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

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The convergent synthesis of the C1–C15 AB-spiroacetal subunit **2** of altohyrtin A/spongistatin 1 (**1**) is described. This highly stereocontrolled synthesis relies on matched boron aldol reactions of chiral methyl ketones, under Ipc_2BCl mediation, to establish the C5, C9 and C11 stereocentres, and formation of the desired thermodynamic spiroacetal under acidic conditions. The scalable synthetic sequence developed provided access to multi-gram quantities of **2**, thus enabling the successful completion of the total synthesis of altohyrtin A/spongistatin 1, as reported in Part 4.

Introduction

Marine organisms, particularly invertebrates such as sponges, have become a key source of novel biologically-active compounds.[1] Many of these marine-derived natural products exhibit exceptional levels of biological activity, combined with unique modes of action, which may have value as lead structures for the development of new medicines.

The first members of the spongipyran family of antimitotic marine macrolides were reported independently by three research groups in 1993. Bioassay-guided fractionation by Pettit and co-workers of extracts of *Spongia* sp. and *Spirastrella spinispirulifera* led to the identification and partial structure elucidation of spongistatins 1–9 (Fig. 1).[2] Similarly, the Kitagawa/Kobayashi group[3] reported altohyrtins A–C and 5-desacetylaltohyrtin A from *Hyrtios altum* and Fusetani[4] reported the isolation of cinachyrolide A from *Cinachyra* sponges (Fig. 2). Remarkably, each of these groups reported the same gross structures on the basis of extensive NMR experiments performed on extremely small quantities of the natural products (0.5–13.8 mg). However, several discrepancies were apparent in the relative stereochemical relationships attributed to these unprecedented 42-membered macrolides. Furthermore, only the Kitagawa/Kobayashi group proposed the full relative and absolute configuration, the validity of which was verified by subsequent total syntheses (*vide infra*).

The spongipyrans[5] have attracted a great deal of excitement due to their extraordinary biological activity. They are among the most potent cancer cell-growth inhibitory antimitotic agents tested by the US National Cancer Institute (NCI), with altohyrtin A/spongistatin 1 being one of the most active of the series. Typical of the class, this compound displayed sub-nanomolar level cytotoxicity in the NCI 60 human carcinoma cell line screen (mean panel GI_{50} 1.3×10^{-10} M) and enhanced potency against a subset of highly chemoresistant tumour types (GI_{50} 2.5–3.5 $\times$ 10^{-11} M).[2a] Furthermore, *in vivo* human melanoma and ovarian carcinoma xenograft experiments with this compound, showed curative responses at extremely low doses.[2g] Although little data is available concerning the mode of action of these compounds,

† Part 1 of a series of four papers.

‡ 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/b504146e/

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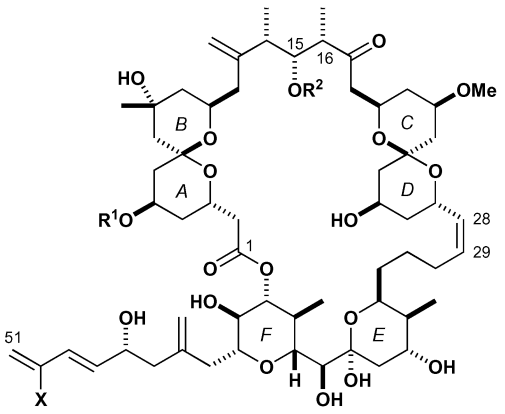
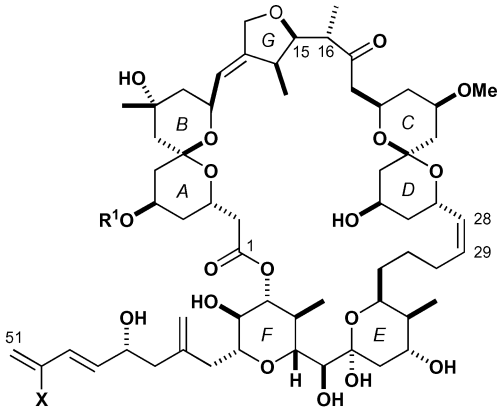


	X	R^1	R^2
spongistatin 1	Cl	Ac	Ac
spongistatin 2	H	Ac	Ac
spongistatin 3	Cl	H	Ac
spongistatin 4	Cl	Ac	H
spongistatin 6	H	Ac	H



	X	R^1
spongistatin 5	Cl	H
spongistatin 7	H	H
spongistatin 8	H	Ac
spongistatin 9	Cl	Ac

Fig. 1 Structures originally proposed for spongistatins 1–9.

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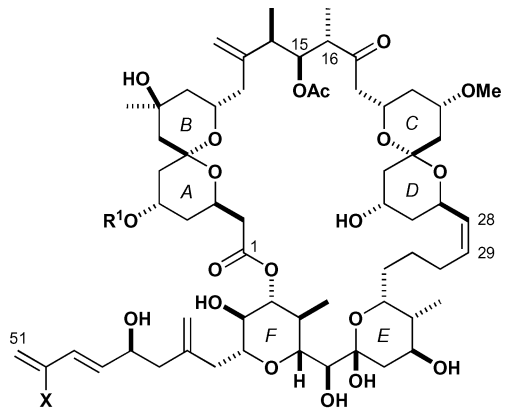
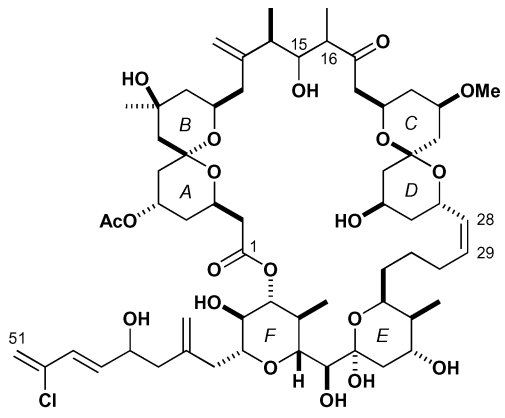


	X	R^1
altohyrtin A	Cl	Ac
altohyrtin B	Br	Ac
altohyrtin C	H	Ac
5-desacetyl-altohyrtin A	Cl	H



cinachyrolide A

Fig. 2 Structures originally proposed for altohyrtins A–C, 5-desacetylaltohyrtin A and cinachyrolide A.

altohyrtin A/spongistatin 1 was shown to inhibit mitosis by binding to tubulin and blocking microtubule assembly.[2h] Despite this enticing biological profile, further biological evaluation has been severely hampered by the extreme paucity of the spongipyrans available from the natural source (*e.g.*, 13.8 mg was isolated by the Pettit group from 400 kg wet sponge).

The spongipyran class of marine macrolides have attracted considerable synthetic interest due to an enticing combination of their promising anticancer properties, the paltry supply from the natural source and, most significantly, their unprecedented molecular architecture. To date, six research groups have reported successful total syntheses of members of the spongipyran family. The first reported synthesis of altohyrtin C/spongistatin 2 by Evans[6] in 1997 was followed soon after by the synthesis of altohyrtin A/spongistatin 1 by Kishi,[7] and both these elegant studies served to confirm the full stereochemical assignments of the Kitagawa/Kobayashi group shown in Fig. 2, and established that the altohyrtins and spongistatins had identical structures. Subsequent total syntheses have been reported by the Smith,[8] Paterson,[9] Crimmins[10] and Heathcock[11] groups, in addition to a formal total synthesis by Nakata and co-workers[12] and numerous synthetic approaches by other groups.[13] In this series of four papers, we provide a full account of our studies in this area leading to a highly stereocontrolled total synthesis of altohyrtin A/spongistatin 1, as well as access to novel structural analogues for biological evaluation.

Retrosynthetic analysis

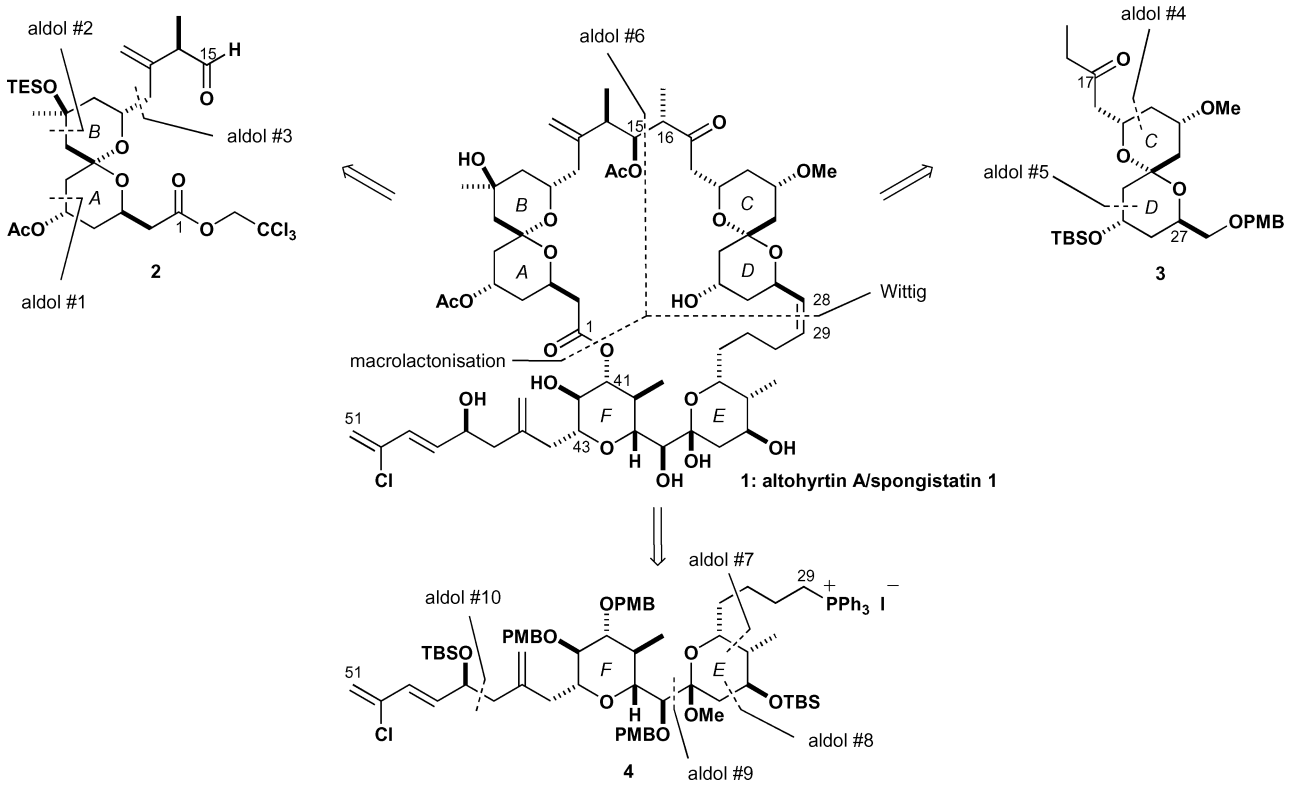
At the onset of this project in 1995, our synthetic plan for the spongipyrans was designed to be highly flexible, due to the initial uncertainty over the stereochemical assignment as discussed in the introduction, and to allow for the production of useful quantities of altohyrtin A/spongistatin 1, along with enabling access to novel structural analogues for SAR studies.

The spongipyran family present a significant synthetic challenge, due primarily to the unprecedented array of functionality and the high level of oxygenation which necessitates careful attention to chemoselectivity issues and the selection of a workable protecting group strategy. The control of stereochemistry is also essential if a useful amount of the target structure is to be accessed. Altohyrtin A/spongistatin 1 (**1**, Scheme 1) bears 24 stereogenic centres distributed around the 42-membered macrolactone core and the sensitive chlorotrienol side-chain. Two spiroacetals, only one of which benefits from two stabilising anomeric effects, and a highly oxygenated bis-tetrahydropyran portion are also present.

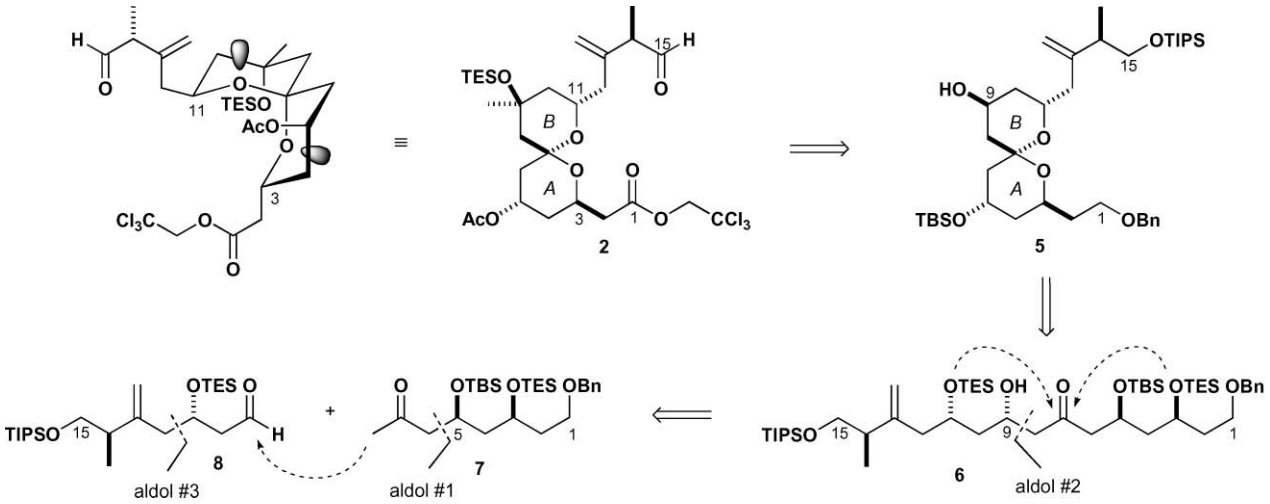
Taking all these factors into consideration, our retrosynthetic analysis for altohyrtin A relied on the disassembly of the molecule *via* three principal disconnections (Scheme 1). In a forward sense, fragment coupling of the AB- and CD-spiroacetal subunits, **2** and **3** respectively, was planned *via* formation of the C15–C16 bond, and the associated stereocentres, by a stereoselective aldol reaction, while a challenging Wittig coupling would then be employed to unite an advanced ABCD aldehyde subunit with the fully elaborated C29–C51 EF phosphonium salt **4**. Finally, macrolactonisation of a suitable *seco*-acid derivative at the C41 hydroxyl was anticipated to proceed selectively to complete the fully functionalised spongipyran framework. A cornerstone of our synthetic strategy was the late-stage coupling of highly functionalised subunits, allowing for an optimum level of convergency and a succinct end-game to the synthesis. Furthermore, our retrosynthetic analysis revealed 10 potential disconnection sites for the use of stereoselective aldol methodology to form key C–C bonds and establish oxygen-bearing stereocentres, as indicated by the labels "aldols #1–10".

The AB-spiroacetal

The C1–C15 fragment of altohyrtin A (**1**), comprising the AB-spiroacetal, benefits from two stabilising anomeric effects arising from the "axial–axial" disposition of the two acetal oxygen atoms at C7, as shown in segment **2** (Scheme 2). As such, it was reasoned that the desired spiroacetal would be obtained under thermodynamic conditions of acid-catalysed acetal formation from a linear precursor. The fully functionalised AB-spiroacetal aldehyde **2** would be obtained from the simpler spiroacetal system **5** by a series of functional group interconversions and stereoselective methyl addition to a C9 ketone. In turn, spiroacetal **5** would be the thermodynamic product of an acid-mediated, selective bis-desilylation of linear precursor **6** with concomitant spiroacetal formation. Aldol disconnection of **6** to ketone **7** and aldehyde **8** provides a convergent strategy for union of the C1–C8 and C9–C15 segments. Examination of **7** and **8** reveals two further aldol disconnections of methyl ketones. Particular synthetic challenges presented by the C1–C15 fragment include the development of efficient methods for the construction of the stereochemically dense, polyacetate framework and differentiation of the oxygen functionality by means of selective protection or differences in oxidation state.



Scheme 1 Retrosynthetic analysis for altohyrtin A/spongistatin 1 (**1**), showing proposed aldol disconnections.



Scheme 2 Retrosynthetic analysis for the AB-spiroacetal subunit **2**.

Results and discussion

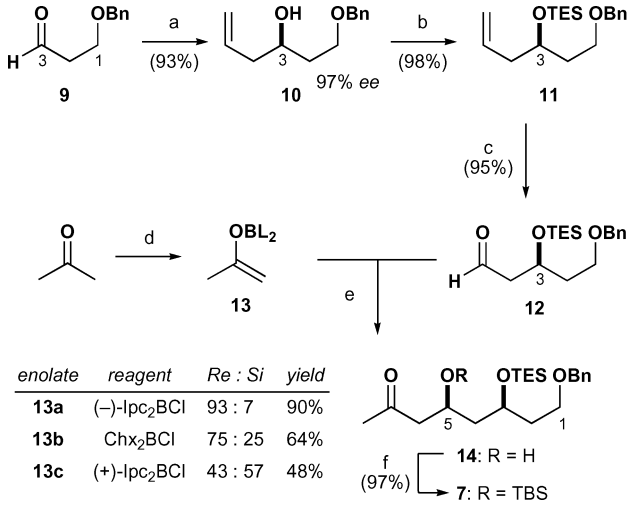
The C1–C8 chiral ketone 7

Our synthesis of the C1–C15, AB-spiroacetal-containing subunit **2** began with the Brown asymmetric allylation of **9** (Scheme 3), employing *B*-allylbis(2-isocaranyl)borane (2-^{d}Icr$_2$BAll),[14] providing homoallylic alcohol **10** in excellent yield (93%) and high enantiomeric excess (97% ee by ^{1}H NMR analysis of the derived MTPA esters[15]). Protection as the triethylsilyl (TES) ether **11** and subsequent ozonolysis, provided aldehyde **12**, poised for the first boron aldol reaction[16] of our synthetic endeavour.

Enolisation of acetone with (−)-*B*-chlorodiisopinocampheylborane [(−)-Ipc$_2$BCl] and Et$_3$N, under standard conditions (0 °C, Et$_2$O),[17] provided enol borinate **13a**, which was used *in situ* in a matched aldol reaction with aldehyde **12**. The nature of the Ipc ligands on boron reinforces the inherent diastereofacial bias of aldehyde **12**, providing 1,3-*syn* **14** as the major diastereomer (93 : 7 dr). By comparison, without the chiral ligands on boron, *i.e.*, using dicyclohexylboron enolate **13b**, derived from *B*-chlorodicyclohexylborane (Chx$_2$BCl) and Et$_3$N,[18] aldol product **14** was provided with significantly reduced diastereoselectivity (75 : 25 dr). The mismatched situation, using enolate **13c**, prepared from (+)-Ipc$_2$BCl, resulted in a weak preference for the corresponding 1,3-*anti* aldol adduct. Protection of the C5 alcohol as the *tert*-butyldimethylsilyl (TBS) ether produced C1–C8 ketone **7**, ready for aldol coupling with the C9–C15 aldehyde subunit.

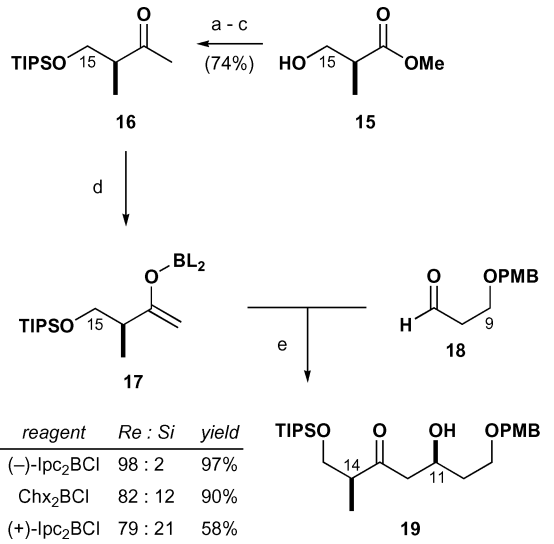
The C9–C15 subunit

The synthesis of the C9–C15 fragment commenced with the triisopropylsilyl (TIPS) protection of methyl (*S*)-3-hydroxy-2-methylpropionate **15** (Roche ester), and conversion into the corresponding methyl ketone **16**, *via* the Weinreb amide[19] (Scheme 4). This previously-reported,[9c] three-step procedure



enolate	reagent	Re : Si	yield
13a	(–)-Ipc$_2$BCl	93 : 7	90%
13b	Chx$_2$BCl	75 : 25	64%
13c	(+)-Ipc$_2$BCl	43 : 57	48%

Scheme 3 *Reagents and conditions*: (a) 2-^{d}Icr$_2$BOMe, $H_2C{=}CHCH_2$-MgBr, Et_2O, −78 °C, 4 h, then H_2O_2, NaOH, H_2O, reflux, 16 h; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; (c) O_3, $NaHCO_3$, CH_2Cl_2, −78 °C, then PPh_3, rt, 3.5 h; (d) L_2BCl, Et_3N, Et_2O, 0 °C, 45 min; (e) **12**, −78 → −20 °C, 20 h, then pH 7 buffer, H_2O_2, MeOH, 0 °C → rt, 1 h; (f) TBSCl, Im, DMF, rt, 16 h.

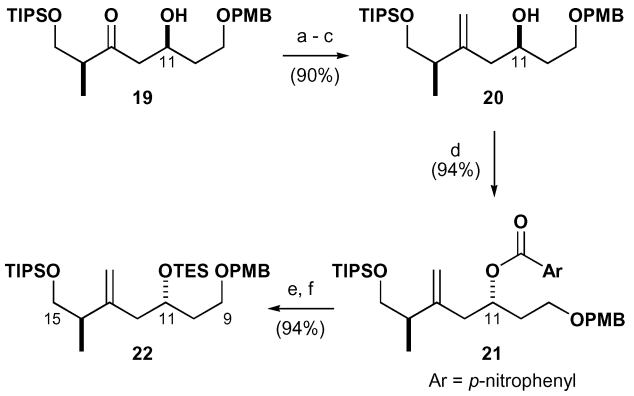


enolate	reagent	Re : Si	yield
17a	(–)-Ipc$_2$BCl	98 : 2	97%
17b	Chx$_2$BCl	82 : 12	90%
17c	(+)-Ipc$_2$BCl	79 : 21	58%

Scheme 4 *Reagents and conditions*: (a) TIPSCl, Im, DMAP, CH_2Cl_2, 0 °C → rt, 16 h; (b) MeONHMe–HCl, *i*-PrMgCl, THF, −20 → −10 °C, 4 h; (c) MeMgBr, THF, −78 → 0 °C, 3 h; (d) L_2BCl, Et_3N, Et_2O, −78 → 0 °C, 1 h; (e) **18**, Et_2O, −78 → −20 °C, 19 h, then H_2O_2, MeOH, pH 7 buffer, 0 °C → rt, 2 h.

could be performed easily on 40 g of **15**, with distillation of ketone **16** being the only purification step required in the sequence. Previously, we had demonstrated that the boron-mediated aldol reactions of certain α-chiral methyl ketones can proceed with high levels of 1,4-*syn* diastereoselection, and that this could be enhanced by the appropriate choice of Ipc ligand chirality.[20] The spongipyrans require a 1,4-*anti* relationship between C11 and C14, which was best achieved by the application of a highly 1,4-*syn* selective, matched aldol reaction and subsequent Mitsunobu inversion[21] at C11. To this end, conversion of methyl ketone **16** into enol borinate **17a** by reaction with (−)-Ipc$_2$BCl and Et_3N, and *in situ* reaction with aldehyde **18**, afforded the desired 1,4-*syn* aldol product **19** (98 : 2 dr) in excellent yield (97%). Reaction under purely substrate control, using Chx$_2$BCl (enolate **17b**), or using the mismatched (+)-Ipc$_2$BCl reagent (enolate **17c**) led to lower levels of 1,4-*syn* selectivity.

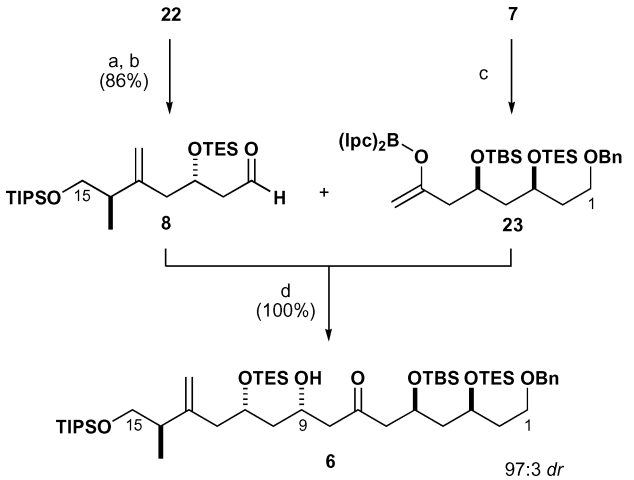
The inversion of configuration at C11 was not possible directly on **19**, as Mitsunobu conditions led only to elimination, providing the corresponding α,β-unsaturated ketone. Furthermore, attempts to methylenate **19** under a variety of conditions (*e.g.*, Wittig, Petasis), resulted in substantial decomposition *via* elimination and retro-aldol pathways. The optimal procedure required initial protection of **19** as the corresponding TES ether, followed by methylenation (Scheme 5). In earlier work, the methylenation was conveniently carried out using the Petasis reagent Cp_2TiMe_2 in good yield (79%).[9c] However, application of the modified Takai procedure[22] (Zn, CH_2I_2, $TiCl_4$, cat. PbI_2) proved generally superior in terms of yield (≥92%) and ease of purification, and was particularly amenable to larger scale operations. Removal of the TES protecting group to give **20** (90% yield from **19**), allowed smooth Mitsunobu inversion to take place, affording **21** (94%). Saponification of the *p*-nitrobenzoate and replacement with a TES ether afforded **22** (94%).



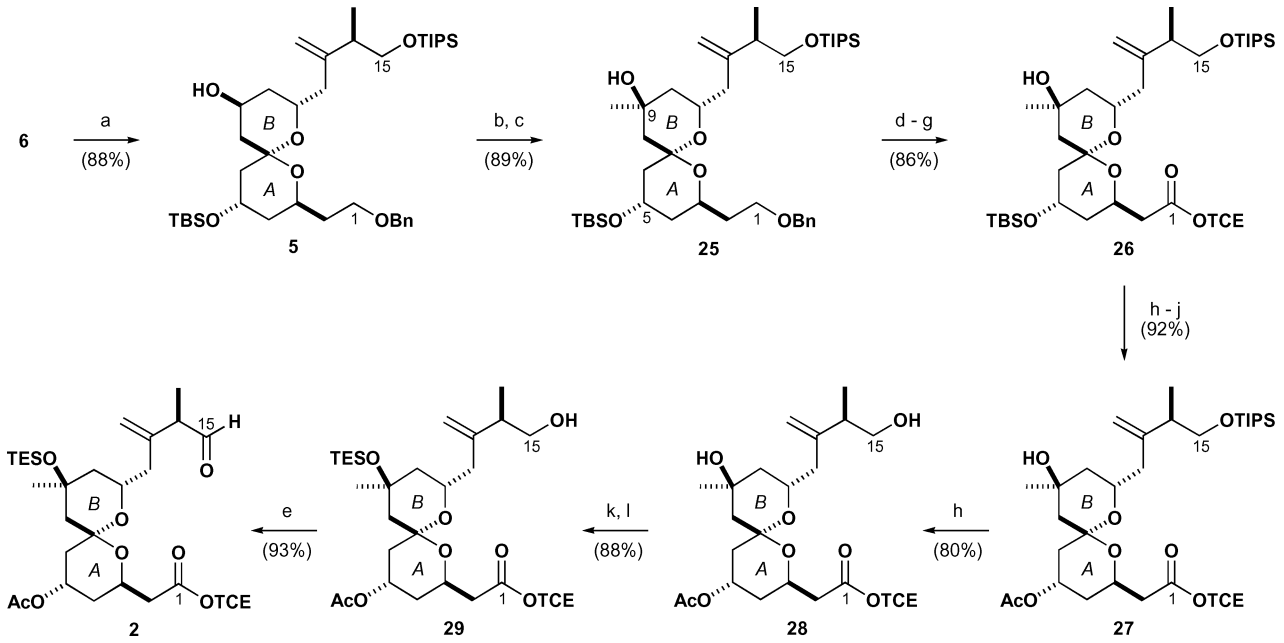
Scheme 5 *Reagents and conditions*: (a) TESOTf, 2,6-lutidine, −78 °C, 2 h; (b) Zn, CH_2I_2, $TiCl_4$, cat. PbI_2, THF–CH_2Cl_2, rt, 3 h; (c) cat. PPTS, CH_2Cl_2–MeOH, 0 °C, 20 min; (d) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, PhMe, rt, 30 min; (e) K_2CO_3, MeOH, rt, 16 h; (f) TESCl, Im., DMF, rt, 16 h.

Aldol coupling of the C1–C8 and C9–C15 subunits, and spiroacetal formation

Formation of the proposed linear precursor to the AB-spiroacetal, *via* aldol union of the C1–C8 and C9–C15 fragments, required conversion of **22** into the corresponding C9 aldehyde **8**. This was achieved by careful treatment of **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of pH 7 buffer, followed by oxidation of the resultant 1° alcohol with the Dess–Martin periodinane[23] (Scheme 6). This two-step procedure illustrates a pair of recurring challenges faced in our synthesis of altohyrtin A. Firstly, removal of a



Scheme 6 *Reagents and conditions*: (a) DDQ, 10 : 1 CH_2Cl_2–pH 7 buffer, 0 °C, 45 min; (b) Dess–Martin periodinane, pyr, CH_2Cl_2, rt, 30 min; (c) (−)-Ipc$_2$BCl, Et_3N, Et_2O, 0 °C, 40 min; (d) **8**, Et_2O, −78 → −20 °C, 19 h, then H_2O_2, MeOH, pH 7 buffer, 0 °C → rt, 2.5 h.



Scheme 7 *Reagents and conditions*: (a) cat. PPTS, CH_2Cl_2–MeOH, rt, 40 min, then separation and resubjection; (b) Dess–Martin periodinane, pyr, CH_2Cl_2, rt, 30 min; (c) MeMgBr, THF, −78 → 0 °C, 50 min; (d) LiDBB, THF, −78 °C, 1 h; (e) Dess–Martin periodinane, CH_2Cl_2, rt, 1–2 h; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O, 0 °C → rt, 16 h; (g) 2,2,2-trichloroethanol, DCC, cat. DMAP, CH_2Cl_2, rt, 2 h; (h) 40% aq. HF, MeCN, rt, 0.75–2 h; (i) TIPSCl, Im., cat. DMAP, CH_2Cl_2, rt, 6 h; (j) Ac_2O, DMAP, CH_2Cl_2, rt, 3 h; (k) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 → 0 °C, 3 h; (l) cat. PPTS, CH_2Cl_2–MeOH, 0 °C, 1 h.

p-methoxybenzyl (PMB) protecting group proved problematic in several instances where acid-sensitive functional groups are present in the substrate, *e.g.*, the TES ether in **22** was found to be somewhat labile under standard DDQ-mediated oxidative deprotection conditions. Gratifyingly, in most instances the acid-mediated, unwanted side reactions could be limited by careful optimisation of reaction conditions. In particular, the use of pH 7 buffer, rapid mixing of the biphasic mixture and portion-wise addition of an excess of DDQ gave the best results. Secondly, our synthetic route to **1** required the oxidation of several complex 1° and 2° alcohols to the corresponding carbonyl compounds, in the presence of sensitive functional groups, or potentially labile α-stereocentres. In most instances, the Dess–Martin periodinane, sometimes buffered with pyridine, proved to be the oxidant *par excellence*.

With aldehyde **8** and ketone **7** in hand, the aldol union of these fragments could proceed, exploiting triple asymmetric induction,[24] wherein the stereodirecting influence from all three chiral components (aldehyde, ketone[25] and boron reagent) were matched. Enolisation of **7** with (–)-Ipc_2BCl and Et_3N, to give enol borinate **23** *in situ*, followed by treatment with aldehyde **8** gave the desired aldol adduct **6** cleanly in near quantitative yield (97 : 3 dr). In this reaction, the 1,3-*syn* preference of aldehyde **8**, the 1,5-*anti* preference[26,27] of ketone **7** and the stereodirecting influence of the boron reagent act in a synergistic fashion, resulting in an excellent level of stereoselectivity.

Selective bis-desilylation of **6** and concomitant spiroacetal formation were achieved by subjection to catalytic pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2–MeOH, providing the desired, thermodynamically favoured, AB-spiroacetal **5** (Scheme 7). The spiroacetal stereochemistry was assigned on the basis of NOESY results for a closely related system,[9a] and confirmed at a later point in the AB-spiroacetal synthesis, *vide infra*.

Further functionalisation of the AB-spiroacetal

Oxidation of **5** to the corresponding C9 ketone **24**, with the Dess–Martin periodinane, was followed by equatorial addition of MeMgBr to give the 3° alcohol **25** as the sole product. In this Grignard addition reaction, axial attack of the reagent on ketone **24** is blocked by the bulky C1–C6 portion of the spiroacetal (Fig. 3).

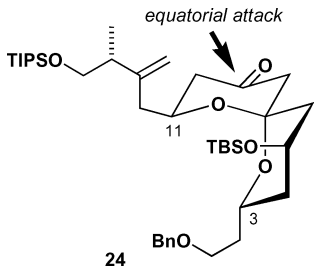


Fig. 3 Equatorial attack of Grignard reagent on **24**.

Although **25** embodies the complete carbon skeleton of the AB-spiroacetal of the spongipyrans, in keeping with our synthetic strategy for altohyrtin A, we required C1 at the acid oxidation state and acetylation of the C5 hydroxyl group. To this end, debenzylation of **25** with lithium 4,4′-di(*tert*-butyl)biphenylide (LiDBB)[28] was followed by two-step oxidation to the carboxylic acid and esterification with 2,2,2-trichloroethanol to provide **26**. The 2,2,2-trichloroethyl (TCE) ester protecting group was chosen on the basis that it would be readily removed in the final stages of the synthesis, using mild, reductive conditions, compatible with the manifold sensitive functionality of the targeted *seco*-compound. Earlier model studies with a simple methyl ester had proven this to be unsuitable, due to inability to remove it chemoselectively under mild conditions at a late stage, *e.g.*, by using potassium trimethylsilanolate (KOTMS).

After the investigation of several conditions for the selective removal of the TBS ether in **26** in the presence of the TIPS group, a high yielding two-step sequence of bis-desilylation, mono-silylation was finally employed. This allowed selective acetylation of the hindered 2° alcohol at C5 under carefully optimised conditions (Ac_2O, DMAP, CH_2Cl_2), to yield **27**. Although our synthetic strategy called for acetylation at this point, it is envisaged that access to several other spongipyran congeners, *e.g.*, desacetylaltohyrtin A/spongistatin 3, would be possible by retaining a silyl protecting group at the C5 hydroxyl,

which would ultimately be removed in a global deprotection step at the conclusion of the synthesis.

Removal of the TIPS ether from **27** (aq. HF, MeCN) provided diol **28**, the stereochemistry of which was confirmed by NOESY (Fig. 4). Protection of the 3° alcohol at C9 as the TES ether, chosen for ease of removal in the final step of the synthesis, was achieved by a two-step sequence, to afford **29**.

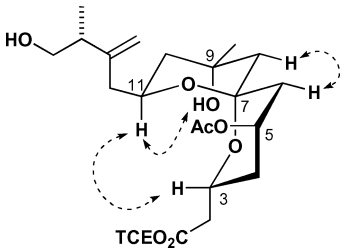


Fig. 4 Key NOE interactions for **28**.

The success of any multi-step total synthesis endeavour relies on strategic "stockpiling" of highly stable intermediates at key points. The synthesis of **29** outlined here proved robust and was able to be scaled up to the extent that multi-gram quantities of **29** could be produced in a single campaign. Conversion of alcohol **29** to the corresponding, fully functionalised, C1–C15 AB-spiroacetal aldehyde **2** was efficiently performed, as needed, using the Dess–Martin periodinane (93% yield).

Conclusions

The synthesis of the C1–C15 AB-spiroacetal segment reported herein requires 24 steps in the longest linear sequence from methyl ketone **16**, and gives a 27% overall yield of **2**. The challenge of introducing a number of stereogenic centres on a largely polyacetate-derived backbone was dealt with by the application of Brown's allylation methodology and boron-mediated aldol reactions of methyl ketones, where substrate control was matched with appropriate choice of Ipc ligand chirality to afford high levels of diastereoselectivity. The developed route allowed access to multi-gram quantities of **2** for completion of the total synthesis of altohyrtin A, as discussed in Parts 2–4 of this series of papers.[29]

Experimental

(*R*)-1-Benzyloxy-hex-5-en-3-ol (10)

To a cold (−78 °C), stirred solution of 2-^{d}Icr$_2$BOMe[14] (10.34 g, 32.68 mmol, 1.7 eq.) in dry Et_2O (62 mL), was added, dropwise, allylmagnesium bromide (0.98 M in Et_2O, 29.0 mL, 28.4 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 **9** (3.15 g, 19.2 mmol, 1.0 eq.) in dry Et_2O (5 mL + 2 × 2 mL for washings) was added *via* cannula. The mixture was stirred at −78 °C for 4 h and then quenched with 3 M aqueous NaOH (13 mL) and a 30% aqueous solution of H_2O_2 (27 mL). The biphasic mixture was refluxed for 16 h, the layers were then separated and the aqueous phase extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine (1 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil thus obtained was flash chromatographed (10 : 90 EtOAc–hexanes) to provide the homoallylic alcohol **10** (3.64 g, 93%), as a colourless oil: R_f: 0.20 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ −4.8 (*c* 2.31, $CHCl_3$); IR (liquid film): 3424, 3071, 3029, 1640 cm^{-1}; ^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.28–7.37 (5H, m, Ar_a), 5.81–5.88 (1H, m, H_5), 5.09, 5.12 (2H, s, d, J = 8.2 Hz, –C=CH_2), 4.53 (2H, s, –OCH_2Ph), 3.87–3.90 (1H, m), 3.64–3.74 (2H, m), 2.86 (1H, d, J = 2.9 Hz, –OH), 2.26 (2H, t, J = 6.3 Hz, H_{4A} and H_{4B}), 1.75–1.80 (2H, m); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 137.9, 134.9, 128.4, 127.8, 127.7, 117.6, 73.3, 70.4, 69.0, 41.9, 35.8; HRMS: (CI, NH_3) Calc. for $C_{13}H_{19}O_2$ (MH^+) 207.1385, found 207.1385.

(4*S*,6*S*)-8-Benzyloxy-4-hydroxy-6-(triethylsiloxy)-2-octanone (14)

Et_3N (3.89 mL, 28.0 mmol) and freshly distilled acetone (2.5 mL, 34.2 mmol) were added to a solution of (−)-Ipc$_2$BCl (7.48 g, 23.3 mmol, previously dried under high vacuum for 1 h to remove traces of HCl) in Et_2O (220 mL) at 0 °C. After stirring for 45 min at 0 °C, the reaction mixture was cooled to −78 °C and a solution of aldehyde **12** (5.0 g, 15.5 mmol) in Et_2O (20 mL and 5 mL washings) was slowly added. The reaction mixture was stirred 4 h at −78 °C before being kept in a freezer (−20 °C) overnight. The reaction was quenched by addition of excess of pH 7 buffer (200 mL) at 0 °C. The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude material was dissolved in MeOH (220 mL) and pH 7 buffer (115 mL) then, H_2O_2 (75 mL of a 30% aq. sol.) was added at 0 °C and the resulting mixture was stirred for 1 h at rt. The reaction mixture was partitioned between Et_2O and pH 7 buffer. The aqueous layer was extracted with Et_2O (2 × 100 mL) and EtOAc (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed *in vacuo*. Purification by flash chromatography (20 : 80 EtOAc–hexanes) afforded the desired aldol **14** (5.31 g, 90%) as a colourless oil: R_f: 0.40 (40 : 60 EtOAc–hexanes); $[\alpha]_D^{20}$ +16.0 (*c* 2.06, $CHCl_3$); IR (liquid film): 3482, 1713 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.28–7.36 (5H, m, *Ar*), 4.46, 4.50 (2H, AB_q, J = 11.9 Hz, –OCH_2Ph), 4.20 (1H, sextet, J = 3.8 Hz, *H*5), 4.12 (1H, qn, J = 6.2 Hz, H_3), 3.53 (2H, t, J = 6.4 Hz, H_{1A} and H_{1B}), 3.45 (1H, br s, –O*H*), 2.51–2.60 (2H, m, H_{6A} and H_{6B}), 2.16 (3H, s, C_7–CH_3), 1.84 (2H, q, J = 6.2 Hz, H_{2A} and H_{2B}), 1.57–1.66 (2H, m), 0.96 (9H, t, J = 8.0 Hz, –OSi(CH$_2$CH_3)$_3$), 0.62 (6H, q, J = 8.0 Hz, –OSi(CH_2CH$_3$)$_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 208.9, 138.3, 128.3, 127.7, 127.6, 73.0, 69.1, 66.6, 66.2, 50.6, 43.1, 37.2, 30.8, 6.8, 5.0; HRMS (+FAB) Calc. for $C_{21}H_{36}O_4Si$ (MH^+) 381.2461, found 381.2442.

(2*S*,5*S*)-5-Hydroxy-7-(*p*-methoxybenzyloxy)-2-methyl-1-(triisopropylsiloxy)-heptan-3-one (19)

A two-necked round bottomed flask containing (−)-Ipc$_2$BCl (5.36 g, 16.71 mmol, 1.8 eq.) was placed under high vacuum for 1 h to remove any traces of HCl. To this flask was added dry Et_2O (150 mL) and the solution was cooled to 0 °C. Dry Et_3N (2.6 mL 18.6 mmol, 2.0 eq.) was added followed by a solution of ketone **16** (2.40 g, 9.28 mmol, 1.0 eq.) in dry Et_2O (2 mL + 2 × 3 mL for washings). The resultant white suspension was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of the aldehyde **18** (2.77 g, 14.27 mmol, 1.5 eq.) in dry Et_2O (2 mL + 2 × 2 mL for washings) was added, *via* cannula, and the suspension was stirred at −78 °C for 5 h and then at −20 °C for 16 h. The reaction was quenched by the addition of pH 7 buffer (100 mL) and after warming to room temperature, the layers were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were concentrated *in vacuo*. The resultant residue was taken up in MeOH (125 mL) and pH 7 buffer (60 mL) and cooled to 0 °C. A 30% aqueous solution of H_2O_2 (50 mL) was added and the mixture was warmed to rt and stirred for 2.5 h. Et_2O (150 mL) and H_2O (100 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 150 mL) and EtOAc (2 × 150 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was flash chromatographed (10 : 90 → 20 : 80 EtOAc–hexanes) to yield a 98 : 2 mixture of the 1,4-*syn* to 1,4-*anti* aldol adducts **19** and 5-epi-**19** (4.08 g, 97%), respectively. Major diastereomer: R_f: 0.30 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ +38.8 (*c* 1.80, $CHCl_3$); IR (liquid film): 3508, 1708, 1613, 1513, 1463 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.6 Hz, Ar*H*), 6.87 (2H, br d, J = 8.6 Hz, Ar*H*), 4.44 (2H, s,

OCH_2Ar), 4.24 (1H, m, 11-C*H*), 3.79–3.84 (1H, m, 15-CH_aH_b), 3.80 (3H, s, OCH_3), 3.72 (1H, dd, $J = 9.7$, 5.2 Hz, 15-CH_aH_b), 3.62 (2H, br sextet, $J = 6.0$ Hz, 9-CH_2), 3.40 (1H, d, $J = 2.9$ Hz, O*H*), 2.79 (1H, br sextet, $J = 7.0$ Hz, 14-C*H*), 2.73 (1H, dd, $J = 17.6$, 4.2 Hz, 12-CH_aH_b), 2.67 (1H, dd, $J = 17.6$, 8.0 Hz, 12-CH_aH_b), 1.70–1.80 (2H, m, 10-CH_2), 1.01–1.10 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 214.4, 159.1, 130.2, 129.2, 113.6, 72.8, 67.5, 66.2, 66.0, 55.2, 49.5, 49.3, 36.1, 17.9, 12.7, 11.8; HRMS (+FAB) Calc. for $C_{25}H_{44}O_5Si$ $[M]^+$ 452.2958, found: 452.2913.

(4*R*)-2-[1-(Triisopropylsiloxy)-prop-2-(*R*)-yl]-6-(*p*-methoxybenzyloxy)-4-(triethylsiloxy)-hex-1-ene (20)

To a cold (−78 °C), stirred solution of alcohol **19** (2.13 g, 4.70 mmol) in dry CH_2Cl_2 (50 mL) was added 2,6-lutidine (1.6 mL, 13.7 mmol, 3 eq.) followed by TESOTf (1.6 mL, 7.1 mmol, 1.5 eq.). The resultant solution was stirred at −78 °C for 2 h and then EtOH (5 mL) was added to quench the excess TESOTf. Saturated aqueous NH_4Cl (50 mL) was added and the reaction was allowed to warm to rt. The layers were separated and the aqueous phase was extracted with Et_2O (4 × 150 mL). The combined organic extracts were washed with pH 7 buffer (2 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was flash chromatographed (10 : 90 Et_2O–hexanes) to yield the desired TES ether (2.62 g, 98%), as a colourless oil: R_f: 0.50 (10 : 90 Et_2O–hexanes); $[\alpha]_D^{20}$ +27.4 (*c* 1.97, $CHCl_3$); IR (liquid film): 1714, 1613, 1586, 1514 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.24 (2H, d, $J = 8.6$ Hz, Ar*H*), 6.86 (2H, d, $J = 8.6$ Hz, Ar*H*), 4.41 (2H, s, OCH_2Ar), 4.37 (1H, quin., $J = 5.4$ Hz, 11-C*H*), 3.80–3.84 (1H, m, 15-CH_aH_b), 3.80 (3H, s, OCH_3), 3.71 (1H, dd, $J = 9.7$, 5.7 Hz, 15-CH_aH_b), 3.50 (2H, t, $J = 6.6$ Hz, 9-CH_2), 2.71–2.78 (2H, m, 12-CH_aH_b + 14-C*H*), 2.62 (1H, dd, $J = 16.7$, 5.4 Hz, 12-CH_aH_b), 1.71–1.83 (2H, m, 10-CH_2), 1.03–1.06 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$), 0.92 (9H, t, $J =$ 7.9 Hz, Si(CH_2CH_3)$_3$), 0.58 (6H, q, $J = 7.9$ Hz, Si(CH_2CH$_3$)$_3$), ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 211.7, 159.0, 130.5, 129.2, 113.6, 72.5, 66.4, 65.8, 65.6, 55.2, 50.6, 49.6, 37.6, 17.9, 12.7, 11.8, 6.8, 4.8; HRMS (+FAB) Calc. for $C_{29}H_{53}O_5Si_2$ $[M–Et]^+$: 537.3431, found: 537.3381.

Diiodomethane (16.3 mL, 0.203 mol, 15 eq.) was added dropwise to a stirred suspension of activated Zn (30.6 g, 0.468 mol, 34 eq., dried at 140 °C under vacuum for 2 h before use) and PbI_2 (2.04 g, 4.43 mmol, 0.325 eq.) in THF (150 mL) and the resulting mixture was maintained at self-reflux during the addition. The reaction mixture was stirred for a further 30 min at rt before cooling to 0 °C. $TiCl_4$ (5.59 mL in 30 mL CH_2Cl_2, 51 mmol, 3.75 eq.) was added dropwise, and the mixture was allowed to stir at rt for a further 1 h after the addition. A solution of TES ether from the above procedure (7.71 g, 13.6 mmol) in THF (20 mL + 2 × 10 mL washings) was added *via* cannula and the resultant mixture was stirred at rt for 4.5 h. The reaction was quenched by slow addition to pH 7 buffer (600 mL) at 0 °C and the layers were separated. The aqueous phase was extracted with Et_2O (4 × 500 mL), combined organics were washed with brine (500 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was filtered through a plug of silica, eluting with Et_2O–light petroleum (50 : 50, 500 mL) and concentrated *in vacuo* to afford a pale yellow oil consisting of the desired alkene and the corresponding TES deprotected compound **20**. This mixture was routinely carried through to the subsequent desilylation reaction without any further purification.

To a solution of this TES ether–alcohol mixture in 1.3 : 1 CH_2Cl_2 (130 mL) and MeOH (100 mL), was added PPTS (cat.). The reaction was stirred at rt for 30 min before addition of Et_3N (200 μL) to neutralise the PPTS. The reaction mixture was concentrated *in vacuo* and purification by flash chromatography (20 : 80 → 40 : 60 Et_2O–light petroleum) afforded alcohol **20** (5.64 g, 92% over two steps) as a colourless oil: R_f: 0.35 (30 : 70 Et_2O–hexanes); $[\alpha]_D^{20}$ +12.8 (*c* 1.97, $CHCl_3$); IR (liquid film): 3473, 1641, 1613, 1514, 1463 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.25 (2H, d, $J = 8.5$ Hz, Ar*H*), 6.87 (2H, d, $J = 8.5$ Hz, Ar*H*), 4.91 (1H, s, C=CH_aH_b), 4.92 (1H, s, C=CH_aH_b), 4.45 (2H, AB_q, $J = 11.6$ Hz, OCH_2Ar), 3.92–3.99 (1H, m, 11-C*H*), 3.80 (3H, s, OCH_3), 3.53–3.72 (4H, m, 9-CH_2 + 15-CH_2), 2.94 (1H, d, $J = 1.8$ Hz, O*H*), 2.33 (1H, sextet, $J = 6.9$ Hz, 14-C*H*), 2.22 (1H, dd, $J = 13.9$, 4.6 Hz, 12-CH_aH_b), 2.16 (1H, dd, $J = 13.9$, 8.5 Hz, 12-CH_aH_b), 1.71–1.82 (2H, m, 10-CH_2), 1.05–1.13 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.02 (3H, d, $J = 6.9$ Hz, 14-CHCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 159.1, 149.2, 130.3, 129.3, 113.7, 112.0, 72.8, 68.1, 68.0, 67.8, 55.2, 44.0, 41.6, 36.3, 18.0, 17.1, 11.9; HRMS (+FAB) Calc. for $C_{26}H_{47}O_4Si$ $[MH]^+$: 451.3243, found: 451.3207.

(4*S*)-2-[1-(Triisopropylsiloxy)-prop-2-(*R*)-yl]-6-(*p*-methoxybenzyloxy)-4-(*p*-nitrobenzoyloxy)-hex-1-ene (21)

To a stirred solution of **20** (2.50 g, 5.55 mmol, 1.0 eq.) in dry benzene (50 mL) was added *p*-nitrobenzoic acid (4.10 g, 24.5 mmol, 4.4 eq.) followed by Ph_3P (7.30 g, 27.45 mmol, 5.0 eq.). To the resultant yellow suspension was added, dropwise over 10 min, diethylazodicarboxylate (4.4 mL, 27.70 mmol, 5.0 eq.). The resultant homogeneous yellow solution was stirred at rt for 20 min and the reaction was then concentrated *in vacuo*. The residue was first passed through a plug of silica (5% EtOAc in hexane) and after concentration *in vacuo*, the resultant oil was flash chromatographed (20 : 80 Et_2O–hexanes) to provide the desired *p*-nitrobenzoate **21** (3.12 g, 94%), as a pale yellow oil: R_f: 0.55 (30 : 70 Et_2O–hexanes); $[\alpha]_D^{20}$ +23.6 (*c* 1.73, $CHCl_3$); IR (liquid film): 3079, 1725, 1610, 1529 cm^{-1}; ^{1}H NMR: δ (500 MHz, $CDCl_3$) 8.22 (2H, d, $J = 8.7$ Hz, Ar*H*), 8.10 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.17 (2H, d, $J = 8.5$ Hz, Ar*H*), 6.77 (2H, d, $J = 8.5$ Hz, Ar*H*), 5.49 (1H, septet, $J = 4.1$ Hz, 11-C*H*), 4.85 (1H, s, C=CH_aH_b), 4.83 (1H, s, C=CH_aH_b), 4.37 (2H, AB_q, $J = 11.6$ Hz, OCH_2Ar), 3.75 (3H, s, OCH_3), 3.65 (1H, dd, $J = 9.4$, 5.9 Hz, 15-CH_aH_b), 3.49–3.54 (3H, m, 9-CH_2 + 15-CH_aH_b), 2.51 (1H, dd, $J = 14.5$, 8.1 Hz, 12-CH_aH_b), 2.46 (1H, dd, $J = 14.5$, 5.3 Hz, 12-CH_aH_b), 2.36 (1H, sextet, $J =$ 6.6 Hz, 14-C*H*), 1.96–2.08 (2H, m, 10-CH_2), 1.03–1.08 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 164.1, 159.0, 150.2, 147.7, 136.0, 130.5, 130.1, 129.3, 123.3, 113.6, 112.2, 72.7, 72.0, 68.1, 66.2, 55.1, 41.6, 41.4, 34.4, 18.0, 16.5, 11.7; HRMS (+FAB) Calc. for $C_{33}H_{48}NO_7Si$ $[M–H]^+$: 598.3200, found: 598.3177.

(3*S*,5*S*,9*S*,11*S*)-1-Benzyloxy-5-(*t*-butyldimethylsiloxy)-9-hydroxy-13-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-3,11-bis-(triethylsiloxy)-tetradec-13-en-7-one (6)

A two-necked flask containing (−)-Ipc_2BCl (1.38 g, 4.31 mmol, 1.5 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 0 °C and Et_3N (681 μL, 4.89 mmol, 1.7 eq.) was added, followed by a solution of ketone **7** (1.42 g, 2.88 mmol) in Et_2O (5 mL + 2 × 3 mL washings) *via* cannula. The reaction mixture was stirred for a further 40 min at 0 °C then cooled to −78 °C before a solution of aldehyde **8** (1.98 g, 4.46 mmol, 1.55 eq.) in Et_2O (5 mL + 2 × 3 mL washings) was added *via* cannula. The reaction was stirred at −78 °C for a further 3 h then at −20 °C for 16 h. The reaction was quenched by the addition of pH 7 buffer (50 mL) at 0 °C and allowed to warm to room temperature. 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 (50 mL), pH7 buffer (25 mL) and cooled to 0 °C. A 30% solution of H_2O_2 (5 mL) was added and the mixture was warmed to rt and stirred for 2.5 h. CH_2Cl_2 (50 mL) and H_2O (50 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL) and combined organics were washed with brine (2 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash

chromatography (2.5 : 97.5 → 25 : 75 Et_2O–light petroleum) afforded recovered aldehyde **8** (608 mg) and aldol product **6** (2.69 g, 100%) as a colourless oil: R_f: 0.80 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ +14.9 (*c* 1.93, $CHCl_3$); IR (liquid film): 3518, 3030, 1711, 1641, 1462 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.27–7.33 (5H, m, Ar*H*), 4.84 (1H, s, C=CH_aH_b), 4.80 (1H, s, C=CH_aH_b), 4.48 (2H, AB_q, J = 11.9 Hz, OCH_2Ph), 4.26 (1H, quin., J = 6.0 Hz), 4.16–4.20 (1H, m), 4.06–4.11 (1H, m), 3.94 (1H, quin., J = 6.0 Hz), 3.70 (1H, dd, J = 9.5, 5.3 Hz), 3.45–3.55 (4H, m, one of which is O*H*), 2.45–2.60 (4H, m), 2.13–2.34 (3H, m), 1.50–1.88 (6H, m), 1.04–1.10 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$), 0.94 (9H, t, J = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.99 (9H, t, J = 8.0 Hz, Si(CH_2CH_3)$_3$), 0.84 (9H, s, SiC(CH_3)$_3$), 0.63 (6H, q, J = 8.0 Hz, Si(C$H_2$$CH_3$)$_3$), 0.58 (6H, q, J = 7.9 Hz, Si(C$H_2$$CH_3$)$_3$), 0.05 (3H, s, SiC$H_3$), 0.00 (3H, s, SiC$H_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 209.2, 148.2, 138.5, 128.3, 127.7, 127.4, 111.8, 73.0, 71.4, 67.7, 66.8, 66.6, 66.1, 51.5, 51.3, 45.4, 44.2, 42.7, 42.5, 37.1, 25.8, 18.0, 17.9, 16.7, 12.0, 6.9, 6.8, 5.1, 5.0, −4.5, −4.6; HRMS (+FAB) Calc. for $C_{51}H_{101}O_7Si_4Na$ [MH + Na]$^+$: 960.6522, found: 960.6589.

(2*S*,4*S*,6*R*,8*S*,10*S*)-8-(2-Benzyloxyethyl)-10-(*t*-butyldimethylsiloxy)-2-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undecan-4-ol (5)

To a stirred solution of the aldol adduct **6** (864 mg, 0.921 mmol, 1.0 eq.) in a 1 : 1 mixture of dry CH_2Cl_2 (20 mL) and dry MeOH (20 mL) was added a catalytic amount of PPTS. The solution was stirred at rt for 40 min (TLC analysis indicated product **5**, hemiacetal and a very small amount of the TBS deprotected diol) and then a few drops of Et_3N were added to neutralise the PPTS. The reaction was concentrated *in vacuo* and the residue was subjected to flash chromatography (10 : 90 → 20 : 80 EtOAc–hexanes) to yield the spiroacetal **57** (405 mg, 63%) followed by the hemiacetal (202 mg, R_f: 0.50 (20% EtOAc in hexane). The hemiacetal (202 mg) was resubjected to the above conditions (CH_2Cl_2 (5 mL), MeOH (5 mL) and a catalytic amount of PPTS) and after flash chromatography (10 : 90 → 20 : 80 EtOAc–hexanes), a further 157 mg of the spiroacetal **5** was recovered. The total spiroacetal **5** obtained was 562 mg (88%): R_f: 0.60 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ −33.2 (*c* 1.20, $CHCl_3$); IR (liquid film): 3526, 1642, 1463 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.27–7.33 (5H, m, Ar*H*), 4.88 (1H, s, C=CH_aH_b), 4.82 (1H, s, C=CH_aH_b), 4.50 (2H, AB_q, J = 12.1 Hz, OCH_2Ph), 4.26–4.28 (1H, m, 3-C*H*), 4.23 (1H, d, J = 10.5 Hz, O*H*), 4.09–4.13 (1H, m, 11-C*H*), 4.07 (1H, br t, J = 3.3 Hz, 5-C*H*), 4.03 (1H, br d, J = 10.5 Hz, 9-C*H*), 3.70 (1H, dd, J = 9.4, 5.4 Hz, 15-CH_aH_b), 3.57 (2H, t, J = 6.3 Hz, 1-CH_2), 3.46 (1H, dd, J = 9.4, 8.0 Hz, 15-CH_aH_b), 2.42 (1H, dd, J = 14.6, 5.1 Hz, 12-CH_aH_b), 2.27 (1H, sextet, J = 6.5 Hz, 14-C*H*), 2.06 (1H, dd, J = 14.6, 7.9 Hz, 12-CH_aH_b), 1.69–1.90 (5H, m, 2-CH_2 + 4-CH_2 + 10-CH_aH_b), 1.49–1.62 (4H, m, 6-CH_2 + 8-CH_2), 1.36 (1H, dt, J = 12.7, 2.6 Hz, 10-CH_aH_b), 1.01–1.12 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.02 (3H, s, Si(CH_3)$_2$); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 147.9, 138.3, 128.3, 127.8, 127.5, 111.3, 98.7, 73.1, 67.7, 65.2, 64.2, 63.5, 63.4, 43.0, 41.7, 41.4, 40.9, 38.8, 37.5, 36.0, 25.8, 18.1, 16.4, 12.0, −4.8, −5.0; HRMS (+FAB) Calc. for $C_{39}H_{70}O_6Si_2$ [M]$^+$: 690.4711, found: 690.4752.

(2*S*,4*S*,6*R*,8*S*,10*S*)-8-(2-Benzyloxyethyl)-10-(*t*-butyldimethylsiloxy)-2-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undecan-4-ol (24)

To a suspension of Dess–Martin periodinane (6.18 g, 14.6 mmol, 2 eq.) in CH_2Cl_2 (80 mL) was added pyridine (5.90 mL, 72.9 mmol, 10 eq.) at rt. The resultant mixture was stirred at rt for a further 15 min before a solution of alcohol **5** (5.03 g, 7.28 mmol) in CH_2Cl_2 (10 mL + 2 × 5 mL washings) was added. The reaction mixture was stirred at rt for a further 30 min and poured into sat. aq. $Na_2S_2O_3$–$NaHCO_3$ (1 : 1, 100 mL). The biphasic mixture was stirred for 15 min, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5 : 95 → 25 : 75 Et_2O–light petroleum) afforded ketone **24** (4.69 g, 94%) as a colourless oil: R_f: 0.75 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ −48.0 (*c* 0.98, $CHCl_3$); IR (liquid film): 1728, 1642, 1463 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.24–7.33 (5H, m, Ar*H*), 4.84 (2H, s, C=CH_2), 4.45 (2H, AB_q, J = 11.9 Hz, OCH_2Ar), 4.17–4.21 (1H, m, 3-C*H*), 4.12 (1H, br t, J = 3.0 Hz, 5-C*H*), 4.05–4.10 (1H, m, 11-C*H*), 3.66 (1H, dd, J = 9.5, 5.7 Hz, 15-CH_aH_b), 3.45–3.55 (3H, m, 1-CH_aCH_b + 15-CH_aH_b), 2.52 (1H, dd, J = 14.5, 4.5 Hz, 12-CH_aH_b), 2.43 (1H, br d, J = 14.3 Hz, 10-CH_aH_b), 2.17–2.40 (4H, m, 8-CH_aH_b + 12-CH_aH_b + 14-C*H*), 2.13 (1H, dd, J = 14.3, 11.5 Hz, 10-CH_aH_b), 1.95 (1H, br d, J = 14.0 Hz, 6-CH_aH_b), 1.73 (2H, br q, J = 7.3 Hz, 2-CH_2), 1.56–1.61 (2H, m, 4-CH_aH_b + 6-CH_aH_b), 1.47 (1H, dt, J = 12.5, 3.0 Hz, 4-CH_aH_b), 1.01–1.08 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$), 0.91 (9H, s, SiC(CH_3)$_3$), 0.04, 0.06 (6H, 2 × s, Si(CH_3)$_2$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 206.4, 147.0, 138.4, 128.3, 127.5, 127.4, 111.9, 99.3, 72.8, 68.2, 67.4, 66.8, 64.1, 62.0, 52.4, 46.2, 42.6, 42.6, 41.5, 41.1, 36.1, 35.7, 25.8, 18.0, 16.4, 11.9, −4.8, −5.0; HRMS (+FAB) Calc. for $C_{39}H_{69}O_6Si_2$ [M + H]$^+$: 689.4633, found: 689.4643.

(2*S*,4*S*,6*R*,8*S*,10*S*)-8-(2-Benzyloxyethyl)-10-(*t*-butyldimethylsiloxy)-4-methyl-2-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undecan-4-ol (25)

To a cold (−78 °C) solution of ketone **24** (3.84 g, 5.57 mmol) in THF (35 mL) was added MeMgBr (3.0 M in Et_2O, 3.72 mL, 11.2 mmol, 2.0 eq.). The reaction mixture was stirred at −78 °C for 20 min then warmed to 0 °C for a further 30 min. The reaction was quenched with sat. aq. NH_4Cl (100 mL) 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 → 25 : 75 Et_2O–light petroleum) afforded 3° alcohol **25** (3.73 g, 95%) as a colourless oil: R_f: 0.75 (20 : 80 EtOAc–hexanes); $[\alpha]_D^{20}$ −34.7 (*c* 1.69, $CHCl_3$); IR (liquid film): 3516, 1642, 1462 cm^{-1}; ^1H NMR: δ (500 MHz, $CDCl_3$) 7.25–7.32 (5H, m, *Ph*), 4.88, 4.82 (2H, s, s, C=CH_2), 4.61 (1H, s, O*H*), 4.51, 4.47 (2H, AB_q, J = 12.0 Hz, OCH_2Ph), 4.26 (1H, br t, J = 9.2 Hz, 3-C*H*), 4.02–4.08 (2H, m, 5-C*H* + 11-C*H*), 3.70 (1H, dd, J = 9.2, 5.4 Hz, 15-CH_aH_b), 3.56 (2H, t, J = 6.4 Hz, 1-CH_2), 3.46 (1H, dd, J = 7.9, 9.2 Hz, 15-CH_aH_b), 2.44 (1H, dd, J = 5.0, 14.7 Hz, 12-CH_aH_b), 2.27 (1H, sextet, J = 6.6 Hz, 14-C*H*), 2.05 (1H, dd, J = 7.9, 14.7 Hz, 12-CH_aH_b), 1.69–1.85 (5H, m, 2-CH_2 + 6-CH_aH_b + 8-CH_aH_b + 10-CH_aH_b), 1.49–1.60 (3H, m, 4-CH_2 + 6-CH_aH_b), 1.44 (1H, d, J = 13.8 Hz, 8-CH_aH_b), 1.20 (1H, t, J = 12.5 Hz, 10-CH_aH_b), 1.15 (3H, s, 9-CCH_3), 1.05–1.10 (24H, m, 14-CHCH_3 + Si(C*H*(CH_3)$_2$)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04, 0.02 (6H, s, s, Si(CH_3)$_2$); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 147.8, 138.4, 128.3, 127.7, 127.4, 111.3, 98.6, 73.1, 68.1, 67.6, 67.5, 65.2, 64.2, 63.2, 46.6, 43.3, 43.0, 41.7, 41.1, 38.8, 35.9, 30.1, 25.8, 18.1, 18.0, 16.4, 12.0, −4.8, −4.9; HRMS (+FAB) Calc. for $C_{40}H_{71}O_6Si_2$ [M–H]$^+$: 703.4789, found: 703.4744; *m/z*: (+FAB) 703 ([M–H]$^+$, 1), 687 (2), 555 (28), 305 (16), 231 (43), 145 (100), 115 (88).

(2*S*,4*S*,6*R*,8*S*,10*S*)-8-(2-Hydroxyethyl)-10-(*t*-butyldimethylsiloxy)-4-methyl-2-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undecan-4-ol

To a cold (−78 °C) solution of benzyl ether **25** (2.29 g, 3.25 mmol) in THF (20 mL) was added a solution of LiDBB[28] (0.5 M in THF, 26.0 mL, 13.0 mmol, 4 eq.), dropwise. The reaction mixture was stirred at −78 °C for 1 h then quenched by addition of sat. aq. $NaHCO_3$ (50 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography

(20 : 80 → 75 : 25 Et_2O–light petroleum) afforded the title compound (1.99 g, 100%) as a colourless oil: R_f: 0.28 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −39.7 (*c* 0.70, $CHCl_3$); IR (liquid film): 3404 (br, OH), 1642,(w, C=C); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 4.89 (1H, s, C=CH_aH_b), 4.82 (1H, s, C=CH_aH_b), 4.31 (1H, m, 3-C*H*), 4.13 (1H, br, s, O*H*), 4.04–4.08 (2H, m, 5-C*H* + 11-C*H*), 3.75–3.76 (2H, m, 1-CH_2), 3.71 (1H, dd, J = 9.1, 5.0 Hz, 15-CH_aH_b), 3.46 (1H, br t, J = 9.1 Hz, 15-CH_aH_b), 2.47 (1H, dd, J = 14.1, 4.4 Hz, 12-CH_aH_b), 2.36 (1H, m, 14-C*H*), 2.27 (1H, br s, O*H*), 2.07 (1H, dd, J = 14.1, 8.4 Hz, 12-CH_aH_b), 1.67–1.74 (3H, m, 4-CH_aH_b + 6-CH_aH_b + 8-CH_aH_b), 1.52–1.60 (3H, m, 4-CH_aH_b + 6-CH_aH_b + 10-CH_aH_b), 1.43 (1H, d, J = 13.8 Hz, 8-CH_aH_b), 1.21 (1H, t, J = 12.1 Hz, 10-CH_aH_b), 1.14 (3H, s, 9-CCH_3), 1.09–1.13 (24H, m, 14-CHCH_3 + Si(CH(CH_3)$_2$)$_3$), 0.95 (9H, s, SiC(CH_3)$_3$), 0.03 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 148.3, 111.3, 98.3, 68.2, 67.8, 64.8, 64.2, 63.3, 60.1, 46.5, 43.2, 42.2, 41.6, 38.9, 38.0, 30.4, 25.8, 18.0, 18.0, 16.9, 12.0, −4.7, −4.9; HRMS (+CI, NH_3) Calc. for $C_{33}H_{67}O_6Si_2$ [MH]$^+$: 615.4476, found : 615.4480; *m/z*: (+CI, NH_3) 615 ([MH]$^+$, 5), 598 (20), 465 (60), 257 (50), 141 (100).

(2*R*,4*S*,6*S*,8*S*,10*S*)-(4-(*t*-Butyldimethylsiloxy)-10-hydroxy-10-methyl-8-{2-[1-methyl-2-(triisopropylsiloxy)-ethyl]-allyl}-1,7-dioxaspiro[5.5]undec-2-yl)-acetaldehyde

To a solution of the alcohol from the above procedure (3.33 g, 5.42 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (4.60 g, 10.8 mmol, 2 eq.) and the resulting suspension was stirred at rt for 2 h. The reaction was poured into sat. aq. $Na_2S_2O_3$–$NaHCO_3$ (1 : 1, 200 mL) and the biphasic mixture was stirred for a further 15 min. The layers were separated and 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 → 75 : 25 Et_2O–light petroleum) afforded the title compound (3.30 g, 99%) as a colourless oil: R_f: 0.36 (30 : 70 EtOAc–hexanes); $[\alpha]_D^{20}$ −34.4 (*c* 0.80, $CHCl_3$); IR (liquid film): 3528 (m, OH), 1729 (s, C=O), 1641, (w, C=C); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 9.81 (1H, m, 1-C*H*O), 4.94 (1H, s, C=CH_aH_b), 4.88 (1H, s, C=CH_aH_b), 4.65 (1H, m, 3-C*H*), 4.12 (2H, m, 5-C*H* + 11-C*H*), 4.01 (1H, br, s, O*H*), 3.72 (1H, dd, J = 9.4, 5.4 Hz, 15-CH_aH_b), 3.48 (1H, dd, J = 9.4, 7.7 Hz, 15-CH_aH_b), 2.61 (1H, ddd, J = 16.5, 8.3, 2.3 Hz, 2-CH_aH_b), 2.56 (1H, m, 2-CH_aH_b), 2.48 (1H, dd, J = 14.6, 4.9 Hz, 12-CH_aH_b), 2.31 (1H, br sextet, J = 6.4 Hz 14-C*H*), 2.06 (1H, dd, J = 14.6, 8.2 Hz, 12-CH_aH_b), 1.74–1.78 (2H, m, 6-CH_aH_b + 10-CH_aH_b), 1.65 (1H, d, J = 14.0 Hz, 8-CH_aH_b), 1.51–1.62 (3H, m, 4-CH_2 + 6-C*H*), 1.43 (1H, d, J = 14.0 Hz, 8-CH_aH_b), 1.20 (1H, m, 10-CH_aH_b), 1.16 (3H, s, 9-CCH_3), 1.04–1.10 (24H, m, Si(CH(CH_3)$_2$)$_3$ + 14-CHCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 199.6, 147.8, 111.4, 98.9, 68.0, 67.6, 65.4, 63.8, 60.2, 49.4, 46.5, 43.1, 41.4, 41.1, 38.3, 30.0, 25.8, 18.0, 18.0, 16.4, 12.0, −4.8, −5.0; HRMS (+CI, NH_3) Calc. for $C_{33}H_{68}NO_6Si_2$ [M + NH_4]$^+$: 630.4585, found: 630.4590; *m/z*: (+CI, NH_3) 630 ([M + NH_4]$^+$, 15), 595 (20), 285 (100), 257 (70), 156 (40).

(2*R*,4*S*,6*S*,8*S*,10*S*)-(4-(*t*-Butyldimethylsiloxy)-10-hydroxy-10-methyl-8-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undec-2-yl)-acetic acid

To a solution of the aldehyde from the above procedure (901 mg, 1.47 mmol) in *t*-BuOH (18 mL) and H_2O (6 mL) at 0 °C was added 2-methyl-2-butene (2.0 M in THF, 4.4 mL, 8.8 mmol, 6 eq.), followed by the dropwise addition of a solution of $NaClO_2$ (technical grade *ca.* 80%, 333 mg, 2.94 mmol, 2 eq.) and NaH_2PO_4·$2H_2O$ (0.92 g, 5.9 mmol, 4 eq.) in H_2O (12 mL). The resulting mixture was warmed to rt and stirred for 16 h and then diluted with H_2O (30 mL) and acidified with AcOH (few drops → pH 6). The mixture was extracted with EtOAc (4 × 15 mL), the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound (924 mg, 100%), as a colourless oil: R_f: 0.28 (40 : 60 EtOAc–hexanes); $[\alpha]_D^{20}$ −28.9 (*c* 0.70, $CHCl_3$); IR (liquid film): 3460 (m, OH), 2800–3200 (br, COOH) 1730 (s, C=O), 1643, (w, C=C); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 4.88 (1H, s, C=CH_aH_b), 4.77 (1H, s, C=CH_aH_b), 4.52 (1H, m, 3-C*H*), 4.11 (1H, m, 5-C*H*), 4.05 (1H, m, 11-C*H*), 3.79 (1H, dd, J = 14.4, 4.4 Hz, 15-CH_aH_b), 3.46 (1H, m, 15-CH_aH_b), 2.38–2.48 (3H, m, 2-CH_2 + 12-CH_aH_b), 2.33 (1H, m, 14-C*H*), 2.20 (1H, m, 12-CH_aH_b), 1.71–1.75 (2H, m, 6-CH_aH_b + 10-CH_aH_b), 1.70 (1H, d, J = 13.7 Hz, 8-CH_aH_b), 1.50–1.63 (4H, m, 4-CH_2 + 6-CH_aH_b + 10-CH_aH_b), 1.45 (1H, d, J = 13.7 Hz, 8-CH_aH_b), 1.14 (3H, s, 9-CCH_3), 1.13 (3H, d, J = 6.7 Hz, 14-CCH_3), 1.08–1.11 (21H, m, Si(CH(CH_3)$_2$)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 173.2, 147.6, 111.4, 98.7, 68.8, 67.8, 64.8, 63.9, 62.4, 46.3, 42.8, 42.7, 41.8, 41.3, 40.9, 38.5, 29.8, 25.8, 18.1, 18.0, 16.8, 12.0, −7.4, −4.9; HRMS (+CI, NH_3) Calc. for $C_{33}H_{65}O_7Si_2$ [MH]$^+$: 629.4269, found: 629.4269; *m/z*: (+CI, NH_3) 629 ([MH]$^+$, 50) 611 (95), 479 (100), 435 (65), 285 (70), 155 (100).

2,2,2-Trichloroethyl (2*R*,4*S*,6*S*,8*S*,10*S*)-(4-(*t*-butyldimethylsiloxy)-10-hydroxy-10-methyl-8-{2-[1-(triisopropylsiloxy)-prop-2-(*R*)-yl]-allyl}-1,7-dioxaspiro[5.5]undec-2-yl)-acetate (26)

To a solution of the acid from the above procedure (3.02 g, 4.81 mmol), 2,2,2-trichloroethanol (0.554 mL, 5.77 mmol, 1.2 eq.) and DMAP (cat.) in CH_2Cl_2 (20 mL) at rt was added a solution of DCC (1.0 M in CH_2Cl_2, 9.62 mL, 9.62 mmol, 2 eq.). The reaction mixture was stirred at rt for 2 h and then quenched by addition of H_2O (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 ($MgSO_4$) and concentrated *in vacuo.* Flash chromatography (5 : 95 → 20 : 80 Et_2O–light petroleum) afforded ester **26** (3.18 g, 87%) as a colourless oil: R_f: 0.23 (10 : 90 EtOAc–hexanes); $[\alpha]_D^{20}$ −26.3 (*c* 1.70, $CHCl_3$); IR (liquid film): 3536 (m, OH), 1760 (s, C=O), 1642, (w, C=C); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 4.93 (1H, s, C=CH_aH_b), 4.87 (1H, s, C=CH_aH_b), 4.80 (1H, d, J = 12.0 Hz, OCH_aH_bCCl$_3$), 4.70 (1H, d, J = 12.0 Hz, OCH_aH_bCCl$_3$), 4.58 (1H, m, 3-C*H*), 4.19–4.23 (2H, m, 11-C*H* + O*H*), 4.10 (1H, m, 5-C*H*), 3.72 (1H, dd, J = 9.5, 5.3 Hz, 15-CH_aH_b), 3.48 (1H, dd, J = 9.5, 7.7 Hz, 15-CH_aH_b), 2.62–2.68 (2H, m, 2-CH_2), 2.48 (1H, dd, J = 14.7, 4.9 Hz, 12-CH_aH_b), 2.31 (1H, m, 14-C*H*), 2.02 (1H, dd, J = 14.7, 8.4 Hz, 12-CH_aH_b), 1.63–1.80 (2H, m, 6-CH_aH_b + 10-CH_aH_b), 1.62 (1H, d, J = 13.4 Hz, 8-CH_aH_b), 1.51–1.58 (2H, m, 4-CH_aH_b + 6-CH_aH_b), 1.42 (1H, d, J = 13.4 Hz, 8-CH_aH_b), 1.28 (1H, t, J = 7.2 Hz, 10-CH_aH_b), 1.13 (3H, s, 9-CCH_3), 1.08 (3H, d, J = 8.8 Hz, 14-CHCH_3), 1.02–1.05 (21H, m, Si(CH(CH_3)$_2$)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3); ^{13}C NMR: δ (62.5 MHz, $CDCl_3$) 169.5, 147.8, 111.3, 98.8, 94.9, 73.9, 68.0, 67.6, 65.2, 63.8, 61.5, 46.5, 43.1, 41.4, 41.1, 40.1, 38.2, 30.2, 25.8, 18.1, 18.0, 16.4, 12.0, −4.8, −5.0; HRMS (+ESI) Calc. for $C_{35}H_{69}NO_7Cl_3Si_2$ [M + NH_4]$^+$: 776.3678, found: 776.3676; *m/z*: (+CI, NH_3) 776–780 ([M + NH_4]$^+$, 20), 740–746 (80), 705–711 (100), 669–675 (40), 609–611 (60), 573–577 (70), 436–438 (50).

2,2,2-Trichloroethyl (2*R*,4*S*,6*S*,8*S*,10*S*)-(4-acetoxy-8-{2-[1-oxo-prop-2-(*R*)-yl]-allyl}-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl)-acetate (2)

To a solution of alcohol **29** (45.9 mg, 71.3 μmol) in CH_2Cl_2 (2 mL) at rt was added Dess–Martin periodinane (60.0 mg, 143 μmol, 2 eq.). The reaction mixture was stirred at rt for 1 h and quenched by pouring into sat. aq. $Na_2S_2O_3$–$NaHCO_3$ (1 : 1, 10 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 × 20 mL), combined organics were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (20 : 80 EtOAc–light petroleum) afforded aldehyde **2** (42.7 mg, 93%) as a colourless oil: R_f: 0.64

(50 : 50 EtOAc–hexanes); $[a]_D^{20}$ −69.0 (*c* 3.00, $CHCl_3$); IR (liquid film): 2954, 1760, 1732 (s, C=O), 1640 (w, C=C); ^{1}H NMR: δ (500 MHz, $CDCl_3$) 9.57 (1H, s, 15-C*H*O), 5.19 (1H, s, C=CH_aH_b), 5.06 (1H, m, 5-C*H*), 4.93 (1H, s, C=CH_aH_b), 4.84 (1H, d, J = 12.0 Hz, OCH_aH_bCCl_3), 4.63 (1H, d, J = 12.0 Hz, OCH_aH_bCCl_3), 4.48 (1H, m, 3-C*H*), 4.33 (1H, m, 11-C*H*), 3.26 (1H, q, J = 6.9 Hz, 14-C*H*), 2.78 (1H, dd, J = 16.6, 6.3 Hz, 2-CH_aH_b), 2.54 (1H, dd, J = 16.6, 6.8 Hz, 2-CH_aH_b), 2.67 (1H, dd, J = 14.2, 6.8 Hz, 12-CH_aH_b), 2.18 (1H, dd, J = 14.2, 5.9 Hz, 12-CH_aH_b), 2.02 (3H, s, COCH_3), 1.82–1.90 (2H, m, 6-CH_aH_b + 4-CH_aH_b), 1.78 (1H, dd, J = 14.2, 1.7 Hz, 8-CH_aH_b), 1.54–1.60 (3H, m, 6-CH_aH_b + 4-CH_aH_b + 10-CH_aH_b), 1.30 (1H, d, J = 14.2 Hz, 8-CH_aH_b), 1.23 (3H, d, J = 6.9 Hz, 14-CHCH_3), 1.21 (4H, m, 10-CH_aH_b + 9-CCH_3), 0.93 (9H, m, Si(CH_2CH_3)$_3$), 0.56 (6H, m, Si(CH_2CH_3)$_3$); ^{13}C NMR: δ (100.6 MHz, $CDCl_3$) 201.2, 170.4, 168.8, 143.0, 125.1, 115.0, 96.6, 94.4, 73.4, 69.7, 66.4, 64.4, 60.2, 52.1, 47.0, 44.1, 41.6, 39.5, 37.9, 33.4, 31.5, 29.8, 29.2, 21.0, 12.7, 6.8, 6.3; HRMS (+CI, NH_3) Calc. for $C_{28}H_{45}O_8Cl_3Si$ [M + Na]$^+$: 665.1847, found: 665.1848.

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