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

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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

§ Current address: School of Chemistry, University of Sydney, NSW 2006, Australia. E-mail: m.coster@chem.usyd.edu.au; Fax: +61 2 9351 3329. detailed preclinical development as a lead structure for cancer chemotherapy.¹ Our strategy² 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 ABspiroacetal 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



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

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[‡] 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/



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 allylation⁶ of aldehyde **15**, employing *B*-allyldiisopinocampheylborane (^dIpc₂BAll), provided homoallylic alcohol **16** in 90% yield and 85% ee (MTPA ester⁷ 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 (TiCl₄, CH₂Cl₂, 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° under Sharpless asymmetric epoxidation¹⁰ conditions, to give enantioenriched (*R*)-19 (40%)



Scheme 3 Reagents and conditions: (a) (-)-Ipc₂BOMe, H₂C=CHCH₂-MgBr, Et₂O, -78 °C, 4 h, then H₂O₂, NaOH, H₂O, rt, 3 d; (b) NaH, MeI, THF, rt, 16 h; (c) O₃, CH₂Cl₂, NaHCO₃, -78 °C, 10 min, then PPh₃, 0 °C, 3 h; (d) H₂C=C(Et)CH₂SiMe₃ (13), TiCl₄, CH₂Cl₂, -100 °C, 20 min; (e) TIPSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 2 h; (f) CSA, MeOH, CH₂Cl₂, rt, 3.5 h.

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 oxidation¹¹ 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 (NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH–H₂O)¹² to convert **21a** to the corresponding acid **21b**, facilitating the isolation of **11** (47%).



Scheme 4 Reagents and conditions: (a) 10 mol% $Ti(Oi-Pr)_4$, 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% PdCl₂, CuCl, O₂, DMF-H₂O (8 : 1), rt, 16 h, then NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH-H₂O (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 reaction¹⁴ with ketone **11** (Scheme 5). Generation of the corresponding dicyclohexylboron enolate **22** from **11** under standard conditions (Chx₂BCl, Et₃N),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, CH₂Cl₂, rt, 30 min; (b) Chx₂BCl, Et₃N, Et₂O, 0 °C, 30 min; (c) 12, $-78 \rightarrow -20$ °C, 21 h, then pH 7 buffer, H₂O₂, MeOH, 0 °C \rightarrow 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 Ipc₂BCl 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, CD₂Cl₂) 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 (CH₂Cl₂, -78 °C, 15 min) allowed isolation of the intermediate alcohol 9. While strong bases such as KOt-Bu also led to the exclusive formation of the undesired spiroacetal 25, under mild, basic conditions (DBU, CH₂Cl₂, 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)-3hydroxybutyric 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 ^dIpc₂BAll 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) (-)-Ipc₂BOMe, H₂C=CHCH₂-MgBr, Et₂O, $-78 \rightarrow 0^{\circ}$ C 3 h, then H₂O₂, NaOH, H₂O, reflux, 16 h; (b) NaH, MeI, THF, 0 °C \rightarrow rt, 16 h; (c) O₃, CH₂Cl₂, -78° C then PPh₃, rt, 16 h; (d) (+)-Ipc₂BOMe, H₂C=CHCH₂MgBr, Et₂O, $-78 \rightarrow -20^{\circ}$ C 18 h, then H₂O₂, NaOH, H₂O, reflux, 20 h; (e) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78° C, 2 h; (f) LiDBB, THF, -78° C, 1 h; (g) Dess-Martin periodinane, CH₂Cl₂, 0° C \rightarrow rt, 1.5 h.

was subjected to allylboration, this time with ${}^{1}\text{Ipc}_{2}\text{BAll}$ (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(2isocaranyl)borane (2- d Icr₂BAll),²² providing homoallylic alcohol **31** in 75% yield with high enantiomeric excess (94% ee by ¹H 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 (–)-Ipc₂BCl and Et₃N 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 (\geq 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 ($CH_2Cl_2-Et_2O$), 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} Icr₂BOMe, H₂C=CHCH₂MgBr, Et₂O, $-78 \degree$ C, 4 h, then H₂O₂, NaOH, H₂O, rt, 3 d; (b) TESOTf, 2,6-lutidine, CH₂Cl₂, $-78 \degree$ C, 2 h; (c) cat. OsO₄, NMO, acetone–H₂O, rt, 3 d; (d) NaIO₄, MeOH, pH 7 buffer, 0 °C \rightarrow rt, 16 h; (e) (–)-Ipc₂BCl, Et₃N, Et₂O, $-78 \rightarrow 0 \degree$ C, 1 h; (f) 7, $-78 \rightarrow -20 \degree$ C, 16 h, then pH 7 buffer, H₂O₂, MeOH, 0 °C \rightarrow rt, 1 h; (g) 40% aq. HF, MeCN, 0 °C, 50 min; (h) cat. HCl, CH₂Cl₂, Et₂O, rt, 30 min, separation and resubjection (x 5); (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, $-78 \degree$ C, 1 h; (j) Ac₂O, DMAP, pyridine, rt, 2 h; (k) cat. OsO₄, NMO, acetone–H₂O, rt, 20 h; (l) NaIO₄, MeOH, pH 7 buffer, rt, 1 h; (m) EtMgBr, Et₂O, $-78 \degree$ C \rightarrow rt, 2 h; (n) Dess–Martin periodinane, CH₂Cl₂, rt, 1 h.



Scheme 9 Reagents and conditions: (a) (+)-Ipc₂BCl, Et₃N, Et₂O, $-78 \rightarrow 0$ °C, 1 h; (b) **38**, $-78 \rightarrow -20$ °C, 17 h, then pH 7 buffer, H₂O₂, MeOH, 0 °C \rightarrow rt, 1 h; (c) cat. SmI₂, 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 boronmediated aldol reaction of ketone 37, readily available in four steps from PHB, with aldehyde 38 (Scheme 9). Enolisation of 37 with (+)-Ipc₂BCl and Et₃N 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-ol²⁵ 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 ¹H 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 reduction²⁶ using catalytic SmI₂ and propionaldehyde provided monoacylated anti 1,3-diol 41 in 90% yield as the only diastereomer by ¹H NMR (>97 : 3 dr).

Methylation of the C21 hydroxyl in **41**, under mild conditions (Me₃OBF₄, Proton-Sponge[®], CH₂Cl₂, 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 CH₂Cl₂–Et₂O afforded an equimolar mixture of the two, separable, spiroacetals. Protection of **47** as the TBS ether and oxidative cleavage of the alkene moiety (cat. OsO₄, NMO; NaIO₄) 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

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

A cooled (-78 °C) solution of (-)-Ipc₂BOMe (22.8 g, 72.0 mmol, 1.5 eq.) in Et₂O (200 mL) was treated with allylmagnesium bromide (1.0 M in Et₂O, 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 Et₂O (20 mL + 2 \times 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% H₂O₂ (60 mL) by dropping funnel. The resultant biphasic mixture was refluxed for 16 h. H₂O (200 mL) was added, the layers were separated and the aqueous phase was extracted with Et₂O (3 \times 100 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. The residue was purified by flash chromatography (5:95 Et₂O-CH₂Cl₂) 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 Et₂O-CH₂Cl₂) 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) (–)-Ipc₂BCl, Et₃N, Et₂O, -78 \rightarrow 0 °C, 1 h; (g) 7, -78 \rightarrow -20 °C, 16 h, then pH 7 buffer, H_2O_2 , MeOH, 0 °C \rightarrow rt, 1 h; (h) 40% aq. HF, MeCN, 0 °C, 40 min; (i) cat. HCl, CH_2Cl_2 , et₂O, rt, 30 min; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2 , -78 °C, 1 h; (k) cat. OsO₄, NMO, acetone–H₂O, rt, 6 h; (l) NaIO₄, MeOH, pH 7 buffer, rt, 1 h.

Downloaded by University of Stellenbosch on 27 February 2013 Published on 24 May 2005 on http://pubs.rsc.org | doi:10.1039/B504148A title compound, sufficiently pure for characterisation purposes. Major diastereomer: $R_{\rm f}$: 0.30 (5 : 95 Et₂O–CH₂Cl₂); $[a]_{\rm D}^{20}$ –55.8 (*c* 1.56, CHCl₃); IR (liquid film): 3443 (br, s), 1641 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.26–7.36 (5H, m, *Ph*), 5.83 (1H, m, 19-CH), 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-CH + 23-CH), 3.63 (1H, br s, OH), 2.21 (2H, m, 20-CH₂), 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-CH₃); ¹³C NMR: δ (62.9 MHz, CDCl₃) 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, NH₃) Calc. for C₁₄H₂₁O₂ [MH]⁺: 221.1542, found: 221.1541; *m/z*: (+CI, NH₃) 221 ([MH]⁺, 100), 179 (7), 130 (68), 108 (100), 106 (69), 91 (57).

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

NaH (60% in mineral oil, 15.4 g, 0.385 mol) was washed with *n*-hexane $(3 \times 50 \text{ mL})$ and suspended in THF (200 mL). The suspension was cooled to 0 $^{\circ}C$ and a solution of (4S,6R)-6benzyloxy-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 H₂O (150 mL) and Et₂O (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% Na₂S₂O₃ (150 mL) then brine (100 mL), dried over MgSO₄ 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 $(2:78:20 \text{ Et}_2\text{O}-\text{CH}_2\text{Cl}_2-\text{hexanes})$ 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): $R_{\rm f}$: 0.45 (5 : 95 Et₂O–CH₂Cl₂); $[a]_{\rm D}^{20}$ –6.3 (c 2.24, CHCl₃); IR (liquid film): 1640 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.25-7.35 (5H, m, Ph), 5.81 (1H, m, 19-CH), 5.06 (2H, app d, J = 13.4 Hz, CH=C H_2), 4.57 (1H, d, J = 11.7 Hz, OC H_aH_bPh), 4.44 (1H, d, J = 11.7 Hz, OCH_aH_bPh), 3.66 (1H, m, 23-CH), 3.38 (1H, m, 21-CH), 3.33 (3H, s, OCH₃), 2.26 (2H, m, 20-CH₂), 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_a $H_{\rm b}$), 1.23 (3H, d, J = 6.1 Hz, 24-C $H_{\rm a}$); ¹³C NMR: δ (62.9 MHz, CDCl₃) 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, NH₃) Calc. for C₁₅H₂₃O₂ [MH]⁺: 235.1698, found: 235.1698; m/z: (+CI, NH₃) 235 ([MH]⁺, 100), 203 (8), 108 (22), 106 (11), 91 (16).

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

A cooled $(-78 \degree C)$ solution of (+)-Ipc₂BOMe (4.10 g, 13.0 mmol,1.9 eq.) in Et₂O (80 mL) was treated with allylmagnesium bromide (1.0 M in Et₂O, 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% H₂O₂ (20 mL) was added to the stirred solution at 0 °C and the resultant biphasic mixture refluxed for 20 h. H₂O (20 mL) was added, the layers were separated and the aqueous phase was extracted with Et₂O (3 \times 20 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated in vacuo. The crude product was purified by flash chromatography (30: 70 EtOAchexanes) 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: $R_{\rm f}$: 0.32 (30 : 70 EtOAc-hexanes); [a]²⁰_D -40.5 (c 2.19, CHCl₃); IR (liquid film): 3389 (br, s), 1641, 1603 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.25-7.37 (5H, m, Ph), 5.80 (1H, m, 17-CH), 5.10 (1H, d, J = 18.6 Hz, trans-CH=CH_aH_b), 5.08 (1H, d, J = 8.6 Hz, *cis*-CH=CH_a H_b), 4.57 (1H, d, J = 11.7 Hz, OC H_a H_bPh), 4.41 $(1H, d, J = 11.7 \text{ Hz}, \text{OCH}_{a}H_{b}\text{Ph}), 3.91 (1H, m, 19-CH), 3.68$ (1H, m, 23-CH), 3.59 (1H, m, 21-CH), 3.34 (3H, s, OCH₃), 2.89 (1H, d, J = 3.2 Hz, OH), 2.19 (2H, m, 18-CH₂), 2.04 (1H, m, 20-CH_aH_b), 1.67 (1H, m, 20-CH_aH_b), 1.53 (2H, m, 22-CH₂), 1.24 (3H, d, J = 6.1 Hz, 24-CH₃); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for $C_{17}H_{27}O_3$ [MH]⁺: 279.1960, found: 279.1960; m/z: (+CI, NH₃) 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 $(-78 \degree C)$ solution of the alcohol from the above procedure (2.05 g, 7.36 mmol), in CH₂Cl₂ (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. NaHCO₃ (20 mL) and warmed to rt. The mixture was concentrated in vacuo and Et₂O (20 mL) was added. The layers were separated and the aqueous phase was extracted with Et₂O (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄) 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: $R_{\rm f}$: 0.36 (10 : 90 EtOAchexanes); $[a]_{D}^{20}$ -46.1 (c 1.39, CHCl₃); IR (liquid film): 1640 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.25–7.36 (5H, m, Ph), 5.81 (1H, m, 17-CH), 5.03 (1H, d, J = 15.2 Hz, trans-CH=CH_aH_b), 5.03 $(1H, d, J = 12.2 \text{ Hz}, cis-CH=CH_aH_b), 4.56 (1H, d, J = 11.7 \text{ Hz},$ $OCH_{a}H_{b}Ph$), 4.45 (1H, d, J = 11.7 Hz, $OCH_{a}H_{b}Ph$), 3.96 (1H, m, 19-CH), 3.60 (1H, m, 23-CH), 3.57 (1H, m, 21-CH), 3.29 $(3H, s, OCH_3), 2.23 (2H, m, 18-CH_2), 2.00 (1H, ddd, J = 14.1, 1)$ 7.5, 5.3 Hz, 20- $CH_{a}H_{b}$), 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-CH₃), 0.88 (9H, s, SiC(CH₃)₃), 0.08 (3H, s, Si(CH₃)_a), 0.07 $(3H, s, Si(CH_3)_b)$; ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₂₃H₄₁O₃Si [MH]⁺: 393.2825, found: 393.2825; *m/z*: (+CI, NH₃) 393 ([MH]⁺, 100), 263 (16), 261 (11), 229 (19), 132 (24), 108 (50), 106 (67), 91 (32).

(2R,4R,6R)-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 LiDBB²¹ (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. NaHCO₃ (50 mL) and warmed to rt. H₂O (20 mL) and Et₂O (50 mL) were added, the layers were separated and the aqueous phase was extracted with Et₂O (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by flash chromatography (5: $95 \rightarrow 25$: 75 EtOAc-hexanes) to afford the title compound (4.83 g, 95%), as a colourless oil: R_f : 0.35 (30 : 70 EtOAc-hexanes); $[a]_D^{20}$ -12.8 (*c* 2.30, CHCl₃); IR (liquid film): 3442 (br, s), 1641 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 5.81 (1H, m, 17-CH), 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-CH), 3.85 (1H, m, 19-CH), 3.53 (1H, m, 21-CH), 3.33 (3H, s, OCH₃), 3.12 (1H, s, O*H*), 2.23 (2H, m, 18-C*H*₂), 1.77 (1H, ddd, *J* = 14.3, 8.4, 6.0 Hz, 20-C*H*_aH_b), 1.65 (1H, app dt, *J* = 15.5, 8.8 Hz, 22-C*H*_aH_b), 1.56 (1H, m, 22-C*H*_aH_b), 1.50 (1H, ddd, *J* = 14.3, 8.0, 6.0 Hz, 20-C*H*_aH_b), 1.18 (3H, d, *J* = 6.2 Hz, 24-C*H*₃), 0.89 (9H, s, SiC(C*H*₃)₃), 0.08 (3H, s, Si(C*H*₃)_a), 0.07 (3H, s, Si(C*H*₃)_b); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₁₆H₃₅O₃Si [MH]⁺: 303.2355, found: 303.2355; *m/z*: (+CI, NH₃) 303 ([MH]⁺, 100), 187 (11), 171 (13), 139 (19), 132 (25), 92 (13).

(4S,6R)-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 CH₂Cl₂ (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. NaHCO₃ (100 mL) followed by 10% $Na_2S_2O_3$ (100 mL) and the biphasic mixture allowed to stir vigorously for 1 h. The CH₂Cl₂ was removed in vacuo, Et₂O (100 mL) was added, the layers were separated and the aqueous phase was extracted with Et₂O (3×50 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) 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: $R_{\rm f}$: 0.44 $(30: 70 \text{ EtOAc-hexanes}); [a]_{D}^{20} - 34.1 (c 1.40, CHCl_3); IR (liquid$ film): 1715 (s), 1640 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 5.79 (1H, m, 17-CH), 5.03 (2H, app d, 13.3 Hz, CH=CH₂), 3.92 (1H, m, 19-CH), 3.83 (1H, m, 21-CH), 3.30 (3H, s, OCH₃), 2.70 (1H, dd, J = 15.6, 6.4 Hz, 22-C H_a H_b), 2.49 (1H, dd, J = 15.6, 5.8 Hz, $22-CH_aH_b$), 2.24 (2H, br t, J = 6.2 Hz, 18-C H_2), 2.16 (3H, s, 24- CH_3 , 1.65 (1H, ddd, $J = 14.2, 8.6, 3.3 \text{ Hz}, 20 - CH_aH_b$), 1.43 (1H, ddd, J = 14.2, 8.8, 3.9 Hz, 20-CH_aH_b), 0.90 (9H, s, SiC(CH₃)₃), 0.08 (6H, s, Si(CH₃)₂); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₁₆H₃₃O₃Si [MH]⁺: 301.2199, found: 301.2199; m/z: (+CI, NH₃) 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*}Icr₂BOMe²² (3.0 g, 9.48 mmol, 1.7 eq.) in dry Et₂O (20 mL) was added, dropwise, allylmagnesium bromide (1.0 M solution in Et₂O, 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 $(3 \times 100 \text{ mL})$. The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) 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: $R_{\rm f}$: 0.35 (30 : 70 EtOAc–hexanes); $[a]_{\rm D}^{2\ell}$ -3.0 (c 2.06, CHCl₃); IR (liquid film): 3443 (br, s), 1641, 1612, 1513 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.26 (2H, d, J = 8.5 Hz, ArH), 6.89 (2H, d, J = 8.5 Hz, ArH), 5.78–5.86 (1H, m, 25-CH), 5.08–5.13 (2H, m, C=CH₂), 4.49 (2H, s, OCH₂Ar), 3.83–3.89 (1H, m, 27-CH), 3.81 (3H, s, OCH₃), 3.49 (1H, dd, $J = 9.3, 3.3 \text{ Hz}, 28 \text{-} CH_a H_b), 3.35 (1H, dd, J = 9.3, 7.6 \text{ Hz}, 28 \text{-}$ CH_aH_b), 2.31 (1H, d, J = 3.1 Hz, OH), 2.25 (2H, t, J = 6.6 Hz, 26-CH₂); ¹³C NMR: δ (62.9 MHz, CDCl₃) 159.3, 134.3, 130.1, 129.4, 117.6, 113.9, 73.6, 73.0, 69.7, 55.3, 37.2; HRMS: (+CI, NH₃) Calc. for C₁₃H₁₉O₃ [MH]⁺: 223.1334, found: 223.1334.

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

A two-necked flask containing (–)-Ipc₂BCl (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 Et₂O (20 mL) was added. The solution was cooled to -78 °C and Et₃N (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 Et₂O (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 $Et_2O(10 \text{ mL} + 2 \times 5 \text{ mL} \text{ washings})$ 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% H₂O₂ (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 CH₂Cl₂ (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 (MgSO₄) and concentrated in *vacuo*. Flash chromatography $(1: 99 \rightarrow 10: 90 \text{ Et}_2\text{O}-\text{CH}_2\text{Cl}_2)$ afforded aldol product 5 (2.01 g, 89%) as colourless oil: R_f : 0.35 (30 : 70 EtOAc-hexanes); $[a]_{D}^{20}$ -7.0 (c 0.90, CHCl₃); IR (liquid film): 3676 (br), 1734 (s), 1639, 1612 cm⁻¹; ¹H NMR: δ (500 MHz, $CDCl_3$) 7.24 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, d, J = 8.6 Hz, ArH), 5.80 (1H, m, 17-CH), 5.03 (1H, d, J = 15.2 Hz, trans- $CH=CH_{a}H_{b}$), 5.03 (1H, d, J = 12.1 Hz, *cis*-CH=CH_aH_b), 4.44 (2H, ab q, J = 12.1 Hz, CH_2Ar), 4.23 (1H, m, 25-CH), 4.08 (1H, br dq, J = 7.2, 5.3 Hz, 27-CH), 3.88 (1H, m, 19-CH),3.84 (1H, m, 21-CH), 3.80 (3H, s, ArOCH₃), 3.51 (1H, d, J = 2.1 Hz, OH), 3.40 (1H, dd, J = 9.7, 5.2 Hz, 28-CH_aH_b), 3.36 $(1H, dd, J = 9.7, 5.2 Hz, 28-CH_aH_b), 3.29 (3H, s, OCH_3), 2.70$ $(1H, dd, J = 15.8, 6.5 Hz, 22-CH_aH_b), 2.60 (1H, dd, J = 16.7, 100)$ 7.9 Hz, 24-C H_aH_b), 2.52 (1H, dd, J = 16.7, 4.3 Hz, 24-C H_aH_b), 2.49 (1H, dd, J = 15.8, 5.5 Hz, 22-CH_aH_b), 2.22 (2H, br t, J =6.1 Hz, 18-CH₂), 1.60–1.72 (3H, m, 26-CH₂ + 20-CH_aH_b), 1.42 (1H, ddd, J = 14.2, 8.7, 4.0 Hz, 20-CH_aH_b), 0.94 (9H, t, J =8.0 Hz, Si(CH₂CH₃)₃), 0.89 (9H, s, SiC(CH₃)₃), 0.61 (6H, q, J = 8.0 Hz, Si(CH₂CH3)₃), 0.08 (6H, s, Si(CH₃)₂); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for $C_{34}H_{63}O_7Si_2$ [MH]⁺: 639.4112, found: 639.4110; *m*/*z*: (+CI, NH₃) 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-10methoxy-2-(*p*-methoxybenzyloxymethyl)-1,7dioxaspiro[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. NaHCO₃ (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 (MgSO₄) and concentrated *in vacuo*. Flash chromatography (50 : 50 \rightarrow 80 : 20 EtOAc–light petroleum) afforded spiroacetals **3** and **4** (1.13 g, 92%) as a 1 : 5 mixture, respectively.

Minor spiroacetal (desired) 3: $R_{\rm f}$: 0.49 (5 : 95 MeOH–CH₂Cl₂); HPLC: $R_{\rm t}$ 35 min (65 : 35 EtOAc–hexane); $[a]_{\rm D}^{20}$ –37.4 (c 0.70, CHCl₃); IR (liquid film): 3525 (br, s), 3053, 1612, 1513 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.27 (2H, d, J = 8.6 Hz, ArH), 6.89 (2H, d, J = 8.6 Hz, ArH), 5.83 (1H, m, 17-CH), 5.17 (1H, d, J = 18.0 Hz, trans-CH=CH_aH_b), 5.14 (1H, d, J = 10.9 Hz, cis-CH=CH_aH_b), 4.53 (2H, s, OCH₂Ar), 4.43 (1H, m, 27-CH), 4.07 (1H, app dt, J = 8.3, 3.0 Hz, 25-CH), 3.81 (3H, s, ArOCH₃), 3.65 (1H, m, 19-CH), 3.50 (2H, m, 28-CH₂), 3.45 (1H, m, 21-CH), 3.33 (3H, s, OCH₃), 2.36 (1H, m, 18-CH_aH_b), 2.25–2.32 (2H, m, 18-CH_a H_b + 24-C H_{eq}), 2.10 (1H, app dd, J = 12.2, 4.4 Hz, 22-C H_{eq}), 2.05 (1H, app dt, J = 12.4, 2.0 Hz, 20-C H_{eq}), 1.77 (1H, dd, J = 13.7, 2.0 Hz, 26-C H_{eq}), 1.66 (1H, dt, J = 13.7, 2.8 Hz, 26-C H_{ax}), 1.41–1.48 (2H, m, 22-C H_{ax} + 24-C H_{ax}), 1.27 (1H, br q, J = 11.8 Hz, 26-C H_{ax}); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₂₂H₃₆NO₆ [M + NH₄]⁺: 410.2543, found: 410.2543; m/z: (+CI, NH₃) 410 ([M + NH₄]⁺, 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-CH₂Cl₂); HPLC: R_t 45 min (65 : 35 EtOAc-hexane); $[a]_{D}^{20}$ +41.3 (c 0.90, CHCl₃); IR (liquid film): 3425 (br, s), 3073, 1641, 1612, 1586, 1513 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.25 (2H, d, J = 8.5 Hz, ArH), 6.88 (2H, d, J = 8.5 Hz, ArH), 5.76 (1H, m, 17-CH), 5.07 (1H, dd, J = 17.5, 1.4 Hz, trans-CH=CH_aH_b), 5.03 $(1H, d, J = 9.8 \text{ Hz}, cis-CH=CH_aH_b), 4.50 (1H, d, J = 11.6 \text{ Hz},$ OCH_aH_bAr), 4.43 (1H, d, J = 11.6 Hz, OCH_aH_bAr), 4.17–4.22 (2H, m, 25-CH + 27-CH), 3.85 (1H, m, 19-CH), 3.81 (3H, s, ArOCH₃), 3.63 (1H, m, 21-CH), 3.58 (1H, dd, *J* = 9.7, 6.2 Hz, 28-C H_aH_b), 3.51 (1H, dd, J = 9.7, 4.0 Hz, 28-C H_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 $(3H, m, 20-CH_{eq} + 24-CH_{eq} 26-CH_{eq}), 1.57 (1H, dt, J = 8.1)$ $3.7 \text{ Hz}, 26\text{-}CH_{ax}), 1.52 (1\text{H}, \text{app dd}, J = 13.0, 9.3 \text{ Hz}, 24\text{-}CH_{ax}),$ $1.21 (1H, br t, J = 12.0 Hz, 22-CH_{ax}), 1.03 (1H, br q, J = 11.7 Hz,$ 20-CH_{ax}); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₂₂H₃₃O₆ [MH]⁺: 393.2277, found: 393.2277; *m*/*z*: (+CI, NH₃) 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 CH₂Cl₂ (35 mL) was added anhydrous HCl (1.0 M in Et₂O, 0.216 mL, 0.216 mmol, 0.05 eq.). The reaction mixture was stirred at rt for 30 min then Et₃N (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 \rightarrow 2.5 : 97.5 MeOH–CH₂Cl₂) allowed the separation of desired spiroacetal **3** and undesired spiroacetal **4**. The undesired spiroacetal **4** was resubjected to the above conditions and after 5 cycles the desired spiroacetal **3** (1.17 g, 69%) was obtained as a colourless oil.

(2R,4S,6R,8R,10S)-[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 H₂O (4 mL) was treated with NMO (347 mg, 2.96 mmol, 1.7 eq.) and OsO4 (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% Na₂S₂O₃ (10 mL) and the mixture stirred for 40 min before the addition of Et₂O (10 mL) and separation of the layers. The aqueous phase was extracted with EtOAc (3 \times 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 (Na₂SO₄) 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 $H_2O(30 \text{ mL})$ was added to dissolve the precipitate. The solution was extracted with Et₂O (3 \times 20 mL), the combined organic extracts were washed with brine (40 mL), dried (Na₂SO₄) and the mixture was filtered through a short pad of silica, washing with 50 : 50 EtOAc-hexanes (2 \times 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); $[a]_{D}^{20}$ -8.2 (c 0.80, CHCl₃); IR (liquid film): 1724 (C=O), 1612, 1586, 1513 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 9.83 (1H, t, J = 1.8 Hz, 17-CHO), 7.25 (2H, d, J = 8.5 Hz, ArH), 6.86 $(2H, d, J = 8.5 \text{ Hz}, \text{Ar}H), 4.50-4.53 (3H, m, \text{OC}H_2\text{Ar} + 27-$ CH), 4.15 (1H, m, 25-CH), 4.01 (1H, m, 19-CH), 3.80 (3H, s, ArOCH₃), 3.45–3.51 (3H, m, 28-CH₂ and 21-CH), 3.32 (3H, s, OCH_3), 2.74 (1H, ddd, J = 17.1, 6.3, 1.7 Hz, 18- CH_aH_b), 2.60 $(1H, ddd, J = 17.1, 6.5, 1.7 Hz, 18-CH_aH_b), 2.03-2.20 (3H, m, m)$ $20-CH_{eq} + 24-CH_{eq} + 22-CH_{eq}$, 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-C H_{ax}), 1.36 (1H, t, J = 11.9 Hz, 22-C H_{ax}), 1.04 (1H, m, $20-CH_{ax}$, 0.85 (9H, s, SiC(CH₃)₃), 0.03 (3H, s, Si(CH₃)_a), 0.01 (3H, s, Si(CH₃)_b); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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 Et₂O (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. NH₄Cl (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 \times 50 mL). The combined organics were washed with brine (50 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude alcohol was taken up in CH₂Cl₂ (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. Na₂S₂O₃-NaHCO₃ 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 Et₂O (3 \times 60 mL), combined organics were washed with brine (50 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (5 : $95 \rightarrow 50$: 50 EtOAc–light petroleum) afforded CD-spiroacetal ethyl ketone 2 (1.53 g, 93% over 2 steps) as a white crystalline solid: $R_{\rm f}$: 0.45 (40 : 60 EtOAchexanes); [a]_D²⁰ -20.3 (c 1.00, CHCl₃); mp 47-49 °C; IR (liquid film): 1713 (s), 1612, 1586, 1513 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.86 (2H, d, *J* = 8.5 Hz, ArH), 4.51–4.52 (3H, m, OCH₂Ar + 28-CH), 4.11 (1H, m, 25-CH), 3.93 (1H, m, 19-CH), 3.80 (3H, s, ArOCH₃), 3.45-3.51 (3H, m, 27-CH₂ + 21-CH), 3.32 (3H, s, OCH₃), 2.84 (1H, dd, $J = 17.1, 3.7 \text{ Hz}, 18\text{-}CH_{a}H_{b}), 2.66 (1H, dd, J = 17.1, 8.9 \text{ Hz},$ 18-CH_a H_b), 2.40 (2H, q, J = 7.3 Hz, 16-C H_2), 2.21 (1H, m, $20-CH_{eq}$, 2.13 (1H, dd, J = 14.3, 3.4 Hz, $24-CH_{a}H_{b}$), 2.03 (1H, dd, J = 11.5, 3.8 Hz, 22-C H_{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-C H_{ax}), 1.36 (1H, t, J = 11.9 Hz, 22-C H_{ax}), 1.04 $(1H, m, 20-CH_{ax}), 1.01 (3H, t, J = 7.3 Hz, CH_2CH_3), 0.85 (9H, 1.01)$ S, SiC(CH₃)₃), 0.03 (3H, s, Si(CH₃)_a), 0.01 (3H, s, Si(CH₃)_b); 13 C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for $C_{29}H_{52}O_7NSi [M + NH_4]^+$: 554.3513, found: 554.3510; m/z: (+CI, NH₃) 554 ([M + NH₄]⁺, 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 CH₂Cl₂ (100 mL) was added a solution of 3-ethyl-3-buten-1-ol²⁵ (801 mg, 8.00 mmol) in CH₂Cl₂ (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 Et₂O (60 mL) and a 1 : 1 mixture of 10% Na₂S₂O₃ (50 mL) and sat. NaHCO₃ (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 Et₂O (2×20 mL). The combined organic extracts were dried (Na₂SO₄), 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 Et₂O, and used without further purification in the subsequent reaction: ¹H NMR: δ (250 MHz, CDCl₃) 9.65 (1H, t, J = 2.6 Hz, 19-CHO), 4.89 (1H, m, C=CH_aH_b), 4.84 (1H, m, C=CH_aH_b), 3.10 (2H, br d, J = 2.0 Hz, 18-CH₂), 2.09 (2H, br q, J = 7.4 Hz, 16-CH₂), 1.05 (3H, t, J = 7.4 Hz, CH₂CH₃).

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

A 100 mL, two-necked flask containing (+)-Ipc₂BCl (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 Et₃N (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 Et₂O ($3 \text{ mL} + 2 \times 1 \text{ mL}$ 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% H₂O₂ solution (3 mL). The reaction was stirred at rt for 1 h, diluted with H₂O (30 mL), the layers were separated and the aqueous layer extracted with Et₂O (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) 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: $R_{\rm f}$: 0.36 (30 : 70 EtOAc-hexanes); $[a]_{\rm D}^{20}$ -38.2 (c 2.28, CHCl₃); IR (liquid film): 3453 (br, s), 1708 (s), 1645 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.26–7.34 (5H, m, *Ph*), 4.85 (1H, d, *J* = 1.5 Hz, C=C H_aH_b), 4.78 (1H, d, J = 0.7 Hz, C=C H_aH_b), 4.56 $(1H, d, J = 11.5 \text{ Hz}, \text{OCH}_{a}\text{H}_{b}\text{Ph}), 4.43 (1H, d, J = 11.5 \text{ Hz},$ OCH_aH_bPh), 4.20 (1H, m, 19-CH), 4.06 (1H, m, 23-CH), 2.81 $(1H, s, OH), 2.80 (1H, dd, J = 15.6, 7.8 Hz, 22-CH_aH_b), 2.63$ $(1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 2.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_aH_b), 3.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_b), 3.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_b), 3.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_b), 3.53 (1H, dd, J = 17.4, 3.2 Hz, 20-CH_b), 3.53 (1H, dd, J = 17.4, 3.5 Hz), 3.53 (1H, dd, J = 17.4, 3.5 Hz), 3.5 Hz)$ 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_aH_b), 2.04 (2H, app q, 16-CH₂), 1.24 (3H, d, J = 6.2 Hz, 24-CH₃), 1.03 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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 SmI₂ (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. NaHCO₃ (10 mL), then diluted with H₂O (20 mL) and $Et_2O(10 \text{ mL})$. The layers were separated and the aqueous phase was extracted with Et₂O (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 EtOAchexanes); [a]_D²⁰ -56.7 (c 1.71, CHCl₃); IR (liquid film): 3504 (br, s), 1736 (s), 1646 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.26–7.34 (5H, m, Ph), 5.24 (1H, m, 19-CH), 4.79 (1H, d, J = 1.4 Hz, C=CH_aH_b), 4.74 (1H, br s, C=CH_aH_b), 4.62 (1H, d, J = 11.6 Hz, OCH_aH_bPh), 4.43 (1H, d, J = 11.6 Hz, OCH_aH_bPh), 3.77 (1H, m, 23-CH), 3.72 (1H, m, 21-CH), 3.57 (1H, d, J = 2.2 Hz, OH), 2.34 (1H, br dd, J = 14.1, 7.7 Hz, 18-CH_aH_b), 2.31 (2H, q, J = 7.6 Hz, COCH₂CH₃), 2.22 (1H, br dd, J = 14.1, 6.4 Hz, 18-CH_aH_b), 2.04 (2H, app q, 16-CH₂), 1.80 (1H, dt, J = 14.3, 8.8 Hz, 22-CH_aH_b), 1.54–1.65 (2H, m, 20-CH₂), 1.51 (1H, m, 22-CH_aH_b), 1.22 (3H, d, J = 6.1 Hz, 24-CH₃), 1.13 (3H, t, J = 7.6 Hz, COCH₂CH₃), 101 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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, NH₃) Calc. for C₂₁H₃₃O₄ [MH]⁺: 349.2379, found: 349.2386; *m*/*z*: (+CI, NH₃) 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)-12tridecen-6-one (45)

A 25 mL flask containing (-)-Ipc₂BCl (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 Et₂O (3 mL) was added. The solution was cooled to $-78\ ^{\circ}\text{C}$ 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 Et₂O (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% H₂O₂ solution (2 mL). The resultant mixture was stirred vigorously at rt for 1 h, and then diluted with H₂O (10 mL) and Et₂O (10 mL), the layers were separated and the aqueous layer was extracted with $Et_2O(3 \times 5 mL)$. The combined organic extracts were washed with sat. NaHCO₃ (10 mL) and brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude material was purified by sequential flash chromatography (20: 80 Et₂O-CH₂Cl₂ then 20 : 80 EtOAc-hexanes) to provide aldol adduct **45** (110.8 mg, 78%) as a colourless oil: R_f : 0.48 (30 : 70 EtOAchexanes), $0.72 (20: 80 \text{ Et}_2\text{O}-\text{CH}_2\text{Cl}_2); [a]_D^{20} - 2.5 (c \ 1.69, \text{CHCl}_3);$ IR (liquid film): 3507 (br), 1710 (s), 1612, 1514 cm⁻¹; ¹H NMR: δ (500 MHz, CDCl₃) 7.24 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, d, J = 8.6 Hz, ArH), 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-CH), 4.07 (1H, m, 27-CH), 3.97 (1H, m, 19-CH), 3.87 (1H, m, 21-CH), 3.80 (3H, s, ArOCH₃), 3.52 (1H, d, J = 2.2 Hz, OH), 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, OCH₃), 2.72 (1H, dd, J =15.8, 6.5 Hz, 22-C H_aH_b), 2.60 (1H, dd, J = 16.7, 7.9 Hz, 24- $CH_{a}H_{b}$), 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, $18-CH_{a}H_{b}$), 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-CH₂), 1.61–1.73 (3H, m, 26-CH₂ + 20-C H_aH_b), 1.34 (1H, ddd, J = 14.2, 8.8, 3.8 Hz, 20-C H_aH_b), 1.02 (3H, t, J = 7.4 Hz, 16-CH₂CH₃), 0.93 (9H, t, J = 8.0 Hz, $Si(CH_2CH_3)_3$, 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, $Si(CH_3)_b$); ¹³C NMR: δ (100.6 MHz, CDCl₃) 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 C₃₆H₆₆O₇Si₂Na [M + Na]⁺: 689.4245, found: 689.4234.

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