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The stereocontrolled total synthesis of altohyrtin A/spongistatin 1: the CD-spiroacetal segment†‡

Ian Paterson,* Mark J. Coster,§ David Y.-K. Chen, Karl R. Gibson and Debra J. Wallace
University Chemical Laboratory, Lensfield Road, University of Cambridge, Cambridge, UK CB2 1EW. E-mail: ip100@cam.ac.uk; Fax: +44 (0)1223 336 362

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Stereocontrolled syntheses of the C16–C28 CD-spiroacetal subunit of altohyrtin A/spongistatin 1 (**1**), relying on kinetic and thermodynamic control of the spiroacetal formation, are described. The kinetic control approach resulted in a slight preference (60 : 40) for the desired spiroacetal isomer. The thermodynamic approach allowed ready access to the desired spiroacetal **2** by acid-promoted equilibration, chromatographic separation of the C23 epimers and resubjection of the undesired isomer to the equilibration conditions. This scalable synthetic sequence provided multi-gram quantities of **2**, thus enabling the successful completion of the total synthesis of altohyrtin A/spongistatin 1, as reported in Part 4 of this series.

Introduction

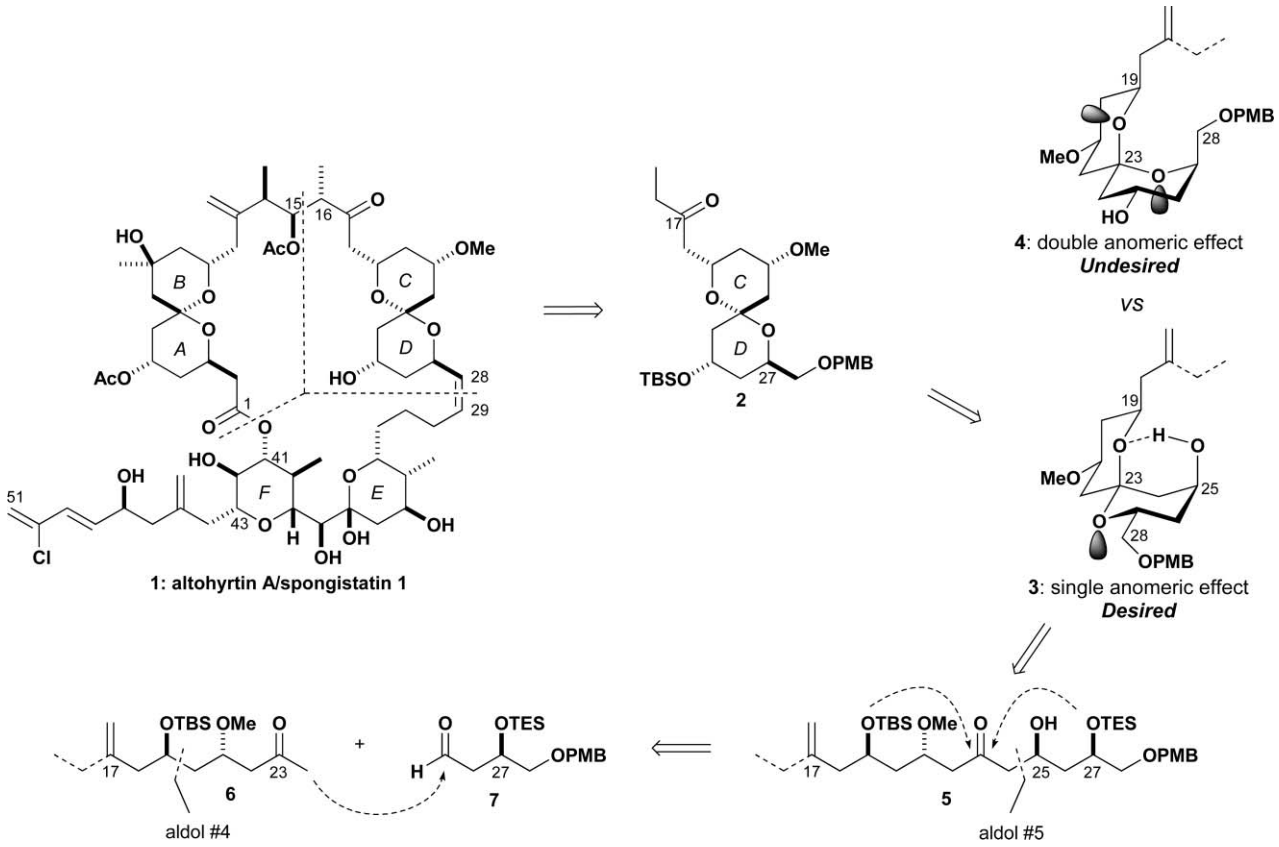
Altohyrtin A/spongistatin 1 (**1**, Scheme 1) is an extraordinarily potent cytotoxic marine macrolide. Unfortunately, the paucity of material available from the sponge sources has precluded its detailed preclinical development as a lead structure for cancer chemotherapy.[1] Our strategy[2] for the total synthesis of this captivating marine natural product involves its disconnection into three fragments, one of which is the C16–C28 CD-spiroacetal subunit **2**.[3–5] Herein, we provide a full account of the various strategies that we have explored for achieving a scalable synthesis of this key segment of the altohyrtins.[2d,g]

The CD-spiroacetal **2** exhibits an "axial–equatorial" arrangement of the acetal oxygen atoms and hence, unlike the AB-spiroacetal system, benefits from only one stabilising anomeric effect, as indicated in structure **3**, in contrast to the presumably more stable epimeric acetal **4**, which has a double anomeric effect. Two distinct approaches to assembling this portion of the spongipyrans were pursued. In a similar manner to that already

† Part 2 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/b504148a/

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



Scheme 1 Retrosynthetic analysis involving thermodynamic control of CD-spiroacetal formation in the synthesis of altohyrtin A/spongistatin 1 (**1**).

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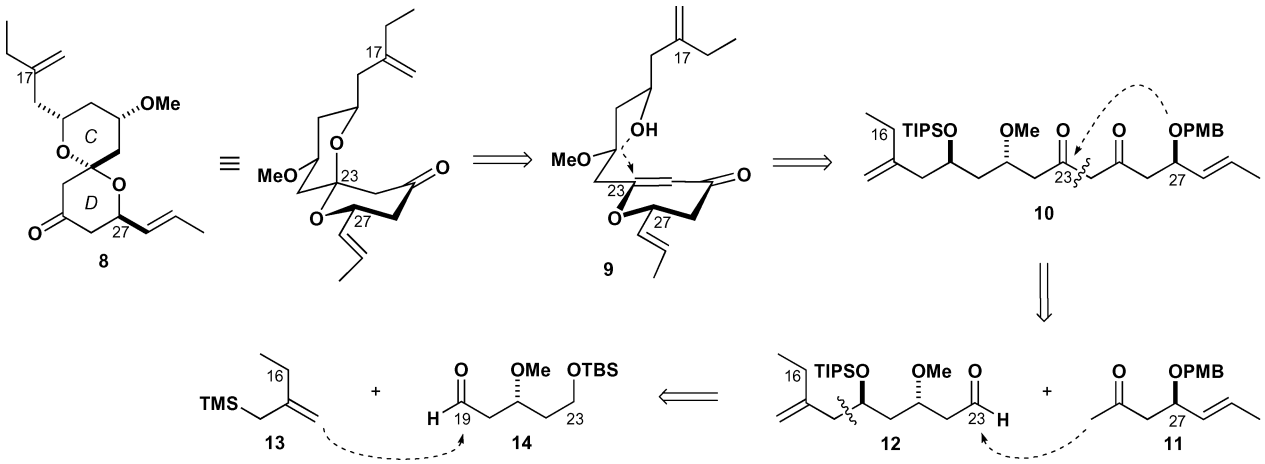


Scheme 2 Retrosynthetic analysis involving kinetic control of CD-spiroacetal formation.

employed for the AB-spiroacetal, the thermodynamic control approach relied on the acid-promoted bis-desilylation of a suitable linear precursor, such as **5**, with concomitant spiroacetal formation. In particular, it was envisaged that using this strategy, the desired spiroacetal **3** might be stabilised to some extent, especially in non-polar solvents, by an intramolecular hydrogen bond between the axial C25 hydroxyl and an acetal oxygen, ameliorating the presence of only one stabilising anomeric effect. In contrast, the undesired spiroacetal isomer **4** cannot form an intramolecular hydrogen bond of this nature and would be destabilised by 1,3-diaxial interactions involving the axially oriented C27 side-chain. In turn, the linear precursor **5** would be available from a stereocontrolled aldol reaction (aldol #5) between methyl ketone **6** and aldehyde **7**. Two alternative strategies for the assembly of ketone **6**, and a C17 ethyl homologue were envisioned, one involving establishment of the C19 and C21 stereocentres by asymmetric allylations, the other approach relying on a stereocontrolled aldol reaction (aldol #4) followed by 1,3-*anti* reduction.

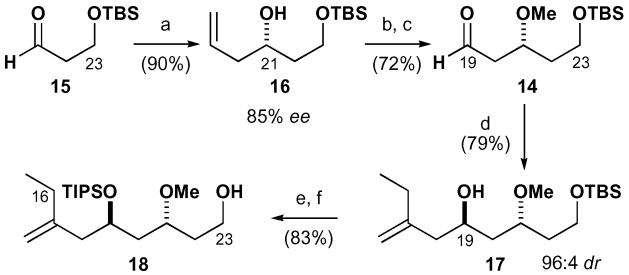
For the kinetic-control approach to the CD-spiroacetal subunit, stepwise construction of the C- and D-rings was prescribed (Scheme 2). Thus, it was proposed that the desired spiroacetal **8** might be obtained from D-ring dihydropyrone **9** by a kinetically-controlled, intramolecular hetero-Michael addition. Unravelling **9** to linear precursor **10** reveals an aldol disconnection to ketone **11** and aldehyde **12**. The latter of these intermediates might, in turn, be obtained as the product of a chelation controlled addition of allylsilane **13** to chiral β-methoxy aldehyde **14**. This kinetic control approach to the CD-spiroacetal will be described first.

Results and discussion

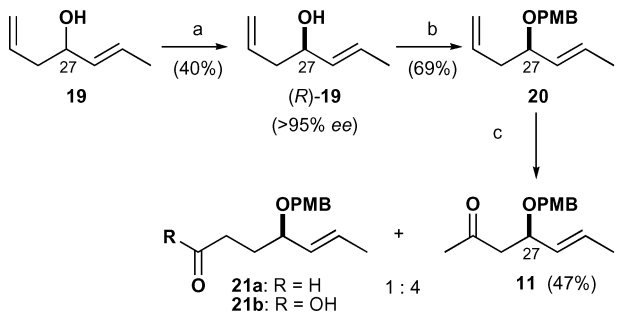
Formation of the CD-spiroacetal under kinetic control

The kinetic approach to the CD-spiroacetal[2d] required the synthesis of aldehyde **14** in enantiomerically enriched form (Scheme 3). Brown asymmetric allylation[6] of aldehyde **15**, employing *B*-allyldiisopinocampheylborane (^{d}Ipc$_2$BAll), provided homoallylic alcohol **16** in 90% yield and 85% ee (MTPA ester[7] analysis). Subsequent *O*-methylation (NaH, MeI) and ozonolysis gave the aldehyde **14** in 72% yield. Reaction of **14** with 2-(trimethylsilylmethyl)-1-butene (**13**)[8] under chelation control conditions ($TiCl_4$, CH_2Cl_2, 0.01 M, −100 °C), afforded the 1,3-*anti* isomer **17** in 79% yield as the major diastereomer (96 : 4 dr). Protection of the C19 hydroxyl as the triisopropylsilyl (TIPS) ether and selective removal of the *tert*-butyldimethylsilyl (TBS) group provided 1° alcohol **18**.

Synthesis of the C24–C28 fragment commenced with the kinetic resolution of alcohol **19**[9] under Sharpless asymmetric epoxidation[10] conditions, to give enantioenriched (*R*)-**19** (40% yield, >95% ee by MTPA ester analysis), which was then protected as the *p*-methoxybenzyl (PMB) ether **20** (Scheme 4). Subjection of this diene to Wacker oxidation[11] conditions provided an *ca.* 4 : 1 mixture of the desired methyl ketone **11** and undesired aldehyde **21a**, respectively. To simplify purification, the crude reaction mixture was subjected to oxidation ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O)[12] to convert **21a** to the corresponding acid **21b**, facilitating the isolation of **11** (47%).

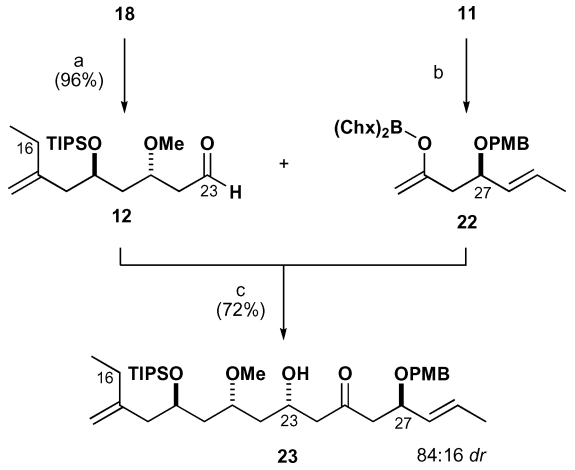


Scheme 3 *Reagents and conditions*: (a) (−)-Ipc$_2$BOMe, H_2C=$CHCH_2$-MgBr, Et_2O, −78 °C, 4 h, then H_2O_2, NaOH, H_2O, rt, 3 d; (b) NaH, MeI, THF, rt, 16 h; (c) O_3, CH_2Cl_2, $NaHCO_3$, −78 °C, 10 min, then PPh_3, 0 °C, 3 h; (d) H_2C=C(Et)CH_2SiMe_3 (**13**), $TiCl_4$, CH_2Cl_2, −100 °C, 20 min; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; (f) CSA, MeOH, CH_2Cl_2, rt, 3.5 h.



Scheme 4 *Reagents and conditions*: (a) 10 mol% Ti(O*i*–Pr)$_4$, 14 mol% diisopropyl L-tartrate, *t*-BuOOH (0.55 eq.), 4 Å mol. sieves, CH_2Cl_2, −20 °C, 20 h; (b) KH, PMBCl, cat. TBAI, rt, 14 h; (c) 8 mol% $PdCl_2$, CuCl, O_2, DMF–H_2O (8 : 1), rt, 16 h, then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O (1 : 1), rt, 2 h.

Oxidation of alcohol **18** with the Dess–Martin periodinane,[13] providing aldehyde **12** in 96% yield, set the stage for the boron aldol coupling reaction[14] with ketone **11** (Scheme 5). Generation of the corresponding dicyclohexylboron enolate **22** from **11** under standard conditions (Chx$_2$BCl, Et_3N),[15] and reaction with aldehyde **12**, provided the aldol adduct **23** in a surprisingly diastereoselective fashion (84 : 16 dr). On the basis of this work and related model studies, and despite the fact that the



Scheme 5 *Reagents and conditions*: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (b) Chx_2BCl, Et_3N, Et_2O, 0 °C, 30 min; (c) **12**, −78 → −20 °C, 21 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 2 h.

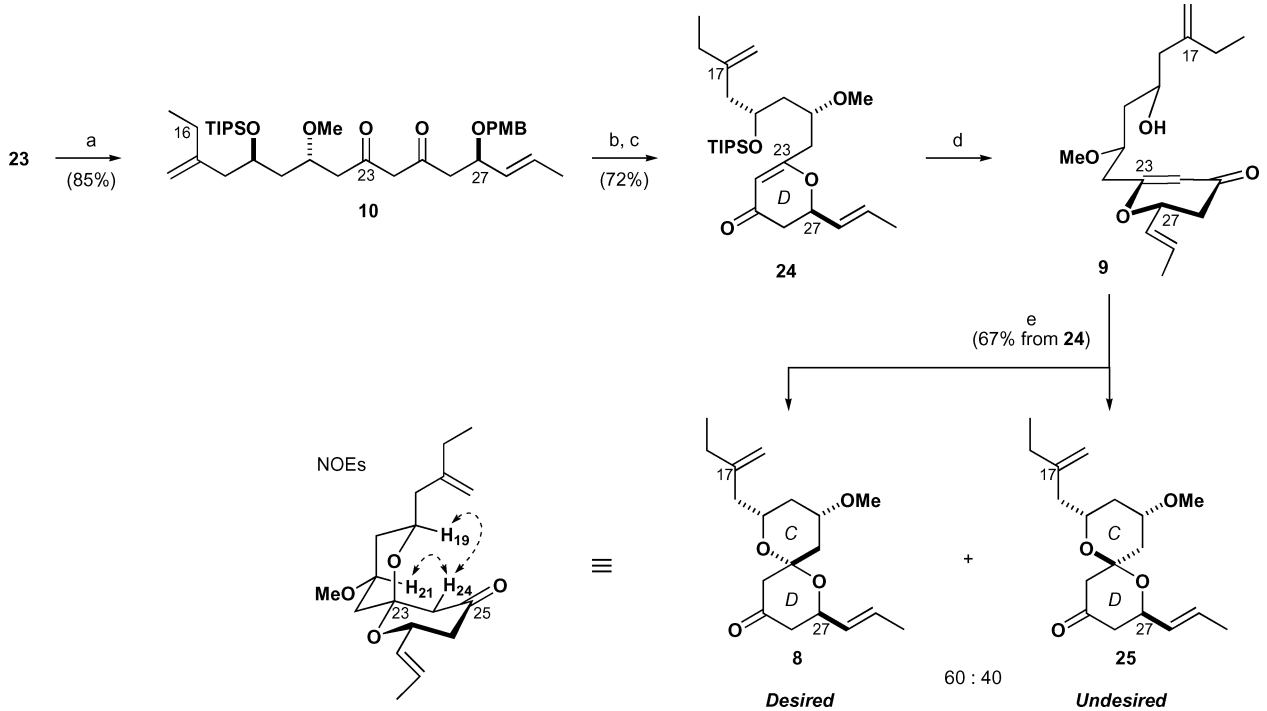
C23 stereocentre is destroyed in the subsequent oxidation of **23**, we decided to further investigate this intriguing case of remote asymmetric induction.

Careful examination of a range of substrates revealed that the boron-mediated aldol reaction of β-alkoxy methyl ketones with simple, achiral aldehydes is highly 1,5-*anti* diastereoselective, particularly when PMB protection of the β-oxygen is utilised.[16] The level of 1,5-induction obtained in these aldol reactions roughly correlated with the steric demand of the aldehyde, where an increase in selectivity was observed on going from acetaldehyde to isobutyraldehyde. Furthermore, enhanced diastereoselectivities were obtained by the use of matched aldol reactions, employing Ipc_2BCl with the appropriate Ipc ligand chirality. In contrast, methyl ketones containing a β-*tert*-butyldimethylsiloxy substituent provided aldol adducts with greatly reduced stereoselectivity (42 : 58–77 : 23 dr). The discovery and development of this remarkably stereoselective subset of methyl ketone aldol reactions proved greatly advantageous in the spongistatin total synthesis and in other total synthesis efforts within our laboratory.[17] Similar results have been reported by Evans and co-workers.[18]

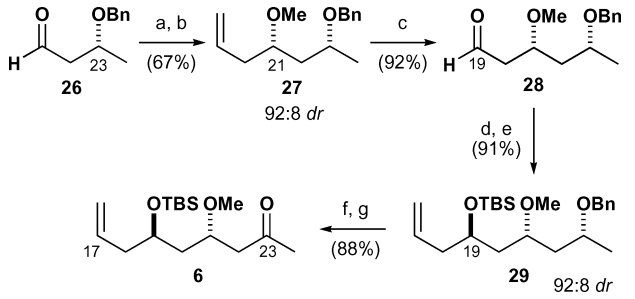
Oxidation of aldol adduct **23** to β-diketone **10** was achieved in 85% yield using the Dess–Martin periodinane (Scheme 6). Removal of the PMB protecting group was followed by dehydrative cyclisation (PPTS, CD_2Cl_2) to give the D-ring dihydropyranone **24** in 72% yield from **10**. Desilylation with HF–pyridine, with concomitant spiroacetalisation, provided only the *undesired* spiroacetal **25**, where presumably acetal equilibration occurred under the reaction conditions. Gratifyingly, treatment of **24** with TMSOTf (CH_2Cl_2, −78 °C, 15 min) allowed isolation of the intermediate alcohol **9**. While strong bases such as KO*t*–Bu also led to the exclusive formation of the undesired spiroacetal **25**, under mild, basic conditions (DBU, CH_2Cl_2, 16 h), **9** underwent intramolecular hetero-Michael reaction to install the C-ring, leading to a small preference (60 : 40) for formation of the *desired*, less stable,[19] spiroacetal **8** over **25**. In both these cases, the stereochemistry was unambiguously determined by extensive NOE studies.

Formation of the CD-spiroacetal under thermodynamic control

Our first reported synthesis of the CD-spiroacetal subunit of the spongipyrans was performed under thermodynamic control, where this involved the use of Brown asymmetric allylations and a fully matched boron-mediated aldol reaction to establish the oxygen-bearing stereocentres.[2d] Minor changes were made to this previously reported route, in order to maximise convergency. The improved thermodynamic route to the CD-spiroacetal started with aldehyde **26**, readily available in enantiomerically pure form in three steps from the biopolymer poly[(*R*)-3-hydroxybutyric acid] (PHB).[20] Although the C23 stereogenic centre is lost in a subsequent oxidation step, the use of enantiomerically pure **26** simplified spectroscopic analysis of subsequent intermediates retaining the C23 stereocentre and facilitated separation of minor diastereomeric components of mixtures. Brown asymmetric allylation of **26** using $^{d}Ipc_2BAll$ provided the desired homoallylic alcohol as the major diastereomer (92 : 8 dr), which was converted into the methyl ether **27** (NaH, MeI) in 67% yield over two steps (Scheme 7). Ozonolytic cleavage of the alkene unit in **27** provided aldehyde **28**, which



Scheme 6 *Reagents and conditions*: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (b) DDQ, 10 : 1 CH_2Cl_2–pH 7 buffer, rt, 1 h; (c) PPTS, CD_2Cl_2, rt, 7 d; (d) TMSOTf, CH_2Cl_2, −78 °C, 15 min; (e) DBU, CH_2Cl_2, rt, 16 h.



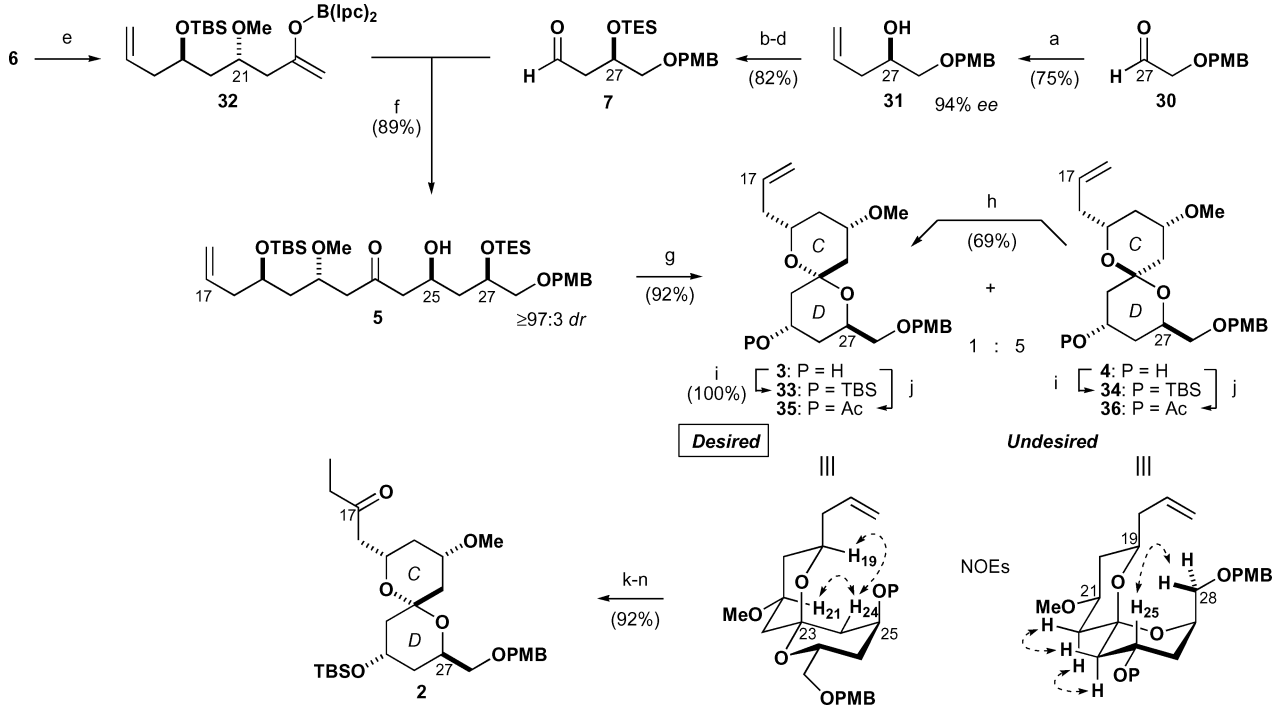
Scheme 7 *Reagents and conditions*: (a) (−)-Ipc$_2$BOMe, H$_2$C=CHCH$_2$-MgBr, Et$_2$O, −78 → 0 °C 3 h, then H$_2$O$_2$, NaOH, H$_2$O, reflux, 16 h; (b) NaH, MeI, THF, 0 °C → rt, 16 h; (c) O$_3$, CH$_2$Cl$_2$, −78 °C then PPh$_3$, rt, 16 h; (d) (+)-Ipc$_2$BOMe, H$_2$C=CHCH$_2$MgBr, Et$_2$O, −78 → −20 °C 18 h, then H$_2$O$_2$, NaOH, H$_2$O, reflux, 20 h; (e) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 2 h; (f) LiDBB, THF, −78 °C, 1 h; (g) Dess–Martin periodinane, CH$_2$Cl$_2$, 0 °C → rt, 1.5 h.

was subjected to allylboration, this time with ^{l}Ipc$_2$BAll (92 : 8 dr). Protection of the resultant alcohol as the TBS ether afforded **29** in 91% yield from **28**. Debenzylation with lithium 4,4′-di(*tert*-butyl)biphenylide (LiDBB)[21] and oxidation of the resultant alcohol with the Dess–Martin periodinane provided ketone **6** (88% yield from **29**), ready for aldol coupling.

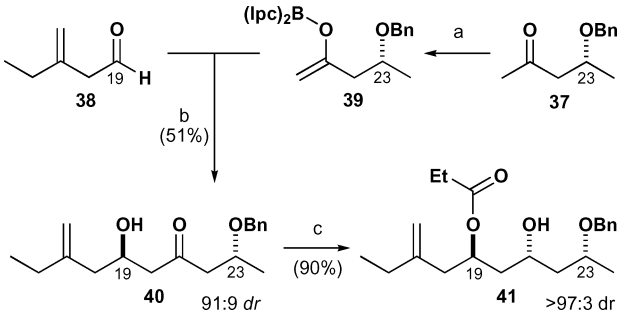
The synthesis of the C25–C28 aldehyde **7** began with the asymmetric allylboration of **30** (Scheme 8), employing *B*-allylbis(2-isocaranyl)borane (2-^{d}Icr$_2$BAll),[22] providing homoallylic alcohol **31** in 75% yield with high enantiomeric excess (94% ee by ^{1}H NMR of the derived MTPA esters). Protection of **31** as the TES ether and oxidative cleavage of the terminal alkene afforded aldehyde **7**. Treatment of methyl ketone **6** with (−)-Ipc$_2$BCl and Et$_3$N resulted in regioselective formation of enol borinate **32**, which underwent facile aldol union with aldehyde **7** to give the adduct **5** in 89% yield and with excellent diastereocontrol (≥97 : 3 dr). This pleasingly high level of diastereoselectivity results from triple asymmetric induction,[23] where the stereodirecting influence of all three chiral components (aldehyde, ketone and boron reagent) are matched. Treatment of **5** with 40% aqueous HF in MeCN effected bis-desilylation with concomitant spiroacetal formation, to yield a *ca.* 5 : 1 mixture of the undesired and desired spiroacetals, **4** and **3**, respectively (92% combined yield). Derivatisation of the C25 hydroxyl as the TBS ether (**33** and **34**) or acetate (**35** and **36**), facilitated chromatographic separation and stereochemical assignment. Extensive NOE studies unambiguously demonstrated that the major diastereomer formed in the HF procedure was the *undesired* "axial–axial" spiroacetal **4**. In particular, NOEs were observed between the equatorial H24 and the axial H19 and H21 in the derivatives **33** and **35**, obtained from the minor spiroacetal **3**. These were absent in the corresponding derivatives **34** and **36**, obtained from the major spiroacetal **4**, which displayed a strong NOE between the axial H25 and both H28 protons. Diagnostic NOEs were observed around the C-ring in all cases, confirming the stereochemical relationship between C19 and C21.

With the stereochemical assignment of spiroacetals **3** and **4** secure, we next focused our attention on procuring more useful quantities of the desired isomer **3**. Gratifyingly, acid-promoted equilibration in a less polar, aprotic solvent mixture (CH$_2$Cl$_2$–Et$_2$O), under carefully-controlled conditions so as to avoid competing decomposition, resulted in an equimolar mixture of **3** and **4**. Although spiroacetals **3** and **4** were separable by HPLC, purification was more readily achieved on up to a gram scale by careful, gradient elution column chromatography. Through five cycles of this equilibration–separation procedure, the desired spiroacetal **3** was isolated in 69% yield.

Further elaboration of the desired TBS protected spiroacetal **33** to the fully functionalised C16–C28 CD-spiroacetal ketone **2** was readily achieved by oxidative cleavage of the alkene moiety (cat. OsO$_4$, NMO; NaIO$_4$), addition of EtMgBr to the resultant aldehyde and oxidation with the Dess–Martin periodinane (92% yield from **33**). This synthetic route to the CD-spiroacetal subunit **2** of the spongipyrans proved robust and readily scalable, affording multi-gram quantities of **2** in a single campaign.



Scheme 8 *Reagents and conditions*: (a) 2-^{d}Icr$_2$BOMe, H$_2$C=CHCH$_2$MgBr, Et$_2$O, −78 °C, 4 h, then H$_2$O$_2$, NaOH, H$_2$O, rt, 3 d; (b) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 2 h; (c) cat. OsO$_4$, NMO, acetone–H$_2$O, rt, 3 d; (d) NaIO$_4$, MeOH, pH 7 buffer, 0 °C → rt, 16 h; (e) (−)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, −78 → 0 °C, 1 h; (f) **7**, −78 → −20 °C, 16 h, then pH 7 buffer, H$_2$O$_2$, MeOH, 0 °C → rt, 1 h; (g) 40% aq. HF, MeCN, 0 °C, 50 min; (h) cat. HCl, CH$_2$Cl$_2$, Et$_2$O, rt, 30 min, separation and resubjection (x 5); (i) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 1 h; (j) Ac$_2$O, DMAP, pyridine, rt, 2 h; (k) cat. OsO$_4$, NMO, acetone–H$_2$O, rt, 20 h; (l) NaIO$_4$, MeOH, pH 7 buffer, rt, 1 h; (m) EtMgBr, Et$_2$O, −78 °C → rt, 2 h; (n) Dess–Martin periodinane, CH$_2$Cl$_2$, rt, 1 h.



Scheme 9 *Reagents and conditions*: (a) (+)-Ipc_2BCl, Et_3N, Et_2O, −78 → 0 °C, 1 h; (b) **38**, −78 → −20 °C, 17 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 1 h; (c) cat. SmI_2, EtCHO, THF, −20 °C, 16 h.

An alternative route to the CD-spiroacetal

An alternative synthetic strategy[2g] for building up the linear CD-spiroacetal precursor arose from our desire to harness the stereocentre derived from the biopolymer PHB and the new options for stereocontrolled 1,3-polyol synthesis afforded by the 1,5-*anti* aldol reaction. This approach began with the boron-mediated aldol reaction of ketone **37**, readily available in four steps from PHB, with aldehyde **38** (Scheme 9). Enolisation of **37** with (+)-Ipc_2BCl and Et_3N under standard conditions,[24] gave enol borinate **39** *in situ*, which underwent smooth aldol reaction with aldehyde **38** (prepared from 3-ethyl-3-buten-1-ol[25] by Dess–Martin oxidation), to afford the desired 1,5-*anti* aldol product **40** in 51% yield, with high diastereoselectivity (91 : 9 dr). The sense and extent of asymmetric induction in this aldol reaction was assessed by high field ^{1}H NMR analysis of the derived MTPA esters.[7] With the desired C19 stereochemistry secured, 1,3-*anti* selective reduction of the carbonyl group in **40** was required. To this end, Evans–Tishchenko reduction[26] using catalytic SmI_2 and propionaldehyde provided monoacylated *anti* 1,3-diol **41** in 90% yield as the only diastereomer by ^{1}H NMR (>97 : 3 dr).

Methylation of the C21 hydroxyl in **41**, under mild conditions (Me_3OBF_4, Proton-Sponge®, CH_2Cl_2, 0 °C),[27] was followed by a protecting group swap at the C19 oxygen, to give TBS ether **42** (Scheme 10). Debenzylation and oxidation with the Dess–Martin periodinane provided ketone **43** (96% yield from **42**), homologous with **6**.

Conversion of ketone **43** into enol borinate **44**, and subsequent aldol reaction with aldehyde **7**, provided **45** in 78% yield and with similarly high diastereoselectivity (≥97 : 3 dr), as for the previously-exploited case using ketone **6**. The remainder of this alternative synthesis of the CD-spiroacetal proceeded in an analogous manner to the thermodynamic approach reported above, *via* desilylation–spiroacetalisation (aq. HF, MeCN) to give a *ca.* 5 : 1 mixture of the undesired and desired spiroacetals, **46** and **47**, respectively. As before, treatment with anhydrous HCl in CH_2Cl_2–Et_2O afforded an equimolar mixture of the two, separable, spiroacetals. Protection of **47** as the TBS ether and oxidative cleavage of the alkene moiety (cat. OsO_4, NMO; $NaIO_4$) provided the CD-spiroacetal subunit **2**, having identical spectroscopic properties to material produced by the previous route.

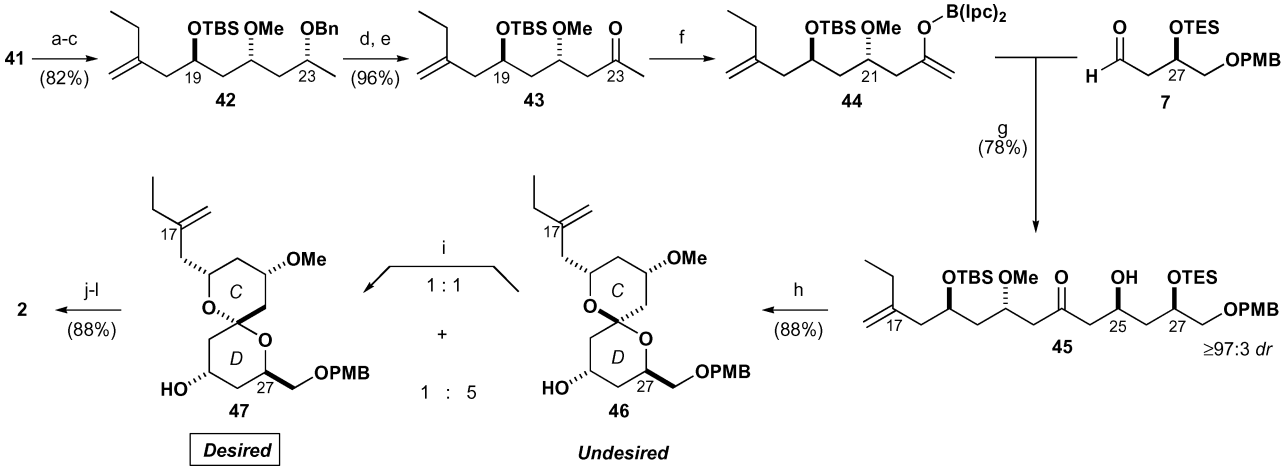
Conclusions

The synthesis of the C16–C28 CD-spiroacetal of the spongipyrans has been achieved by routes involving kinetic and thermodynamic control over the spiroacetalisation process. The thermodynamic control route proved the more practical and useful of the two approaches, due to the readily separable nature of the spiroacetal epimers **3** and **4**, and the robust, reliable and highly selective nature of the reactions utilised in this sequence. The latter route provided gram quantities of **2** for the successful completion of the total synthesis of altohyrtin A/spongistatin 1, as described in Parts 3 and 4 of this series.[28]

Experimental

(4*S*,6*R*)-6-Benzyloxy-1-hepten-4-ol

A cooled (−78 °C) solution of (−)-Ipc_2BOMe (22.8 g, 72.0 mmol, 1.5 eq.) in Et_2O (200 mL) was treated with allylmagnesium bromide (1.0 M in Et_2O, 67.2 mL, 67.2 mmol, 1.4 eq.). The cooling bath was removed and the mixture left to stir at rt for 1 h. The white suspension was re-cooled to −78 °C and a solution of (*R*)-3-benzyloxybutanal (**26**)[29] (48.0 mmol) in Et_2O (20 mL + 2 × 5 mL washings) was added by cannula. The mixture was left to stir at −78 °C for 2 h followed by 1 h at 0 °C. To the vigorously stirred mixture was cautiously added a pre-mixed solution of 10% NaOH (30 mL) and 30% H_2O_2 (60 mL) by dropping funnel. The resultant biphasic mixture was refluxed for 16 h. H_2O (200 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (5 : 95 Et_2O–CH_2Cl_2) to give a colourless oil (32 g), consisting of the homoallylic alcohol and IpcOH, which was used directly in the next reaction. In other experiments, repeated flash chromatography (5 : 95 Et_2O–CH_2Cl_2) gave the



Scheme 10 *Reagents and conditions*: (a) Me_3OBF_4, Proton-Sponge®, CH_2Cl_2, 0 °C, 3 h; (b) K_2CO_3, MeOH, rt, 16 h; (c) TBSCl, Im., DMF, rt, 16 h; (d) LiDBB, THF, −78 °C, 1 h; (e) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 40 min; (f) (−)-Ipc_2BCl, Et_3N, Et_2O, −78 → 0 °C, 1 h; (g) **7**, −78 → −20 °C, 16 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 1 h; (h) 40% aq. HF, MeCN, 0 °C, 40 min; (i) cat. HCl, CH_2Cl_2, Et_2O, rt, 30 min; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; (k) cat. OsO_4, NMO, acetone–H_2O, rt, 6 h; (l) $NaIO_4$, MeOH, pH 7 buffer, rt, 1 h.

title compound, sufficiently pure for characterisation purposes. Major diastereomer: R_f: 0.30 (5 : 95 Et_2O–CH_2Cl_2); $[\alpha]_D^{20}$ −55.8 (*c* 1.56, $CHCl_3$); IR (liquid film): 3443 (br, s), 1641 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.26–7.36 (5H, m, *Ph*), 5.83 (1H, m, 19-C*H*), 5.09 (1H, dd, $J = 18.8$, 1.6 Hz, *trans*-CH=CH_aH_b), 5.08 (1H, dd, $J = 9.3$, 0.8 Hz, *cis*-CH=CH_aH_b), 4.67 (1H, d, $J =$ 11.4 Hz, OCH_aH_bPh), 4.44 (1H, d, $J = 11.4$ Hz, OCH_aH_bPh), 3.78–3.89 (2H, m, 21-C*H* + 23-C*H*), 3.63 (1H, br s, O*H*), 2.21 (2H, m, 20-CH_2), 1.68 (1H, app dt, $J = 14.6$, 9.5 Hz, 22-CH_aH_b), 1.61 (1H, app dt, $J = 14.6$, 3.1 Hz, 22-CH_aH_b), 1.25 (3H, d, $J = 6.0$ Hz, 24-CH_3); ^{13}C NMR: δ (62.9 MHz, $CDCl_3$) 138.1, 135.0, 128.5, 127.81, 127.77, 117.3, 75.8, 70.9, 70.3, 43.2, 42.1, 19.7; HRMS: (+CI, NH_3) Calc. for $C_{14}H_{21}O_2$ $[MH]^+$: 221.1542, found: 221.1541; *m/z*: (+CI, NH_3) 221 ($[MH]^+$, 100), 179 (7), 130 (68), 108 (100), 106 (69), 91 (57).

(4*S*,6*R*)-6-Benzyloxy-4-methoxy-1-heptene (27)

NaH (60% in mineral oil, 15.4 g, 0.385 mol) was washed with *n*-hexane (3 × 50 mL) and suspended in THF (200 mL). The suspension was cooled to 0 °C and a solution of (4*S*,6*R*)-6-benzyloxy-1-hepten-4-ol (from above procedure, *ca.* 48.0 mmol) in THF (30 mL + 2 × 10 mL washings) was added *via* cannula. After stirring for 10 min at 0 °C, MeI (21.5 mL, 0.346 mol) was added and the mixture left to warm slowly to rt overnight. The reaction was quenched by the cautious addition of MeOH (100 mL) at 0 °C followed by H_2O (150 mL) and Et_2O (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with 10% $Na_2S_2O_3$ (150 mL) then brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (80 : 20 CH_2Cl_2–hexanes) removed the IpcOMe. Further flash chromatography (2 : 78 : 20 Et_2O–CH_2Cl_2–hexanes) allowed separation of the diastereomeric methyl ethers, providing the undesired 21-*epi*-**27** (0.45 g, 4%) and desired methyl ether **27** (7.10 g, 63% from **26**): R_f: 0.45 (5 : 95 Et_2O–CH_2Cl_2); $[\alpha]_D^{20}$ −6.3 (*c* 2.24, $CHCl_3$); IR (liquid film): 1640 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.25–7.35 (5H, m, *Ph*), 5.81 (1H, m, 19-C*H*), 5.06 (2H, app d, $J =$ 13.4 Hz, CH=CH_2), 4.57 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 4.44 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 3.66 (1H, m, 23-C*H*), 3.38 (1H, m, 21-C*H*), 3.33 (3H, s, OCH_3), 2.26 (2H, m, 20-CH_2), 1.93 (1H, app dt, $J = 14.1$, 6.7 Hz, 22-CH_aH_b), 1.53 (1H, app dt, 14.1, 6.2 Hz, 22-CH_aH_b), 1.23 (3H, d, $J = 6.1$ Hz, 24-CH_3); ^{13}C NMR: δ (62.9 MHz, $CDCl_3$) 139.0, 134.6, 128.3, 127.7, 127.4, 117.1, 77.5, 72.1, 70.3, 56.4, 40.6, 37.7, 19.7; HRMS: (+CI, NH_3) Calc. for $C_{15}H_{23}O_2$ $[MH]^+$: 235.1698, found: 235.1698; *m/z*: (+CI, NH_3) 235 ($[MH]^+$, 100), 203 (8), 108 (22), 106 (11), 91 (16).

(4*R*,6*S*,8*R*)-8-Benzyloxy-6-methoxy-1-nonen-4-ol

A cooled (−78 °C) solution of (+)-Ipc_2BOMe (4.10 g, 13.0 mmol, 1.9 eq.) in Et_2O (80 mL) was treated with allylmagnesium bromide (1.0 M in Et_2O, 11.5 mL, 11.5 mmol, 1.7 eq.). The cooling bath was removed and the mixture left to stir at rt for 1 h. The white suspension was re-cooled to −78 °C and a solution of aldehyde **28** (1.64 g, 6.94 mmol) in Et_2O (10 mL + 2 × 5 mL washings) was added by cannula. The mixture was left to stir at −78 °C for 2 h followed by 16 h at −20 °C. A solution of 10% NaOH (10 mL) and 30% H_2O_2 (20 mL) was added to the stirred solution at 0 °C and the resultant biphasic mixture refluxed for 20 h. H_2O (20 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (30 : 70 EtOAc–hexanes) to produce the title compound (2.15 g, contaminated with IpcOH) as a colourless oil, used without further purification in the next reaction. A small portion was further purified, for characterisation purposes, by repeated flash chromatography (30 : 70 EtOAc–hexanes). Major diastereomer: R_f: 0.32 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −40.5 (*c* 2.19, $CHCl_3$); IR (liquid film): 3389 (br, s), 1641, 1603 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.25–7.37 (5H, m, *Ph*), 5.80 (1H, m, 17-C*H*), 5.10 (1H, d, $J = 18.6$ Hz, *trans*-CH=CH_aH_b), 5.08 (1H, d, $J = 8.6$ Hz, *cis*-CH=CH_aH_b), 4.57 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 4.41 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 3.91 (1H, m, 19-C*H*), 3.68 (1H, m, 23-C*H*), 3.59 (1H, m, 21-C*H*), 3.34 (3H, s, OCH_3), 2.89 (1H, d, $J = 3.2$ Hz, O*H*), 2.19 (2H, m, 18-CH_2), 2.04 (1H, m, 20-CH_aH_b), 1.67 (1H, m, 20-CH_aH_b), 1.53 (2H, m, 22-CH_2), 1.24 (3H, d, $J = 6.1$ Hz, 24-CH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 138.7, 134.9, 128.4, 127.8, 127.5, 117.4, 76.5, 71.8, 70.3, 68.0, 56.0, 42.2, 40.2, 38.9, 19.9; HRMS: (+CI, NH_3) Calc. for $C_{17}H_{27}O_3$ $[MH]^+$: 279.1960, found: 279.1960; *m/z*: (+CI, NH_3) 279 ($[MH]^+$, 100), 254 (14), 222 (23), 171 (12), 114 (30), 108 (13), 106 (11), 97 (40).

(4*R*,6*R*,8*R*)-8-Benzyloxy-4-(*t*-butyldimethylsiloxy)-6-methoxy-1-nonene (29)

A cooled (−78 °C) solution of the alcohol from the above procedure (2.05 g, 7.36 mmol), in CH_2Cl_2 (60 mL) was treated with 2,6-lutidine (2.6 mL, 22.5 mmol, 3.0 eq.) followed by TBSOTf (3.4 mL, 14.8 mmol, 2.0 eq.). After stirring at −78 °C for 2 h the reaction was quenched by the addition of sat. $NaHCO_3$ (20 mL) and warmed to rt. The mixture was concentrated *in vacuo* and Et_2O (20 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography (8 : 92 EtOAc–hexanes) to yield silyl ether **29** (2.36 g, 91% over 2 steps from **28**) as a colourless oil. Major diastereomer: R_f: 0.36 (10 : 90 EtOAc–hexanes); $[\alpha]_D^{20}$ −46.1 (*c* 1.39, $CHCl_3$); IR (liquid film): 1640 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.25–7.36 (5H, m, *Ph*), 5.81 (1H, m, 17-C*H*), 5.03 (1H, d, $J = 15.2$ Hz, *trans*-CH=CH_aH_b), 5.03 (1H, d, $J = 12.2$ Hz, *cis*-CH=CH_aH_b), 4.56 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 4.45 (1H, d, $J = 11.7$ Hz, OCH_aH_bPh), 3.96 (1H, m, 19-C*H*), 3.60 (1H, m, 23-C*H*), 3.57 (1H, m, 21-C*H*), 3.29 (3H, s, OCH_3), 2.23 (2H, m, 18-CH_2), 2.00 (1H, ddd, $J = 14.1$, 7.5, 5.3 Hz, 20-CH_aH_b), 1.49–1.60 (2H, m, 22-CH_2), 1.43 (1H, ddd, $J = 14.1$, 7.0, 5.2 Hz, 20-CH_aH_b), 1.21 (3H, d, $J = 6.0$ Hz, 24-CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, Si(CH_3)$_a$), 0.07 (3H, s, Si(CH_3)$_b$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 138.9, 134.7, 128.3, 127.6, 127.3, 117.0, 74.4, 71.9, 70.3, 68.4, 55.5, 42.7, 41.9, 40.8, 25.9, 20.0, 18.1, −4.1, −4.6; HRMS: (+CI, NH_3) Calc. for $C_{23}H_{41}O_3Si$ $[MH]^+$: 393.2825, found: 393.2825; *m/z*: (+CI, NH_3) 393 ($[MH]^+$, 100), 263 (16), 261 (11), 229 (19), 132 (24), 108 (50), 106 (67), 91 (32).

(2*R*,4*R*,6*R*)-6-(*t*-Butyldimethylsiloxy)-4-methoxy-8-nonen-2-ol

To a solution of benzyl ether **29** (6.58 g, 16.8 mmol) in degassed THF (30 mL) at −78 °C was added LiDBB[21] (0.5 M, 80 mL, 40 mmol, 2.4 eq.) *via* cannula. The reaction was monitored by TLC to ensure complete consumption of starting material. After 1 h, the reaction was quenched by the addition of sat. $NaHCO_3$ (50 mL) and warmed to rt. H_2O (20 mL) and Et_2O (50 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography (5 : 95 → 25 : 75 EtOAc–hexanes) to afford the title compound (4.83 g, 95%), as a colourless oil: R_f: 0.35 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −12.8 (*c* 2.30, $CHCl_3$); IR (liquid film): 3442 (br, s), 1641 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 5.81 (1H, m, 17-C*H*), 5.07 (1H, d, $J = 15.9$ Hz, *cis*-CH=CH_aH_b), 5.06 (1H, d, $J = 11.5$ Hz, *trans*-CH=CH_aH_b), 3.95 (1H, m, 23-C*H*), 3.85 (1H, m, 19-C*H*), 3.53 (1H, m, 21-C*H*), 3.33 (3H, s, OCH_3), 3.12

(1H, s, O*H*), 2.23 (2H, m, 18-CH_2), 1.77 (1H, ddd, J = 14.3, 8.4, 6.0 Hz, 20-CH_aH$_b$), 1.65 (1H, app dt, J = 15.5, 8.8 Hz, 22-CH_aH$_b$), 1.56 (1H, m, 22-CH$_a$$H_b$), 1.50 (1H, ddd, J = 14.3, 8.0, 6.0 Hz, 20-CH$_a$$H_b$), 1.18 (3H, d, J = 6.2 Hz, 24-CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, Si(CH_3)$_a$), 0.07 (3H, s, Si(CH_3)$_b$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 134.4, 117.3, 78.6, 69.2, 67.3, 55.5, 43.2, 42.4, 41.1, 25.9, 23.7, 18.0, −4.2, −4.6; HRMS: (+CI, NH_3) Calc. for $C_{16}H_{35}O_3Si$ [MH]$^+$: 303.2355, found: 303.2355; m/z: (+CI, NH_3) 303 ([MH]$^+$, 100), 187 (11), 171 (13), 139 (19), 132 (25), 92 (13).

(4*S*,6*R*)-6-(*t*-Butyldimethylsiloxy)-4-methoxy-8-nonen-2-one (6)

To a solution of the alcohol from the above procedure (4.50 g, 14.9 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added Dess–Martin periodinane (7.60 g, 17.9 mmol, 1.2 eq.). The white suspension was warmed to rt and stirred, open to the atmosphere, for 90 min. The reaction was quenched by the addition of sat. $NaHCO_3$ (100 mL) followed by 10% $Na_2S_2O_3$ (100 mL) and the biphasic mixture allowed to stir vigorously for 1 h. The CH_2Cl_2 was removed *in vacuo*, Et_2O (100 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (20 : 80 EtOAc–hexanes) afforded ketone **6** (4.15 g, 93%) as a colourless oil. Major diastereomer: R_f: 0.44 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −34.1 (*c* 1.40, $CHCl_3$); IR (liquid film): 1715 (s), 1640 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 5.79 (1H, m, 17-C*H*), 5.03 (2H, app d, 13.3 Hz, CH=CH_2), 3.92 (1H, m, 19-C*H*), 3.83 (1H, m, 21-C*H*), 3.30 (3H, s, OCH_3), 2.70 (1H, dd, J = 15.6, 6.4 Hz, 22-CH_aH$_b$), 2.49 (1H, dd, J = 15.6, 5.8 Hz, 22-CH$_a$$H_b$), 2.24 (2H, br t, J = 6.2 Hz, 18-CH_2), 2.16 (3H, s, 24-CH_3), 1.65 (1H, ddd, J = 14.2, 8.6, 3.3 Hz, 20-CH_aH$_b$), 1.43 (1H, ddd, J = 14.2, 8.8, 3.9 Hz, 20-CH$_a$$H_b$), 0.90 (9H, s, SiC(C$H_3$)$_3$), 0.08 (6H, s, Si(C$H_3$)$_2$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 207.2, 134.4, 117.2, 74.0, 68.6, 56.3, 48.5, 42.6, 41.9, 30.8, 25.9, 18.0, −4.1, −4.7; HRMS: (+CI, NH_3) Calc. for $C_{16}H_{33}O_3Si$ [MH]$^+$: 301.2199, found: 301.2199; m/z: (+CI, NH_3) 301 ([MH]$^+$, 100), 169 (37), 154 (34), 138 (40), 137 (40), 121 (100), 52 (80).

(*R*)-1-(*p*-Methoxybenzyloxy)-4-penten-2-ol (31)

To a cold (−78 °C), stirred solution of 2-^{d}Icr$_2$BOMe[22] (3.0 g, 9.48 mmol, 1.7 eq.) in dry Et_2O (20 mL) was added, dropwise, allylmagnesium bromide (1.0 M solution in Et_2O, 8.3 mL, 8.30 mmol, 1.5 eq.). The solution was stirred at −78 °C for 15 min and then warmed to rt for 75 min. The resultant white suspension was cooled to −78 °C and a solution of the aldehyde **30** (1.0 g, 5.55 mmol, 1.0 eq.) in dry Et_2O (2 mL + 2 × 2 mL washings) was added *via* cannula. The mixture was stirred at −78 °C for 4 h and then quenched with 3 M aqueous NaOH (8 mL) and 30% aqueous H_2O_2 (11 mL). The biphasic solution was stirred at rt for 3 d (reflux conditions were avoided to suppress the decomposition of the PMB–ether functionality). The layers were then separated and the aqueous phase extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil thus obtained was flash chromatographed (20 : 80 EtOAc–hexanes) to provide the homoallylic alcohol **31** (928 mg, 75%), as a colourless oil: R_f: 0.35 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −3.0 (*c* 2.06, $CHCl_3$); IR (liquid film): 3443 (br, s), 1641, 1612, 1513 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.26 (2H, d, J = 8.5 Hz, Ar*H*), 6.89 (2H, d, J = 8.5 Hz, Ar*H*), 5.78–5.86 (1H, m, 25-C*H*), 5.08–5.13 (2H, m, C=CH_2), 4.49 (2H, s, OCH_2Ar), 3.83–3.89 (1H, m, 27-C*H*), 3.81 (3H, s, OCH_3), 3.49 (1H, dd, J = 9.3, 3.3 Hz, 28-CH_aH$_b$), 3.35 (1H, dd, J = 9.3, 7.6 Hz, 28-CH$_a$$H_b$), 2.31 (1H, d, J = 3.1 Hz, O*H*), 2.25 (2H, t, J = 6.6 Hz, 26-CH_2); ^{13}C NMR: δ (62.9 MHz, $CDCl_3$) 159.3, 134.3, 130.1, 129.4, 117.6, 113.9, 73.6, 73.0, 69.7, 55.3, 37.2; HRMS: (+CI, NH_3) Calc. for $C_{13}H_{19}O_3$ [MH]$^+$: 223.1334, found: 223.1334.

(2*R*,4*S*,8*S*,10*R*)-10-(*t*-Butyldimethylsiloxy)-4-hydroxy-8-methoxy-1-(*p*-methoxybenzyloxy)-2-(triethylsiloxy)-12-tridecen-6-one (5)

A two-necked flask containing (−)-Ipc$_2$BCl (1.48 g, 4.62 mmol, 1.3 eq.) was placed under vacuum for 1 h to remove any traces of HCl. The flask was charged with argon and Et_2O (20 mL) was added. The solution was cooled to −78 °C and Et_3N (0.743 mL, 5.33 mmol, 1.5 eq.) was added, followed by a solution of ketone **6** (1.07 g, 3.55 mmol) in Et_2O (10 mL + 2 × 5 mL washings) *via* cannula. The reaction mixture was allowed to warm to 0 °C and stirred for a further 1 h. The reaction mixture was then cooled to −78 °C before a solution of aldehyde **7** (1.36 g, 4.01 mol, 1.13 eq.) in Et_2O (10 mL + 2 × 5 mL washings) was added *via* cannula. The reaction 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 (20 mL), MeOH (20 mL) and 30% H_2O_2 (10 mL) at 0 °C and allowed to warm to rt and stirred vigorously for 1 h. The reaction mixture was diluted with water (50 mL) and CH_2Cl_2 (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (1 : 99 → 10 : 90 Et_2O–CH_2Cl_2) afforded aldol product **5** (2.01 g, 89%) as colourless oil: R_f: 0.35 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −7.0 (*c* 0.90, $CHCl_3$); IR (liquid film): 3676 (br), 1734 (s), 1639, 1612 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.24 (2H, d, J = 8.6 Hz, Ar*H*), 6.87 (2H, d, J = 8.6 Hz, Ar*H*), 5.80 (1H, m, 17-C*H*), 5.03 (1H, d, J = 15.2 Hz, *trans*-CH=CH_aH$_b$), 5.03 (1H, d, J = 12.1 Hz, *cis*-CH=CH$_a$$H_b$), 4.44 (2H, ab q, J = 12.1 Hz, CH_2Ar), 4.23 (1H, m, 25-C*H*), 4.08 (1H, br dq, J = 7.2, 5.3 Hz, 27-C*H*), 3.88 (1H, m, 19-C*H*), 3.84 (1H, m, 21-C*H*), 3.80 (3H, s, ArOCH_3), 3.51 (1H, d, J = 2.1 Hz, O*H*), 3.40 (1H, dd, J = 9.7, 5.2 Hz, 28-CH_aH$_b$), 3.36 (1H, dd, J = 9.7, 5.2 Hz, 28-CH$_a$$H_b$), 3.29 (3H, s, OC$H_3$), 2.70 (1H, dd, J = 15.8, 6.5 Hz, 22-CH_aH$_b$), 2.60 (1H, dd, J = 16.7, 7.9 Hz, 24-CH_aH$_b$), 2.52 (1H, dd, J = 16.7, 4.3 Hz, 24-CH$_a$$H_b$), 2.49 (1H, dd, J = 15.8, 5.5 Hz, 22-CH$_a$$H_b$), 2.22 (2H, br t, J = 6.1 Hz, 18-CH_2), 1.60–1.72 (3H, m, 26-CH_2 + 20-CH_aH$_b$), 1.42 (1H, ddd, J = 14.2, 8.7, 4.0 Hz, 20-CH$_a$$H_b$), 0.94 (9H, t, J = 8.0 Hz, Si(CH$_2$CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.61 (6H, q, J = 8.0 Hz, Si(CH_2CH3)$_3$), 0.08 (6H, s, Si(CH_3)$_2$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 209.0, 159.0, 134.5, 130.0, 129.3, 117.2, 113.8, 76.5, 74.2, 73.9, 73.0, 70.6, 68.6, 66.0, 56.5, 55.3, 50.9, 48.5, 42.5, 41.9, 41.1, 25.9, 18.0, 5.0, −4.1, −4.6; HRMS: (+CI, NH_3) Calc. for $C_{34}H_{63}O_7Si_2$ [MH]$^+$: 639.4112, found: 639.4110; m/z: (+CI, NH_3) 639 ([MH]$^+$, 10), 356 (100), 353 (60), 318 (68).

(2*R*,4*S*,6*R*,8*R*,10*S*)- and (2*R*,4*S*,6*S*,8*R*,10*S*)-8-Allyl-10-methoxy-2-(*p*-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-4-ol (4 and 3)

To a cold (0 °C) solution of ketone **5** (2.01 g, 3.15 mmol) in MeCN (50 mL) was added HF (40% aq., 12.0 mL). The reaction mixture was stirred at 0 °C for 50 min then cautiously quenched with sat. aq. $NaHCO_3$ (200 mL). EtOAc (100 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (50 : 50 → 80 : 20 EtOAc–light petroleum) afforded spiroacetals **3** and **4** (1.13 g, 92%) as a 1 : 5 mixture, respectively.

Minor spiroacetal (desired) **3**: R_f: 0.49 (5 : 95 MeOH–CH_2Cl_2); HPLC: R_t 35 min (65 : 35 EtOAc–hexane); $[\alpha]_D^{20}$ −37.4 (*c* 0.70, $CHCl_3$); IR (liquid film): 3525 (br, s), 3053, 1612, 1513 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.27 (2H, d, J = 8.6 Hz, Ar*H*), 6.89 (2H, d, J = 8.6 Hz, Ar*H*), 5.83 (1H, m, 17-C*H*), 5.17 (1H, d, J = 18.0 Hz, *trans*-CH=CH_aH$_b$), 5.14 (1H, d, J = 10.9 Hz, *cis*-CH=CH$_a$$H_b$), 4.53 (2H, s, OC$H_2$Ar), 4.43 (1H, m, 27-C*H*), 4.07 (1H, app dt, J = 8.3, 3.0 Hz, 25-C*H*), 3.81 (3H, s, ArOCH_3), 3.65 (1H, m, 19-C*H*), 3.50 (2H, m, 28-CH_2), 3.45 (1H, m, 21-C*H*), 3.33 (3H, s, OCH_3), 2.36 (1H, m, 18-CH_aH$_b$), 2.25–2.32 (2H, m,

18-CH_aH_b + 24-CH_{eq}), 2.10 (1H, app dd, J = 12.2, 4.4 Hz, 22-CH_{eq}), 2.05 (1H, app dt, J = 12.4, 2.0 Hz, 20-CH_{eq}), 1.77 (1H, dd, J = 13.7, 2.0 Hz, 26-CH_{eq}), 1.66 (1H, dt, J = 13.7, 2.8 Hz, 26-CH_{ax}), 1.41–1.48 (2H, m, 22-CH_{ax} + 24-CH_{ax}), 1.27 (1H, br q, J = 11.8 Hz, 26-CH_{ax}); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.1, 134.0, 130.3, 129.3, 118.8, 113.7, 99.8, 73.6, 72.9, 72.5, 71.0, 64.9, 64.7, 55.5, 55.2, 42.6, 40.6, 36.9, 34.4, 34.1; HRMS: (+CI, NH_3) Calc. for $C_{22}H_{36}NO_6$ [M + NH_4]$^+$: 410.2543, found: 410.2543; *m/z*: (+CI, NH_3) 410 ([M + NH_4]$^+$, 57), 393 ([MH]$^+$, 5), 378 (12), 361 (30), 343 (26), 154 (32), 138 (50), 121 (100).

Major spiroacetal (undesired) **4**: R_f: 0.16 (5 : 95 MeOH–CH_2Cl_2); HPLC: R_t 45 min (65 : 35 EtOAc–hexane); $[\alpha]_D^{20}$ +41.3 (*c* 0.90, $CHCl_3$); IR (liquid film): 3425 (br, s), 3073, 1641, 1612, 1586, 1513 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.5 Hz, Ar*H*), 6.88 (2H, d, J = 8.5 Hz, Ar*H*), 5.76 (1H, m, 17-C*H*), 5.07 (1H, dd, J = 17.5, 1.4 Hz, *trans*-CH=CH_aH_b), 5.03 (1H, d, J = 9.8 Hz, *cis*-CH=CH_aH_b), 4.50 (1H, d, J = 11.6 Hz, OCH_aH_bAr), 4.43 (1H, d, J = 11.6 Hz, OCH_aH_bAr), 4.17–4.22 (2H, m, 25-C*H* + 27-C*H*), 3.85 (1H, m, 19-C*H*), 3.81 (3H, s, ArOCH_3), 3.63 (1H, m, 21-C*H*), 3.58 (1H, dd, J = 9.7, 6.2 Hz, 28-CH_aH_b), 3.51 (1H, dd, J = 9.7, 4.0 Hz, 28-CH_aH_b), 3.32 (3H, s, OCH_3), 2.32 (1H, ddd, J = 12.7, 4.5, 1.9 Hz, 22-CH_{eq}), 2.26 (1H, m, 18-CH_aH_b), 2.18 (1H, m, 18-CH_aH_b), 2.00–2.07 (3H, m, 20-CH_{eq} + 24-CH_{eq} 26-CH_{eq}), 1.57 (1H, dt, J = 8.1, 3.7 Hz, 26-CH_{ax}), 1.52 (1H, app dd, J = 13.0, 9.3 Hz, 24-CH_{ax}), 1.21 (1H, br t, J = 12.0 Hz, 22-CH_{ax}), 1.03 (1H, br q, J = 11.7 Hz, 20-CH_{ax}); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.1, 134.4, 130.1, 129.2, 117.2, 113.7, 99.8, 72.7, 72.6, 71.7, 71.4, 68.5, 61.5, 55.4, 55.2, 44.8, 41.5, 40.5, 36.5, 34.7; HRMS: (+CI, NH_3) Calc. for $C_{22}H_{33}O_6$ [MH]$^+$: 393.2277, found: 393.2277; *m/z*: (+CI, NH_3) 410 ([M + NH_4]$^+$, 28), 393 ([MH]$^+$, 7), 378 (20), 361 (40), 343 (26), 154 (24), 138 (50) 121 (100).

Equilibration of the CD-spiroacetals (4 and 3)

To a mixture of spiroacetals **4** and **3** (1.69 g, 4.31 mmol) in CH_2Cl_2 (35 mL) was added anhydrous HCl (1.0 M in Et_2O, 0.216 mL, 0.216 mmol, 0.05 eq.). The reaction mixture was stirred at rt for 30 min then Et_3N (0.06 mL, 0.43 mmol) was added to neutralise the HCl. The mixture was concentrated *in vacuo* and flash chromatography (1.25 : 98.75 → 2.5 : 97.5 MeOH–CH_2Cl_2) allowed the separation of desired spiroacetal **3** and undesired spiroacetal **4**. The undesired spiroacetal **4** was re-subjected to the above conditions and after 5 cycles the desired spiroacetal **3** (1.17 g, 69%) was obtained as a colourless oil.

(2*R*,4*S*,6*R*,8*R*,10*S*)-1[10-(*t*-Butyldimethylsiloxy)-4-methoxy-8-(*p*-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-ethanal

A solution of alkene **33** (880 mg, 1.74 mmol) in 2.5 : 1 acetone (10 mL) and H_2O (4 mL) was treated with NMO (347 mg, 2.96 mmol, 1.7 eq.) and OsO_4 (0.1 M in *t*-BuOH, 0.87 mL, 0.087 mmol, 5 mol%) and the resultant mixture stirred at rt for 20 h. The remaining oxidant was quenched by the addition of 10% $Na_2S_2O_3$ (10 mL) and the mixture stirred for 40 min before the addition of Et_2O (10 mL) and separation of the layers. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic extracts were washed with brine (10 mL) and the brine was back-extracted with EtOAc (5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 2 : 1 MeOH (10 mL) and pH 7 buffer (5 mL). The resultant solution was treated with $NaIO_4$ (744 mg, 3.48 mmol, 2 eq.) and the mixture was allowed to stir at rt for 1 h. The mixture was concentrated *in vacuo* and H_2O (30 mL) was added to dissolve the precipitate. The solution was extracted with Et_2O (3 × 20 mL), the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4) and the mixture was filtered through a short pad of silica, washing with 50 : 50 EtOAc–hexanes (2 × 10 mL). The solvent was removed *in vacuo* to provide the title compound (875 mg, 99% from **33**) as a colourless oil: R_f: 0.39 (40 : 60 EtOAc–hexanes); $[\alpha]_D^{20}$ −8.2 (*c* 0.80, $CHCl_3$); IR (liquid film): 1724 (C=O), 1612, 1586, 1513 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 9.83 (1H, t, J = 1.8 Hz, 17-C*H*O), 7.25 (2H, d, J = 8.5 Hz, Ar*H*), 6.86 (2H, d, J = 8.5 Hz, Ar*H*), 4.50–4.53 (3H, m, OCH_2Ar + 27-C*H*), 4.15 (1H, m, 25-C*H*), 4.01 (1H, m, 19-C*H*), 3.80 (3H, s, ArOCH_3), 3.45–3.51 (3H, m, 28-CH_2 and 21-C*H*), 3.32 (3H, s, OCH_3), 2.74 (1H, ddd, J = 17.1, 6.3, 1,7 Hz, 18-CH_aH_b), 2.60 (1H, ddd, J = 17.1, 6.5, 1.7 Hz, 18-CH_aH_b), 2.03–2.20 (3H, m, 20-CH_{eq} + 24-CH_{eq} + 22-CH_{eq}), 1.68 (1H, td, J = 11.4, 3.4 Hz, 26-CH_{ax}), 1.59 (1H, m 26-CH_{eq}), 1.51 (1H, dd, J = 14.6, 3.9 Hz, 24-CH_{ax}), 1.36 (1H, t, J = 11.9 Hz, 22-CH_{ax}), 1.04 (1H, m, 20-CH_{ax}), 0.85 (9H, s, SiC(CH_3)$_3$), 0.03 (3H, s, Si(CH_3)$_a$), 0.01 (3H, s, Si(CH_3)$_b$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 201.4, 159.1, 130.5, 129.2, 113.7, 98.4, 73.7, 72.9, 72.6, 65.9, 64.9, 64.5, 55.5, 55.2, 49.8, 43.2, 37.2, 35.3, 35.0, 26.0, 18.4, −4.7, −5.0; HRMS: (+FAB) Calc. for $C_{27}H_{44}O_7NaSi$ [M + Na]$^+$: 531.2754, found: 531.2726; *m/z*: (+FAB) 531 ([M + Na]$^+$, 100), 387 (25), 241 (60), 201 (60).

(2*R*,4*S*,6*R*,8*R*,10*S*)-1-[10-(*t*-Butyldimethylsiloxy)-4-methoxy-8-(*p*-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-butan-2-one (2)

To a cold (−78 °C) solution of the aldehyde from the above procedure (1.56 g, 3.07 mmol), in Et_2O (40 mL) was added EtMgBr (2.0 M in THF, 3.07 mL, 6.13 mmol, 2.0 eq.). The reaction mixture was warmed to rt and stirred for 2 h then cooled to −78 °C before being quenched by addition of sat. aq. NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude alcohol was taken up in CH_2Cl_2 (30 mL) and Dess–Martin periodinane (2.60 g, 6.13 mmol, 2.0 eq.) was added. The reaction mixture was stirred at rt for 1 h and quenched by pouring into a sat. aq. $Na_2S_2O_3$–$NaHCO_3$ solution (1 : 1, 50 mL). The biphasic mixture was stirred for a further 15 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 60 mL), combined organics were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 50 : 50 EtOAc–light petroleum) afforded CD-spiroacetal ethyl ketone **2** (1.53 g, 93% over 2 steps) as a white crystalline solid: R_f: 0.45 (40 : 60 EtOAc–hexanes); $[\alpha]_D^{20}$ −20.3 (*c* 1.00, $CHCl_3$); mp 47–49 °C; IR (liquid film): 1713 (s), 1612, 1586, 1513 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.5 Hz, Ar*H*), 6.86 (2H, d, J = 8.5 Hz, Ar*H*), 4.51–4.52 (3H, m, OCH_2Ar + 28-C*H*), 4.11 (1H, m, 25-C*H*), 3.93 (1H, m, 19-C*H*), 3.80 (3H, s, ArOCH_3), 3.45–3.51 (3H, m, 27-CH_2 + 21-C*H*), 3.32 (3H, s, OCH_3), 2.84 (1H, dd, J = 17.1, 3.7 Hz, 18-CH_aH_b), 2.66 (1H, dd, J = 17.1, 8.9 Hz, 18-CH_aH_b), 2.40 (2H, q, J = 7.3 Hz, 16-CH_2), 2.21 (1H, m, 20-CH_{eq}), 2.13 (1H, dd, J = 14.3, 3.4 Hz, 24-CH_aH_b), 2.03 (1H, dd, J = 11.5, 3.8 Hz, 22-CH_{eq}), 1.68 (1H, td, J = 13.7, 3.6 Hz, 26-CH_{ax}), 1.59 (1H, m, 26-CH_{eq}), 1.50 (1H, dd, J = 14.3, 3.7 Hz, 24-CH_{ax}), 1.36 (1H, t, J = 11.9 Hz, 22-CH_{ax}), 1.04 (1H, m, 20-CH_{ax}), 1.01 (3H, t, J = 7.3 Hz, CH_2CH_3), 0.85 (9H, S, SiC(CH_3)$_3$), 0.03 (3H, s, Si(CH_3)$_a$), 0.01 (3H, s, Si(CH_3)$_b$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 209.3, 159.1, 130.5, 129.2, 113.7, 98.4, 73.9, 72.9, 72.6, 66.6, 65.1, 64.3, 55.6, 55.3, 48.6, 43.2, 37.0, 36.9, 35.5, 35.1, 25.9, 18.1, 7.7, −4.91, −4.95; HRMS: (+CI, NH_3) Calc. for $C_{29}H_{52}O_7NSi$ [M + NH_4]$^+$: 554.3513, found: 554.3510; *m/z*: (+CI, NH_3) 554 ([M + NH_4]$^+$, 48), 138 (60), 121 (100).

3-Ethyl-3-butenal (38)

To a cold (0 °C), stirred suspension of Dess–Martin periodinane (3.73 g, 8.79 mmol, 1.1 eq.) in CH_2Cl_2 (100 mL) was added a solution of 3-ethyl-3-buten-1-ol[25] (801 mg, 8.00 mmol) in CH_2Cl_2 (10 mL + 2 × 5 mL washings) *via* cannula. The cooling bath was removed and the reaction left at rt, open to the atmosphere

for 2.5 h. The mixture was cautiously concentrated *in vacuo* (bath temperature 0 °C), diluted with Et_2O (60 mL) and a 1 : 1 mixture of 10% $Na_2S_2O_3$ (50 mL) and sat. $NaHCO_3$ (50 mL) added. The biphasic mixture was left to stir vigorously for 1 h, the layers were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a plug of silica and the solution carefully concentrated *in vacuo* (bath temperature 0 °C). Aldehyde **38** was obtained as a concentrated solution (*ca.* 5 mL) in Et_2O, and used without further purification in the subsequent reaction: ^{1}H NMR: δ (250 MHz, $CDCl_3$) 9.65 (1H, t, $J = 2.6$ Hz, 19-C*H*O), 4.89 (1H, m, C=CH_aH_b), 4.84 (1H, m, C=CH$_a$$H_b$), 3.10 (2H, br d, $J = 2.0$ Hz, 18-CH_2), 2.09 (2H, br q, $J = 7.4$ Hz, 16-CH_2), 1.05 (3H, t, $J = 7.4$ Hz, CH_2CH_3).

(2*R*,6*R*)-2-Benzyloxy-8-ethyl-6-hydroxy-8-nonen-4-one (40)

A 100 mL, two-necked flask containing (+)-Ipc$_2$BCl (1.88 g, 5.85 mmol, 1.3 eq.) was placed under vacuum for 30 min to remove any traces of HCl. The flask was charged with argon and Et_2O (20 mL) was added. The solution was cooled to −78 °C and Et_3N (0.94 mL, 6.75 mmol, 1.5 eq.) was added, followed by a solution of ketone **37** (865 mg, 4.50 mmol) in Et_2O (3 mL + 2 × 1 mL washings) *via* cannula. The reaction was stirred for 1 h at 0 °C then re-cooled to −78 °C. Aldehyde **38** (in excess, from above procedure) in Et_2O (3 mL + 2 × 1 mL washings) was added *via* cannula and the reaction stirred at −78 °C for 90 min. The mixture was warmed to −20 °C and stored at this temperature for 16 h. The reaction was quenched by the addition of pH 7 buffer solution (3 mL), MeOH (3 mL) and 30% H_2O_2 solution (3 mL). The reaction was stirred at rt for 1 h, diluted with H_2O (30 mL), the layers were separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by flash chromatography (25 : 75 EtOAc–hexanes) to provide hydroxyketone **40** (660 mg, 51%, 91 : 9 dr by MTPA ester analysis) as a colourless oil: R_f: 0.36 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −38.2 (*c* 2.28, $CHCl_3$); IR (liquid film): 3453 (br, s), 1708 (s), 1645 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.26–7.34 (5H, m, *Ph*), 4.85 (1H, d, $J =$ 1.5 Hz, C=CH_aH_b), 4.78 (1H, d, $J = 0.7$ Hz, C=CH$_a$$H_b$), 4.56 (1H, d, $J = 11.5$ Hz, OCH_aH$_b$Ph), 4.43 (1H, d, $J = 11.5$ Hz, OCH$_a$$H_b$Ph), 4.20 (1H, m, 19-C*H*), 4.06 (1H, m, 23-C*H*), 2.81 (1H, s, O*H*), 2.80 (1H, dd, $J = 15.6$, 7.8 Hz, 22-CH_aH$_b$), 2.63 (1H, dd, $J = 17.4$, 3.2 Hz, 20-CH_aH$_b$), 2.53 (1H, dd, $J = 17.4$, 8.7 Hz, 20-CH$_a$$H_b$), 2.47 (1H, dd, $J = 15.6$, 5.0 Hz, 22-CH$_a$$H_b$), 2.22 (1H, dd, $J = 13.9$, 7.8 Hz, 18-CH_aH$_b$), 2.14 (1H, dd, $J =$ 13.9, 5.6 Hz, 18-CH$_a$$H_b$), 2.04 (2H, app q, 16-C$H_2$), 1.24 (3H, d, $J = 6.2$ Hz, 24-CH_3), 1.03 (3H, t, $J = 7.4$ Hz, CH_2CH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 210.1, 147.6, 138.3, 128.4, 127.8, 127.6, 111.1, 71.6, 70.9, 65.5, 50.6, 50.1, 43.6, 28.6, 19.8, 12.2.

(2*R*,4*R*,6*R*)-2-Benzyloxy-8-ethyl-6-propionoxy-8-nonen-4-ol (41)

EtCHO (3.0 mL, 42 mmol, 20 eq.) in THF (8 mL) at −20 °C was treated with SmI_2 (*ca.* 0.1 M in THF, 6.2 mL, 0.62 mmol, 0.3 eq.). After stirring for 10 min, a solution of hydroxyketone **40** (600 mg, 2.07 mmol) in THF (5 mL + 2 × 2 mL washings) was added *via* cannula, the mixture was allowed to warm to 0 °C, then left at −20 °C for 16 h. The reaction was quenched by the addition of sat. $NaHCO_3$ (10 mL), then diluted with H_2O (20 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude material by flash chromatography (20 : 80 EtOAc–hexanes) afforded propionate **41** (647 mg, 90%) as a colourless oil: R_f: 0.48 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −56.7 (*c* 1.71, $CHCl_3$); IR (liquid film): 3504 (br, s), 1736 (s), 1646 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.26–7.34 (5H, m, *Ph*), 5.24 (1H, m, 19-C*H*), 4.79 (1H, d, $J =$ 1.4 Hz, C=CH_aH_b), 4.74 (1H, br s, C=CH$_a$$H_b$), 4.62 (1H, d, $J =$ 11.6 Hz, OCH_aH$_b$Ph), 4.43 (1H, d, $J = 11.6$ Hz, OCH$_a$$H_b$Ph), 3.77 (1H, m, 23-C*H*), 3.72 (1H, m, 21-C*H*), 3.57 (1H, d, $J =$ 2.2 Hz, O*H*), 2.34 (1H, br dd, $J = 14.1$, 7.7 Hz, 18-CH_aH$_b$), 2.31 (2H, q, $J = 7.6$ Hz, COCH_2CH$_3$), 2.22 (1H, br dd, $J = 14.1$, 6.4 Hz, 18-CH$_a$$H_b$), 2.04 (2H, app q, 16-C$H_2$), 1.80 (1H, dt, $J =$ 14.3, 8.8 Hz, 22-CH_aH$_b$), 1.54–1.65 (2H, m, 20-CH_2), 1.51 (1H, m, 22-CH_aH$_b$), 1.22 (3H, d, $J = 6.1$ Hz, 24-CH_3), 1.13 (3H, t, $J = 7.6$ Hz, COCH$_2$CH_3), 1.01 (3H, t, $J = 7.4$ Hz, CH$_2$CH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 174.8, 147.1, 138.4, 128.4, 127.7, 127.6, 111.0, 74.4, 70.2, 69.5, 66.5, 44.0, 42.4, 42.0, 28.6, 27.8, 19.6, 12.2, 9.3; HRMS: (+CI, NH_3) Calc. for $C_{21}H_{33}O_4$ $[MH]^+$: 349.2379, found: 349.2386; *m*/*z*: (+CI, NH_3) 349 ($[MH]^+$, 11), 331 (2), 222 (9), 196 (19), 167 (13), 108 (45), 106 (68), 91 (100), 74 (69), 52 (56).

(2*R*,4*S*,8*S*,10*R*)-10-(*t*-Butyldimethylsiloxy)-12-ethyl-4-hydroxy-8-methoxy-1-(*p*-methoxybenzyloxy)-2-(triethylsiloxy)-12-tridecen-6-one (45)

A 25 mL flask containing (−)-Ipc$_2$BCl (95 mg, 0.296 mmol, 1.4 eq.) was placed under vacuum for 30 min to remove any traces of HCl. The flask was charged with argon and Et_2O (3 mL) was added. The solution was cooled to −78 °C and Et_3N (50 μL, 0.359 mmol, 1.7 eq.) was added, followed by a solution of ketone **43** (69.6 mg, 0.212 mmol) in Et_2O (1 mL + 2 × 0.5 mL washings) *via* cannula. The mixture was stirred for 1 h at 0 °C then re-cooled to −78 °C. Aldehyde **7** (93 g, 0.275 mmol, 1.3 eq.) in Et_2O (1 mL + 2 × 0.5 mL washings) was added *via* cannula. The reaction mixture was stirred at −78 °C for 90 min then left at −20 °C for 16 h. The reaction was quenched by the addition of pH 7 buffer solution (4 mL), MeOH (2 mL) and 30% H_2O_2 solution (2 mL). The resultant mixture was stirred vigorously at rt for 1 h, and then diluted with H_2O (10 mL) and Et_2O (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by sequential flash chromatography (20 : 80 Et_2O–CH_2Cl_2 then 20 : 80 EtOAc–hexanes) to provide aldol adduct **45** (110.8 mg, 78%) as a colourless oil: R_f: 0.48 (30 : 70 EtOAc–hexanes), 0.72 (20 : 80 Et_2O–CH_2Cl_2); $[\alpha]_D^{20}$ −2.5 (*c* 1.69, $CHCl_3$); IR (liquid film): 3507 (br), 1710 (s), 1612, 1514 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.24 (2H, d, $J = 8.6$ Hz, Ar*H*), 6.87 (2H, d, $J = 8.6$ Hz, Ar*H*), 4.77 (1H, d, $J = 1.4$ Hz, C=CH_aH$_b$), 4.72 (1H, br s, C=CH$_a$$H_b$), 4.44 (2H, s, C$H_2$Ar), 4.23 (1H, m, 25-C*H*), 4.07 (1H, m, 27-C*H*), 3.97 (1H, m, 19-C*H*), 3.87 (1H, m, 21-C*H*), 3.80 (3H, s, ArOCH_3), 3.52 (1H, d, $J = 2.2$ Hz, O*H*), 3.41 (1H, dd, $J = 9.7$, 5.1 Hz, 28-CH_aH$_b$), 3.37 (1H, dd, $J =$ 9.7, 5.1 Hz, 28-CH$_a$$H_b$), 3.28 (3H, s, OC$H_3$), 2.72 (1H, dd, $J =$ 15.8, 6.5 Hz, 22-CH_aH$_b$), 2.60 (1H, dd, $J = 16.7$, 7.9 Hz, 24-CH_aH$_b$), 2.53 (1H, dd, $J = 16.7$, 4.3 Hz, 24-CH$_a$$H_b$), 2.48 (1H, dd, $J = 15.8$, 5.5 Hz, 22-CH$_a$$H_b$), 2.30 (1H, dd, $J = 13.6$, 4.7 Hz, 18-CH_aH$_b$), 2.10 (1H, dd, $J = 13.6$, 4.7 Hz, 18-CH$_a$$H_b$),1.99 (2H, br q, $J = 7.3$ Hz, 16-CH_2), 1.61–1.73 (3H, m, 26-CH_2 + 20-CH_aH$_b$), 1.34 (1H, ddd, $J = 14.2$, 8.8, 3.8 Hz, 20-CH$_a$$H_b$), 1.02 (3H, t, $J = 7.4$ Hz, 16-CH$_2$CH_3), 0.93 (9H, t, $J = 8.0$ Hz, Si(CH$_2$CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.60 (6H, q, $J = 8.0$ Hz, Si(CH_2CH$_3$)$_3$), 0.08 (3H, s, Si(CH_3)$_a$), 0.07 (3H, s, Si(CH_3)$_b$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 209.1, 159.2, 147.9, 130.1, 129.3, 113.7, 110.8, 74.2, 73.9, 73.0, 70.6, 67.9, 66.0, 56.4, 55.2, 50.8, 48.5, 45.4, 42.0, 41.1, 29.0, 25.9, 18.0, 12.2, 6.8, 4.9, −4.1, −4.6; HRMS: (+ESI) Calc. for $C_{36}H_{66}O_7Si_2Na$ $[M + Na]^+$: 689.4245, found: 689.4234.

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