 280 atm effected carbonylation, releasing a mixture of α,β- and β,γ-unsaturated lactones, **124** and **125**, respectively. Hydrogenation of this mixture employing Adam's catalyst[82] was followed by methylation at C11 via the lithium enolate of **126**, which unfortunately proceeded with little selectivity, and in favour of the undesired epimer **127**. However, it was possible to recycle some of this material to the desired advanced intermediate (**128**) by separation (HPLC) and a deprotonation/protonation sequence. Further elaboration to the original retrosynthetic target **3** was possible (see Supporting Information), but these last reactions were complicated by facile epimerisation at C11. Consequently, it proved necessary to reduce the lactone to the corresponding lactol and to protect this as the TBS ether (**129**). With this in hand, a standard sequence was employed to convert the C15-primary benzyl ether to the corresponding methyl ketone **130** (Scheme 24).



Scheme 24. a) $Ti(OiPr)_4$, (+)-diethyl tartrate, *t*BuOOH, −25 °C, 75 %, *ee* 92 %; b) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 0 °C→RT, 80 %; c) LiCl, $(EtO)_2P(O)CH_2CO_2CH_3$, DBU, CH_3CN, RT, 66 %; d) DIBAL-H, CH_2Cl_2, −78 °C; e) PivCl, Py, CH_2Cl_2, 0 °C, 69 % over 2 steps; f) NaH, CH_3I, 0 °C, 94 %; g) DIBAL-H, CH_2Cl_2, −78 °C, 88 %; h) $Ti(OiPr)_4$, (−)-diethyl tartrate, *t*BuOOH, 4 Å MS, CH_2Cl_2, −23 °C, 80 %; i) TPAP, NMO, CH_2Cl_2, CH_3CN, 4 Å MS, RT, 60 %; j) Ph_3PCH_3Br, KHMDS, THF, 0 °C→RT, 83 %; k) $[Fe_2(CO)_9]$, THF, RT, 72 %; l) CO (280 atm), PhH, 70 °C, 85 %; m) PtO_2, H_2 (1 atm), EtOAc, RT, 82 %; n) LDA, THF, CH_3I, −78 °C, 84 %, **127**/**128** 60:40; o) LDA, THF, −78 °C, then H_2O, 94 %, **127**/**128** 60:40; p) DIBAL-H, $PhCH_3$, −78 °C; q) TBSCl, Im, DMAP, DMF, RT, 92 % over 2 steps; r) $Pd(OH)_2$, H_2 (1 atm), EtOAc, RT, 100 %; s) TPAP, NMO, 4 Å MS, CH_2Cl_2, CH_3CN, RT, 100 %; t) MeMgBr, THF, −78 °C, 74 %, dr 3:1; u) TPAP, NMO, 4 Å MS, CH_2Cl_2, CH_3CN, RT, 92 %. Pr = propyl, DBU = diaza(1,3)bicyclo[5.4.0]undecane, Piv = pivaloyl.

With a successful route to **130** developed, we began to scale up this chemistry to provide synthetically useful quantities of material. However, in doing so, a number of drawbacks in the approach became apparent. For example, the poor selectivity obtained in introducing the C11-methyl function necessitated a difficult and tedious separation of diastereomers by HPLC, resulting in a substantial bottleneck in material throughput. Furthermore, the toxicity of $[Fe_2(CO)_9]$ and the high pressure of carbon monoxide required by the iron carbonyl chemistry led us to seek alternative methodologies on scale. As a consequence, a modified route was developed which would rely on the convergent union of sulfone **136** and epoxide **134** to generate the carbon skeleton of **130** (Scheme 25).



Scheme 25. a) $Ti(OiPr)_4$, (+)-diethyl tartrate, *t*BuOOH, −25 °C, 75 %, *ee* 92 %; b) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, 0 °C→RT; c) Ph_3PCH_3Br, KHMDS, THF, 0 °C→RT, 52 % over 2 steps; d) DIBAL-H, $PhCH_3$, −78 °C, 94 %; e) *n*BuLi, Et_2O, RT, then Boc-ON, THF, RT, 100 %; f) IBr, $PhCH_3$, CH_2Cl_2, −85 °C, 50 %, dr > 11:1; g) K_2CO_3, MeOH, RT, 90 %; h) CH_3I, Ag_2O, DMF, RT, 75–95 %; i) DHP, PPTS, CH_2Cl_2, RT, 100 %; j) $LiAlH_4$, Et_2O, −20 °C, 100 %; k) PMBCl, NaH, DMF, RT, 100 %; l) Amberlite IR 120, MeOH, RT, 82 %; m) TsCl, Py, 0 °C→RT, 90 %; n) PhSH, K_2CO_3, THF, RT, reflux, 100 %; o) *m*CPBA, CH_2Cl_2, 0 °C→RT, 100 %. Boc-ON = [2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile], *m*CPBA = *meta*-chloroperbenzoic acid.

Construction of the latter epoxide once again used benzyl ether **118** as a convenient starting point. Sharpless epoxidation, followed by oxidation and methylenation (in place of the previous Horner–Wadsworth–Emmons homologation) afforded terminal olefin **131**. After regioselective reductive ring-opening of the epoxide, the released secondary alcohol at C16 was used productively to install the corresponding iodocarbonate (**133**) in good selectivity for the 1,3-*syn* isomer, following Smith's IBr electrophilic cyclisation procedure.[83] Nucleophilic cleavage of the carbonate with basic methanol spontaneously formed the terminal epoxide, whilst the remaining free alcohol was subsequently methylated with methyl iodide and silver oxide to furnish **134**. The remaining fragment, sulfone **136**, was readily prepared from (*R*)-Roche ester through a standard set of synthetic operations as shown in Scheme 25.

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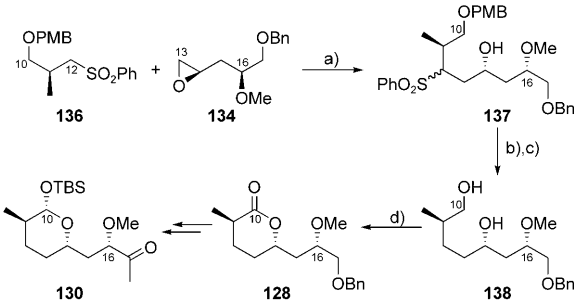
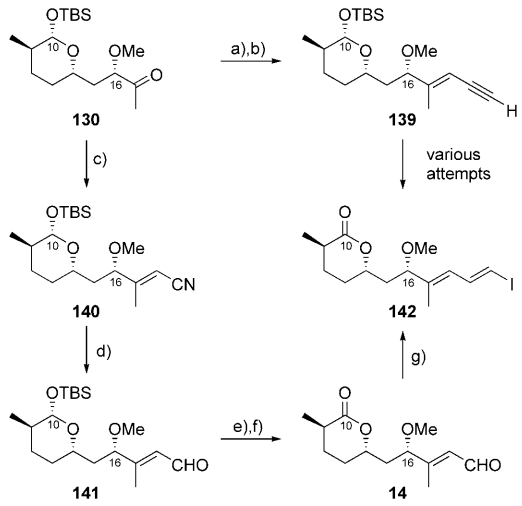
Treatment of sulfone **136** with *n*BuLi generated the corresponding α-litho anion, which in the presence of **134** and $BF_3{\cdot}OEt_2$ resulted in the smooth opening of the terminal epoxide in quantitative yield (relative to **134**), provided that a substantial excess of **136** was employed. Following reductive desulfonylation of **137** and cleavage of the PMB ether, oxidation of the ensuing diol (**138**) with TPAP generated the desired lactone (**128**) via an intermediate hemiacetal. This material was identical in all regards to that prepared through the previous iron carbonyl approach (cf. Scheme 24). However, this revised sequence was more convergent, higher yielding and easily scalable, and crucially avoided any HPLC purification by prior introduction of the C11-methyl stereocentre. Further elaboration of **128** to ketone **130** was then accomplished using the same approach as previously developed (Scheme 26).



Scheme 26. a) **136**, *n*BuLi, THF, −78 °C, then **134**, then $BF_3{\cdot}OEt_2$, −78 °C→RT, 100 %; b) 1 M lithium naphthalenide, THF, −90 °C, 93 %; c) DDQ, H_2O, CH_2Cl_2, RT, 100 %; d) TPAP, NMO, CH_2Cl_2, 4 Å MS, RT, 90 %.

Based upon earlier experience in preparing model dienyl iodides for cross-coupling studies (e.g. **114**), further elaboration of **130** to the required C10–C20 lactone (**142**) was not expected to be eventful. Accordingly, the *E*-homologated enyne **139** could be readily prepared via reaction of **130** with Gibson's modified Horner–Wadsworth–Emmons reagent,[84] followed by base-induced desilylation. However, in contrast to reports by Smith during his synthesis of rapamycin,[6m] all efforts to introduce the requisite vinyl iodide functionality by hydrozirconation or by radical or metal-catalysed hydrostannylation were disappointing, giving unacceptably low yields and/or poor *E*/*Z* selectivity (Scheme 27).[85] Attempts to address the regioselectivity problems associated with palladium-catalysed hydrostannylations through use of the 1-bromoalkyne derivatives[86] were also unsuccessful.

After investigation of a variety of other chain extension strategies, it was found that condensation of ketone **130** with the sodium anion of diethyl phosphonoacetonitrile[87] gave **140** in good yield, albeit in a modest ratio of olefin isomers (*E*/*Z* 7:1). Importantly, the major isomer could be readily separated and subsequently reduced cleanly with DIBAL-H to afford the corresponding enal (**141**) as a single stereoisomer. Regeneration of the C10-lactone through sequential



Scheme 27. a) $(Et_2O)P(O)CH_2{-}C{\equiv}C{-}TMS$, NaHMDS, THF, −78 °C, then **130**, 84 %, (*E*/*Z* > 10:1); b) K_2CO_3, MeOH, RT, 97 %; c) $(EtO)_2P(O)CH_2CN$, NaHMDS, THF, 0 °C, then **130**, −78 °C, 85 % (*E*/*Z* 7:1); d) DIBAL-H, $PhCH_3$, −78 °C, 91 %; e) TBAF, THF/AcOH/H_2O, RT; f) TPAP, NMO, 4 Å MS, CH_2Cl_2, 85 % over 2 steps; g) $CrCl_2$, CHI_3, THF/dioxane, 0 °C, 80 % (*E*/*Z* 6:1). TMS = Trimethylsilyl.

deprotection and oxidation of the intermediate lactol furnished dicarbonyl **14**, which had been obtained previously via degradation (cf. Scheme 2). Compound **14** was subsequently converted to the corresponding vinyl iodide **142** as a 6:1 mixture of geometric isomers through Takai olefination (Scheme 27).

Stille coupling and introduction of the catechol template: Although the *E*/*Z* ratio of **142** remained low (6:1) following Takai olefination, we nevertheless chose to proceed and to use this material in preliminary coupling studies with the C21–C42 stannane **117**. In the event, union of these two advanced fragments was readily accomplished (**10**) using the same conditions previously employed for the introduction of the C21 stannyl moiety. This material had identical spectroscopic properties with the same triene that had been obtained originally through the degradation of rapamycin (**1**) (cf. Scheme 1). Interestingly, despite using an isomeric mixture (6:1) of lactone dienyl iodides **142**, no minor geometric isomers could be detected in the ^1H NMR spectrum of the crude Stille coupled product. We have postulated that this unexpected result may most likely be due to isomerisation of the minor *Z*-component of **142** to the *E*-dienyl iodide under the reaction conditions. Alternatively, given that an excess of the iodide is employed, the *Z* isomer may react more slowly than the *E*-isomer. All attempts to further utilise **10** directly were ultimately unsuccessful, with reaction conditions either resulting in β-elimination of the pipecolinic unit, or frequently epimerisation at C11. However, on the basis of work undertaken during the preliminary degradative studies on rapamycin (**1**), we were able to selectively reduce the C32 carbonyl functionality in **10** using LiAlH-

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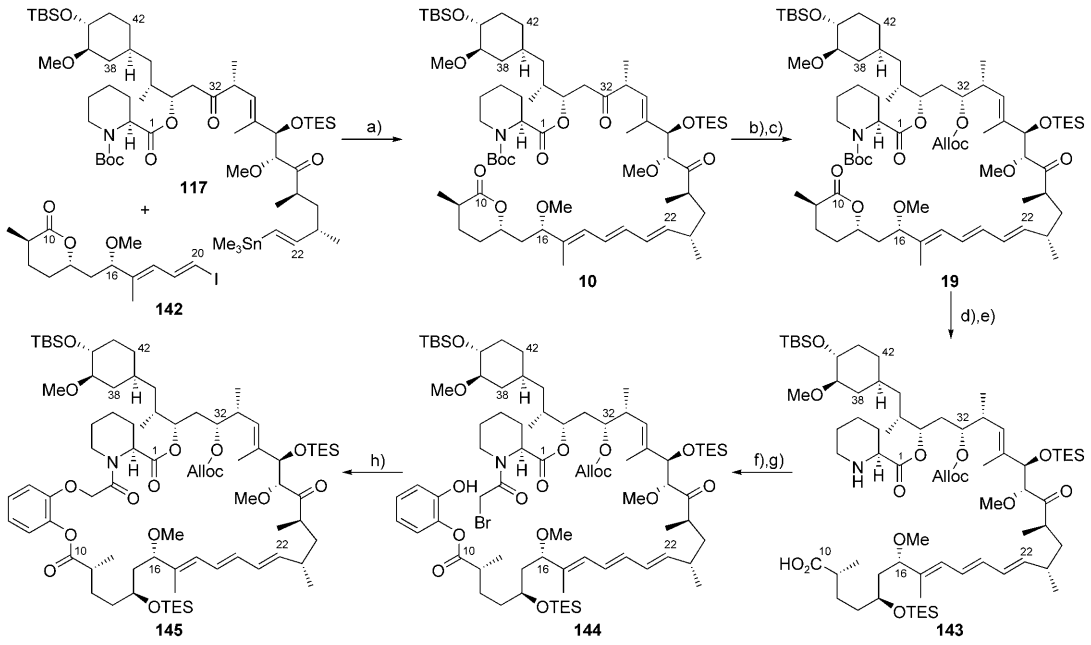
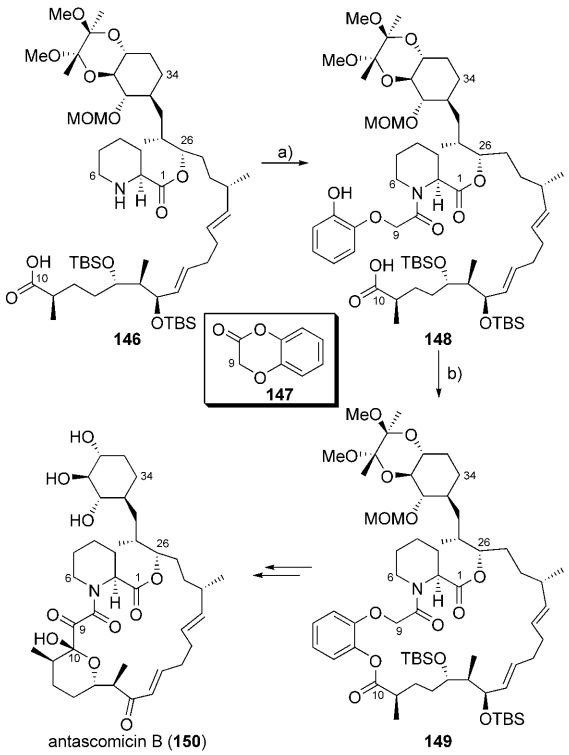


Scheme 28. a) $[Pd(PFur_3)_2Cl_2]$, **142**, NMP, dark, RT, 69%; b) $LiAlH(OtBu)_3$, THF, −10°C, 81%; c) AllocCl, PPy, CH_2Cl_2, RT, 81%; d) LiOH (aq), THF, 0°C, 89%; e) TESOTf, 2,6-lut., CH_2Cl_2, −20°C→RT, 88%; f) $BrCH_2C(O)Br$, 2,6-lut., CH_2Cl_2, −20°C, 66%; g) catechol, DCC, DMAP, CH_2Cl_2, 0°C→RT, 88%; h) K_2CO_3, DMF, RT, 70%.

$(OtBu)_3$[32] and subsequently protect the new (*R*)-carbinol as its Alloc derivative without difficulty, and in good yields. Basic hydrolysis of the lactone in **19** was followed by TES protection of the liberated C14-hydroxyl functionality. This latter reaction occurred with concomitant cleavage of the *N*-Boc group via breakdown of the corresponding silyl carbamate during workup, to furnish **143** wherein either of the N7 and C10 termini are available for installation of the catechol template. This latter sequence of events was crucial to maintain the stereochemical integrity at C11; attempts to cleave the *N*-Boc group prior to hydrolysis of the lactone resulted in considerable epimerisation of the sensitive methyl group (Scheme 28).

We had previously demonstrated the benefits of using a catechol-templated macrocyclisation strategy in our synthesis of the related macrolide antascomicin B (**150**) (Scheme 29).[88] On that occasion, from a similar situation (**146**) containing both free amine and carboxylic acid functionalities, we chose to introduce the template through the nitrogen terminus. This amide formation was readily achieved using commercially-available benzo-[1,4]dioxin-2-one (**147**), which also installed the remaining C8 and C9 centres whilst simultaneously exposing the second alcohol of the tether. Completion of the linkage was then achieved without difficulty via high-dilution macroesterification (0.001 M). However, in our rapamycin (**1**) synthesis program, we deliberately sought to demonstrate additional scope in this methodology by completing the catechol template via a less common macroetherification. We thus desired to install the tethering moiety initially at the carboxylic acid terminus (C10), and promote cyclisation through carbon-oxygen bond formation at C9. Accordingly, amide formation upon **143** with α-bromoacetyl bromide successfully introduced the remaining two carbons (C8, C9) of the rapamycin framework. This was followed by a standard DCC-mediated coupling of



Scheme 29. a) **147**, DMAP, CH_2Cl_2, RT, 90%; b) EDCI, CH_2Cl_2, RT, 71%. EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride.

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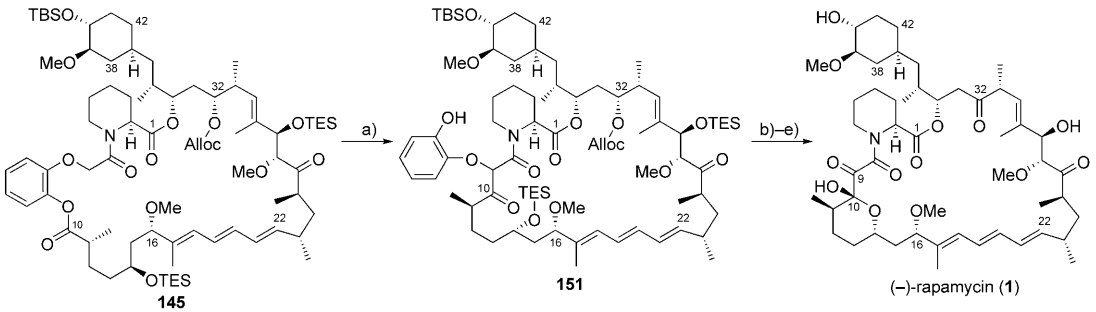

Scheme 30. a) LiHMDS, THF, −78 °C→−20 °C, 78 %; b) $[Pd(PPh_3)_4]$, dimedone, THF, RT, 80 %; c) $PhI(OAc)_2$, $MeCN/H_2O$ (10:1), 0 °C; d) DMP, Py, CH_2Cl_2, RT, 61 % over 2 steps; e) HF·Py, THF, 50 °C, 61 %. DMP = Dess–Martin periodinane.

catechol with the free carboxylic acid to attach one end of the template (**144**) and prepare for the crucial alkylative ring closure. We were very pleased to observe that treatment of **144** with K_2CO_3 resulted in smooth and problem-free macrocyclisation to construct the desired linkage in 81 % yield (Scheme 28). Although in the event the overall step count to install the tether was higher through this approach than for the sequence used in our synthesis of antascomicin B, this alternative macroetherification strategy has successfully highlighted additional flexibility in the introduction of the catechol moiety and the subsequent crucial macrocyclisation.

Completion of the total synthesis of rapamycin (1): With the catechol tether in place (**145**), we sought to complete the parent macrocycle of rapamycin through a Dieckmann-like condensation of a C9-anion upon C10. In the event, treatment of **145** with LiHMDS under conditions previously optimised in the synthesis of antascomicin B afforded the 29-membered ring without incident (**151**), and in an excellent 78 % yield. Of all the various reported approaches to this core motif of rapamycin,[6c,g,j,k] this templated strategy is the highest yielding. More specifically, direct comparison with the only previous example of macrocyclisation via direct carbon–carbon bond formation (11 % via aldol formation of the C26–C27 bond)[6j] serves best to demonstrate the power of this templating methodology (Scheme 30).

With the framework of **1** in place, all that remained to complete the total synthesis was a four step sequence of protecting group removal and oxidation state adjustments. Thus, after removal of the Alloc and catechol moieties, oxidation of the C9 and C32 alcohols using Dess–Martin reagent and a final global silyl ether cleavage using HF·Py yielded rapamycin, identical in all regards with an authentic sample of the natural product (Scheme 30).

Conclusions

This total synthesis of rapamycin (**1**) represents the culmination of one of the major synthesis programs within our research group. It is a true testament to this remarkable natural product that it has kept us intrigued and fascinated for many years, just as it continues to inspire chemists and biologists alike to this day.

We have used this complex molecule as a platform to develop and to demonstrate a wide variety of methodologies developed within our group, including iron-carbonyl chemistry, the intramolecular addition of allylsilanes to oxonium ions, a butane-2,3-diacetal-controlled aldol condensation, and a highly-efficient catechol-templated intramolecular macrocycle construction. However, whilst the end result is one of success and satisfaction, we have also met with considerable disappointment and frustration along the way. We have been thwarted by rigidly stable cyclic acetals, labile pipecolinate residues, epimerisable stereocentres and stubborn protecting groups, and were forced to re-evaluate the strategy on numerous occasions. However, such is the lure of rapamycin that we have persevered to complete this convergent total synthesis, and hope that this will prove an engaging addition to a field of enduring interest.

Experimental Section

General information: All non-aqueous reactions were performed under an atmosphere of argon and carried out using oven-dried (200 °C) glassware; synthetic intermediates were dried in vacuo before use. All reagents were obtained from commercial sources and used as supplied unless otherwise stated. Solvents were of reagent-grade and freshly distilled before use. Flash column chromatography was performed using Merck 60 Kieselgel (230–400 mesh) under pressure unless otherwise indicated. Florisil refers to 200–300 mesh Florisil (BDH). Analytical thin layer chromatography (TLC) was performed using precoated glass-backed plates (Merck Kieselgel 60 F254), and visualised by ultraviolet radiation (254 nm) and/or by oxidative staining with aqueous acidic ammonium molybdate or acidic potassium permanganate and heating as necessary. Petrol refers to petroleum ether b.p. 40–60 °C. Melting points were performed on a Reichert hot stage apparatus equipped with a digital thermometer. Specific optical rotations were recorded on Optical Activity AA-1000 and Perkin–Elmer 343 digital polarimeters using a sodium lamp (589 nm) as the light source. $[\alpha]_D^{25}$ values are reported in 10^{-1} deg cm^2 g^{-1} (concentration, c in g per 100 mL). ^{1}H NMR spectra were recorded at 27 °C on Bruker AM-200, Bruker AM-250, Jeol GFX 270, Bruker AM-400, Bruker DPX-400, Bruker AM-500, Bruker DRX-500, Bruker Avance 500 (with dual cryoprobe) or Bruker DRX-600 spectrometers, operating at 200, 250, 270, 400, 500 and 600 MHz respectively, as stated with each experiment. Chemical shift data is quoted in ppm to the nearest 0.01 ppm, and given relative to residual protic solvent where $\delta(CDCl_3) = 7.26$ and $\delta(C_6D_6) = 7.15$ ppm. Multiplicities (J) are recorded

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in Hertz (Hz). ^{13}C NMR spectra were recorded on Bruker AM-200, Bruker AM-250, Bruker AM-400, Bruker DPX-400, Bruker AM-500, Bruker DRX-500, Bruker Avance 500 (with dual cryoprobe) or Bruker DRX-600 spectrometers, operating at 50, 62.5, 100, 125 and 150 MHz, respectively, as stated with each experiment. Chemical shift data is quoted in ppm to the nearest 0.1 ppm, and given relative to residual deuterated solvent where $\delta(CDCl_3)=77.0$ and $\delta(C_6D_6)=128.6$ ppm. NMR spectra were assigned using information obtained from DEPT, COSY, HMBC, HMQC and nOe experiments. These assignments are given according to the recognised numbering of rapamycin (**1**). Infrared spectra (IR) were recorded as thin films using Perkin–Elmer FTIR 983G, FTIR 1600, FTIR 1620 or Spectrum One spectrometers. High-resolution mass spectrometry (HRMS) was conducted with Kratos Concept, Bruker BIOAPEX 4.7T FTICR or Waters Micromass LCT Premier spectrometers using electron impact (EI) or electrospray (ESI) ionisation techniques. Additional spectra were run by the EPSRC Mass Spectrometry Service, Swansea. Microanalyses were performed in the microanalytical laboratories at Imperial College London and at the University of Cambridge, and additionally by Medac Ltd. at the Department of Chemistry, Brunel University. Chiral HPLC analysis was performed on an Agilent 1100 series HPLC using AD Chiralpak or OD Chiralcel columns, HPLC grade solvents and UV detection ($\lambda=225$, 254 and 280 nm) at RT.

Sulfone 25: A solution of Oxone (138 g, 0.225 mol) in aqueous pH 4 buffer solution (750 mL) was added dropwise to a stirred solution of methoxymethyl phenyl sulfide (22.5 mL, 0.150 mol) in MeOH (750 mL). The white slurry was stirred overnight at RT, then diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Recrystallisation of the crude white residue from Et_2O gave sulfone **25** as white needles (18.0 g, 70%). $R_f=$ 0.35 (30% EtOAc/petrol); m.p. 68–70°C; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.98$–7.91 (m, 2H, ArH), 7.72–7.65 (m, 1H, ArH), 7.63–7.55 (m, 2H, ArH), 4.52 (s, 2H, $2\times H_{39}$), 3.68 ppm (s, 3H, C_{39}-OCH_3); IR (thin film): $\tilde{\nu}=1443$, 1328, 1199, 1142, 1118, 1078, 908, 748, 686 cm^{-1}.

Alcohols 26 and 27: To a stirred solution of sulfone **25** (41.0 g, 0.220 mol) in 1,2-dimethoxyethane (600 mL) at −78°C was added *t*BuLi (1.7 M in pentane, 142 mL, 0.242 mol) dropwise over 1 h. After addition was complete, the solution was stirred for 10 min at −78°C, then a solution of ester **24**[36] (24.5 g, 0.115 mol) in 1,2-dimethoxyethane (50 mL) was added dropwise. The reaction mixture was stirred for 45 min at −78°C, warmed to RT over 2 h, then stirred for an additional 30 min. The reaction was quenched by careful addition of saturated NH_4Cl solution. The bulk of the solvent was removed in vacuo, and the residue taken up with Et_2O. The solution was washed with H_2O and with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude residue by flash chromatography (15% EtOAc/petrol) gave, in order of elution, the desired β-ketosulfone as a pale yellow oil which solidified on standing (35.4 g, 87%), followed by the recovered sulfone **25** (13.2 g). $R_f=0.29$ (15% EtOAc/petrol); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta=7.85$ (dd, $J=7.8$, 1.2 Hz, 2H, ArH), 7.69 (dd, $J=6.3$, 1.2 Hz, 1H, ArH), 7.56 (m, 2H, ArH), 4.70 (s, 1H, H_{39}), 4.49 (d, $J=1.3$ Hz, 2H, $2\times H_{38}$), 3.71 (s, 3H, OCH_3), 2.84 (m, 1H, H_{41}), 2.51 (m, 1H, H_{41}), 2.10 (m, 2H, $2\times H_{42}$), 1.47 (s, 2H, $2\times H_{36}$), 0.00 ppm (s, 9H, TBS); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta=$ 200.7 (C_{40}), 145.6 (C_{37}), 136.0 (Ar), 134.5 (Ar), 129.6 (Ar), 129.2 (Ar), 107.4 (C_{38}), 100.3 (C_{39}), 61.7 (OCH_3), 38.7 (C_{41}), 31.0 (C_{42}), 27.0 (C_{36}), −1.4 ppm (TBS); IR (thin film): $\tilde{\nu}=2952$, 2900, 1633, 1477, 1447, 1323, 1309, 1247, 854 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{26}O_4SSi$: C 57.59, H 7.39; found: C 57.62, H 7.50.

BH_3·DMS (0.58 mL, 6.00 mmol) was added to a solution of the ketone prepared above (2.90 g, 8.18 mmol) and freshly-prepared (*S*)-CBS catalyst (1.0 M in $PhCH_3$, 0.80 mL, 0.80 mmol) in THF at −78°C. After 2 h, additional BH_3·DMS (0.19 mL, 0.19 mmol) was added and the reaction stirred for a further 2 h 30 min. It was then quenched by the addition of methanol, the cooling bath removed, and the solution stirred for 30 min before being concentrated in vacuo. The residue was dissolved in Et_2O, washed with HCl (1.0 N), saturated aqueous $NaHCO_3$, H_2O and with brine, dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR of this indicated the crude residue to be essentially pure, and as a mixture of diastereoisomers (3.00 g, 100%, **26**/**27** 1:2). These could be separated by flash chromatography on Florisil (12.5% EtOAc/petrol).

Data for alcohol **26**: $R_f=0.44$ (20% EtOAc/petrol); $[\alpha]_D^{25}=+11.0$ ($c=$ 2.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta=7.93$–7.91 (m, 2H, ArH), 7.72–7.68 (m, 1H, ArH), 7.61–7.57 (m, 2H, ArH), 4.54 (s, 1H, H_{38}), 4.49 (s, 1H, H_{38}), 4.09 (d, $J=7.8$ Hz, 1H, H_{39}), 3.73 (ddd, including $J=8.0$ Hz, 1H, H_{40}), 3.61 (s, 3H, OCH_3), 3.31 (s, 1H, OH), 2.17–2.11 (m, 1H, H_{41}), 2.04–1.96 (m, 1H, H_{41}), 1.84–1.77 (m, 1H, H_{42}), 1.59–1.52 (m, 1H, H_{42}), 1.48 (s, 2H, $2\times H_{36}$), 0.00 ppm (s, 9H, TMS); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=137.6$ (C_{37}), 137.4 (Ar), 134.1 (Ar), 129.3 (Ar), 129.2 (Ar), 110.2 (C_{38}), 98.5 (C_{39}), 69.4 (C_{40}), 62.5 (OCH_3), 32.7 (C_{41}), 31.1 (C_{42}), 26.6 (C_{36}), −1.6 ppm (TMS); IR (thin film): $\tilde{\nu}=3341$, 2929, 1558, 1539, 1457, 1006 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{29}O_4SSi$: 357.1556; found: 357.1558 $[M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{28}O_4SSi$: C 57.20, H 7.92; found: C 57.35, H 7.83.

Data for alcohol **27**: $R_f=0.38$ (20% EtOAc/petrol); $[\alpha]_D^{25}=-1.7$ ($c=1.49$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta=7.93$–7.91 (m, 2H, ArH), 7.70–7.65 (m, 1H, ArH), 7.60–7.55 (m, 2H, ArH), 4.58 (s, 1H, H_{38}), 4.53 (s, 1H, H_{38}), 4.11 (ddd, including $J=2.1$ Hz, 1H, H_{40}), 4.10 (d, $J=2.0$ Hz, 1H, H_{39}), 3.61 (s, 3H, OCH_3), 2.13 (s, 1H, OH), 2.16–2.12 (m, 1H, H_{41}), 2.03–1.97 (m, 1H, H_{41}), 1.77–1.74 (m, 2H, $2\times H_{42}$), 1.51 (s, 2H, $2\times H_{36}$), 0.0 ppm (s, 9H, TMS); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=146.5$ (C_{37}), 137.4 (Ar), 134.1 (Ar), 129.7 (Ar), 129.0 (Ar), 107.7 (C_{38}), 99.4 (C_{39}), 69.2 (C_{40}), 62.5 (OCH_3), 34.0 (C_{41}), 32.4 (C_{42}), 26.8 (C_{36}), −1.3 ppm (TMS); HRMS (ESI): m/z: calcd for $C_{17}H_{29}O_4SSi$: 357.1556; found: 357.1546 $[M+H]^+$.

The undesired epimer **27** could be recycled as follows: To a mixture of alcohol **27** (120 mg, 0.34 mmol) and pre-dried 4 Å MS in CH_2Cl_2 (3 mL) was added PCC (181 mg, 0.84 mmol). The dark suspension was stirred vigorously at RT for 45 min, then filtered through a pad of Florisil (eluting with EtOAc). The filtrate was concentrated in vacuo, and the crude residue purified by flash chromatography (15% EtOAc/petrol) to return the ketone prepared above, as a colourless oil (60 mg, 50%), which could be reduced to a mixture of **26** and **27** in the same manner. The observed analytical data was identical in all respects to that reported above.

***trans*-Cyclohexane 28**: A solution of alcohol **26** (5.34 g, 15.0 mmol), pyridine (1.50 mL, 18.8 mmol) and DMAP (183 mg, 1.50 mmol) in CH_2Cl_2 (75 mL) was cooled to 0°C, and TBSOTf (3.80 mL, 16.5 mmol) was added. The reaction was stirred for 1 h 15 min, then quenched by the addition of saturated aqueous Na_2CO_3 and diluted with Et_2O. The organic layer was separated and washed sequentially with HCl (1.0 N), H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, then dried over $MgSO_4$ and concentrated in vacuo to afford the desired silyl ether as a colourless oil (6.70 g, 95% material balance). A small sample of the crude residue was purified by flash chromatography (0–5% EtOAc/petrol) to afford the desired silyl ether as a colourless oil (4.93 g, 70%). $R_f=0.81$ (20% EtOAc/petrol); ^{1}H NMR (500 MHz, $CDC1_3$). $\delta=7.94$–7.92 (m, 2H, ArH), 7.68–7.65 (m, 1H, ArH), 7.58–7.55 (m, 2H, ArH), 4.47 (2s, 2H, $2\times H_{38}$), 4.26 (m, 1H, H_{40}), 4.23 (d, 1H, $J=2.0$ Hz, H_{39}), 3.44 (s, 3H, OCH_3), 2.05 (m, 1H, H_{42}), 1.85 (m, 1H, H_{42}), 1.68 (m, 1H, H_{41}), 1.53 (m, 1H, H_{41}), 1.46 (s, 2H, $2\times H_{36}$), 0.88 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.08 (s, 3H, TBS), 0.00 ppm (s, 9H, TMS); ^{13}C NMR (62.5 MHz, $CDC1_3$): $\delta=147.1$ (C_{37}), 138.0 (Ar), 133.9 (Ar), 129.4 (Ar), 129.1 (Ar), 107.1 (C_{38}), 101.3 (C_{39}), 70.9 (OCH_3), 62.5 (C_{40}), 34.3 (C_{41}), 30.3 (C_{42}), 27.0 (C_{36}), 25.8 (TBS), 17.9 (TBS), −1.3 (TMS), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}=$ 2954, 1190, 1150, 1077, 909 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{23}H_{43}O_4SSi_2$: 471.2420; found: 471.2421 $[M+H]^+$; elemental analysis calcd (%) for $C_{23}H_{42}O_4SSi_2$: C 58.67, H 8.99; found: C 58.80, H 8.96.

To a cooled (−78°C) solution of the silyl ether prepared above (6.70 g, 14.2 mmol) in CH_2Cl_2 (120 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 28.4 mL, 28.4 mmol) over 45 min. After addition was complete, the reaction was stirred for an additional 10 min, then poured into aqueous HCl (3.0 N) and extracted with petrol. The organic layer was washed sequentially with H_2O, saturated aqueous $NaHCO_3$, H_2O and with brine, dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR of the crude product indicated a 5:1 mixture of diastereoisomers **28**/**29**. The crude residue was purified by flash chromatography (1% EtOAc/petrol) to afford the desired cyclohexane as a colourless oil (2.10 g, **28**/**29** 5:1, 58% over 2 steps). An improved single step yield of 90% could be achieved for this cyclisa-

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tion using the same protocol when starting from purified silyl ether. R_f= 0.45 (5% EtOAc/petrol); ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.68 (d, 2H, 2×H_{36}), 3.73 (m, 1H, H_{39}), 3.38 (s, 3H, OCH_3), 3.11 (s, 1H, H_{40}), 2.58–2.30 (m, 2H, 2×H_{38}), 2.18–1.90 (m, 2H, 2×H_{41}), 1.72 (m, 1H, H_{42}), 1.45 (m, 1H, H_{42}), 0.88 (s, 9H, TBS), 0.09 ppm (s, 6H, TBS); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=145.6 (C_{37}), 109.1 (C_{36}), 82.8 (C_{39}), 71.0 (OCH_3), 57.2 (C_{40}), 36.0 (C_{38}), 32.0 (C_{41}), 30.5 (C_{42}), 25.9 (TBS), 18.2 (TBS), −4.5 (TBS), −4.7 ppm (TBS); HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{29}O_2Si$: 257.1936; found: 257.1954 $[M+H]^+$ elemental analysis calcd (%) for $C_{14}H_{28}O_2Si$: C 65.57, H 11.00; found: C 65.72, H 11.08.

Aldehyde 30: 9-BBN (0.5 M in THF, 60.0 mL, 30.0 mmol) was added dropwise to a solution of methylene cyclohexane **28** (2.56 g, 10.0 mmol) in THF (30 mL) at 0 °C. After the addition was complete, the cooling bath was removed and the solution stirred at RT for 3 h. After cooling back to 0 °C, the reaction quenched by the successive addition of THF/EtOH 1:1, NaOH (2.5 N), and finally 30% aqueous H_2O_2. The mixture was stirred for 3 h at RT, then poured into aqueous pH 7 phosphate buffer and extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (15% EtOAc/petrol) gave the desired alcohol as a colourless oil (2.09 g, 76%). R_f= 0.29 (20% EtOAc/petrol); $[\alpha]_D^{25}$=−5.6 (*c*=2.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=3.47 (d, *J*=6.0 Hz, 2H, 2×H_{36}), 3.40 (m, 1H, H_{40}), 3.40 (s, 3H, OCH_3), 2.96 (m, 1H, H_{39}), 2.11 (m, 1H, H_{38}), 1.71 (m, 1H, H41), 1.66–1.44 (m, 3H, H_{41}, H_{37}, H_{42}), 1.40 (m, 1H, H_{42}), 0.98 (s, 9H, TBS), 0.07 (s, 3H, TBS), 0.06 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=84.3 (C_{39}), 75.5 (OCH_3), 67.8 (C_{36}), 58.0 (C_{40}), 38.8 (C_{37}), 33.5 and 33.0 (C_{28}, C_{41}), 27.1 (C_{42}), 26.0 (TBS), 18.3 (TBS), −4.4 (TBS), −4.6 ppm (TBS); IR (thin film): $\tilde{\nu}$=3625, 3423, 3017, 2929, 1471, 1251, 1215, 1105, 1070, 836, 758 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{31}O_3Si$: 275.2042; found: 275.2049 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{30}O_3Si$: C 61.26, H 11.02; found: C 61.88, H 10.88.

A solution of DMSO (5.0 mL, 71.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of $(COCl)_2$ (3.0 mL, 34.0 mmol) in CH_2Cl_2 (250 mL) at −78 °C. After 30 min, a solution of the alcohol prepared above (7.20 g, 26.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise over ca. 1 h 30 min. After addition was complete, the reaction was stirred for 15 min, then triethylamine (20.0 mL, 145 mmol) was added dropwise. The cooling bath was removed, and the reaction allowed to warm gradually to RT, then H_2O was added and the biphasic mixture transferred to a separating funnel. The organic phase was washed with saturated aqueous NH_4Cl (×3), dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by rapid flash chromatography (20% Et_2O/petrol) gave the desired aldehyde **30** as a pale yellow oil (6.50 g, 92%). R_f=0.69 (20% EtOAc/petrol); $[\alpha]_D^{25}$=−30.0 (*c*=2.01, $CHCl_3$) [ref. [6]=−31.1 (*c*= 0.67, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.60 (s, 1H, CHO), 3.49 (m, 1H, H_{40}), 3.33 (s, 3H, C_{39}-OCH_3), 2.99 (m, 1H, H_{39}), 2.25–2.12 (m, 2H, H_{38}, H_{39}), 1.89–1.80 (m, 2H, H_{39}, H_{42}), 1.48–1.28 (m, 3H, H_{42}, 2× H_{41}), 0.85 (s, 9H, TBS), 0.04 ppm (s, 6H, TBS). The observed data was consistent with that previously reported.[6d]

Alkene 31: (*E*)-2-Butene was condensed directly into a flask containing KO*t*Bu (1.0 M in THF, 0.46 mL, 0.46 mmol) at −78 °C via cannula. *n*BuLi (2.5 M in hexanes, 0.18 mL, 0.46 mmol) was then added and the mixture stirred at −45 °C for 30 min. After cooling back to −78 °C, a solution of (−)-Ipc_2BOMe (175 mg, 0.56 mmol) in Et_2O (0.5 mL) was added, and the solution stirred for 1 h, before cooling to −100 °C. BF_3·OEt_2 (70 μL, 0.67 mmol) was added dropwise, before aldehyde **30** (100 mg, 0.37 mmol) was introduced as a solution in Et_2O (0.5+0.25 mL). The reaction was stirred at −100 °C for 3 h, and at −20 °C for 1 h, then warmed to 0 °C and quenched by the addition of aqueous NaOH (3 N) and 27.5% H_2O_2. After stirring overnight, the mixture was partitioned between aqueous pH 7 phosphate buffer and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography gave the desired alkene **31** as a colourless oil that solidified into fine crystals on standing (87.0 mg, 71%). R_f=0.16 (10% EtOAc/petrol); $[\alpha]_D^{25}$=−38.0 (*c*=1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=5.75 (ddd, *J*=17.0, 10.2, 7.8 Hz, 1H, H_{34}), 5.10 (m, 2H, 2×H_{33}), 3.41 (s, 3H, OCH_3), 3.39 (m, 1H, H_{40}), 3.14 (m, 1H, OH), 2.88 (m, 1H, H_{39}), 2.34 (m, 1H, H_{36}), 2.14 (m, 1H, H_{38}), 1.87 (m, 1H, H_{35}), 1.58 (m, 1H, H_{41}), 1.46 (m, 1H, H_{37}), 1.31 (m, 1H, H_{42}), 1.20 (m, 1H, H_{41}), 1.03 (d, *J*=7.0 Hz, C_{35}-CH_3), 1.00 (m, 1H, H_{42}), 0.88 (s, 9H, TBS), 0.87 (m, 1H, H_{38}), 0.06 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=140.3 (C_{34}), 116.6 (C_{33}), 84.7 (C_{39}), 78.0 (C_{36}), 75.5 (OCH_3), 58.0 (C_{40}), 41.4 (C_{35}), 38.7 (C_{37}), 33.7 and 33.5 (C_{38}, C_{41}), 26.0 (TBS), 24.5 (C_{42}), 18.3 (TBS), 17.1 (C_{35}-CH_3), −4.4 (TBS), −4.6 ppm (TBS); HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{37}O_3Si$: 329.2512; found: 329.2522 $[M+H]^+$.

Attempts to increase the scale of this reaction led to reduced product yields and/or diastereoselectivity. As an alternative, **31** could be prepared on scale as follows: (*E*)-2-Butene (8.5 mL, 90.0 mmol) was condensed into a cooled (−78 °C) graduated cylinder and transferred via cannula to a solution of KO*t*Bu (9.60 g, 85.0 mmol) in THF (60 mL) at −78 °C. *n*BuLi (2.5 M in hexanes, 34.0 mL, 85.0 mmol) was then added dropwise, before the reaction mixture was warmed to −50 °C. After 15 min at this temperature, it was cooled back to −78 °C and $B(OiPr)_3$ (19.6 mL, 85.0 mmol) added. The mixture was stirred for 10 min, then quenched by pouring into HCl (1.0 N, saturated with NaCl). The solution was acidified to pH 1 with HCl (3.0 N), then (+)-diisopropyl tartrate (20.0 g, 85.0 mmol) in Et_2O (30 mL) was added, and the mixture stirred vigorously. The layers were separated, and the aqueous phase extracted with Et_2O (×4). The combined organic extracts were dried over $MgSO_4$, filtered under an argon blanket, and concentrated in vacuo to afford Roush's boronate reagent as a pale yellow oil (23.0 g, 90%) that was stored in the fridge, under argon, as a solution in $PhCH_3$.

A precooled (−78 °C) solution of aldehyde **30** (5.41 g, 20.0 mmol) in $PhCH_3$ (75 mL) was added dropwise via cannula to a freshly-prepared mixture of Roush's diisopropyl tartrate modified boronate prepared above (0.45 M in $PhCH_3$, 48.0 mL, 22.0 mmol) and pre-dried 4 Å MS at −78 °C. The reaction was stirred for 4 h, then quenched by the addition of aqueous NaOH (2.5 M) and warmed to 0 °C. The biphasic mixture was stirred for 45 min, then filtered through a pad of Celite (washing with Et_2O). The filtrate was washed with H_2O and with brine, dried over K_2CO_3 and concentrated in vacuo. Purification of the crude residue by flash chromatography (8–10% Et_2O/petrol) gave the desired alkene **31** as a colourless oil (3.95 g, 60%). The observed analytical data was identical in all respects to that reported above.

Epoxide 32: To a stirred solution of homoallylic alcohol **31** (4.00 g, 12.2 mmol) in CH_2Cl_2 (150 mL) containing pre-dried 3 Å MS was added *t*BuOOH (3.0 M in isooctane, 8.0 mL, 24.0 mmol). After 5 min, $VO(acac)_2$ (323 mg, 10 mol%) was introduced, and the resulting dark red solution stirred at RT for 30 h. The reaction was quenched by the addition of 10% aqueous $Na_2S_2O_3$, then stirred vigorously for 30 min. The mixture was filtered through a pad of Celite, and the filtrate washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20% EtOAc/petrol) gave the desired epoxide **32** as a colourless oil (2.95 g, 71%). R_f=0.13 (20% EtOAc/petrol); $[\alpha]_D^{25}$=−25.0 (*c*=1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ= 3.40 (m, 2H, H_{40}, H_{36}), 3.39 (s, 3H, OCH_3), 2.93 (m, 2H, H_{40}, H_{34}), 2.76 (dd, *J*=5.2, 8.0 Hz, 1H, H_{33}), 2.46 (dd, *J*=2.0, 5.1 Hz, 1H, H_{33}), 2.26 (d, *J*=4.2 Hz, 1H, OH), 2.03 (ddd, *J*=2.1, 8.8, 9.0 Hz, 1H, H_{38}), 1.88 (m, 1H, H_{35}), 1.59 (m, 1H, H_{41}), 1.42–1.28 (m, 3H, H_{37}, H_{41}, H_{42}), 1.09 (m, 1H, H_{42}), 0.98 (d, *J*=7.1 Hz, 3H, C_{35}-CH_3), 0.89 (s, 9H, TBS), 0.85 (m, 1H, H_{38}), 0.04 ppm (s, 6H, TBS); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ=85.4 (C_{39}), 78.6 (C_{36}), 75.3 (C_{40}), 58.0 (C_{34}), 54.8 (OCH_3), 45.2 (C_{33}), 39.4 (C_{37}), 38.6 (C_{35}), 33.6 (C_{38}), 29.7 (C_{42}), 27.3 (C_{41}), 25.9 (TBS), 18.2 (TBS), 13.5 (C_{35}-CH_3), −4.5 (TBS), −4.7 ppm (TBS); HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{37}O_4Si$: 345.2461; found: 345.2455 $[M+H]^+$.

Epoxide 6: *n*BuLi (1.6 M in hexanes, 3.1 mL, 5.02 mmol) was added dropwise to a cooled (−20 °C) solution of epoxyalcohol **32** (1.73 g, 5.02 mmol) in THF (50 mL). After stirring for 25 min, phenyl chlorothioformate (0.76 mL, 5.50 mmol) was added dropwise and the mixture stirred for 1 h. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 and warmed to RT. The volatiles were removed in vacuo and the residue dissolved in Et_2O, and the organic layer was washed with H_2O and with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (8% Et_2O/petrol) to

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afford, in order of elution, the desired thionocarbonate as a colourless oil (2.05 g, 85%) and recovered epoxyalcohol **32** (87 mg, 4%). R_f=0.76 (20% EtOAc/petrol); $[\alpha]_D^{25}$=−45.2 (c=1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.42 (m, 2H, ArH), 7.28 (m, 1H, ArH), 7.12 (m, 2H, ArH), 5.50 (dd, J=6.1, 7.0 Hz, 1H, H_{36}), 3.43 (s, 3H, OCH_3), 3.41 (m, 1H, H_{40}), 3.02 (ddd, J=2.0, 4.9, 7.2 Hz, 1H, H_{34}), 2.93 (ddd, J=2.1, 8.9, 9.0 Hz, 1H, H_{39}), 2.74 (dd, J=5.2, 7.8 Hz, 1H, H_{33}), 2.45 (dd, 1H, J=2.1, 5.0 Hz, 1H, H_{33}), 2.12 (m, 1H, H_{38}), 2.04 (m, 1H, H_{35}), 1.88 (m, 1H, H_{41}), 1.78 (m, 2H, H37, H_{42}), 1.42 (m, 1H, H_{41}), 1.21 (m, 1H, H_{42}), 1.06 (d, J=7.2 Hz, 3H, C_{35}-CH_3), 0.89 (s, 9H, TBS), 0.86 (m, 1H, H_{38}), 0.05 (s, 3H, TBS), 0.04 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ=196.0 (C=S), 153.5 (Ar), 129.5 (Ar), 126.5 (Ar), 122.0 (Ar), 90.4 (C_{36}), 84.2 (C_{39}), 75.2 (C_{40}), 58.1 (C_{34}), 52.9 (OCH_3), 44.9 (C_{33}), 38.7 (C_{37}), 38.1 (C_{35}), 33.4 (C_{38}), 31.3 (C_{42}), 27.2 (C_{41}), 25.9 (TBS), 18.2 (TBS), 13.5 (C_{35}-CH_3), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}$=3051, 2930, 1740, 1591, 1490, 1461, 1416, 1266, 1201, 1106 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{31}O_5SSi$: 423.1661; found: 423.1680 $[M-t\mathrm{Bu}]^+$.

To a solution of the thionocarbonate prepared above (2.10 g, 4.37 mmol) and AIBN (cat.) in PhH (80 mL) was added tri-*n*-butyltin hydride (2.35 mL, 8.75 mmol), and the mixture heated to reflux. After 30 min, the reaction was allowed to cool to RT and quenched by the addition of CCl_4. The mixture was stirred for 10 min, then concentrated in vacuo. The residue was dissolved in EtOAc, and saturated aqueous KF added. The resulting biphasic mixture was stirred vigorously for 45 min, then filtered. The layers were separated, and the organic phase washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (0–5% Et_2O/petrol) to afford the deoxygenated epoxide **6** as a colourless oil (1.23 g, 86%). R_f=0.48 (10% EtOAc/petrol); $[\alpha]_D^{25}$=−21.0 (c=0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.39 (s, 3H, OCH_3), 3.38 (m, 1H, H_{39}), 2.89 (ddd, including J=8.8, 2.0 Hz, 1H, H_{40}), 2.67 (m, 2H, 2×H_{33}), 2.45 (ddd, J=2.8, 5.0, 6.1 Hz, 1H, H_{34}), 2.02 (ddd, J=2.0, 2.1, 9.0 Hz, 1H, H_{38}), 1.82 (m, 1H, H_{35}), 1.67 (m, 1H, H_{41}), 1.48 (m, 1H, H_{42}), 1.45–1.35 (m, 3H, H_{36}, H_{37}, H_{41}), 1.22 (m, 1H, H_{36}), 0.91 (m, 1H, H_{42}), 0.90 (d, J=6.7 Hz, 3H, C_{35}-CH_3), 0.88 (s, 9H, TBS), 0.83 (m, 1H, H_{38}), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=84.5 (C_{39}), 75.7 (C_{40}), 58.0 (C_{34}), 57.2 (OCH_3), 45.5 (C_{33}), 41.7 (C_{36}), 36.6 (C_{38}), 33.9 (C_{41}), 33.5 (C_{37}), 33.2 (C_{35}), 31.3 (C_{42}), 25.9 (TBS), 18.2 (TBS), 16.1 (C_{35}-CH_3), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}$=2927, 2855, 1460, 1386, 1359, 1251, 1190, 1145, 1110, 1078, 924, 875, 834, 775 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{36}O_3Si$: 328.2434; found: 328.2405 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{36}O_3Si$: C 65.80, H 11.04; found: C 68.99, H 11.07.

Dithiane 73: To a cooled (−78°C) solution of oxalyl chloride (5.23 mL, 60.2 mmol) in CH_2Cl_2 (200 mL) was added DMSO (10.6 mL, 150 mmol) dropwise over 20 min. After addition was complete, the reaction was stirred for 30 min before adding trityl alcohol **72**[89] (10.0 g, 30.1 mmol) as a pre-cooled (−78°C) solution in CH_2Cl_2 (40+20 mL) via cannula over 20 min. The reaction was stirred for 30 min, then DIPEA (21 mL, 120 mmol) was added by syringe over 15 min. After a further 30 min at −78°C, the cooling bath was removed and the reaction vessel allowed to warm to RT. After 20 min at RT, the reaction was quenched by addition of aqueous pH 7 phosphate buffer solution and diluted with CH_2Cl_2. The organic layer was separated, and washed sequentially with saturated aqueous NH_4Cl (× 2) and pH 7 phosphate buffer solution, then dried over $MgSO_4$ and concentrated in vacuo. The bulk of the crude aldehyde product was used directly in the next reaction without further purification (purity >95%). A small sample was purified by rapid flash chromatography (10% EtOAc/hexanes) to afford the desired product as a white solid. R_f=0.64 (30% Et_2O/petrol); m.p. 84–86°C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ=9.60 (d, J=1.2 Hz, 1H, CHO), 7.34 (d, J=7.8 Hz, 6H, ArH), 7.22 (t, J=7.8 Hz, 6H, ArH), 7.16 (t, J=7.2 Hz, 3H, ArH), 3.29 (dd, J=9.0, 4.8 Hz, 1H, H_{30}), 3.26 (dd, J=9.0, 6.6 Hz, 1H, H_{30}), 2.56–2.49 (m, 1H, H_{31}), 1.04 ppm (d, J=6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=204.3 (C_{32}), 143.9 (Ar), 129.8 (Ar), 128.1 (Ar), 127.3 (Ar), 86.9 (C(Ph)$_3$), 63.9 (C_{30}), 47.3 (C_{31}), 11.0 ppm (CH_3); IR (thin film): $\tilde{\nu}$=3025, 2874, 1724, 1490, 1448, 1069, 1035 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{23}H_{22}O_2Na$: 353.1517; found: 353.1530 $[M+\mathrm{Na}]^+$.

To a cooled solution (−78°C) of freshly prepared aldehyde (≈30.1 mmol) in CH_2Cl_2 (150 mL) was added 1,3-propanedithiol (6.02 mL, 60.2 mmol), followed by BF_3·OEt_2 (7.61 mL, 60.2 mmol) dropwise. The reaction was stirred for 30 min at −78°C, then warmed to RT and stirred for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the biphasic mixture stirred until CO_2 evolution ceased. After extraction with CH_2Cl_2 (×3), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (10–100% Et_2O/petrol) to afford dithiane **73** as a light yellow oil (5.30 g, 99% over 2 steps). R_f=0.14 (40% Et_2O/petrol); $[\alpha]_D^{25}$=−5.0 (c=1.80, $CHCl_3$) [ref. [90]=−4.8 (c=1.00, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 600 MHz): δ=4.29 (d, J=4.9 Hz, 1H, H_{32}), 3.68 (m, 2H, 2×H_{30}), 2.92–2.85 (m, 4H, dithiane), 2.10 (m, 2H, H_{31} and dithiane), 1.86 (m, 2H, C_{30}-OH, dithiane), 1.09 ppm (d, J=7.0 Hz, 3H, C_{31}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=65.2 (C_{30}), 51.8 (C_{32}), 40.7 (C_{31}), 30.9 (dithiane), 30.6 (dithiane), 26.2 (dithiane), 14.1 ppm (C_{31}-CH_3); IR (thin film): $\tilde{\nu}$=3388, 2931, 2894, 1455, 1422, 1380, 1275, 1243, 1187, 1033, 985, 907, 874, 767 cm^{-1}; HMRS (ESI): m/z: calcd for $C_7H_{14}OS_2Na$: 201.0384; found: 201.0380 $[M+\mathrm{Na}]^+$.

Dithiane aldehyde 74: A solution of SO_3·Py (5.36 g, 33.6 mmol) in DMSO (35+5 mL) was added to a cooled (0°C) solution of **73** (2.0 g, 11.2 mmol) in CH_2Cl_2 (70 mL) via cannula. The reaction was left for 90 min then quenched with a solution of aqueous pH 7 phosphate buffer and diluted with Et_2O. The organic layer was separated, then washed sequentially with saturated aqueous $CuSO_4$ (×2), saturated aqueous NH_4Cl, and again with pH 7 phosphate buffer. The separate aqueous washes were back-extracted individually with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product **74** appeared as a light yellow oil (2.00 g, 99%) and was used directly in the subsequent reaction without further purification (purity >95%). R_f=0.35 (40% Et_2O/petrol); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=9.70 (d, J=1.5 Hz, 1H, H_{30}), 4.40 (d, J=5.9 Hz, 1H, H_{32}), 2.89 (m, 4H, dithiane), 2.73 (m, 1H, H_{31}), 2.12 (m, 1H, dithiane), 1.89 (m, 1H, dithiane), 1.28 ppm (d, J=7.1 Hz, 3H, C_{31}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=201.5 (C_{30}), 50.7 (C_{31}), 48.5 (C_{32}), 30.6 (dithiane), 30.5 (dithiane), 25.8 (dithiane), 11.8 ppm (C_{31}-CH_3); IR (thin film): $\tilde{\nu}$=2899, 1720, 1660, 1580, 1421, 1276, 1184, 907, 767 cm^{-1}; HMRS (ESI): m/z: calcd for $C_7H_{12}OS_2Na$: 199.0227; found: 199.0233 $[M+\mathrm{Na}]^+$. NMR and IR data were consistent with those previously reported for the (31*R*)-enantiomer.[91]

Bromoolefin 76: KHMDS (0.5 M in $PhCH_3$, 33.6 mL, 16.8 mmol) was added to a stirred solution of methyl P,P-bis(2,2,2-trifluoroethyl)phosphonoacetate (3.56 mL, 16.8 mmol) in THF (250 mL) immersed in a H_2O bath at RT. After 15 min, Br_2 (1.72 mL, 33.6 mmol) was added dropwise, and the mixture stirred for 10 min. To this was added a pre-mixed solution (5 min at RT, then 15 min −45°C) of [18]crown-6 (9.76 g, 37.0 mmol) and KHMDS (33.6 mL, 16.8 mmol) in THF (30 + 10 mL) via cannula. After 30 min at RT, the reaction mixture was cooled to −45°C and the freshly prepared aldehyde **74** (≈11.2 mmol) was added as a solution in THF (20+10 mL) via cannula. Stirring was continued for 18 h at −45°C, then the solution was diluted with Et_2O and poured into a 1:1 mixture of saturated aqueous NH_4Cl and saturated aqueous $Na_2S_2O_3$. The organic phase was separated, and the aqueous layer back-extracted with Et_2O (× 2). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue was purified by flash chromatography (10–20% Et_2O/petrol) to afford the desired trisubstituted olefin **76** as a light yellow oil (3.36 g, 96%). R_f=0.42 (40% Et_2O/petrol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=6.67 (d, J=10.4 Hz, 1H, H_{30}), 4.00 (d, J=6.4 Hz, 1H, H_{32}), 3.81 (s, 3H, CO_2Me), 3.63 (ddq, J=10.4, 6.4, 6.8 Hz, 1H, H_{31}), 2.88–2.80 (m, 4H, dithiane), 2.12–2.03 (m, 1H, dithiane), 1.92–1.79 (m, 1H, dithiane), 1.23 ppm (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=163.2 (CO), 149.8 (C_{30}), 111.5 (C_{29}), 53.2 (CO_2CH_3), 52.8 (C_{32}), 40.5 (C_{31}), 30.4 (dithiane), 30.2 (dithiane), 26.0 (dithiane), 17.7 ppm (CH_3); IR (thin film): $\tilde{\nu}$=2898, 1716, 1434, 1351, 1230, 1172, 1106, 960 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{10}H_{15}BrO_2S_2$: 328.0037; found: 328.0037 $[M+\mathrm{H}]^+$.

Allylic alcohol 77: To a cooled (−78°C) solution of ester **76** (3.35 g, 10.8 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (1.0 M in CH_2Cl_2,

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32.3 mL, 32.3 mmol) over 10 min. The resulting mixture was stirred for 2 h at −78 °C, then warmed to 0 °C. After 30 min, an equal volume of saturated aqueous Rochelle's salts was added, and the biphasic mixture stirred vigorously for 14 h. The reaction mixture was then diluted with CH_2Cl_2, the organic phase separated, and the aqueous layer back-extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography (30–50 % Et_2O/petrol) to afford allylic alcohol **77** as a colourless oil (2.93 g, 96 %). R_f = 0.14 (40 % Et_2O/petrol); $[\alpha]_D^{25}$ = +64.3 (c = 3.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.91 (d, J = 10.2 Hz, 1H, H_{30}), 4.29 (dd, J = 13.2, 5.4 Hz, 1H, C_{29}-CH_2OH), 4.21 (dd, J = 13.8, 7.8 Hz, 1H, C_{29}-CH_2OH), 3.92 (d, J = 6.6 Hz, 1H, H_{32}), 2.85–2.74 (m, 5H, H_{31}, dithiane), 2.04–1.97 (m, 2H, OH and dithiane), 1.82–1.73 (m, 1H, dithiane), 1.14 ppm (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 136.5 (C_{30}), 125.9 (C_{29}), 63.3 (C_{29}-CH_2OH), 53.1 (C_{32}), 39.8 (C_{31}), 30.8 (dithiane), 30.6 (dithiane), 25.9 (dithiane), 18.8 ppm (CH_3); IR (thin film): $\tilde{\nu}$ = 3385, 2898, 1640, 1450, 1421, 1375, 1275, 1183, 1145, 1037, 970, 907, 874, 772 cm^{-1}; HMRS (ESI): m/z: calcd for $C_9H_{15}BrOS_2$: 304.9640; found: 304.9640 $[M+H]^+$.

Allylic bromide 78: To a cooled (0 °C) solution of **77** (1.00 g, 3.53 mmol) in CH_2Cl_2 (20 mL) was added sequentially DMAP (43 mg, 0.35 mmol), Et_3N (1.47 mL, 10.6 mmol), and MsCl (0.68 mL, 1.48 mmol). After 1 h, DMF (20 mL) and LiBr (3.07 g, 35.3 mmol) were added, then the cooling bath removed and the reaction mixture allowed to warm to RT where it was stirred for 14 h. The reaction mixture was diluted with Et_2O/petrol 1:1, washed with saturated aqueous NH_4Cl (×3), and the aqueous layers back-extracted with Et_2O/petrol (1:1). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography (10 % EtOAc/hexanes) to afford allylic bromide **78** as a colourless oil (884 mg, 72 %). R_f = 0.51 (10 % Et_2O/petrol); $[\alpha]_D^{25}$ = +25.7 (c = 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.08 (d, J = 10.5 Hz, 1H, H_{30}), 4.44 (d, J = 12.4 Hz, 1H, C_{29}-CH_2Br), 4.24 (d, J = 12.4 Hz, 1H, C_{29}-CH_2Br), 4.02 (d, J = 6.6 Hz, 1H, H_{32}), 2.87–2.80 (m, 5H, H_{31}, dithiane), 2.16–2.09 (m, 1H, dithiane), 1.87–1.83 (m, 1H, dithiane), 1.23 ppm (d, J = 5.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 139.5 (C_{30}), 120.4 (C_{29}), 53.1 (C_{32}), 45.6 (C_{29}-CH_2Br), 40.2 (C_{31}), 30.9 (dithiane), 30.7 (dithiane), 25.7 (dithiane), 18.3 ppm (CH_3); IR (thin film): $\tilde{\nu}$ = 3399, 2903, 1637, 1421, 1255, 1180, 1003, 952, 907, 857, 814, 772, 722 cm^{-1}; HMRS (EI): m/z: calcd for $C_9H_{14}S_2Br_2$: 345.8883; found: 345.8888 $[M]^+$.

Vinyl bromide 69: To a cooled (0 °C) solution of **78** (750 mg, 2.17 mmol) in THF (20 mL) was added $LiEt_3BH$ (1.0 M in THF, 10.8 mL, 10.8 mmol). After 2 h the reaction was quenched by the addition of an equal volume of saturated aqueous Rochelle's salts, and the resulting mixture stirred for 1 h. Et_2O was added, and the organic phase separated. The aqueous layer was back-extracted with Et_2O, and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (0–10 % Et_2O/petrol) to afford the desired vinyl bromide intermediate **69** as a colourless oil (540 mg, 99 %). R_f = 0.59 (10 % Et_2O/petrol); $[\alpha]_D^{25}$ = +70.6 (c = 0.53, $CHCl_3$);^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.82 (d, J = 10.2 Hz, 1H, H_{30}), 4.00 (d, J = 6.6 Hz, 1H, H_{32}), 2.88–2.80 (m, 4H, dithiane), 2.70 (ddq, J = 10.2, 6.6, 6.6 Hz, H_{31}), 2.24 (s, 3H, C_{29}-CH_3), 2.11–2.05 (m, 1H, dithiane), 1.86–1.77 (m, 1H, dithiane), 1.16 ppm (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 134.0 (C_{30}), 120.9 (C_{29}), 54.0 (C_{32}), 39.9 (C_{31}), 30.9 (dithiane), 30.7 (dithiane), 26.1 (dithiane), 23.9 (C_{29}-CH_3), 18.2 ppm (CH_3); IR (thin film): $\tilde{\nu}$ = 2925, 2898, 1696, 1649, 1599, 1421, 1378, 1275, 1094, 1035, 907, 851, 771 cm^{-1}; HMRS (ESI): m/z: calcd for $C_9H_{15}BrS_2$: 265.9793; found: 265.9792 $[M]^+$.

Aldehyde 87: To a cooled solution of alcohol **38** (see Supporting Information) (4.00 g, 22.9 mmol) in CH_2Cl_2 (125 mL) was added DIPEA (16.0 mL, 91.8 mmol) via syringe. A solution of SO_3·Py (11.0 g, 68.9 mmol) in DMSO (50+10 mL) was then introduced via cannula, and stirring continued for 90 min. The reaction was quenched by the addition of an equal volume of aqueous pH 7 phosphate buffer, and diluted with Et_2O. The organic phase was separated, and washed sequentially with saturated aqueous $CuSO_4$, saturated aqueous NH_4Cl and aqueous pH 7 phosphate buffer. The separate aqueous layers were then back-extracted individually with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford aldehyde **87** as a light yellow oil which was used immediately in the subsequent reaction without further purification (yield ≈99 %, purity > 95 %). The observed analytical data was identical in all respects to that reported previously for the preparation of **87** en route to **39** (see Supporting Information).

Diol 90: To a cooled (−78 °C) solution of allyl methyl ether (3.54 mL, 37.8 mmol) in THF (50 mL) was added *s*BuLi (1.1 M in cyclohexane, 30.9 mL, 34.4 mmol) dropwise over 15 min. The resulting bright yellow solution was stirred for 15 min, then (−)-Ipc_2BOMe (11.2 g, 35.5 mmol) was added as a solution in THF (50+10 mL) via cannula. After 1 h BF_3·OEt_2 (5.63 mL, 45.8 mmol) was introduced dropwise, followed immediately by a solution of freshly prepared aldehyde **87** (≈22.9 mmol) in THF (20+10 mL) via cannula. The reaction mixture was stirred at −78 °C for 14 h, then aqueous NaOH (1.0 N) was added followed by 30 % H_2O_2. The biphasic mixture was allowed to warm slowly to RT. After stirring for 14 h, the mixture was diluted with Et_2O, and the organic layer was separated, washed with saturated aqueous NH_4Cl (×2), then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was used directly without further purification as the desired product was not readily separable from the pinenol produced during the work-up.

The concentrated reaction mixture was diluted with MeOH (65 mL), and K_2CO_3 (12.7 g, 91.6 mmol) was added. After 24 h the solvent was removed in vacuo. The residue was taken up in a mixture of H_2O and EtOAc and the organic layer isolated. The aqueous layer was back-extracted with EtOAc (×3), and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (50–80 % Et_2O/petrol) to afford the desired diol **90** as a viscous colourless oil (1.96 g, 40 % over 2 steps). R_f = 0.19 (80 % Et_2O/petrol); $[\alpha]_D^{25}$ = −4.3 (c = 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.66 (ddd, J = 17.4, 10.2, 8.4 Hz, 1H, H_{28}), 5.33 (d, J = 10.2 Hz, 1H, H_{29}), 5.30 (d, J = 17.4 Hz, 1H, H_{29}), 3.54 (t, J = 7.2 Hz, 1H, H_{27}), 3.51 (dd, J = 10.8, 4.2 Hz, 1H, H_{22}), 3.37 (dd, J = 10.8, 6.6 Hz, 1H, H_{22}), 3.31–3.29 (m, 1H, H_{26}), 3.29 (s, 3H, C_{27}-OCH_3), 2.16 (2H, br s, 2×OH), 1.73–1.65 (m, 2H, H_{25}, $H2_2$), 1.52 (ddd, J = 14.1, 9.0, 3.6 Hz, 1H, H_{24}), 1.07 (ddd, J = 14.1, 9.6, 4.8 Hz, 1H, H_{24}), 0.99 (d, J = 6.6 Hz, 3H, CH_3), 0.96 ppm (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 135.5 (C_{28}), 119.8 (C_{29}), 84.3 (C_{27}), 78.4 (C_{25}), 67.3 (C_{22}), 56.5 (C_{27}-OCH_3), 34.8 (C_{24}), 33.5 (C_{23}), 32.6 (C_{26}), 18.7 (CH_3), 17.9 ppm (CH_3); IR (thin film): $\tilde{\nu}$ = 3387, 2925, 1459, 1093, 975, 928 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{11}H_{22}O_3Na$: 225.1467; found: 225.1457 $[M+Na]^+$.

For the purpose of characterisation, a small amount of C22 acetate was prepared as follows: To a cooled (0 °C) solution of **90** (100 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added DMAP (6.0 mg, 0.05 mmol), Et_3N (136 μL, 0.98 mmol) and Ac_2O (69 μL, 0.74 mmol). After 1 h, the reaction was quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was separated, and the aqueous phase back-extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (15–40 % EtOAc/hexanes) gave the desired C22 acetate as a colourless oil (99 mg, 83 %). R_f = 0.43 (30 % EtOAc/hexanes); $[\alpha]_D^{25}$ = +25.9 (c = 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.57 (ddd, J = 18.0, 10.4, 8.4 Hz, 1H, H_{28}), 5.26 (d, J = 10.4 Hz, 1H, H_{29}), 5.22 (d, J = 17.2 Hz, 1H, H_{29}), 3.92 (dd, J = 10.8, 4.8 Hz, 1H, H_{22}), 3.69 (dd, J = 10.8, 6.8 Hz, 1H, H_{22}), 3.45 (t, J = 7.2 Hz, 1H, H_{27}), 3.26–3.20 (m, 1H, H_{26}), 3.23 (s, 3H, C_{27}-OCH_3), 2.52 (d, J = 3.2 Hz, 1H, OH), 1.97 (s, 3H, Ac-CH_3), 1.85–1.75 (m, 1H, H_{23}), 1.71–1.58 (m, 1H, H_{25}), 1.42 (ddd, J = 13.6, 9.6, 3.6 Hz, 1H, H_{24}), 1.09 (ddd, J = 14.8, 10.4, 4.8 Hz, 1H, H_{24}), 0.94 (d, J = 6.8 Hz, 3H, CH_3), 0.90 ppm (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.4 (Ac-CO), 135.3 (C_{28}), 119.9 (C_{29}), 84.4 (C_{27}), 78.2 (C_{26}), 68.8 (C_{22}), 56.4 (C_{27}-OCH_3), 34.7 (C_{25}), 32.3 (C_{26}), 30.3 (C_{23}), 21.1 (Ac-CH_3), 18.9 (CH_3), 17.6 ppm (CH_3); IR (thin film): $\tilde{\nu}$ = 3506, 2934, 1735, 1371, 1235, 1092, 1035, 988 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{13}H_{24}O_4Na$: 267.1572; found: 267.1576 $[M+Na]^+$.

To determine the relative configuration of **90**, the bis-*para*-nitrobenzoate ester was prepared as follows: To a cooled (0 °C) solution of **90** (100 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added DMAP (18.0 mg, 0.15 mmol),

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Et_3N (271 μL, 1.96 mmol), and *p*-nitrobenzoyl chloride (275 mg, 1.48 mmol). After 30 min, the reaction mixture was warmed to RT, and stirred for 6 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and diluted with Et_2O. The organic layer was separated, and washed sequentially with saturated aqueous NH_4Cl and with saturated aqueous $NaHCO_3$ (×2), then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (10–30% EtOAc/hexanes) to afford the bis-*para*-nitrobenzoate as a viscous colourless oil (231 mg, 95%). This material could be crystallised by the slow evaporation of an Et_2O/hexanes solution, and X-ray analysis confirmed the stereochemical assignment as shown in **90**.[68] R_f=0.54 (30% EtOAc/hexanes); m.p. 100–102°C; $[\alpha]_D^{25}$=+8.5 (c=1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.18–8.00 (m, 8H, ArH), 5.57 (ddd, J=17.2, 10.4, 7.2 Hz, 1H, H_{28}), 5.22 (d, J=17.2 Hz, 1H, H_{29}), 5.17 (d, J=10.4 Hz, 1H, H_{29}), 5.03 (t, J=5.6 Hz, 1H, H_{26}), 4.19 (dd, J=10.8, 4.8 Hz, 1H, H_{22}), 4.04 (dd, J=10.8, 6.4 Hz, 1H, H_{22}), 3.79 (d, J=5.6 Hz, 1H, H_{27}), 3.19 (s, 3H, C_{27}-OCH_3), 2.20–2.10 (m, 1H, H_{25}), 2.06–1.96 (m, 1H, H_{23}), 1.56 (ddd, J=13.6, 9.6, 3.6 Hz, 1H, H_{24}), 1.16 (ddd, J=14.4, 10.4, 4.8 Hz, 1H, H_{24}), 1.01 (d, J=6.8 Hz, 3H, CH_3), 1.00 ppm (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=164.7 (CO), 164.6 (CO), 150.7 (Ar), 150.6 (Ar), 135.71 (Ar), 135.69 (Ar), 134.2 (C_{28}), 130.9 (Ar), 130.7 (Ar), 123.62 (Ar), 123.60 (Ar), 119.7 (C_{29}), 82.1 (C_{27}), 80.7 (C_{26}), 69.8 (C_{22}), 56.9 (OCH_3), 36.3 (C_{24}), 31.8 (C_{25}), 30.4 (C_{23}), 18.9 (CH_3), 16.9 ppm (CH_3); IR (thin film): $\tilde{\nu}$=2965, 1723, 1527, 1347, 1268, 1241, 1100 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{25}H_{28}N_2O_9Na$: 523.1693; found: 523.1711 $[M+Na]^+$.

Bis-PMB aldehyde 91: To a cooled (0°C) solution of **90** (380 mg, 1.87 mmol) in DMF (20 mL) was added NaH (60% dispersion in oil, 225 mg, 5.64 mmol) and the resulting mixture stirred for 30 min. TBAI (69.0 mg, 0.19 mmol) and PMBCl (0.77 mL, 5.64 mmol) were then introduced, and the reaction stirred for 1 h at 0°C, and for 48 h at RT. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with Et_2O/petrol (1:1, ×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (30→50% EtOAc/hexanes) gave the desired bis-PMB ether as a colourless oil (825 mg, 99%). R_f=0.62 (100% Et_2O); $[\alpha]_D^{25}$=+13.9 (c=1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.28 (d, J=8.4 Hz, 2H, ArH), 7.24 (d, J=8.4 Hz, 2H, ArH), 6.86 (t, J=8.4 Hz, 4H, ArH), 5.73 (ddd, J=17.4, 10.2, 7.8 Hz, 1H, H_{28}), 5.24 (d, J=17.4 Hz, 1H, H_{29}), 5.22 (d, J=10.2 Hz, 1H, H_{29}), 4.72 (d, J=11.4 Hz, 1H, Ar -CH_2), 4.50 (d, J=11.4 Hz, 1H, Ar -CH_2), 4.40 (d, J=11.4 Hz, 1H, Ar -CH_2), 4.38 (d, J=11.4 Hz, 1H, Ar -CH_2), 3.79 (s, 3H, Ar -OCH_3), 3.78 (s, 3H, Ar -OCH_3), 3.70 (t, J=7.0 Hz, 1H, H_{27}), 3.33 (dd, J=9.0, 4.8 Hz, 1H, H_{22}), 3.29 (s, 3H, OCH_3), 3.16 (dd, J=6.0, 4.8 Hz, 1H, H_{26}), 3.09 (dd, J=9.0, 7.8 Hz, 1H, H_{22}), 1.85–1.76 (m, 2H, H_2, H_{25}), 1.48 (ddd, J=13.8, 9.6, 3.6 Hz, 1H, H_{24}), 1.07 (ddd, J=14.4, 10.2, 4.2 Hz, 1H, H_{24}), 0.96 (d, J=7.2 Hz, 3H, CH_3), 0.95 ppm (d, J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=159.2 (2×Ar), 136.0 (C_{28}), 131.6 (Ar), 131.1 (Ar), 129.6 (Ar), 129.2 (Ar), 118.1 (C_{29}), 113.8 (Ar), 113.7 (Ar), 86.4 (C_{26}), 85.4 (C_{27}), 75.2 (C_{22}), 74.7 (Ar -CH_2), 72.8 (Ar -CH_2), 56.7 (C_{27}-OCH_3), 55.4 (2× Ar -OCH_3), 35.9 (C_{24}), 32.6 (C_{23}), 31.2 (C_{25}), 19.4 (CH_3), 17.6 ppm (CH_3); IR (thin film): $\tilde{\nu}$=2931, 2874, 1612, 1586, 1512, 1462, 1359, 1301, 1244, 1171, 1079, 1034, 928, 818, 756, 709 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{27}H_{38}O_5Na$: 465.2617; found: 465.2626 $[M+Na]^+$.

To a solution of the alkene prepared above (700 mg, 1.58 mmol) in acetone (28 mL) and H_2O (14 mL) was added NMO (251 mg, 2.13 mmol) and then OsO_4 (2.5% in *t*BuOH, 0.98 mL). After stirring for 16 h, the reaction was quenched by the addition of solid Na_2SO_3, and stirred for a further 2 h. The mixture was then diluted with H_2O and extracted with CH_2Cl_2 (×4). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo, and the crude residue purified by flash chromatography (50% EtOAc/hexanes) to afford the desired diol as a colourless oil and as a single diastereoisomer by NMR (590 mg, 78%). R_f=0.09 (50% EtOAc/hexanes); $[\alpha]_D^{25}$=+3.4 (c=1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.18 (m, 4H, 4×ArH), 6.78 (m, 4H, 4×ArH), 4.47 (s, 2H, Ar-CH_2), 4.34 (d, J=2.4 Hz, 2H, Ar-CH_2), 3.72 (m, 7H, H_{28}, 2×Ar-OCH_3), 3.59 (s, 2H, C_{28}-CH_2OH), 3.43–3.31 [m, 5H, including 3.38 (s, 3H, C_{27}-OCH_3), H_{27}, H_{26}], 3.23 (dd, J=5.2, 9.1 Hz, 1H, H_{22}), 3.15 (dd, J=6.3, 9.0 Hz, 1H, H_{22}), 2.95 (brs, 1H, OH), 2.13 (brs, 1H, OH), 1.88 (m, 1H, H_{23}), 1.76 (m, 1H, H_{25}), 1.54 (m, 1H, H_{24}), 1.03–087 [m, 7H, including 0.93 (d, J=6.8 Hz, 3H, C_{25}-CH_3), 0.89 ppm (d, J=6.7 Hz, 3H, C_{23}-CH_3), H_{24}); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=159.4 (Ar), 159.1 (Ar), 130.8 (Ar), 130.2 (Ar), 129.7 (Ar), 129.1 (Ar), 113.8 (Ar), 113.7 (Ar), 82.5 (C_{26}), 81.6 (C_{27}), 75.1 (C_{22}), 73.0 (Ar-CH_2), 72.7 (Ar-CH_2), 71.2 (C_{28}), 63.7 (C_{28}-CH_2OH), 59.7 (C_{27}-OCH_3), 55.3 (Ar-OCH_3), 55.2 (Ar-OCH_3), 37.0 (C_{24}), 31.9 (C_{23}), 31.0 (C_{25}), 19.0 (C_{23}-CH_3), 15.2 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu}$=3418, 2933, 1612, 1586, 1512, 1461, 1360, 1301, 1245, 1173, 1064, 1032, 967, 818, 757, 734, 708 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{27}H_{41}O_7$: 477.2852; found: 477.2866 $[M+H]^+$.

To a solution of the diol prepared above (274 mg, 0.58 mmol; azeotroped with PhH and dried in vacuo prior to use) in PhH (5 mL) at 0°C was added $Pb(OAc)_4$ (331 mg, 0.75 mmol). The cooling bath was removed, and the reaction allowed to warm to RT. After stirring for 1 h, it was filtered through a pad of Celite, and the organic filtrate washed with saturated aqueous $NaHCO_3$ and with aqueous pH 7 phosphate buffer, then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was azeotroped with PhH and dried in vacuo to afford the desired aldehyde **91** as a colourless oil (260 mg, 99%) that was used directly in the subsequent reaction without further purification (purity >95%). R_f=0.46 (50% EtOAc/hexanes); H NMR ($CDCl_3$, 600 MHz): δ=9.78 (d, J=1.4 Hz, 1H, CHO), 7.33 (m, 2H, 2×ArH), 7.24 (m, 2H, 2×ArH), 6.89 (m, 2H, 2×ArH), 6.86 (d, J=8.5 Hz, 2H, 2×ArH), 4.57 (d, J=10.9 Hz, 1H, Ar-CH_2), 4.51 (d, J=10.9 Hz, Ar-CH_2), 4.40 (d, J=4.5 Hz, 2H, 2× Ar-CH_2), 3.63 (d, J=1.1 Hz, 1H, H_{27}), 3.59 (m, 1H, H_{26}), 3.40 (s, 3H, Ar-OCH_3), 3.38 (s, 3H, Ar-OCH_3), 3.33 (m, 1H, H_{22}), 3.27 (m, 1H, H_{22}), 3.19 (s, 3H, C_{27}-OCH_3), 2.18 (m, 1H, H_{25}), 1.92 (m, 1H, H_{23}), 1.88 (m, 1H, H_{24}), 1.49 (m, 1H, H_{24}), 1.10 (d, J=6.6 Hz, C_{25}-CH_3), 1.03 ppm (d, J=6.8 Hz, C_{23}-CH_3); HRMS (ESI): m/z: calcd for $C_{26}H_{36}O_6Na$: 467.2410; found: 467.2412 $[M+Na]^+$.

PMB-aldehyde 92: To a cooled (0°C) solution of acetate **38** (see Supporting Information) (12.3 g, 70.5 mmol) in CH_2Cl_2 (200 mL) was added imidazole (9.60 g, 141 mmol) and TBSCl (11.7 g, 77.6 mmol). The heterogeneous mixture was stirred for 4 h, then an equal volume of saturated aqueous NH_4Cl was added and the reaction contents diluted with Et_2O. The layers were separated and the aqueous layer back-extracted with Et_2O (×2). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. A small amount of the crude material was purified by flash chromatography (20–40% Et_2O/petrol) to facilitate characterisation, affording the desired TBS ether as a colourless oil. The remainder of the material was used directly in the subsequent reaction without further purification (purity >95%). R_f=0.69 (70% Et_2O/petrol); $[\alpha]_D^{25}$=+5.4 (c=2.30, $CHCl_3$) [ref. [92]=+5.6 (c=0.24, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=3.92 (dd, J=10.0, 5.6 Hz, 1H, H_{22}), 3.78 (dd, J=10.8, 6.8 Hz, 1H, H_{22}), 3.39 (dd, J=10.0, 5.6 Hz, 1H, H_{26}), 3.33 (dd, J=9.6, 6.0 Hz, 1H, H_{26}), 2.00 (s, 3H, Ac-CH_3), 1.92–1.90 (m, 1H, H_{23}), 1.71–1.60 (m, 1H, H_{25}), 1.42 (ddd, J=13.6, 6.8, 6.8 Hz, 1H, H_{24}), 0.94–0.84 [m, 16H, including; 0.91 (d, J=6.8 Hz, 3H, H_{23}-CH_3), 0.86 (d, J=6.8 Hz, 3H, H_{25}-CH_3), 0.86 (s, 9H, TBS), H_{24}], 0.00 ppm (s, 6H, TBS); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=171.2 (Ac-CO), 69.5 (C_{22}), 68.2 (C_{26}), 37.6 (C_{24}), 33.3 (C_{25}), 30.3 (C_{23}), 26.1 (TBS), 21.0 (Ac-CH_3), 18.4 (TBS), 18.0 (C_{23}-CH_3), 17.7 (C_{25}-CH_3), −5.3 (TBS), −5.27 ppm (TBS); IR (thin film): $\tilde{\nu}$=2956, 1741, 1467, 1365, 1236, 1093, 1035, 835, 774 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{15}H_{32}O_3SiNa$: 311.2018; found: 311.2007 $[M+Na]^+$. The observed data was consistent with that previously reported.[92]

The crude mixture consisting primarily of freshly prepared TBS ether (≈70.5 mmol) was taken up in MeOH (250 mL) and solid K_2CO_3 (29.2 g, 212 mmol) was added. After 2 h, Et_2O was added, and the mixture washed with saturated aqueous NH_4Cl (×2). The aqueous layers were back-extracted with Et_2O (×2), and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (30–40% Et_2O/petrol) to afford the desired deacetylated product as a colourless oil (16.9 g, 98% over 2 steps). R_f=0.50 (70% Et_2O/petrol); $[\alpha]_D^{25}$=−1.7 (c=5.40, $CHCl_3$) [lit.[93]=−1.3 (c=1.40, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=3.49 (dd, J=10.4, 5.2 Hz, 1H, H_{22}), 3.43 (dd, J=9.6, 5.6 Hz, 1H, H_{26}), 3.40 (dd, J=10.4, 6.4 Hz, 1H, H_{26}), 3.36 (dd, J=10.0, 6.4 Hz, 1H, H_{22}), 1.77–1.65 (m, 2H, H_{23}, H_{25}), 1.64 (s, 1H, C_{22}-OH), 1.43 (ddd, J=13.6, 6.8, 6.8 Hz, H_{24}), 0.96–0.87 [m, 16H,

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including; 0.94 (d, $J=6.8$ Hz, 3H, C_{23}-CH_3), 0.89 (d, $J=6.8$ Hz, 3H, C_{25}-CH_3), 0.89 (s, 9H, C_{26}-OSiC(CH_3)$_3$), H_{24}], 0.04 ppm (s, 6H, 2×C_{26}-OSiCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=68.5$ (C_{26}), 68.4 (C_{22}), 37.5 (C_{24}), 33.5 (C_{23}), 33.5 (C_{25}), 26.2 (TBS), 18.6 (TBS), 18.0 (C_{25}-CH_3), 17.9 (C_{23}-CH_3), −5.2 ppm (TBS); IR (thin film): $\tilde{\nu}=3336$, 2955, 1463, 1251, 1092, 834, 773 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{13}H_{31}O_2Si$: 247.2093; found: 247.2085 $[M+H]^+$. The observed data was consistent with that previously reported.[93]

To a cooled (0 °C) solution of the revealed primary alcohol (16.9 g, 69.1 mmol) in DMF (60 mL) was added NaH (60% dispersion in oil, 4.16 g, 103 mmol) portionwise. When the addition was complete, the reaction was stirred for 30 min, then TBAI (1.28 g, 3.46 mmol) and PMBCl (13.9 mL, 103 mmol) were introduced. The cooling bath was removed, and the reaction allowed to warm to RT and stirred for 14 h. The reaction was quenched by the careful addition of H_2O, then diluted with petrol. The organic layer was separated, and the aqueous layer back-extracted with petrol (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography (20% Et_2O/petrol) to afford the desired TBS/PMB ether as a colourless oil (25.3 g, 99%). $R_f=0.70$ (40% Et_2O/petrol); $[\alpha]_D^{25}=+2.2$ ($c=1.07$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.22$ (d, $J=8.4$ Hz, 2H, ArH), 6.83 (d, $J=8.4$ Hz, 2H, ArH), 4.40 (d, $J=11.6$ Hz, 1H, Ar-CH_2), 4.37 (d, $J=12.0$ Hz, 1H, Ar-CH_2), 3.74 (s, 3H, Ar-OCH_3), 3.44 (dd, $J=10.0$, 5.6 Hz, 1H, H_{26}), 3.30 (dd, $J=9.6$, 6.4 Hz, 1H, H_{22}), 3.29 (dd, $J=9.2$, 5.2 Hz, 1H, H_{26}), 3.14 (dd, $J=8.8$, 7.2 Hz, 1H, H_{22}), 1.90–1.77 (m, 1H, H_{23}), 1.72–1.61 (m, 1H, H_{25}), 1.41 (ddd, $J=13.6$, 6.8, 6.8 Hz, 1H, H_{24}), 0.93 (d, $J=6.8$ Hz, 3H, C_{23}-CH_3), 0.90–0.84 [m, 13H, including; 0.88 (s, 9H, C_{26}-OSiC(CH_3)$_3$), 0.88 (d, $J=6.8$ Hz, 3H, C_{25}-CH_3), H_{24}], 0.04 ppm (s, 6H, 2×C_{26}-OSiCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=159.2$ (Ar), 131.1 (Ar), 129.1 (Ar), 113.9 (Ar), 76.0 (C_{22}), 72.8 (Ar-CH_2), 68.4 (C_{26}), 55.3 (Ar-OCH_3), 38.0 (C_{24}), 33.4 (C_{25}), 31.2 (C_{23}), 26.1 (TBS), 18.5 (TBS), 18.4 (C_{23}-CH_3), 17.9 (C_{25}-CH_3), −5.2 ppm (TBS); IR (thin film): $\tilde{\nu}=2925$, 1614, 1513, 1423, 1248, 1092, 835, 774 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{21}H_{38}O_3SiNa$: 389.2488; found: 389.2500 $[M+Na]^+$.

To a cooled (0 °C) solution of the TBS/PMB ether as prepared above (25.0 g, 68.1 mmol) in THF (200 mL) was added TBAF (1.0 M in THF, 71.5 mL, 71.5 mmol), and the resulting mixture allowed to warm to RT and stirred for 18 h. H_2O and Et_2O were then added, the organic layer separated, and the aqueous phase back-extracted with Et_2O (×2). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography (20–40% Et_2O/petrol) to afford the PMB alcohol as a light yellow oil (15.9 g, 93%). $R_f=0.31$ (70% Et_2O/petrol); $[\alpha]_D^{25}=+7.0$ ($c=2.46$, $CHCl_3$) [ref. [94] $=+2.5$ ($c=2.97$, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.25$ (d, $J=8.8$ Hz, 2H, ArH), 6.88 (d, $J=8.4$ Hz, 2H, ArH), 4.44 (d, $J=12.3$ Hz, 1H, Ar-CH_2), 4.41 (d, $J=12.8$ Hz, 1H, Ar-CH_2), 3.80 (s, 3H, Ar-OCH_3), 3.52–3.44 (m, 1H, H_{26}), 3.44–3.35 (m, 1H, H_{26}), 3.29 (dd, $J=8.8$, 6.0 Hz, 1H, H_{22}), 3.22 (dd, $J=8.8$, 6.8 Hz, 1H, H_{22}), 1.90–1.80 (m, 1H, H_{25}), 1.76–1.62 (m, 2H, H_{23}), 1.47 (ddd, $J=13.6$, 6.4, 6.4 Hz, 1H, H_{24}), 1.00–0.89 [m, 7H, including; 0.95 (d, $J=6.4$ Hz, 3H, C_{23}-CH_3), 0.95 ppm (d, $J=6.4$ Hz, 3H, C_{23}-CH_3), H_{24}]; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=159.3$ (Ar), 131.0 (Ar), 129.4 (Ar), 114.0 (Ar), 75.8 (C_{22}), 72.9 (Ar-CH_2), 68.2 (C_{26}), 55.5 (Ar-OCH_3), 37.9 (C_{24}), 33.5 (C_{23}), 31.3 (C_{25}), 18.4 (C_{25}-CH_3), 17.8 ppm (C_{23}-CH_3); IR (thin film): $\tilde{\nu}=3403$, 2911, 1612, 1512, 1461, 1245, 1088, 1034, 819 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{15}H_{24}O_3Na$: 275.1623; found: 275.1616 $[M+Na]^+$; HPLC [Chiralcel OD, hexanes/*i*PrOH 97:3, 1.0 mL min^{-1}, 25 °C], t_R^1 (major) = 18.4 min, t_R^2 (minor) = 20.2 min; *ee* 96.8%. The observed data was consistent with that previously reported.[94]

To confirm the HPLC retention times, a racemic sample of the mono-PMB alcohol above was prepared as follows: To a solution of *meso*-2,4-dimethylpentane-1,5-diol (prepared by the reduction of **37** (220 mg, 1.66 mmol, see Supporting Information) in DMF (3 mL) was added NaH (60% dispersion in oil, 66 mg, 1.66 mmol). After 30 min, TBAI (63 mg, 0.17 mmol) and PMBCl (225 μL, 1.66 mmol) were added, and the reaction mixture stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with 1:1 Et_2O/petrol. The organic layer was separated, and washed with saturated aqueous NH_4Cl (×2), then dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (50–60% Et_2O/petrol) gave the racemic PMB-alcohol as a light yellow oil (361 mg, 86%). The observed analytical data was identical in all respects (aside from optical rotation) to that reported above.

To a cooled (0 °C) solution of the C22-PMB ether prepared above (5.00 g, 19.8 mmol) in CH_2Cl_2 (150 mL) was added DIPEA (13.8 mL, 79.2 mmol) via syringe. A solution of SO_3·Py (9.46 g, 59.4 mmol) in DMSO (50+10 mL) was then introduced via cannula, and stirred for 1 h 30 min. The reaction mixture was diluted with an equal volume of aqueous pH 7 phosphate buffer and Et_2O, and the organic layer separated. This was washed sequentially with saturated aqueous $CuSO_4$, saturated aqueous NH_4Cl, and aqueous pH 7 phosphate buffer. The separate aqueous layers were back-extracted individually with Et_2O, and the combined organic extracts then washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the desired product aldehyde **92** as a light yellow oil that was used directly in the subsequent reaction without further purification (≈99%, purity >95%). $R_f=0.38$ (10% Et_2O/petrol); $[\alpha]_D^{25}=-7.4$ ($c=1.00$, $CHCl_3$) [ref. [95] $=-6.7$ ($c=1.02$, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=9.56$ (d, $J=2.4$ Hz, 1H, H_{26}), 7.24 (d, $J=8.4$ Hz, 2H, ArH), 6.87 (d, $J=8.4$ Hz, 2H, ArH), 4.40 (s, 2H, 2×Ar-CH_2), 3.79 (s, 3H, Ar-OCH_3), 3.26 (d, $J=6.0$ Hz, 2H, 2×<z_{22}), 2.48–2.42 (m, 1H, H_{25}), 1.91–1.85 (m, 1H, H_{24}), 1.86–1.80 (m, 1H, H_{23}), 1.18–1.12 (m, 1H, H_{24}), 1.08 (d, $J=7.2$ Hz, 3H, C_{25}-CH_3), 0.94 ppm (d, $J=6.6$ Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=205.2$ (C_{26}), 159.3 (Ar), 130.8 (Ar), 129.2 (Ar), 113.8 (Ar), 75.2 (C_{22}), 72.8 (Ar-CH_2), 55.4 (Ar-OCH_3), 44.3 (C_{25}), 35.2 (C_{24}), 31.4 (C_{23}), 17.7 (C_{23}-CH_3), 14.5 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu}=2961$, 1721, 1612, 1512, 1245, 1086, 1034, 818 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{15}H_{22}O_3Na$: 273.1467; found: 273.1473 $[M+Na]^+$. The observed data was consistent with that previously reported.[95]

PMB–BDA adduct 95: LiHMDS (1.0 M in THF, 13.1 mL, 13.1 mmol) was added portionwise to a solution of (*R*,*R*)-BDA glycolate **93**[96] (2.26 g, 11.9 mmol) in THF (120 mL) at −78 °C, After a further 5 min, a solution of aldehyde **92** (3.00 g, 11.2 mmol) in THF (15 mL) was added dropwise over 10 min and the mixture left stirring for 10 min. The reaction was quenched at −78 °C with AcOH (1.40 mL, 24.4 mmol), then allowed to warm to RT before diluting with Et_2O. The mixture was filtered through a pad of silica (eluting with EtOAc), then concentrated in vacuo. Purification of the crude residue by flash chromatography (10–25% Et_2O/petrol) afforded BDA aldol adduct **95** as a colourless oil (4.83 g, 92%). $R_f=0.25$ (50% Et_2O/petrol); $[\alpha]_D^{25}=-69.5$ ($c=0.98$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=7.28$–7.24 (m, 2H, ArH), 6.88–6.85 (m, 2H, ArH), 4.43 (s, 2H, 2×Ar-CH_2), 4.16 (d, $J=5.9$ Hz, 1H, H_{27}), 3.80 (s, 3H, Ar-OCH_3), 3.69 (t, $J=5.7$ Hz, 1H, H_{26}), 3.43–3.39 [m, 4H, including; 3.42 (s, 3H, BDA-OCH_3), H_{22}], 3.31 (s, 3H, BDA-OCH_3), 3.21 (dd, $J=9.1$, 7.3 Hz, H_{22}), 2.10–2.02 (m, 1H, H_{25}), 1.94–1.87 (m, 1H, H_{23}), 1.60–1.53 (m, 1H, H_{24}), 1.49 (s, 3H, BDA-CH_3), 1.39 (s, 3H, BDA-CH_3), 1.06–1.00 (m, 1H, H_{24}), 0.98 (d, $J=6.7$ Hz, 3H, CH_3), 0.96 ppm (d, 3H, $J=6.7$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=169.3$ (C_{28}), 159.0 (Ar), 131.0 (Ar), 129.1 (Ar), 113.7 (Ar), 105.0 (BDA), 98.0 (BDA), 75.3 (C_{22}), 74.8 (C_{26}), 72.6 (Ar-CH_2), 71.7 (C_{27}), 55.2 (Ar-OCH_3), 50.2 (BDA-OCH_3), 49.2 (BDA-OCH_3), 37.4 (C_{24}), 30.9 (C_{25}), 30.8 (C_{23}), 18.4 (C_{23}-CH_3), 17.8 (BDA-CH_3), 16.9 (BDA-CH_3), 14.5 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu}=3511$, 2955, 2841, 1753, 1613, 1586, 1513, 1462, 1379, 1301, 1246, 1219, 1148, 1117, 1097, 1034, 992, 969, 916, 861, 821, 758 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{23}H_{36}O_8Na$: 463.2308; found: 465.2300 $[M+Na]^+$; elemental analysis calcd (%) for $C_{23}H_{36}O_8$: C 62.71, H 8.24; found: C 62.81, H 8.15.

bis-PMB–BDA adduct 96: Trityl tetrafluoroborate (41.0 mg, 0.13 mmol) was added to a solution of alcohol **95** (1.10 g, 2.50 mmol) and PMBTCA (2.12 g, 7.50 mmol) in THF (20 mL) at RT. After stirring for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with saturated aqueous NH_4Cl and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (0–10% EtOAc/PhCH_3) allowed the recovery of starting alcohol **95**

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(490 mg, 45%), and a second purification of the remaining mixture by flash chromatography (0–25% Et_2O/petrol) afforded bis-PMB ether **96** as a pale orange oil (665 mg, 47%). $R_f = 0.36$ (50% Et_2O/petrol); $[\alpha]_D^{25} = -106.8$ ($c = 0.37$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 7.29$–7.22 (m, 4H, ArH), 6.87–6.82 (m, 4H, ArH), 4.66 (d, $J = 11.3$ Hz, 1H, Ar-CH_2), 4.46 (d, $J = 11.3$ Hz, 1H, Ar-CH_2), 4.39 (d, $J = 5.2$ Hz, 2H, 2×Ar-CH_2), 4.36 (d, $J = 3.7$ Hz, 1H, H_{27}), 3.79 (s, 3H, Ar-OCH_3), 3.78 (s, 3H, Ar-OCH_3), 3.71 (t, $J = 4.1$ Hz, 1H, H_{26}), 3.33 (s, 3H, BDA-OCH_3), 3.28–3.24 [m, 4H, including; 3.26 (s, 3H, Ar-OCH_3), H_{22}], 3.12 (dd, $J = 9.0$, 7.2 Hz, 1H, H_{22}), 1.99–1.93 (m, 1H, H_{25}), 1.82–1.75 (m, 1H, H_{23}), 1.49–1.41 [m, 4H, including; 1.47 (s, 3H, BDA-CH_3), H_{24}], 1.39 (s, 3H, BDA-CH_3), 1.01 (d, $J = 6.7$ Hz, 3H, C_{25}-CH_3), 0.94–0.88 [m, 4H, including; 0.90 ppm (d, $J = 6.6$ Hz, 3H, C_{23}-CH_3), H_{24}]; ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 167.9$ (C_{28}), 159.1 (Ar), 159.0 (Ar), 131.0 (Ar), 130.6 (Ar), 129.7 (Ar), 129.1 (Ar), 113.7 (Ar), 113.6 (Ar), 105.1 (BDA), 98.3 (BDA), 81.8 (C_{26}), 75.3 (C_{22}), 73.2 (Ar-CH_2), 72.6 (Ar-CH_2), 71.7 (C_{27}), 55.2 (Ar-OCH_3), 49.7 (BDA-OCH_3), 49.0 (BDA-OCH_3), 38.5 (C_{24}), 32.4 (C_{25}), 30.8 (C_{23}), 17.9 (BDA-CH_3), 17.9 (C_{23}-CH_3), 17.0 (BDA-CH_3), 15.7 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu} = 2930$, 2103, 1752, 1613, 1586, 1513, 1462, 1379, 1302, 1248, 1172, 1147, 1103, 1035, 969, 824 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{31}H_{44}O_9Na$: 583.2883; found: 583.2867 $[M+Na]^+$.

Methyl ester 97: (±)-CSA (1.73 g, 7.40 mmol) was added to a solution of BDA-adduct **96** (3.76 g, 6.70 mmol) in MeOH (67 mL) at RT. After stirring for 14 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and Et_2O was added. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (33–50% Et_2O/petrol) afforded α-hydroxyester **97** as a colourless oil (2.48 g, 80%). $R_f = 0.21$ (50% Et_2O/petrol); $[\alpha]_D^{25} = +9.8$ ($c = 0.31$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 7.23$ (m, 4H, ArH), 6.85 (m, 4H, ArH), 4.50 (dd, $J = 28.4$, 11.0 Hz, 2H, 2×Ar-CH_2), 4.41 (d, $J = 3.5$ Hz, 2H, 2×Ar-CH_2), 4.35 (dd, $J = 6.5$, 5.2 Hz, 1H, H_{27}), 3.79 (s, 6H, 2×Ar-OCH_3), 3.74 (s, 3H, C_{28}-OCH_3), 3.46 (t, $J = 4.9$ Hz, H_{26}), 3.26 (dd, $J = 9.0$, 5.4 Hz, 1H, H_{22}), 3.19 (dd, $J = 9.0$, 6.6 Hz, 1H, H_{22}), 2.81 (d, $J = 6.7$ Hz, C_{27}-OH), 1.93 (m, 1H, H_{25}), 1.85–1.77 (m, 1H, H_{23}), 1.53 (td, $J = 13.5$, 6.7 Hz, 1H, H_{24}), 0.99 (d, $J = 6.8$ Hz, 3H, C_{25}-CH_3), 0.96 (m, 1H, H_{24}), 0.93 ppm (d, $J = 6.7$ Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 174.1$ (C_{28}), 159.2 (Ar), 159.0 (Ar), 130.8 (Ar), 130.4 (Ar), 129.4 (Ar), 129.0 (Ar), 113.7 (Ar), 113.7 (Ar), 83.6 (C_{26}), 75.2 (C_{22}), 73.7 (Ar-CH_2), 72.7 (Ar-CH_2), 71.9 (C_{27}), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 52.4 (C_{28}-OCH_3), 38.1 (C_{24}), 32.2 (C_{25}), 31.0 (C_{23}), 18.1 (C_{23}-CH_3), 15.6 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu} =$ 3462, 2955, 2857, 1736, 1612, 1586, 1513, 1463, 1441, 1361, 1301, 1246, 1173, 1084, 1033, 973, 820, 758 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{26}H_{36}O_7Na$: 483.2359; found: 483.2367 $[M+Na]^+$.

Methyl ether 98: Iodomethane (2.16 mL, 34.7 mmol) was added to a tube containing alcohol **97** (800 mg, 1.74 mmol), freshly-prepared Ag_2O (1.21 g, 5.20 mmol) and CH_2Cl_2 (4 mL). The tube was sealed, and heated at 50 °C for 18 h. After cooling to RT, the reaction mixture was filtered through a pad of Celite (washing with CH_2Cl_2), and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–50% Et_2O/petrol) gave, in order of elution, methyl ether **98** as a colourless oil (614 mg, 74%), along with recovered starting alcohol **97** (193 mg, 24%). $R_f = 0.49$ (50% Et_2O/petrol); $[\alpha]_D^{25} = -41.0$ ($c = 0.30$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 7.25$–7.22 (m, 2H, ArH), 7.18 (d, $J =$ 8.5 Hz, 2H, ArH), 6.85–6.81 (m, 4H, ArH), 4.45 (s, 2H, 2×Ar-CH_2), 4.41 (d, $J = 1.1$ Hz, 2H, 2×Ar-CH_2), 3.86 (d, $J = 7.0$ Hz, 1H, H_{27}), 3.79 (s, 3H, Ar-OCH_3), 3.78 (s, 3H, Ar-OCH_3), 3.72 (s, 3H, C_{28}-OCH_3), 3.58 (dd, $J =$ 6.9, 3.3 Hz, 1H, H_{26}), 3.36 (s, 3H, C_{27}-OCH_3), 3.27 (dd, $J = 9.0$, 5.6 Hz, 1H, H_{22}), 3.20 (dd, $J = 9.0$, 6.6 Hz, 1H, H_{22}), 1.99–1.93 (m, 1H, H_{25}), 1.89–1.82 (m, 1H, H_{23}), 1.58 (td, $J = 13.6$, 6.8 Hz, 1H, H_{24}), 1.00 (td, $J = 17.3$, 5.3 Hz, 1H, H_{24}), 0.96–0.92 ppm (m, 6H, C_{25}-CH_3, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 172.4$ (C_{28}), 159.1 (Ar), 159.0 (Ar), 130.9 (Ar), 130.6 (Ar), 129.4 (Ar), 129.0 (Ar), 113.7 (Ar), 113.6 (Ar), 82.0 (C_{26}), 81.9 (C_{27}), 75.5 (C_{22}), 73.9 (Ar-CH_2), 72.7 (Ar-CH_2), 58.2 (C_{27}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 51.8 (C_{28}-OCH_3), 38.2 (C_{24}), 32.0 (C_{25}), 31.0 (C_{23}), 18.0 (C_{23}-CH_3), 15.0 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu} = 2933$, 2836, 1743, 1612, 1586, 1512, 1462, 1442, 1399, 1358, 1301, 1245, 1200, 1172, 1110, 1088, 1033, 819, 755, 710 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{27}H_{38}O_7Na$: 497.2515; found: 497.2540 $[M+Na]^+$.

Weinreb amide 99: LiHMDS (1.0 M in THF, 5.50 mL, 5.50 mmol) was added dropwise over ca. 10 min to a stirred mixture of ester **98** (530 mg, 1.11 mmol) and MeO(Me)NH·HCl (272 mg, 2.79 mmol) in THF (15 mL) at −20 °C. After addition was complete, the reaction was stirred at −20 °C for 20 min, and at −10 °C for a further 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl and diluted with Et_2O. After warming to RT, the organic layer was separated and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with H_2O and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (50–67% Et_2O/petrol) afforded Weinreb amide **99** as a colourless oil (543 mg, 97%). $R_f = 0.09$ (50% Et_2O/petrol); $[\alpha]_D^{25} = -16.2$ ($c = 1.90$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 7.23$ (d, $J = 8.5$ Hz, 2H, ArH), 7.15 (d, $J = 8.5$ Hz, 2H, ArH), 6.84–6.78 (m, 4H, ArH), 4.45–4.34 (m, 5H, 2×Ar-CH_2, 2×Ar-CH_2, H_{27}), 3.78 (s, 3H, Ar-OCH_3), 3.77 (s, 3H, Ar-OCH_3), 3.70 (dd, $J = 8.8$, 1.8 Hz, 1H, H_{26}), 3.56 (s, 3H, C_{28}-$NOCH_3$), 3.32 (s, 3H, C_{27}-CH_3), 3.27 (dd, $J = 9.0$, 5.9 Hz, 1H, H_{22}), 3.23–3.17 [m, 4H, including; 3.21 (s, 3H, C_{28}-NCH_3), H_{22}], 2.05–1.97 (m, 1H, H_{25}), 1.93–1.86 (m, 1H, H_{23}), 1.60 (td, $J = 13.7$, 7.0 Hz, 1H, H_{24}), 1.09–1.03 (m, 1H, H_{24}), 0.96 (d, $J = 6.7$ Hz, 3H, C_{25}-CH_3), 0.94 ppm (d, $J = 6.6$ Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 172.8$ (C_{28}), 159.0 (Ar), 159.0 (Ar), 131.0 (Ar), 130.9 (Ar), 129.5 (Ar), 129.0 (Ar), 113.7 (Ar), 113.4 (Ar), 81.2 (C_{26}), 76.1 (C_{27}), 75.8 (C_{22}), 74.3 (Ar-CH_2), 72.6 (Ar-CH_2), 61.3 (C_{28}-$NOCH_3$), 57.4 (C_{27}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 38.4 (C_{24}), 32.0 (C_{28}-NCH_3), 31.7 (C_{25}), 30.9 (C_{23}), 17.8 (C_{23}-CH_3), 14.5 ppm (C_{25}-CH_3); IR (thin film): $\tilde{\nu} = 2934$, 2874, 2308, 1662, 1612, 1586, 1513, 1462, 1388, 1301, 1245, 1173, 1109, 1078, 1033, 995, 958, 818, 758, 715, 635, 575 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{27}H_{38}NO_7Na$: 497.2515; found: 497.2540 $[M+Na]^+$.

Diastereoisomeric alcohols 105 and 106: Vinyl bromide **69** (307 mg, 1.15 mmol) was azeotroped with PhH (×2) and dried in vacuo for 2 h. THF (3 mL) was added, and the solution cooled to −100 °C (N_2/Et_2O). To this was added *t*BuLi (1.8 M in hexanes, 1.28 mmol, 2.30 mmol) over 3 min, during which time the solution turned dark yellow/orange. The reaction mixture was stirred for 10 min, after which the freshly prepared and dried aldehyde **91** (256 mg, ≈0.58 mmol) was introduced as a solution in THF (1+1 mL) via cannula. Stirring was continued for 1 h at −100 °C, and then for 1 h at −78 °C before an equal volume of saturated aqueous NH_4Cl was added and the resulting mixture allowed to warm to RT. The mixture was diluted with Et_2O, and the organic layer separated. The aqueous phase was back-extracted with Et_2O (×2), and the combined organic extracts washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude residue by flash chromatography (10–30% EtOAc/hexanes) gave the coupled product as a 3:1 mixture of partially separable diastereoisomers **105** and **106** in favour of the undesired C28 epimer **105** (254 mg overall, 70%). A small amount of this major diastereoisomer was separated for characterisation purposes whilst the remainder of the mixture was used directly in the next step without further purification (purity >95%).

Data for the major diastereoisomer **105**: $R_f = 0.17$ (30% EtOAc/hexanes); $[\alpha]_D^{25} = +8.4$ ($c = 0.72$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta =$ 7.27 (d, $J = 9.0$ Hz, 2H, ArH), 7.22 (d, $J = 8.4$ Hz, 2H, ArH), 6.86 (d, $J =$ 8.4 Hz, ArH), 6.85 (d, $J = 8.4$ Hz, 2H, ArH), 5.43 (d, $J = 9.6$ Hz, 1H, H_{30}), 4.61 (d, $J = 10.8$ Hz, 1H, Ar-CH_2), 4.50 (d, $J = 10.8$ Hz, 1H, Ar-CH_2), 4.39 (s, 2H, 2×Ar-CH_2), 4.02 (d, $J = 6.6$ Hz, 1H, H_{32}), 5.98 (br d, 6.0 Hz, 1H, H_{28}), 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 3.50 (s, 3H, C_{27}-OCH_3), 3.37–3.34 (m, 2H, H_{27}, H_{26}), 3.29 (dd, $J = 9.0$, 4.8 Hz, 1H, H_{22}), 3.16 (dd, $J = 8.4$, 6.0 Hz, 1H, H_{22}), 2.90–2.73 (m, 5H, H_{31}, dithiane), 2.63 (d, $J = 6.6$ Hz, 1H, C_{28}-OH), 2.12–2.04 (m, 1H, dithiane), 1.92–1.85 (m, 1H, H_{25}), 1.85–1.76 (m, 2H, H_{23}, dithiane), 1.62 (s, 3H, C_{29}-CH_3), 1.46 (ddd, $J = 13.8$, 10.2, 4.8 Hz, 1H, H_{24}), 1.15 (ddd, $J = 13.8$, 10.2, 4.8 Hz, 1H, H_{24}), 1.11 (d, $J = 7.2$ Hz, 3H, H_{31}-CH_3), 1.00 (d, $J = 6.6$ Hz, 3H, C_{25}-CH_3), 0.96 ppm (d, $J = 6.6$ Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta =$ 159.3 (Ar), 159.3 (Ar), 136.0 (C_{29}), 131.5 (Ar), 131.0 (Ar), 129.8 (Ar), 129.3 (Ar), 128.5 (C_{30}), 113.9 (2×Ar), 84.1 and 82.8 (C_{26} and C_{27}), 75.7 (C_{28}), 75.0 (C_{22}), 74.3 (Ar-CH_2), 73.0 (Ar-CH_2), 61.2 (C_{27}-OCH_3), 55.5

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(2× Ar-OCH_3), 55.0 (C_{32}), 37.7 (C_{31}), 35.8 (C_{24}), 32.3 (C_{25}), 31.1 (C_{23}), 31.1 (dithiane), 30.9 (dithiane), 26.3 (dithiane), 19.3 (C_{25}-CH_3), 18.5 (C_{31}-CH_3), 17.4 (C_{22}-CH_3), 13.6 ppm (C_{29}-CH_3); IR (thin film): $\tilde{\nu}$ = 3486, 2957, 1612, 1512, 1245, 1070, 1034, 818 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{35}H_{53}O_6S_2$: 633.3284; found: 633.3289 $[M+H]^+$.

For data related to **106**, see below.

Dithiane 107: A solution of the diastereoisomeric mixture of alcohols (**105/106** 3:1, 176 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this was added a pre-mixed solution of SO_3·Py (132 mg, 0.83 mmol) and DIPEA (194 μL, 1.11 mmol) in DMSO (2+1 mL) via cannula. After 1 h an equal volume of aqueous pH 7 phosphate buffer was added, and the reaction mixture diluted with Et_2O. The organic phase was washed with aqueous pH 7 phosphate buffer, saturated aqueous $CuSO_4$, saturated aqueous NH_4Cl and once more with aqueous pH 7 phosphate buffer. The separate aqueous layers were then back-extracted individually with Et_2O, and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20% EtOAc/hexanes) gave the C28-enone as a colourless oil (170 mg, 97%). R_f = 0.26 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = +24.3 (*c* = 2.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24 (d, *J* = 8.8 Hz, 2H, ArH), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 6.85 (d, *J* = 8.8 Hz, 2H, ArH), 6.80 (d, *J* = 8.4 Hz, 2H, ArH), 6.66 (d, *J* = 8.8 Hz, 1H, H_{30}), 4.53 (d, *J* = 3.6 Hz, 1H, H_{27}), 4.42 (d, *J* = 11.6 Hz, 1H, Ar-CH_2), 4.38 (s, 2H, 2× Ar-CH_2), 4.37 (d, *J* = 11.2 Hz, 1H, Ar-CH_2), 4.08 (d, *J* = 6.4 Hz, 1H, H_{32}), 3.80–3.74 [m, 7H, including; 3.79 (s, 3H, Ar-OCH_3), 3.77 (s, 3H, Ar-OCH_3), H_{26}], 3.37–3.30 [m, 4H, including; 3.36 (s, 3H, C_{27}-OCH_3), H_{22})], 3.12 (dd, *J* = 8.8, 7.2 Hz, 1H, H_{22}), 3.01–2.91 (m, 1H, H_{31}), 2.86–2.79 (m, 4H, dithiane), 2.13–2.04 (m, 1H, dithiane), 2.01–1.90 (m, 1H, H_{25}), 1.90–1.77 [m, 5H, including; 1.82 (s, 3H, C_{29}-CH_3), dithiane, H_{23}], 1.63–1.54 (m, 1H, H_{24}), 1.16 (d, *J* = 6.8 Hz, 3H, C_{31}-CH_3), 1.05–0.91 [m, 7H, including; 0.99 (d, *J* = 6.8 Hz, 3H, C_{25}-CH_3), 0.94 ppm (d, *J* = 6.4 Hz, 3H, C_{23}-CH_3), H_{24}]; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.6 (C_{28}), 159.2 (2× Ar), 143.9 (C_{30}), 136.9 (C_{29}), 131.2 (Ar), 131.1 (Ar), 129.8 (Ar), 129.3 (Ar), 113.9 (Ar), 113.7 (Ar), 84.6 (C_{27}), 84.3 (C_{26}), 75.6 (C_{22}), 73.0 (Ar-CH_2), 72.9 (Ar-CH_2), 58.7 (C_{27}-OCH_3), 55.5 (2× Ar-OCH_3), 53.8 (C_{32}), 38.7 (C_{31}), 37.5 (C_{24}), 32.7 (C_{25}), 31.3 (C_{23}), 30.7 (dithiane), 30.6 (dithiane), 26.2 (dithiane), 19.3 (C_{25}-CH_3), 17.6 (C_{31}-CH_3), 17.0 (C_{23}-CH_3), 12.3 ppm (C_{29}-CH_3); IR (thin film): $\tilde{\nu}$ = 2929, 1684, 1612, 1513, 1245, 1071, 1034, 819 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{35}H_{50}O_6S_2Na$: 653.2947; found: 653.2942 $[M+Na]^+$.

To a cooled (0 °C) suspension of $NaBH_4$ (378 mg, 10.0 mmol) in Et_2O (5 mL) was added $ZnCl_2$ (1.0 M in Et_2O, 5.0 mL, 5.0 mmol) over 5 min. The ice bath was removed and the reaction warmed to RT where it was stirred vigorously for 60 h. Stirring was discontinued to allow the salts to settle, to afford an ethereal solution of $Zn(BH_4)_2$ (theoretical molarity = 0.5 M).

To a cooled (−20 °C) solution of the enone prepared above (175 mg, 0.28 mmol) in Et_2O (4 mL) was added a freshly prepared solution of $Zn(BH_4)_2$ (0.5 M in Et_2O, 2.5 mL, 1.25 mmol), and the reaction mixture stirred for 18 h at −20 °C. An additional portion of $Zn(BH_4)_2$ (1.5 mL, 0.75 mmol) was added, and stirring continued for 24 h. The reaction mixture was then warmed to 0 °C, and an equal volume of saturated aqueous NH_4Cl added carefully. The biphasic mixture was stirred for 30 min at 0 °C, then 6 h at RT before dilution with Et_2O. The organic layer was separated, and washed with saturated aqueous NH_4Cl and with saturated aqueous $NaHCO_3$. The separate aqueous layers were extracted individually with Et_2O, and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (10–20% EtOAc/hexanes) gave the desired alcohol **106** as a colourless oil (140 mg, 80%). R_f = 0.22 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = +9.2 (*c* = 2.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.28 (d, *J* = 8.4 Hz, 2H, ArH), 7.24 (d, *J* = 8.4 Hz, 2H, ArH), 6.86 (d, *J* = 8.4 Hz, 2H, ArH), 6.85 (d, *J* = 8.4 Hz, 2H, ArH), 5.54 (d, *J* = 9.6 Hz, 1H, H_{30}), 4.51 (d, *J* = 11.4 Hz, 1H, Ar-CH_2), 4.49 (d, *J* = 11.4 Hz, 1H, Ar-CH_2), 4.42 (d, *J* = 11.4 Hz, 1H, Ar-CH_2), 4.40 (d, *J* = 11.4 Hz, 1H, Ar-CH_2), 4.24 (t, *J* = 3.2 Hz, 1H, H_{28}), 4.01 (d, *J* = 7.2 Hz, 1H, H_{32}), 3.79 (s, 6H, 2× Ar-OCH_3), 3.44–3.41 [m, 4H, including; 3.43 (s, 3H, C_{27}-OCH_3), H_{26}), 3.35 (t, *J* = 4.2 Hz, 1H, H_{27}), 3.30 (dd, *J* = 9.0, 5.4 Hz, 1H, H_{22}), 3.19 (dd, *J* = 8.4, 6.6 Hz, 1H, H_{22}), 3.12 (d, *J* = 5.4 Hz, 1H, C_{28}-OH), 2.87–2.77 (m, 5H, H_{31}, dithiane), 2.11–2.05 (m, 1H, dithiane), 2.01–1.94 (m, 1H, H_{25}), 1.87–1.75 (m, 2H, H_{23}, dithiane), 1.66 (s, 3H, C_{29}-CH_3), 1.49 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1H, H_{24}), 1.14 (d, *J* = 7.2 Hz, 3H, C_{31}-CH_3), 1.03 (ddd, *J* = 14.4, 9.0, 6.0 Hz, 1H, H_{24}), 0.99 (d, *J* = 6.6 Hz, 3H, C_{25}-CH_3), 0.95 ppm (d, *J* = 6.6 Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.5 (Ar), 159.3 (Ar), 135.9 (C_{29}), 131.1 (Ar), 130.8 (Ar), 130.1 (Ar), 129.7 (C_{30}), 129.3 (Ar), 114.0 (Ar), 113.9 (Ar), 81.7 (C_{27} and C_{26}), 75.6 (C_{28}), 75.3 (C_{22}), 73.0 (Ar-CH_2), 72.8 (Ar-CH_2), 59.0 (C_{27}-OCH_3), 55.5 (Ar-OCH_3), 55.48 (Ar-OCH_3), 54.9 (C_{32}), 37.6 (C_{31}), 37.2 (C_{24}), 31.8 (C_{25}), 31.2 (C_{23}), 31.1 (dithiane), 30.9 (dithiane), 26.3 (dithiane), 19.0 (C_{25}-CH_3), 18.6 (C_{31}-CH_3), 16.8 (C_{23}-CH_3), 14.0 ppm (C_{29}-CH_3); IR (thin film): $\tilde{\nu}$ = 2931, 1613, 1514, 1459, 1248, 1174, 1082 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{35}H_{53}O_6S_2$: 633.3284; found: 633.3273 $[M+H]^+$.

To a cooled (−78 °C) solution of **106** (130 mg, 206 μmol) in CH_2Cl_2 was added 2,6-lutidine (96.0 μL, 823 μmol) followed by TESOTf (70.0 μL, 309 μmol). After 40 min, an equal volume of saturated aqueous $NaHCO_3$ was added, and the reaction mixture allowed to warm to RT. Et_2O was added, and the organic layer separated and washed sequentially with saturated aqueous $NaHCO_3$, saturated aqueous $CuSO_4$, and saturated aqueous NH_4Cl. The separate aqueous layers were back-extracted individually with Et_2O, and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (5–10% EtOAc/hexanes) gave TES ether **107** as a light yellow oil (152 mg, 99%). R_f = 0.58 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = +22.7 (*c* = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.29 (d, *J* = 8.4 Hz, 2H, ArH), 7.25 (d, *J* = 8.4 Hz, 2H, ArH), 6.86 (d, *J* = 9.0 Hz, 2H, ArH), 6.85 (d, *J* = 9.0 Hz, 2H, ArH), 5.35 (d, *J* = 9.6 Hz, 1H, H_{30}), 4.68 (d, *J* = 10.8 Hz, 1H, Ar-CH_2), 4.47 (d, *J* = 11.4 Hz, 1H, Ar-CH_2), 4.44 (s, 2H, 2× Ar-CH_2), 4.10 (d, *J* = 5.4 Hz, 1H, H_{28}), 3.99 (d, *J* = 6.6 Hz, 1H, H_{32}), 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 3.48 (s, 3H, C_{27}-OCH_3), 3.41–3.35 (m, 2H, H_{26}, H_{22}), 3.33 (t, *J* = 5.4 Hz, 1H, H_{27}), 3.15 (dd, *J* = 8.4, 7.8 Hz, 1H, H_{22}), 2.87–2.77 (m, 5H, H_{31}, dithiane), 2.10–2.03 (m, 1H, dithiane), 1.92–1.78 (m, 3H, H_{25}, H_{23}, dithiane), 1.72 (s, 3H, C_{29}-CH_3), 1.45–1.39 (m, 1H, H_{24}), 1.20–1.12 [m, 4H, including; 1.14 (d, *J* = 6.6 Hz, 3H, C_{31}-CH_3), H_{24}], 0.97 (d, *J* = 6.6 Hz, 3H, C_{23}-CH_3), 0.96 (d, *J* = 6.6 Hz, 3H, C_{25}-CH_3), 0.93 (t, *J* = 7.8 Hz, 9H, TES), 0.56 ppm (q, *J* = 7.8 Hz, 6H, TES); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.2 (Ar), 159.1 (Ar), 137.1 (C_{29}), 132.2 (Ar), 131.2 (Ar), 130.6 (C_{30}), 129.5 (Ar), 129.1 (Ar), 113.9 (Ar), 113.7 (Ar), 85.3 (C_{27}), 83.1 (C_{26}), 78.4 (C_{28}), 75.3 (C_{22}), 74.1 (Ar-CH_2), 72.8 (Ar-CH_2), 60.8 (C_{27}-OCH_3), 55.4 (2× Ar-OCH_3), 55.1 (C_{32}), 37.6 (C_{31}), 35.8 (C_{24}), 32.5 (C_{25}), 31.0 (2× dithiane), 30.9 (C_{23}), 26.3 (dithiane), 19.4 (C_{23}-CH_3), 18.0 (C_{31}-CH_3), 17.4 (C_{25}-CH_3), 13.3 (C_{29}-CH_3), 7.2 (TES), 5.2 ppm (TES); IR (thin film): $\tilde{\nu}$ = 2955, 1612, 1513, 1459, 1245, 1036, 819 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{41}H_{67}O_6S_2SiNa$: 747.4148; found: 747.4151 $[M+Na]^+$.

Enone 108: *t*BuLi (1.75 M in pentane, 1.82 mL, 3.19 mmol) was added carefully to a solution of vinyl bromide **69** (425 mg, 1.59 mmol; azeotroped with PhH and dried in vacuo prior to reaction) in THF (20 mL) at −100 °C. After addition was complete, the intense yellow solution was stirred for a further 15 min. A solution of Weinreb amide **99** (400 mg, 0.79 mmol, azeotroped with PhH and dried in vacuo prior to reaction) in THF (8 mL) was then added dropwise over ca. 3 min. Stirring was continued at −100 °C for 15 min, and at −78 °C for 1 h 30 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and diluted with Et_2O. After warming to RT, the organic layer was separated and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (10–35% Et_2O/petrol) afforded enone **108** as a colourless oil (399 mg, 80%). R_f = 0.40 (50% Et_2O/petrol); $[\alpha]_D^{25}$ = +10.0 (*c* = 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.22 (d, *J* = 8.5 Hz, 2H ArH), 7.13 (d, *J* = 8.5 Hz, 2H, ArH), 6.84–6.79 (m, 4H, ArH), 6.77 (d, *J* = 9.9 Hz, 1H, H_{30}), 4.49 (d, *J* = 7.5 Hz, 1H, H_{27}), 4.42–4.36 (m, 3H, 3× Ar-CH_2), 4.30 (d, *J* = 10.9 Hz, 1H, Ar-CH_2), 3.89 (d, *J* = 6.1 Hz, 1H, H_{32}), 3.78 (s, 3H, Ar-OCH_3), 3.77 (s, 3H, Ar-OCH_3), 3.68 (dd, *J* = 7.4, 1.6 Hz, 1H, H_{26}), 3.28 (s, 3H, C_{27}-OCH_3), 3.25 (dd, *J* = 8.8, 6.0 Hz, 1H, H_{22}), 3.17 (dd, *J* = 8.8, 6.9 Hz, 1H, H_{22}), 2.96–2.88 (m, 1H, H_{31}), 2.80–2.71 (m, 4H,dithiane), 2.06–1.99 (m, 1H, dithiane), 1.97–1.90 (m, 1H, H_2), 1.89–1.73 [m, 5H, including; 1.82 (s, 3H, C_{29}-CH_3), H_{23}, dithiane), 1.62–1.55 (m, 1H, H_{24}), 1.18 (d, *J* =

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6.9 Hz, 3H, C_{31}-CH_3), 1.05–0.97 [m, 4H, including; 1.00 (d, J=6.8 Hz, 3H, C_{25}-CH_3), H_{24}], 0.91 ppm (d, J=6.6 Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=201.9 (C_{28}), 159.0 (Ar), 158.9 (Ar), 144.7 (C_{30}), 137.4 (C_{29}), 130.9 (Ar), 130.9 (Ar), 129.1 (Ar), 129.0 (Ar), 113.6 (Ar), 113.5 (Ar), 82.0 (C_{26}), 82.0 (C_{27}), 75.8 (C_{22}), 73.4 (Ar-CH_2), 72.6 (Ar-CH_2), 57.7 (C_{27}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 53.1 (C_{32}), 38.6 (C_{31}), 38.5 (C_{24}), 32.0 (C_{25}), 30.9 (C_{23}), 30.4 (dithiane), 30.2 (dithiane), 25.9 (dithiane), 17.8 (C_{23}-CH_3), 17.1 (C_{31}-CH_3), 15.0 (C_{25}-CH_3), 12.0 ppm (C_{29}-CH_3); IR (thin film): $\tilde{\nu}$=3648, 2958, 2930, 1670, 1635, 1613, 1586, 1513, 1462, 1422, 1374, 1301, 1246, 1172, 1092, 1034, 968, 909, 820, 757 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{35}H_{51}O_6S_2$: 631.3127; found: 631.3135 $[M+H]^+$.

Dithiane 109: Freshly prepared $Zn(BH_4)_2$ (0.5 M in Et_2O, 3.30 mL, 1.65 mmol) was added slowly to a stirred solution of enone **108** (344 mg, 0.55 mmol) in Et_2O (20 mL) at −20 °C. After 3 h at this temperature, the reaction was quenched with H_2O and diluted with saturated aqueous NH_4Cl and Et_2O. After warming to RT, the organic layer was separated and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20–30% Et_2O/petrol) afforded the desired C28-(*R*)-allylic alcohol as a colourless oil (285 mg, 83%). R_f=0.37 (50% Et_2O/petrol); $[\alpha]_D^{25}$=+40.9 (c=2.00, $CHCl_3$);^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.25–7.20 (m, 4H, ArH), 6.85–6.81 (m, 4H, ArH), 5.52 (d, J=9.5 Hz, 1H, H_{30}), 4.57 (q, J=10.6 Hz, 2H, 2×Ar-CH_2), 4.41 (s, 2H, 2× Ar-CH_2), 4.12 (d, J=7.4 Hz, 1H, H_{28}), 4.04 (d, J=6.9 Hz, 1H, H_{32}), 3.78 (s, 3H, Ar-OCH_3), 3.78 (s, 3H, Ar-OCH_3), 3.58 (s, 1H, C_{28}-OH), 3.55 (dd, J=6.9, 1.5 Hz, 1H, H_{26}), 3.36 (s, 3H,c C_{27}-OCH_3), 3.29 (dd, J=8.8, 6.0 Hz, 1H, H_{22}), 3.23 (dd, J=8.6, 6.8 Hz, 1H, H_{22}), 3.19 (t, J=7.3 Hz, 1H, H_{27}), 2.88–2.77 (m, 5H, dithiane, H_{31}), 2.10–2.03 (m, 1H, dithiane), 2.03–1.97 (m, 1H, H_{25}), 1.96–1.89 (m, 1H, H_{23}), 1.86–1.77 (m, 1H, dithiane), 1.73 (s, 3H, C_{29}-CH_3), 1.70–1.64 (m, 1H, H_{24}), 1.16 (d, J=6.8 Hz, 3H, C_{31}-CH_3), 1.11–1.04 (m, 1H, H_{24}), 1.00 (d, J=6.8 Hz, 3H, C_{25}-CH_3), 0.95 ppm (d, J=6.6 Hz, 3H, C_{23}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=159.3 (Ar), 159.0 (Ar), 135.7 (C_{29}), 130.8 (Ar), 130.3 (C_{30}), 130.2 (Ar), 129.5 (Ar), 129.0 (Ar), 113.8 (Ar), 113.7 (Ar), 84.4 (C_{26}), 82.1 (C_{27}), 78.8 (C_{28}), 75.6 (C_{22}), 74.2 (Ar-CH_2), 72.7 (Ar-CH_2), 59.6 (C_{27}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 54.6 (C_{32}), 39.1 (C_{24}), 37.5 (C_{31}), 32.6 (C_{25}), 31.1 (C_{23}), 30.9 (dithiane), 30.6 (dithiane), 26.1 (dithiane), 18.2 (C_{31}-CH_3), 17.9 (C_{23}-CH_3), 15.4 (C_{25}-CH_3), 13.3 ppm (C_{29}-CH_3); IR (thin film): $\tilde{\nu}$=3442, 3957, 2930, 2902, 1612, 1586, 1512, 1462, 1422, 1372, 1301, 1276, 1245, 1172, 1090, 1034, 955, 910, 820, 768, 757, 733 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{35}H_{53}O_6S_2$: 633.3284; found: 633.3293 $[M+H]^+$.

Imidazole (110 mg, 1.62 mmol) and then TESCl (202 μL, 1.20 mmol) were added to a solution of the C28-(*R*)-allylic alcohol prepared above (254 mg, 0.40 mmol) in DMF (5 mL), and the reaction mixture heated at 50 °C for 3 h. After cooling to RT, 10% (w/v) aqueous LiCl and Et_2O were added. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with saturated aqueous NH_4Cl and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20% Et_2O/petrol) afforded silyl ether **109** as a colourless oil (278 mg, 93%). R_f=0.26 (20% Et_2O/petrol); $[\alpha]_D^{25}$=+10.4 (c=1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.29–7.18 (m, 4H, ArH), 6.90–6.82 (m, 4H, ArH), 5.24 (d, J=9.6 Hz, 1H, H_{30}), 4.61 (dd, J=61.2, 11.3 Hz, 2H, 2×Ar-CH_2), 4.40 (q, J=11.6 Hz, 2H, 2×Ar-CH_2), 4.31 (d, J=2.9 Hz, 1H, H_{28}), 4.01 (d, J=6.3 Hz, 1H, H_{32}), 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 3.54–3.49 [m, 4H, including; 3.51 (s, 3H, C_{27}-OCH_3), H_{26}], 3.34–3.29 (m, 2H, H_{27}, H_{22}), 3.16–3.11 (m, 1H, H_{22}), 2.85 (ddd, J=13.9, 9.8, 6.9 Hz, 1H, H_{31}), 2.81–2.74 (m, 4H, dithiane), 2.06 (m, 1H, H_{23}), 2.02–1.94 (m, 2H, H_{25}, dithiane), 1.82–1.69 [m, 4H, including; 1.73 (s, 3H, C_{29}-CH_3), dithiane], 1.62–1.53 (m, 1H, H_{24}), 1.10 (d, J=6.8 Hz, 3H, C_{31}-CH_3), 1.08–1.01 (m, 1H, H_{24}), 0.96–0.86 (m, 15H, TES, C_{23}-CH_3, C_{25}-CH_3), 0.53 ppm (q, J=7.9 Hz, 6H, TES); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=158.9 (Ar), 158.7 (Ar), 137.5 (C_{29}), 132.1 (Ar), 131.0 (Ar), 129.9 (C_{30}), 128.9 (Ar), 128.7 (Ar), 113.6 (Ar), 113.5 (Ar), 86.2 (C_{27}), 80.7 (C_{26}), 79.4 (C_{28}), 76.0 (C_{22}), 72.7 (Ar-CH_2), 72.6 (Ar-CH_2), 60.6 (C_{27}-OCH_3), 55.3 (Ar-OCH_3), 55.2 (Ar-OCH_3), 54.9 (C_{32}), 39.1 (C_{24}), 37.3 (C_{31}), 31.4 (C_{23}), 31.0 (C_{25}), 30.7 (dithiane), 30.6 (dithiane), 26.1 (dithiane), 18.1 (C_{23}-CH_3), 17.9 (C_{31}-CH_3), 15.2 (C_{25}-CH_3), 13.2 (C_{29}-CH_3), 6.9 (TES), 4.9 ppm (TES); IR (thin film): $\tilde{\nu}$=2954, 2932, 2909, 2875, 2047, 1613, 1586, 1513, 1461, 1421, 1372, 1301, 1275, 1246, 1171, 1091, 1037, 1008, 974, 909, 879, 846, 819, 745, 728, 685 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{41}H_{66}O_6S_2SiNa$: 769.3968; found: 769.3965 $[M+Na]^+$.

Alcohol 110: A 5 mL round bottom flask was charged with dithiane **107** (17.4 mg, 23.4 μmol) and epoxide **6** (10.0 mg, 30.0 μmol) and the resulting mixture azeotroped with PhH (×2) and dried in vacuo for 1 h 30 min. The flask was filled with argon, THF (300 μL) and HMPA (50 μL) were added, and the resulting solution was cooled to −78 °C. To this was added *t*BuLi (1.85 M in pentane, 17.0 μL, 31.5 μmol). During addition, the reaction mixture darkened progressively to orange. After the addition was complete, stirring was continued for 2 min at this temperature before the reaction vessel was immersed in a controlled dry-ice/acetone bath at −45 °C and stirred for an additional 40 min. H_2O was then added and the reaction allowed to warm to RT where it was diluted further with H_2O and Et_2O. The organic layer was separated, washed with H_2O (×2), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (2.5–20% EtOAc/hexanes) to afforded alcohol **110** as a viscous colourless oil (19.5 mg, 77%). When the reaction was repeated on a larger scale (110 mg of dithiane **107**, 146 μmol) and the other reagents/solvents scaled appropriately, the desired product **110** was isolated in a diminished yield of 51% (80.3 mg). However, the majority (>90%) of unreacted epoxide **6** and dithiane **107** were recovered and could be recycled. R_f=0.16 (20% EtOAc/hexanes); $[\alpha]_D^{25}$=+6.1 (c=1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.28 (d, J=8.4 Hz, 2H, ArH), 7.25 (d, J=8.4 Hz, 2H, ArH), 6.85 (t, J=7.2 Hz, 4H, ArH), 5.67 (d, J=9.6 Hz, 1H, H_{30}), 4.70 (d, J=10.8 Hz, 1H, Ar-CH_2), 4.50–4.39 (m, 3H, 3×Ar-CH_2), 4.14 (d, J=3.6 Hz, 1H, H_{28}), 3.86 (brs, 1H, H_{34}), 3.79 (s, 6H, 2×Ar-OCH_3), 3.74 (brs, 1H, C_{34}-OH), 3.51 (s, 3H, C_{27}-OCH_3), 3.45–3.33 [m, 7H, including; 3.41 (s, 3H, C_{39}-OCH_3), H_{40}, H_{27}, H_{26}, H_{22}], 3.16 (t, J=8.1 Hz, 1H, H_{22}), 3.11 (t, J=7.8 Hz, 1H, H_{31}), 3.03 (t, J=11.7 Hz, 1H, dithiane), 2.96 (t, J=11.4 Hz, 1H, dithiane), 2.93–2.86 (m, 1H, H_{39}), 2.73 (d, J=14.4 Hz, 1H, dithiane), 2.66 (d, J=13.8 Hz, 1H, dithiane), 2.38 (dd, J=15.0, 9.6 Hz, 1H, H_{33}), 2.12–2.08 (m, 3H, dithiane, H_{38}, H_{33}), 1.95–1.87 (m, 1H, H_{25}), 1.87–1.80 (m, 3H, dithiane, H_{41}, H_{23}), 1.77–1.67 [m, 4H, including; 1.76 (s, 3H, C_{29}-CH_3), H_{35}], 1.66–1.60 (m, 1H, H_{42}), 1.46–1.37 (m, 2H, H_{24}. H_{37}), 1.36–1.08 (m, 7H, including; 1.09 (d, J=6.6 Hz, 3H, C_{31}-CH_3), H_{41}, H_{36}, H_{36}, H_{24}], 0.99–0.81 [m, 28H, including; 0.93 (t, J=7.8 Hz, 9H, TES), 0.90 (s, 9H, TBS), C_{35}-CH_3, C_{25}-CH_3, C_{23}-CH_3, H_{42}], 0.76 (q, J=12.0 H, 1H, H_{38}), 0.57 (q, J=7.8 Hz, 6H, TES), 0.08 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=159.2 (Ar), 159.1 (Ar), 137.2 (C_{29}), 132.2 (Ar), 131.2 (Ar), 129.6 (Ar), 129.5 (C_{30}), 129.2 (Ar), 113.9 (Ar), 113.8 (Ar), 85.8 (C_{27}), 84.8 (C_{39}), 83.4 (C_{26}), 78.8 (C_{28}), 76.0 (C_{40}), 75.0 (C_{22}), 74.4 (Ar-CH_2), 72.8 (Ar-CH_2), 72.1 (C_{34}), 60.9 (C_{27}-OCH_3), 58.2 (C_{39}-OCH_3), 57.4 (C_{32}), 55.5 (2×Ar-OCH_3), 39.2 (C_{36}), 38.8 (C_{31}), 38.5 (C_{33}), 36.9 (C_{35}), 36.3 (C_{38}), 35.4 (C_{24}), 34.3 (C_{41}), 33.7 (C_{37}), 32.7 (C_{25}), 32.3 (C_{42}), 31.1 (C_{23}), 26.6 (dithiane), 26.1 (TBS), 25.9 (dithiane), 25.0 (dithiane), 19.5 (C_{23}-CH_3), 18.4 (TBS), 17.7 (C_{25}-CH_3), 15.5 (C_{35}-CH_3), 15.0 (C_{31}-CH_3), 13.3 (C_{29}-CH_3), 7.2 (TES), 5.2 (TES), −4.3 (TBS), −4.5 ppm (TBS); IR (thin film): $\tilde{\nu}$=3448, 2928, 1613, 1513, 1461, 1247, 1109, 1038, 836 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{59}H_{102}O_9S_2Si_2Na$: 1097.6396; found: 1097.6420 $[M+Na]^+$.

Alcohol 111: Dithiane **109** (174 mg, 0.233 mmol) was split into two batches, and each batch treated as follows: HMPA (0.2 mL) was added to a solution of dithiane **109** (87.0 mg, 116 μmol, azeotroped with PhH and dried in vacuo prior to reaction) and epoxide **6** (49.3 mg, 150 μmol, azeotroped with PhH and dried in vacuo prior to reaction) in THF (1.8 mL) at −78 °C. After stirring for 5 min, *t*BuLi (1.75 M in pentane, 115 μL, 201 μmol) was added and the resulting dark orange solution stirred at this temperature for a further 5 min, and at −40 °C for 10 min. The reaction mixture was then quenched with D_2O, and diluted with H_2O and Et_2O. After warming to RT, the organic layer was separated and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. After combining both batches, purification of the combined crude residues by flash chromatography (10–20% Et_2O/petrol) afforded alcohol **111** as a colourless oil (207 mg, 81%). R_f=0.28 (25% Et_2O/petrol); $[\alpha]_D^{25}$=+0.5 (c=1.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.29 (d,

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$J=8.3$ Hz, 2H, ArH), 7.21 (d, $J=8.3$ Hz, 2H, ArH), 6.85 (d, $J=8.4$ Hz, 2H, ArH), 6.83 (d, $J=8.4$ Hz, 2H, ArH), 5.65 (d, $J=9.5$ Hz, 1H, H_{30}), 4.80 (d, $J=11.0$ Hz, 1H, Ar-CH_2), 4.58 (d, $J=11.1$ Hz, 1H, Ar-CH_2), 4.42–4.34 (m, 3H, 2×Ar-CH_2, H_{28}), 3.85 (app dd, $J=9.0$, 3.7 Hz, 1H, H_{34}), 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 3.59 (d, $J=6.5$ Hz, 1H, H_{26}), 3.53 (s, 3H, C_{27}-OCH_3), 3.43–3.37 [4H, m, including; 3.41 (s, 3H, C_{39}-OCH_3), H_{40}], 3.34 (dd, $J=7.5$, 2.9 Hz, 1H, H_{27}), 3.30 (dd, $J=8.7$, 5.3 Hz, 1H, H_{22}), 3.18–3.10 (m, 2H, H_{22}, H_{31}), 3.00–2.87 (m, 3H, H_{39}, dithiane), 2.75–2.64 (m, 2H, dithiane), 2.34 (dd, $J=15.1$, 9.5 Hz, 1H, H_{33}), 2.12–2.02 (m, 3H, H_{38}, H_{33}, H_{25}), 1.99–1.89 (m, 2H, H_{23}, dithiane), 1.87–1.81 (m, 1H, H_{41}), 1.79–1.56 [m, 7H, including; 1.76 (s, 3H, C_{29}-CH_3), dithiane, H_{35}, H_{42}, H_{24}), 1.45–1.24 (m, 3H, H_{37}, H_{41}, H_{36}), 1.17–1.01 [m, 5H, including; 1.09 (d, $J=6.8$ Hz, 3H, C_{31}-CH_3), H_{36}, H_{24}), 1.00–0.85 [m, 28H, including; 0.95 (d, $J=6.8$ Hz, 3H, C_{25}-CH_3), H_{42}, C_{35}-CH_3, C_{23}-CH_3, TBS, TES], 0.74 (q, $J=12.0$ Hz, 1H, H_{38}), 0.54 (q, $J=7.9$ Hz, 6H, TES), 0.08 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=$ 158.9 (Ar), 158.8 (Ar), 137.6 (C_{29}), 132.0 (Ar), 131.0 (Ar), 129.0 (C_{30}), 128.9 (Ar), 128.7 (Ar), 113.6 (Ar), 113.5 (Ar), 86.4 (C_{27}), 84.6 (C_{39}), 80.4 (C_{26}), 79.7 (C_{28}), 76.0 (C_{22}), 75.8 (C_{40}), 72.9 (Ar-CH_2), 72.7 (Ar-CH_2), 71.8 (C_{34}), 60.6 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), 57.2 (C_{32}), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 39.1 (C_{24}), 38.9 (C_{36}), 38.5 (C_{31}), 38.4 (C_{33}), 36.7 (C_{35}), 36.0 (C_{38}), 34.1 (C_{41}), 33.4 (C_{37}), 32.0 (C_{42}), 31.2 (C_{25}), 31.0 (C_{23}), 26.3 (dithiane), 25.9 (TBS), 25.6 (dithiane), 24.9 (dithiane), 18.2 (TBS), 18.1 (C_{23}-CH_3), 15.2 (C_{25}-CH_3), 15.2 (C_{31}-CH_3), 14.8 (C_{35}-CH_3), 13.0 (C_{29}-CH_3), 6.9 (TES), 4.9 (TES), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}=$ 3725, 3528, 2955, 2927, 2874, 2347, 2157, 2025, 1613, 1587, 1514, 1458, 1370, 1301, 1248, 1172, 1111, 1037, 975, 876, 835, 774, 746 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{59}H_{102}O_9S_2Si_2Na$: 1097.6396; found: 1097.6351 $[M+Na]^+$.

Aldehyde 12 prepared from alcohol 110: To a cooled (0 °C) solution of **110** (90.0 mg, 83.7 μmol) in THF/MeOH/H_2O 10:9:1 (10 mL), was added $PhI(O_2CCF_3)_2$ (178 mg, 465 μmol). The reaction was stirred for 30 min, then quenched by the addition of saturated aqueous $NaHCO_3$, and diluted with Et_2O. The layers were separated, and the organic phase washed with saturated aqueous $Na_2S_2O_3$ and H_2O. The separate aqueous layers were back-extracted individually with ether (×2), and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (10–20% EtOAc/hexanes) to afford the desired C32-ketone as a colourless oil (69.2 mg, 84%). $R_f=$ 0.46 (30% EtOAc/hexanes); $[\alpha]_D^{25}=-49.9$ ($c=1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=7.25$ (d, $J=7.2$ Hz, 2H, ArH), 7.24 (d, $J=9.0$ Hz, 2H, ArH), 6.85 (t, $J=8.1$ Hz, 4H, ArH), 5.29 (d, $J=9.6$ Hz, 1H, H_{30}), 4.59 (d, J 10.8 Hz, 1H, Ar-CH_2), 4.44 (d, $J=10.8$ Hz, 1H, Ar-CH_2), 4.41 (s, 2H, 2×Ar-CH_2), 4.14 (d, $J=6.6$ Hz, 1H, H_{28}), 3.85–3.81 (m, 1H, H_{34}), 3.79 (s, 6H, 2×Ar-OCH_3), 3.47–3.41 (m, 1H, H_{31}), 3.40–3.35 (m, 8H, H_{26}, H_{40}, 2×-OCH_3), 3.33 (dd, $J=9.0$, 4.8 Hz, 1H, H_{22}), 3.24 (dd, $J=6.6$, 4.2 Hz, 1H, H_{27}), 3.16 (dd, $J=9.0$, 7.2 Hz, 1H, H_{22}), 2.90–2.85 (m, 1H, H_{39}), 2.56 (dd, $J=17.4$, 1.8 Hz, 1H, H_{33}), 2.48 (dd, $J=18.0$, 10.2 Hz, 1H, H_{33}), 2.07–2.01 (m, 1H, H_{38}), 1.92–1.79 (m, 3H, H_{23}, H_{25}, H_{41}), 1.75 (s, 3H, C_{29}-CH_3), 1.66–1.49 (m, 3H, H_{24}, H_{35}, H_{42}), 1.37–1.24 (m, 3H, H_{36}, H_{37}, H_{41}), 1.14 (d, $J=6.6$ Hz, 3H, C_{31}-CH_3), 1.12–1.03 (m, 2H, H_{24}, H_{36}), 0.98–0.85 [m, 25H, including; 0.96 (d, $J=7.2$ Hz, 3H, C_{25}-CH_3), 0.92 (t, $J=7.2$ Hz, 9H, TES), 0.89 (s, 9H, TBS), 0.87 (d, $J=7.2$ Hz, 3H, C_{23}-CH_3), H_{42}], 0.70 (q, $J=12.0$ Hz, 1H, H_{38}), 0.54 (q, $J=7.4$ Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.06 ppm (TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=$ 213.3 (C_{32}), 159.2 (Ar), 159.16 (Ar), 139.7 (C_{29}), 131.8 (Ar), 131.1 (Ar), 129.4 (Ar), 129.2 (Ar), 127.1 (C_{30}), 113.9 (Ar), 113.8 (Ar), 84.7 (C_{39}), 83.1 (C_{27}), 82.7 (C_{26} or C_{40}), 78.0 (C_{28}), 75.9 (C_{26} or C_{40}), 75.4 (C_{22}), 73.5 (Ar-CH_2), 72.8 (Ar-CH_2), 72.0 (C_{34}), 60.0 (C_{27}-OCH_3 or C_{39}-OCH_3), 58.1 (C_{27}-OCH_3 or C_{39}-OCH_3), 55.5 (2×Ar-OCH_3), 47.1 (C_{31}), 44.0 (C_{33}), 39.2 (C_{36}), 36.6 (C_{24}), 36.1 (C_{38}), 35.6 (C_{35}), 34.2 (C_{41}), 33.6 (C_{37}), 32.7 (C_{23} or C_{25}), 32.2 (C_{42}), 31.2 (C_{23} or C_{25}), 26.1 (TBS), 19.1 (C_{23}-CH_3 or C_{25}-CH_3), 18.4 (TBS), 17.1 (TES), 16.0 (C_{31}-CH_3), 15.6 (C_{23}-CH_3 or C_{25}-CH_3), 13.3 (C_{29}-CH_3), 7.1 (TES), 5.2 (TES), −4.3 (TBS), −4.5 ppm (TBS); IR (thin film): $\tilde{\nu}=3508$, 2930, 1707, 1611, 1514, 1460, 1248, 1110, 835 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{56}H_{96}O_{10}Si_2Na$: 1007.6434; found: 1007.6403 $[M+Na]^+$.

To a cooled (−5 °C) solution of the C32-ketone prepared above (62.0 mg, 63.1 μmol) in CH_2Cl_2 (4 mL) was added *N*-Boc-L-pipecolinic acid (**9**; 86.5 mg, 377 μmol), DCC (78 mg, 377 μmol), and DMAP (4.5 mg, 37 μmol). After stirring for 24 h, saturated aqueous NH_4Cl was added and the reaction contents diluted with Et_2O. The layers were separated, the organic phase washed with saturated aqueous $NaHCO_3$ (×2), and the separate aqueous layers back-extracted individually with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography (10–15% EtOAc/hexanes) to afford the desired C34-ester as a colourless oil and as a 1:1 mixture of rotamers (63.5 mg, 84%). $R_f=0.58$ (30% EtOAc/hexanes); $[\alpha]_D^{25}=-73.3$ ($c=1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=$ 7.26–7.22 (m, 4H, ArH), 6.86–6.83 (m, 4H, ArH), 5.27 (brs, 0.5H, 0.5 of H_{34}), 5.25 (d, $J=9.7$ Hz, 1H, H_{30}), 5.19 (brs, 0.5H, 0.5 of H_{34}), 4.84 (brs, 0.5H, 0.5 of H_2), 4.69 (brs, 0.5H, 0.5 of H_2), 4.59 (d, $J=11.0$ Hz, 1H, Ar-CH_2), 4.44 (d, $J=11.1$ Hz, 1H, Ar-CH_2), 4.41 (d, $J=2.5$ Hz, 2H, 2×Ar-CH_2), 4.15 (d, $J=7.0$ Hz, 1H, H_{28}), 4.01 (brd, 0.5H, 0.5 of H_6), 3.84 (brd, 0.5H, H_6), 3.79 (s, 6H, 2×Ar-OCH_3), 3.42–3.32 [m, 10H, including 3.60 (s, 6H, C_{27}-OCH_3, C_{39}-OCH_3), H_{31}, H_{27}, H_{40}, H_{26}], 3.26 (dd, $J=4.0$, 6.9 Hz, 1H, H_{22}), 3.15 (brt, 1H, H_{22}), 2.90–2.80 (m, 1.5H, H_{39}, 0.5 of H_6), 2.73–2.61 [m, 1.5H, including; 2.69 (dd, $J=16.8$, 9.1 Hz, 1H, H_{33}), 0.5 of H_6], 2.44 (dd, $J=16.8$, 3.0 Hz, 1H, H_{33}), 2.19 (brm, 1H, H_3), 1.99–0.84 [m, 60H, including; 1.78 (brs, 3H, C_{29}-CH_3), 1.44 (s, 9H, Boc), 1.10 (brd, $J=$ 6.1 Hz, 3H, C_{31}-CH_3), 0.96 (d, $J=6.7$ Hz, 3H, C_{25}-CH_3), 0.89 (s, 9H, TBS), 0.84 (brd, $J=6.6$ Hz, 3H, C_{35}-CH_3), H_{38}, H_{25}, H_{35}, H_{23}, 2×H_{42}, H_3, 2×H_{24}, H_{37}, 2×H_{41}, 2×H_4, 2×H_5, 2×H_{36})], 0.72 (m, 1H, H_{38}), 0.49 (q, $J=$ 8.0 Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=$(208.4, 208.1) (C_{32}), (171.4, 171.3) (C_1), 159.2 (Ar), 159.2 (Ar), (155.9, 155.4) (C_8), (139.7, 139.7) (C_{29}), 131.7 (Ar), 131.1 (Ar), 129.3 (Ar), 129.2 (Ar), (127.2, 127.1) (C_{30}), 113.9 (Ar), 113.8 (Ar), 84.6 (C_{27}), 84.6 (C_{39}), 83.0 (C_{26}), (80.2, 80.1) (Boc), 78.2 (C_{28}), 75.9 (C_{40}), 75.4 (C_{22}), (74.7, 74.5) (C_{34}), 73.6 (Ar-CH_2), 72.8 (Ar-CH_2), 60.0 (C_{27}-OCH_3), 58.2 (C_{39}-OCH_3), 55.5 (Ar-OCH_3), 55.5 (Ar-OCH_3), (55.1, 53.9) (C_2), 47.4 (C_{31}), (42.2, 41.4) (C_6), (41.1, 40.6) (C_{33}), 39.3 (C_{24}), 39.0 (C_{36}), (36.4, 36.3) (C_{38}), 34.1 (C_{41}), 33.3 (C_{35}), 32.7 (C_{25}), (31.7, 31.6) (C_5), 31.2 (C_{23}), 29.9 (C_{37}), (28.6, 28.6) (Boc), 27.0 (C_3), 26.1 (TBS), (25.0, 24.8) (C_4), (20.9, 20.8) (C_{42}), 19.2 (C_{23}-CH_3), 18.4 (TBS), 17.2 (C_{25}-CH_3), 15.6 (C_{35}-CH_3), (15.3, 15.2) (C_{31}-CH_3), 13.2 (C_{29}-CH_3), 7.2 (TES), 5.2 (TES), −4.3 (TBS), −4.5 ppm (TBS); IR (thin film): $\tilde{\nu}=$2931, 1736, 1699, 1614, 1514, 1460, 1366, 1248, 1159, 1111 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{67}H_{113}NO_{13}Si_2Na$: 1218.7643; found: 1218.7646 $[M+Na]^+$.

To a solution of the C34-ester prepared above (62.0 mg, 52.0 μmol) in CH_2Cl_2/pH 7 phosphate buffer 8:1 (4.5 mL) was added DDQ (29.4 mg, 130 μmol) as a solid. The reaction was stirred rapidly for 2 h, then diluted with aqueous pH 7 phosphate buffer and CH_2Cl_2. The organic layer was separated and the aqueous phase back-extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (×2), dried over $NaSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20–30% EtOAc/hexanes) gave the desired diol as a colourless oil and as a 1:1 mixture of rotamers (46.0 mg, 93%). $R_f=0.23$ (30% EtOAc/hexanes); $[\alpha]_D^{25}=-93.4$ ($c=1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=5.36$ (d, $J=9.5$ Hz, 1H, H_{30}), 5.29 (brs, 0.5H, 0.5 of H_{34}), 5.19 (brs, 0.5H, 0.5 of H_{34}), 4.83 (brs, 0.5H, 0.5 of H_2), 4.68 (brs, 0.5H, 0.5 of H_2), 4.21 (d, $J=5.5$ Hz, 1H, H_{28}), 3.99 (brm, 0.5H, 0.5 of H_6), 3.87 (brm, 0.5H, 0.5 of H_6), 3.53–3.45 (m, 2H, H_{26}, H_{31}), 3.42–3.33 [m, 9H, including; 3.40 (s, 3H, C_{39}-OCH_3), 3.39 (s, 3H, C_{27}-OCH_3), H_{40}, 2×H_{22}], 3.15 (brd, $J=5.5$ Hz, 1H, H_{27}), 2.97–2.82 (m, 1.5H, H_{39}, 0.5 of H_6), 2.72–2.59 (m, 1.5H, including 2.68 (dd, $J=8.8$, 16.9 Hz, H_{33}), 0.5 of H_6], 2.51–2.44 (m, 1H, H_{33}), 2.17 (m, 1H, H_3), 1.99–1.55 [m, 16H, including 1.75 (s, 3H, C_{29}-CH_3), H_{38}, H_{25}, H_{35}, H_{41}, H_{23}, H_{24}, 2×H_5, H_3], 1.46–0.82 [m, 44H, including 1.44 (brs, 9H, Boc), 1.13 (brd, $J=6.4$ Hz, 3H, C_{31}-CH_3), 0.88 (s, 9H, TBS), 0.84 (d, $J=6.7$ Hz, 3H, C_{23}-CH_3), C_{25}-CH_3, C_{35}-CH_3, TES], 0.76 (m, 1H, H_{38}), 0.57 (q, $J=7.9$ Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=$(208.3, 208.0) (C_{32}), (171.4, 171.3) (C_1), (155.9, 155.4) (C_8), (138.5, 138.4) (C_{29}), (126.9, 126.7) (C_{30}), 84.6 (C_{39}), 81.0 (C_{28}), 80.2 (C_{27}), (80.1, 80.0) (Boc), 75.9 (C_{40}), 74.9 (C_{26}), 74.5 (C_{34}), 67.6 (C_{22}), 59.5 (C_{27}-OCH_3), 58.3 (C_{39}-OCH_3), (55.1, 54.0) (C_2), (47.1, 47.0) (C_{31}), 42.2 (C_6), (41.4, 40.6) (C_{33}), (39.2, 38.8) (C_{36}), 37.5 (C_{24}), (36.4, 36.3) (C_{38}), 34.4 (C_{41}), 33.8 (C_{23}), 33.4 (C_{35}), 33.3 (C_{25}), (31.9, 31.7) (C_5), 29.9 (C_{37}), (28.6, 28.6) (Boc), 27.0 (C_3), 26.1 (TBS), 25.1 (C_4), 20.8 (C_{42}), (18.8, 18.4)

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(TBS), 17.4 (C_{23}-CH_3), 16.0 (C_{31}-CH_3), (15.9, 15.6) (C_{35}-CH_3), 15.3 (C_{25}-CH_3), 13.6 (C_{29}-CH_3), 7.0 (TES), 4.9 (TES), −4.3 (TBS), −4.5 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 3460, 2931, 2877, 1736, 1699, 1457, 1392, 1249, 1159, 1110, 836 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{51}H_{97}NO_{11}Si_2Na$: 978.6498; found: 978.6460 $[M+Na]^+$.

To a solution of DMSO (52.0 μL, 730 μmol) in CH_2Cl_2 (0.5 mL) at −78 °C was added $(COCl)_2$ (32.0 μL, 370 μmol), and the resulting mixture stirred for 30 min. A pre-cooled (−78 °C) solution of the diol prepared above (7.0 mg, 7.3 μmol) in CH_2Cl_2 (0.5+0.5 mL) was added via cannula. After 45 min, Et_3N (200 μL, 1.46 mmol) was added dropwise, and the reaction stirred for an additional 30 min. The cooling bath was then removed and the reaction mixture allowed to warm to RT where it was stirred for 30 min, then diluted with Et_2O and saturated aqueous NH_4Cl. The layers were separated, and the organic phase washed sequentially with saturated aqueous NH_4Cl and with H_2O, then dried over $MgSO_4$ and concentrated in vacuo to obtain the desired bis-oxidation product **12** as a light yellow oil and as a 1:1 mixture of rotamers (7.0 mg, 99 %) which was used directly in the subsequent reaction. The observed analytical data was identical in all respects to that reported for the preparation of **12** by degradation (see Supporting Information), including mixed material NMR studies.

Aldehyde 12 prepared from alcohol 111: Alcohol **111** (203 mg, 189 μmol) was split into two batches, and each batch treated as follows: PhI-$(O_2CCF_3)_2$ (203 mg, 473 μmol) was added to a stirred solution of **111** (102 mg, 94.5 μmol) in THF/MeOH/H_2O (10:9:1, 12 mL) at 0 °C. After 25 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and Et_2O was added. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with 20 % (w/v) aqueous $Na_2S_2O_3$, with H_2O, and with brine, dried over $MgSO_4$ and concentrated in vacuo. After combining both batches, purification of the crude residue by flash chromatography (25–30 % Et_2O/petrol) afforded the desired C32-ketone as a colourless oil (155 mg, 83 %). R_f = 0.52 (50 % Et_2O/petrol); $[\alpha]_D^{25}$ = −74.3 (*c* = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.23 (d, *J* = 8.7 Hz, 2H, ArH), 7.21 (d, *J* = 8.6 Hz, 2H, ArH), 6.87–6.81 (m, 4H, ArH), 5.15 (d, *J* = 9.6 Hz, 1H, H_{30}), 4.51–4.35 (m, 4H, 4×Ar-CH_2), 4.20 (d, *J* = 5.1 Hz, 1H, H_{28}), 3.85–3.76 [m, 7H, including; 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), H_{34}], 3.45–3.35 [m, 9H, including; 3.42 (s, 3H, C_{39}-OCH_3), 3.39 (s, 3H, C_{27}-OCH_3), H_{27}, H_{31}, H_{40}], 3.35–3.27 (m, 2H, H_{22}, H_{26}), 3.14 (t, *J* = 8.1 Hz, 1H, H_{22}), 2.91–2.84 (m, 1H, H_{39}), 2.58 (d, *J* = 17.3 Hz, 1H, H_{33}), 2.48 (dd, *J* = 17.3, 9.8 Hz, 1H, H_{33}), 2.07–2.03 (m, 1H, H_{38}), 2.01–1.93 (m, 1H, H_{25}), 1.90–1.80 (m, 2H, H_{23}, H_{41}), 1.74 (s, 3H, C_{29}-CH_3), 1.67–1.55 (m, 2H, H_{35}, H_{42}), 1.49 (td, *J* = 13.2, 6.5 Hz, 1H, H_{24}), 1.26–1.40 (m, 3H, H_{37}, H_{41}, H_{36}), 1.11–1.01 [m, 5H, including; 1.09 (d, *J* = 6.7 Hz, 3H, C_{31}-CH_3), H_{24}, H_{36}], 0.98 (d, *J* = 6.7 Hz, 3H, C_{25}-CH_3), 0.94 (d, *J* = 6.6 Hz, 3H, C_{23}-CH_3), 0.93–0.88 (m, 19H, TBS, TES, H_{42}), 0.86 (d, *J* = 6.7 Hz, 3H, C_{35}-CH_3), 0.71 (q, *J* = 11.9 Hz, 1H, H_{38}), 0.54 (q, *J* = 7.9 Hz, 6H, TES), 0.08 (s, 3H, TBS), 0.06 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 213.3 (C_{32}), 159.0 (Ar), 158.9 (Ar), 139.5 (C_{29}), 131.4 (Ar), 130.9 (Ar), 128.9 (Ar), 128.8 (Ar), 126.2 (C_{30}), 113.7 (Ar), 113.5 (Ar), 84.6 (C_{27}), 84.5 (C_{39}), 81.9 (C_{26}), 78.0 (C_{28}), 75.7 (C_{40}), 75.5 (C_{22}), 72.6 (Ar-CH_2), 72.4 (Ar-CH_2), 71.8 (C_{34}), 59.8 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), 46.7 (C_{31}), 43.7 (C_{33}), 39.2 (C_{24}), 39.0 (C_{36}), 35.9 (C_{38}), 35.4 (C_{35}), 34.0 (C_{41}), 33.4 (C_{37}), 32.0 (C_{42}), 31.7 (C_{25}), 31.1 (C_{23}), 25.9 (TBS), 18.6 (C_{23}-CH_3), 18.2 (TBS), 15.8 (C_{25}-CH_3 and C_{31}-CH_3), 15.3 (C_{35}-CH_3), 12.9 (C_{29}-CH_3), 6.9 (TES), 4.9 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 3710, 3501, 2955, 2931, 2876, 2855, 2366, 2235, 1707, 1613, 1587, 1514, 1462, 1377, 1360, 1301, 1247, 1172, 1110, 1038, 1008, 977, 874, 834, 776, 742 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{56}H_{96}O_{10}Si_2Na$: 1007.6434; found: 1007.6392 $[M+Na]^+$.

DCC (247 mg, 1.20 mmol), **9** (275 mg, 1.20 mmol) and then DMAP (14.6 mg, 120 μmol) were added to a solution of the C32 ketone prepared above (118 mg, 120 μmol) in CH_2Cl_2 (6 mL) at −5 °C. After stirring for 20 h, the reaction was quenched with saturated aqueous NH_4Cl, diluted with Et_2O and allowed to warm to RT. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (×2) and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (22–28 % Et_2O/petrol) afforded the desired C34-ester as a colourless oil and as a 1:1 mixture of rotamers (143 mg, 99 %). R_f = 0.72 (50 % Et_2O/petrol); $[\alpha]_D^{25}$ = −79.1 (*c* = 2.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.25–7.19 (m, 4H, ArH), 6.86–6.82 (m, 4H, ArH), 5.27 (brs, 0.5H, 0.5 of H_{34}), 5.21 (brs, 0.5H, 0.5 of H_{34}), 5.11 (d, *J* = 9.7 Hz, 1H, H_{30}), 4.84 (brs, 0.5H, 0.5 of H_2), 4.69 (brs, 0.5H, 0.5 of H_2), 4.47 (d, *J* = 11.2 Hz, 1H, Ar-CH_2), 4.44–4.37 (m, 3H, 3×Ar-CH_2), 4.16 (d, *J* = 5.5 Hz, 1H, H_{28}), 4.03–3.97 (brm, 0.5H, 0.5 of H_6), 3.90–3.83 (brm, 0.5H, H_6), 3.80 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 3.42 (s, 3H, C_{27}-OCH_3), 3.40–3.29 [m, 8H, including; 3.38 (s, 3H, C_{39}-OCH_3), H_{31}, H_{27}, H_{40}, H_{22}, H_{26}], 3.15–3.11 (m, 1H, H_{22}), 2.90–2.83 (m, 1H, H_{39}), 2.83–2.79 (brm, 0.5H, 0.5 of H_6), 2.73–2.64 [m, 1.5H, including; 2.69 (dd, *J* = 16.9, 9.0 Hz, 1H, H_{33}), 0.5 of H_6], 2.49 (dd, *J* = 17.0, 3.1 Hz, 1H, H_{33}), 2.23–2.15 (m, 1H, H_3), 2.05–0.65 [m, 61H, including; 1.77–1.74 (brm, 3H, C_{29}-CH_3), 1.45 (s, 9H, Boc), 1.05 (brd, *J* = 6.1 Hz, 3H, C_{31}-CH_3), 0.99 (d, *J* = 6.8 Hz, 3H, C_{25}-CH_3), 0.94 (d, *J* = 6.6 Hz, 3H, C_{23}-CH_3), 0.90 (t, *J* = 8.0 Hz, 9H, TES), 0.88 (s, 9H, TBS), 0.86–0.82 (brm, 3H, C_{35}-CH_3), H_{38}, H_{25}, H_{35}, H_{23}, 2×H_{42}, H_3, 2×H_{24}, H_{37}, 2×H_{41}, 2×H_4, 2×H_5, 2×H_{36}, H_{38})] 0.53 (q, *J* = 8.0 Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = (208.3, 208.0) (C_{32}), (171.1, 171.1) (C_1), 159.0 (Ar), 158.9 (Ar), (155.6, 155.2) (C_8), 139.5 (C_{29}), 130.9 (Ar), 128.9 (Ar), 128.9 (Ar), (126.3, 126.2) (C_{30}), 113.7 (Ar), 113.5 (Ar), 84.5 (C_{27}), 84.3 (C_{39}), 82.0 (C_{26}), (79.8, 79.7) (Boc), 78.0 (C_{28}), 75.6 (C_{40}), 75.4 (C_{22}), (74.6, 74.3) (C_{34}), 72.6 (Ar-CH_2), 72.3 (Ar-CH_2), 59.8 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), 55.2 (Ar-OCH_3), 55.2 (Ar-OCH_3), (54.9, 53.8) (C_2), 46.9 (C_{31}), (42.0, 40.8) (C_6), (41.0, 40.4) (C_{33}), 39.2 (C_{24}), (39.0, 38.8) (C_{36}), (36.2, 36.1) (C_{38}), 33.9 (C_{41}), 33.1 (C_{35}), 31.7 (C_{25}), (31.5, 31.4) (C_5), 31.1 (C_{23}), 29.7 (C_{37}), (28.4, 28.3) (Boc), (26.8, 26.7) (C_3), 25.8 (TBS), (24.9, 24.7) (C_4), (20.7, 20.6) (C_{42}), 18.6 (C_{23}-CH_3), 18.1 (TBS), 15.8 (C_{25}-CH_3), 15.3 (C_{35}-CH_3), (15.1, 15.0) (C_{31}-CH_3), 12.9 (C_{29}-CH_3), 6.9 (TES), 5.0 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2952, 2930, 2876, 2855, 1738, 1698, 1613, 1514, 1460, 1390, 1365, 1300, 1247, 1181, 1159, 1110, 1038, 1004, 976, 930, 874, 835, 776, 745 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{67}H_{113}NO_{13}Si_2Na$: 1218.7643; found: 1218.7661 $[M+Na]^+$.

DDQ (59.8 mg, 263 μmol) was added to a rapidly stirring solution of the C34-ester prepared above (126 mg, 105 μmol) in CH_2Cl_2/pH 7 phosphate buffer (10:1, 11 mL). After 2 h, the reaction was diluted with pH 7 buffer and CH_2Cl_2. The organic layer was separated, and the aqueous phase extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (33–50 % Et_2O/petrol) afforded the desired diol as a colourless oil and as a 1:1 mixture of rotamers (91.0 mg, 90 %). R_f = 0.23 (50 % Et_2O/petrol); $[\alpha]_D^{25}$ = −44.6 (*c* = 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.32 (d, *J* = 9.6 Hz, 1H, H_{30}), 5.28–5.24 (brs, 0.5H, 0.5 of H_{34}), 5.20–5.15 (brs, 0.5H, 0.5 of H_{34}), 4.85–4.80 (brs, 0.5H, 0.5 of H_2), 4.71–4.66 (brs, 0.5H, 0.5 of H_2), 4.28 (d, *J* = 4.3 Hz, 1H, H_{28}), 4.02–3.97 (brm, 0.5H, 0.5 of H_6), 3.89–3.83 (brm, 0.5H, 0.5 of H_6), 3.51 (d, *J* = 8.7, 1H, H_{26}), 3.49–3.34 [m, 10H, including; 3.40 (s, 6H, C_{27}-OCH_3, C_{39}-OCH_3), 2×H_{22}, H_{31}, H_{40}], 3.17 (dd, *J* = 8.8, 5.2 Hz, 1H, H_{27}), 2.92–2.79 (m, 1.5H, H_{39}, 0.5 of H_6), 2.73 (dd, *J* = 17.1, 8.8 Hz, 1H, H_{33}), 2.69–2.63 (brm, 0.5H, 0.5 of H_6), 2.53–2.46 (m, 1H, H_{33}), 2.23–2.14 (m, 1H, H_3), 2.13–1.79 (m, 4H, H_{38}, H_{25}, H_{35}, H_{41}), 1.77 (s, 3H, C_{29}-CH_3), 1.75–0.79 [m, 53H, including; 1.44 (s, 9H, Boc), 1.14 (brs, 3H, C_{31}-CH_3), 0.88 (s, 9H, TBS), 0.85 (d, *J* = 6.8 Hz, 3H, C_{23}-CH_3), H_{23}, H_3, 2×H_{42}, 2×H_{24} H_{41}, 2×H_4, 2×H_5, H_{37}, 2×H_{36}, C_{25}-CH_3, C_{35}-CH_3, TES], 0.76–0.66 (m, 1H, H_{38}), 0.59 (q, *J* = 7.8 Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = (208.9, 208.7) (C_{32}), (171.3, 171.1) (C_1), (155.7, 155.1) (C_8), (138.9, 138.8) (C_{29}), (126.5, 126.4) (C_{30}), 84.3 (C_{39}), 82.7 (C_{27}), (80.7, 80.6) (C_{28}), (79.9, 79.8) (Boc), 75.6 (C_{40}), (74.3, 73.9) (C_{34}), (73.2, 73.2) (C_{26}), 68.5 (C_{22}), (59.8, 59.7) (C_{27}-OCH_3), 58.0 (C_{39}-OCH_3), (54.8, 53.8) (C_2), (46.4, 46.3) (C_{31}), (42.0, 40.9) (C_6), (41.4, 40.8) (C_{33}), (38.9, 38.6) (C_{36}), 37.8 (C_{24}), (36.2, 36.1) (C_{38}), 33.9 (C_{41}), 33.1 (C_{35}), 33.1 (C_{23}), (31.6, 31.4) (C_5), 31.1 (C_{25}), 30.3 (C_{37}), (28.4, 28.3) (Boc), (26.8, 26.7) (C_3), 25.8 (TBS), (24.8, 24.6) (C_4), (20.7, 20.5) (C_{42}), 18.1 (TBS), 17.8 (C_{23}-CH_3), (16.1, 16.0) (C_{31}-CH_3), (15.4, 15.1) (C_{35}-CH_3), 14.1 (C_{25}-CH_3), (12.9, 12.8) (C_{29}-CH_3), 6.7 (TES), 4.7 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 3414, 2923, 2852, 1735, 1699, 1461, 1366, 1337,

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1278, 1249, 1187, 1159, 1113, 1041, 1004, 930, 874, 836, 776 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{51}H_{98}NO_{11}Si_2$: 956.6678; found: 956.6713 $[M+H]^+$.

DMSO (179 μL, 2.52 mmol) was added dropwise to a solution of oxalyl chloride (110 μL, 1.26 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C. After 30 min, a solution of the diol prepared above (24.1 mg, 25.2 μmol) in CH_2Cl_2 (1 + 0.5 + 0.5 mL), precooled to −78 °C, was added via cannula. After stirring for 40 min, Et_3N (702 μL, 5.04 mmol) was added. The mixture was stirred for 30 min at −78 °C before warming to RT and stirring for a further 30 min. The reaction was quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were washed with saturated aqueous NH_4Cl, with H_2O, and with brine, dried over $MgSO_4$ and concentrated in vacuo to afford aldehyde **12** as a yellow oil and as a 1:1 mixture of rotamers (24.0 mg, 99 %) which was used directly in the subsequent reaction without further purification (purity >95 %). The observed analytical data was identical in all respects to that reported for the preparation of **12** by degradation (see Supporting Information), and from alcohol **110**, including mixed material NMR studies.

Vinyl stannane 117: A solution of aldehyde **12** (36.0 mg, 37.8 μmol) and iodoform (45.0 mg, 114 μmol) in THF (0.5 mL) was added via cannula to a rapidly stirred solution of $CrCl_2$ (70.0 mg, 568 μmol) in THF (1.0 mL) at 0 °C. Stirring was continued at 0 °C for 2 h, then the mixture was allowed to warm to RT over 30 min. H_2O was added, and the mixture extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo, and the crude residue purified by flash chromatography (10–50 % Et_2O/petrol) to give the desired vinyl iodide as a colourless oil and as a 1:1 mixture of rotamers (33.5 mg, 82 %). $[\alpha]_D^{25} = -101.6$ ($c = 0.50$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta =$ 6.35 (dd, $J = 14.5$, 9.0 Hz, 1H, H_{21}), 6.07 (d, $J = 14.5$ Hz, 1H, H_{22}), 5.27 (apparent d, $J = 10.0$ Hz, 1.5H, H_{30}, 0.5 of H_{34}), 5.19 (br s, 0.5H, 0.5 of H_{34}), 4.83 (br s, 0.5H, 0.5 of H_2), 4.68 (br s, 0.5H, 0.5 of H_2), 4.18 (d, $J =$ 7.0 Hz, 1H, H_{28}), 3.99 (m, 0.5H, 0.5 of H_6), 3.85–3.82 [m, 1.5H, including; 3.83 (d, $J = 7.0$ Hz, 1H, H_{27}), 0.5 of H_6], 3.39–3.30 [m, 5H, including; 3.39 (s, 3H, C_{39}-OCH_3), H_{31}, H_{40}], 3.26 (s, 3H, C_{27}-OCH_3), 2.90–2.83 (m, 1.5H, H_{39}, 0.5 of H_6), 2.65 (apparent dd, $J = 17.0$, 9.0 Hz, 1.5H, H_{33}, 0.5 of H_6), 2.51–2.45 (m, 1H, H_{33}), 2.36–2.28 (m, 1H, H_{23}), 2.22–2.17 (m, 1H), 2.01–1.75 [m, 6H, including; 1.77 (s, 3H, C_{29}-CH_3)], 1.69–1.56 (m, 6H), 1.48–1.00 [m, 25H, including; 1.45 (s, 9H, Boc), 1.10 (d, $J = 6.5$ Hz, 3H, C_{31}-CH_3), 1.04 (d, $J = 6.5$ Hz, 3H, C_{23}-CH_3), 1.02 (d, $J = 6.5$ Hz, 3H, C_{25}-CH_3)], 0.84–0.83 [m, 21H, including; 0.88 (s, 9H, TBS), 0.85 (d, $J =$ 6.0 Hz, 3H, C_{35}-CH_3)], 0.75–0.66 (m, 1H, H_{38}), 0.53 (q, $J = 8.0$ Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 212.8$ (C_{26}), (207.9, 207.6) (C_{32}), 171.0 (C_1), (155.6, 155.2) (C_8), 150.6 (C_{22}), 137.8 (C_{29}), (127.8, 127.7) (C_{30}), (85.0, 84.9) (C_{27}), 84.4 (C_{39}), (79.9, 79.7) (Boc), 78.8 (C_{28}), 75.6 (C_{40}), 74.5 (C_{21} and C_{34}), 74.2 (C_{34}), 58.1 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), (54.9, 53.8) (C_2), (47.0, 46.9) (C_{31}), 42.5 (C_{25}), (42.0, 40.9) (C_6), 40.1 (C_{33}), 39.0 (C_{23}), 38.6, 38.1, 36.2, 33.1, 33.0, 31.3, 28.4 and 28.3 (Boc), 26.8, 25.8 (TBS), 24.9, 24.7, 20.7, 20.5, 18.1, 15.2, 15.0, 14.2, 12.0, 6.8 (TES), 4.9, 4.7 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu} = 3852$, 3418, 2932, 2360, 1699, 1652, 1558, 1540, 1506, 1456, 1248, 1159, 1111, 874, 836 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{52}H_{94}INO_{10}Si_2Na$: 1098.5360; found: 1098.5450 $[M+Na]^+$.

Tri-2-furylphosphine (1.04 g, 4.47 mmol) was added to a solution of $[Pd(CH_3CN)_2Cl_2]$ (565 mg, 2.18 mmol) in acetone/H_2O (1:1, 20 mL). The mixture was stirred at RT for 45 min, then extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give bis(tri-2-furylphosphine) dichloride as a yellow powder and as a 3:2 mixture of *cis*:*trans* isomers (650 mg, 46 %). The observed spectral data was consistent with that reported previously.[78]

$[Pd(PFur_3)_2Cl_2]$ (3 mM stock solution in NMP, 310 μL, 10 mol %) was added to the vinyl iodide prepared above (10.0 mg, 9.3 μmol) at RT. After 15 min, hexamethyldistannane (10.0 μL, 47.0 μmol) was added and the mixture stirred in the dark for 16 h. H_2O was then added and the mixture extracted with Et_2O (×3). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and the crude residue purified by flash chromatography (20–50 % Et_2O/petrol) to furnish the desired vinyl stannane **117** as a colourless oil and as a 1:1 mixture of rotamers (8.5 mg, 82 %). $[\alpha]_D^{25} = -57.0$ ($c = 0.10$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 5.98$ (d, $J = 19.0$ Hz, 1H, H_{21}), 5.77 (dd, $J = 19.0$, 7.5 Hz, 1H, H_{22}), 5.24 [m, 1.5H, including; 5.25 (d, $J = 10.0$ Hz, 1H, H_{30}), 0.5 of H_{34}], 5.19 (br s, 0.5H, 0.5 of H_{34}), 4.83 (br s, 0.5H, 0.5 of H_2), 4.69 (br s, 0.5H, 0.5 of H_2), 4.14 (d, $J = 7.5$ Hz, 1H, H_{28}), 4.03–3.97 (m, 0.5H, 0.5 of H_6), 3.87 (apparent d, $J = 7.5$ Hz, 1.5H, H_{27}, 0.5 of H_6), 3.41–3.29 [m, 5H, including; 3.39 (s, 3H, C_{39}-OCH_3), H_{40}, H_{31}], 3.24 (s, 3H, C_{27}-OCH_3), 2.91–2.83 (m, 1.5H, H_{39}, 0.5 of H_6), 2.83–2.77 (m, 1H, H_{25}), 2.65 (apparent dd, $J = 17.0$, 9.0 Hz, 1.5H, H_{33}, 0.5 of H_6), 2.54–2.46 (m, 1H, H_{33}), 2.33–2.25 (m, 1H, H_{23}), 2.22–2.16 (m, 1H), 2.02–1.80 (m, 3H), 1.76 (s, 3H, C_{29}-CH_3), 1.70–1.56 (m, 3H), 1.45 (s, 9H, Boc), 1.43–1.00 [m, 19H, including; 1.10 (d, $J = 6.5$ Hz, 3H, C_{31}-CH_3), 1.03 (2×d, $J = 6.5$ Hz, 6H, C_{25}-CH_3, C_{23}-CH_3)], 0.95–0.82 [m, 21H, including; 0.88 (s, 9H, TBS), 0.85 (d, $J = 6.5$ Hz, 3H, C_{35}-CH_3)], 0.76–0.67 (m, 1H, H_{38}), 0.51 (q, $J = 8.0$ Hz, 6H, TES), 0.14 (s, 9H, $SnMe_3$), 0.07 (s, 3H, TBS), 0.06 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 213.8$ (C_{26}), (207.9, 207.7) (C_{32}), 171.1 (C_1), (155.7, 155.2) (C_8), 153.0 (C_{22}), 138.0 (C_{29}), 128.2 (C_{21}), 128.0 (C_{30}), 84.4 (C_{39}), 84.1 (C_{27}), (79.8, 79.6) (Boc), 79.2 (C_{28}), 75.6 (C_{40}), (74.7, 74.3) (C_{34}), 57.9 (C_{27}-OCH_3 and C_{39}-OCH_3), (54.9, 53.8) (C_2), 47.1 (C_{31}), 43.2 (C_{25}), (41.9, 40.9) (C_6), 39.1 (C_{23}), 38.6, 38.5, 36.1, 33.9, 33.1, 32.9, 31.3, (28.4, 28.3) (Boc), 26.8, 25.8 (TBS), 24.9, 24.7, 21.4, 20.5, 18.1, 15.2, 15.1, 15.0, 14.0, 11.6, 6.7 (TES), 4.7 (TES), 1.0, −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu} = 2926$, 1722, 1707, 1462, 1415, 1369, 1270, 1169, 1109 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{55}H_{103}NO_{10}Si_2Sn$: 1136.6040; found: 1136.6141 $[M+H]^+$.

Enoate 119: A solution of distilled $Ti(OiPr)_4$ (126 mL, 0.42 mol) and L-(+)-diethyl tartrate (96.0 g, 0.50 mol) in CH_2Cl_2 (800 mL) was stirred for 30 min at −25 °C. *t*BuOOH (3.0 M in isooctane, 280 mL, 0.84 mol) was added and the solution stirred for a further 1 h. A solution of *cis*-4-benzyloxybut-2-en-1-ol (75.0 g, 0.42 mol) in CH_2Cl_2 (400 mL) was then added via cannula over a period of 30 min and the resulting mixture stirred at −25 °C for 3 d. The reaction was warmed to 0 °C and quenched by the addition of an aqueous solution (500 mL) of ferrous sulfate heptahydrate (150 g) and tartaric acid (50 g). After stirring vigorously for 15 min, the layers were separated and the brown aqueous phase back-extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with H_2O and with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (50–80 % Et_2O/petrol) gave the desired epoxyalcohol as a colourless oil (65.0 g, 75 %, *ee* 92 % by comparison of optical rotation[97]) $[\alpha]_D^{25} = -26.5$ ($c = 1.28$, $CHCl_3$) [lit. (*ee* 90 %)[97] $= -26.5$ ($c = 0.80$, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 200 MHz): $\delta =$ 7.36–7.28 (m, 5H, ArH), 4.62 (d, $J = 11.8$ Hz, 1H, Ar-CH_2), 4.51 (d, $J =$ 11.8 Hz, Ar-CH_2), 3.74–3.65 (m, 4H, 2×H_{14}, 2×H_{17}), 3.32–3.16 (m, 2H, H_{15}, H_{16}), 2.52 ppm (t, $J = 6.3$ H, 1H, C_{14}-OH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.7$ (Ar), 128.4 (Ar), 127.9 (Ar), 127.7 (Ar), 73.4 (Ar-CH_2), 68.0 and 60.6 (C_{14} and C_{17}), 55.7 and 54.7 ppm (C_{15} and C_{16}); IR (thin film): $\tilde{\nu} = 3419$, 2990, 2862, 1453, 1256, 1093, 847 cm^{-1}; HMRS (EI): *m/z*: calcd for $C_{11}H_{14}O_3$: 194.0943; found: 194.0944 $[M]^+$. The observed data was consistent with that previously reported.[97]

To a solution of the epoxyalcohol prepared above (9.80 g, 50.0 mmol), DMSO (60 mL), and Et_3N (28.0 mL, 250 mmol) in CH_2Cl_2 (240 mL) at 0 °C was added SO_3·Py (32.0 g, 201 mmol) in two portions. After 1 h, the brown mixture was diluted with Et_2O until a precipitate was evident and then washed with H_2O. The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by rapid flash chromatography (50 % Et_2O/petrol) to afford the desired epoxyaldehyde as a colourless oil (7.70 g, 80 %). $[\alpha]_D^{25} = -96.8$ ($c = 1.80$, $CHCl_3$) [ref. [97] $= +104.3$ ($c = 0.94$, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 9.43$ (d, $J =$ 4.7 Hz, 1H, H_{14}), 7.38–7.34 (m, 5H, ArH), 4.55 (s, 2H, 2×Ar-CH_2), 3.83 (dd, $J = 13.1$, 4.7 Hz, H_{17}), 3.75 (dd, $J = 12.4$, 5.1 Hz, 1H, H_{17}), 3.49 (q, $J =$ 4.5 Hz, 1H, H_{16}), 3.40 ppm (t, $J = 4.7$ Hz, 1H, H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 197.6$ (C_{14}), 137.0 (Ar), 128.4 (Ar), 127.9 (Ar), 127.7 (Ar), 73.4 (Ar-CH_2), 66.1 (C_{17}), 57.9 and 57.2 ppm (C_{15} and C_{16}); IR (thin film): $\tilde{\nu} = 2864$, 1737, 1495, 1242, 1095, 941, 847 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{11}H_{11}O_3$: 191.0708; found: 191.0704 $[M-H]^-$; elemental analysis calcd (%) for $C_{11}H_{12}O_3$: C 68.74, H 6.29; found: C 68.44, H 6.45. The observed NMR and IR data was consistent with that previously reported.[97]

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To a stirred suspension of LiCl (3.90 g, 93.0 mmol) in CH_3CN (600 mL) at RT was added sequentially methyl diethylphosphonate (17.0 mL, 93.0 mmol), DBU (11.5 mL, 74.0 mmol), and the epoxyaldehyde prepared above (12.0 g, 62.0 mmol). After 10 min, saturated aqueous NH_4Cl was added, and the layers separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography gave the desired enoate **119** as a colourless oil (10.2 g, 66%, $E/Z > 95:5$). $[\alpha]_D^{25} = +7.4$ ($c = 1.44$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.33$ (m, 5H, ArH), 6.77 (dd, $J = 15.7$, 6.6 Hz, 1H, H_{14}), 6.14 (dd, $J = 15.7$, 0.9 Hz, 1H, H_{15}), 4.56 (d, $J = 7.9$ Hz, 2H, 2×Ar-CH_2), 3.75 (s, 3H, C_{12}-OCH_3), 3.68–3.40 ppm (m, 4H, 2×H_{17}, H_{16}, H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 165.7$ (C_{12}), 141.3 (C_{14}), 137.4 (Ar), 128.5 (Ar), 127.8 (C_{13}), 125.1 (Ar), 73.3 (Ar-CH_2), 67.4 (C_{17}), 57.5 and 54.20 (C_{15} and C_{16}), 51.1 ppm (C_{12}-OCH_3); IR (thin film): $\tilde{\nu} = 2950$, 2860, 1723, 1689, 1657, 1274, 1098 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{14}H_{17}O_4$. 249.1127; found: 249.1142 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{16}O_4$: C 67.71, H 6.53; found: C 67.99, H 6.50.

Diol 120: DIBAL-H (1.5 M in $PhCH_3$, 160 mL, 240 mmol) was added dropwise to a solution of enoate **119** (10.0 g, 40.0 mmol) in CH_2Cl_2 (300 mL) at −78 °C. The resulting mixture was stirred for 1 h, then H_2O was added carefully, and the reaction mixture allowed to warm to RT. EtOAc and sodium sulfate were added, and stirring continued for 1 h. The mixture was then filtered through a pad of Celite (washing with EtOAc) and the filtrate concentrated in vacuo to afford the desired diol **120** as a colourless oil (9.00 g, 100%) that was used in the subsequent reaction without further purification (purity >95%). $[\alpha]_D^{25} = +2.0$ ($c = 1.5$, $CHCl_3$) [ref. [98] $= +2.7$ ($c = 1.50$, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.31$ (m, 5H, ArH), 5.70 (m, 2H, H_{13}, H_{14}), 4.54 (s, 2H, 2×Ar-CH_2), 4.07 (br s, 2H, 2×H_{12}), 3.84 (m, 1H, H_{16}), 3.45 (m, 2H, 2×H_{17}), 2.24 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 137.5$ (Ar), 132.2 (C_{14}), 128.4 (Ar), 128.0 (C_{13}), 127.8 (Ar), 73.9 and 73.4 (C_{12} and Ar-CH_2), 69.8 (C_{16}), 63.4 (C_{17}), 31.2 ppm (C_{15}); IR (thin film): $\tilde{\nu} = 3373$, 2861, 1453, 1093 cm^{-1}; HMRS (EI): m/z: calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1260 $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{18}O_3$: C 70.23, H 8.17; found: C 70.27, H 8.22. The observed data was consistent with that previously reported.[98]

Methyl ether 121: To a solution of diol **120** (8.30 g, 37.3 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added sequentially pivaloyl chloride (4.90 mL, 40.0 mmol) and pyridine (16.0 mL, 200 mmol). The mixture was warmed to RT and stirred for 2 h, then treated with HCl (3.0 M) and brine. The layers were separated, and the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography gave the desired C12-pivoyl ester as a colourless oil (8.50 g, 69% over 2 steps). $[\alpha]_D^{25} = +1.4$ ($c = 1.62$, $CHCl_3$) [ref. [98] $= +2.8$ ($c = 1.70$, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.33$ (m, 5H, ArH), 5.84–5.56 (m, 2H, H_{13}, H_{14}), 4.55 (s, 2H, 2×Ar-CH_2), 4.50 (d, $J = 5.6$ Hz, 2H, 2×H_{12}), 3.87 (m, 1H, H_{16}), 3.50 (dd, $J = 9.4$, 3.4 Hz, 1H, H_{17}), 3.35 (dd, $J = 9.4$, 7.8 Hz, 1H, H_{17}), 2.26 (t, $J = 6.0$ Hz, 2H, 2×H_{15}), 1.23 (br s, 1H, OH), 1.19 ppm (s, 9H, Piv); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 178.2$ (Piv), 137.8 (Ar), 130.5 (C_{14}), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 127.3 (C_{13}), 73.7 and 73.4 (C_{12} and Ar-CH_2), 69.7 (C_{16}), 64.6 (C_{17}), 38.7 (Piv), 36.3 (C_{15}), 27.2 ppm (Piv); IR (thin film): $\tilde{\nu} = 3465$, 2972, 1727, 1282, 1156 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{18}H_{27}O_4$: 307.1909; found: 307.1920 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{26}O_4$: C 70.55, H 8.56; found: C 70.19, H 8.56. The observed data was consistent with that previously reported.[98]

To a solution of the C12-pivoyl ester prepared above (8.50 g, 27.7 mmol) in iodomethane (50 mL) at 0 °C was added NaH (60% dispersion in oil, 1.70 g, 42.5 mmol). The resulting mixture was stirred for 2 h, then quenched carefully with HCl (3.0 M). Brine was added, and the mixture further diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was washed with CH_2Cl_2 (×2). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography gave the corresponding C16-methyl ether as a colourless oil (8.40 g, 94%). $[\alpha]_D^{25} = +3.1$ ($c = 1.20$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.33$ (m, 5H, ArH), 5.78–5.54 (m, 2H, H_{13}, H_{14}), 4.54 (s, 2H, ×Ar-CH_2), 4.50 (dd, $J = 5.8$, 1.0 Hz, 2H, ×H_{12}), 3.41 (s, 3H, C_{16}-OCH_3), 3.49–3.36 (m, 3H, H_{16}, ×H_{17}), 2.30 (t, $J = 6.0$ Hz, 2H, ×H_{15}), 1.19 ppm (s, 9H, Piv); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 178.3$ (Piv), 138.2 (Ar), 130.9 (C_{14}), 128.4 (Ar), 127.7 (Ar), 127.6 (C_{13}), 126.9 (Ar), 79.6 (C_{16}), 73.4, 71.4, and 64.7 (C_{12}, C_{17}, and Ar-CH_2), 57.5 (C_{16}-OCH_3), 38.7 (Piv), 34.2 (C_{15}), 27.2 ppm (Piv); IR (thin film): $\tilde{\nu} = 2972$, 2931, 1728, 1479, 1454, 1281, 1152 cm^{-1}; HMRS (EI): m/z: calcd for $C_{19}H_{28}O_4$: 320.1987; found: 320.1958 $[M]^+$; elemental analysis calcd (%) for $C_{19}H_{28}O_4$: C 71.21, H 8.81; found: C 71.46, H 8.93.

DIBAL-H (1.5 M in $PhCH_3$, 36.0 mL, 54 mmol) was added dropwise to a solution of the C16-methyl ether prepared above (7.00 g, 21.8 mmol) in CH_2Cl_2 (200 mL) at −78 °C and the resulting mixture stirred for 1 h. H_2O was then added carefully, the reaction mixture warmed to RT, and EtOAc and sodium sulphate introduced. After stirring for 1 h, the reaction contents were filtered, concentrated in vacuo, and the crude residue purified by flash chromatography to afford alcohol **121** as a colourless oil (4.54 g, 88%). $[\alpha]_D^{25} = +3.9$ ($c = 1.62$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.33$ (m, 5H, ArH), 5.68–5.63 (m, 2H, H_{13}, H_{14}), 4.53 (s, 2H, 2×Ar-CH_2), 4.04 (br s, 2H, ×H_{12}), 3.40 (s, 3H, C_{16}-OCH_3), 3.45–3.39 (m, 3H, H_{16}, ×H_{17}), 2.30 ppm (m, 3H, ×H_{15}, C_{12}-OH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 138.2$ (Ar), 131.8 (C_{14}), 128.4 (Ar), 128.0 (Ar), 127.7 (C_{13}), 79.6 (C_{16}), 73.4, 71.3, and 63.4 (C_{12}, C_{17}, and Ar-CH_2), 57.4 (C_{16}-OCH_3), 34.0 ppm (C_{15}); IR (thin film): $\tilde{\nu} = 3416$, 3087, 3062, 3029, 1496, 1453, 1006 cm^{-1}; HMRS (EI): m/z: calcd for $C_{14}H_{20}O_3$: 236.1412; found: 236.1427 $[M]^+$.

Vinyl epoxide 122: To a suspension of D-(−)-diethyl tartrate (485 mg, 14 mol%) and pre-dried 4 Å MS in CH_2Cl_2 (80 mL) at −23 °C was added freshly distilled Ti(O*i*Pr)$_4$ (0.50 mL, 10 mol%) followed by *t*BuOOH (11.5 mL, 34.0 mmol). The resulting mixture was stirred for 1 h, at which point a solution of methyl ether **121** (4.00 g, 16.9 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was stirred for 2 d at −23 °C, then warmed to 0 °C and H_2O added. After 30 min, aqueous NaOH (2.5 M) and brine were added and stirring continued for 1 h at 0 °C. The mixture was filtered through a pad of Celite, and the layers separated. The aqueous phase was back-extracted with CH_2Cl_2, and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography gave the desired epoxide as a colourless oil (3.41 g, 80%). $[\alpha]_D^{25} = +21.0$ ($c = 0.97$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.33$ (m, 5H, ArH), 4.56 (s, 2H, 2×Ar-CH_2), 3.91–3.81 (m, 1H, H_{16}), 3.56 (d, $J = 1.0$ Hz, 2H, 2×H_{17}), 3.65–3.49 (m, 2H, 2×H_{12}), 3.41 (s, 3H, C_{16}-OCH_3), 3.04 (dd, $J = 11.3$, 2.5 Hz, 1H, H_{14}), 2.92 (dt, $J = 4.2$, 2.5 Hz, 1H, H_{13}), 1.89–1.90 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 138.1$ (Ar), 128.4 (Ar), 127.7 (2×Ar), 77.8 (C_{16}), 73.5, 71.5, and 61.6 (C_{12}, C_{17}, and Ar-CH_2), 58.1 and 57.4 (C_{13} and C_{14}), 52.9 (C_{16}-OCH_3), 33.5 ppm (C_{15}); IR (thin film): $\tilde{\nu} = 3468$, 2926, 2864, 1454, 1365, 1094 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{14}H_{20}O_4$: 252.1352; found: 252.1361 $[M]^+$.

The epoxide prepared above (2.00 g, 7.93 mmol) was added to a mixture of NMO (1.40 g, 11.9 mmol) and pre-dried 4 Å MS in CH_3CN/CH_2Cl_2 (1:1, 40 mL). The resulting mixture was stirred for 1 h at RT before the addition of TPAP (280 mg, 0.79 mmol). The green solution was stirred for 1 h, then filtered through Celite and concentrated in vacuo. Purification of the crude residue by rapid flash chromatography afforded the desired C12-aldehyde as a colourless oil (1.19 g, 60%). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.98$ (d, $J = 6.3$ Hz, 1H, H_{12}), 7.33 (m, 5H, ArH), 4.56 (s, 2H, 2×Ar-CH_2), 3.56 (s, 2H, 2×H_{17}), 3.60–3.50 (m, 1H, H_{16}), 3.41 (s, 3H, C_{16}-OCH_3), 3.34 (ddd, $J = 8.1$, 4.9, 2.0 Hz, 1H, H_{14}), 3.16 (dd, $J = 6.4$, 2.1 Hz, 1H, H_{13}), 1.98–1.88 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 198.2$ (C_{12}), 138.0 (Ar), 128.5 (ArH), 127.8 (2×Ar), 77.3 (C_{16}), 73.5 (Ar-CH_2), 70.8 (C_{17}), 58.8 and 57.5 (C_{13} and C_{14}), 53.9 ppm (C_{16}-OCH_3), 33.4 (C_{14}); IR (thin film): $\tilde{\nu} = 2862$, 1726, 1099 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{19}O_4$: 251.1283; found: 251.1277 $[M+H]^+$.

KHMDS (0.5 M in $PhCH_3$, 16.0 mL, 8.00 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.90 g, 8.00 mmol) in THF (100 mL) at 0 °C. The bright yellow mixture was stirred for 30 min, then the C12-aldehyde prepared above (1.00 g, 4.00 mmol) in THF (15+5 mL) was added via cannula. After stirring for 1 h, brine was added, the layers separated, and the aqueous phase extracted with Et_2O (×2). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the crude residue purified by flash chromatography

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to afford the desired vinyl epoxide **122** as a light yellow oil (824 mg, 83%). $[\alpha]_D^{25}=+12.4$ ($c=1.50$, $CHCl_3$);^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=$ 7.33 (m, 5H, ArH), 5.59–5.38 (m, 2H, 2×H_{11}), 5.24 (dd, $J=10.0$, 2.8 Hz, 1H, H_{12}), 4.56 (s, 2H, 2×Ar-CH_2), 3.56 (d, $J=1.5$ Hz, 2H, 2×H_{17}), 3.58–3.50 (m, 1H, H_{16}), 3.41 (s, 3H, C_{16}-OCH_3), 3.10 (dd, $J=6.8$, 2.1 Hz, 1H, H_{13}), 2.91 (td, $J=6.5$, 2.3 Hz, 1H, H_{14}), 1.96–1.79 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=138.0$ (Ar), 135.6 (C_{12}), 128.4 (Ar), 127.7 (2×Ar), 119.2 (C_{11}), 77.9 (C_{16}), 73.5 (Ar-CH_2), 71.4 (C_{17}), 58.5 and 57.5 (C_{13} and C_{14}), 57.3 (C_{16}-OCH_3), 33.9 ppm (C_{15}); IR (thin film): $\tilde{\nu}=2927$, 2863, 1454, 1102 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{15}H_{21}O_3$: 249.1490; found: 249.1503 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{20}O_3$: C 72.54, H 8.12; found: C 72.31, H 8.01.

Iron carbonyl intermediate 123: A solution of vinyl epoxide **122** (820 mg, 3.30 mmol) in degassed THF (100 mL) was added to a suspension of diironnonacarbonyl (2.40 g, 6.60 mmol) at RT and stirring continued for 2 h. The dark green reaction mixture was filtered through Celite, $PhCH_3$ was added and the solution was concentrated in vacuo at RT. Purification of the crude residue by flash chromatography (0–20% Et_2O/petrol) gave the desired ferrilactone **123** as a brown oil (1.00 g, 72%). $[\alpha]_D^{25}=-94.5$ ($c=0.80$, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): $\delta=7.33$ (m, 5H, ArH), 4.30 (s, 2H, 2×Ar-CH_2), 4.19 (dd, $J=12.0$, 5.0 Hz, 1H, H_{14}), 3.86 (dd, $J=$ 8.0, 5.0, Hz, 1H, H_{13}), 3.62 (dt, $J=13.2$, 8.0 Hz, 1H, H_{12}), 3.34 (d, $J=$ 1.5 Hz, 2H, 2×H_{17}), 3.41–3.28 (m, 1H, H_{16}), 3.15 (s, 3H, C_{16}-OCH_3), 2.77 (dd, $J=8.4$, 1.5 Hz, 1H, $H_{11,exo}$), 2.72 (dd, $J=13.2$, 1.5 Hz, 1H, $H_{11,eno}$), 1.74 ppm (dd, $J=7.0$, 5.0 Hz, 2H, 2×H_{15}); ^{13}C NMR (C_6D_6, 100 MHz): $\delta=208.8$, 207.1, 203.8, 200.1 (4×CO), 139.0 (Ar), 128.9 (Ar), 127.8 (2× Ar), 90.8 (C_{12}), 82.3, 78.1 (C_{16}), 73.8, 73.4, 71.4, 58.5, 57.0 (C_{16}-OCH_3), 38.8 ppm (C_{15}); IR (thin film): $\tilde{\nu}=2925$, 2081, 2017, 1670, 1091, 1008 cm^{-1}.

α,β- and β,γ-Unsaturated lactones 124 and 125: A solution of ferrilactone **123** (1.10 g, 2.63 mmol) in degassed PhH (40 mL) was heated at 70°C under 280 atm of carbon monoxide in an agitated high pressure steel reaction vessel for 10 h. The reaction mixture was then allowed to cool to RT, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography to give a mixture of lactones **124** and **125** as a light brown oil (618 mg, 85%, **124**/**125** 2.2:1) along with a small amount of the corresponding γ,δ-unsaturated lactone (≈5%) which was easily separated during purification.

Data for **124**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.32$ (m, 5H, ArH), 5.89–5.82 (m, 2H, H_{12}, H_{13}), 5.05 (m, 1H, H_{14}), 4.55 (d, $J=12.2$ Hz, 2H, 2×Ar-CH_2), 3.58–3.54 (m, 3H, H_{16}, 2×H_{17}), 3.37 (s, 3H, C_{16}-OCH_3), 3.04 (m, 2H, 2×H_{11}), 2.09–1.84 ppm (m, 2H, 2×H_{17}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=168.9$ (C_{10}), 138.0 (Ar), 128.3 (Ar), 127.6 (2×Ar), 126.6 and 121.2 (C_{12} and C_{13}), 76.9, 76.2, 73.3, and 70.6 (C_{14}, C_{16}, C_{17}, Ar-CH_2), 57.3 (C_{16}-OCH_3), 37.3 (C_{11}), 29.9 ppm (C_{15}); IR (thin film): $\tilde{\nu}=2920$, 1723, 1382, 1247 cm^{-1}; HRMS (EI): m/z: calcd for $C_{16}H_{20}O_4$: 276.1362; found: 276.1348 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{20}O_4$: C 69.55, H 7.30; found: C 69.58, H 7.47.

Data for **125**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.31$ (m, 5H, ArH), 6.85 (dt, $J=9.8$, 4.0 Hz, 1H, H_{12}), 5.98 (dt, $J=9.8$, 1.8 Hz, 1H, H_{11}), 4.58–4.43 (m, 3H, H_{14}, 2×Ar-CH_2), 3.60–3.50 (m, 3H, H_{16}, 2×H_{17}), 3.38 (s, 3H, C_{16}-OCH_3), 2.39–2.32 (m, 2H, 2×H_{13}), 2.16–1.91 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=164.3$ (C_{10}), 145.1 (C_{12}), 138.0 (Ar), 128.3 (Ar), 127.6 (2×Ar), 121.2 (C_{11}), 76.0, 75.1, 73.3 and 70.4 (C_{14}, C_{16}, C_{17}, and Ar-CH_2), 57.1 (C_{16}-OCH_3), 36.2 (C_{13}), 29.3 ppm (C_{15}); HRMS (ESI): m/z: calcd for $C_{16}H_{21}O_4$: 277.1440; found: 277.1451 $[M+H]^+$.

Lactone 126: The mixture of lactones **124** and **125** (600 mg, 2.17 mmol) was dissolved in EtOAc (15 mL) and PtO_2 (20 mg, 4 mol%) added. The flask was purged with hydrogen and the reaction stirred for 3 h at RT under an atmosphere of H_2 (1 atm). The mixture was then filtered, the solvent removed in vacuo and the residue purified by flash chromatography to afford the saturated lactone **126** as a colourless oil (495 mg, 82%). $[\alpha]_D^{25}=+26.3$ ($c=1.50$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.33$ (m, 5H, ArH), 4.55 (d, $J=8.1$ Hz, 2H, 2×Ar-CH_2), 4.39–4.25 (m, 1H, H_{14}), 3.62–3.51 (m, 3H, H_{16}, 2×H_{17}), 3.39 (s, 3H, C_{16}-OCH_3), 2.59–2.36 (m, 2H, 2×H_{11}), 2.08–1.47 ppm (m, 6H, 2×H_{12}, 2×H_{13}, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=171.7$ (C_{10}), 138.0 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 77.4 and 76.1 (C_{14} and C_{16}), 73.2 and 70.4 (C_{17} and Ar-CH_2), 57.1 (C_{16}-OCH_3), 37.2 (C_{11}), 29.2, 27.8 and 18.3 ppm (C_{12}, C_{13}, and C_{15}); IR (thin film): $\tilde{\nu}=2930$, 1734, 1241, 1100 cm^{-1}; HMRS (EI): m/z: calcd for $C_{16}H_{22}O_4$: 258.1518; found: 258.1527 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.85, H 7.98.

α-Methyl lactones 127 and 128: To a cooled (−78°C) solution of lactone **126** (400 mg, 1.43 mmol) in THF (10 mL) was added a solution of freshly prepared LDA (0.5 M, 3.0 mL, 1.50 mmol). After 1 h, then iodomethane (0.90 mL, 14.5 mmol) was added dropwise and the mixture stirred at −78°C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, warmed to RT and diluted with Et_2O. The layers were separated, and the aqueous phase back-extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR of the crude mixture indicated a 60:40 diastereoisomeric mixture at the new α-methyl stereocentre, in favour of the undesired C11-(*S*) epimer. Purification by flash chromatography removed minor impurities to give a mixture of **127** and **128** as a colourless oil (351 mg, 84%). Preparative HPLC could be used to achieve separation of small amounts of material. In this fashion, **127** could be recycled to a mixture of **127** and **128** through a deprotonation (LDA, THF, −78°C)/protonation strategy in 94% yield wherein the same 60:40 ratio of **127**/**128** was obtained.

Data for the desired C11-(*R*) epimer **128**: $[\alpha]_D^{25}=+16.8$ ($c=0.72$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.42$–7.29 (m, 5H, ArH), 4.58 (d, $J=$ 12.1 Hz, 1H, Ar-CH_2), 4.48 (d, $J=12.1$ Hz, 1H, Ar-CH_2), 4.38–4.23 (m, 1H, H_{14}), 3.63–3.43 (m, 3H, H_{16}, 2×H_{17}), 3.37 (s, 3H, C_{16}-OCH_3), 2.69–2.32 (m, 1H, H_{11}), 2.03–1.82 (m, 3H, H_{12}, H_{13}, and H_{15}), 1.70–1.44 (m, 3H, H_{12}, H_{13}, and H_{15}), 1.26 ppm (d, $J=7.1$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=174.1$ (C_{10}), 138.2 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 78.9, 76.4, 73.3, and 70.5 (C_{14}, C_{16}, C_{17} and Ar-CH_2), 57.2 (C_{16}-OCH_3), 37.7, 36.1, 29.5, and 28.5 (C_{11}, C_{12}, C_{13}, and C_{15}), 17.4 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu}=2932$, 2873, 1728, 1604, 1495, 1454, 1376, 1284, 1241, 1177, 1092, 1008, 932, 853, 749, 699, 665 cm^{-1}; HMRS (EI): m/z: calcd for $C_{17}H_{24}O_4$: 292.1674; found: 292.1670 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{24}O_4$: C 69.84, H 8.27; found: C 69.87, H 8.20.

Confirmation of the structure of 128 by conversion to 3: A suspension of palladium hydroxide (20% on carbon, 10 mg) in a solution of lactone **128** (100 mg, 0.34 mmol) in EtOAc (2 mL) was stirred under a hydrogen atmosphere (1 atm) at RT for 14 h. The mixture was filtered through a pad of silica (eluting with EtOAc), concentrated in vacuo and purified by flash chromatography (100% EtOAc) to furnish the corresponding C17-alcohol as a colourless oil (68.0 mg, 100%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=4.43$–4.37 (m, 1H, H_{14}), 3.76 (d, $J=9.6$ Hz, 1H, H_{17}), 3.56–3.50 (m, 2H, H_{16}, H_{17}), 3.36 (s, 3H, C_{16}-OCH_3), 2.46–2.38 (m, 1H, H_{11}), 2.23 (s, 1H, C_{17}-OH), 2.03–1.88 (m, 3H, H_{12}, H_{13}, H_{15}), 1.82–1.51 (m, 3H, H_{12}, H_{13}, H_{15}), 1.27 ppm (d, $J=7.1$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=174.1$ (C_{10}), 78.7 and 77.5 (C_{14} and C_{16}), 62.5 (C_{17}), 56.8 (C_{16}-OCH_3), 36.1 (C_{11}), 36.8, 29.5, and 28.5 (C_{12}, C_{13}, and C_{15}), 17.4 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu}=3446$, 2934, 2827, 1727, 1460, 1378, 1334, 1286, 1242, 1179, 1094, 1005, 933, 851 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{10}H_{19}O_4$: 203.1283; found: 203.1283 $[M+H]^+$; elemental analysis calcd (%) for $C_{10}H_{18}O_4$: C 59.39, H 8.97; found: C 59.15, H 9.05.

DMP (197 mg, 0.46 mmol), pyridine (39.0 μL, 460 μmol) and *t*BuOH (45.0 μL, 460 μmol) were added to a stirred solution of the C17 alcohol prepared above (68.0 mg, 336 μmol) in CH_2Cl_2 (3 mL) at RT. After 1 h, the reaction was quenched by the addition of a mixture of aqueous sodium thiosulfate and sodium hydrogen carbonate solutions (1:1) and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography on Florisil (50% EtOAc/petrol) gave the corresponding C17 aldehyde as a colourless oil (68.0 mg, 100%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=9.74$ (d, $J=1.3$ Hz, 1H, H_{17}), 4.54–4.49 (m, 1H, H_{14}), 3.79 (td, $J=5.5$, 1.2 Hz, 1H, H_{16}), 3.47 (s, 3H, C_{16}-OCH_3), 2.46–2.39 (m, 1H, H_{11}), 2.09–1.92 (m, 3H, H_{12}, H_{13}, H_{15}), 1.69–1.53 (m, 3H, H_{12}, H_{13}, H_{15}), 1.29 ppm (d, $J=7.1$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=203.0$ (C_{17}), 173.4 (C_{10}), 81.7 (C_{16}), 77.2 (C_{14}), 58.3 (C_{16}-OCH_3), 35.7 (C_{11}), 36.0, 29.1 and 28.4 (C_{12}, C_{13}, and C_{15}), 17.4 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu}=2932$, 2875, 2828, 1734, 1458, 1376, 1327, 1243, 1174, 1095, 1046, 1005, 934, 894, 837, 734 cm^{-1}; HMRS (EI): m/z: calcd for $C_{10}H_{16}O_4$: 200.1049; found: 200.1049 $[M]^+$.

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MeMgBr (3.0 M in Et_2O, 63.0 μL, 189 μmol) was added dropwise to a stirred solution of the C17 aldehyde prepared above (35.0 mg, 175 μmol) in THF (4.5 mL) at −78 °C. After 30 min, a second aliquot of MeMgBr (3.0 M in Et_2O, 63 μL, 189 μmol) was added and the reaction stirred for an additional 30 min. The reaction was quenched with saturated aqueous NH_4Cl, warmed to RT, and extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–50% EtOAc/petrol) afforded the desired C_{17}-secondary alcohol as a colourless oil and as a 2:1 mixture of inseparable diastereoisomers (14.0 mg, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.55–4.38 (m, 1H, H_{14}), 4.85–3.93 (m, 0.33H, 0.33×H_{16}), 3.73–3.62 (m, 0.66H, 0.66×H_{16}), 3.41 (s, 2H, C_{16}-OCH_3), 3.37 (s, 1H, C_{16}-OCH_3), 3.22 (m, 1H, H_{17}), 2.53–2.48 (m, 0.33H, 0.33H_{11}), 2.47–2.41 (m, 0.66H, 0.66×H_{11}), 2.14 (s, 1H, C_{17}-OH), 2.07–1.73 (m, 3H, H_{12}, H_{13}, H_{15}), 1.68–1.49 (m, 3H, H_{12}, H_{13}, H_{15}), 1.29 (d, J = 7.1 Hz, 3H, C_{11}-CH_3), 1.22 (d, J = 6.5 Hz, 2H, C_{17}-CH_3), 1.17 ppm (d, J = 6.4 Hz, 1H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, only major diastereoisomer reported) δ = 174.0 (C_{10}), 79.2, 78.6, and 68.2 (C_{14}, C_{16}, and C_{17}), 57.9 (C_{16}-OCH_3), 36.1 (C_{11}), 36.3, 29.7, and 28.5 (C_{12}, C_{13}, and C_{15}), 17.4 (C_{11}-CH_3), 14.3 ppm (C_{17}-CH_3); IR (thin film): $\tilde{\nu}$ = 3474, 2925, 1727, 1459, 1378, 1241, 1181, 1094, 933, 734 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{11}H_{19}O_3$: 199.1345; found: 199.1344 $[M-OH]^+$; elemental analysis calcd (%) for $C_{11}H_{20}O_4$: C 61.09, H 9.32; found: C 61.34, H 9.51.

DMP (101 mg, 250 μmol), pyridine (17.0 μL, 250 μmol), and tBuOH (19.0 μL, 250 μmol) were added to a solution of the diastereoisomeric mixture of alcohols prepared above (10.0 mg, 46.2 μmol) in CH_2Cl_2 (1.8 mL) at RT. After 5 min, the reaction was quenched by the addition of a mixture of aqueous sodium thiosulfate and sodium hydrogen carbonate solutions (1:1) and extracted with CH_2Cl_2 (×3). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (50% EtOAc/petrol) gave the desired ketone **3** as a colourless oil (10.0 mg, 100%). The observed analytical data was identical in all respects to that reported for the preparation of **3** by degradation (see Supporting Information), including mixed material NMR studies.

Silylated lactol 129: To a solution of lactone **128** (123 mg, 0.42 mmol) in $PhCH_3$ (2.5 mL) at −78 °C was added DIBAL-H (1.5 M in $PhCH_3$, 0.30 mL, 0.45 mmol). The reaction was stirred for 30 min at −78 °C then quenched by the addition of H_2O. The mixture was allowed to warm to RT and then diluted with EtOAc. Sodium bicarbonate (250 mg) was added and the suspension was stirred for 0.5 h. The reaction was filtered through a pad of silica (eluting with EtOAc) and the solvent removed in vacuo to leave afford the C10-lactol as a clear oil. This was dissolved in DMF (2.5 mL) and then imidazole (31.0 mg, 0.45 mmol), TBSCl (68.0 mg, 0.45 mmol) and DMAP (2 mg, cat.) were added sequentially. The reaction was stirred at RT for 24 h, then H_2O was added and the mixture extracted with Et_2O (×4). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25% Et_2O/petrol) furnished the desired silylated lactol **129** as a clear oil (158 mg, 92%). $[\alpha]_D^{25}$ = −7.0 (c = 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.35–7.30 (m, 4H, ArH), 7.29–7.26 (m, 1H, ArH), 4.51 (d, J = 12.2 Hz, 1H, Ar-CH_2), 4.51 (d, J = 12.2 Hz, 1H, Ar-CH_2), 4.13 (d, J = 8.1 Hz, 1H, H_{10}), 3.59–3.53 (m, 2H, H_{16}, H_{17}), 3.50 (dd, J = 10.3, 5.0 Hz, 1H, H_{17}), 3.36 (s, 3H, C_{16}-OCH_3), 3.35–3.30 (m, 1H, H_{14}), 1.90–1.85 (m, 1H, H_{15}), 1.75–1.71 (m, 1H, H_{12}), 1.69–1.63 (m, 1H, H_{15}), 1.50–1.46 (m, 1H, H_{13}), 1.43–1.37 (m, 1H, H_{11}), 1.31–1.26 (m, 1H, H_{13}), 1.12 (qd, J = 12.9, 3.9 Hz, 1H, H_{12}), 0.90 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.10 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 138.4 (Ar), 128.3 (Ar), 127.7 (Ar), 127.5 (Ar), 102.0 (C_{10}), 77.2 (C_{16}), 73.3 (Ar-CH_2), 73.0 (C_{14}), 71.1 (C_{17}), 57.1 (C_{16}-OCH_3), 37.8 (C_{11}), 36.9 (C_{15}), 31.5 (C_{13}), 30.9 (C_{12}), 25.8 (TBS), 18.0 (TBS), 16.9 (C_{11}-CH_3), −3.7 (TBS), −5.3 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2951, 2928, 2856, 1164, 1065 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{23}H_{40}O_4SiNa$: 431.2588; found: 431.2591 $[M+Na]^+$.

Ketone 130: To a stirred solution of silyl lactol ether **129** (90.0 mg, 0.22 mmol) in EtOAc (4 mL) was added a suspension of palladium hydroxide on carbon (Degussa type) (4.6 mg, cat.) in EtOAc (1 mL). The reaction was purged with hydrogen, and stirred for 24 h under H_2 (1 atm), then filtered through a pad of silica (eluting with EtOAc). The solvent was removed in vacuo, and the crude residue purified by flash chromatography (50% Et_2O/petrol) to give the corresponding C17-alcohol as a clear oil (70.0 mg, 100%). $[\alpha]_D^{25}$ = −10.5 (c = 3.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.12 (d, J = 8.1 Hz, 1H, H_{10}), 3.75–3.70 (m, 1H, H_{17}), 3.56–3.51 (m, 2H, H_{16}, H_{17}), 3.50–3.43 (m, 1H, H_{14}), 3.34 (s, 3H, C_{16}-OCH_3), 2.27 (br s, 1H, C_{17}-OH), 1.94–1.89 (m, 1H, H_{15}), 1.76–1.71 (m, 1H, H_{12}), 1.63–1.57 (m, 1H, H_{15}), 1.50–1.45 (m, 1H, H_{13}), 1.44–1.38 (m, 1H, H_{11}), 1.37–1.30 (m, 1H, H_{13}), 1.17 (qd, J = 13.0, 4.1 Hz, 1H, H_{12}), 0.90 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.10 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 102.0 (C_{10}), 78.3 (C_{16}), 72.8 (C_{14}), 63.2 (C_{17}), 56.7 (C_{16}-OCH_3), 37.7 (C_{11}), 35.9 (C_{15}), 31.7 (C_{13}), 30.9 (C_{12}), 25.7 (TBS), 18.0 (TBS), 16.9 (C_{11}-CH_3), −3.9 (TBS), −5.3 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 3672, 3585, 3464, 2930, 2857, 1161, 1063 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{16}H_{34}O_4SiNa$: 341.2119; found: 341.2102 $[M+Na]^+$.

To a flask containing pre-dried 4 Å MS (100 mg) was added NMO (40.0 mg, 340 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 10 min, and a solution of the C17 alcohol prepared above (35.0 mg, 110 μmol) in CH_2Cl_2 (1 mL) was then added. A solution of TPAP (4.0 mg, 11 μmol) in CH_3CN (0.2 mL) was added dropwise and the reaction stirred at RT for 1 h. The reaction was then filtered through a small pad of silica (eluting with Et_2O) and the solvent removed in vacuo. This resultant oil was dissolved in Et_2O (25 mL), filtered through a small pad of silica (eluting with Et_2O) and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (33% Et_2O/petrol) to give the corresponding C17-aldehyde as a clear oil (35.2 mg, 100%). $[\alpha]_D^{25}$ = −25.0 (c = 3.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.66 (d, J = 1.7 Hz, 1H, H_{17}), 4.13 (d, J = 8.1 Hz, 1H, H_{10}), 3.77–3.72 (m, 1H, H_{16}), 3.57–3.52 (m, 1H, H_{14}), 3.42 (s, 3H, C_{16}-OCH_3), 1.97 (ddd, J = 14.2, 8.9, 5.1 Hz, H_{15}), 1.84 (ddd, J = 14.2, 7.3, 3.8 Hz, H_{15}), 1.77–1.72 (m, 1H, H_{12}), 1.53–1.47 (m, 1H, H_{13}), 1.45–1.39 (m, 1H, H_{11}), 1.31 (tdd, J = 13.1, 11.2, 3.9 Hz, H_{13}), 1.17 (qd, J = 13.0, 4.0 Hz, 1H, H_{12}), 0.91 (s, 9H, TBS), 0.85 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.12 (s, 3H, TBS), 0.08 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 202.8 (C_{17}), 102.0 (C_{10}), 82.5 (C_{16}), 71.5 (C_{14}), 58.0 (C_{16}-OCH_3), 37.7 (C_{11}), 36.2 (C_{15}), 31.3 (C_{13}), 30.8 (C_{12}), 25.7 (TBS), 18.0 (TBS), 16.9 (C_{11}-CH_3), −4.0 (TBS), −5.4 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2955, 2930, 2857, 1732, 1161, 1063 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{16}H_{32}O_4SiNa$: 339.1962; found: 339.1970 $[M+Na]^+$.

To a stirred solution of the C17-aldehyde prepared above (27.0 mg, 85.3 μmol) in THF (1 mL) at −78 °C was added methyl magnesium bromide (3.0 M in Et_2O, 40.0 μL, 120 μmol). The reaction was stirred for 1 h at −78 °C, then a further portion of methyl magnesium bromide (3.0 M in Et_2O, 40.0 μL, 120 μmol) was added. The reaction was stirred for 1 h at −78 °C and then allowed to warm to RT and quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (×2), dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR analysis of the resultant oil indicated a 3:1 mixture of diastereoisomers at C17, along with ca. 10% of unreacted starting aldehyde. Purification of this crude residue by flash chromatography (50% Et_2O/petrol) gave the corresponding tertiary alcohol as a clear oil (21.2 mg, 74%, dr 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz, major diastereoisomer): δ = 4.24 (d, J = 8.1 Hz, 1H, H_{10}), 3.77–3.71 (m, 1H, H_{17}), 3.53–3.48 (m, 1H, H_{14}), 3.37 (s, 3H, C_{16}-OCH_3), 3.21–3.16 (m, 1H, H_{16}), 2.27 (d, J = 6.1 Hz, 1H, C_{17}-OH), 1.85–1.80 (m, 1H, H_{15}), 1.78–1.70 (m, 2H, H_{12}, H_{15}), 1.55–1.50 (m, 1H, H_{13}), 1.45–1.40 (m, 1H, H_{11}), 1.38–1.32 (m, 1H, H_{13}), 1.20 (d, J = 6.3 Hz, 3H, C_{17}-CH_3), 1.20–1.15 (m, 1H, H_{12}), 0.92 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.10 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); (minor diastereoisomer): δ = 4.27 (d, J = 8.1 Hz, 1H, H_{10}), 3.86–3.82 (m, 1H, H_{17}), 3.57–3.52 (m, 1H, H_{14}), 3.34 (s, 3H, C_{16}-OCH_3), 3.24–3.19 (m, 1H, H_{16}), 2.63 (d, J = 5.0 Hz, 1H, C_{17}-OH), 1.95–1.89 (m, 1H, H_{15}), 1.79–1.73 (m, 1H, H_{12}), 1.66–1.62 (m, 1H, H_{15}), 1.51–1.45 (m, 1H, H_{13}), 1.45–1.40 (m, 1H, H_{11}), 1.38–1.32 (m, 1H, H_{13}), 1.17 (d, J = 6.5 Hz, 3H, C_{17}-CH_3), 1.20–1.15 (m, 1H, H_{12}), 0.92 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.14 (s, 3H, TBS), 0.08 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz, major diastereoisomer): δ = 102.0 (C_{10}), 81.8 (C_{16}), 72.9 (C_{14}), 68.3 (C_{17}), 57.5 (C_{16}-OCH_3), 37.8 (C_{11}), 34.7 (C_{15}), 31.8 (C_{13}), 31.0 (C_{12}), 25.7 (TBS_3), 19.6 (C_{17}-CH_3), 18.1 (TBS), 16.9 (C_{11}-CH_3), −3.8 (TBS), −5.3 ppm (TBS); (minor diastereoisomer): δ = 101.9 (C_{10}), 82.3 (C_{16}), 72.7 (C_{14}), 67.4 (C_{17}), 57.2 (C_{16}-

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OCH_3), 37.8 (C_{11}), 34.2 (C_{15}), 31.7 (C_{13}), 31.0 (C_{12}), 25.7 (TBS), 18.1 (C_{17}-CH_3), 18.0 (TBS), 17.0 (C_{11}-CH_3), −4.1 (TBS), −5.2 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 3625, 2935, 2856, 1162, 1090, 1064 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{17}H_{36}O_4SiNa$: 355.2275; found: 355.2264 $[M+Na]^+$.

To a flask containing pre-dried 4 Å MS was added NMO (25.2 mg, 215 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 10 min, and then a solution of the diastereoisomeric alcohols prepared above (21.0 mg, 590 μmol) in CH_2Cl_2 (1 mL) was added. A solution of TPAP (4.0 mg, 11.0 μmol) in CH_3CN (0.2 mL) was added dropwise and the reaction was stirred at RT for 1 h. The reaction was filtered through a small pad of silica (eluting with Et_2O) and the solvent removed in vacuo. The resultant oil was dissolved in Et_2O, filtered through a small pad of silica (eluting with Et_2O) and the solvent was removed in vacuo. Purification of the crude residue by flash chromatography (33% Et_2O/petrol) gave the desired ketone **130** as a clear oil (18.0 mg, 92%). $[\alpha]_D^{25} = -15.5$ (c = 2.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ = 4.02, (d, J = 8.1 Hz, 1H, H_{10}), 3.75 (t, J = 6.6 Hz, 1H, H_{16}), 3.46–3.41 (m, 1H, H_{14}), 3.33 (s, 3H, C_{16}-OCH_3), 2.18 (s, 3H, C_{17}-CH_3), 1.93 (ddd, J = 14.0, 7.8, 6.2 Hz, 1H, H_{15}), 1.77–1.70 (m, 2H, H_{12}, H_{15}), 1.54–1.50 (m, 1H, H_{13}), 1.46–1.37 (m, 1H, H_{11}), 1.36–1.28 (m, 1H, H_{13}), 1.17 (qd, J = 12.9, 4.0 Hz, 1H, H_{12}), 0.90 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.12 (s, 3H, TBS), 0.10 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 210.3 (C_{17}), 102.0 (C_{10}), 83.9 (C_{16}), 72.3 (C_{14}), 57.8 (C_{16}-OCH_3), 37.7 (C_{11}), 37.5 (C_{15}), 31.1 (C_{13}), 30.8 (C_{12}), 25.8 (TBS), 25.2 (C_{17}-CH_3), 18.0 (TBS), 16.8 (C_{11}-CH_3), −3.8 (TBS), −5.3 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2955, 2931, 2857, 1713, 1605, 1160, 1063 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{17}H_{34}O_4SiNa$: 353.2124; found: 353.2107 $[M+Na]^+$.

Benzyl ether alkene 131: To a cooled (0 °C) solution of the epoxyalcohol prepared during the synthesis of **119** (see below; 58.0 g, 0.30 mol) in a mixture of CH_2Cl_2 (1.0 L), DMSO (233 mL) and Et_3N (210 mL, 1.50 mol) was added solid SO_3·Py (191 g, 1.20 mol) portionwise. The reaction was allowed to warm gradually to RT over 1 h, then diluted with CH_2Cl_2 (1.8 L) and washed with saturated aqueous $CuSO_4$ (×3), H_2O, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford the corresponding C14-aldehyde as a pale yellow oil (57.7 g, 100%) that was used immediately in the subsequent reaction without further purification (purity > 95%). The observed analytical data was identical in all respects to that reported above en route to **119**.

A stirred suspension of methyl triphenylphosphonium bromide (319 g, 0.90 mol) in THF (2.0 L) was cooled to 0 °C and a solution of KHMDS (166 g, 0.84 mol) in THF (1.0 L) added via cannula. The resulting suspension was stirred for 1 h, after which a solution of the aldehyde prepared above (57.7 g, 0.30 mol) in THF (500 mL) was added via cannula over 30 min. The reaction mixture was allowed to warm to RT and stirred for 16 h, then filtered through a pad of Celite (washing with Et_2O). The solvent was removed in vacuo and the crude residue diluted with petrol. This mixture was filtered through a pad of Celite (washing repeatedly with 10% Et_2O/petrol) and the solvent removed in vacuo. Purification of the crude residue by flash chromatography (10% Et_2O/petrol) gave the desired alkene **131** as a pale yellow oil (29.6 g, 52% over 2 steps). $[\alpha]_D^{25} = +16.0$ (c = 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.37–7.25 (m, 5H, ArH), 5.68 (ddd, J = 17.1, 10.1, 6.7 Hz, 1H, H_{14}), 5.48 (ddd, J = 17.1, 2.0, 0.5 Hz, 1H, H_{13}), 5.25 (ddd, J = 9.9, 2.0, 0.6 Hz, 1H, H_{13}), 4.63 (d, J = 11.9 Hz, 1H, Ar-CH_2), 4.53 (d, J = 11.9 Hz, 1H, Ar-CH_2), 3.68 (dd, J = 11.2, 4.5 Hz, 1H, H_{17}), 3.57 (dd, J = 11.2, 6.0 Hz, 1H, H_{17}), 3.49 (dd, J = 6.0, 4.5 Hz, 1H, H_{15}), 3.35 ppm (dt, J = 6.0, 4.5 Hz, 1H, H_{16}); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 137.7 (Ar), 131.8 (C_{14}), 128.3 (Ar), 127.9 (Ar), 127.7 (Ar), 120.7 (C_{13}), 73.1 (Ar-CH_2), 67.8 (C_{17}), 56.7 and 56.0 ppm (C_{15} and C_{16}); IR (thin film): $\tilde{\nu}$ = 3087, 3062, 2859, 1640, 1603, 1495, 1388, 1250, 1097, 986 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.73, H 7.31.

Homoallylic alcohol 132: To a cooled (−78 °C) solution of the epoxide **131** (18.1 g, 95.1 mmol) in CH_2Cl_2 (350 mL) was added DIBAL-H (1.5 M in $PhCH_3$, 95.0 mL, 143 mmol) dropwise over 2 h. The temperature was slowly raised to 0 °C, at which point sodium sulfate decahydrate (43.2 g, 134 mmol) was added cautiously and the resulting suspension stirred at RT for 1 h. The white granular solid was removed by filtration, washed with EtOAc, and the combined organic phase concentrated in vacuo. Purification of the crude residue by flash chromatography (25% Et_2O/petrol) gave the desired homoallylic alcohol **132** as a colourless oil (17.1 g, 94%). $[\alpha]_D^{25} = +1.7$ (c = 2.58, $CHCl_3$) [ref. [99] = +2.0 (c = 2.30, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.37–7.28 (m, 5H, ArH), 5.83 (ddd, J = 17.1, 10.0, 7.1, 1H, H_{14}), 5.17–5.05 (m, 2H, 2×H_{13}), 4.56 (s, 2H, 2×Ar-CH_2), 3.94–3.79 (m, 1H, H_{16}), 3.52 (dd, J = 9.5, 3.4 Hz, 1H, H_{17}), 3.38 (dd, J = 9.5, 7.1 Hz, 1H, H_{17}), 2.38–2.18 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 137.9 (Ar), 134.2 (C_{14}), 128.4 (Ar), 127.7 (2×Ar), 117.7 (C_{13}), 73.8 and 73.3 (C_{17} and Ar-CH_2), 69.7 (C_{16}), 37.9 ppm (C_3); IR (thin film): $\tilde{\nu}$ = 3418, 3069, 2908, 1639, 1604, 1102 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.87, H 8.54. The observed data was consistent with that previously reported.[100]

Iodocarbonate 133: A solution of alcohol **132** (18.0 g, 93.6 mmol) in Et_2O (360 mL) was treated with *n*BuLi (2.5 M in hexanes, 45.0 mL, 113 mmol) dropwise at RT. The resulting dark green solution was then added via cannula to a solution of Boc-ON (30.0 g, 122 mmol) in THF (360 mL). After stirring for 14 h, the reaction mixture was diluted with Et_2O and washed with aqueous NaOH (2.0 M, ×2). The aqueous layer was back-extracted with Et_2O (×3) and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (1% EtOAc/petrol) yielded the desired Boc-protected homoallylic alcohol as a yellow oil (27.3 g, 100%). $[\alpha]_D^{25} = +2.9$ (c = 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.24–7.37 (m, 5H, ArH), 5.77 (ddd, J = 17.1, 10.1, 7.0 Hz, 1H, H_{14}), 5.17–5.04 (m, 2H, 2×H_{13}), 4.96–4.84 (m, 1H, H_{16}), 4.59 (d, J = 12.0 Hz, 1H, Ar-CH_2), 4.51 (d, J = 12.0 Hz, 1H, Ar-CH_2), 3.56 (d, J = 5.2 Hz, 2H, 2×H_{17}), 2.45–2.37 (m, 2H, 2×H_{15}), 1.48 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 153.2 (Boc), 137.9 (Ar), 132.9 (C_{14}), 128.3 (Ar), 127.6 (Ar), 126.1 (Ar), 118.1 (C_{13}), 82.0 (Boc), 74.8 and 73.1 (C_{17} and Ar-CH_2), 70.5 (C_{16}), 35.4 (C_{15}), 27.3 ppm (Boc); IR (thin film): $\tilde{\nu}$ = 2933, 2866, 1737, 1643, 1601, 1475, 1279, 1098, 920, 840, 738 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{17}H_{25}O_4$: 293.1757; found: 293.1745 $[M+H]^+$.

A solution of the Boc-protected alcohol prepared above (553 mg, 1.89 mmol) in $PhCH_3$ (15 mL) was cooled to −85 °C and IBr (1.0 M in CH_2Cl_2, 3.78 mL, 3.78 mmol) added. The reaction mixture was stirred in the dark for 2 h, then warmed to 0 °C, diluted with Et_2O and quenched by the addition of an aqueous solution (25 mL) of sodium thiosulfate (6.0 g) and sodium hydrogen carbonate (1.5 g). The layers were separated, and the aqueous phase back-extracted with Et_2O (×2). The combined organic extracts were washed with brine (×2), dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (100% Et_2O) gave, in order of elution, the undesired *anti*-iodocarbonate as a yellow oil (29 mg, 4%) followed by the desired *syn*-iodocarbonate **133** as a yellow oil (315 mg, 46%).

Data for the *anti*-iodocarbonate: $[\alpha]_D^{25} = +5.4$ (c = 1.62, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.39–7.24 (m, 5H, ArH), 4.69–4.47 (m, 4H, H_{14}, H_{16}, 2×Ar-CH_2), 3.75 (d, J = 4.6 Hz, 2H, 2×H_{17}), 3.44–3.21 (m, 2H, 2×H_{13}), 2.39–2.06 ppm (m, 2H, 2×H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 148.2 (carbonate), 137.0 (Ar), 128.6 (Ar), 127.9 (Ar), 127.7 (Ar), 78.4, 74.9, 70.6, and 73.6 (C_{14}, C_{16}, C_{17}, and Ar-CH_2), 28.1 ppm (C_{15}), 5.0 (C_{13}); IR (thin film): $\tilde{\nu}$ = 2933, 2869, 1730, 1495, 1453, 1378, 1252, 1181, 1137, 1052, 851, 732, 669 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{13}H_{14}IO_4$: 360.9939; found: 360.9951 $[M-H]^-$.

Data for the *syn*-iodocarbonate **133**: $[\alpha]_D^{25} = +10.9$ (c = 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.40–7.29 (m, 5H, ArH), 4.38–4.66 (m, 4H, H_{14}, H_{16}, 2×Ar-CH_2), 3.64 (d, J = 4.4 Hz, 2H, 2×H_{17}), 3.39 (dd, J = 10.6, 4.5 Hz, 1H, H_{13}), 3.26 (dd, J = 10.6, 7.2 Hz, 1H, H_{13}), 2.41 (dt, J = 14.2, 3.1 Hz, 1H, H_{15}), 1.89 ppm (dt, J = 14.5, 11.7 Hz, 1H, H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 148.0 (carbonate), 137.3 (Ar), 128.3 (Ar), 127.9 (Ar), 127.7 (Ar), 77.0, 73.7, 70.5, and 65.8 (C_{14}, C_{16}, C_{17}, and Ar-CH_2), 29.9 (C_{15}), 5.1 ppm (C_{13}); IR (thin film): $\tilde{\nu}$ = 2926, 2866, 1746, 1527, 1495, 1453, 1395, 1243, 1189, 1137, 1055, 849, 738, 655 cm^{-1}; HMRS (ESI): *m/z*: calcd for $C_{13}H_{16}IO_4$: 363.0095; found: 363.0068 $[M+H]^+$.

The remainder of the mass balance for this reaction was accounted for by side-products derived from the competitive formation of tetrahydrofurans, via cyclisation of the C17-benzyl ether. A second purification of the remaining material by flash chromatography (80–100% Et_2O/petrol) gave, in order of elution, *tert*-butyl (3*S*,5*R*)-5-(iodomethyl)tetrahydro-

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furan-3-yl carbonate as a yellow oil (229 mg, 37%), followed by *tert*-butyl (3*S*,5*S*)-5-(iodomethyl)tetrahydrofuran-3-yl carbonate as a yellow oil (80.9 mg, 13%).

Data for *tert*-butyl (3*S*,5*R*)-5-(iodomethyl)tetrahydrofuran-3-yl carbonate: $[\alpha]_D^{25} = -5.2$ ($c = 1.10$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.19$–5.17 (m, 1H), 4.18 (dd, $J = 10.6$, 4.5 Hz, 1H), 4.14–4.10 (m, 1H), 3.92 (d, $J = 10.6$ Hz, 1H), 3.28 (d, $J = 5.4$ Hz, 2H), 2.30 (dd, $J = 14.0$, 5.6 Hz, 1H), 1.87 (ddd, $J = 14.2$, 9.5, 5.9 Hz, 1H), 1.50 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 152.9$ (Boc-CO), 81.7, 77.8, 77.2, 73.7, 39.0, 27.7, 9.3 ppm; IR (thin film): $\tilde{\nu} = 2980$, 1738, 1459, 1394, 1369, 1278, 1160, 1091, 955, 912, 836, 733, 648 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for C_5H_8IO: 210.9622; found: 210.9615 $[M-OBoc]^+$.

Data for *tert*-butyl (3*S*,5*S*)-5-(iodomethyl)tetrahydrofuran-3-yl carbonate: $[\alpha]_D^{25} = -24.8$ ($c = 0.42$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.17$–5.14 (m, 1H), 4.16–4.14 (m, 1H0, 4.10 (d, $J = 10.7$ Hz, 1H), 3.92 (dd, $J = 10.7$, 4.7 Hz, 1H), 3.32 (dd, $J = 9.9$, 6.0 Hz, 1H), 3.22 (dd, $J = 9.8$, 7.3 Hz, 1H), 2.44 (dt, $J = 14.3$, 7.0 Hz, 1H), 1.99 (ddd, $J = 14.4$, 4.4, 2.6 Hz, 1H), 1.48 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 153.2$ (Boc-CO), 82.7, 78.9, 77.2, 73.6, 37.8, 27.8, 8.5 ppm; IR (thin film): $\tilde{\nu} = 2981$, 1738, 1458, 1394, 1369, 1280, 1161, 1104, 956, 911, 848, 733, 648 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for C_5H_8O: 210.9622; found: 210.9611 $[M-OBoc]^+$.

Attempts to scale up this reaction resulted both in diminished yields of iodocarbonate product and reduced diastereoselectivity in favour of the desired *anti*-iodocarbonate **133**. Consequently, a batch approach for the synthesis of **133** was adopted.

Methyl ether epoxide 134: K_2CO_3 (3.70 g, 26.7 mmol) was added to iodocarbonate **133** (9.65 g, 26.7 mmol) in MeOH (400 mL) at RT. After 16 h, the reaction was diluted with Et_2O and washed with a mixture of aqueous sodium hydrogen carbonate and sodium thiosulfate (1:1). The aqueous layer was back-extracted with Et_2O (×2), and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–50% Et_2O/petrol) afforded the corresponding epoxide as a colourless oil (5.00 g, 90%). $[\alpha]_D^{25} = +7.6$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.41$–7.24 (m, 5H, ArH), 4.56 (s, 2H, 2×Ar-CH_2), 4.11–3.97 (m, 1H, H_{16}), 3.53 (dd, $J = 9.6$, 3.9 Hz, 1H, H_{17}), 3.44 (dd, $J = 9.5$, 7.0 Hz, 1H, H_{17}), 3.15–3.06 (m, 1H, H_{14}), 2.77 (t, $J = 4.1$ Hz, 1H, H_{13}), 2.57 (d, $J = 3.3$ Hz, 1H, C_{16}-OH), 2.51 (dd, $J = 5.0$, 2.7 Hz, 1H, H_{13}), 1.83 (dt, $J = 14.4$, 4.6 Hz, 1H, H_{15}), 1.65 ppm (dt, $J = 14.0$, 7.0 Hz, 1H, H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.7$ (Ar), 128.3 (Ar), 127.6 (2×Ar), 73.8 and 73.2 (C_{17} and Ar-CH_2), 68.4 (C_{16}), 49.5 (C_{14}), 46.5 (C_{13}), 35.8 ppm (C_{15}); IR (thin film): $\tilde{\nu} = 3439$, 2920, 2339, 1717, 1653, 1602, 1495, 1453, 1205, 1027, 741, 699, 668 cm^{-1}; HMRS (EI): *m*/*z*: calcd for $C_{12}H_{16}O_3$: 208.1099; found: 208.1085 $[M]^+$.

A suspension of the epoxide prepared above (141 mg, 0.67 mmol), iodomethane (625 μL, 10.2 mmol) and freshly prepared Ag_2O (472 mg, 2.03 mmol) in DMF (2 mL) was stirred at RT in the dark for 16 h. The reaction mixture was filtered through Celite (washing with Et_2O) and the collected organics washed with H_2O and with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude residue by flash chromatography (25% Et_2O/petrol) furnished the desired methyl ether **134** as a colourless oil (141 mg, 95%). When the reaction was repeated on a larger scale (6.60 g of epoxide, 31.7 mmol) and the other reagents/solvents scaled appropriately, the desired product **134** was isolated in a diminished yield (5.30 g, 75%). However, the majority of unreacted starting material (>90%) was recovered and could be recycled. $[\alpha]_D^{25} = +7.6$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.35$–7.25 (m, 5H, ArH), 4.56 (s, 2H, 2×Ar-CH_2), 3.59–3.51 (m, 3H, 2×H_{17}, H_{16}), 3.44 (s, 3H, C_{16}-OCH_3), 3.01–2.98 (m, 1H, H_{14}), 2.77 (t, $J = 4.1$ Hz, 1H, H_{13}), 2.51 (dd, $J = 5.0$, 2.7 Hz, 1H, H_{13}), 1.83 (dt, $J = 14.2$, 4.6 Hz, 1H, H_{15}), 1.65 ppm (dt, $J = 14.2$, 7.0 Hz, 1H, H_{15}); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.7$ (Ar), 128.3 (Ar), 127.6 (2×Ar), 73.8 and 73.2 (C_{17} and Ar-CH_2), 68.4 (C_{16}), 57.4 (C_{16}-OCH_3), 49.5 (C_{14}), 46.5 (C_{13}), 35.8 ppm (C_3); IR (thin film): $\tilde{\nu} = 2925$, 1759, 1605, 1496, 1453, 1365, 1257, 1202, 1027, 911, 738, 698, 665 cm^{-1}; HMRS (EI): *m*/*z*: calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1262 $[M]^+$.

Sulfone 136: A solution of **135**[6e] (20.3 g, 96.4 mmol) and *para*-toluenesulfonyl chloride (36.7 g, 190 mmol) in pyridine (170 mL) was stirred at RT for 20 h. The mixture was then diluted with CH_2Cl_2 and H_2O, and stirred vigorously for 15 min. The layers were separated, the aqueous phase back-extracted with CH_2Cl_2 (×3) and the combined organic extracts washed with HCl (1.0 M ×3), H_2O (×3), and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (10% Et_2O/petrol) to afford the desired corresponding C12-tosylate as a yellow oil (32.7 g, 90%). $[\alpha]_D^{25} = +2.5$ ($c = 1.14$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.81$–7.74 (m, 2H, ArH), 7.35–7.25 (m, 2H, ArH), 7.19–7.12 (m, 2H, ArH), 6.88–6.81 (m, 2H, ArH), 4.33 (s, 2H, 2×Ar-CH_2), 4.40 (dd, $J = 9.2$, 5.4 Hz, 1H, H_{12}), 3.96 (dd, $J = 9.2$, 5.6 Hz, 1H, H_{12}), 3.80 (s, 3H, Ar-OCH_3), 3.32 (dd, $J = 9.3$, 5.6 Hz, 1H, H_{10}), 3.27 (dd, $J = 9.3$, 6.5 Hz, 1H, H_{10}), 2.43 (s, 3H, Ts-CH_3), 2.13–2.04 (m, 1H, H_{11}), 0.92 ppm (d, $J = 6.9$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 159.1$ (Ar), 144.6 (Ar), 133.0 (Ar), 130.3 (Ar), 129.8 (Ar), 129.0 (Ar), 127.9 (Ar), 113.7 (Ar), 72.7, 72.3, 70.8 (C_{10}, C_{12}, Ar-CH_2), 56.2 (Ar-OCH_3), 33.6 (C_{11}), 21.6 (Ts-CH_3), 13.6 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu} = 2961$, 2862, 1611, 1598, 1512, 1463, 1357, 1302, 1247, 1175, 1097, 974, 813, 792 cm^{-1}; HMRS (EI): *m*/*z*: calcd for $C_{19}H_{24}O_5S$: 364.1344; found: 364.1329 $[M]^+$; elemental analysis calcd (%) for $C_{19}H_{24}O_5S$: C 62.61, H 6.64; found: C 62.67, H 6.87.

A suspension of thiophenol (19.1 mL, 180 mmol) and K_2CO_3 (28.0 g, 200 mmol) in THF (300 mL) was stirred at RT for 1 h. To this was added a solution of the tosylate prepared above (32.7 g, 89.8 mmol) in THF (300 mL) via cannula and the reaction heated at reflux for 2 h. After cooling to RT, CH_2Cl_2 was added and the reaction contents poured into saturated aqueous NH_4Cl. The layers were separated, and the organic phase washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (0–5% Et_2O/petrol) gave the corresponding sulfide as a yellow oil (27.1 g, 100%). $[\alpha]_D^{25} = -9.2$ ($c = 1.92$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.42$–7.11 (m, 7H, ArH), 4.92–6.84 (m, 2H, ArH), 4.42 (s, 2H, 2×Ar-CH_2), 3.81 (s, 3H, Ar-OCH_3), 3.41 (d, $J = 5.9$ Hz, 2H, 2×H_{10}), 3.51 (dd, $J = 12.9$, 5.7 Hz, 1H, H_{12}), 2.79 (dd, $J = 12.9$, 7.4 Hz, 1H, H_{12}), 2.15–1.96 (m, 1H, H_{11}), 1.06 ppm (d, $J = 6.8$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 159.1$ (Ar), 140.0 (Ar), 130.6 (Ar), 129.2 (Ar), 129.1 (Ar), 128.8 (Ar), 128.7 (Ar), 125.5 (Ar), 114.0 (Ar), 113.7 (Ar), 73.7 and 72.7 (C_{10} and Ar-CH_2), 55.2 (Ar-OCH_3), 37.5 (C_{12}), 33.8 (C_{11}), 16.3 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu} = 2956$, 2930, 1613, 1584, 1480, 1469, 1439, 1422, 1359, 1245, 1172, 1146, 1034, 910, 823, 691 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{22}O_2S$: C 71.49, H 7.33; found: C 71.26, H 7.38.

*m*CPBA (ca. 90%, 37.5 g, 200 mmol) was added cautiously to a stirred solution of the sulfide prepared above (27.1 g, 89.8 mmol) in CH_2Cl_2 (1.0 L) at 0°C followed by pyridine (28.2 mL, 0.36 mol). After stirring for 24 h at RT, the reaction contents were poured into H_2O. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (×3). The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ (×3), saturated aqueous $CuSO_4$ (×3), and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (10% Et_2O/petrol) gave the desired sulfone **136** as a pale yellow oil (30.0 g, 100%). $[\alpha]_D^{25} = -8.3$ ($c = 2.06$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.94$–7.88 (m, 2H, ArH), 7.69–7.50 (m, 3H, ArH), 7.21–7.14 (m, 2H, ArH), 6.89–6.82 (m, 2H, ArH), 4.34 (s, 2H, 2×Ar-CH_2), 3.80 (s, 3H, Ar-OCH_3), 3.48 (dd, $J = 14.1$, 7.0 Hz, 1H, H_{12}), 3.38 (dd, $J = 9.4$, 5.0 Hz, 1H, H_{10}), 3.27 (dd, $J = 9.4$, 6.4 Hz, 1H, H_{10}), 2.91 (dd, $J = 14.1$, 7.8 Hz, 1H, H_{12}), 2.45–2.29 (m, 1H, H_{11}), 1.10 ppm (d, $J = 6.8$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 159.1$ (Ar), 140.0 (Ar), 133.5 (Ar), 130.1 (Ar), 129.2 (Ar), 129.1 (Ar), 127.8 (Ar), 113.9 (Ar), 113.7 (Ar), 73.2 and 72.5 (C_{10} and Ar-CH_2), 59.3 (C_{12}), 55.2 (Ar-OCH_3), 29.3 (C_{11}), 17.1 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu} = 2960$, 2932, 1612, 1585, 1513, 1462, 1446, 1405, 1360, 1247, 1207, 1174, 1147, 1085, 999, 820, 740, 689 cm^{-1}; HMRS (EI): *m*/*z*: calcd for $C_{18}H_{22}O_4S$: 334.1239; found: 334.1235 $[M]^+$.

Coupled product 137: A solution of sulfone **136** (2.47 g, 7.38 mmol) in THF (15 mL) was cooled to −78°C and *n*BuLi (2.5 M in hexanes, 3.10 mL, 8.12 mmol) was added dropwise. After 10 min, a solution of epoxide **133** (328 mg, 1.48 mmol) in THF (5 mL) was added via cannula, followed by $BF_3{\cdot}OEt_2$ (0.20 mL, 1.48 mmol). The reaction was allowed to warm slowly to RT and stirred for 16 h, then quenched by the addition of

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saturated aqueous NH_4Cl. This was extracted with CH_2Cl_2 (×3), and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–75% Et_2O/petrol) gave, in order of elution, the starting material sulfone **136** (1.97 g), followed by the desired coupling product **137** as a pale yellow oil and as a mixture of sulfone diastereoisomers (824 mg, 100%, dr 2:1). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.90$–7.83 (m, 2H, ArH), 7.61–7.47 (m, 3H, ArH), 7.34–7.11 (m, 7H, ArH), 6.89–6.81 (m, 2H, ArH), 4.52 (s, 2H, Ar-CH_2), 4.39 (s, 1.3H, major diastereoisomer, Ar-CH_2), 4.28 (s, 0.7H, minor diastereoisomer, Ar-CH_2), 3.79–3.73 (m, 4H, Ar-OCH_3, H_{14}), 3.58–3.42 (m, 5H, 2×H_{10}, 2×H_{17}, H_{16}), 3.37–3.26 (m, 4H, H_{12}, C_{16}-OCH_3), 2.59–1.42 (m, 5H, H_{11}, 2×H_{13}, 2×H_{15}), 1.08 (d, J = 7.0 Hz, 1H, minor diastereoisomer, C_{11}-CH_3), 0.99 ppm (d, J = 7.0 Hz, 2H, major diastereoisomer, C_{11}-CH_3); IR (thin film): $\tilde{\nu}$ = 3494, 2932, 2867, 1612, 1585, 1514, 1462, 1446, 1365, 1301, 1247, 1175, 1144, 1082, 738, 721, 691, 621 cm^{-1}; HMRS (EI): m/z: calcd for $C_{31}H_{40}O_7S$: 556.2494; found: 556.2473 $[M]^+$; elemental analysis calcd (%) for $C_{31}H_{40}O_7S$: C 66.88, H 7.24; found: C 66.73, H 7.20.

Diol 138: A solution of the diastereoisomeric mixture of sulfone coupling products **137** (263 mg, 0.47 mmol) in THF (5 mL) was cooled to −90 °C and treated with freshly prepared lithium naphthalenide (1.0 M in THF) at such a rate as to maintain the internal temperature below −85 °C and until the dark green colour of the reaction mixture persisted (ca. 1.20 mL, 1.20 mmol). The reaction was then quenched by the addition of H_2O/EtOH 1:9 and warmed to RT, where it was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (50% Et_2O/petrol) furnished the desulfonylated material as a colourless oil (182 mg, 93%). $[\alpha]_D^{25} = -13.2$ (c = 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.36$–7.23 (m, 7H, ArH), 6.88–6.84 (m, 2H, ArH), 4.55 (s, 2H, 2×Ar-CH_2), 4.42 (s, 2H, 2×Ar-CH_2), 3.79–3.67 (m, 4H, H_{14}, Ar-OCH_3), 3.62–3.57 (m, 1H, H_{16}), 3.51–3.49 (m, 3H, 2×H_{17}, C_{14}-OH), 3.45 (s, 3H, C_{16}-OCH_3), 3.31 (dd, J = 9.1, 6.0 Hz, 1H, H_{10}), 3.20 (dd, J = 9.0, 6.7 Hz, 1H, H_{10}), 1.82–1.11 (m, 7H, H_{11}, 2×H_{12}, 2×H_{13}, 2×H_{15}), 0.93 ppm (d, J = 6.7 Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 159.4$ (Ar), 138.9 (Ar), 131.3 (Ar), 129.1 (Ar), 128.4 (Ar), 127.9 (Ar), 127.7 (Ar), 113.7 (Ar), 80.9, 75.5, 73.5, 72.6, 71.8, and 71.4 (C_{17}, C_{16}, C_{14}, C_{10}, 2×Ar-CH_2), 57.6 (C_{16}-OCH_3), 55.3 (Ar-OCH_3), 38.8, 35.0, 33.5, and 29.4 (C_{15}, C_{13}, C_{12}, and C_{11}), 17.2 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu}$ = 3443, 2928, 2855, 1611, 1586, 1513, 1496, 1454, 1363, 1301, 1247, 1206, 1172, 1092, 1034, 819, 738, 698, 671 cm^{-1}; HMRS (EI): m/z: calcd for $C_{25}H_{36}O_5$: 416.2563; found: 416.2568 $[M]^+$; elemental analysis calcd (%) for $C_{25}H_{36}O_5$: C 72.08, H 8.71; found: C 72.05, H 8.60.

DDQ (77.0 mg, 0.34 mmol) was added to a solution of the desulfonylated material prepared above (141 mg, 0.34 mmol) in a mixture of CH_2Cl_2 (5 mL) and H_2O (1 mL) at RT. The reaction was stirred for 1 h, then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ (×2) and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (100% Et_2O) furnished the desired diol **138** as a colourless oil (100 mg, 100%). $[\alpha]_D^{25} = -12.4$ (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.37$–7.28 (m, 5H, ArH), 4.54 (s, 2H, 2×Ar-CH_2), 3.81–3.73 (m, 1H, H_{14}), 3.67–3.45 (m, 5H, H_{16}, 2×H_{17}, 2×H_{10}), 3.45 (s, 3H, C_{16}-OCH_3), 1.70–1.10 (m, 9H, H_{11}, 2×H_{12}, 2×H_{13}, 2×H_{15}, C_{10}-OH, C_{14}-OH), 0.92 ppm (d, J = 6.6 Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.9$ (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 80.9, 73.5, 71.7, 71.6, 68.0 (C_{17}, C_{16}, C_{14}, C_{10} and Ar-CH_2), 57.6 (C_{16}-OCH_3), 38.1, 35.8, 34.8, 28.7 (C_{11}, C_{12}, C_{13} and C_{15}), 16.7 ppm (C_{11}-CH_3); IR (thin film): $\tilde{\nu}$ = 3384, 2923, 1610, 1523, 1453, 1364, 1259, 1198, 1094, 1027, 800, 736, 698 cm^{-1}; HMRS (EI): m/z: calcd for $C_{17}H_{26}O_3$: 278.1880; found: 278.1881 $[M-H_2O]^+$; elemental analysis calcd (%) for $C_{17}H_{28}O_4$: C 68.89, H 9.52; found: C 69.0%, H 9.56.

Lactone 128 prepared by oxidation: NMO (104 mg, 0.92 mmol) and predried powdered 4 Å MS (111 mg) were added to a solution of diol **138** (90.9 mg, 0.31 mmol) in CH_2Cl_2 (2.4 mL) at RT. The mixture was stirred for 10 min, then TPAP (10.4 mg, 31.0 μmol) was added portionwise. After 1 h, the reaction was purified directly by flash chromatography (50% Et_2O/petrol) to furnish lactone **128** as a colourless oil (81.2 mg, 90%). The observed analytical data was identical in all respects to that reported above for **128** (obtained by alkylation and purification by HPLC).

Nitrile 140: To a solution of diethyl cyanomethylphosphonate (55.0 mg, 310 μmol) in THF (1.4 mL) at 0 °C was added NaHMDS (0.5 M in $PhCH_3$, 0.60 mL, 300 μmol). The resulting solution (0.15 M) was stirred for 15 min, then 0.50 mL (75 μmol) of this added to a stirred solution of ketone **130** (24.0 mg, 72.6 mmol) in $PhCH_3$ (1 mL) at −78 °C. The mixture was stirred for 3 h at −78 °C, then allowed to warm to RT. The reaction was quenched by the addition of saturated aqueous NH_4Cl, extracted with Et_2O (×2), and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. ^1H NMR analysis of the crude mixture indicated an E/Z ratio of 7:1 (85%), however the minor geometrical impurity could be removed by flash chromatography (25% Et_2O/petrol) to give the desired (E)-alkene **140** as a clear oil (19.2 mg, 75%) $[\alpha]_D^{25} = -10.1$ (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 5.36$ (s, 1H, H_{18}), 4.23, (d, J = 8.1 Hz, 1H, H_{10}), 3.81 (t, J = 6.6 Hz, 1H, H_{16}), 3.36–3.30 (m, 1H, H_{14}), 3.19 (s, 3H, C_{16}-OCH_3), 1.99 (s, 3H, C_{17}-CH_3, 1.88 (ddd, J = 14.1, 7.6, 6.4 Hz, 1H, H_{15}), 1.78–1.72 (m, 1H, H_{12}), 1.64 (ddd, J = 14.1, 6.9, 4.7 Hz, 1H, H_{15}), 1.50–1.44 (m, 1H, H_{13}), 1.44–1.36 (m, 1H, H_{11}), 1.30 (tdd, J = 13.0, 11.6, 4.0 Hz, 1H, H_{13}), 1.16 (qd, J = 13.0, 4.0 Hz, 1H, H_{12}), 0.90 (s, 9H, TBS), 0.86 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.10 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 163.8$ (C_{17}), 116.4 (C_{19}), 102.0 (C_{10}), 97.1 (C_{18}), 81.4 (C_{16}), 72.5 (C_{14}), 56.8 (C_{16}-OCH_3), 39.6 (C_{15}), 37.8 (C_{11}), 31.1 (C_{13}), 30.8 (C_{12}), 25.8 (TBS), 18.0 (TBS), 16.8 (C_{11}-CH_3), 16.1 (C_{17}-CH_3), −3.6 (TBS), −5.1 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2953, 2929, 2856, 2221, 1634, 1162, 1062 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{19}H_{35}NO_3SiNa$: 376.2284; found: 376.2266 $[M+Na]^+$.

Enal 141: To a stirred solution of nitrile **140** (22.3 mg, 63.1 μmol) in $PhCH_3$ (1 mL) at −78 °C, was added DIBAL-H (1.5 M in $PhCH_3$, 60.0 μL, 90.0 μmol). The reaction was stirred for 3 h at −78 °C then quenched by the addition of H_2O. Solid sodium bicarbonate was added and the suspension was stirred for 30 min. The reaction was filtered through a pad of silica (eluting with EtOAc) and the solvent removed in vacuo to leave a clear oil which was purified by flash chromatography (25% Et_2O/petrol) to furnish enal **141** as a clear oil (20.5 mg, 91%). $[\alpha]_D^{25} = -4.5$ (c = 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 10.09$ (d, J = 7.8 Hz, 1H, H_{19}), 6.03 (d, J = 7.8 Hz, 1H, H_{18}), 4.20, (d, J = 8.1 Hz, 1H, H_{10}), 3.82 (t, J = 6.7 Hz, 1H, H_{16}), 3.37–3.32 (m, 1H, H_{14}), 3.21 (s, 3H, C_{16}-OCH_3), 2.10 (s, 3H, C_{17}-CH_3), 1.93 (ddd, J = 14.1, 7.8, 6.4 Hz, 1H, H_{15}), 1.77–1.72 (m, 1H, H_{12}), 1.66 (ddd, J = 14.1, 7.2, 4.7 Hz, 1H, H_{15}), 1.52–1.46 (m, 1H, H_{13}), 1.45–1.38 (m, 1H, H_{11}), 1.34 (tdd, J = 13.0, 11.2, 4.0 Hz, 1H, H_{13}), 1.15 (qd, J = 13.0, 4.1 Hz, 1H, H_{12}), 0.90 (s, 9H, TBS), 0.85 (d, J = 6.6 Hz, 3H, C_{11}-CH_3), 0.15 (s, 3H, TBS), 0.10 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 191.0$ (C_{19}), 161.1 (C_{17}), 128.1 (C_{18}), 102.0 (C_{10}), 82.8 (C_{16}), 72.6 (C_{14}), 56.8 (C_{16}-OCH_3), 39.6 (C_{15}), 37.8 (C_{11}), 31.1 (C_{13}), 30.8 (C_{12}), 25.8 (TBS), 18.0 (TBS), 16.8 (C_{11}-CH_3), 12.3 (C_{17}-CH_3), −3.6 (TBS), −5.1 ppm (TBS); IR (thin film): $\tilde{\nu}$ = 2928, 2855, 1679, 1163, 1063 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{19}H_{36}O_4SiNa$: 379.2281; found: 379.2274 $[M+Na]^+$.

Lactone 14: To a solution of TBAF (1.0 M in THF, 9.0 mL, 9.0 mmol) was added acetic acid (1 mL) to give a clear solution of pH 5. An aliquot of this solution (1.0 mL) was added to enal **142** (15.1 mg, 42.3 μmol) in THF (1 mL) at RT. The reaction was stirred for 24 h at RT, then quenched by the addition of H_2O (1 mL) and extracted with Et_2O (×2). The combined organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo to leave a mixture of the epimeric lactols as a clear oil. This was dissolved in CH_2Cl_2 (1 mL) and added to a flask containing pre-dried 4 Å MS (25 mg) and NMO (18.1 mg, 155 μmol) in CH_2Cl_2 (1 mL). A solution of TPAP (2.2 mg, 5.5 μmol) in CH_2Cl_2 (0.5 mL) was added dropwise and the reaction stirred at RT for 1 h. The reaction was then filtered through a short pad of silica (eluting with Et_2O) and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (Et_2O) to give the desired lactone **14** as a colourless oil (8.7 mg, 85%). The observed analytical data was identical in all respects to that reported for the preparation of **14** by degradation (see Supporting Information).

Dienyl iodide 142: To a stirred slurry of $CrCl_2$ (173 mg, 1.40 mmol) in dioxane/THF (3:2, 1 mL) at 0 °C was added a solution of enal **14** (28.0 mg,

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117 μmol) and iodoform (138 mg, 351 μmol) in dioxane (0.6 mL) via cannula. The reaction was stirred for 5 h at 0 °C, then allowed to warm to RT and stirred for 1 h. The reaction mixture was quenched by the addition of H_2O, then extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (20–50% Et_2O/petrol) furnished the dienyl iodide **142** as a colourless oil (34.1 mg, 80%) and as an inseparable 6:1 mixture of *E*/*Z* isomers. ^{1}H NMR ($CDCl_3$, 600 MHz, major isomer): $\delta = 7.28$ (dd, $J = 14.0$, 11.0 Hz, 1H, H_{19}), 6.37 (d, $J = 14.0$ Hz, 1H, H_{20}), 6.03 (d, $J = 11.0$ Hz, 1H, H_{18}), 4.25–4.18 (m, 1H, H_{14}), 3.78 (t, $J = 7.0$ Hz, 1H, H_{16}), 3.15 (s, 3H, C_{16}-OCH_3), 2.45–2.40 (m, 1H, H_{11}), 2.06–1.98 (m, 2H, H_{12}, H_{15}), 1.89 (dd, $J = 14.0$, 3.5 Hz, 1H, H_{13}), 1.76–1.45 (m, 3H, H_{12}, H_{13}, H_{15}), 1.64 (s, 3H, C_{17}-CH_3), 1.29 ppm (d, $J = 6.6$ Hz, 3H, C_{11}-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz, major isomer): $\delta =$ 174.0 (C_{10}), 141.0 (C_{19}), 137.1 (C_{17}), 128.6 (C_{18}), 82.4 (C_{16}), 80.4 (C_{20}), 78.5 (C_{14}), 56.0 (C_{16}-OCH_3), 39.8 (C_{15}), 36.1 (C_{11}), 29.2 (C_{13}), 28.4 (C_{12}), 17.3 (C_{11}-CH_3), 11.2 ppm (C_{17}-CH_3); IR (thin film): $\tilde{\nu} = 2929$, 2860, 1729, 1653, 1173, 1084 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{14}H_{21}IO_3Na$: 387.0435; found: 387.0438 $[M+Na]^+$.

Triene 10: $[Pd(PFur_3)_2Cl_2]$ (3.3 mM stock solution in NMP, 300 μL, 1.0 μmol, 15 mol%) was added to a flask containing vinyl stannane **117** (8.0 mg, 7.2 μmol) and dienyl iodide **144** (*E*/*Z* 6:1, 3.5 mg, 10 μmol), and the reaction stirred in the dark for 24 h. H_2O was added and the mixture extracted with Et_2O (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by preparative TLC (67% Et_2O/petrol) afforded triene **10** as a colourless oil and as a single *E*,*E*,*E*-isomer (6.0 mg, 69%). The observed analytical data was identical in all respects to that reported for the preparation of **10** by degradation (see Supporting Information), including mixed material NMR studies.

(*R*)-C32 Alcohol 18: Lithium tri(*tert*-butoxy)aluminium hydride (1.0 M in THF, 150 μL, 0.150 mmol) was added to a stirred solution of triene **10** (149 mg, 0.126 mmol) in THF (5 mL) at −10 °C. After 3 h, EtOAc and sodium sulfate decahydrate were added and the mixture allowed to warm to RT with vigorous stirring. After 30 min, the reaction contents were filtered through Celite and concentrated in vacuo, and the crude residue purified by flash chromatography (45–70% Et_2O/petrol) to afford alcohol **18** as a white foam and as a 2:1 mixture of rotamers (121 mg, 81%). The observed analytical data was identical in all respects to that reported for the preparation of **18** by degradation (see Supporting Information).

Allyl chloroformate (50.0 μL, 0.47 mmol) was added to a stirred solution of the alcohol prepared above (116 mg, 0.097 mmol) and 4-pyrrolidinopyridine (220 mg, 1.48 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h, then diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl. After separation of the organic phase, the aqueous layer was back-extracted with CH_2Cl_2 (×2) and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–50% Et_2O/petrol) furnished the desired C32-protected alcohol **19** as a white foam and as a 2:1 mixture of rotamers (100 mg, 81%). The observed analytical data was identical in all respects to that reported for the preparation of **19** by degradation (see Supporting Information).

TES ether 143: To a solution of lactone **19** (92.0 mg, 72.3 μmol) in THF (5 mL) at 0 °C was added aqueous LiOH (0.2 M; 540 μL, 108 μmol) and stirring continued at this temperature for 1 h. The reaction mixture was then poured into saturated aqueous NH_4SO_4 and extracted with EtOAc (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by flash chromatography (25–50% THF/hexanes) furnished the desired carboxylic acid as a clear oil (82.6 mg, 89%). $R_f = 0.55$ (67% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 6.36$ (dd, $J = 11.0$, 14.5 Hz, 1H, H_{19}), 6.19 (dd, $J = 10.4$, 14.3, 1H, H_{20}), 6.13 (dd, $J = 10.5$, 14.7, 1H, H_{21}), 6.02 (dd, including $J = 11.1$ Hz, 1H, H_{18}), 5.93 (ddd, $J = 5.5$, 10.8, 16.3, 1H, Alloc), 5.51 (dd, $J = 8.7$, 14.7 Hz, 1H, H_{22}), 5.34 (dd, $J = 1.5$, 17.2 Hz, 1H, Alloc), 5.26–5.24 (m, 1H, Alloc), 4.93 (brs, 1H, H_{30}), 4.88 (brs, 0.6H, 0.6 of H_2), 4.72 (brs, 0.4H, 0.4 of H_2), 4.63–4.59 (m, 2H, Alloc), 4.57 (brs, 1H, H_{32}), 4.10–4.09 (m, 1H, H_{28}), 4.04 (brd, 0.4H,0.4 of H_6), 3.91 (brd, 0.6H, 0.6 of H_6), 3.83 (m, 1H, H_{14}), 3.79 (dd, $J = 2.8$, 10.0 Hz, 1H, H_{16}), 3.76 (d, $J = 7.5$ Hz, 1H, H_{27}), 3.44 (ddd, $J = 4.9$, 8.5, 11.0 Hz, 1H, H_{40}), 3.41 (s, 3H, C_{39}-OCH_3), 3.21 (s, 3H, C_{27}-OCH_3), 3.19 (s, 3H, C_{16}-OCH_3), 2.96 (brt, 0.6H, 0.6 of H_6), 2.88 (ddd, including $J = 4.5$, 8.6 Hz, 1H, H_{39}), 2.85 (brs, 0.4H, 0.4 of H_6), 2.76–2.74 (m, 2H, H_{25}, H_{31}), 2.50–2.48 (m, 1H, H_{11}), 2.31 (m, 1H, H_{23}), 2.17 (m, 1H, H_3), 1.86–1.74 [m, 6H, including 2.05–2.04 (m, 1H, H_{38})], 1.69–1.17 [m, 32H, including 1.69 (s, 3H, C_{17}-CH_3), 1.61 (s, 3H, C_{29}-CH_3), 1.45–1.43 (2s, 9H, Boc), 1.18 (d, $J = 7.0$ Hz, 3H, C_{11}-CH_3)], 1.16–0.81 [m, 33H, including 1.05 (d, $J = 6.7$ Hz, 3H, C_{23}-CH_3), 1.03 (d, $J = 6.7$ Hz, 3H, C_{31}-CH_3), 0.96 (d, $J = 6.8$ Hz, 3H, C_{25}-CH_3), 0.89 (s, 9H, TBS), 0.85 (t, $J = 8.0$ Hz, 9H, TES)], 0.74 (app q, $J = 12.0$ Hz, H_{38}), 0.48 (q, $J = 7.9$, 6H, TES), 0.07 ppm (2s, 6H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta =$ (213.2, 213.1) (C_{26}), 180.2 (C_{10}), 171.4 (C_1), (155.5, 155.1) (Boc), 154.8 (Alloc), 139.4 (C_{22}), 136.2, 135.8, 133.2 (C_{20}), (131.8, 131.7) (Alloc), (130.2, 130.1) (C_{21}), 129.9 (C_{30}), 127.8 (C_{18}), 126.6 (C_{19}), (118.7, 118.6) (Alloc), 88.1 (C_{16}), 84.5 (C_{39}), 84.0 (C_{27}), (79.7, 79.6) (Boc), 79.3 and 79.1 (C_{28}, C_{32}), 75.8 and 75.6 (C_{34}, C_{40}), 71.5 (C_{14}), 68.3 (Alloc), 57.9 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), 55.8 (C_{16}-OCH_3), (55.0, 53.8) (C_2), 43.0 (C_{25} or C_{31}), (41.9, 40.9) (C_6), 40.5 (C_{12}), (39.0, 38.9) (C_{11}), (37.7, 37.5), 36.1 (C_{25} or C_{31}), (35.8, 35.6) (C_{38}), (35.0, 34.9) (C_{23}), 34.7, 34.0, (33.2, 33.1), (32.4, 32.1), 31.8, 29.3, 28.4 (Boc), (27.0, 26.9) (C_3), 25.9 (TBS), (24.9, 24.6), 22.6, 21.6 (C_{23}-CH_3), (21.0, 20.7), 19.4, 18.1 (TBS), 17.1 (C_{11}-CH_3), 15.6, (15.5, 15.2) (C_{31}-CH_3), (14.2, 14.1) (C_{25}-CH_3), 11.6 and 11.4 (C_{17}-CH_3, C_{29}-CH_3), 6.7 (TES), 4.7 (TES), −4.6 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu} = 3487$, 2934, 2390, 1741, 1734, 1717, 1700, 1684, 1653, 1574, 1540, 1520, 1507, 1457, 1365, 1256, 1159, 1108, 989, 836, 750 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{70}H_{123}NO_{16}Si_2Na$: 1312.8273; found: 1312.8243 $[M+Na]^+$.

To a solution of the hydroxyacid prepared above (82.6 mg, 64.0 μmol) and 2,6-lutidine (60.0 μL, 515 μmol) in CH_2Cl_2 (2.5 mL) at −20 °C was added TESOTf (72 μL, 318 μmol). After stirring at this temperature for 10 min, the reaction was allowed to warm to RT and stirring continued for 1 h. The reaction was quenched by addition of H_2O (1 drop) and filtered through a pad of SiO_2, washing with THF. The eluant was concentrated in vacuo, and the crude residue purified by flash chromatography (20% EtOAc/hexanes, then 67% THF/hexanes) to afford TES ether **143** as a clear oil (73.7 mg, 88%). ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 6.37$ (m, 1H, H_{19}), 6.18–6.11 (m, 2H, H_{20}, H_{21}), 6.01 (d, $J = 11.0$ Hz, 1H, H_{18}), 5.93 (m, 1H, Alloc), 5.42 (dd, $J = 9.1$, 14.0 Hz, 1H, H_{22}), 5.37–5.22 [m, 4H, including 5.35 (d, $J = 17.2$ Hz, 1H, Alloc), 5.23 (d, $J = 9.8$ Hz, 1H, H_{30}), Alloc, NH], 4.93 (m, 1H, H_{34}), 4.60–4.54 (m, 3H, 2×Alloc, H_{32}), 4.14 (d, $J = 7.4$ Hz, 1H, H_{28}), 3.78 (d, $J = 7.3$ Hz, H_{27}), 3.73 (m, 1H, H_{14}), 3.59 (dd, $J = 2.8$, 10.0 Hz, 1H, H_{16}), 3.54 (m, 1H), 3.41 [m, 4H, including 3.41 (s, 3H, C_{39}-OCH_3), H_{40}], 3.22 (s, 3H, C_{27}-OCH_3), 3.13 (s, 3H, C_{16}-OCH_3), 3.05 (m, 1H), 2.88 (m, 1H), 2.78–2.65 (m, 3H, H_{31}, H_{25}), 2.35–2.30 (m, 2H, H_{11}, H_{23}), 1.97 (brd, 1H), 1.83 (brm, 1H), 1.79–1.41 [m, 24H, including 1.67 (s, 3H, C_{17}-CH_3), 1.61 (s, 3H, C_{29}-CH_3)], 1.33–1.14 [m, 8H, including 1.15 (d, $J = 6.9$ Hz, 3H, C_{11}-CH_3)], 1.05 (m, 6H, C_{25}-CH_3, C_{23}-CH_3), 0.96–0.81 [m, 34H, including 0.89 (s, 9H, TBS), C_{31}-CH_3, 2×TES], 0.71 (dd, $J = 12.0$, 14.0 Hz, 1H, H_{38}), 0.58 (q, $J = 7.9$ Hz, 6H, TES), 0.50 (q, $J = 7.9$ Hz, 6H, TES), 0.07 (s, 3H, TBS), 0.06 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 212.6$ (C_{26}), 180.2 (C_{10}), 172.2 (C_1), 154.8 (Alloc), 139.1 (C_{22}), 137.4, 136.0, 132.5 (C_{20}), 131.7 (Alloc), 130.4 (C_{21}), 129.6 (C_{30}), 127.8 (C_{18}), 127.0 (C_{19}), 118.8 (Alloc), 84.4 (C_{16}), 84.4 (C_{39}), 84.0 (C_{27}), 79.9 and 78.8 (C_{28}, C_{32}), 76.0 and 75.6 (C_{34}, C_{40}), 69.4 (C_{14}), 68.3 (Alloc), 58.0 (C_{27}-OCH_3), 57.9 (C_{39}-OCH_3), 56.7 (C_{16}-OCH_3), 55.9 (C_2), 43.7 (C_{25} or C_{31}), 43.2 (C_6), 41.0 (C_{12}), 38.9 (C_{11}), 38.0, 36.2 (C_{25} or C_{31}), 35.8 (C_{38}), 35.2 (C_{23}), 34.7, 34.0, 33.6, 33.2, 32.1, 31.8, 29.7, 29.1, 27.6 (C_3), 25.9 (TBS), 24.7, 22.9, 21.9 (C_{11}-CH_3), 18.1 (TBS), 17.6 (C_{23}-CH_3), 15.8 (C_{31}-CH_3), 15.6, 14.2 (C_{25}-CH_3), 11.8 and 11.0 (C_{17}-CH_3, C_{29}-CH_3), 6.9 (TES), 6.7 (TES), 5.3 (TES), 4.7 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu} = 3300$, 2960, 2929, 2865, 1746, 1616, 1456, 1378, 1267, 1109, 1006, 988, 874, 837, 778, 746, 666 cm^{-1}; HMRS (ESI): *m*/*z*: calcd for $C_{71}H_{130}NO_{14}Si_3$: 1304.8794; found: 1304.8833 $[M+H]^+$.

Catechol ester 144: To a solution of amine **143** (73.7 mg, 56.5 μmol) and 2,6-lutidine (40.0 μL, 343 μmol) in CH_2Cl_2 (3.5 mL) at −20 °C was added α-bromoacetyl bromide (15.0 μL, 172 μmol). After stirring at this temperature for 30 min, the reaction was concentrated in vacuo and the crude residue purified by preparative TLC (40% EtOAc/hexanes; plate eluted ×2) to afford the desired α-bromoamide as a clear oil (53.3 mg, 66%).

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R_f=0.76 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=6.38 (dd, J=13.5, 14.0 Hz, 1H, H_{19}), 6.21–6.12 (m, 2H, H_{20}, H_{21}), 6.01 (d, J=11.1 Hz, 1H, H_{18}), 5.93 (m, 1H, Alloc), 5.52 (dd, J=8.6, 14.4 Hz, 1H, H_{22}), 5.35 (d, J=17.3 Hz, 1H, Alloc), 5.29–5.23 (m, 2.6H, H_{30}, Alloc, 0.6 of H_2), 4.93 (m, 1H, H_{34}), 4.62–4.58 (m, 3.4H, 2×Alloc, H_{32}, 0.4 of H_2), 4.50 (br d, 0.4H, 0.4 of H_6), 4.11 (m, 1H, H_{28}), 3.95 (d, J=10.6 Hz, 1H, H_9), 3.89 (d, J=10.7 Hz, 1H, H_9), 3.80–3.75 (m, 2.6H, H_{27}, H_{14}, 0.6 of H_6), 3.59 (dd, J=5.0, 8.1 Hz, 1H, H_{16}), 3.54 (m, 1H), 3.42 [m, 4H, including 3.42 (s, 3H, C_{39}-OCH_3), H_{40}], 3.34 (br t, 0.6H, 0.6 of H_6), 3.22 (s, 3H, C_{27}-OCH_3), 3.13 (s, 3H, C_{16}-OCH_3), 2.89–2.74 (m, 3.4H, H_{39}, H_{31}, H_{25}, 0.4 of H_6), 2.44 (m, 1H, H_{11}), 2.27 (m, 2H, H_3, H_{23}), 2.07 (br d, 1H, H_{38}), 1.89–1.42 [m, 19H, including 1.67 (s, 3H, C_{17}-CH_3), 1.63 (s, 3H, C_{29}-CH_3)], 1.34–1.15 [m, 11H, including 1.19 (d, J=6.9 Hz, 3H, C_{11}-CH_3)], 1.06–0.74 [m, 41H, including 0.89 (s, 9H, TBS), 0.76 (m, 1H, H_{38}), C_{23}-CH_3, C_{25}-CH_3, 2×TES], 0.59 (q, J=7.9 Hz, 6H, TES), 0.49 (q, J=7.9 Hz, 6H, TES), 0.08 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=213.4 (C_{26}), 179.7 (C_{10}), (170.2, 169.9) (C_1), (166.8, 166.5) (C_8), 154.8 (Alloc), 138.9 (C_{22}), (137.3, 137.3), 135.8, 132.6 (C_{20}), (131.8, 131.6) (Alloc), 130.4 (C_{21}), 129.8 (C_{30}), 127.5 (C_{18}), 126.9 (C_{19}), (118.9, 118.6) (Alloc), 84.5 (C_{16}), 84.4 (C_{39}), 84.4 (C_{27}), 79.4 and 79.3 (C_{28}, C_{32}), 76.3 and 75.6 (C_{34}, C_{40}), 69.2 (C_{14}), (68.5, 68.4) (Alloc), (58.1, 58.0) (C_{27}-OCH_3), (58.0, 57.9)(C_{39}-OCH_3), 55.8 (C_{16}-OCH_3), 52.5 (C_2), 44.7 (C_{25} or C_{31}), (43.1, 39.2) (C_6), 41.2 (C_{12}), 38.9 (C_{11}), 38.0, 35.8 (C_{25} or C_{31}), 35.7 (C_{38}), 34.9 (C_{23}), 34.1, (34.0, 33.9), 33.9, 33.4, 33.2, 32.1, (31.8, 31.8), 29.7, 28.8, 26.4 (C_3), (25.9, 25.9) (TBS), 25.1, 21.7 (C_{11}-CH_3), 20.8, 18.1 (TBS), 17.1 (C_{23}-CH_3), (15.6, 15.5) (C_{31}-CH_3), 15.2, 14.1 (C_{25}-CH_3), 11.5 and 11.3 (C_{17}-CH_3, C_{29}-CH_3), 6.9 (TES), 6.7 (TES), (5.2, 5.1) (TES), 4.7 (TES), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}$=3341, 2984, 2950, 2872, 1742, 1729, 1706, 1652, 1456, 1377, 1257, 1107, 1005, 876, 836, 744 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{73}H_{130}BrNO_{15}Si_3Na$: 1446.7824; found: 1446.7724 $[M+Na]^+$.

To a mixture of the acid prepared above (53.3 mg, 37.4 μmol), catechol (21.0 mg, 191 μmol) and DMAP (cat.) in CH_2Cl_2 (2 mL) at 0°C was added DCC (23.0 mg, 111 μmol). The reaction was allowed to warm to RT and stirred for 30 min. The reaction was then concentrated in vacuo and the crude residue purified by preparative TLC (40% EtOAc/hexanes) to afford catechol ester **144** as a clear oil (49.7 mg, 88%). R_f=0.56 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.11 (m, 1H, ArH), 7.04 (dd, J=8.0, 1.3 Hz, ArH), 7.00 (m, 1H, ArH), 6.90 (m, 1H, ArH), 6.36 (dd, J=13.5, 11.4 Hz, 1H, H_{19}), 6.19–6.11 (m, 2H, H_{20}, H_{21}), 6.05 (s, 1H, ArOH), 6.00 (d, J=11.0 Hz, 1H, H_{18}), 5.93 (m, 1H, Alloc), 5.52 (dd, J=8.7, 14.2 Hz, 1H, H_{22}), 5.35 (d, J=17.1 Hz, 1H, Alloc), 5.30–5.23 (m, 2.6H, H_{30}, Alloc, 0.6×H_2), 4.93 (m, 1H, H_{34}), 4.62–4.58 (m, 3.4H, 2×Alloc, H_{32}, 0.4 of H_2), 4.50 (br d, 0.4H, 0.4 of H_6), 4.11 (m, 1H, H_{28}), 3.95 (m, 1H, H_9), 3.87–3.75 [m, 3.6H, including 3.86 (d, J=10.7 Hz, 1H, H_9), H_{27}, H_{14}, 0.6 of H_6], 3.60 (dd, J=4.1, 8.9 Hz, 1H, H_{16}), 3.42 [m, 4H, including 3.42 (s, 3H, C_{39}-OCH_3), H_{40}], 3.34 (br t, 0.6H, 0.6 of H_6), 3.22 (s, 3H, C_{27}-OCH_3), 3.11 (s, 3H, C_{16}-OCH_3), 2.85 (m, 1.4H, H_{39}, 0.4 of H_6), 2.77–2.71 (m, 3H, H_{11}, H_{25}, H_{31}), 2.32 (br m, 1H, H_{23}), 2.25 (br d, 1H), 2.03–1.52 [m, 20H, including 1.68 (s, 3H, C_{17}-CH_3), 1.62 (s, 3H, C_{29}-CH_3)], 1.36–1.21 [m, 10H, including 1.35 (d, J=7.0 Hz, 3H, C_{11}-CH_3)], 1.06–0.71 [m, 44H, including 0.89 (s, 9H, TBS), 0.73 (m, 1H, H38), C_{23}-CH_3, C_{25}-CH_3, C_{31}-CH_3, 2×TES], 0.62 (q, J=7.9 Hz, 6H, TES), 0.49 (q, J=7.9 Hz, 6H, TES), 0.08 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=213.0 (C_{26}), 174.7 (C_{10}), 170.6 (C_1), 166.5 (C_8), 154.8 (Alloc), 147.4 (Ar), 138.9 (C_{22}), 138.7 (Ar),137.2, 135.8, 132.7 (C_{20}), (131.8, 131.6) (Alloc), 130.3 (C_{21}), 129.9 (C_{30}), 127.4 (C_{18}), 126.9 (Ar), 126.8 (C_{19}), 122.5 (Ar), 120.7 (Ar), (118.7, 118.6) (Alloc), 118.0 (Ar), 84.5 (C_{16}), 84.4 (C_{39}), (83.9, 83.7) (C_{27}), 79.3 and 79.2 (C_{28}, C_{32}), 76.3 and 75.6 (C_{34}, C_{40}), 69.3 (C_{14}), (68.5, 68.4) (Alloc), 58.0 (C_{27}-OCH_3), 58.0 (C_{39}-OCH_3), 55.8 (C_{16}-OCH_3), 52.4 (C_2), 44.7 (C_{25} or C_{31}), 41.6 (C_6), 40.2 (C_{12}), 38.9 (C_{11}), (38.1, 38.0), 35.8 (C_{25} or C_{31}), 35.7 (C_{38}), 34.9 (C_{23}), 34.2, (34.1, 34.0), 33.9, 33.4, 33.2, 32.1, (31.9, 31.8), 29.7, 29.2, (26.4, 26.3) (C_3), (26.0, 25.9) (TBS), 25.1, 21.6 (C_{11}-CH_3), 20.8, 18.1 (TBS), 17.6 (C_{23}-CH_3), (15.7, 15.6) (C_{31}-CH_3), 15.2, 14.1 (C_{25}-CH_3), 11.6 and 11.5 (C_{17}-CH_3, C_{29}-CH_3), 6.9 (TES), 6.7 (TES), (5.1, 5.0) (TES), 4.7 (TES), −4.5 (TBS), −4.7 ppm (TBS); IR (thin film): $\tilde{\nu}$=3380, 2959, 2934, 2888, 1744, 1659, 1650, 1631, 1575, 1519, 1501, 1641, 1378, 1257, 1106, 877, 834, 776, 744, 726 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{79}H_{134}BrNO_{16}Si_3Na$: 1538.8086; found: 1538.8026 $[M+Na]^+$.

Catechol-templated rap 145: Finely powdered K_2CO_3 (11.3 mg, 81.8 μmol) was added to DMF (80 mL) and the suspension sonicated at RT until homogenous. To this was added a solution of catechol ester **144** (49.7 mg, 32.7 μmol) in DMF (1 mL), dropwise over 1 h. After stirring for an additional 30 min, the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc and filtered through a pad of silica (washing with EtOAc), and the eluant concentrated in vacuo. The crude residue was purified by preparative TLC (25% EtOAc/hexanes) to afford catechol-templated rap **145** as a clear oil (33.0 mg, 70%). R_f=0.36 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.17 (m, 1H, ArH), 7.04 (m, 2H, ArH), 6.98 (m, 1H, ArH), 6.34 (m, 1H, H_{19}), 6.16–6.11 (m, 2H, H_{20}, H_{21}), 5.97–5.99 (m, 2H, H_{18}, Alloc), 5.43 (dd, J=9.1, 13.9 Hz, 1H, H_{22}), 5.35–5.21 [m, 3H, including 5.24 (dd, J=15.0, 17.2 Hz, Alloc)], 4.92 (m, 1H, H_{34}), 4.79–4.50 [m, 5.4H, including 4.74 (d, J=12.2, 1H, H_9)], 4.10 (d, J=8.0 Hz, 1H, H_{28}), 3.88 (br m, 1H), 3.76 (m, 1.6H), 3.55 (m, 1H, H_{16}), 3.41 [m, 4H, including 3.41 (s, 3H, C_{39}-OCH_3), H_{40}], 3.33 (br t, 0.6H, 0.6 of H_6), 3.19 (s, 3H, C_{27}-OCH_3), 3.10 (s, 3H, C_{16}-OCH_3), 2.88 (m, 1H), 2.80 (m, 0.6H, 0.6 of H_6), 2.69 (m, 1H, H_{34}), 2.22 (m, 2H), 2.03 (m, 1.4H), 1.85–1.53 [m, 23.4H, including 1.67 (s, 3H, C_{17}-CH_3), 1.59 (s, 3H, C_{29}-CH_3)], 1.45–1.19 (m, 10H), 1.06–0.83 [m, 42H, including 1.05 (d, J=7.1 Hz, 3H, C_{23}-CH_3), 0.89 (s, 9H, TBS), C_{25}-CH_3, 2×TES], 0.73 (m, 1H, H_{38}), 0.61 (m, 6H, TES), 0.49 (m, 6H, TES), 0.08 (s, 3H, TBS), 0.07 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=213.1 (C_{26}), (174.5, 174.4) (C_{10}), 170.3 (C_1), (167.7, 167.2) (C_8), 154.8 (Alloc), 149.9 (Ar), 140.0 (Ar), 139.5 (C_{22}), (137.6, 137.4), 135.8, (132.9, 132.7) (C_{20}), (131.7, 131.6) (Alloc), 130.4 (C_{21}), (130.2, 130.0) (C_{30}), 128.0 (C_{18}), 126.8 (Ar), 126.7 (C_{19}), (123.0, 122.9) (Ar), 121.7 (Ar), (118.9, 118.7) (Alloc), (114.0, 113.9) (Ar), 84.5 (C_{16}), 84.4 (C_{39}), (83.7, 83.4) (C_{27}), 79.1 and 79.0 (C_{28}, C_{32}), 76.1 and 75.6 (C_{34}, C_{40}), 68.7 (C_{14}), (68.5, 68.3) (Alloc), 58.0 (C_{27}-OCH_3), 58.0 (C_{39}-OCH_3), (55.9, 55.6) (C_{16}-OCH_3), 52.3 (C_2), 43.4 (C_{25} or C_{31}), (41.4, 41.2) (C_6), (39.7, 39.6) (C_{12}), (39.0, 38.7) (C_{11}), (38.3, 38.2), 35.9 (C_{25} or C_{31}), 35.5 (C_{38}), 35.4 (C_{23}), 34.2, (34.0, 34.0), 33.9, 33.4, (33.2, 33.1), 32.6, (31.9, 31.8), 29.7, (28.4, 28.3), (27.2, 26.7) (C_3), 25.9 (TBS), 25.2, 22.1 (C_{11}-CH_3), 20.9, (18.1, 18.0) (TBS), 17.6 (C_{23}-CH_3), (15.4, 15.4) (C_{31}-CH_3), 15.0, (14.3, 14.1) (C_{25}-CH_3), 11.4 and 11.3 (C_{17}-CH_3, C_{29}-CH_3), 6.9 (TES), 6.7 (TES), 5.1 (TES), 4.7 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu}$=2934, 2878, 1745, 1682, 1652, 1606, 1559, 1542, 1501, 1456, 1376, 1256, 1190, 1111, 1005, 875, 836, 816, 778, 745, 727, 666 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{79}H_{133}NO_{16}Si_3Na$: 1458.8824; found: 1458.8727 $[M+Na]^+$.

Macrocyclisation product 151: To a solution of catechol-templated rap **145** (14.7 mg, 10.2 μmol) in THF (0.6 mL) at −78°C was added LiHMDS (1.0 M in THF; 23.0 μL, 23.0 μmol). The reaction was warmed to −20°C and stirred for 3 min, before it was cooled back to −78°C and quenched with saturated aqueous NH_4Cl (1 drop). After warming gradually to RT, the reaction mixture was concentrated in vacuo and the crude residue purified by preparative TLC to afford the macrocyclisation product **151** as a clear oil and as an undetermined mixture of rotamers and of stereoisomers at C9 (11.4 mg, 78%). R_f=0.68 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.03–6.78 (m, 4H, 4×ArH), 6.39–6.25 (m, 2H), 6.18–5.90 (m, 4H), 5.47–5.17 (m, 5H), 4.90 (m, 1H), 4.79 (m, 1H, H_{34}), 4.63–4.50 (m, 4H), 4.43 (br d, 0.6H), 4.31 (m, 0.4H), 4.20–4.08 [m, 2H, including 4.12 (d, J=6.7 Hz, part of H_{28}), 4.10 (d, J=7.8 Hz, part of H_{28})], 3.83–3.67 (m, 2H), 3.60–3.03 (m, 11H, including 3.41 (s, part of C_{39}-OCH_3), 3.20 (s, part of C_{27}-OCH_3), 3.09 (s, part of C_{16}-OCH_3)], 2.92–2.54 (m, 3H), 2.32–2.17 (m, 2H), 2.05–0.66 [m, 73H, including 1.70 (s, part of C_{17}-CH_3), 0.89 (s, part of TBS), 0.72 (m, 1H, H_{38})], 0.64–0.46 (m, 12H, 2×TES), 0.07 ppm (2s, 6H, 2×TBS); IR (thin film): $\tilde{\nu}$=3350, 2954, 2934, 2875, 1745, 1736, 1718, 1701, 1652, 1646, 1637, 1558, 1540, 1496, 1456, 1259, 1107, 1006, 876, 836, 778, 745, 726, 666 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{79}H_{133}NO_{16}Si_3Na$: 1458.8824; found: 1458.8727 $[M+Na]^+$.

(−)-Rapamycin (1): To a solution of Alloc-protected alcohol **153** (10.6 mg, 7.4 μmol) and dimedone (10.3 mg, 73.5 μmol) in THF (0.6 mL) was added $[Pd(PPh_3)_4]$ (1.5 mg, 18 mol%). After stirring for 15 min, the reaction was diluted with EtOAc and filtered through a pad of SiO_2, washing with EtOAc, and the eluant concentrated in vacuo. The crude

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residue was purified by preparative TLC (25% EtOAc/hexanes) to afford the corresponding C32-alcohol as a colourless oil and as an undetermined mixture of rotamers and of stereoisomers at C9 (8.0 mg, 80%). $R_f = 0.22$ (25% EtOAc/hexanes); $[\alpha]_D^{25} = -58.8$ ($c = 0.80$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 7.02$–6.79 (m, 4H, 4×ArH), 6.43–6.25 (m, 1.6H), 6.21–6.09 (m, 1.4H), 6.04–5.89 (m, 1H), 5.52–4.78 (m, 5H), 4.56 (br d, 0.2H), 4.42 (br t, 0.3H), 4.21–4.04 [m, 1.5H, including 4.07 (d, $J = 7.8$ Hz, part of H_{28}), 4.05 (d, $J = 7.9$ Hz, part of H_{28})], 3.85–3.64 (m, 2H), 3.62–3.32 [m, 5H, including 3.41 (s, part of C_{39}-OCH_3)], 3.28–2.99 [m, 6H, including 3.24 (s, part of C_{27}-OCH_3), 3.24 (s, part of C_{27}-OCH_3), 3.20 (s, part of C_{27}-OCH_3), 3.11 (s, part of C_{16}-OCH_3), 3.10 (s, part of C_{16}-OCH_3)], 2.90–2.63 (m, 2H), 2.54–2.11 (m, 6H), 1.88–0.66 [m, 75H, including 1.60 (s, part of C_{29}-CH_3), 0.90 (s, part of TBS), 0.89 (s, part of TBS), 0.88 (s, part of TBS), 0.71 (m, 1H, H_{38})], 0.63–0.48 (m, 12H, 2× TES), 0.08–0.05 ppm [m, 6H, including 0.08 (s, part of TBS), 0.06 (s, part of TBS)]; IR (thin film): $\tilde{\nu} = 3400$, 2955, 2931, 2875, 1735, 1718, 1653, 1646, 1637, 1559, 1541, 1496, 1457, 1247, 1106, 836, 745, 666 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{75}H_{129}NO_{14}Si_3Na$: 1374.8613; found: 1374.8620 $[M+Na]^+$.

To a solution of the C32-alcohol prepared above (7.4 mg, 5.5 μmol) in CH_3CN/H_2O (10:1, 0.7 mL) at 0°C was added $PhI(OAc)_2$ (7.0 mg, 21.7 μmol) and the mixture stirred at this temperature for 1 h 15 min. The reaction was then diluted with EtOAc and hexanes, and filtered through a pad of SiO_2 (washing with 50% EtOAc/hexanes). The eluant was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and pyridine (36.0 μL, 445 μmol) added, followed by DMP (46.0 mg, 108 μmol). After stirring for 3 h 30, the reaction was filtered through a pad of silica (washing with 50% EtOAc/hexanes). The eluant was concentrated in vacuo, and the crude residue purified by preparative TLC (33% EtOAc/hexanes) to afford the corresponding C32-ketone as a white solid (4.2 mg, 61% over 2 steps). $R_f = 0.56$ (33% EtOAc/hexanes); $[\alpha]_D^{25} = -160.0$ ($c = 0.38$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 6.43$–6.38 [m, 1H, including 6.40 (dd, $J = 14.3$, 11.1 Hz, part of H_{19})], 6.26–6.08 (m, 2H, H_{20}, H_{21}), 6.05–5.98 [m, 1H, including 6.03 (d, $J = 10.9$ Hz, part of H_{18})], 5.49–5.43 [m, 1H, including 5.47 (dd, $J = 9.0$, 14.7 Hz, part of H_{22})], 5.31–5.13 (m, 4H), 4.51–4.25 (m, 1H), 4.12–3.50 [m, 3H, including 4.05 (d, $J = 8.2$ Hz, part of H_{28})], 3.41–3.11 [m, 10H, including 3.40 (s, part of C_{39}-OCH_3), 3.23 (s, part of C_{27}-OCH_3), 3.15 (s, part of C_{16}-OCH_3)], 2.99–2.68 (m, 3H), 2.48–2.19 (m, 2H), 2.09–1.92 (m, 2H), 1.87–0.70 [m, 73H, including 1.67 (s, part of C_{17}-CH_3), 1.55 (s, part of C_{29}-CH_3), 0.89 (s, part of TBS), 0.88 (s, part of TBS)], 0.63–0.47 [m, 12H, including 0.61 (q, $J = 7.5$ Hz, 6H, TES), TES], 0.07 (s, 3H, TBS), 0.05 ppm (s, 3H, TBS); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 213.4$ (C_{26}), 208.2 (C_{32}), 202.4 (C_{10}), 185.5 (C_9), 168.8 (C_1), 165.3 (C_8),139.5 (C_{22}), 135.0 (C_{17}),132.7 (C_{20}), 130.9 (C_{21}), 130.0 (C_{18}), 128.7, 128.1 (C_{30}), 126.8 (C_{19}), 84.6 (C_{27}), 84.3 (C_{39}), 83.3 (C_{16}), 80.2 (C_{28}), 75.6 and 74.7 (C_{34}, C_{40}), 69.1 (C_{14}), 58.0 and 57.8 (C_{27}-OCH_3, C_{39}-OCH_3), 56.0 (C_{16}-OCH_3), 51.7 (C_2), 47.0 (C_{31}), 44.0 (C_{25}), 43.2, 41.0 (C_6), 40.4 (C_{24}), 40.1, 39.8 (C_{12}), (39.1, 39.0) (C_{11}), 36.5, 36.1 (C_{38}), 34.4, 33.9 (C_{41}), 33.4, 33.1 (C_{35}), 32.3, 29.7, 27.3 (C_3), 25.8 (TBS), 25.4, 21.8 (C_{11}-CH_3), 20.7, 18.1 (TBS), 17.6 (C_{23}-CH_3), 15.8 (C_{31}-CH_3), (14.5, 14.2) (C_{35}-CH_3), 13.8 (C_{25}-CH_3), 11.0 and 10.6 (C_{17}-CH_3, C_{29}-CH_3), 6.9 (TES), 6.7 (TES), 5.1 (TES), 4.7 (TES), −4.5 (TBS), −4.8 ppm (TBS); IR (thin film): $\tilde{\nu} = 2956$, 2933, 2874, 1734, 1718, 1652, 1647, 1559, 1541, 1507, 1457, 1248, 1108, 878, 836, 777, 745, 729, 666 cm^{-1}; HMRS (ESI): m/z: calcd for $C_{69}H_{121}NO_{13}Si_3Na$: 1278.8038; found: 1278.7959 $[M+Na]^+$.

To a solution of the ketone prepared above (3.6 mg, 2.9 μmol) in THF (70 μL) was added HF·Py (500 μL) and the reaction mixture heated to 50°C. After stirring for 4 h, the solution was poured into saturated aqueous $NaHCO_3$ and the product extracted with THF (×5). The combined organic extracts were dried over K_2CO_3 and concentrated in vacuo. The crude residue was purified by preparative TLC (50% THF/hexanes) to afford (−)-rapamycin **1** as a white solid and as a 4:1 mixture of rotamers (1.6 mg, 61%). The observed analytical data was identical in all respects to that obtained for an authentic sample of the natural product of (−)-rapamycin (**1**). $R_f = 0.25$ (30% acetone/petrol); $[\alpha]_D^{25} = -70.8$ ($c = 0.15$, MeOH) [ref. [6] $= -65.0$ ($c = 0.21$, MeOH)]; ^{1}H NMR ($CDCl_3$, 600 MHz, major rotamer): $\delta = 6.38$ (dd, $J = 11.3$, 14.7 Hz, 1H, H_{19}), 6.31 (dd, $J =$ 11.0, 15.3 Hz, 1H, H_{20}), 6.14 (dd, $J = 10.5$, 15.3 Hz, 1H, H_{21}), 5.96 (d, $J =$ 11.0 Hz, 1H, H_{18}), 5.54 (dd, $J = 8.8$, 15.2 Hz, 1H, H_{22}), 5.41 (d, $J = 9.8$ Hz, 1H), 5.29 (d, $J = 5.0$ Hz, 1H), 5.17 (dd, $J = 6.0$, 10.3 Hz, 1H), 4.81 (s, 1H), 4.17 (d, $J = 5.8$ Hz, 1H), 3.85 (m, 1H), 3.70 (d, $J = 6.1$ Hz, 1H), 3.66 (m, 1H), 3.57 (d, $J = 11.6$ Hz, 1H), 3.47–3.31 [m, 9H, including 3.41 (s, 3H, C_{39}-OCH_3), 3.34 (s, 3H, C_{27}-OCH_3)], 3.14 (s, 3H, C_{16}-OCH_3), 2.94 (m, 1H), 2.79–2.71 [m, 2H, inlcuding 2.74 (dd, $J = 6.2$, 17.0 Hz, 1H)], 2.62 (m, 1H), 2.36–2.30 (m, 2H), 2.10 (m, 1H), 2.01–1.96 (m, 3H), 1.87–0.80 [m, 42H, including 1.65 (s, 3H, C_{17}-CH_3), 1.10 (d, $J = 6.8$ Hz, 3H, C_{31}-CH_3), 1.05 (d, $J = 6.5$ Hz, 3H, C_{23}-CH_3), 1.00 (d, $J = 6.5$ Hz, 3H, C_{25}-CH_3), 0.95 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H)], 0.66 ppm (m, 1H, H_{38}); (minor rotamer): $\delta = 6.24$ (dd, $J = 10.8$, 14.7 Hz, 1H), 5.89 (d, $J = 10.7$ Hz, 1H, H_{18}), 5.49 (dd, $J = 9.3$, 14.3 Hz, 1H, H_{22}), 5.11 (m, 1H), 4.43 (d, $J =$ 14.1 Hz, 1H), 4.29 (m, 1H), 4.21 (d, $J = 7.8$ Hz, 1H), 3.40 (s, 3H, C_{39}-OCH_3), 3.37 (s, 3H, C_{27}-OCH_3), 1.74 (s, 3H), 1.15 (d, $J = 6.8$ Hz, 3H), 0.83 ppm (d, $J = 6.6$ Hz, 1H); HMRS (ESI): m/z: calcd for $C_{51}H_{79}NO_{13}Na$: 936.5443; found: 936.5439 $[M+Na]^+$.

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[1] a) C. Vezina, A. Kudelski, S. N. Sehgal, *J. Antibiot.* **1975**, *28*, 721; b) S. N. Sehgal, H. Baker, C. Vezina, *J. Antibiot.* **1975**, *28*, 727.

[2] D. C. N. Swindells, P. S. White, J. A. Findlay, *Can. J. Chem.* **1978**, *56*, 2491.

[3] a) J. A. Findlay, L. Radics, *Can. J. Chem.* **1980**, *58*, 579; b) J. B. McAlpine, S. J. Swanson, M. Jackson, D. N. Whittern, *J. Antibiot.* **1991**, *44*, 688; c) T. G. Pagano, *Magn. Reson. Chem.* **2005**, *43*, 174.

[4] R. R. Martel, J. Klicius, S. Galet, *Can. J. Physiol. Pharmacol.* **1977**, *55*, 48.

[5] a) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, T. Taga, *J. Am. Chem. Soc.* **1987**, *109*, 5031; b) T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, M. Kosaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, *40*, 1249; c) T. Kino, H. Hatanaka, S. Miyata, N. Inamura, M. Nishiyama, T. Yajima, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, T. Ochiai, *J. Antibiot.* **1987**, *40*, 1256.

[6] Nicolaou: a) A. D. Piscopio, N. Minowa, T. K. Chakraborty, K. Koide, P. Bertinato, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1993**, 617; b) K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, N. Minowa, *J. Chem. Soc. Chem. Commun.* **1993**, 619; c) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419; d) K. C. Nicolaou, A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, K. Koide, *Chem. Eur. J.* **1995**, *1*, 318; Schreiber: e) S. D. Meyer, T. Miwa, M. Nakatsuka, S. L. Schreiber, *J. Org. Chem.* **1992**, *57*, 5058; f) D. Romo, D. D. Johnson, L. Plamondon, T. Miwa, S. L. Schreiber, *J. Org. Chem.* **1992**, *57*, 5060; g) D. Romo, S. D. Meyer, D. D. Johnson, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 7906; Danishefsky: h) C. M. Hayward, M. J. Fisher, D. Yohannes, S. J. Danishefsky, *Tetrahedron Lett.* **1993**, *34*, 3989; i) R. F. Horvath, R. G. Linde, C. M. Hayward, J. Joglar, D. Yohannes, S. J. Danishefsky, *Tetrahedron Lett.* **1993**, *34*, 3993; j) C. M. Hayward, D. Yohannes, S. J. Danishefsky, *J. Am. Chem. Soc.* **1993**, *115*, 9345; Smith: k) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1995**, *117*, 5407;

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l) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, *119*, 947; m) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, *119*, 962; n) For an extensive recent review of the synthesis of rapamycin within the context of other pipecolinic natural products, see: M. L. Maddess, M. N. Tackett, S. V. Ley in *Progress in Drug Research, Vol. 66* (Eds.: F. Petersen, R. Amstutz), Birkhäuser Verlag, Basel, **2008**, pp. 15–186.

[7] a) W. Braun, J. Kallen, V. Mikol, M. D. Walkinshaw, K. Wuthrich, *FASEB J.* **1995**, *9*, 63; b) C. R. Kissinger, H. E. Parge, D. R. Knighton, C. T. Lewis, L. A. Pelletier, A. Tempczyk, V. J. Kalish, K. D. Tucker, R. E. Showalter, *Nature* **1995**, *378*, 641; c) F. J. Dumont, M. J. Staruch, S. L. Koprak, J. J. Siekierka, C. S. Lin, R. Harrison, T. Sewell, V. M. Kindt, T. R. Beattie, *J. Exp. Med.* **1992**, *176*, 751; d) S. L. Schreiber, *Science* **1991**, *251*, 283.

[8] J. W. Becker, J. Rotonda, B. M. McKeever, H. K. Chan, A. I. Marcy, G. Wiederrecht, J. D. Hermes, J. P. Springer, *J. Biol. Chem.* **1993**, *268*, 11335.

[9] a) M. Morisaki, T. Arai, *J. Antibiot.* **1992**, *45*, 126; b) H. Hatanaka, M. Iwami, T. Kino, T. Goto, M. Okuhara, *J. Antibiot.* **1988**, *41*, 1586; c) H. Hatanaka, T. Kino, S. Miyata, N. Inamura, A. Kuroda, T. Goto, H. Tanaka, M. Okuhara, *J. Antibiot.* **1988**, *41*, 1592.

[10] a) M. He, B. Haltli, M. Summers, X. Feng, J. Hucul, *Gene* **2006**, *377*, 109; b) G. M. Salituro, D. L. Zink, A. Dahl, J. Nielsen, E. Wu, L. Huang, C. Kastner, F. J. Dumont, *Tetrahedron Lett.* **1995**, *36*, 997.

[11] a) Y. S. Or, R. F. Clark, Q. Xie, J. McAlpine, D. N. Whittern, R. Henry, J. R. Luly, *Tetrahedron* **1993**, *49*, 8771; b) T. Arai, Y. Koyama, T. Suenaga, H. Honda, *J. Antibiot.* **1962**, *15*, 231.

[12] T. Fehr, J. J. Sanglier, W. Schuler, L. Gschwind, M. Ponelle, W. Schilling, C. Wioland, *J. Antibiot.* **1996**, *49*, 230.

[13] For recent reviews, see: a) A. M. Arsham, T. P. Neufeld, *Curr. Opin. Cell Biol.* **2006**, *18*, 589; b) C. K. Tsang, H. Qi, L. F. Liu, X. F. S. Zheng, *Drug Disc. Today* **2007**, *12*, 112; c) S. Wullschleger, R. Loewith, M. N. Hall, *Cell* **2006**, *124*, 471.

[14] For a recent review, see: D. A. Young, C. L. Nickerson-Nutter, *Curr. Opin. Pharmacol.* **2005**, *5*, 418.

[15] R. T. Abraham, C. H. Eng, *Exp. Opin. Ther. Targets* **2008**, *12*, 209.

[16] For recent reviews, see: a) S. Vignot, S. Faivre, D. Aguirre, E. Raymond, *Ann. Oncol.* **2005**, *16*, 525; b) D. A. Guertin, D. M. Sabatini, *Cancer Cell* **2007**, *12*, 9; c) S. Faivre, G. Kroemer, E. Raymond, *Nat. Rev. Drug Discovery* **2006**, *5*, 671.

[17] a) B. Rini, S. Kar, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2007**, *6*, 599; b) D. Simpson, M. P. Curran, *Drugs* **2008**, *68*, 631.

[18] a) D. M. Sabatini, H. Erdjument-Bromage, M. Lui, P. Tempst, S. H. Snyder, *Cell* **1994**, *78*, 35; b) E. J. Brown, M. W. Albers, T. B. Shin, K. Ichikawa, C. T. Keith, W. S. Lane, S. L. Schreiber, *Nature* **1994**, *369*, 756.

[19] J. Choi, J. Chen, S. L. Schreiber, J. Clardy, *Science* **1996**, *273*, 239.

[20] a) J. C. Anderson, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, *35*, 2087; b) C. Kouklovsky, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, *35*, 2091; c) S. V. Ley, J. Norman, C. Pinel, *Tetrahedron Lett.* **1994**, *35*, 2095.

[21] S. V. Ley, C. Kouklovsky, *Tetrahedron* **1994**, *50*, 835.

[22] M. L. Maddess, M. N. Tackett, H. Watanabe, P. E. Brennan, C. D. Spilling, J. S. Scott, D. P. Osborn, S. V. Ley, *Angew. Chem.* **2007**, *119*, 597; *Angew. Chem. Int. Ed.* **2007**, *46*, 591.

[23] An ever-increasing number of reagents are available nowadays to achieve stereoselectivity in acetate aldol reacions; for examples, see: *Modern Aldol Reactions, Vol. 1* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**. Nevertheless, this remains a difficulty in organic synthesis, and was even moreso when we first developed our retrosynthesis of rapamycin (**1**) in 1990, before the discovery of most modern aldol catalysts and auxiliaries.

[24] R. J. Steffan, R. M. Kearney, D. C. Hu, A. A. Failli, J. S. Skotnicki, R. A. Schiksnis, J. F. Mattes, K. W. Chan, C. E. Caufield, *Tetrahedron Lett.* **1993**, *34*, 3699.

[25] a) D. Yohannes, S. J. Danishefsky, *Tetrahedron Lett.* **1992**, *33*, 7469; b) D. Yohannes, C. D. Myers, S. J. Danishefsky, *Tetrahedron Lett.* **1993**, *34*, 2075.

[26] The unselective formation of C28, C40-bis-OTBS-rapamycin has previously been reported. See M. T. Goulet, J. Boger, *Tetrahedron Lett.* **1990**, *31*, 4845.

[27] J. I. Luengo, L. W. Rozamus, D. A. Holt, *Tetrahedron Lett.* **1993**, *34*, 4599.

[28] a) S. Mukherjee, Ph.D. thesis, Imperial College of Science Technology and Medicine (London, U.K.), **1988**; b) S. V. Ley, A. Armstrong, D. Diezmartin, M. J. Ford, P. Grice, J. G. Knight, H. C. Kolb, A. Madin, C. A. Marby, S. Mukherjee, A. N. Shaw, A. M. Z. Slawin, S. Vile, A. D. White, D. J. Williams, M. Woods, *J. Chem. Soc. Perkin Trans. 1* **1991**, 667.

[29] Lactone fragment **3** has previously been prepared by an alternative degradation of rapamycin (**1**), see reference [26].

[30] Aldehyde **16** has previously been prepared by an alternative degradation of rapamycin (**1**), see reference [26].

[31] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226.

[32] J. I. Luengo, L. W. Rozamus, D. A. Holt, *Tetrahedron Lett.* **1994**, *35*, 6469.

[33] J. I. Luengo, A. L. Konialian, D. A. Holt, *Tetrahedron Lett.* **1993**, *34*, 991.

[34] a) S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511; b) S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945.

[35] D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099.

[36] R. Ahmed-Schofield, P. S. Mariano, *J. Org. Chem.* **1985**, *50*, 5667.

[37] E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925.

[38] a) D. Cremer, J. Gauss, R. F. Childs, C. Blackburn, *J. Am. Chem. Soc.* **1985**, *107*, 2435; b) C. Blackburn, R. F. Childs, D. Cremer, J. Gauss, *J. Am. Chem. Soc.* **1985**, *107*, 2442.

[39] H. C. Brown, P. V. Ramachandran, *J. Organomet. Chem.* **1995**, *500*, 1.

[40] W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339.

[41] E. D. Mihelich, K. Daniels, D. J. Eickhoff, *J. Am. Chem. Soc.* **1981**, *103*, 7690.

[42] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.

[43] a) J. A. Labinger, D. W. Hart, W. E. Seibert, III, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 3851; b) D. W. Hart, J. Schwartz, *J. Am. Chem. Soc.* **1974**, *96*, 8115.

[44] D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679.

[45] P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., O. Weaver, U. C. Quarck, R. R. Chauvette, R. Monahan, *J. Am. Chem. Soc.* **1957**, *79*, 6062.

[46] E. Prusov, H. Rohm, M. E. Maier, *Org. Lett.* **2006**, *8*, 1025.

[47] G. M. R. Tombo, H. P. Schaer, X. F. Busquets, O. Ghisalba, *Tetrahedron Lett.* **1986**, *27*, 5707.

[48] A. K. Ghosh, X. Xu, *Org. Lett.* **2004**, *6*, 2055.

[49] A. M. Doherty, S. V. Ley, B. Lygo, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1371.

[50] S. Current, K. B. Sharpless, *Tetrahedron Lett.* **1978**, *19*, 5075.

[51] H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, D. F. Wendelborn, *J. Org. Chem.* **1978**, *43*, 1697.

[52] a) Y. Kishi, *Pure Appl. Chem.* **1992**, *64*, 343; b) P. Cintas, *Synthesis* **1992**, 248.

[53] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.

[54] T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, *24*, 2653.

[55] Y. Murata, K. Inomata, H. Kinoshita, H. Kotake, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2539.

[56] In contrast to our observations, Kotake et al. had previously reported that the hydrolysis of dithioketal monosulfones requires stong

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conditions (e.g. $CuCl_2$, SiO_2, or anodic hydrolysis) and long reaction times; see reference [55].
[57] D. R. Mootoo, V. Date, B. Fraser-Reid, *J. Am. Chem. Soc.* **1988**, *110*, 2662.
[58] F. L. Qing, X. G. Zhang, *Tetrahedron Lett.* **2001**, *42*, 5929.
[59] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405.
[60] Y. L. Bennani, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 2079.
[61] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.* **1992**, *57*, 2768.
[62] The chemistry at C26 and C27 was inferred as shown (**83**), based on literature precedent for similar substrates; see reference [61].
[63] M. K. Gurjar, A. S. Mainkar, P. Srinivas, *Tetrahedron Lett.* **1995**, *36*, 5967.
[64] a) S. David, S. Hanessian, *Tetrahedron* **1985**, *41*, 643; b) N. Nagashima, M. Ohno, *Chem. Pharm. Bull.* **1991**, *39*, 1972.
[65] For a review on this methodology, see: A. R. Katritzky, M. Piffl, H. Lang, E. Anders, *Chem. Rev.* **1999**, *99*, 665.
[66] D. A. Evans, G. C. Andrews, B. Buckwalter, *J. Am. Chem. Soc.* **1974**, *96*, 5560.
[67] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535.
[68] a) The preparation of the bis-*para*-nitrobenzoate ester of **90** as a crystalline solid enabled X-ray analysis to confirm the stereochemistry as shown. See also reference [68b]; b) CCDC 696859 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[69] For a recent review on BDA chemistry, see: S. V. Ley, A. Polara, *J. Org. Chem.* **2007**, *72*, 5943.
[70] S. V. Ley, E. Diez, D. J. Dixon, R. T. Guy, P. Michel, G. L. Nattrass, T. D. Sheppard, *Org. Bio. Chem.* **2004**, *2*, 3608.
[71] a) N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139; b) I. Paterson, D. Y. K. Chen, M. J. Coster, J. L. Acena, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross, *Angew. Chem.* **2001**, *113*, 4179; *Angew. Chem. Int. Ed.* **2001**, *40*, 4055.
[72] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U. H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461.
[73] For an extensive review on the use of 1,3-dithianes in organic synthesis, see: A. B. Smith, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365.
[74] M. Kinoshita, M. Taniguchi, M. Morioka, H. Takami, Y. Mizusawa, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2147.
[75] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287.
[76] a) T. Okazoe, K. Takai, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 951; b) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408.
[77] V. Farina, S. R. Baker, D. A. Benigni, C. Sapino, *Tetrahedron Lett.* **1988**, *29*, 5739.
[78] C. M. Hettrick, W. J. Scott, *J. Am. Chem. Soc.* **1991**, *113*, 4903.
[79] For a review on the utility of this methodology, see: S. V. Ley, L. R. Cox, G. Meek, *Chem. Rev.* **1996**, *96*, 423.
[80] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[81] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.
[82] V. Voorhees, R. Adams, *J. Am. Chem. Soc.* **1922**, *44*, 1397.
[83] J. J. W. Duan, A. B. Smith, *J. Org. Chem.* **1993**, *58*, 3703.
[84] A. W. Gibson, G. R. Humphrey, D. J. Kennedy, S. H. B. Wright, *Synthesis* **1991**, 414.
[85] Our observations were in contrast to the success reported by Smith et al. when employing an AIBN-catalysed thermal hydrostannylation to install the C17–C20 (*E*,*E*)-dienyl moiety; see reference [6m].
[86] C. D. J. Boden, G. Pattenden, T. Ye, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2417; In an attempt to investigate the poor yields and *E*/*Z* selectivities observed during the hydrostannylation of enyne **139**, a related bromoenyne was synthesised (wherein C10 already supports a carbonyl). This was prepared from ketone **3** (obtainable both via synthesis and degradation); see Supporting Information A. In the event, the bromoenyne offered no practical advantage and this approach was not pursued.
[87] For other examples of use of this reagent with ketones that have an α-hydroxy functionality, see: a) S. Jendrzejewski, P. Ermann, *Tetrahedron Lett.* **1993**, *34*, 615; b) T. Tsukuda, I. Umeda, K. Masubuchi, M. Shirai, N. Shimma, *Chem. Pharm. Bull.* **1993**, *41*, 1191.
[88] D. E. A. Brittain, C. M. Griffiths-Jones, M. R. Linder, M. D. Smith, C. McCusker, J. S. Barlow, R. Akiyama, K. Yasuda, S. V. Ley, *Angew. Chem.* **2005**, *117*, 2792; *Angew. Chem. Int. Ed.* **2005**, *44*, 2732.
[89] G. Ehrlich, M. Kalesse, *Synlett* **2005**, 655.
[90] A. Pasquarello, G. Poli, D. Potenza, C. Scolastico, *Tetrahedron: Asymmetry* **1990**, *1*, 429.
[91] A. B. Smith, III, S. A. Lodise, *Org. Lett.* **1999**, *1*, 1249.
[92] T. Nagamitsu, D. Takano, T. Fukuda, K. Otoguro, I. Kuwajima, Y. Harigaya, S. Omura, *Org. Lett.* **2004**, *6*, 1865.
[93] I. Shin, H. Q. Zhou, N. L. S. Que, H. W. Liu, P. D. Swedenborg, R. L. Jones, *J. Org. Chem.* **1993**, *58*, 2923.
[94] C. Herber, B. Breit, *Chem. Eur. J.* **2006**, *12*, 6684.
[95] C. C. Aldrich, L. Venkatraman, D. H. Sherman, R. A. Fecik, *J. Am. Chem. Soc.* **2005**, *127*, 8910.
[96] P. Michel, S. V. Ley, *Synthesis* **2003**, 1598.
[97] J. M. Escudier, M. Baltas, L. Gorrichon, *Tetrahedron* **1993**, *49*, 5253.
[98] K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4672.
[99] G. E. Keck, D. Krishnamurthy, *Org. Synth.* **1997**, *75*, 12.
[100] A. K. Ghosh, H. Lei, *J. Org. Chem.* **2000**, *65*, 4779.

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