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Synthesis of the FG ring fragment of pectenotoxins **1**–**9**

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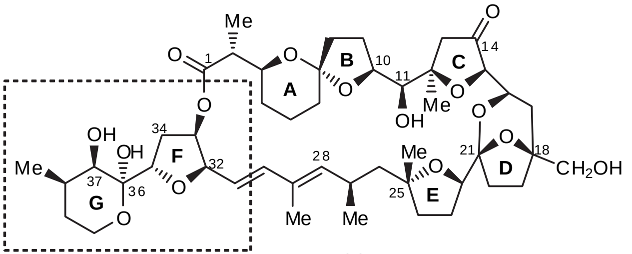
The synthesis of the FG ring fragment common to pectenotoxins **1**–**9** is reported. The successful, convergent synthesis relied on high yielding routes to access two key intermediates; aldehyde **1** and phosphonium salt **2**. A *Z*-selective Wittig reaction gave access to advanced linear precursor **3**, which was converted to FG ring fragment **4** using two sequential cyclization reactions.

1. Introduction

The pectenotoxins (PTX) typified by pectenotoxin-4 (PTX-4 (**5**), Figure 1) are a family of structurally complex polyether marine toxins. These compounds are produced by dinoflagellates and subsequently accumulate in the shellfish and marine sponges that feed on them. The toxins can be transferred to humans upon consumption of contaminated shellfish. PTX-1 and PTX-2, the first members of the PTXs to be characterized, were collected off the coast of Japan from contaminated scallops *Patinopectin yessoensis*.[1]



PTX-4 (**5**)

Figure 1. PTX-4 (**5**).

Interest in the PTXs was initially sparked due to their suspected involvement in diarrhoetic food poisoning, but it is now known that the PTXs do not cause diarrhoetic shellfish poisoning (DSP), but induce toxicity via a specific interaction with the actin cytoskeleton,[2] causing severe liver injuries in mice.[3] This mechanism of biological activity was irrefutably established when an X-ray crystal structure of actin co-crystallized with PTX-2 revealed a novel binding site and was shown to exert its activity by capping the barbed end of F-actin, resulting in depolymerization, but not the severing of actin filaments.[4] In 1995, it was demonstrated that PTX-2 exhibited potent and selective cytotoxicity towards lung, colon, CNS, skin, ovarian, renal and breast cancer cell lines with LC_{50} values in the nanomolar range.[5] The selectivity of PTX towards cancer cell lines was later demonstrated to arise from its ability to induce apoptosis in p53 deficient tumour cells.[6]

These studies indicate that PTX or synthetic analogues thereof, have the potential to be used as potent, selective chemotherapeutic agents thus prompting considerable attention from several synthetic research groups.[7–21] To date, only one elegant total synthesis of the PTXs (PTX-4 and PTX-8) has been completed by Evans et al.[22,23] Access to the FG ring fragment is desirable, not only as part of the total synthesis of PTX, but also, this fragment is considered to be significant since it was observed that the FG ring moiety occupies a narrow cavity in the actin protein binding site.[4] This small fragment could therefore potentially mimic the biological activity of the more complex parent macrolide structure.

2. Results and discussion

2.1. Retrosynthesis

The synthesis of the FG ring fragment reported herein completes our combined synthesis of all the major ring systems present in the PTXs that are embedded within the macrocyclic ring.[24] The ABC spiroacetal ring system was produced in 2005,[25,26] and most

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recently, the DE ring fragment appended to a model C ring was completed in 2009.[27]

The FG ring fragment **4** (Fig. 2) was chosen as the target compound and is representative of the FG rings present in PTX-1 to PTX-9. Protecting groups at O-33 and O-31 were chosen to be orthogonal such that further manipulation will allow future unification with the ABC and DE fragments previously prepared by our research group.

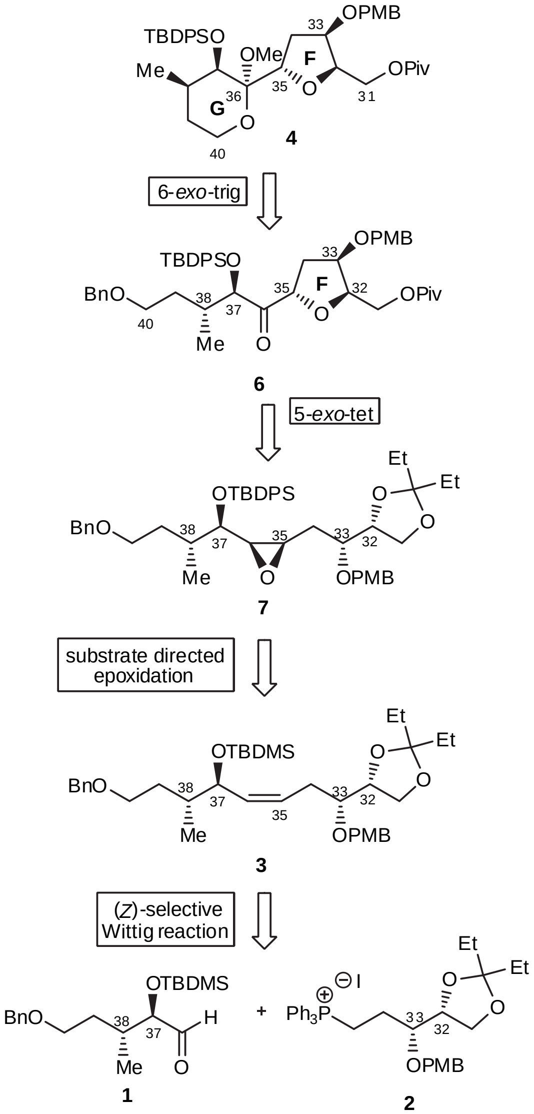


Figure 2. Retrosynthesis of FG ring fragment **4**.

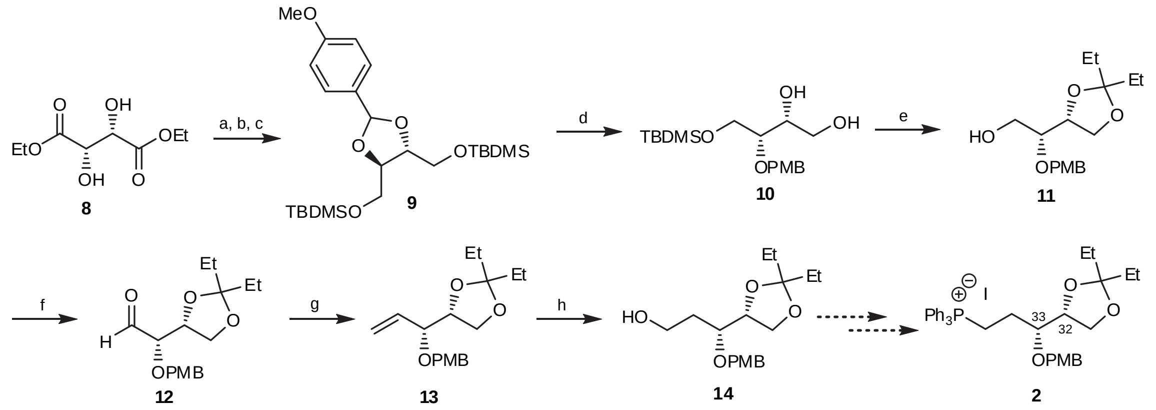
We envisaged a convergent approach to access the FG ring fragment, which hinges on the preparation and subsequent unification of two key fragments; aldehyde **1** and phosphonium iodide **2**. Key late stage disconnections (Fig. 2) of the FG fragment comprise a 6-*exo-trig* cyclization to form the tetrahydropyran G ring preceded by a 5-*exo*-tet cyclization to afford the tetrahydrofuran F ring **6**. The linear cyclization precursor, epoxide **7**, is obtained by substrate-directed epoxidation of (*Z*)-olefin **3**, itself obtained by (*Z*)-selective Wittig reaction between aldehyde **1** and the phosphorous ylide derived from phosphonium salt **2**.

Although originally planned to make use of chiral pool materials to access phosphonium salt **2**, this initial pathway was met with difficulties and an alternative route utilizing a robust Sharpless asymmetric dihydroxylation reaction was used. This revised pathway effectively generated key *syn* stereocentres at C-32 and C-33, thus providing a unique focal point for the synthesis of the FG ring fragment.

2.2. Synthesis

The initial synthesis of phosphonium salt **2** (Scheme 1) was designed to use the chiral pool starting material D-(−)-diethyl tartrate **8** to provide both key C-32 and C-33 stereocentres. This route ultimately proved to be impractical due to low yielding Wittig and hydroboration reactions at the end of the synthetic route.

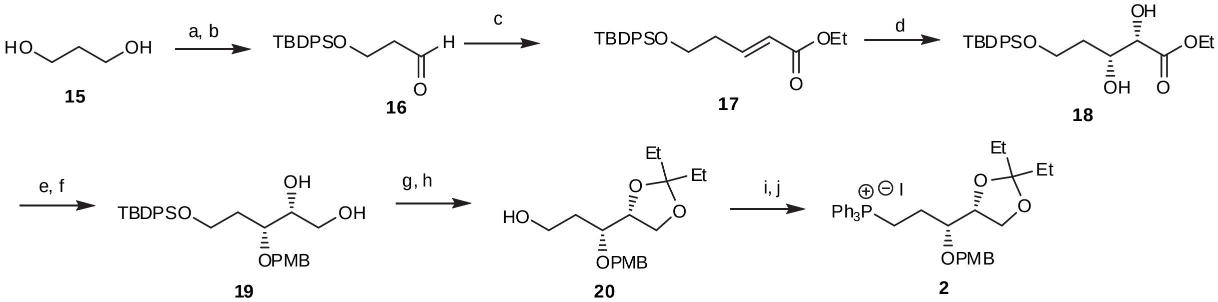
D-(−)-Diethyl tartrate **8** was protected as a benzylidene acetal by reaction with the dimethoxyacetal of *p*-anisaldehyde and catalytic *p*-TsOH under reduced pressure. The resulting diester was reduced to the corresponding diol ($NaBH_4$, LiCl, THF, 92%), which was then protected as the bis-TBDMS ether **9** (TBDMSCl, imidazole, CH_2Cl_2, 84%). Regioselective reduction using DIBAL-H, afforded 1,2-diol **10**. This reaction effected selective cleavage of one silyl ether and also installed the resultant secondary PMB protecting group at the desired position. Side products were avoided by careful adjustment of temperature conditions, with the best results being achieved when the reaction was maintained at −78 °C for 45 min followed by 45 min at 0 °C. With 1,2-diol **10** eventually obtained in 83% yield, the diol moiety was then protected as a 1,3-dioxolane by reaction with 3,3-dimethoxypentane and catalytic CSA. These conditions also had the desired effect of removing the remaining TBDMS protecting group to afford alcohol **11**. The rate of silyl ether deprotection relative to the diol protection had to be controlled; a mixture of 1,2-, 1,3- and 1,4-protected systems was observed if the TBDMS ether was cleaved before the 1,2-diol was protected.



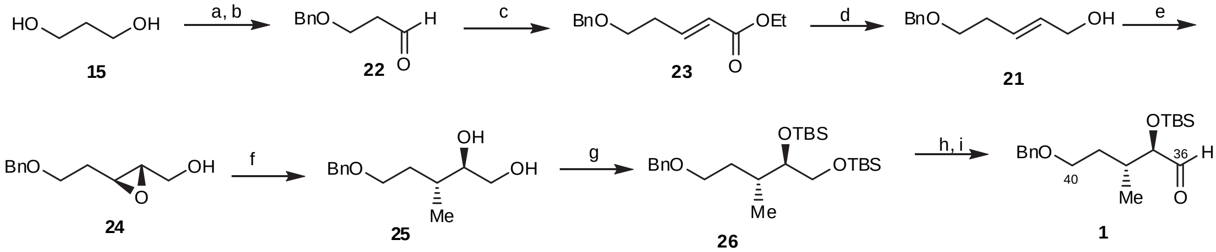
Scheme 1. Attempted synthesis of phosphonium salt **2**. Reagents and conditions: (a) $MeO(C_6H_4)CH(OMe)_2$, *p*-TsOH, DMF, 5 h, 50 °C, 18 Torr, 99%; (b) $NaBH_4$, LiCl, THF, 18 h, rt, 92%; (c) TBDMSCl, im, CH_2Cl_2, 15 h, rt, 84%; (d) DIBAL-H, CH_2Cl_2, 45 min, −78 °C then 45 min, 0 °C, 83%; (e) $Et_2C(OMe)_2$, CSA (cat), PhH, 3 h, rt, 64%; (f) DMP, CH_2Cl_2, 2 h, rt, 96%; (g) Ph_3PMeBr, *n*-BuLi, 1 h, 0 °C, 2 h, rt, 48%; $BH_3 \cdot Me_2S$, THF, H_2O_2, NaOH, 15 min, reflux, 32%.

At this point, methods to extend the backbone of the compound by one carbon unit were sought. The primary alcohol **11** was transformed into a variety of leaving groups e.g., tosylate, mesylate and iodide so that cyanide displacements could be investigated, but unfortunately, only low yields of the nitrile were obtained. In an alternative approach, the primary alcohol was oxidized to the corresponding aldehyde **12** (DMP, CH_2Cl_2, 96%) followed by immediate Wittig olefination using $Ph_3P{=}CH_2$ to introduce the additional one carbon fragment, thus affording olefin **13**. Disappointingly, the yield of this Wittig reaction was only moderate (48%) and subsequent attempts to convert the newly formed terminal olefin **13** into the corresponding primary alcohol **14** by hydroboration, using a variety of boranes ($BH_3 \cdot Me_2S$, 9-BBN, catecholborane) proceeded in low yields (32% at best). With a sequence of difficult steps and low yielding transformations, it was decided to revise the synthesis of coupling partner **2**.

The revised synthetic plan to obtain the Wittig coupling partner, phosphonium salt **2**, (Scheme 2) relied on the use of a robust Sharpless asymmetric dihydroxylation reaction, and accordingly phosphonium salt **2** was successfully synthesized in 10 high yielding steps.



Scheme 2. Synthesis of phosphonium salt **2**. Reagents and conditions: (a) NaH, THF, rt, 1 h then TBDPSCl, 0 °C to rt, 92%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then NEt_3, rt, 88%; (c) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, Et_2O, H_2O, 0 °C to rt, 86%; (d) $K_3Fe(CN)_6$, $(DHQD)_2Phal$, $MeSO_2NH_2$, *t*-BuOH/H_2O, K_2CO_3, OsO_4, rt, 2 h then olefin 17, 0 °C to rt, 93%, 94% ee; (e) MeO$(C_6H_4)CH(OMe)_2$, CSA, PhH, rt, 170 mbar, 76%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 77%; (g) 3,3-dimethoxypentane, PTSA, PhH, rt, 70%; (h) TBAF, THF, rt, 84%; (i) PPh_3, im, I_2, CH_2Cl_2, rt, 85%; (j) PPh_3, DIPEA, MeCN, reflux, 60%.



Scheme 3. Synthesis of aldehyde **1**. Reagents and conditions: (a) KOH, BnBr, rt, 73%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then NEt_3, rt, 88%; (c) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, Et_2O, H_2O, 0 °C to rt, 86%; (d) DIBAL-H, CH_2Cl_2, −78 °C, 87%; (e) Ti(*i*-PrO)$_4$, (+)-DET, 4 Å MS, CH_2Cl_2, −20 °C, 30 min then TBHP, 91%; (f) $AlMe_3$, CH_2Cl_2, 0 °C to rt, 66%; (g) TBDMSOTf, lut, CH_2Cl_2, 0 °C, 89%; (h) HF/py, THF, 0 °C to rt, 100%; (i) DMP, py, THF, rt, 96%.

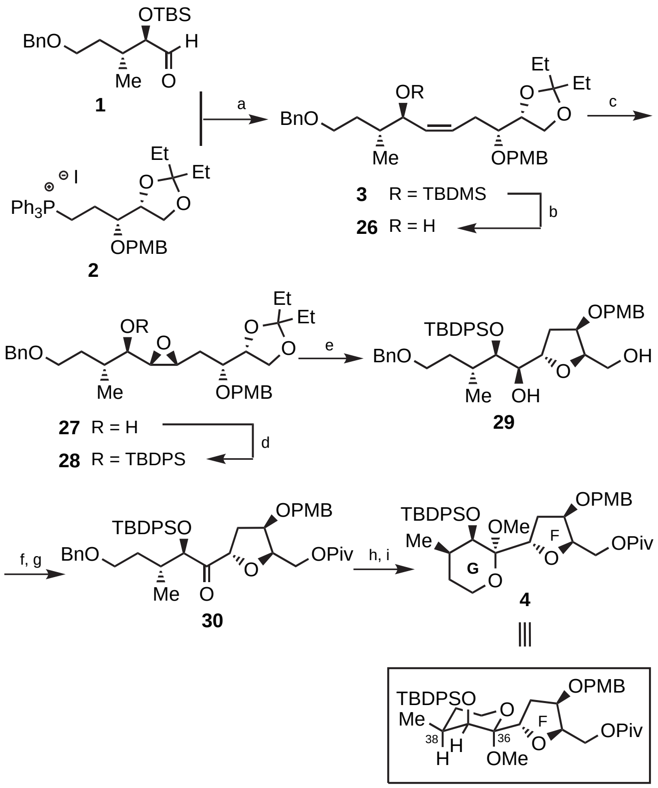
The synthesis (Scheme 2) started with propane-1,3-diol **15**, which was converted to the mono-protected TBDPS ether. After oxidation to the corresponding aldehyde **16** using a Swern oxidation, Horner/Wadsworth/Emmons olefination with triethyl phosphonoacetate using sodium hydride as base afforded olefin **17** in 67% yield. The reaction was then optimized using conditions reported by Codero et al.[28] The reaction was carried out under biphasic, aqueous conditions utilizing potassium carbonate as base. Using this procedure, (*E*)-olefin **17** was consistently obtained in high yield (86%). Sharpless asymmetric dihydroxylation of (*E*)-olefin **17** using $(DHQD)_2Phal$ routinely afforded the desired *syn* diol **18** in high yield and high enantiomeric excess (93%, >94% ee).

The secondary *para*-methoxybenzyl protecting group was then introduced at the desired position by a two step manipulation that first converted diol **18** to the corresponding benzylidene acetal. Chelation controlled, regioselective DIBAL-H reduction of the newly formed acetal with concomitant reduction of the ethyl ester afforded the desired 1,2-diol **19** with none of the undesired 1,3-diol being observed. The 1,2-diol was then protected as the corresponding 1,3-dioxolane by reaction with 3,3-dimethoxypentane. It was decided to use this less common diethyl substituted protecting group due to its enhanced stability over the dimethyl variant. This protecting group was required to withstand seven further transformations but must then be removed easily to effect the acid catalyzed 5-*exo*-tet cyclization reaction. The TBDPS protecting group was removed (TBAF, THF, 84%) and the resultant primary alcohol **20** converted to the corresponding iodide (PPh_3, I_2, imidazole, CH_2Cl_2, 85%). Generation of phosphonium iodide salt **2** was effected by heating the primary alkyl iodide under reflux with triphenylphosphine and Hünig's base in acetonitrile. The salt was easily purified by flash column chromatography then azeotroped with benzene and dried under high vacuum immediately before use.

With phosphonium iodide **2** in hand, we next sought to access aldehyde coupling partner **1**. The two key stereocentres were installed by Sharpless asymmetric epoxidation of allyl alcohol **21** (Scheme 3). Thus aldehyde **1** was obtained in nine steps also starting from propane-1,3-diol **15**. Desymmetrization of **15** was achieved by mono-benzylation via addition of solid potassium hydroxide to neat propane-1,3-diol followed by the addition of benzyl bromide (0.2 mol equiv).[29] Oxidation of the primary alcohol to the corresponding aldehyde **22** using Swern oxidation was conducted on a large scale (~30 g).

Again, the simple Horner/Wadsworth/Emmons procedure of Codero et al.[28] was employed to access α,β-unsaturated ester **23**, affording exclusively the *E* isomer. Reduction of ethyl ester **23** (DIBAL-H, CH_2Cl_2, 87%) afforded the desired allyl alcohol **21**. Sharpless asymmetric epoxidation of allyl alcohol **21** utilizing (+)-DET as the chiral ligand afforded (*S*,*S*)-epoxy alcohol **24**. Regioselective epoxide opening using trimethylaluminium afforded the 1,2-diol **25**, with none of the regiomeric 1,3-diol being observed. Next, attempts to access aldehyde **1** in two steps instead of three by selectively oxidizing primary alcohol **25** in the presence of a secondary alcohol were unsuccessful thus necessitating the required protection of both exposed primary and secondary alcohols (TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 89%) thus affording bis-silyl ether **26**. Selective deprotection of the primary silyl protecting group (HF/pyridine) afforded the corresponding alcohol. The desired aldehyde **1** was then obtained by oxidation of the primary alcohol with Dess/Martin periodinane.

With both aldehyde **1** and phosphonium salt **2** in hand, attention turned to the coupling of these two fragments using a (*Z*)-selective Wittig reaction (Scheme 4). The key Wittig reaction proceeded smoothly to afford olefin-(*Z*) **3**, in 93% yield using *n*-BuLi to generate the ylide, combined with the lithium ion sequestering reagent HMPA. After TBDMS deprotection using TBAF, the stereochemistry of the Wittig reaction was confirmed to be (*Z*) by the observation of the total line width of both overlapping olefinic protons in the ^1H NMR spectrum to be 10.7 Hz.



Scheme 4. Synthesis of epoxy alcohol **27**, en route to FG ring fragment **4**. Reagents and conditions: (a) *n*-BuLi, HMPA, THF, −78 °C, 93%; (b) TBAF, THF, rt, 81%; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 99%, >95% de; (d) TBDPSCl, im, CH_2Cl_2, rt, 85%; (e) 50% aq TFA, CH_2Cl_2, rt, 62%; (f) PivCl, py, CH_2Cl_2, −5 °C, 97%; (g) DMP, py, CH_2Cl_2, rt, 99%; (h) W-5 Raney Nickel, EtOH, H_2, rt; (i) CSA, $CH(OMe)_3$, MeOH, rt, 70%, two steps.

Silyl deprotection to afford allyl alcohol **26** was followed by substrate-directed epoxidation (*m*-CPBA, CH_2Cl_2, 0 °C) affording epoxy alcohol **27** as the sole diastereomer (as determined by NMR analysis) in high yield (99%). It now remained to reprotect secondary alcohol **27** (Scheme 4). The protecting group at this position had to withstand the impending acid catalyzed cyclization reaction. The TBDMS protecting group was found to be unstable to the cyclization conditions, and a complex mixture of products was observed upon exposure to various acids (TFA, CSA, PPTS). The acetate protecting group was also investigated, but acid catalysed cyclization did not result in formation of the desired product. It was therefore decided to reprotect the secondary alcohol as a TBDPS ether **28**. The TBDPS protecting group remained intact during the acid catalyzed 5-*exo*-tet cyclization (50% aq TFA), affording the desired tetrahydrofuran **29** in 62% yield. Protection of the newly formed primary alcohol as the pivalate ester (PivCl, py, CH_2Cl_2, −15 °C, 97%) proceeded smoothly, allowing the remaining secondary alcohol to be oxidized to the corresponding ketone **30** (DMP, py, CH_2Cl_2, rt, 99%).

Initial attempts to induce cyclization to form a tetrahydropyran ring by careful debenzylation in the presence of the *para*-methoxybenzyl protecting group (Pd/C, H_2, EtOH) were unsuccessful. This transformation was eventually achieved by reaction of **30** with freshly prepared W-5 Raney nickel[30] allowing concomitant hemiacetal formation. The successful 6-*exo-trig* cyclization resulted in a single diastereoisomer as was evident by NMR analysis. The crude reaction mixture was not purified, but immediately subjected to acid catalyzed methylation (CSA, $CH(OMe)_3$, MeOH, rt, 2 h). Methyl acetal **4** was then easily purified by flash chromatography. Only one diastereomer was observed in the ^1H and ^{13}C NMR spectrum. Due to the equilibrating conditions employed for the methyl acetal formation step, it was assumed that the thermodynamically stabilized acetal diastereomer formed in which the methoxy group occupies the anomerically stabilized axial position (Scheme 4). Further evidence for this was obtained by comparison of the ^1H NMR data with that reported by Murai et al. during the synthesis of an *ent*-FG ring fragment,[7] that was similar in structure to compound **4** produced in the present work.

3. Conclusion

The FG ring fragment of the PTXs was synthesized in a convergent manner from propane-1,3-diol. Initial attempts to use a chiral pool based strategy were unsuccessful. Revision of the synthetic route made use of a robust Sharpless asymmetric dihydroxylation reaction to introduce two key stereocentres in phosphonium salt **2**. A Sharpless asymmetric epoxidation reaction was used to introduce two further stereocentres in aldehyde **1**. A (*Z*)-selective Wittig olefination afforded the required linear backbone. 5-*exo*-tet and 6-*exo-trig* cyclization reactions were then used to afford the FG ring fragment **4**.

4. Experimental

4.1. General details

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen in oven dried glassware equipped with a magnetic stirrer bar and a rubber septum. Solvents were distilled before use and commercial reagents were used without further purification unless otherwise noted.

*4.1.1. (2S,3R)-Ethyl 5-(tert-butyldiphenylsilyloxy)-2,3-dihydroxypentanoate (**18**).* To a stirred solution of potassium ferricyanide (13.4 g, 40.8 mmol), potassium carbonate (5.64 g, 40.8 mmol), $(DHQD)_2Phal$ (530 mg, 0.680 mmol, 5 mol %) and methanesulfonamide (1.29 g, 13.6 mmol) in *t*-BuOH/H_2O (120 mL, 1:1 v/v), was added osmium tetroxide (6.80 mL, 0.054 mmol, 0.4 mol %, 2.5% wt in 2-methyl-2-propanol) and the resultant suspension stirred at room temperature for 2 h. The mixture was then cooled to 0 °C and a solution of olefin **17** (5.20 g, 13.6 mmol) in *t*-BuOH (20 mL) added dropwise. The resultant mixture was allowed to stir at 0 °C for 15 min then at room temperature for 24 h. The reaction mixture was quenched by the addition of saturated aqueous sodium sulfite solution (50 mL) and stirred for 30 min at room temperature. The mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (3:2) as eluent to afford the *title* *compound* **18** (5.24 g, 93%) as a transparent yellow oil. R_f (40% EtOAc/hexane) 0.55; $[\alpha]_D^{20}$ +5.9 (*c* 2.85, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3479 (OH), 3050, 2958, 2857, 1739 (C=O), 1427, 1243, 1111, 703; δ_H (400 MHz, $CDCl_3$): 1.14 (9H, s), 1.31 (3H, t, *J* 7.2 Hz), 1.84–1.89 (1H, m), 2.02–2.09 (1H, m), 3.20 (1H, br s), 3.55 (1H, br s), 3.89–3.99 (2H, m), 4.17 (1H, d, *J* 7.2 Hz), 4.32–4.37 (3H, m, H-3), 7.40–7.50 (6H, m), 7.74–7.78 (4H, m); δ_C (100 MHz, $CDCl_3$): 14.1, 19.0, 26.7, 35.4, 61.8, 62.0, 71.4, 73.5, 127.7, 129.8, 133.0, 133.1, 135.5, 135.5, 173.2; ESI HRMS found: MH$^+$, 417.2094, $C_{23}H_{33}O_5Si$ requires 417.2097.

*4.1.2. (2R,3R)-5-(tert-Butyldiphenylsilyloxy)-3-(p-methoxybenzyloxy)pentane-1,2-diol (**19**).* To a stirred solution of camphorsulfonic acid (69.0 mg, 0.300 mmol) and diol **18** (6.14 g, 15.0 mmol) in benzene (40 mL) at reduced pressure (170 mbar) was added $MeO(C_6H_4)CH(OMe)_2$ (13.3 mL, 74.0 mmol) and the mixture stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3×80 mL). The combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (9:1) as eluent to afford the corresponding benzylidene acetal (5.61 g, 76%) as a pale yellow liquid. The above ester (3.08 g, 5.80 mmol) was taken up in CH_2Cl_2 (30 mL) and cooled to −78 °C. DIBAL-H (20.2 mL, 1 mol L^{-1} in hexane) was added dropwise and the mixture stirred for 30 min. The reaction was warmed to 0 °C and stirred for 1 h then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched at 0 °C by the addition of saturated Rochelle salts (50 mL) then diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL) and stirred for 1 h. The organic solvents were evaporated under reduced pressure and the remaining residue dissolved in diethyl ether (100 mL) and H_2O (50 mL). The aqueous portion was then extracted with diethyl ether (3×60 mL). The combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (3:2) as eluent to afford the *title compound* **19** (2.21 g, 77%) as a thick colourless liquid. R_f (40% EtOAc/hexane) 0.27; $[\alpha]_D^{20}$ −11.7 (*c* 3.95, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3408 (OH), 2931, 1613, 1513, 1427, 1248, 1111, 1036, 823, 702; δ_H (400 MHz, $CDCl_3$): 1.06 (9H, s), 1.78–1.95 (2H, m), 2.04 (1H, br s), 2.81 (1H, br s), 3.58–3.62 (3H, m), 3.68–3.72 (1H, m), 3.78–3.81 (5H, m), 4.38 (1H, d, *J* 11.1 Hz), 4.54 (1H, d, *J* 11.1 Hz), 6.83–6.86 (2H, m), 7.17–7.19 (2H, m), 7.40–7.44 (6H, m), 7.65–7.68 (4H, m); δ_C (100 MHz, $CDCl_3$): 19.1, 26.8, 33.2, 55.2, 60.1, 64.1, 72.0, 72.9, 76.6, 113.9, 127.7, 129.6, 129.7, 130.0, 133.4, 133.4, 135.5, 159.4; ESI HRMS found: MH$^+$, 495.2560, $C_{29}H_{39}O_5Si$ requires 495.2567.

*4.1.3. (2R,3R)-5-Benzyloxy-3-methylpentane-1,2-diol (**25**).* To a solution of trimethylaluminium (1 mL, 2 mol L^{-1} in toluene) at 0 °C was added dropwise a solution of epoxide **24** (100 mg, 0.480 mmol) in CH_2Cl_2 (1 mL) and the resultant solution stirred for 10 min. The mixture was allowed to warm to room temperature and stirred for a further 2.5 h. The reaction was cooled to 0 °C, diluted by the addition of diethyl ether (2 mL) and quenched by the addition of HCl 10% aqueous solution (2 mL). The mixture was stirred vigorously for 30 min after which the aqueous portion was extracted with CH_2Cl_2 (3×50 mL). The organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated and the resultant crude product purified by flash column chromatography using hexane/ethyl acetate (2:3) as eluent to afford the title compound **25** (71 mg, 66%) as a colourless liquid. R_f (60% EtOAc/hexane) 0.31; $[\alpha]_D^{20}$ +4.1 (*c* 3.02, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3390 (O–H), 2872, 1737, 1454, 1365, 1242, 1075, 736, 698; δ_H (400 MHz, $CDCl_3$): 0.89 (3H, d, *J* 6.8 Hz), 1.59–1.65 (1H, m), 1.72–1.82 (2H, m), 2.76 (1H, br s), 3.41–3.52 (3H, m), 3.56–3.69 (3H, m), 4.51 (2H, s), 7.26–7.36 (5H, m); δ_C (100 MHz, $CDCl_3$): 16.3, 32.9, 33.9, 64.8, 68.2, 73.1, 75.9, 127.7, 128.4, 137.8; ESI HRMS found: MH$^+$, 224.1408, $C_{13}H_{20}O_3$ requires 224.1412.

*4.1.4. (2R,3R)-1,2-Di-tert-butyldimethylsilyloxy-3-methyl-5-benzyloxypentane (**26**).* To a stirred solution of diol **25** (4.78 g, 21.3 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added 2,6-lutidine (10 mL, 85.3 mmol) and the solution stirred for stirred for 10 min. The solution was then cooled to 0 °C and *tert*-butyldimethylsilyl triflate (15 mL, 63.9 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated sodium bicarbonate (50 mL) and H_2O (20 mL). The aqueous portion was extracted with CH_2Cl_2 (3×100 mL) and the organic extracts washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and the resultant crude residue purified by flash column chromatography using hexane/ethyl acetate (1:4) as eluent to afford the *title compound* **26** (8.60 g, 89%) as a colourless liquid. R_f (80% EtOAc/hexane) 0.90; $[\alpha]_D^{20}$ +8.7 (*c* 3.67, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2955, 2856, 1471, 1462, 1361, 1254, 1099; δ_H (300 MHz, $CDCl_3$): 0.04 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.07 (3H, s), 0.89 (3H, s), 0.90 (9H, s) 0.91 (9H, m), 1.40–1.52 (1H, m), 1.78–1.92 (2H, m), 3.48–3.63 (5H, m), 4.49 (1H, d, *J* 12.0 Hz), 4.56 (1H, d, *J* 12.0 Hz), 7.26–7.36 (5H, m); δ_C (75 MHz, $CDCl_3$): −5.4, −5.3, −4.9, −4.1, 16.4, 18.1, 18.1, 25.9, 26.0, 30.7, 33.0, 65.1, 69.1, 72.8, 77.1, 127.4, 127.6, 128.3 138.7; ESI HRMS found: MH$^+$, 453.3228, $C_{25}H_{49}O_3Si_2$ requires 453.3220.

*4.1.5. (2R,3R)-5-Benzyloxy-2-tert-butyldimethylsilyloxy-3-methylpentan-1-al (**1**).* To a stirred solution of bis-silyl ether **26** (196 mg, 0.430 mmol) in dry tetrahydrofuran (8 mL) and pyridine (652 μL) cooled to 0 °C was added hydrofluoric acid (326 μL, 13.0 mmol, 70% in pyridine). The reaction was then allowed to warm to room temperature and was stirred for a further 10 h. Although starting material remained, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (3 mL) at 0 °C before significant amounts of bis-deprotected compound had formed. The mixture was extracted with ethyl acetate (3×30 mL), washed with brine (2 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude residue purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the corresponding primary alcohol (69 mg, 100% BORSM) as a transparent yellow oil.

A mixture of the above primary alcohol (372 mg, 1.10 mmol), dry pyridine (0.890 mL, 11.0 mmol) and Dess/Martin periodinane (930 mg, 2.20 mmol) was stirred in dry CH_2Cl_2 (5 mL) at room temperature for 45 min. Saturated aqueous $Na_2S_2O_3$ solution (3 mL) and saturated aqueous $NaHCO_3$ solution (3 mL) were added and the mixture allowed to stir for an additional 15 min. The mixture was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to afford the *title compound* **1** (355 mg, 96%) as a colourless liquid. R_f (30% EtOAc/hexane) 0.85; $[\alpha]_D^{20}$ +18.1 (*c* 3.05, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2956, 2929, 2857, 1735 (C=O), 1471, 1462, 1362, 1254, 1099, 838; δ_H (300 MHz, $CDCl_3$): 0.07 (3H, s), 0.08 (3H, s), 0.94 (9H, s), 1.00 (3H, d, *J* 7.2 Hz), 1.46–1.57 (1H, m), 1.76–1.87 (1H, m), 2.10–2.23 (1H, m), 3.47–3.52 (2H, m), 3.86 (1H, dd, *J* 4.2, 1.7 Hz), 4.44 (1H, d, *J* 11.9 Hz), 4.50 (1H, d, *J* 11.9 Hz), 7.26–7.35 (5H, m), 9.61 (1H, d, *J* 1.7 Hz); δ_C (75 MHz, $CDCl_3$): −5.1, −4.6, 16.3, 18.2, 25.7, 31.0, 33.6, 68.1, 72.8, 81.5, 127.5, 127.6, 128.3, 138.4, 204.5; ESI HRMS found: MH$^+$, 337.2201, $C_{19}H_{33}O_3Si$ requires 337.2199.

*4.1.6. ((R)-3-((R)-2′,2′-Diethyl-1′,3′-dioxolane-4′-yl)-3-(p-methoxybenzyloxy)propyl)triphenylphosphonium iodide (**2**).* To a stirred suspension of imidazole (2.17 g, 31.9 mmol) and triphenylphosphine (5.02 g, 19.1 mmol) in CH_2Cl_2 (45 mL) was added a solution of alcohol **20** (1.03 g, 3.20 mmol) in CH_2Cl_2 (20 mL). Iodine (2.20 g, 17.0 mmol) was added and the reaction stirred at room temperature for 45 min protected from the light. The crude reaction mixture was filtered through a short plug of silica, which was then washed with hexane/ethyl acetate (1:1) (300 mL). The solvent was evaporated and the resultant white sticky solid purified by flash column chromatography using hexane/ethyl acetate (19:1) as eluent to afford the corresponding iodide (1.17 g, 85%) as a colourless liquid. A mixture of the above iodide (1.75 g, 4.03 mmol), triphenylphosphine (5.29 g, 20.0 mmol), diisopropylethylamine (1.10 mL, 8.06 mmol) and dry acetonitrile (6 mL) was heated under reflux for 24 h. The mixture was allowed to cool and the solvent evaporated under reduced pressure. The resultant crude residue was purified by flash column chromatography using gradient elution of $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH (95:5) as eluent to afford the *title compound* **2** (1.70 g, 60%) as a pale yellow gum. R_f (5% MeOH/CH_2Cl_2) 0.30; ESI HRMS found: $[M-I]^+$, 569.2818, $C_{36}H_{42}O_4P$ requires 569.2821.

*4.1.7. (3R,4R,8R,Z)-1-(Benzyloxy)-8-(R)-(2′,2′-diethyl-1′,3′-dioxolan-4′-yl)-8-(4-methoxybenzyloxy)-3-methyl-4-(tert-butyldimethylsilyloxy)oct-5-ene (**3**).* To a solution of phosphonium salt **2** (1.58 g, 2.27 mmol) in dry tetrahydrofuran (15 mL, 7% HMPA) at −78 °C was added *n*-BuLi (2.27 mL, 1.60 mol L^{-1} in hexane, 3.60 mmol) affording a bright orange solution. The resultant ylide was allowed to stir for 30 min at −78 °C then 5 min at room temperature. The solution was then cooled to −78 °C and a solution of aldehyde **1** (0.910 g, 2.70 mmol) in dry tetrahydrofuran (10 mL, 7% HMPA) added dropwise down the side of the flask. The mixture was stirred at −78 °C for 40 min then at room temperature for 40 min. The solvent was removed under reduced pressure then the crude residue was dissolved in CH_2Cl_2 (250 ml) and washed with water (2×50 mL). The aqueous fractions were extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the mixture purified by flash column chromatography using hexane/ethyl acetate (9:1) as eluent to afford the *title compound* **3** (980 mg, 93%) as a yellow oil. R_f (10% EtOAc/hexane) 0.46; $[\alpha]_D^{20}$ +7.2 (*c* 7.20, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3433, 2929, 2856, 1613, 1514, 1463, 1249, 1083, 835, 775; δ_H (300 MHz, $CDCl_3$): 0.02 (3H, s), 0.03 (3H, s), 0.85–0.94 (18H, m), 1.25–1.30 (1H, m), 1.61–1.71 (5H, m), 1.82–1.94 (1H, m), 2.10–2.30 (2H, m), 3.45–3.50 (3H, m), 3.60–3.67 (1H, m), 3.80 (3H, s), 3.94–4.00 (1H, m), 4.17–4.20 (2H, m), 4.49–4.71 (4H, m), 5.40–5.54 (2H, m), 6.86–6.89 (2H, m), 7.26–7.35 (7H, m); δ_C (75 MHz, $CDCl_3$): −4.8, −4.2, 8.1, 8.3, 15.4, 18.1, 25.8, 29.2, 29.6, 31.6, 37.3, 55.2, 66.4, 68.9, 72.6, 72.8, 72.6, 78.5, 79.1, 113.2, 113.7, 125.4, 127.4, 127.6, 128.3, 129.4, 130.7, 134.0, 138.7, 159.2; ESI HRMS found: $M-H^+$, 625.3919, $C_{37}H_{57}O_6Si$ requires 625.3924.

*4.1.8. (3R,4R,8R,Z)-1-(Benzyloxy)-8-((R)-2′,2′-diethyl-1′,3′-dioxolan-4′-yl)-8-(p-methoxybenzyloxy)-3-methyloct-5-en-4-ol (**26**).* To a solution of silyl ether **3** (206 mg, 0.330 mmol) in dry tetrahydrofuran (3 mL) was added a solution of tetrabutylammonium fluoride (300 mg, 1.15 mmol) in dry tetrahydrofuran (3 mL). The mixture was allowed to stir at room temperature for 5 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and the mixture extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **26** (135 mg, 81%) as a colourless wax. R_f (20% EtOAc/hexane) 0.15 $[\alpha]_D^{20}$ +5.1 (*c* 1.60, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3444 (OH), 2968, 2932, 1613, 1514, 1462, 1248, 1173, 1084, 1035; δ_H (300 MHz, $CDCl_3$): 0.85–0.93 (9H, m), 1.51–1.70 (7H, m), 2.20–2.42 (2H, m), 2.82 (1H, br s), 3.44–3.55 (3H, m), 3.65 (1H, dd, *J* 7.8, 6.6 Hz), 3.79 (3H, s), 3.95 (1H, dd, *J* 7.8, 6.6 Hz), 4.14–4.18 (2H, m), 4.50–4.63 (4H, m), 5.52–5.55 (2H, m), 6.84–6.87 (2H, m), 7.28–7.33 (7H, m); δ_C (75 MHz, $CDCl_3$): 8.1, 8.1, 15.5, 29.1, 29.5, 29.5, 32.6, 36.4, 55.1, 66.3, 68.4, 71.0, 72.2, 72.9, 78.3, 78.3, 113.3, 113.7, 127.5, 127.6, 128.3, 129.5, 130.4, 133.8, 138.3, 159.1; ESI HRMS found: MH^+, 513.3208, $C_{31}H_{45}O_6$ requires 513.3216.

*4.1.9. (3R,4R,5R,6R,8R)-1-(Benzyloxy)-8-((R)-2′,2′-diethyl-1′,3′-dioxolan-4′-yl)-8-(p-methoxybenzyloxy)-5,6-epoxy-3-methyloctan-4-ol (**27**).* To a solution of allyl alcohol **26** (32 mg, 0.06 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C was added a solution of *m*-chloroperbenzoic acid (32 mg, 0.19 mmol) in dry CH_2Cl_2 (1 mL) and the resultant solution stirred for 9 h. Saturated aqueous $Na_2S_2O_3$ solution (3 mL), saturated aqueous $NaHCO_3$ solution (3 mL) and CH_2Cl_2 (5 mL) were added and the mixture stirred vigorously for 30 min. The layers were separated and the organic layer washed with dilute $NaHCO_3$ (3 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to afford the *title compound* **27** (32 mg, 99%) as a colourless wax. R_f (40% EtOAc/hexane) 0.45; $[\alpha]_D^{20}$ +26.4 (*c* 1.65, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3459 (OH), 2926, 1612, 1514, 1462, 1248, 1173, 1248, 1173, 1085, 1036, 919; δ_H (300 MHz, $CDCl_3$): 0.88–0.94 (9H, m), 1.62–1.68 (6H, m), 1.85–1.89 (3H, m), 2.80 (1H, d, *J* 4.4 Hz), 3.00 (1H, dd, *J* 7.2, 4.4 Hz), 3.24–3.30 (2H, m), 3.49–3.63 (3H, m), 3.68–3.75 (1H, m), 3.78 (3H, s), 3.95 (1H, dd, *J* 8.0, 6.4 Hz), 4.14–4.21 (1H, m), 4.47 (1H, d, *J* 12.0 Hz), 4.52 (1H, d, *J* 12.0 Hz), 4.60 (1H, d, *J* 11.0 Hz), 4.78 (1H, d, *J* 11.0 Hz), 6.84–6.87 (2H, m), 7.26–7.33 (7H, m); δ_C (75 MHz, $CDCl_3$): 8.1, 8.3, 15.7, 29.2, 29.6, 30.4, 32.2, 35.2, 55.3, 55.3, 59.6, 66.3, 68.1, 72.8, 73.0, 73.3, 77.6, 78.9, 113.4, 113.8, 127.6, 127.7, 128.4 129.6, 130.6, 138.2, 159.3; ESI HRMS found: MH^+, 529.3155, $C_{31}H_{45}O_7$ requires 529.3165.

*4.1.10. (3R,4R,5R,6R,8R)-1-(Benzyloxy)-8-((R)-2′,2′-diethyl-1′,3′-dioxolan-4′-yl)-8-(p-methoxybenzyloxy)-5,6-(epoxy)-3-methyl-4-(tert-butyldiphenylsilyloxy)octane (**28**).* To a stirred solution of epoxy alcohol **27** (50 mg, 0.09 mmol), CH_2Cl_2 (2 mL) and imidazole (80.0 mg, 1.18 mmol) was added *tert*-butyldiphenylsilyl chloride (50 μL, 0.78 mmol) and the reaction stirred for 6 h at room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous portion extracted with CH_2Cl_2 (3×30 mL). The combined organic portions were washed with brine (10 mL) and dried over over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography using hexane/ethyl acetate (9:1) as eluent to afford the *title compound* **28** (62 mg, 85%) as a pale yellow oil. R_f (10% EtOAc/hexane) 0.26; $[\alpha]_D^{20}$ +14.6 (*c* 3.04, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3069, 2931, 2856, 1612, 1514, 1462, 1248, 1111, 1085; δ_H (400 MHz, $CDCl_3$): 0.84–0.90 (9H, m), 1.07 (9H, s), 1.46–1.81 (9H, m), 3.11–3.15 (2H, m), 3.20–3.27 (2H, m), 3.36–3.38 (1H, m), 3.42–3.47 (2H, m), 3.65–3.68 (1H, m), 3.69 (3H, s), 3.93–3.95 (1H, m), 4.39–4.52 (3H, m) 4.73 (1H, d, *J* 10.9 Hz), 6.83 (2H, d, *J* 8.6 Hz) 7.22–7.41 (13H, m), 7.70–7.72 (4H, m); δ_C (100 MHz, $CDCl_3$): 8.0, 8.2, 15.7, 19.6, 27.1, 29.4, 29.6, 30.9, 31.4, 54.4, 55.2, 58.9, 66.4, 68.4, 72.9, 73.2, 76.0, 77.8, 79.41, 113.3, 113.7, 127.2, 127.3, 127.5, 127.5, 128.3, 129.4, 129.5, 129.6, 130.8, 133.8, 133.9, 136.1, 136.2, 138.4, 159.2; ESI HRMS found: M^+, 766.4279, $C_{47}H_{62}O_7Si$ requires 766.4265.

*4.1.11. (1R,2R,3R)-5-(Benzyloxy)-2-(tert-butyldiphenylsilyloxy)-1-((2′S,4′R,5′R)-5′-(hydroxymethyl)-4′-(p-methoxybenzyloxy)tetrahydrofuran-2′-yl)-3-methylpentan-1-ol (**29**).* To a stirred solution of acetal

28 (33 mg, 0.043 mmol) in CH_2Cl_2 (3 mL) was added aqueous trifluoroacetic acid (50% v/v, 200 μL) and the resultant solution stirred vigorously at room temperature for 50 min. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (3 mL) and diluted with H_2O (2 mL) and CH_2Cl_2 (2 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine (10 mL) and dried over over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture purified by flash column chromatography using hexane/ethyl acetate (3:2) as eluent to afford the *title compound* **29** (16 mg, 62%) as a colourless wax. R_f (40% EtOAc/hexane) 0.30; $[\alpha]_D^{20}$ −6.9 (*c* 1.75, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3469 (OH), 3069, 2930, 2856, 1612, 1513, 1247, 1110; δ_H (300 MHz, $CDCl_3$): 0.99 (3H, d, *J* 6.8 Hz), 1.08 (9H, s), 1.41–1.61 (2H, m), 1.65–1.69 (2H, dd, *J* 11.5, 4.0 Hz), 1.50–1.72 (1H, m), 2.20–2.27 (1H, br s), 2.66 (1H, d, *J* 8.0 Hz), 3.15–3.34 (2H, m), 3.34–3.42 (1H, m), 3.56–3.72 (3H, m), 3.80 (3H, s), 3.88 (1H, m), 4.06–4.10 (2H, m) 4.22 (1H, d, *J* 11.5 Hz), 4.35–4.41 (2H, m) 4.44 (1H, d, *J* 11.5 Hz), 6.85–6.88 (2H, m), 7.16–7.37 (13H, m), 7.66–7.69 (4H, m); δ_C (75 MHz, $CDCl_3$): 15.4, 19.6, 27.2, 32.5, 33.9, 34.7, 55.3, 62.0, 68.6, 71.1, 72.0, 72.9, 76.5, 79.2, 79.8, 81.5, 113.9, 127.5, 127.5, 127.6, 128.3, 129.0, 129.8, 129.8, 133.6, 133.7, 136.0, 136.1, 138.4, 159.3; ESI HRMS found: MH^+, 699.3721, $C_{42}H_{55}O_7Si$ requires 699.3717.

*4.1.12. (2R,3R)-5-(Benzyloxy)-2-(tert-butyldiphenylsilyloxy)-1-((2′S,4′R,5′R)-5′-(tert-butylcarbonyloxymethyl)-4′-(p-methoxybenzyloxy)tetrahydrofuran-2′-yl)-3-methylpentan-1-one (**30**).* To a stirred solution of diol **29** (86 mg, 0.123 mmol) in pyridine (250 μL) cooled to −15 °C was added pivaloyl chloride (20 μL, 0.162 mmol) and the mixture stirred for 6 h. The reaction mixture was quenched by the addition of H_2O (2 mL), cooled to 0 °C, and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3×30 mL). The combined organic portions were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the corresponding pivalate ester (80 mg, 83%) as a colourless liquid. A mixture of the above secondary alcohol (77 mg, 0.098 mmol), dry pyridine (0.210 mL, 2.70 mmol) and Dess/Martin periodinane (120 mg, 0.280 mmol) was stirred in dry CH_2Cl_2 (2.5 mL) at room temperature for 45 min. Saturated $Na_2S_2O_3$ solution (3 mL) and saturated $NaHCO_3$ solution (3 mL) was added and the mixture allowed to stir for an additional 15 min. The mixture was extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **30** (76 mg, 99%) as a colourless liquid. R_f (20% EtOAc/hexane) 0.50; $[\alpha]_D^{20}$ −41.3 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2959, 2857, 1728 (C=O), 1613 (C=O), 1514, 1162, 1112; δ_H (300 MHz, $CDCl_3$): 1.09 (9H, s), 1.12 (3H, m), 1.17 (9H, s), 1.23–1.34 (1H, m), 1.50–1.59 (1H, m), 1.68–1.74 (1H, m), 1.91–2.00 (1H, m), 2.24–2.42 (1H, m), 3.33–3.37 (1H, m), 3.39–3.50 (2H, m), 3.62–3.63 (1H, m) 3.78 (3H, s), 4.08–4.20 (3H, m) 4.34–4.46 (3H, m), 4.50 (1H, t, *J* 7.9 Hz), 4.66 (1H, d, *J* 2.4 Hz), 6.83–7.35 (19H, m); δ_C (75 MHz, $CDCl_3$): 18.1, 19.8, 27.1, 27.1, 30.4, 33.8, 38.6, 38.6, 55.2, 62.7, 68.2, 70.8, 72.7, 77.8, 80.0, 80.2, 80.7, 113.8, 127.3, 127.4, 127.4, 127.5, 128.3, 129.0, 129.4, 129.5, 129.8, 133.7, 133.7, 136.2, 138.6, 159.2, 178.1, 211.2; ESI HRMS found: MH^+, 781.4121, $C_{47}H_{61}O_8Si$ requires 781.4136.

*4.1.13. (3R,4R)-3-(tert-Butyldiphenylsilyloxy)-2-((2′S,4′R,5′R)-4′-(p-methoxybenzyloxy)-5′-(tert-butylcarbonyloxymethyl)tetrahydrofuran-2′-yl)-4-methyltetrahydro-2H-2-methoxypyran (**4**).* To a stirred slurry of freshly prepared W-5 Raney nickel (∼5 mg, 0.09 mmol) in ethanol (2 mL) was added a solution of benzyl ether **30** (24 mg, 0.031 mmol) in ethanol (2 mL) and the mixture was stirred vigorously for 22 h under an atmosphere of H_2. The solution was filtered through a plug of Celite that was then washed with methanol (15 mL) and ethyl acetate (15 mL). The solvent was removed under reduced pressure and the crude hemiacetal used without further purification. To a stirred solution of the above crude hemiacetal in methanol (1.0 mL) was added trimethyl orthoformate (1.0 mL, 8.39 mmol) and camphorsulphonic acid (15 mg, 0.064 mmol). The mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$ (10 mL) then diluted with water (5 mL) and ethyl acetate (5 mL). The mixture was extracted with ethyl acetate (3×30 mL) and diethyl ether (1×30 mL). The combined organic extracts were washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography using hexane/ethyl acetate (9:1), 0.5% triethylamine as eluent to afford the *title compound* **4** (5 mg, 70%, two steps) as a colourless oil. R_f (10% EtOAc/hexane) 0.30; $[\alpha]_D^{20}$ −6.0 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2932, 1729 (C=O), 1613, 1514, 1428, 1248, 1170, 1093, 821, 703; δ_H (300 MHz, $CDCl_3$): 1.05 (3H, s), 1.14 (3H, s), 1.15–1.17 (1H, m), 1.21 (3H, d, *J* 7.1 Hz), 1.24–1.27 (1H, m), 1.32–1.43 (1H, m), 1.63–1.76 (1H, m), 1.99–2.09 (1H, m), 3.39 (3H, s), 3.42–3.47 (1H, m), 3.61 (1H, d, *J* 5.0 Hz), 3.73–3.77 (1H, m), 3.80 (3H, s), 3.93–3.98 (1H, m), 4.04 (1H, d, *J* 11.8 Hz), 4.11–4.17 (2H, m), 4.23 (1H, d, *J* 11.8 Hz), 4.39–4.45 (1H, m), 6.82–6.86 (2H, m), 7.09–7.12 (2H, m), 7.30–7.42 (6H, m), 7.65–7.76 (4H, m); δ_C (75 MHz, $CDCl_3$): 14.1, 19.7, 27.1, 27.2, 30.4, 31.6, 32.6, 50.4, 55.3, 56.4, 63.0, 70.4, 73.0, 78.2, 79.8, 80.0, 100.6, 113.8, 127.4, 127.5, 128.8, 129.5, 129.6, 130.3, 133.8, 134.1, 136.2, 136.2, 159.1, 178.2; ESI HRMS found: $[M-H]^+$, 703.3670, $C_{41}H_{55}O_8Si$ requires 703.3666.

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