ARTICLE

OBC
www.rsc.org/obc

The stereocontrolled total synthesis of altohyrtin A/spongistatin 1: the southern hemisphere EF segment†‡

Ian Paterson,* Mark J. Coster,§ David Y.-K. Chen, José L. Aceña, Jordi Bach, Linda E. Keown and Thomas Trieselmann

University Chemical Laboratory, Lensfield Road, University of Cambridge, Cambridge, UK CB2 1EW. E-mail: ip100@cam.ac.uk; Fax: +44 (0)1223 336 362

Received 22nd March 2005, Accepted 3rd May 2005
First published as an Advance Article on the web 24th May 2005

The fully functionalised C29–C51 southern hemisphere of altohyrtin A/spongistatin 1 (**1**), incorporating the E- and F-ring tetrahydropyran rings and the unsaturated side chain, has been synthesised in a highly convergent and stereocontrolled manner. Key steps in the synthesis of this phosphonium salt include four highly diastereoselective, substrate-controlled, boron aldol reactions to establish key C–C bonds and accompanying stereocentres, where the introduction of the chlorodiene side chain and the C47 hydroxyl-bearing centre were realised by exploiting remote stereoinduction from the F-ring tetrahydropyran.

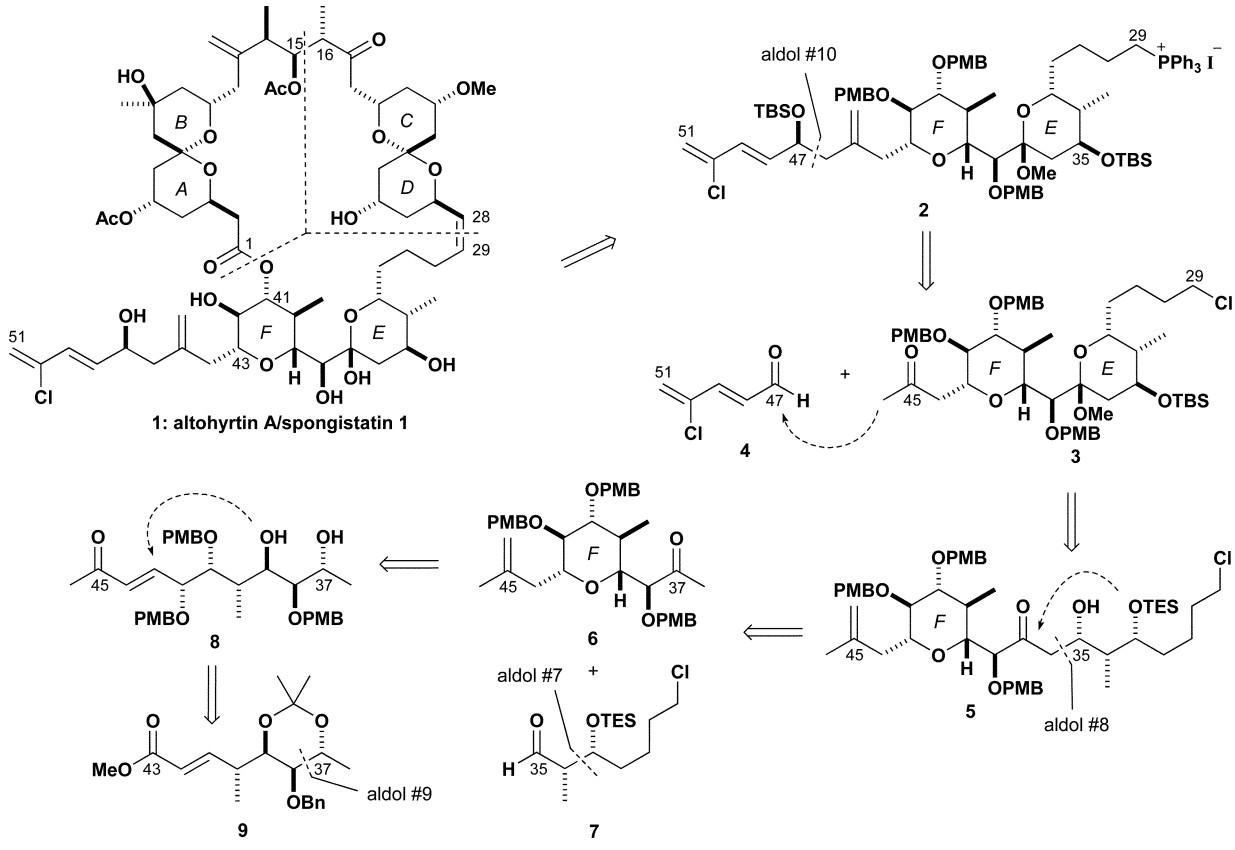
Introduction

Altohyrtin A/spongistatin 1 (**1**, Scheme 1) is a remarkably cytotoxic marine macrolide that is in limited supply from its sponge sources.[1] Our strategy[2] for the synthesis of this structurally complex polyketide natural product involves its disconnection into three major fragments, one of which is the C29–C51 southern hemisphere EF-subunit **2**, incorporating the sensitive chloro-triene side chain.[3–5] Herein, we provide a full account of our synthesis of this segment, which proved by far to be the most challenging part of the spongipyran molecular architecture that we had to assemble.[2b,f] Our synthesis of the fully functionalised C29–C51 phosphonium salt **2** was designed to minimise functional group manipulations subsequent to late stage Wittig coupling with the C1–C28 northern hemisphere ABCD-subunit. It was planned that **2** would be derived, in the forward sense, from a stereocontrolled boron aldol reaction[6] between complex methyl ketone **3** and aldehyde **4**, followed by hydroxyl protection, ketone methylenation and conversion of the

† Part 3 of a series of four papers.[1]

‡ Electronic supplementary information (ESI) available: general experimental information and procedures for the synthesis of compounds not detailed in the Experimental section of this paper. See http://www.rsc.org/suppdata/ob/b5/b504149j/

§ Current address: School of Chemistry, University of Sydney, NSW 2006, Australia. Email: m.coster@chem.usyd.edu.au; Fax: +61 2 9351 3329.



Scheme 1 Retrosynthetic analysis for the C29–C51 southern hemisphere EF-subunit of altohyrtin A/spongistatin 1 (**1**).

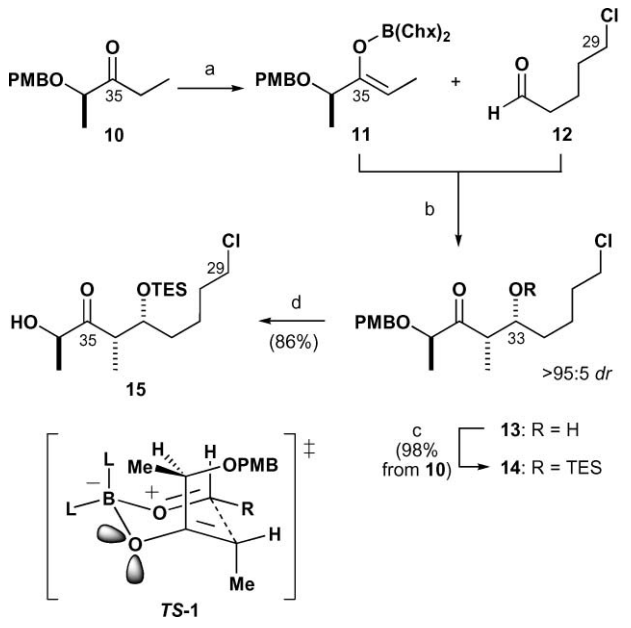
DOI: 10.1039/b504149j

primary alkyl chloride to the corresponding phosphonium salt. The E-ring of **3** would be formed by acetalisation of **5**, which in turn might be obtained by a stereocontrolled aldol reaction between F-ring methyl ketone **6** and aldehyde **7**, the latter of which is simplified by a further aldol disconnection. It was proposed that the formation of the F-ring in **6** would be achieved by intramolecular hetero-Michael addition of **8**, which might be derived from **9** using Sharpless asymmetric dihydroxylation and chain extension as key steps. Finally, the stereo-tetrad present in **9** is well suited to the application of an asymmetric aldol-stereoselective reduction sequence, as previously developed in our laboratory.

Results and discussion

Synthesis of the C29–C35 segment 7

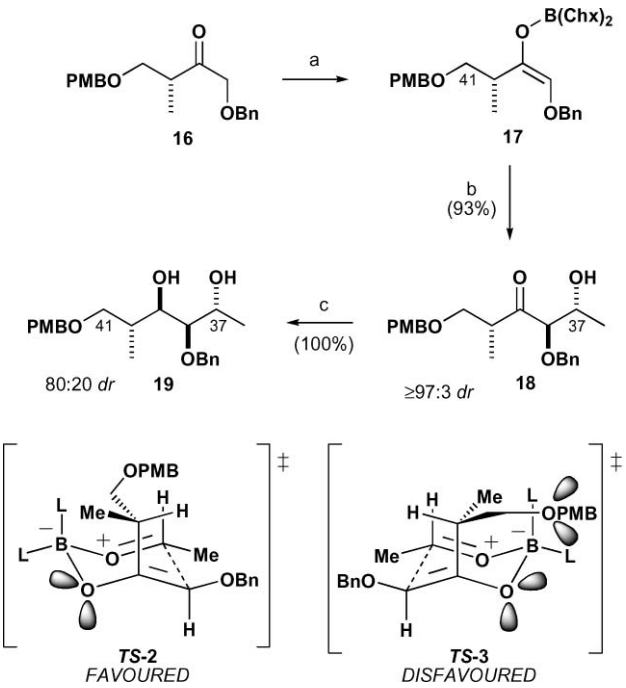
Our synthesis of C29–C35 aldehyde **7** utilised *syn*-selective aldol methodology of a lactate-derived ethyl ketone,[7] to establish the C34 and C35 stereocentres. To this end, (*Z*)-selective enolisation of ketone **10** under the standard conditions (Chx_2BCl, Et_3N, Et_2O)[7,8] provided the dicyclohexylboron enolate **11**, *in situ* (Scheme 2). This underwent a highly diastereoselective aldol reaction with 5-chloropentanal (**12**), to provide **13** (>95 : 5 dr), which was protected as the triethylsilyl (TES) ether **14** (98% from **10**). The stereochemical assignment of aldol adduct **13** was made by analogy with our extensive previous work with aldol reactions of such lactate-derived ethyl ketones,[7] and by NMR analysis of a cyclic derivative prepared later in the synthesis, *vide infra*. The aldol reaction to form **13** is believed to proceed *via TS*-**1**, where the PMB ether and enolate oxygens are directed away from each other, and the smaller of the two remaining groups at the stereogenic centre (H *vs.* Me), is directed inwards. Removal of the *p*-methoxybenzyl (PMB) group from **14** was achieved using DDQ, providing α-hydroxy ketone **15** in preparation for conversion to the corresponding C35 aldehyde.



Scheme 2 *Reagents and conditions*: (a) Chx_2BCl, Et_3N, Et_2O, −78 °C, 1 h; (b) **12**, −78 → −20 °C, 17 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 2 h; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; (d) DDQ, CH_2Cl_2–pH 7 buffer (10 : 1), 0 °C, 2 h.

Synthesis of the C36–C46 F-ring ketone 6

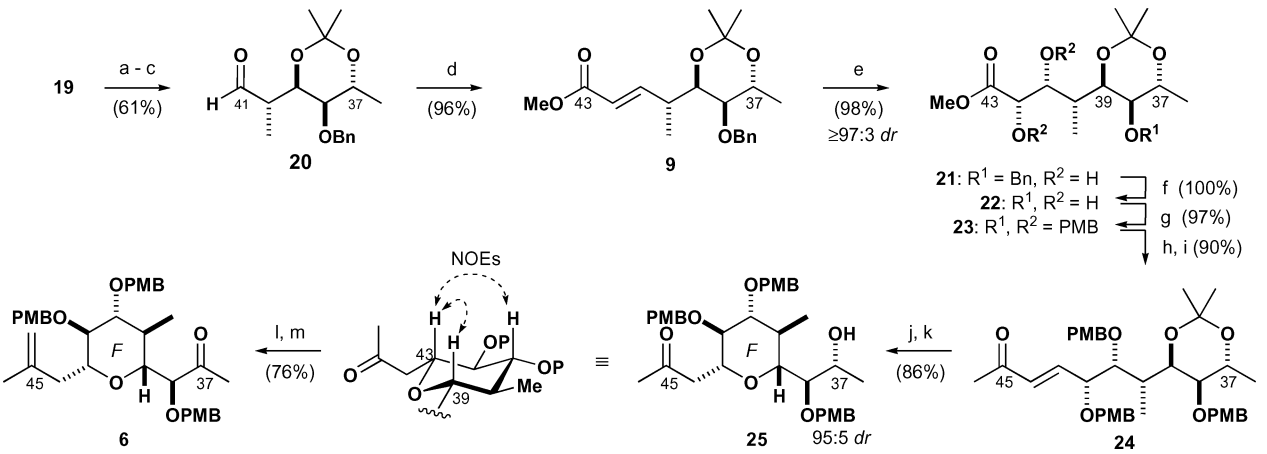
Ketone **16**, derived from methyl (*R*)-3-hydroxy-2-methylpropionate (Roche ester),[2b,9b] was subjected to (*E*)-selective enolisation under conditions previously employed with a number of closely related α-chiral alkoxymethyl ketones,[9] to provide the boron enolate **17**, *in situ* (Scheme 3). Reaction with acetaldehyde in a substrate-controlled aldol reaction provided the 1,2-*anti*-2,4-*anti* adduct **18** with excellent diastereocontrol (≥97 : 3 dr) in 93% yield. While the configuration of **18** was confidently predicted on the basis of previous work by our group,[9] the large vicinal coupling constant (^3J = 6.4 Hz) between protons of the newly formed stereocentres validated the 1,2-*anti* stereochemistry and ^{1}H NMR analysis of the derived MTPA esters[10] confirmed the (37*R*)-configuration. The contra-steric preference for reaction *via TS*-**2**, in which A(1,3) strain is minimised,[11] could be a result of unfavourable repulsion between the oxygen lone pairs of the boron enolate and ether (PMB) in the diastereomeric chair-like transition state *TS*-**3**. There may also be a favourable formyl hydrogen bond[12] between the aldehydic hydrogen and the PMB ether oxygen contributing to stabilisation of *TS*-**2**. Next, stereoselective 1,3-*anti* reduction of β-hydroxy ketone **18** was achieved with tetramethylammonium triacetoxyborohydride {$Me_4NBH(OAc)_3$} in MeCN–AcOH,[13] to yield the desired diol **19** as the major diastereomer (80 : 20 dr). Separation of the unwanted 1,3-*syn* diastereomer was readily achieved at a later stage, *vide infra*.



Scheme 3 *Reagents and conditions*: (a) Chx_2BCl, Et_3N, Et_2O, −78 → 0 °C, 2 h; (b) MeCHO, −78 → −20 °C, 16 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C, 3 h; (c) $Me_4NBH(OAc)_3$, MeCN–AcOH (1 : 1), 4 °C, 60 h.

With the requisite diol **19** in hand, conversion to aldehyde **20** was achieved in three steps by firstly acetonide protection[14] {cat. *p*-toluenesulfonic acid (PTSA), $Me_2C(OMe)_2$} and PMB removal by DDQ to reveal the C41 primary alcohol (Scheme 4). At this stage, the desired compound and the corresponding, undesired C39 epimer were readily separable. Oxidation of the primary alcohol using the Dess–Martin periodinane[15] then provided aldehyde **20** (61% from **19**).

Horner–Wadsworth–Emmons (HWE) chain extension of α-chiral aldehyde **20** to the (*E*)-alkene **9** was best achieved under the Masamune–Roush conditions,[16] using trimethylphosphonoacetate, LiCl and *i*-Pr_2NEt in MeCN (96% yield), with no detectable epimerisation at C40. Although sluggish to react under standard conditions, Sharpless asymmetric dihydroxylation[17] of **9** using enriched AD-mix-β,[17b] with added $MeSO_2NH_2$, provided the desired diol **21** in 98% yield with excellent diastereoselectivity (≥97 : 3 dr). Protection of the C38 hydroxyl as a benzyl ether was crucial to obtain good stereoselectivity in this asymmetric dihydroxylation. By comparison, an analogue with *tert*-butyldimethylsilyl (TBS) protection of the C38 hydroxy group



Scheme 4 *Reagents and conditions*: (a) $Me_2C(OMe)_2$, cat. PTSA, CH_2Cl_2, rt, 16 h; separate from starting materials, 5 cycles; (b) DDQ, CH_2Cl_2–pH 7 buffer (5 : 1), 0 °C, 1.5 h; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; (d) $(MeO)_2P(O)CH_2CO_2Me$, LiCl, *i*-Pr_2NEt, MeCN, rt, 16 h; (e) enriched AD-mix-β, *t*-BuOH–H_2O (1 : 1), $MeSO_2NH_2$, rt, 16 h; (f) H_2, cat. $Pd(OH)_2$–C, $NaHCO_3$, MeOH, rt, 20 h; (g) $PMBOC(NH)CCl_3$, cat. Ph_3CBF_4, THF, 0 °C, 0.5 h; (h) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (i) $(MeO)_2P(O)CH_2COCH_3$, $Ba(OH)_2$, THF–H_2O (40 : 1), rt, 16 h; (j) AcOH–THF–H_2O (9 : 1 : 1), rt, 60 h; (k) KOH, MeOH, rt, 20 h; (l) Cp_2TiMe_2, PhMe, 110 °C, 2 h; (m) cat. TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2, 0 °C → rt, 2 h.

gave an unsatisfactory *ca.* 2 : 1 mixture of diastereomers under the same dihydroxylation conditions.

At this juncture, it became necessary to make a judicious choice of protecting groups for the C41 and C42 hydroxyl groups and to re-appraise the C38 hydroxyl protecting group. Our previously reported synthesis of the C36–C46 segment of altohyrtin A,[2b] utilised the β-(trimethylsilyl)ethoxymethyl (SEM) protecting group for the C41 and C42 hydroxyls and a benzyl (Bn) ether at C38. Through model studies and the results of experiments on other advanced intermediates, the PMB group was chosen for protection of the C38, C41 and C42 hydroxyls. Hence, our synthetic plan for **1** would involve the removal of all three PMB ethers on a sensitive fully-protected *seco*-compound, prior to regioselective macrolactonisation at the C41 hydroxyl on the resultant triol. Although PMB ethers can be problematic to remove on sensitive substrates, we were reasonably confident, on the basis of extensive prior work using this protecting group (as well as from the Kishi synthesis[3f] of altohyrtin A, which involved removal of two PMB ethers), that appropriately mild deprotection conditions would be developed for the late-stage *tris*-PMB removal.

With the protecting group strategy mapped out, debenzylation of **21** to provide triol **22**, was achieved by hydrogenolysis (H_2, $Pd(OH)_2$–C, MeOH) in the presence of $NaHCO_3$, in order to prevent adventitious acid-promoted removal of the sensitive acetonide moiety.[18] Subjection of triol **22** to an excess of *p*-(methoxybenzyl)trichloroacetimidate (PMBTCA)[19] and catalytic trityl tetrafluoroborate (Ph_3CBF_4)[20] in THF effected smooth protection of all three hydroxyl groups to afford **23** (97% yield). The excellent yield obtained in this *tris*-PMB protection highlights the superior nature of Ph_3CBF_4 as a catalyst for etherifications of this type, on delicate acid-sensitive substrates. Reduction of **23** directly to the corresponding aldehyde using diisobutylaluminium hydride (DIBAL-H), which is presumably assisted by chelation of the intermediate aluminium species by a neighbouring alkoxy group, was followed by HWE chain extension with $(MeO)_2P(O)CH_2COCH_3$ to the α,β-unsaturated methyl ketone **24**, this time using activated $Ba(OH)_2$ in aq. THF[21] (90% from **23**).

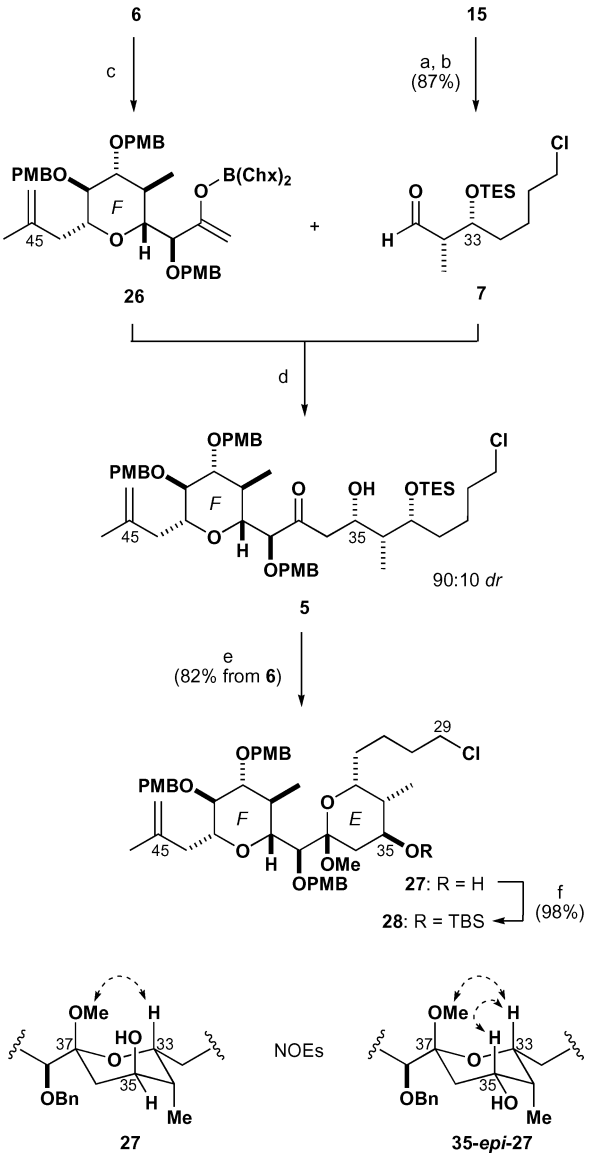
With the stage set for formation of the F-ring of altohyrtin A (**1**), **24** was exposed to AcOH–THF–H_2O, unmasking the C37 and C39 hydroxyls, with concomitant intramolecular hetero-Michael addition to give a *ca.* 1 : 1 mixture of C43 epimeric tetrahydropyrans. Base-promoted equilibration of this mixture could be achieved with either Triton methoxide ($BnNMe_3OMe$) in THF–MeOH or with KOH in MeOH. The latter procedure proved superior on scaling up, cleanly providing the desired, all-equatorial tetrahydropyran **25** as the major diastereomer (95 : 5 dr, 86% yield from **24**), the stereochemistry of which was confirmed by analysis of NOESY spectra.

At this point, it was possible, in principle, to construct the remainder of the southern hemisphere fragment **2** by aldol reactions at either the C36 or C46 terminus. In order to minimise the number of synthetic operations conducted in the presence of the sensitive chloro-trienol side-chain, extension *via* initial aldol reaction at the C36 terminus was exploited. In preparation for this aldol reaction, **25** was methylenated using the Petasis reagent[22] (Cp_2TiMe_2, PhMe, 110 °C). Subsequent oxidation at C37 (TPAP, NMO)[23] provided ketone **6** (76% yield from **25**), ready for aldol reaction with the C29–C35 segment.

Aldol union of the C29–C35 and C36–C46 segments and formation of the F-ring

In preparation for the aldol reaction to unite the C29–C35 and C36–C46 fragments, α-hydroxy ketone **15** was reduced to a diastereomeric mixture of vicinal diols with $LiAlH_4$ (Scheme 5), which were subsequently cleaved oxidatively to the aldehyde **7** as needed, using $Pb(OAc)_4$ (87% from **15**). With the requisite ketone **6** and aldehyde **7** in hand, realisation of the desired aldol reaction proved to be demanding. In simplified model systems, the required Felkin–Anh selective aldol reaction was achievable using Mukaiyama conditions, or by using tin(II), boron and lithium enolates. However, all attempts to effect the Mukaiyama aldol reaction of aldehyde **7** with the trimethylsilyl (TMS) enol ether of **6**, under a variety of conditions, were unsuccessful. Standard conditions for the aldol reaction of **6** with **7** using tin(II) and boron enolates (Chx_2BCl, Et_3N) also failed to deliver any aldol product. Furthermore, the lithium-mediated aldol reaction provided the undesired anti-Felkin–Anh diastereomer in low yield.

Success in the aldol union of **6** with **7** was finally achieved by using a more reactive boron Lewis acid, Chx_2BBr, in the enolate preparation. As such, ketone **6** was transformed into the boron enolate **26** (Chx_2BBr, Et_3N, Et_2O, −78 °C), *in situ*, followed by reaction with aldehyde **7** to afford the desired aldol product **5** with good diastereoselectivity (90 : 10 dr). Although **5** could be separated from the corresponding C35 epimer by careful column chromatography at this stage, it was more convenient to first subject **5** to a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in MeOH–$(MeO)_3CH$ to effect TES deprotection and formation of the E-ring as a methyl acetal **27** (82% from **6**), which was readily separated from its C35 epimer. At this point, analysis of NOESY spectra obtained for **27** and 35-*epi*-**27** confirmed the

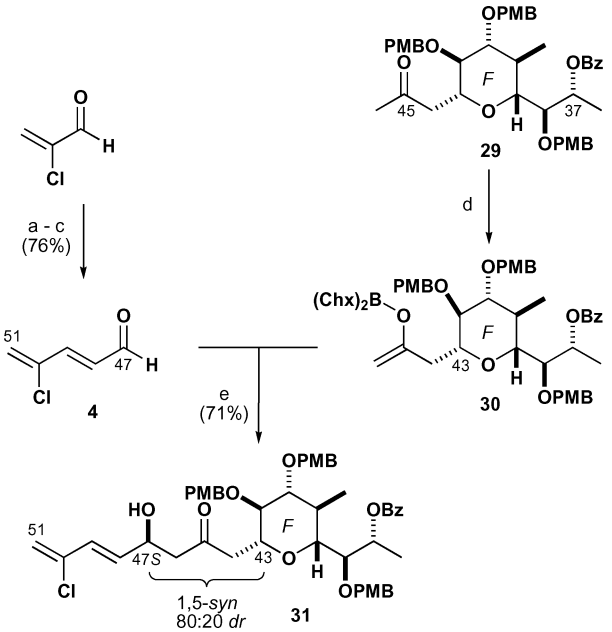


Scheme 5 *Reagents and conditions*: (a) $LiAlH_4$, THF, −78 °C, 0.5 h; (b) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C, 40 min; (c) Chx_2BBr, Et_3N, Et_2O, −78 °C, 2.5 h; (d) **7**, −78 → −20 °C, 17 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 2 h; (e) cat. PPTS, MeOH–$(MeO)_3CH$ (10 : 1), rt, 2 h; (f) TBSCl, Et_3N, Im, DMF, rt, 48 h.

assigned stereochemistry, established in the aldol reaction of **6** with **7**. At this stage, recycling of the undesired diastereomer 35-*epi*-**27** could be achieved by oxidation (TPAP, NMO) followed by stereoselective reduction with L-Selectride to give a *ca.* 4 : 1 ratio of **27** and 35-*epi*-**27**, respectively (63% yield). Finally, the axial C35 hydroxyl was protected as the TBS ether under carefully defined conditions (TBSCl, Et_3N, Im, DMF), providing **28** in 98% yield.

Installation of the chloro-trienol side-chain and final steps to construct the southern hemisphere phosphonium salt 2

Model studies for the key aldol reaction to install the C47–C51 chlorodiene segment were carried out on C36–C46 F-ring ketone **29** (Scheme 6). The required C47–C51 aldehyde **4** was synthesised in three steps from 2-chloroacrolein[24] by HWE chain extension, DIBAL-H reduction and Swern oxidation[25] in 76% overall yield. Conversion of ketone **29** into the dicyclohexylboron enolate **30**, under the standard conditions, and reaction with (*E*)-4-chloro-2,4-pentadienal (**4**) provided the desired aldol product **31** with surprisingly good diastereoselectivity (80 : 20 dr). Notably, this outcome is in the 1,5-*syn* sense, in contrast to



Scheme 6 *Reagents and conditions*: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, catechol, THF, −78 → −20 °C, 19 h; (b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (c) $(COCl)_2$, DMSO, −78 °C, 20 min; then Et_3N, −78 °C, 1 h; (d) Chx_2BCl, Et_3N, Et_2O, −78 → −40 °C, 1.5 h; (e) **4**, −78 → −20 °C, 16 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C, 2.5 h.

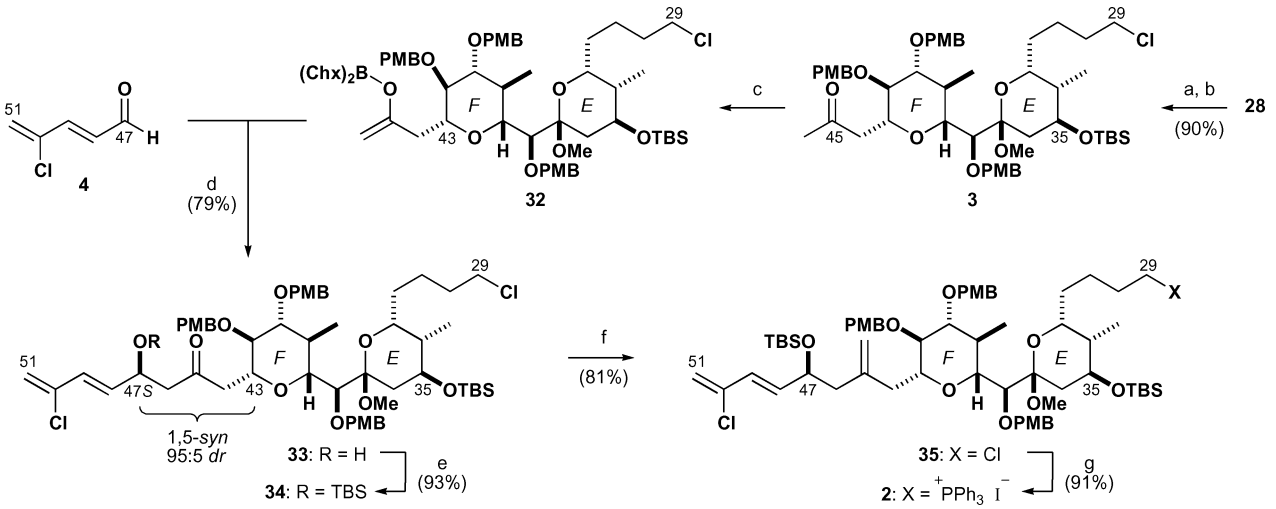
the 1,5-*anti* stereoinduction typically observed for boron aldol reactions of simple β-alkoxy methyl ketones,[26,27] indicating the overriding influence, in this more complex case, of the more remote stereocentres. This serendipitous result was certainly welcome and greatly simplified the introduction of the C47 stereocentre, particularly relative to the more elaborate strategies employed by other research groups.[3–5]

Following on from these promising model studies, the C29–C46 EF-subunit **28** was converted into the corresponding C45 ketone **3** in 90% yield (Scheme 7). Regioselective enolisation of **3** provided the boron enolate **32**, *in situ*, which underwent smooth aldol reaction with **4**. After careful oxidative workup, the desired (47*S*)-adduct **33** was isolated in 79% yield as the major diastereomer (95 : 5 dr). The (47*S*)-configuration was determined by ^1H NMR analysis of the derived MTPA esters.[10] The enhanced stereoselectivity in this aldol reaction compared to the case with F-ring ketone **29**, both of which are under substrate control, illustrates a reinforcing stereodirecting effect of the E-ring. In both these cases, the corresponding lithium aldol reaction (LiHMDS) gave no measurable induction.

Towards completion of the fully elaborated southern hemisphere segment **2**, the C47 hydroxyl was protected as the corresponding TBS ether **34** (93% yield), and methylenation of this highly functionalised compound was achieved in 81% yield, providing **35**, by using a modified Takai procedure under carefully controlled conditions (Zn, cat. PbI_2, TMSCl, CH_2I_2, $TiCl_4$).[28] Finally, conversion of the chloride **35** to the corresponding phosphonium salt **2** was readily achieved in 91% yield by heating with Ph_3P in the presence of NaI. Notably, the selection of a chloride substituent at C29, as opposed to a protected hydroxyl group, served to streamline the synthetic sequence.

Conclusions

The functionally and stereochemically dense C29–C51 EF southern hemisphere subunit **2** has been synthesised in a highly stereoselective manner, providing access to multi-gram quantities. Key steps include two substrate-controlled boron aldol reactions of elaborately functionalised methyl ketones, **6** and **3**, to install the E-ring linear precursor and chlorodienol



Scheme 7 *Reagents and conditions*: (a) cat. OsO_4, $Me_3N{\rightarrow}O$, acetone–H_2O (8 : 1), rt, 16 h; (b) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C, 40 min; (c) Chx_2BCl, Et_3N, Et_2O, −78 → −40 °C, 1.5 h; (d) **4**, −78 → −20 °C, 16 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C, 2.5 h; (e) TBSCl, Im, DMF, rt, 2 h; (f) Zn, cat. PbI_2, TMSCl, CH_2I_2, $TiCl_4$, THF–CH_2Cl_2, rt, 1.75 h, then **34**, THF, rt, 4 h; (g) PPh_3, NaI, *i*-Pr_2NEt, MeCN–MeOH (9 : 1), Δ, 19 h.

side-chains, respectively. Notably, the late-stage incorporation of the C47–C51 side-chain segment and the remote C47 hydroxyl-bearing stereocentre by a remarkably stereoselective (1,5-*syn*) aldol reaction should allow ready access to the C50 protio- and bromo-altohyrtin/spongistatin congeners, by appropriate choice of aldehyde coupling partner. At this stage, we had assembled the three major fragments of altohyrtin A by scalable routes and were poised to examine their sequential coupling and elaboration, as described in Part 4 of this series.[29]

Experimental

(2*R*,4*S*,5*R*)-9-Chloro-5-hydroxy-2-(*p*-methoxybenzyloxy)-4-methyl-nonan-3-one (13)

To a cold (−78 °C) solution of Chx_2BCl (1.89 mL, 8.62 mmol, 1.3 eq.) in Et_2O (30 mL) was added Et_3N (1.39 mL, 9.97 mmol, 1.5 eq.) followed by a solution of ketone **10** (1.48 g, 6.64 mmol) in Et_2O (5 mL + 2 × 2 mL washings) *via* cannula. The reaction mixture was stirred at −78 °C for 1 h before a solution of aldehyde **12** (*ca.* 1.3 eq.) in PhMe was added. The mixture was stirred at −78 °C for a further 1.5 h then at −20 °C for 16 h. The reaction was quenched at 0 °C by the addition of pH 7 buffer (15 mL) and MeOH (60 mL), followed by 30% H_2O_2 solution (10 mL). The reaction mixture was allowed to warm to rt and stirred for a further 2 h before being diluted with H_2O (50 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (80 mL) and brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (10 : 90 → 50 : 50 EtOAc–light petroleum) afforded aldol product **13** (2.53 g) as a colourless oil which contained a small amount of ChxOH and was carried to the subsequent step without further purification. Further purification by column chromatography allowed production of analytically pure material for characterisation purposes: R_f: 0.25 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ +16.3 (*c* 1.50, $CHCl_3$); IR (film): 3493 (br, OH), 2937, 2867, 1713 (C=O) cm^{-1}; ^1H NMR: δ (400 MHz, $CDCl_3$) 7.26 (2H, d, J = 8.6 Hz, ArH), 6.89 (2H, d, J = 8.6 Hz, ArH), 4.47 (2H, s, OCH_2Ar), 4.02 (1H, q, J = 6.9 Hz, 36-C*H*), 3.81 (3H, s, $ArOCH_3$), 3.80–3.83 (1H, m, 33-C*H*), 3.52 (2H, t, J = 6.7 Hz, 29-CH_2), 2.98 (1H, qd, J = 7.2, 2.9 Hz, 34-C*H*), 2.83 (1H, d, J = 2.7 Hz, O*H*), 1.77 (2H, qn, J = 6.9 Hz, 30-CH_2), 1.45–1.60 (4H, m, 31-CH_2 + 32-CH_2), 1.36 (3H, d, J = 6.9 Hz, 36-CHCH_3), 1.11 (3H, d, J = 7.2 Hz, 34-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 217.2, 159.5, 129.4, 129.4, 113.9, 79.2, 71.4, 70.8, 55.3, 45.2, 44.9, 33.2, 32.4, 23.4, 17.3, 10.1; HRMS: (+ES) Calc. for $C_{18}H_{31}ClNO_4$ [M + NH_4]$^+$: 360.1942, found: 360.1944; *m*/*z*: (+CI, NH_3) 360 ([M + NH_4]$^+$, 5), 240 (40), 138 (40), 121 (100).

(2*R*,4*S*,5*R*)-9-Chloro-5-triethylsiloxy-2-(*p*-methoxybenzyloxy)-4-methyl-nonan-3-one (14)

To a cold (−78 °C) solution of aldol product **13**–ChxOH (2.53 g, max. 6.64 mmol) in CH_2Cl_2 (60 mL) was added 2,6-lutidine (1.72 mL, 14.8 mmol, 2.2 eq.), followed by TESOTf (2.50 mL, 11.1 mmol, 1.67 eq.). The reaction mixture was stirred at −78 °C for 1 h then quenched by the addition of sat. aq. K_2CO_3 (50 mL). The mixture was allowed to warm to rt and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL), combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 20 : 80 EtOAc–light petroleum) afforded TES ether **14** (2.97 g, 98% over two steps from **10**) as a colourless oil: R_f: 0.37 (15 : 85 EtOAc–hexanes); $[\alpha]_D^{20}$ +31.5 (*c* 1.80, $CHCl_3$); IR (film): 2952, 2875, 1716 (C=O) cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.27 (2H, d, J = 8.5 Hz, Ar*H*), 6.88 (2H, d, J = 8.6 Hz, Ar*H*), 4.47 (2H, s, OCH_2Ar), 4.04 (1H, q, J = 6.7 Hz, 36-C*H*), 3.96–4.00 (1H, m, 33-C*H*), 3.80 (3H, s, $ArOCH_3$), 3.46 (2H, t, J = 6.6 Hz, 29-CH_2), 3.05 (1H, quin., J = 6.8 Hz, 34-C*H*), 1.64–1.76 (2H, m, 30-CH_2), 1.36–1.43 (4H, m, 31-CH_2 + 32-CH_2), 1.33 (3H, d, J = 6.7 Hz, 36-CHCH_3), 1.07 (3H, d, J = 7.0 Hz, 34-CHCH_3), 0.94 (9H, t, J = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.58 (6H, q, J = 8.0 Hz, $Si(CH_2CH_3)_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 213.6, 159.4, 129.8, 129.5, 113.9, 78.9, 72.6, 70.9, 55.3, 47.1, 44.9, 35.0, 32.7, 22.4, 16.4, 12.9, 6.9, 5.2; HRMS: (+ES) Calc. for $C_{24}H_{42}ClO_4Si$ [M + H]$^+$: 457.2541, found: 457.2538; *m*/*z*: (+CI, NH_3) 474 ([M + NH_4]$^+$, 5), 240 (40), 138 (35), 121 (100).

(2*R*,4*R*,5*R*)-4-Benzyloxy-5-hydroxy-1-(*p*-methoxybenzyloxy)-2-methyl-3-hexanone (18)

To a cold (−78 °C) solution of Chx_2BCl (10.6 mL, 48.4 mmol, 1.2 eq.) in Et_2O (200 mL) was added Et_3N (8.4 mL, 60.3 mmol, 1.5 eq.) followed by a solution of ketone **16** (13.2 g, 40.2 mmol) in Et_2O (10 mL + 2 × 5 mL washings) *via* cannula. The reaction mixture was stirred for 2 h at 0 °C and then cooled to −78 °C before MeCHO (9.0 mL, 161 mmol, 4 eq.) was added. The mixture was stirred at −78 °C for a further 30 min, then at −20 °C for 16 h. The reaction was quenched by the addition of pH 7 buffer (200 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the

combined organics were concentrated *in vacuo*. The residue was taken up in MeOH (150 mL) and pH 7 buffer (50 mL) and cooled to 0 °C. A 30% H_2O_2 solution (50 mL) was added and the mixture was stirred for a further 3 h at 0 °C. The reaction mixture was diluted with H_2O (200 mL) and CH_2Cl_2 (100 mL). Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Removal of the ChxOH by Kugelrohr short-path distillation (50 °C, 0.2 mmHg) for 16 h afforded aldol adduct **18** (13.9 g, 93%) as a slightly yellow oil, which was carried to the subsequent step without further purification: R_f: 0.23 (50 : 50 Et_2O–hexane); $[a]_D^{20}$ +28.6 (*c* 0.90, $CHCl_3$); IR (liquid film): 3452 (s, br), 1717 (s), 1612 (s), 1586 (m), 1513 (s), 1454 cm^{-1} (s); ^1H NMR: δ (400 MHz, $CDCl_3$) 7.27–7.36 (5H, m, Ar*H*), 7.19 (2H, d, J = 8.6 Hz, Ar*H*), 6.86 (2H, d, J = 8.6 Hz, Ar*H*), 4.59 (1H, d, J = 11.6 Hz, OCH_aH_bAr), 4.35–4.43 (3H, m, OCH_2Ar + OCH_aH_bAr), 4.02–4.09 (1H, m, 37-C*H*), 3.79 (3H, s, $ArOCH_3$), 3.73 (1H, d, J = 6.4 Hz, 38-C*H*), 3.65 (1H, m, 40-C*H*), 3.43 (2H, m, 41-CH_2), 3.04 (1H, d, J = 6.3 Hz, O*H*), 1.20 (3H, d, J = 6.4 Hz, 36-CH_3), 1.00 (3H, d, J = 6.6 Hz, 40-$CHCH_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 214.3, 159.4, 137.3, 129.5, 129.0, 128.4, 127.9, 127.8, 113.8, 89.8, 73.3, 73.1, 72.9, 67.1, 55.2, 41.1, 19.1, 13.8; HRMS: (+FAB) Calc. for $C_{22}H_{29}O_5$ [M + H]$^+$: 373.2015, found: 373.2026; *m/z*: (+CI, NH_3) 373 ([M + H]$^+$, 47), 307 (100).

(2*R*,3*R*,4*R*,5*R*)- and (2*R*,3*R*,4*S*,5*R*)-3-Benzyloxy-6-(*p*-methoxybenzyloxy)-5-methyl-hexane-2,4-diol (19 and 39-*epi*-19)

To a solution of $Me_4NBH(OAc)_3$ (53.5 g, 203 mmol, 3 eq.) in MeCN (80 mL) was added AcOH (80 mL) and the resultant mixture was stirred at rt for 1 h. The mixture was then cooled to −20 °C and a solution of hydroxyketone **18** (25.3 g, 67.8 mmol) in MeCN (20 mL + 2 × 5 mL washings) was added *via* cannula. The reaction mixture was stirred at −20 °C for 1 h and then at 4 °C for 60 h. The reaction was quenched by pouring into a sodium potassium tartrate solution (0.5 M, 500 mL) and vigorously stirred for 1 h. The resultant mixture was diluted with CH_2Cl_2 (100 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL) and the combined organics were washed with sat. aq. $NaHCO_3$ until aqueous washing attained a neutral pH. The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 25 : 75 EtOAc–light petroleum) afforded a *ca.* 4 : 1 mixture of diols **19** and 39-*epi*-**19** (23.0 g, 91% over 2 steps from **16**) as a colourless oil: R_f: 0.29 (50 : 50 EtOAc–hexanes); IR (liquid film): 3442 (m, br), 1612 (m), 1513 (s), 1455 cm^{-1} (m); The following NMR data corresponds to the major (*anti*) diastereomer **19**: ^1H NMR: δ (400 MHz, $CDCl_3$) 7.26–7.38 (5H, m, Ar*H*), 7.24 (2H, d, J = 8.6 Hz, Ar*H*), 6.87 (2H, d, J = 8.6 Hz, Ar*H*), 4.79 (1H, d, J = 11.5 Hz, OCH_aCH_bAr), 4.53 (1H, d, J = 11.5 Hz, OCH_aH_bAr), 4.44 (2H, s, OCH_2Ar), 4.18–4.27 (1H, m, 37-C*H*), 3.84 (1H, br s, 39-C*H*), 3.79 (3H, s, $ArOCH_3$), 3.53 (2H, d, J = 6.0 Hz, 41-CH_2), 3.40 (1H, br s, O*H*), 3.27–3.30 (1H, m, 38-C*H*), 2.17–2.27 (1H, m, 40-C*H*), 1.27 (3H, d, J = 6.5 Hz, 36-CH_3), 0.78 (3H, d, J = 6.9 Hz, 40-$CHCH_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.3, 138.2, 130.0, 129.2, 128.4, 128.0, 127.8, 113.9, 80.4, 75.5, 74.3, 73.1, 72.1, 67.3, 55.3, 35.5, 19.8, 13.9; HRMS: (+CI, NH_3) Calc. for $C_{22}H_{31}O_5$ [M + H]$^+$: 375.21715, found: 375.2171: *m/z*: (+CI, NH_3) 375 ([M + H]$^+$, 14), 121 (100).

Methyl (2*E*,4*R*)-4-[5-(*R*)-benzyloxy-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-pent-2-enoate (9)

To a suspension of LiCl (dried at 140 °C under vacuum for 5 h, 1.89 g, 44.6 mmol, 2.5 eq.) in MeCN (40 mL) was added trimethyl phosphonoacetate (4.35 mL, 26.9 mmol, 1.5 eq.) and $^iPr_2NEt$ (4.06 mL, 23.3 mmol, 1.3 eq.). The mixture was stirred at rt for 10 min before a solution of aldehyde **20** (5.24 g, 17.9 mmol) in MeCN (5 mL + 2 × 2 mL washings) was added *via* cannula. The resultant mixture was then stirred at rt for 16 h before being quenched by addition of sat. aq. NH_4Cl (50 mL). The mixture was diluted with Et_2O and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL), combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (2.5 : 97.5 → 50 : 50 Et_2O–light petroleum) afforded enoate **9** (5.99 g, 96%) as a colourless oil: R_f: 0.57 (30 : 70 EtOAc–hexanes); $[a]_D^{20}$ −12.2 (*c* 1.05, $CHCl_3$); IR (liquid film): 1718 (m), 1660 (w), 1454 (w), 1436 (w), 1380 (w), 1265 cm^{-1} (s); ^1H NMR: δ (500 MHz, $CDCl_3$) 7.28–7.36 (5H, m, *Ph*), 7.05 (1H, dd, J = 15.8, 7.6 Hz, 41-C*H*), 5.85 (1H, d, J = 15.8 Hz, 42-C*H*), 4.65 (1H, d, J = 11.5 Hz, OCH_aH_bPh), 4.47 (1H, d, J = 11.5 Hz, OCH_aH_bPh), 3.86–3.93 (1H, m, 37-C*H*), 3.71 (3H, s, OCH_3), 3.59 (1H, dd, J = 9.3, 3.2 Hz, 39-C*H*), 3.39 (1H, dd, J = 5.5, 3.2 Hz, 38-C*H*), 2.80–2.87 (1H, m, 40-C*H*), 1.39 (3H, s, CMe_aMe_b), 1.32 (3H, d, J = 6.4 Hz, 36-CH_3), 1.28 (3H, s, CMe_aMe_b), 0.99 (3H, d, J = 6.8 Hz, 40-$CHCH_3$); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 167.3, 152.3, 138.0, 128.4, 127.8, 127.7, 120.3, 100.8, 82.2, 73.7, 72.9, 69.7, 51.3, 35.4, 24.9, 23.8, 21.2, 15.6; HRMS: (+CI, NH_3) Calc. for $C_{20}H_{29}O_5$ [MH]$^+$: 349.2015, found: 349.2015; *m/z*: (+CI, NH_3) 349 ([MH]$^+$, 14), 308 (18), 291 (28).

Methyl (2*S*,3*R*,4*R*)-4-[5-(*R*)-benzyloxy-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-2,3-dihydroxy-pentanoate (21)

To a cold (0 °C) solution of enoate **9** (8.58 g, 24.6 mmol) in ^{t}BuOH–H_2O (1 : 1, 250 mL) was added freshly prepared, enriched AD-mix-β (36.9 g, 1.5 g mmol^{-1} substrate) and $MeSO_2NH_2$ (4.68 g, 49.2 mmol, 2 eq.). The reaction mixture was allowed to warm to rt and stirred vigorously for 16 h. Sodium sulfite (37.0 g, 294 mmol, 12 eq.) was added and the reaction stirred for a further 1 h. The mixture was diluted with water (200 mL) and EtOAc (200 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 200 mL), combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (20 : 80 → 80 : 20 EtOAc–light petroleum) afforded diol **21** (9.20 g, 98%) as a colourless oil: R_f: 0.25 (40 : 60 EtOAc–hexanes); $[a]_D^{20}$ −17.8 (*c* 0.39, $CHCl_3$); IR (liquid film): 3464 (s, br), 1739 (s), 1454 (m), 1380 (m) cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.28–7.36 (5H, m, Ar*H*), 4.68 (1H, d, J = 11.4 Hz, OCH_aH_bAr), 4.45 (1H, d, J = 11.4 Hz, OCH_aH_bAr), 4.26–4.28 (1H, m, 42-C*H*), 4.07–4.10 (1H, m, 41-C*H*), 4.04 (1H, dd, J = 9.9, 3.0 Hz, 39-C*H*), 3.92–3.97 (1H, m, 37-C*H*), 3.79 (3H, s, OCH_3), 3.36 (1H, dd, J = 5.0, 3.1 Hz, 38-C*H*), 3.28 (1H, d, J = 7.8 Hz, O*H*), 3.09 (1H, d, J = 6.2 Hz, O*H*), 2.37–2.44 (1H, m, 40-C*H*), 1.41 (3H, s, CMe_aMe_b), 1.38 (3H, s, CMe_aMe_b), 1.34 (3H, d, J = 6.5 Hz, 36-CH_3), 0.93 (3H, d, J = 6.9 Hz, 40-$CHCH_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 174.3, 138.1, 128.4, 127.8, 127.6, 100.9, 81.9, 73.5, 72.8, 72.7, 72.5, 69.8, 52.7, 35.2, 25.5, 24.0, 21.4, 11.2; HRMS: (+CI, NH_3) Calc. for $C_{20}H_{31}O_7$ [M + H]$^+$: 383.2070, found: 383.2070; *m/z*: (+CI, NH_3) 383 ([M + H]$^+$, 7), 235 (38), 217 (100).

Methyl (2*S*,3*R*,4*R*)-2,3-dihydroxy-4-[5-(*R*)-hydroxy-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-pentanoate (22)

To a solution of diol **21** (4.23 g, 11.1 mmol) in MeOH (70 mL) was added $NaHCO_3$ (1.86 g, 22.1 mmol, 2 eq.) and $Pd(OH)_2/C$ (20% w/w on carbon, 3.86 g, 5.54 mmol, 0.5 eq.). The system was evacuated and then filled with H_2. The procedure was repeated twice more and then the reaction was left under an atmosphere of H_2 for 20 h. The reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. Flash chromatography (80 : 20 EtOAc–light petroleum → 100% EtOAc) afforded triol **22** (3.28 g, 100%) as a colourless oil: R_f: 0.09 (65 : 35 EtOAc–hexanes); $[a]_D^{20}$ −23.9 (*c* 0.90, $CHCl_3$); IR (liquid film): 3435 (broad, OH), 2985, 2935, 1738 (C=O), 1440, 1381, 1225 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 4.30–4.32 (1H, m, 42-C*H*), 3.96–4.00 (2H, m, 39-C*H* + 41-C*H*), 3.79 (3H, s, OCH_3),

3.59–3.64 (1H, m, 37-C*H*), 3.42–3.45 (2H, m, 38-C*H* + 41-CHO*H*), 3.33–3.37 (1H, m, 42-CHO*H*), 2.18–2.23 (1H, m, 40-C*H*), 1.36 (3H, s, C*Me*$_a$Me$_b$), 1.35 (3H, s, CMe$_a$*Me*$_b$), 1.29 (3H, d, J = 6.4 Hz, 36-CH_3), 0.99 (3H, d, J = 6.9 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 174.2, 101.1, 74.6, 73.6, 72.8, 72.4, 71.9, 52.8, 35.3, 25.0, 24.4, 19.6, 11.3; HRMS: (+CI, NH_3) Calc. for $C_{13}H_{25}O_7$ [M + H]$^+$: 293.1600, found: 293.1609; *m/z*: (+CI, NH_3) 310 ([M + NH_4]$^+$, 80), 293 ([M + H]$^+$, 20), 218 (70), 202 (100).

Methyl (2*S*,3*R*,4*R*)-2,3-bis-(*p*-methoxybenzyloxy)-4-[5-(*R*)-(*p*-methoxybenzyloxy)-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-pentanoate (23)

To a cold (0 °C) solution of triol **22** (3.56 g, 12.2 mmol) in THF (120 mL) was added PMBTCA[19] (20.7 g, 73.3 mmol, 6 eq.), followed by a solution of Ph_3CBF_4 (weighed into a dry flask in the glovebox, 80 mg, 0.242 mmol, 2.0 mol%) in THF (2 mL) *via* cannula. The reaction mixture was stirred at 0 °C for a further 30 min before being quenched by addition of sat. aq. $NaHCO_3$ (100 mL) and Et_2O (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). Combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude was dissolved in the minimum amount of CH_2Cl_2 and then hexane was added slowly until precipitation of the trichloroacetamide occurred. After filtration, the filtrate was concentrated *in vacuo*. Flash chromatography (15 : 85 → 30 : 70 EtOAc–light petroleum) afforded the *tris*-PMB ether **23** (7.73 g, 97%) as a colourless oil: R_f: 0.31 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −28.5 (*c* 1.10, $CHCl_3$); IR (liquid film): 2935, 1733 (C=O), 1613, 1514, 1248 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.18–7.27 (6H, m, Ar*H*), 6.78–6.88 (6H, m, Ar*H*), 4.92 (1H, d, J = 11.1 Hz, OCH_aH$_b$Ar), 4.57 (1H, d, J = 11.3 Hz, OCH_aH$_b$Ar), 4.54 (1H, d, J = 11.9 Hz, OCH_aH$_b$Ar), 4.51 (1H, d, J = 11.4 Hz, OCH$_a$$H_b$Ar), 4.40 (1H, d, J = 11.1 Hz, OCH$_a$$H_b$Ar), 4.34 (1H, d, J = 10.9 Hz, OCH$_a$$H_b$Ar), 4.21 (1H, d, J = 7.2 Hz, 42-C*H*), 4.17 (1H, dd, J = 7.2, 1.7 Hz, 41-C*H*), 3.84–3.90 (1H, m, 37-C*H*), 3.80 (6H, s, 2 × ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.76–3.79 (1H, m, 39-C*H*), 3.64 (3H, s, CO_2CH_3), 3.34 (1H, dd, J = 5.4, 3.2 Hz, 38-C*H*), 1.98–2.08 (1H, m, 40-C*H*), 1.34 (3H, s, C*Me*$_a$Me$_b$), 1.32 (3H, d, J = 6.4 Hz, 36-CH_3), 1.26 (3H, s, CMe$_a$*Me*$_b$), 0.94 (3H, d, J = 6.8 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 171.6, 159.4, 159.2, 158.8, 131.7, 130.5, 129.9, 129.5, 129.1, 128.5, 113.8, 113.7, 113.6, 100.6, 83.5, 81.8, 78.5, 74.1, 72.7, 72.5, 71.7, 69.7, 55.3, 55.3, 55.2, 51.8, 34.5, 25.6, 24.1, 21.4, 9.9; HRMS: (+CI, NH_3) Calc. for $C_{37}H_{52}NO_{10}$ [M + NH_4]$^+$: 670.3591, found: 670.3579; *m/z*: (+CI, NH_3) 670 ([M + NH_4]$^+$, 20), 396 (40), 275 (100).

(2*S*,3*R*,4*R*)-2,3-Bis-(*p*-methoxybenzyloxy)-4-[5-(*R*)-(*p*-methoxybenzyloxy)-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-pentanal

To a cold (−78 °C) solution of ester **23** (4.16 g, 6.38 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (1.0 M in CH_2Cl_2, 16.0 mL, 16.0 mmol, 2.5 eq.) dropwise. The reaction mixture was stirred at −78 °C for 1.5 h before being quenched by addition of a solution of sat. aq. potassium sodium tartrate (150 mL). The resultant mixture was stirred vigorously for 30 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL), combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 40 : 60 EtOAc–light petroleum) afforded the title aldehyde (3.73 g, 94%) as a colourless oil: R_f: 0.29 (35 : 65 EtOAc–hexanes); $[\alpha]_D^{20}$ −26.4 (*c* 1.00, $CHCl_3$); IR (liquid film): 2984, 1729 (C=O), 1612, 1514, 1248, 1032 cm^{-1}; ^{1}H NMR: δ (400 MHz, $CDCl_3$) 9.64 (1H, d, J = 3.0 Hz, 43-C*H*O), 7.18–7.27 (6H, m, Ar*H*), 6.81–6.89 (6H, m, Ar*H*), 4.78 (1H, d, J = 10.9 Hz, OCH_aH$_b$Ar), 4.58 (1H, d, J = 11.1 Hz, OCH_aH$_b$Ar), 4.57 (1H, d, J = 11.3 Hz, OCH_aH$_b$Ar), 4.51 (2H, m, 2 × OCH$_a$$H_b$Ar), 4.38 (1H, d, J = 11.1 Hz, OCH$_a$$H_b$Ar), 4.24 (1H, dd, J = 6.7, 2.0 Hz, 41-C*H*), 3.99 (1H, dd, J = 6.7, 3.0 Hz, 42-C*H*), 3.85–3.92 (1H, m, 37-C*H*), 3.81 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.78–3.80 (1H, m, 39-C*H*), 3.35 (1H, dd, J = 5.1, 3.1 Hz, 38-C*H*), 2.16–2.24 (1H, m, 40-C*H*), 1.39 (3H, s, C*Me*$_a$Me$_b$), 1.32 (3H, d, J = 6.5 Hz, 36-CH_3), 1.29 (3H, s, CMe$_a$*Me*$_b$), 0.91 (3H, d, J = 6.8 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 202.2, 159.5, 159.3, 159.0, 131.2, 130.3, 129.8, 129.4, 129.3, 128.6, 113.9, 113.8, 113.7, 100.7, 87.0, 81.4, 77.3, 73.9, 72.8, 72.4, 71.2, 69.9, 55.3, 55.2, 34.2, 25.7, 24.1, 21.4, 9.7; HRMS: (+CI, NH_3) Calc. for $C_{36}H_{50}NO_9$ [M + NH_4]$^+$: 640.3486, found: 640.3485; *m/z*: (+CI, NH_3) 640 ([M + NH_4]$^+$, 20), 571 (100).

(3*E*,5*R*,6*R*,7*R*)-5,6-Bis-(*p*-methoxybenzyloxy)-7-[5-(*R*)-(*p*-methoxybenzyloxy)-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-oct-3-en-2-one (24)

$Ba(OH)_2 \cdot 8H_2O$ (dried at 140 °C under vacuum for 4 h before the reaction) was added to a solution of dimethyl(2-oxopropyl)phosphonate (87 μL, 0.63 mmol) in THF (7.5 mL) and the resulting mixture was stirred for 30 min at rt. A solution of the aldehyde from the above procedure (196 mg, 0.315 mmol) in THF (7.3 mL) and water (0.4 mL) was then added *via* cannula and the resulting mixture was stirred for 4 h before quenching the reaction by addition of excess of $NaHCO_3$ solution (20 mL). The mixture was partitioned between aqueous $NaHCO_3$ sol. and Et_2O (20 mL) and the aqueous layer was washed with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (20 : 80 EtOAc–hexanes) afforded enone **24** (199 mg, 96%) as a colourless oil: R_f: 0.24 (35 : 65 EtOAc–hexanes); $[\alpha]_D^{20}$ −7.3 (*c* 1.40, $CHCl_3$); IR (liquid film): 2984, 2936, 2835, 1678 (C=O), 1612, 1514, 1248, 1034 cm^{-1}; ^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.13–7.27 (6H, m, Ar*H*), 6.80–6.88 (6H, m, Ar*H*), 6.60 (1H, dd, J = 16.2, 7.5 Hz, 43-C*H*), 6.24 (1H, d, J = 16.2 Hz, 44-C*H*), 4.99 (1H, d, J = 11.2 Hz, OCH_aH$_b$Ar), 4.58 (1H, d, J = 11.0 Hz, OCH_aH$_b$Ar), 4.52 (1H, d, J = 11.2 Hz, OCH_aH$_b$Ar), 4.47 (1H, d, J = 11.0 Hz, OCH$_a$$H_b$Ar), 4.35 (1H, d, J = 11.0 Hz, OCH$_a$$H_b$Ar), 4.31 (1H, d, J = 11.0 Hz, OCH$_a$$H_b$Ar), 4.19 (1H, t, J = 7.5, Hz, 42-C*H*), 4.02 (1H, dd, J = 7.5, 1.4 Hz, 41-C*H*), 3.85–3.91 (1H, m, 37-C*H*), 3.80 (6H, s, 2 × ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.75–3.80 (1H, m, 39-C*H*), 3.34 (1H, dd, J = 5.2, 3.2 Hz, 38-C*H*), 2.22 (3H, s, 46-CH_3), 2.04–2.12 (1H, m, 40-C*H*), 1.38 (3H, s, C*Me*$_a$Me$_b$), 1.33 (3H, d, J = 6.5 Hz, 36-CH_3), 1.27 (3H, s, CMe$_a$*Me*$_b$), 0.82 (3H, d, J = 6.8 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 198.5, 159.3, 159.3, 158.8, 143.5, 132.6, 131.8, 130.3, 130.0, 129.6, 129.0, 128.3, 113.8, 113.7, 113.6, 100.7, 83.5, 81.6, 79.3, 73.9, 72.5, 71.3, 70.9, 69.8, 55.3, 55.3, 55.2, 34.3, 26.9, 25.7, 24.2, 21.4, 9.3; HRMS: (+CI, NH_3) Calc. for $C_{39}H_{54}NO_9$ [M + NH_4]$^+$: 680.3799, found: 680.3795; *m/z*: (+CI, NH_3) 680 ([M + NH_4]$^+$, 50), 287 (50), 274 (100).

(2*S*,3*S*,4*R*,5*R*,6*R*)- and (2*R*,3*S*,4*R*,5*R*,6*R*)-6-(2-(*R*)-Hydroxy-1-(*R*)-[*p*-methoxybenzyloxy)-prop-1-yl]-3,4-bis(*p*-methoxybenzyloxy)-5-methyl-2-(propanone)-tetrahydropyran (25 and 43-*epi*-25)

To a solution of enone **24** (5.38 g, 8.12 mmol) in THF–H_2O (1 : 1, 20 mL) was added AcOH (90 mL) and the resultant mixture was stirred at rt for 60 h. The reaction was quenched by careful addition to sat. aq. $NaHCO_3$ (500 mL) and diluted with EtOAc (300 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organics were washed with brine (250 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (30 : 70 → 80 : 20 EtOAc–light petroleum) afforded a mixture of tetrahydropyrans **25** and 43-*epi*-**25** (*ca.* 1 : 1, 4.58 g, 91%) as a colourless oil.

Equilibration of the mixture of tetrahydropyrans (25 and 43-*epi*-25)

The mixture of tetrahydropyran epimers **25** and 43-*epi*-**25** (181 mg, 0.291 mmol) was dissolved in dry MeOH (14 mL). Separately, KOH (2.00 g, 35.6 mmol) was dissolved in dry MeOH (5 mL) to make a *ca.* 7 M solution. Of this KOH solution, 3 mL (*ca.* 21 mmol) was added to the stirred solution of substrate, and the reaction left at rt for 20 h. The mixture was cooled (0 °C) and H_2O (100 mL) was slowly added, followed by EtOAc (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered through a short pad of silica and concentrated *in vacuo* to yield a *ca.* 95 : 5 ratio of desired and undesired THPs (170 mg, 94%), **25** and 43-*epi*-**25**, respectively, as a colourless oil. Major diastereomer: R_f: 0.05 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ +8.8 (*c* 1.13, $CHCl_3$); IR (liquid film): 3518 (br), 2964, 2909, 2836, 1712 (C=O), 1612, 1514, 1249, 1082, 1034 cm^{-1}; ^1H NMR: δ (400 MHz, $CDCl_3$) 7.21–7.32 (6H, m, Ar*H*), 6.82–6.92 (6H, m, Ar*H*), 4.86 (1H, d, J = 11.1 Hz, OCH_aH$_b$Ar), 4.85 (1H, d, J = 10.5 Hz, OCH_aH$_b$Ar), 4.61 (1H, d, J = 11.1 Hz, OCH_aH$_b$Ar), 4.59 (1H, d, J = 10.5 Hz, OCH$_a$$H_b$Ar), 4.54 (1H, d, J = 11.1 Hz, OCH$_a$$H_b$Ar), 4.47 (1H, d, J = 11.1 Hz, OCH$_a$$H_b$Ar), 3.93–4.01 (1H, m, 37-C*H*), 3.81 (6H, s, 2 × ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.60–3.69 (1H, m, 43-C*H*), 3.48 (1H, dd, J = 10.3, 2.2 Hz, 39-C*H*), 3.18–3.32 (4H, m, 38-C*H* + 41-C*H* + 42-C*H* + O*H*), 2.71 (1H, dd, J = 17.8, 2.0 Hz, 44-CH_aH$_b$), 2.49 (1H, dd, J = 17.8, 10.2 Hz, 44-CH$_a$$H_b$), 2.10–2.18 (1H, m, 40-C*H*), 2.06 (3H, s, 46-C*H*), 1.27 (3H, d, J = 6.4 Hz, 36-CH_3), 0.88 (3H, d, J = 6.5 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 207.2, 159.5, 159.4, 159.3, 130.5, 130.3, 130.2, 129.8, 129.7, 129.6, 113.9, 113.8, 86.9, 81.4, 81.2, 80.3, 75.3, 75.1, 74.5, 72.6, 66.8, 55.3, 44.8, 37.9. 30.5, 20.4, 12.8; HRMS: (+CI, NH_3) Calc. for $C_{36}H_{50}NO_9$ $[M + NH_4]^+$: 640.3486, found: 640.3488; *m/z*: (+CI, NH_3) 640 ($[M + NH_4]^+$, 100), 520 (30).

(2*R*,3*R*,4*R*,5*R*,6*R*)-6-[2-(*R*)-Hydroxy-1-(*R*)-(*p*-methoxybenzyloxy)-prop-1-yl]-3,4-bis(*p*-methoxybenzyloxy)-5-methyl-2-(2-methylallyl)-tetrahydropyran

To a solution of hydroxyketone **25** (140 mg, 0.225 mmol) in PhMe (1.8 mL), Cp_2TiMe_2 (10 wt% in 1 : 1 PhMe–THF, 1.4 mL, 0.67 mmol, 3 eq.) was added. The mixture was heated at 120 °C for 2 h, shielded from light, before being cooled to rt and concentrated *in vacuo*. The crude was dissolved in CH_2Cl_2 and adsorbed onto silica. Flash chromatography (10 : 90 → 60 : 40 EtOAc–hexanes) yielded the title compound (98.5 mg, 71%). The same procedure was repeated on a larger scale (194 mg, 0.312 mmol of **25**) to afford a further batch of the title compound (172 mg, 89%). The two batches were combined to yield the title compound (270 mg, 81%) as a yellow oil: R_f: 0.16 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −4.5 (*c* 1.00, $CHCl_3$); IR (liquid film): 3514 (br, OH), 2965, 2933 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.29 (2H, d, J = 8.6 Hz, Ar*H*), 7.26 (2H, d, J = 8.4 Hz, Ar*H*), 7.25 (2H, d, J = 8.3 Hz, Ar*H*), 6.89 (2H, d, J = 8.9 Hz, Ar*H*), 6.87 (2H, d, J = 8.7 Hz, Ar*H*), 6.86 (2H, d, J = 8.4 Hz, Ar*H*), 4.87 (1H, s, C=CH_aH$_b$), 4.86 (1H, d, J = 10.4 Hz, OCH_aH$_b$Ar), 4.82 (1H, d, J = 10.4 Hz, OCH$_a$$H_b$Ar), 4.81 (1H, s, C=CH$_a$$H_b$), 4.73 (1H, d, J = 11.7 Hz, OCH_aH$_b$Ar), 4.58 (1H, d, J = 10.6 Hz, OCH_aH$_b$Ar), 4.57 (1H, d, J = 10.6 Hz, OCH$_a$$H_b$Ar), 4.42 (1H, d, J = 11.7 Hz, OCH$_a$$H_b$Ar), 4.15–4.17 (1H, m, 37-C*H*), 3.81 (3H, s, ArOCH_3), 3.80 (6H, s, 2 × ArOCH_3), 3.33–3.38 (2H, m, 39-C*H* + 43-C*H*), 3.27 (1H, t, J = 9.0 Hz, 42-C*H*), 3.15–3.21 (3H, m, 38-C*H* + 41-C*H* + O*H*), 2.54 (1H, d, J = 14.0 Hz, 44-CH_aH$_b$), 2.16–2.21 (2H, m, 40-C*H* + 44-CH$_a$$H_b$), 1.73 (3H, s, 46-C$H_3$), 1.16 (3H, d, J = 6.5 Hz, 36-CH_3), 0.74 (3H, d, J = 6.5 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.4, 159.3, 159.3, 142.1, 130.7, 130.3, 130.1, 129.8, 129.6, 129.6, 113.9, 113.9, 113.7, 113.7, 86.5, 82.9, 81.6, 77.7, 77.1, 75.0, 74.8, 70.4, 66.1, 55.3, 55.3, 55.3, 40.2, 37.7, 21.8, 20.4, 12.5; HRMS: (+CI, NH_3) Calc. for $C_{37}H_{52}NO_8$ $[M + NH_4]^+$: 638.3693, found: 638.3689; *m/z*: (+CI, NH_3) 638 ($[M + NH_4]^+$, 1), 154 (100), 137 (50), 121 (70).

(2*R*,3*R*,4*R*,5*R*,6*R*)-6-[1-(*S*)-(*p*-Methoxybenzyloxy)-propanone]-3,4-bis(*p*-methoxybenzyloxy)-5-methyl-2-(2-methylallyl)-tetrahydropyran (6)

To a cold (0 °C) solution of the 2° alcohol from the above procedure (1.17 g, 1.88 mmol), in CH_2Cl_2 (23.0 mL) was added activated (heated under vacuum) powdered 4 Å molecular sieves (1.64 g), NMO (663 mg, 5.66 mmol, 3.0 eq.) and TPAP (65 mg, 0.19 mmol, 10 mol%). The reaction mixture was stirred at rt for 2 h, filtered through a pad of silica, eluted with EtOAc (100 mL) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 70 : 30 Et_2O–light petroleum) afforded ketone **6** (1.10 g, 94%) as a colourless oil: R_f: 0.31 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −15.7 (*c* 1.00, $CHCl_3$); IR (liquid film): 2932, 1710 (C=O) cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.27 (2H, d, J = 8.6 Hz, Ar*H*), 7.24 (2H, d, J = 8.5 Hz, Ar*H*), 7.23 (2H, d, J = 8.5 Hz, Ar*H*), 6.89 (2H, d, J = 8.2 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 6.86 (2H, d, J = 8.7 Hz, Ar*H*), 4.83 (1H, d, J = 10.6 Hz, OCH_aH$_b$Ar), 4.80 (1H, d, J = 10.6 Hz, OCH_aH$_b$Ar), 4.72 (1H, s, C=CH_aH$_b$), 4.71 (1H, d, J = 11.6 Hz, OCH_aH$_b$Ar), 4.67 (1H, s, C=CH$_a$$H_b$), 4.57 (1H, d, J = 10.6 Hz, OCH$_a$$H_b$Ar), 4.54 (1H, d, J = 10.6 Hz, OCH$_a$$H_b$Ar), 4.25 (1H, d, J = 11.6 Hz, OCH$_a$$H_b$Ar), 3.81 (3H, s, ArOC$H_3$), 3.80 (3H, s, ArOC$H_3$), 3.79 (3H, s, ArOC$H_3$), 3.71 (1H, d, J = 2.2 Hz, 38-C*H*), 3.22–3.28 (3H, m, 39-C*H* + 42-C*H* + 43-C*H*), 3.14 (1H, dd, J = 10.3, 8.4 Hz, 41-C*H*), 2.49 (1H, d, J = 14.6 Hz, 44-CH_aH$_b$), 2.20 (3H, s, 36-CH_3), 2.17 (1H, dd, J = 14.5, 10.0 Hz, 44-CH$_a$$H_b$), 2.02–2.05 (1H, m, 40-C*H*), 1.63 (3H, s, 46-CH_3), 0.61 (3H, d, J = 6.5 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 213.4, 159.7, 159.3, 159.3, 142.5, 130.6, 130.4, 130.3, 129.6, 129.6, 128.7, 113.9, 113.9, 113.9, 112.3, 86.2, 83.1, 83.0, 82.6, 78.1, 75.1, 74.7, 73.1, 55.3, 55.3, 55.3, 39.7, 37.9, 27.8, 22.0, 12.2; HRMS: (+CI, NH_3) Calc. for $C_{37}H_{50}NO_8$ $[M + NH_4]^+$: 636.3536, found: 636.3544; *m/z*: (+CI, NH_3) 636 ($[M + NH_4]^+$, 5), 154 (100), 137 (60), 121 (75).

(1*S*,4*S*,5*R*,6*R*)- and (1*S*,4*R*,5*R*,6*R*)-10-chloro-4-hydroxy-1-(*p*-methoxybenzyloxy)-1-[4,5-(*R*,*R*)-bis(*p*-methoxybenzyloxy)-3-(*R*)-methyl-6-(*R*)-(2-methylallyl)-tetrahydropyran-2-(*R*)-yl]-5-methyl-6-(triethylsiloxy)-decan-2-one (5 and 35-*epi*-5)

To a cold (−78 °C) solution of Chx_2BBr (1.14 mL, 5.23 mmol, 3.5 eq.) in Et_2O (20 mL) was added Et_3N (1.25 mL, 8.97 mmol, 6 eq.) followed by a solution of ketone **6** (921 mg, 1.49 mmol) in Et_2O (5 mL + 2 × 2 mL washings) *via* cannula. The reaction mixture was stirred at −78 °C for 2.5 h before a solution of aldehyde **7** (1.75 g, 5.96 mmol, 4 eq.) in Et_2O (2 mL + 2 × 1 mL washings) was added *via* cannula. The reaction was stirred at −78 °C for a further 1 h and then at −20 °C for 16 h. The reaction was quenched at 0 °C by the addition of pH 7 buffer (30 mL) and allowed to warm to rt. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organics were concentrated *in vacuo* and the resultant residue was taken up in MeOH–pH7 buffer (3 : 1, 100 mL) and cooled to 0 °C. A 30% solution of H_2O_2 (5.5 mL) was added and the mixture was warmed to rt and stirred for 2 h. Et_2O (100 mL) and H_2O (100 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL), combined organics were washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 50 : 50 EtOAc–light petroleum) afforded aldol product **5** and diastereomer 35-*epi*-**5** contaminated with ChxOH. The mixture was used in the subsequent step without further purification.

Major diastereomer **5**: R_f: 0.34 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −23.8 (*c* 1.30, $CHCl_3$); IR (liquid film): 3530 (br, OH), 2954, 1712 (C=O) cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.22–7.26 (6H, m, Ar*H*), 6.85–6.89 (6H,m, Ar*H*), 4.82 (1H, d,

J = 11.7 Hz, OCH_aH$_b$Ar), 4.80 (1H, d, J = 11.4 Hz, OCH_aH$_b$Ar), 4.78 (1H, d, J = 11.7 Hz, OCH$_a$$H_b$Ar), 4.63 (2H, s, C=C$H_2$), 4.56 (1H, d, J = 11.0 Hz, OCH_aH$_b$Ar), 4.53 (1H, d, J = 11.0 Hz, OCH$_a$$H_b$Ar), 4.34 (1H, d, J = 9.5 Hz, 35-CH), 4.28 (1H, d, J = 11.4 Hz, OCH$_a$$H_b$Ar), 3.90–3.95 (1H, m, 33-CH), 3.80 (6H, s, 2 × ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.75 (1H, s, 38-CH), 3.54 (2H, t, J = 6.5 Hz, 29-CH_2), 3.19–3.27 (3H, m, 39-CH + 42-CH + 43-CH), 3.05–3.15 (3H, m, 36-CH_aH$_b$ + 41-CH + OH), 2.44–2.50 (2H, m, 36-CH$_a$$H_b$ + 44-CH_aH$_b$), 2.15 (1H, dd, J = 14.4, 10.2 Hz, 44-CH$_a$$H_b$), 1.98–2.05 (1H, m, 40-CH), 1.78 (2H, quin., J = 6.9 Hz, 30-CH_2), 1.61 (3H, s, 46-CH_3), 1.46–1.59 (3H, m, 32-CH_2 + 34-CH), 1.36–1.44 (2H, m, 31-CH_2), 0.98 (9H, t, J = 7.7 Hz, Si(CH$_2$CH_3)$_3$), 0.90 (3H, d, J = 6.9 Hz, 34-CHCH_3), 0.64 (6H, q, J = 7.8 Hz, Si(CH_2CH$_3$)$_3$), 0.59 (3H, d, J = 6.5 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 214.3, 159.7, 159.3, 159.3, 142.9, 130.6, 130.5, 130.4, 130.3, 129.8, 129.6, 129.6, 128.8, 113.9, 113.9, 113.7, 111.9, 86.2, 82.8, 82.8, 82.5, 77.9, 77.7, 75.1, 74.7, 72.8, 69.8, 55.3, 55.3, 55.3, 45.3, 44.8, 40.4, 39.5, 37.9, 33.9, 32.7, 22.8, 22.3, 12.2, 6.9, 6.7, 5.4; HRMS: (+ESI) Calc. for $C_{51}H_{75}O_{10}ClSiNa$ [M + Na]$^+$: 933.4716, found: 933.4749.

Minor diastereomer 35-*epi*-**5**: R_f: 0.42 (30 : 70 EtOAc–hexanes); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.20–7.25 (6H, m, ArH), 6.84–6.89 (6H, m, ArH), 4.83 (1H, d, J = 10.7 Hz, OCH_aH$_b$Ar), 4.79 (1H, d, J = 11.0 Hz, OCH_aH$_b$Ar), 4.76 (1H, d, J = 11.9 Hz, OCH_aH$_b$Ar), 4.71 (1H, s, C=CH_aH$_b$), 4.69 (1H, s, C=CH$_a$$H_b$), 4.56 (1H, d, J = 11.0 Hz, OCH$_a$$H_b$Ar), 4.54 (1H, d, J = 10.7 Hz, OCH$_a$$H_b$Ar), 4.28 (1H, d, J = 11.9 Hz, OCH$_a$$H_b$Ar), 3.99 (1H, t, J = 9.0 Hz, 35-CH), 3.92–3.96 (1H, m, 33-CH), 3.85–3.91 (2H, m, 38-CH + OH), 3.81 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.79 (3H, s, ArOCH_3), 3.54 (2H, t, J = 6.7 Hz, 29-CH_2), 3.33 (1H, d, J = 11.4 Hz, 39-CH), 3.20–3.29 (2H, m, 42-CH + 43-CH), 3.14 (1H, dd, J = 9.7, 8.3 Hz, 41-CH), 2.75 (1H, d, J = 16.1 Hz, 36-CH_aH$_b$), 2.43–2.53 (2H, m, 36-CH$_a$$H_b$ + 44-CH_aH$_b$), 2.14 (1H, dd, J = 14.2, 9.8 Hz, 44-CH$_a$$H_b$), 2.00–2.08 (1H, m, 40-CH), 1.78 (2H, quin., J = 6.9 Hz, 30-CH_2), 1.65–1.72 (1H, m, 34-CH), 1.64 (3H, s, 46-CH_3), 1.46–1.58 (3H, m, 31-CH_aH$_b$ + 32-CH_2), 1.35–1.44 (1H, m, 31-CH$_a$$H_b$), 0.98 (9H, t, J = 7.7 Hz, Si(CH$_2$CH_3)$_3$), 0.75 (3H, d, J = 6.8 Hz, 34-CHCH_3), 0.60–0.66 (9H, m, 40-CHCH_3 + Si(CH_2CH$_3$)$_3$).

(2*R*,4*S*,5*R*,6*R*)- and (2*R*,4*R*,5*R*,6*R*)-6-(4-chlorobutyl)-2-methoxy-2-[[4,5-(*R*,*R*)-bis-(*p*-methoxybenzyloxy)-3-(*R*)-methyl-6-(*R*)-(2-methylallyl)-tetrahydropyran-2-(*R*)-yl]-((*S*)-*p*-methoxybenzyloxy)-methyl]-5-methyl-tetrahydropyran-4-ol (27 and 35-*epi*-27)

To a solution of aldol products **5** and 35-*epi*-**5** (from above procedure, max. 1.49 mmol) in MeOH–(MeO)$_3$CH (10 : 1, 33 mL) was added PPTS (cat.). The reaction mixture was stirred at rt for 2 h then quenched by the addition of sat. aq. $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 50 : 50 EtOAc–light petroleum) afforded methyl acetal **27** (849 mg, 70%) and the diastereomer 35-*epi*-**27** (142 mg, 12%) as colourless oils. The combined yield was 991 mg, 82% over two steps from ketone **6**.

Major diastereomer **27**: R_f: 0.24 (30 : 70 EtOAc–hexanes); $[a]_D^{20}$ +14.7 (*c* 0.80, $CHCl_3$); IR (liquid film): 3531 (br, OH), 2935, 1612 (C=C) cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.29 (2H, d, J = 8.5 Hz, ArH), 7.25 (2H, d, J = 7.9 Hz, ArH), 7.25 (2H, d, J = 8.6 Hz, ArH), 6.88 (2H, d, J = 8.6 Hz, ArH), 6.86 (4H, d, J = 8.2 Hz, ArH), 4.80 (2H, s, C=CH_2), 4.77–4.82 (3H, m, 2 × OCH_aH$_b$Ar + OCH$_a$$H_b$Ar), 4.66 (1H, d, J = 11.4 Hz, OCH$_a$$H_b$Ar), 4.57 (1H, d, J = 10.6 Hz, OCH_aH$_b$Ar), 4.52 (1H, d, J = 10.6 Hz, OCH$_a$$H_b$Ar), 4.02–4.06 (1H, m, 33-CH), 3.81 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.75 (1H, d, J = 8.0 Hz, OH), 3.66–3.71 (1H, m, 35-CH), 3.61 (2H, t, J = 6.3 Hz, 29-CH_2), 3.48 (1H, s, 38-CH), 3.35 (1H, t, J = 9.5 Hz, 43-CH), 3.22 (1H, t, J = 8.8 Hz, 42-CH), 3.19 (3H, s, 37-COCH_3), 3.10 (1H, t, J = 9.5 Hz, 41-CH), 3.06 (1H, d, J = 10.3 Hz, 39-CH), 2.51 (1H, d, J = 14.3 Hz, 44-CH_aH$_b$), 2.26 (1H, dd, J = 14.5, 10.3 Hz, 44-CH$_a$$H_b$), 2.17 (2H, d, J = 2.5 Hz, 36-CH_2), 1.88 (2H, quin., J = 6.8 Hz, 30-CH_2), 1.78–1.88 (2H, m, 31-CH_aH$_b$ + 40-CH), 1.74 (3H, s, 46-CH_3), 1.66–1.76 (2H, m, 32-CH_aH$_b$ + 34-CH), 1.52–1.60 (1H, m, 31-CH$_a$$H_b$), 1.40–1.48 (1H, m, 32-CH$_a$$H_b$), 0.89 (3H, d, J = 7.1 Hz, 34-CHCH_3), 0.42 (3H, d, J = 6.4 Hz, 40-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.4, 159.3, 159.2, 142.7, 131.1, 130.7, 130.5, 130.1, 129.7, 129.5, 113.9, 113.9, 113.7, 112.8, 104.2, 86.8, 82.8, 80.2, 78.1, 74.7, 74.6, 73.9, 72.8, 70.5, 67.6, 55.3, 55.3, 55.3, 47.6, 45.0, 39.7, 38.3, 37.3, 32.7, 32.3, 29.1, 23.6, 22.1, 12.4, 10.7; HRMS: (+ESI) Calc. for $C_{46}H_{63}O_{10}ClNa$ [M + Na]$^+$: 833.4007, found: 833.4037.

Minor diastereomer 35-*epi*-**27**: R_f: 0.12 (30 : 70 EtOAc–hexanes); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.30 (2H, d, J = 8.4 Hz, ArH), 7.25 (2H, d, J = 8.1 Hz, ArH), 7.24 (2H, d, J = 8.5 Hz, ArH), 6.85–6.90 (6H, m, ArH), 4.77–4.81 (5H, m, C=CH_2 + 2 × OCH_aH$_b$Ar + OCH$_a$$H_b$Ar), 4.67 (1H, d, J = 11.4 Hz, OCH$_a$$H_b$Ar), 4.57 (1H, d, J = 10.6 Hz, OCH_aH$_b$Ar), 4.51 (1H, d, J = 10.6 Hz, OCH$_a$$H_b$Ar), 4.03–4.07 (1H, m, 35-CH), 3.81 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.80 (3H, s, ArOCH_3), 3.57–3.61 (3H, m, 29-CH_2 + 33-CH), 3.55 (1H, s, 38-CH), 3.35 (1H, td, J = 9.2, 2.0 Hz, 43-CH), 3.21 (1H, t, J = 9.0 Hz, 42-CH), 3.12 (3H, s, 37-COCH_3), 3.04–3.15 (2H, m, 39-CH + 41-CH), 2.50 (1H, d, J = 14.1 Hz, 44-CH_aH$_b$), 2.27 (1H, dd, J = 14.2, 10.1 Hz, 44-CH$_a$$H_b$), 2.12 (1H, dd, J = 13.7, 4.7 Hz, 36-CH_aH$_b$), 1.93 (1H, t, J = 13.5 Hz, 36-CH$_a$$H_b$), 1.80–1.90 (4H, m, 30-CH_2 + 34-CH + 40-CH), 1.74 (3H, s, 46-CH_3), 1.68–1.78 (2H, m, 31-CH_aH$_b$ + 32-CH_aH$_b$), 1.50–1.58 (1H, m, 31-CH$_a$$H_b$), 1.44–1.50 (1H, m, 32-CH$_a$$H_b$), 1.08 (1H, d, J = 4.9 Hz, OH), 0.88 (3H, d, J = 6.8 Hz, 34-CHCH_3), 0.43 (3H, d, J = 6.4 Hz, 40-CHCH_3).

(4*S*)-1-[6-[[4-(*S*)-(*t*-Butyldimethylsiloxy)-6-(*R*)-(4-chlorobutyl)-2-(*R*)-methoxy-5-(*S*)-methyl-tetrahydropyran-2-yl]-(*S*)-(*p*-methoxybenzyloxy)-methyl]-(6*R*)-3,4-(*R*,*R*)-bis-(*p*-methoxybenzyloxy)-5-(*R*)-methyl-tetrahydropyran-2-(*R*)-yl]-7-chloro-4-hydroxy-octa-5,7-dien-2-one (33)

To a cooled (−78 °C) solution of ketone **3** (23.8 mg, 25.7 μmol) in Et_2O (500 μL) were added Et_3N (29 μL, 208 μmol, 8 eq.) followed by Chx_2BCl (23 μL, 105 μmol, 4 eq.). The resultant mixture was stirred at −78 °C for 30 min before warming to −40 °C. After stirring at −40 °C for 1 h, the mixture was cooled back to −78 °C and a solution of aldehyde **4** (22.4 mg, 192 μmol, 7.5 eq.) in Et_2O (250 μL + 2 × 125 μL) was added *via* cannula. The reaction was stirred at −78 °C for 2 h before being warmed to −20 °C and was stored at this temperature for 14 h. To the cooled solution (0 °C) was added a premixed solution of 3 : 1 MeOH (900 μL) and pH 7 buffer (300 μL). The mixture was stirred for 10 min before the dropwise addition of a premixed solution of 2 : 1 pH 7 buffer (800 μL) and 30% H_2O_2 (400 μL). The resultant mixture was stirred vigorously at 0 °C for 2.5 h before dilution with H_2O (5 mL). Et_2O (3 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 2 mL), the combined organic extracts were washed with $NaHCO_3$ (2 × 2 mL) and brine (2 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash chromatography (20 : 80 → 35 : 65 EtOAc–hexanes) gave the aldol adduct **33** (21.2 mg, 79%) as a colourless oil, which was found to decompose over time (noticeable decomposition after 1 week at −20 °C): R_f: 0.25 (30 : 70 EtOAc–hexanes); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.5 Hz, ArH), 7.25 (2H, d, J = 8.5 Hz, ArH), 7.23 (2H, d, J = 8.5 Hz, ArH), 6.86 (6H, d, J = 8.3 Hz, ArH), 6.29 (1H, d, J = 14.9 Hz, 49-CH), 5.94 (1H, dd, J = 14.9, 4.6 Hz, 48-CH), 5.33 (1H, s, 51-CH_aH$_b$), 5.31

(1H, s, 51-CH$_a$H$_b$), 4.84 (1H, d, J = 10.9 Hz, OCH$_a$H$_b$Ar), 4.78 (1H, d, J = 11.2 Hz, OCH$_a$H$_b$Ar), 4.77 (1H, d, J = 10.4 Hz, OCH$_a$H$_b$Ar), 4.66 (1H, d, J = 11.2 Hz, OCH$_a$H$_b$Ar), 4.61 (1H, d, J = 10.9 Hz, OCH$_a$H$_b$Ar), 4.54–4.58 (1H, m, 47-CH), 4.52 (1H, d, J = 10.4 Hz, OCH$_a$H$_b$Ar), 4.10–4.14 (1H, m, 33-CH), 3.80 (3H, s, ArOCH$_3$), 3.79 (6H, s, 2 × ArOCH$_3$), 3.76–3.80 (1H, m, 35-CH), 3.66–3.73 (1H, m, 43-CH), 3.60 (2H, t, J = 6.3 Hz, 29-CH$_2$), 3.49 (1H, s, 38-CH), 3.37 (1H, d, J = 2.7 Hz, OH), 3.22–3.28 (2H, m, 39-CH + 42-CH), 3.12 (3H, s, 37-COCH$_3$), 3.10–3.13 (1H, m, 41-CH), 2.70 (1H, dd, J = 15.1, 5.0 Hz, 44-CH$_a$H$_b$), 2.58–2.63 (2H, m, 44-CH$_a$H$_b$ + 46-CH$_a$H$_b$), 2.48 (1H, dd, J = 17.1, 9.7 Hz, 46-CH$_a$H$_b$), 2.08 (1H, dd, J = 15.1, 3.5 Hz, 36-CH$_a$H$_b$), 1.87 (2H, qn, J = 6.8 Hz, 30-CH$_2$), 1.68–1.78 (2H, m, 31-CH$_a$H$_b$ + 40-CH), 1.46–1.66 (4H, m, 31-CH$_a$H$_b$ + 32-CH$_a$H$_b$ + 34-CH + 36-CH$_a$H$_b$), 1.36–1.42 (1H, m, 32-CH$_a$H$_b$), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.86 (3H, d, J = 7.2 Hz, 34-CHCH$_3$), 0.51 (3H, d, J = 6.3 Hz, 40-CHCH$_3$), 0.07 (3H, s, Si(CH$_3$)$_a$), 0.01 (3H, s, Si(CH$_3$)$_b$); HRMS: (+ESI) Calc. for $C_{56}H_{80}O_{12}Cl_2SiNa$ [M + Na]$^+$: 1065.4688, found: 1065.4654.

(4*S*)-1-[6-[[4-(*S*)-(*t*-Butyldimethylsiloxy)-6-(*R*)-(4-chlorobutyl)-2-(*R*)-methoxy-5-(*S*)-methyl-tetrahydropyran-2-yl]-(*S*)-(*p*-methoxybenzyloxy)-methyl]-(6*R*)-3,4-(*R*,*R*)-bis-(*p*-methoxybenzyloxy)-5-(*R*)-methyl-tetrahydropyran-2-(*R*)-yl]-4-(*t*-butyldimethylsiloxy)-7-chloro-2-methylene-octa-5,7-diene (35)

To a stirred suspension of Zn (4.27 g, 65.3 mmol, 180 eq.) and PbI_2 (300 mg, 0.65 mmol, 1.8 eq.) in THF (25 mL) was added TMSCl (0.42 mL, 3.31 mmol, 9.0 eq.). The resulting suspension was stirred at rt for 15 min before diiodomethane (2.92 mL, 36.2 mmol, 100 eq.) was added dropwise. The reaction was maintained at self-reflux during the addition and stirred for a further 30 min at rt before cooling to 0 °C. $TiCl_4$ (1 M in CH_2Cl_2, 7.25 mL, 7.25 mmol, 20 eq.) was added dropwise and the reaction mixture was warmed to rt and stirred for a further 1 h. A solution of TBS ether **34** (420 mg, 0.36 mmol) in THF (10 mL + 2 × 5 mL washings) was added *via* cannula and the resultant mixture was stirred at rt for 4 h. The reaction was quenched by slow addition to a cold (0 °C) sodium potassium tartrate solution. It was allowed to warm to rt and vigorously stirred for 30 min. The layers were separated and the aqueous phase was extracted with Et_2O (4 × 150 mL), combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 40 : 60 EtOAc–light petroleum) afforded triene **35** (342 mg, 81%) as a colourless oil: R_f: 0.26 (7 : 30 : 63 Et_2O–CH_2Cl_2–hexanes); $[\alpha]_D^{20}$ +16.8 (*c* 1.03, $CHCl_3$); IR (liquid film): 2931, 2856, 1612, 1514 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.31 (2H, d, J = 8.4 Hz, ArH), 7.23 (4H, d, J = 7.8 Hz, ArH), 6.83–6.87 (6H, m, ArH), 6.21 (1H, d, J = 14.9 Hz, 49-CH), 6.10 (1H, dd, J = 14.9, 5.2 Hz, 48-CH), 5.29 (1H, br s, 51-CH$_a$H$_b$), 5.24 (1H, br s, 51-CH$_a$H$_b$), 4.92 (1H, br s, 45-C=CH$_a$H$_b$), 4.83 (1H, br s, 45-C=CH$_a$H$_b$), 4.81 (2H, app. d, J = 11 Hz, 2 × OCH$_a$H$_b$Ar), 4.76 (1H, d, J = 10.6 Hz, OCH$_a$H$_b$Ar), 4.72 (1H, d, J = 11.4 Hz, OCH$_a$H$_b$Ar), 4.55 (1H, d, J = 10.8 Hz, OCH$_a$H$_b$Ar), 4.50 (1H, d, J = 10.6 Hz, OCH$_a$H$_b$Ar), 4.32 (1H, td, J = 6.2, 5.2 Hz, 47-CH), 4.13 (1H, br t, J = 6.9 Hz, 33-CH), 3.80 (6H, s, 2 × ArOCH$_3$), 3.79 (3H, s, ArOCH$_3$), 3.73 (1H, m, 35-CH), 3.59 (2H, t, J = 6.3 Hz, 29-CH$_2$), 3.45 (1H, s, 38-CH), 3.30 (1H, br t, J = 8.7 Hz, 43-CH), 3.16 (1H, t, J = 9.0 Hz, 42-CH), 3.10 (3H, s, 37-COCH$_3$), 3.02–3.13 (2H, m, 39-CH + 41-CH), 2.51 (1H, br d, J = 14.8 Hz, 44-CH$_a$H$_b$), 2.32 (1H, dd, J = 13.6, 6.5 Hz, 46-CH$_a$H$_b$), 2.15–2.22 (2H, m, 44-CH$_a$H$_b$ + 46-CH$_a$H$_b$), 2.12 (1H, dd, J = 15.5, 3.7 Hz, 36-CH$_a$H$_b$), 1.85 (2H, m, 30-CH$_2$), 1.72–1.77 (2H, m, 31-CH$_a$H$_b$ + 40-CH), 1.60–1.69 (3H, m, 31-CH$_a$H$_b$ + 32-CH$_a$H$_b$ + 36-CH$_a$H$_b$), 1.34–1.46 (2H, m, 32-CH$_a$H$_b$ + 34-CH), 0.86–0.88 (21H, m, 34-CHCH$_3$ + 2 × SiC(CH$_3$)$_3$), 0.41 (3H, d, J = 6.4 Hz, 40-CHCH$_3$), 0.02 (3H, s, SiCH$_3$), 0.01 (3H, s, SiCH$_3$), −;0.01 (6H, 2 × s, 2 × SiCH$_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.7, 159.6, 159.5, 142.7, 138.8, 138.4, 131.5, 131.1, 131.0, 129.9, 129.6, 126.2, 115.5, 115.0, 114.2, 114.2, 114.2, 114.0, 102.9, 87.2, 83.0, 80.0, 78.8, 74.9, 74.7, 74.3, 73.4, 71.3, 70.6, 67.1, 55.6, 55.6, 55.6, 47.5, 45.7, 45.4, 38.8, 38.5, 38.4, 33.1, 32.6, 31.1, 26.2, 26.1, 23.9, 18.6, 18.2, 12.9, 10.5, −4.2, −4.2, −4.4, −4.4; HRMS: (+ESI) Calc. for $C_{63}H_{96}O_{11}Cl_2Si_2Na$ [M + Na]$^+$: 1177.5760, found: 1177.5694.

(4*S*)-1-[6-[[4-(*S*)-(*t*-Butyldimethylsiloxy)-6-(*R*)-(4-(triphenylphosphonium)-butyl)-2-(*R*)-methoxy-5-(*S*)-methyl-tetrahydropyran-2-yl]-(*S*)-(*p*-methoxybenzyloxy)-methyl]-(6*R*)-3,4-(*R*,*R*)-bis-(*p*-methoxybenzyloxy)-5-(*R*)-methyl-tetrahydropyran-2-(*R*)-yl]-4-(*t*-butyldimethylsiloxy)-7-chloro-2-methylene-octa-5,7-diene iodide (2)

To a solution of **35** (9.7 mg, 8.39 μmol) in 9 : 1 MeCN (450 μL) and MeOH (50 μL) were added *i*-Pr$_2$NEt (3 μL, 17.2 μmol, 2 eq.), NaI (19 mg, 127 μmol, 15 eq.) and PPh_3 (88 mg, 336 μmol, 40 eq.). The resultant mixture was heated at reflux for 11 h at which point TLC analysis showed that a small amount of starting material **35** remained. A further portion of PPh_3 (44 mg, 118 μmol, 20 eq.) was added and the mixture heated at reflux for an additional 8 h. The mixture was cooled to rt and the solvent was removed *in vacuo* before the addition of CH_2Cl_2 (1 mL) and the resultant suspension was filtered through cotton wool, washing with CH_2Cl_2 (3 × 0.5 mL). The resultant filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography (10 : 90 → 60 : 40 MeCN–EtOAc). The residue was dissolved in CH_2Cl_2 and filtered through cotton wool. The filtrate was concentrated *in vacuo* to afford a glassy solid. Lyophilisation with C_6H_6 (2x) provided phosphonium salt **2** (11.5 mg, 91%) as a white powder: R_f: 0.54 (70 : 30 MeCN–EtOAc); $[\alpha]_D^{20}$ +12.2 (*c* 1.15, $CHCl_3$); IR: (neat) 2929, 2855, 1612, 1513, 1438 cm^{-1}; ^{1}H NMR: δ (500 MHz, C_6D_6) 7.83–7.85 (6H, m, ArH), 7.74 (3H, dd, J = 11.6, 7.3 Hz, ArH), 7.57 (2H, d, J = 8.3 Hz, ArH), 7.34 (2H, d, J = 8.4 Hz, ArH), 7.27 (2H, d, J = 8.4 Hz, ArH), 7.14–7.20 (2H, m, ArH), 7.03 (2H, d, J = 6.1 Hz, ArH), 6.97–7.01 (2H, m, ArH), 6.96 (2H, d, J = 8.3 Hz, ArH), 6.84 (2H, d, J = 8.1 Hz, ArH), 6.83 (2H, d, J = 8.1 Hz, ArH), 6.45 (1H, dd, J = 14.9, 5.0 Hz, 48-CH), 6.37 (1H, d, J = 14.9 Hz, 49-CH), 5.10–5.13 (4H, m, OCH$_a$H$_b$Ar + 51-CH$_a$H$_b$ + 45-C=CH$_2$), 5.02 (1H, br s, 51-CH$_a$H$_b$), 4.94 (1H, d, J = 12.4 Hz, OCH$_a$H$_b$Ar), 4.93 (1H, d, J = 10.8 Hz, OCH$_a$H$_b$Ar), 4.91 (1H, d, J = 11.1 Hz, OCH$_a$H$_b$Ar), 4.63–4.68 (1H, m, 29-CH$_a$H$_b$), 4.61 (1H, d, J = 10.8 Hz, OCH$_a$H$_b$Ar), 4.54 (1H, d, J = 11.1 Hz, OCH$_a$H$_b$Ar), 4.50 (1H, app. q, J = 6.2 Hz, 47-CH), 4.30 (1H, br d, J = 9.7 Hz, 33-CH), 4.22–4.25 (1H, m, 29-CH$_a$H$_b$), 4.05 (1H, br s, 38-CH), 3.95 (1H, br d, J = 1.9 Hz, 35-CH), 3.56 (1H, br t, J = 8.9 Hz, 43-CH), 3.42 (1H, m, 39-CH), 3.42 (3H, s, OCH$_3$), 3.39 (3H, s, OCH$_3$), 3.34 (1H, m, 42-CH), 3.33 (3H, s, OCH$_3$), 3.31 (3H, s, OCH$_3$), 3.19 (1H, br t, J = 9.5, 41-CH), 2.74 (1H, br d, J = 14.6 Hz, 44-CH$_a$H$_b$), 2.66 (1H, dd, J = 13.5, 6.7 Hz, 46-CH$_a$H$_b$), 2.56 (1H, dd, J = 15.3, 3.4 Hz, 36-CH$_a$H$_b$), 2.52 (1H, dd, J = 13.5, 6.9 Hz, 46-CH$_a$H$_b$), 2.44 (1H, m, 30-CH$_a$H$_b$), 2.30 (1H, dd, J = 14.6, 9.1 Hz, 44-CH$_a$H$_b$), 2.19 (1H, m, 40-CH), 1.99 (1H, br d, J = 15.3 Hz, 36-CH$_a$H$_b$), 1.90 (1H, m, 30-CH$_a$H$_b$), 1.72 (1H, m, 32-CH$_a$H$_b$), 1.55–1.64 (3H, 31-CH$_2$ + 34-CH), 1.20 (1H, m, 32-CH$_a$H$_b$), 1.08 (9H, s, SiC(CH$_3$)$_3$), 1.05 (3H, d, J = 6.2 Hz, 40-CHCH$_3$), 1.02 (3H, d, J = 7.1 Hz, 34-CHCH$_3$), 1.01 (9H, s, SiC(CH$_3$)$_3$), 0.25 (3H, s, SiCH$_3$), 0.15 (3H, s, SiCH$_3$), 0.13 (3H, s, SiCH$_3$), 0.09 (3H, s, SiCH$_3$); ^{13}C NMR: δ (125.7 MHz, C_6D_6) 159.7, 159.6, 143.3, 138.9, 138.8, 134.4, 134.4, 132.4 (d, $^2J_{P\text{-}C}$ = 9.7 Hz, C *ortho* to P$^+$), 131.5, 131.0, 130.2 (d, $^3J_{P\text{-}C}$ = 12.2 Hz, C *meta* to P$^+$), 129.5, 129.3, 126.4, 119.1 (d, $^1J_{P\text{-}C}$ = 85.2 Hz, C *ipso* to P$^+$), 115.0, 114.3, 114.1, 102.9, 87.5, 83.2, 80.1, 78.6, 76.5, 75.1, 74.7, 74.5, 71.4, 71.3, 66.6, 55.0, 54.8, 54.7, 48.7, 46.2, 39.4, 39.4, 39.0, 33.7, 31.7, 27.4 (d, $^3J_{P\text{-}C}$ = 16.2 Hz, 31-*C*), 26.2, 26.2, 23.4, 23.1 (d, $^1J_{P\text{-}C}$ = 48.8 Hz, 29-*C*), 18.5, 18.4, 14.0, 10.9, −4.1, −4.3, −4.4; ^{31}P NMR: δ (162 MHz, C_6D_6) 25.6; HRMS: (+ESI) Calc. for $C_{81}H_{111}O_{11}ClPSi_2$ [M]$^+$: 1381.7076, found: 1381.7173.

Acknowledgements

Financial support was provided by the EPSRC (GR/L41646), EC (Marie Curie Fellowship to J.L.A.), DFG (Postdoctoral Fellowship to T.T.), Cambridge Commonwealth Trust (M.J.C.), King's College and Sim's Fund, Cambridge (D.Y.-K.C.). We thank Merck, AstraZeneca and Novartis Pharmaceuticals for generous support, and Dr Anne Butlin (AZ) for valuable assistance.

References

1 For a full introduction and background, see the preceding papers in this series: I. Paterson, M. J. Coster, D. Y.-K. Chen, R. M. Oballa, D. J. Wallace and R. D. Norcross, *Org. Biomol. Chem.*, 2005, **3**, DOI: 10.1039/b504146e; I. Paterson, M. J. Coster, D. Y.-K. Chen, K. R. Gibson and D. J. Wallace, *Org. Biomol. Chem.*, 2005, **3**, DOI: 10.1039/b504148a.

2 For previous communications of our work, see: (*a*) I. Paterson, R. M. Oballa and R. D. Norcross, *Tetrahedron Lett.*, 1996, **37**, 8581–8584; (*b*) I. Paterson and L. E. Keown, *Tetrahedron Lett.*, 1997, **38**, 5727–5730; (*c*) I. Paterson and R. M. Oballa, *Tetrahedron Lett.*, 1997, **38**, 8241–8244; (*d*) I. Paterson, D. J. Wallace and K. R. Gibson, *Tetrahedron Lett.*, 1997, **38**, 8911–8914; (*e*) I. Paterson, D. J. Wallace and R. M. Oballa, *Tetrahedron Lett.*, 1998, **39**, 8545–8548; (*f*) 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 and R. D. Norcross, *Angew. Chem., Int. Ed.*, 2001, **40**, 4055–4060; (*g*) I. Paterson and M. J. Coster, *Tetrahedron Lett.*, 2002, **43**, 3285–3289; (*h*) I. Paterson, J. L. Acena, J. Bach, D. Y.-K. Chen and M. J. Coster, *Chem. Commun.*, 2003, 462–463; (*i*) I. Paterson and M. J. Coster, in *Strategy and Tactics in Organic Synthesis*, ed. M. Harmata, Elsevier, Oxford, 2004, vol. 4, ch. 8, pp. 211–245.

3 Completed altohyrtin/spongistatin total syntheses: (*a*) D. A. Evans, P. J. Coleman and L. C. Dias, *Angew. Chem., Int. Ed.*, 1997, **36**, 2738–2741; (*b*) D. A. Evans, B. W. Trotter, B. Cote and P. J. Coleman, *Angew. Chem., Int. Ed.*, 1997, **36**, 2741–2744; (*c*) D. A. Evans, B. W. Trotter, B. Cote, P. J. Coleman, L. C. Dias and A. N. Tyler, *Angew. Chem., Int. Ed.*, 1997, **36**, 2744–2747; (*d*) D. A. Evans, B. W. Trotter, P. J. Coleman, B. Cote, L. C. Dias, H. A. Rajapakse and A. N. Tyler, *Tetrahedron*, 1999, **55**, 8671–8726; (*e*) J. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 187–192; (*f*) M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. Guo and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 192–196; (*g*) A. B. Smith, III, V. A. Doughty, Q. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama and M. Sobukawa, *Angew. Chem., Int. Ed.*, 2001, **40**, 191–195; (*h*) A. B. Smith, III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase and K. Nakayama, *Angew. Chem., Int. Ed.*, 2001, **40**, 196–199; (*i*) A. B. Smith, III, V. A. Doughty, C. Sfouggatakis, C. S. Bennett, J. Koyanagi and M. Takeuchi, *Org. Lett.*, 2002, **4**, 783–786; (*j*) A. B. Smith, III, W. Zhu, S. Shirakami, C. Sfouggatakis, V. A. Doughty, C. S. Bennett and Y. Sakamoto, *Org. Lett.*, 2003, **5**, 761–764; (*k*) M. T. Crimmin and D. G. Washburn, *Tetrahedron Lett.*, 1998, **39**, 7487–7490; (*l*) M. T. Crimmin, J. D. Katz, L. C. McAtee, E. A. Tabet and S. J. Kirincich, *Org. Lett.*, 2001, **3**, 949–952; (*m*) M. T. Crimmin and J. D. Katz, *Org. Lett.*, 2000, **2**, 957–960; (*n*) M. T. Crimmin, J. D. Katz, D. G. Washburn, S. P. Allwein and L. F. McAtee, *J. Am. Chem. Soc.*, 2002, **124**, 5661–5663; (*o*) J. L. Hubbs and C. H. Heathcock, *J. Am. Chem. Soc.*, 2003, **125**, 12836–12843; (*p*) C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes and G. R. Ott, *J. Am. Chem. Soc.*, 2003, **125**, 12844–12849.

4 Formal total synthesis of altohyrtin C/spongistatin 2 by Nakata and co-workers: T. Terauchi, T. Terauchi, I. Sato, W. Shoji, T. Tsukada, T. Tsunoda, N. Kanoh and M. Nakata, *Tetrahedron Lett.*, 2003, **44**, 7741–7745; T. Terauchi, T. Tanaka, T. Terauchi, M. Morita, K. Kimijima, I. Sato, W. Shoji, Y. Nakamura, T. Tsukada, T. Tsunoda, G. Hayashi, N. Kanoh and M. Nakata, *Tetrahedron Lett.*, 2003, **44**, 7747–7751.

5 Syntheses of E- and/or F-ring subunits by other groups: J. C. Anderson and B. P. McDermott, *Tetrahedron Lett.*, 1999, **40**, 7135–7138; J. C. Anderson, B. P. McDermott and E. J. Griffin, *Tetrahedron*, 2000, **56**, 8747–8767; R. Dunkel, J. Treu, H. Martin and R. Hoffmann, *Tetrahedron: Asymmetry*, 1999, **10**, 1539–1549; H. Kim and H. M. R. Hoffmann, *Eur. J. Org. Chem.*, 2000, 2195–2201; E. Fernandez-Megia, N. Gourlaouen, S. V. Ley and G. J. Rowlands, *Synlett*, 1998, 991–994; I. H. Cho and L. A. Paquette, *Heterocycles*, 2002, **58**, 43–46; S. A. Hermitage, S. M. Roberts and D. J. Watson, *Tetrahedron Lett.*, 1998, **39**, 3567–3570; P. D. Kary, S. M. Roberts and D. J. Watson, *Tetrahedron: Asymmetry*, 1999, **10**, 213–216; P. D. Kary and S. M. Roberts, *Tetrahedron: Asymmetry*, 1999, **10**, 217–219; G. C. Micalizio and W. R. Roush, *Tetrahedron Lett.*, 1999, **40**, 3351–3354; G. C. Micalizio, A. N. Pinchuk and W. R. Roush, *J. Org. Chem.*, 2000, **65**, 8730–8736; M. Samadi, C. Munoz-Letelier, S. Poigny and M. Guyot, *Tetrahedron Lett.*, 2000, **41**, 3349–3353; S. Lemaire-Audoire and P. Vogel, *Tetrahedron Lett.*, 1998, **39**, 1345–1348.

6 C. J. Cowden and I. Paterson, *Org. React.*, 1997, **51**, 1–200; I. Paterson, C. J. Cowden, and D. J. Wallace, in *Modern Carbonyl Chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, 2000, pp. 249–297.

7 I. Paterson, D. J. Wallace and S. M. Velazquez, *Tetrahedron Lett.*, 1994, **35**, 9083–9086; I. Paterson and D. J. Wallace, *Tetrahedron Lett.*, 1994, **35**, 9087–9090; I. Paterson and D. J. Wallace, *Tetrahedron Lett.*, 1994, **35**, 9477–9480; I. Paterson, D. J. Wallace and C. J. Cowden, *Synthesis*, 1998, 639–652.

8 H. C. Brown, R. K. Dhar, K. Ganesan and B. Singaram, *J. Org. Chem.*, 1992, **57**, 499–504.

9 (*a*) I. Paterson and R. D. Tillyer, *J. Org. Chem.*, 1993, **58**, 4182–4184; (*b*) I. Paterson and T. Nowak, *Tetrahedron Lett.*, 1996, **37**, 8243–8246.

10 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543–2549; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512–519; I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092–4096.

11 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841–1860.

12 E. J. Corey, D. Barnes-Seeman and T. W. Lee, *Tetrahedron Lett.*, 1997, **38**, 4351–4354, and references cited therein.

13 D. A. Evans and K. T. Chapman, *Tetrahedron Lett.*, 1986, **27**, 5939–5942; D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560–3578.

14 Analysis of these acetonides by ^{13}C NMR confirmed the 1,3-*anti* selectivity in the $Me_4NBH(OAc)_3$ reduction step: S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945–948; S. D. Rychnovsky, B. Rogers and G. Yang, *J. Org. Chem.*, 1993, **58**, 3511–3515; D. A. Evans, D. L. Rieger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099–7100.

15 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156; D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277–7287.

16 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183–2186.

17 (*a*) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768–2771; (*b*) Z. M. Wang and K. B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 8225–8228; (*c*) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev*, 1994, **94**, 2483–2547.

18 All compounds in this series bearing an acetonide protecting group were found to be sensitive to even mildly acidic conditions, presumably due to the sterically unfavourable 1,2-*cis*-1,3-*trans*- nature of the substituents on the 1,3-dioxane ring.

19 N. Nakajima, K. Horita, R. Abe and O. Yonemitsu, *Tetrahedron Lett.*, 1988, **29**, 4139–4142.

20 R. E. Ireland, L. Liu and T. D. Roper, *Tetrahedron*, 1997, **53**, 13221–13256.

21 C. Alvarez-Ibarra, S. Arias, G. Banon, M. J. Fernandez, M. Rodriguez and V. Sinisterra, *J. Chem. Soc., Chem. Commun.*, 1987, 1509–1511; I. Paterson, K. S. Yeung and J. B. Smaill, *Synlett*, 1993, 774–776.

22 N. A. Petasis and E. I. Bzowej, *J. Am. Chem. Soc.*, 1990, **112**, 6392–6394.

23 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666.

24 K. Griesbaum, A. R. Bandyopadhyay and M. Meister, *Can. J. Chem.*, 1986, **64**, 1553–1559.

25 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165–185.

26 I. Paterson, K. R. Gibson and R. M. Oballa, *Tetrahedron Lett.*, 1996, **37**, 8585–8588; I. Paterson and L. A. Collett, *Tetrahedron Lett.*, 2001, **42**, 1187–1191.

27 D. A. Evans, P. J. Coleman and B. Côté, *J. Org. Chem.*, 1997, **62**, 788–789; D. A. Evans, B. Cote, P. J. Coleman and B. T. Connell, *J. Am. Chem. Soc.*, 2003, **125**, 10893–10898.

28 K. Takai, T. Kakiuchi, Y. Kataoka and K. Utimoto, *J. Org. Chem.*, 1994, **59**, 2668–2670.

29 I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach and D. J. Wallace, *Org. Biomol. Chem.*, 2005, **3**, DOI: 10.1039/b504151a.