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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5008527 • Publication Date (Web): 16 May 2014

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Total Synthesis of Virgatolide B *via* Exploitation of Intramolecular Hydrogen Bonding

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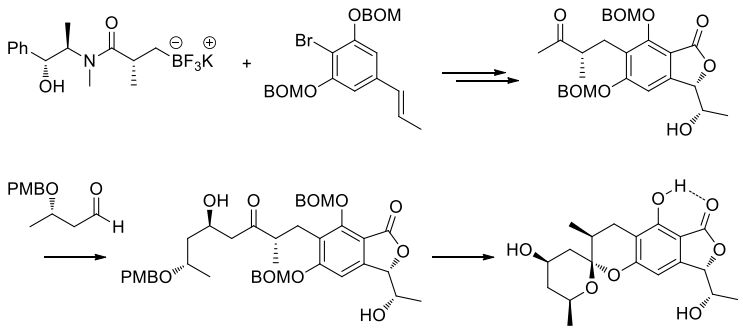


Abstract: A full account of the enantioselective total synthesis of virgatolide B is reported. Key features of the synthesis include an sp^3-sp^2 Suzuki-Miyaura cross-coupling of a β-trifluoroboratoamide with an aryl bromide, regioselective intramolecular carboalkoxylation and a 1,3-*anti*-selective Mukaiyama aldol reaction. Intramolecular hydrogen bonding governed the regioselectivity of the key spiroketalisation step, affording the natural product as a single regioisomer.

Introduction

Virgatolides A-C (**1**-**3**, Figure 1) are a family of [6,6]-benzannulated spiroketals, isolated in 2011 by Che et al. during an investigation into fungal metabolites produced by the genus *Pestalotiopsis*.[1] During preliminary biological screening, an ethyl acetate extract of a

fermentation culture of *P. virgatula* (L147) exhibited cytotoxicity towards HeLa (cervical epithelium) cells. Separation of the constituents furnished virgatolides A-C (IC_{50} 19.0, 22.5, and 20.6 μM respectively) together with previously described pestaphthalides A and B (**4** and **5**).[2] Virgatolides A-C share a common tetracyclic core and differ only in their stereochemistry and substitution at C-4 and C-13. The structure and relative stereochemistry of **1** was unambiguously secured by X-ray crystallography, and the absolute stereochemistry then determined by comparison of the CD-spectrum to those of **4** and **5**. The structures of **2** and **3**, including their relative and absolute stereochemistry, were established by NMR and HRMS analysis and by comparison of their CD-spectra with **1**, **4** and **5**. Importantly, the stereochemical information at C-4 and C-5 in **2** and **3** could not be directly correlated with that of the spiroketal moiety. The absolute configuration of the spiroketal ring system in **2** and **3** was therefore assumed to be analogous to that present in **1** in view of the likely biosynthetic connection between compounds **1**-**3**.[1] Naturally occurring [6,6]-benzannulated spiroketals are rare, with the only other known examples being chaetoquadrins A-C,[3] citreoviranol,[4] demethylcitreoviranol,[4] the dimeric cyandiones[5] dehydrocollatolic acid,[6] peniphenone A[7] and the peniciketals.[8] The novel molecular architecture, biological activity and unconfirmed stereochemical assignments of **1**-**3** captured our interest, and we were thus inspired to develop a synthetic approach to the virgatolides. We herein report the full details of this synthetic undertaking.[9]

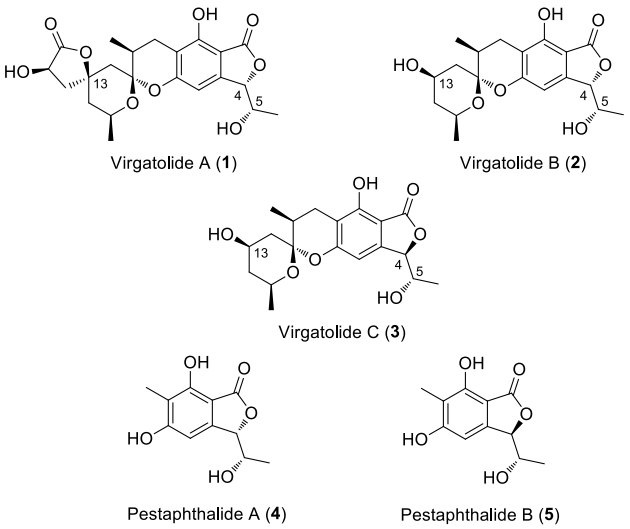
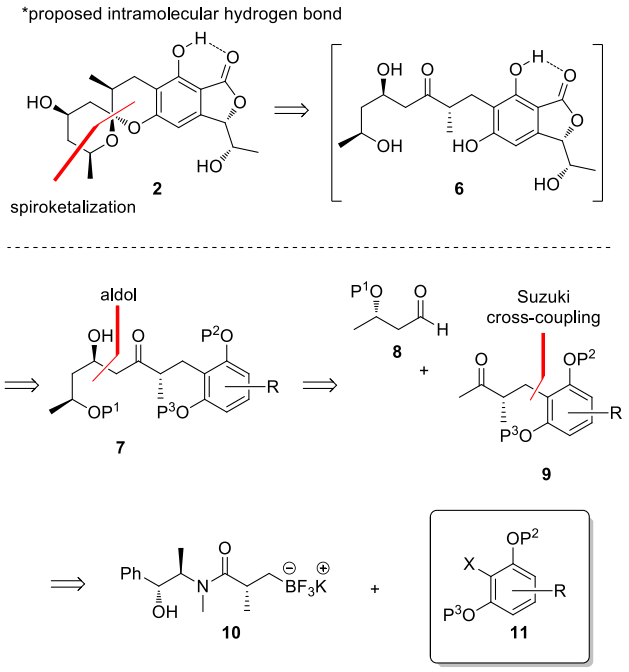


Figure 1. Virgatolides A-B (1-3), and pestaphthalides A (4) and B (5).

Retrosynthetic analysis

Virgatolide B (**2**) was chosen as the structural prototype of the virgatolides and a synthetic strategy was developed with the expectation that a successful synthesis would also enable access to the remaining two congeners (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Virgatolide B (2).



Retrosynthetically, disconnection of the spiroketal ring system in virgatolide B (**2**) provides ketone **6**. It was postulated that intramolecular hydrogen bonding between the phthalide carbonyl and the neighbouring phenol would result in an energetic differential between **2** and the spiroketal regioisomer formed upon spirocyclisation of the alternate phenolic oxygen. We hypothesized that this would favour formation of **2** *via* acid-catalysed equilibration of the spiroketal core. The acyclic spiroketal precursor **7** is accessed *via* a diastereoselective aldol reaction between methyl ketone **9** and aldehyde **8**. Aldehyde **8** is readily available from commercially available ethyl (*S*)-3-hydroxybutyrate *via* known chemistry.[10-11]

Methyl ketone **9** contains an α-chiral β-arylated ketone side chain, a motif posing some synthetic challenges. There are few direct methods for the construction of such subunits,[12-14] which have to date been accessed by benzylation of enolates,[15-16] conjugate addition of aryl organometallics,[17] Negishi cross-coupling[18-20] or catalytic asymmetric hydrogenation of α,β-unsaturated carbonyls compounds.[21-24] Each of these methods suffer from non-trivial drawbacks.[12] Our synthetic strategy sought to employ methodology developed by Molander et al.[12] for the Suzuki cross-coupling of enantiomerically-enriched potassium β-trifluoroboratoamide **10** with a suitable aryl halide coupling partner **11**. The remaining consideration was the level of substitution of the aryl halide coupling partner, i.e. whether the phthalide moiety was fully assembled prior to cross-coupling, or whether the aryl halide contained a suitable handle for elaboration to the phthalide at a later stage.

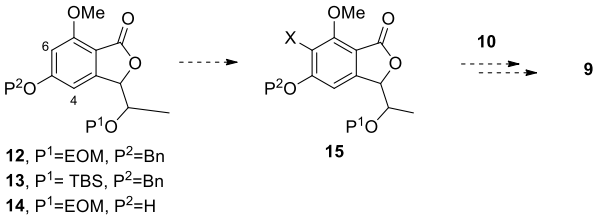
Results and Discussion

Attempted Preparation of a Fully Substituted Halo-Phthalide Coupling Partner

Our initial strategy sought to employ a fully substituted halo-phthalide coupling partner in the key Suzuki cross-coupling. We therefore focussed on regioselective halogenation of

phthalides **12-14**, hoping to introduce a bromide or iodide selectively at C-6. The resulting halide would then undergo Suzuki cross-coupling with trifluoroboratoamide **10** (Scheme 2).

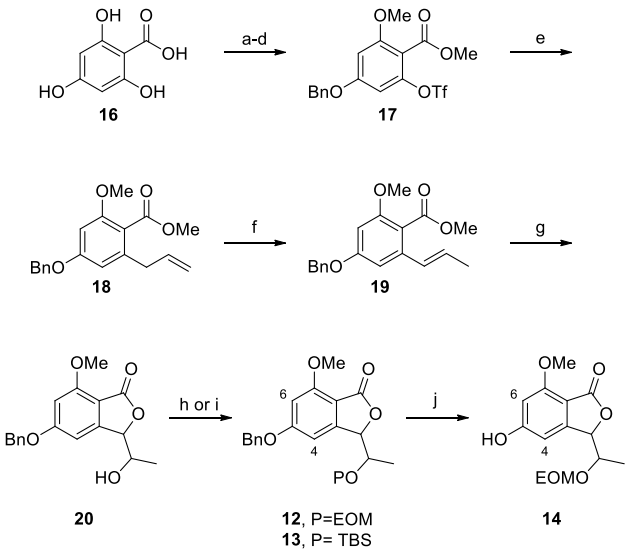
Scheme 2. Proposed Coupling of Halo-Phthalide 15 with 10



12, P^1=EOM, P^2=Bn
13, P^1= TBS, P^2=Bn
14, P^1=EOM, P^2=H

Toward that end, phthalides **12-14** were prepared from commercially available 2,4,6-trihydroxybenzoic acid **16** (Scheme 3), analogous to the work of Kitahara et al.[25] Selective esterification,[26] benzylation,[27] and methylation followed by conversion of the remaining hydroxyl group to the triflate provided **17** in moderate yield over four steps. Stille cross-coupling with allyltributyltin and base-mediated isomerization to the thermodynamically favoured *E*-alkene **19** completed the installation of the carbon framework. For the purposes of our initial investigation, phthalide **20** was generated as a racemic mixture *via* osmium-catalysed *cis*-dihydroxylation of olefin **19**. EOM and TBS protected phthalides **12** and **13** were prepared from **20**. Phthalide **14** was then formed by hydrogenolysis of the benzyl ether present in **12**.

Scheme 3. Synthesis of Phthalides 12-14

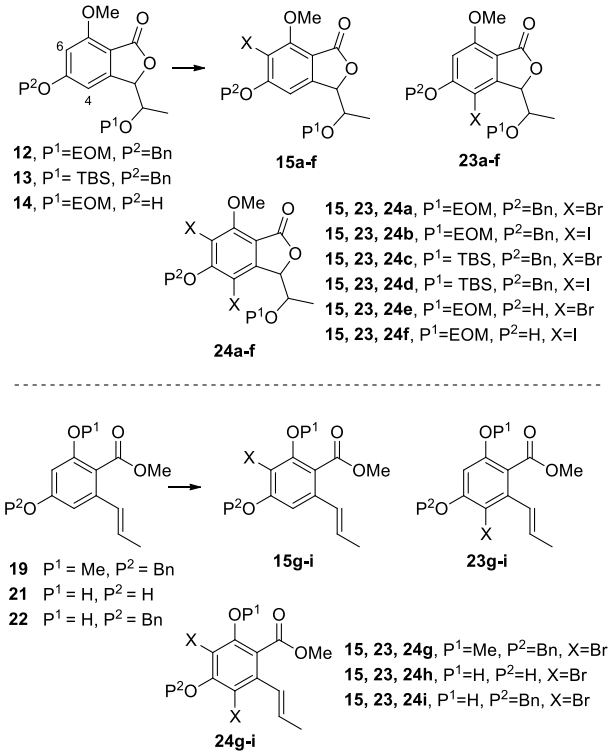


Reagents and conditions: a) Me_2SO_4, K_2CO_3, acetone, rt, 16 h, 56%; b) BnBr, K_2CO_3, NaI, acetone, reflux, 3 h, 62%; c) DIAD, PPh_3, MeOH, THF, rt, 2 h, 64%; d) $PhNTf_2$, NEt_3, CH_2Cl_2, reflux, 48 h, 96% e) allyltributyltin, $Pd(PPh_3)_4$, LiCl, THF, reflux, 48 h; f) *t*-BuOK, THF, 40 °C, 24 h, 83% over two steps; g) OsO_4, NMO, acetone-water (10:1), rt, 16 h, 90%; h) EOMCl, DIPEA, DMAP, CH_2Cl_2, rt, 48 h, quant.; i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 4 h, quant.; j) H_2, Pd/C, MeOH, rt, 24 h, 89%.

Selective halogenation of phthalides **12-14** at C-6 was required to generate the correct carbon framework upon cross-coupling with **10**. However, prediction of the preferred site for electrophilic aromatic substitution based on simple substituent-directing considerations was challenging for these substrates. Halogenation of **12-14** was conducted with both NBS and iodine. However, despite some literature precedent,[28-29] in all cases halogenation occurred exclusively at C-4 (Table 1). Attempted halogenation of several phthalide precursors (**19**, **21,** **22**) also proved unsuccessful, resulting in either selective halogenation at C-4 or halogenation

at both positions leading to inseparable product mixtures. These results indicated an inherent bias towards halogenation at C-4 which would likely be difficult to overturn.

Table 1. Attempted Synthesis of 15a-i



Entry	Substrate	Method[a]	Yield (%)		
			15	**23**	**24**
1	12	A	-	93	-
2	12	B	-	96	-
3	13	A	-	93	-
4	13	B	-	88	-
5	14	A	-	62	15
6	14	B	-	56	21
7	19	A	-	82	-
8	21	A	-	-	46[b]
9	22	A	3 component mixture		

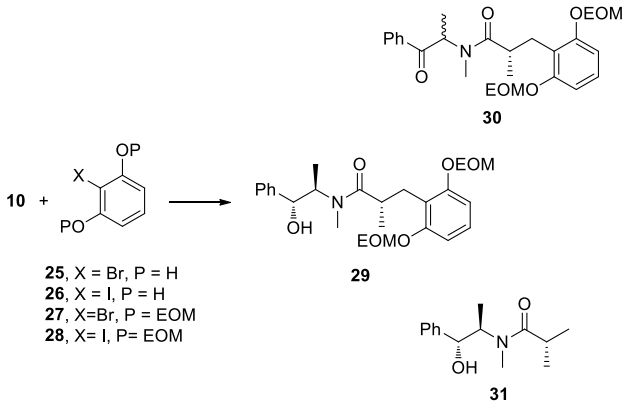
[a]Method A: NBS, CH_2Cl_2, 0 °C to rt. Method B: I_2, AgO_2CF_3, CH_2Cl_2, 0 °C to rt. [b]Remaining material was isolated as an inseparable mixture of **21** and monobrominated species.

Use of a Simplified Halide Coupling Partner for the Suzuki Coupling

Following unsuccessful efforts to achieve the synthesis of compounds **15a-i**, we noted that use of a simpler, rotationally symmetric halide coupling partner would remove the requirement for regioselective functionalisation of the aromatic nucleus. The required functionalisation was envisioned to be possible *via* iridium-catalysed CH-borylation at a later stage.[12,30-32] Attention therefore now focussed on the cross-coupling of halo-resorcinol derivatives **25**-**28** with trifluoroboratoamide **10**.

Trifluoroboratoamide **10** was prepared by the method of Molander[12] and the key Suzuki cross-coupling reaction investigated with resorcinol derivatives **25**-**28**[33-34] (Table 2). Attempted cross-coupling of **10** with bromide **25** resulted in the formation of protodeboronated amide **31**, identified by NMR and HRMS (entry 1). Use of iodide **26** resulted in the formation of a complex mixture (entry 2). However, use of protected aryl bromide **27** resulted in a pleasing 60% yield of coupled product **29**, despite the electron-rich, *ortho*-disubstituted nature of the coupling partner (entry 3). Low levels (10-20%) of oxidised amide **30** were also obtained. Amide **30** co-eluted with a catalyst-derived species and thus could not be obtained in an analytically pure form, but was identified using a combination of NMR and HRMS. Coupling of iodide **28** with **10** afforded amide **29** only in low yields even using extended reaction times (entry 4).

Table 2. Suzuki Cross-Coupling of 10 and Aryl Halides 25-28.



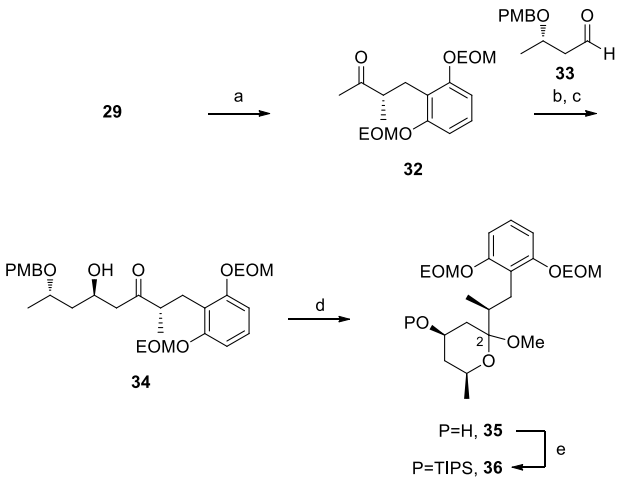
Entry	Conditions	Yield (%)		
		29	**30**	**31**
1	**25**, $Pd(OAc)_2$, RuPhos, K_2CO_3, toluene-H_2O, 85 °C, 3 h	-	-	76
2	**26**, $Pd(OAc)_2$, RuPhos, K_2CO_3, toluene-H_2O, 85 °C, 19 h	-	-	-
3	**27**, $Pd(OAc)_2$, RuPhos, K_2CO_3, toluene-H_2O, 85 °C, 3 h	60	10	-
4	**28**, $Pd(OAc)_2$, RuPhos, K_2CO_3, toluene-H_2O, 85 °C, 22 h	10	-	-

Pleased with the successful union of **10** and **27**, we now sought to investigate the construction of the spiroketal core prior to further functionalisation of the aromatic ring. Treatment of amide **29** with methyllithium generated methyl ketone **32** in good yield (Scheme 5).[35-36] Attention then turned to the key aldol reaction between **32** and aldehyde **33**.

An initial investigation into Paterson-type aldol reactions ((+)-Ipc_2BCl, NEt_3) to effect union of ketone **32** with aldehyde **33** provided aldol products only with moderate diastereoselectivity (d.r.~2:1) prompting the investigation of other methods.[37-38] Pleasingly, conversion of **32** to the corresponding TMS-enol ether, followed by reaction with aldehyde **33** in a substrate-controlled Mukaiyama aldol reaction afforded **34** as a single diastereomer in excellent yield. The stereochemistry of the newly generated chiral center was not assigned at

this stage, since cyclisation would allow assignment of the configuration by NOESY analysis. With the carbon framework required for the spiroketal core in place, the key spirocyclisation process was now investigated to ascertain whether the desired spiroketalisation would be possible on a more advanced intermediate.

Scheme 4. Synthesis of Acetals 35 and 36



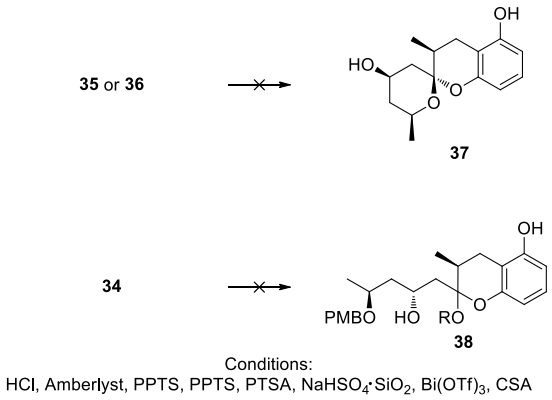
Reagents and conditions: a) MeLi, Et_2O, −78 °C to 0 °C, 30 min then diisopropylamine, AcOH, 80%; b) TMSOTf, NEt_3, CH_2Cl_2, 0 °C, 30 min; c) **33**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 2 min then add silyl enol ether, 1.5 h, 82% over two steps; d) H_2, $Pd(OH)_2/C$, MeOH, rt, 1 h, 90%; e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 40 min, 75%.

The PMB group in aldol product **34** was removed first, allowing formation of a cyclic acetal that would hopefully minimize the propensity for acid-catalysed elimination to take place. Hydrogenolysis of **34** in methanol afforded methoxy acetal **35** as a 3:1 mixture of anomers at C-2 (Scheme 4). Fortunately, treatment of **35** with TIPSOTf afforded TIPS ether **36** as a single diastereomer.

A survey of acidic deprotection conditions was now undertaken to effect spirocyclisation of **35** and TIPS ether **36** (Scheme 5). Unfortunately, treatment of **35** and **36** with $NaHSO_4{\cdot}SiO_2$,[39] PPTS,[40] HCl, CSA, Amberlyst®-15[41] or $Bi(OTf)_3$[42] all failed to effect

formation of spiroketal **37**. NMR analysis revealed the formation of complex product mixtures containing olefinic resonances, presumably resulting from acid-catalysed elimination. Reactions in methanol generated methylated by-products likely formed *via* elimination and subsequent addition of a solvent molecule. Realising that masking the ketone as an acetal did not remove the tendency of the molecule to undergo subsequent elimination; the deprotection sequence of the PMB and EOM groups was reversed (i.e. **34→38**). However, similar results were also obtained in this case.

Scheme 5. Attempted Formation of Spiroketal 37.

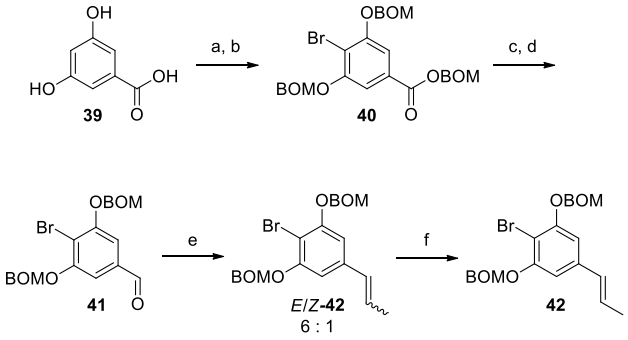


Revised Halide Coupling Partner for the Suzuki Coupling

Although formation of spiroketal **37** from acetals **35** and **36** was unsuccessful, we were satisfied with the success achieved in the key Suzuki cross-coupling and aldol reactions. We therefore sought to modify the aryl halide coupling partner to allow construction of the spiroketal core. The revised aryl bromide coupling partner **42** contains an (*E*)-alkene side chain (Scheme 6). The alkene side-chain facilitates construction of the phthalide moiety by Sharpless asymmetric dihydroxylation, halogenation and palladium-catalysed carboalkoxylation later in the synthesis. BOM was chosen as the desired protecting group as it was expected to be well tolerated in the key Suzuki cross-coupling step and cleavage *via*

hydrogenolysis would obviate the problems associated with the use of acid-mediated deprotection conditions.

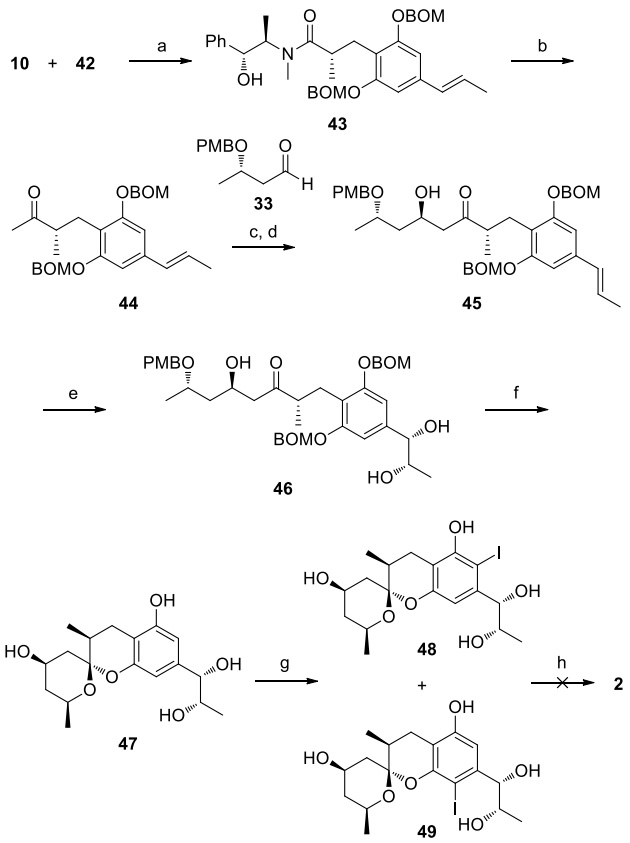
Scheme 6. Synthesis of Bromide 42



Reagents and conditions: a) Br_2, 20% aq. HCl, reflux, 2 h, 99%; b) BOMCl, DIPEA, CH_2Cl_2, rt, 16 h, 87%: c) DIBAL-H, CH_2Cl_2, −78°C to 0 °C, 20 min, 95%; d) SO_3·py, DIPEA, DMSO, 0 °C, 15 min, quant.; e) ethyltriphenylphosphonium iodide, KO^{t}Bu, 18-crown-6, CH_2Cl_2, rt, 89%; f) $Ru(CO)ClH(PPh_3)_3$, toluene, reflux, 24 h, 90%.

The synthesis of aryl bromide **42** was therefore undertaken from 3,5-dihydroxybenzoic acid **39**. Selective bromination[43] of **39** followed by global BOM protection provided ester **40**. Reduction of **40** with DIBAL-H followed by Parikh-Doehring oxidation[44] generated aldehyde **41** which underwent smooth Wittig reaction with ethyltriphenylphosphonium iodide affording *E*/*Z* alkene **42** as an inseparable 6:1 mixture of isomers. Isomerisation to **42** was readily achieved by subjecting the mixture to ruthenium (II) catalysis in refluxing toluene.[45]

Scheme 7. Synthesis of Spiroketal 47 and Attempted Conversion to Virgatolide B (2)



Reagents and conditions: a) $Pd(OAc)_2$, RuPhos, K_2CO_3, toluene-H_2O, (4:1), 85°C, 1.5 h, 55%; b) MeLi, THF, −78°C to 0°C, 30 min, 85%; c) TMSOTf, NEt_3, DMAP, CH_2Cl_2, 0°C, 30 min; d) **33**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 2 min, then add silyl enol ether, −78 °C, 3 h, 58% over two steps; e) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), 0 °C, 18 h, 90%; f) H_2, Pd/C, EtOAc, rt, 4 h, 55%; g) NIS, DMF, −40 °C, 24 h, 60%; h) CO, $PdCl_2(PPh_3)_2$, $N_2H_4{\cdot}H_2O$, K_2CO_3, 60°C or rt, 3 h or 24 h.

Despite the increased steric demand of **42**, Suzuki coupling with **10** proceeded cleanly, furnishing amide **43** which was readily elaborated to methyl ketone **44** (Scheme 7). **44** underwent Mukaiyama aldol reaction with aldehyde **33** furnishing aldol **45** as a single diastereomer. Asymmetric dihydroxylation of **45** then afforded **46** as a single diastereomer by NMR.

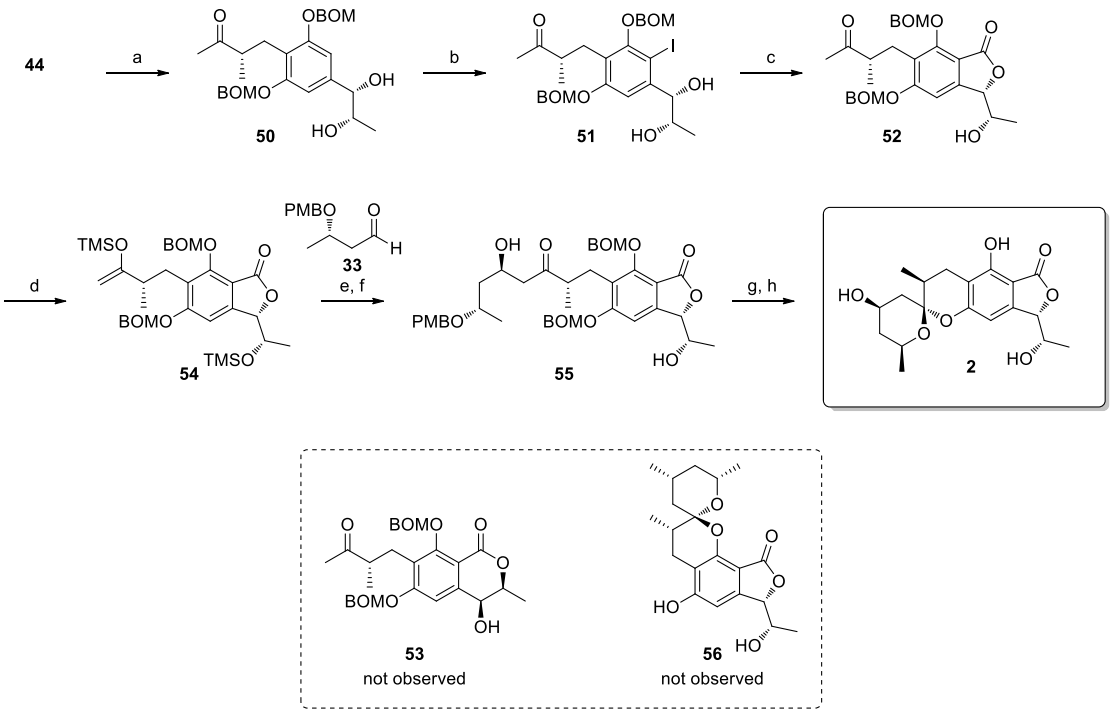
Pleasingly, the BOM groups were readily removed by hydrogenolysis, allowing successful formation of spiroketal **47** following global deprotection. Having successfully formed the spiroketal core of the virgatolide skeleton, all that remained was to complete the installation of the phthalide moiety. Iodination of **47** was non-selective, forming an inseparable regioisomeric mixture of iodides **48** and **49** although we postulated that upon installation of the carbonyl group, hydrogen-bonding would facilitate convergence to **2** *via* acid-catalysed equilibration. Disappointingly however, attempted carbonylation of **48**/**49** to give **2** resulted only in protodehalogenation, regenerating spiroketal **47** thus preventing construction of the phthalide moiety.

Revised Synthetic Strategy

Although the use of BOM groups had enabled access to the spiroketal core of virgatolide B (**2**), late stage construction of the phthalide moiety had proven problematic. It was noted that the free phenol *ortho* to the iodide could be contributing to the protodehalogenation observed upon attempted carbonylation. Rather than introduce unnecessary protecting group chemistry, it was decided to conduct the carbonylation step prior to the aldol reaction, re-ordering the sequence of synthetic events. Critically, it was noted that carbonylation of the rotationally symmetric aromatic nucleus prior to spiroketalisation would avoid the requirement to effect regioselective functionalisation of the aromatic ring and hopefully prevent any protodehalogenation taking place during the carboalkoxylation step. The intramolecular hydrogen bonding would then govern the regioselectivity of the spiroketalisation.

Attention therefore next focussed on assembly of methyl ketone phthalide **52** (Scheme 8), which would be converted to a silyl enol ether to effect the key Mukaiyama aldol reaction with aldehyde **33** to provide spirocyclisation precursor **55**.

Scheme 8. Synthesis of Virgatolide B (2)



Reagents and conditions: a) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), 0 °C to rt, 18 h, 87%; b) I_2, CF_3CO_2Ag, 0 °C, 1, h, 72%; c) CO, $Pd(PPh_3)_4$, DIPEA, 100°C, 18 h, 75%; d) TMSOTf, NEt_3 DMAP, CH_2Cl_2, 0°C, 15 min; e) **33**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 2 min. then **54**, −78 °C, 1.5 h; f) sat. aq. K_2CO_3 (5 drops), MeOH, rt, 30 min, 65% over three steps; g) H_2, Pd/C, EtOAc, rt, 3 h; h) CSA, CH_2Cl_2, 16 h, 55% over 2 steps.

Accordingly, Sharpless asymmetric dihydroxylation[46-47] of **44** using AD-mix α afforded diol **50** in high yield as a single diastereoisomer as determined by ^1H and ^{13}C NMR analysis (Scheme 8). Selective mono-iodination of the aromatic ring afforded iodide **51** with only traces of the easily separable di-iodinated product being formed. The formation of a single diastereoisomer in the asymmetric dihydroxylation was confirmed by subjecting a sample of **44** to non-selective *cis*-dihydroxylation followed by monoiodination. Inspection of the ^{13}C NMR in this case clearly revealed the presence of two diastereoisomers due to the pre-

existing chiral centre. Carbonylation of homochiral iodide **51** with concomitant intramolecular alkoxylation[48-53] afforded phthalide **52** in 75% yield. Gratifyingly, the cyclisation process was found to be completely selective for formation of **52** over isochromanone **53**, even at the elevated temperature at which the reaction was conducted, indicating a strong kinetic preference for formation of the five membered ring.

Attention finally turned to the key aldol reaction to unite phthalide **52** with aldehyde **33**. Simultaneous conversion of **52** to the TMS enol ether and protection of the secondary alcohol as a TMS ether was effected with TMSOTf. Reaction of the crude enol ether with aldehyde **33** was conducted analogously to the procedure used to construct aldol product **34** (Scheme 4). Upon completion of the reaction, the crude aldol adduct was dissolved in methanol and treated with saturated aqueous potassium carbonate, liberating the latent alcohol functionality. Ketone **55** was isolated in 65% yield over three steps as a single diastereomer.

Finally, global deprotection followed by equilibration with a catalytic quantity of CSA yielded the target natural product, virgatolide B (**2**) in 55% over two steps. Pleasingly, the spiroketal isomer **56** was not observed, fully consistent with our postulation that intramolecular hydrogen-bonding would govern the spirocyclisation step. Spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS analyses) for synthetic virgatolide B (**2**) were in full agreement with those reported for the natural product.[1] Furthermore, the absolute stereochemistry of naturally occurring virgatolide B was confirmed by comparison of the optical rotation values ($[\alpha]_D^{25}$ +19.1 (c 0.25 in MeOH), {lit. +25.0, (c 0.07 in MeOH)}.

Conclusion

In summary, the first total synthesis of virgatolide B (**2**) has been achieved in a concise manner (16 steps longest linear sequence) confirming the stereochemical assignment of the natural product. The carbon framework was assembled using an sp^3-sp^2 Suzuki Miyaura

cross-coupling of a chiral trifluoroboratoamide and an aryl bromide, and a highly diastereoselective 1,3-*anti* Mukaiyama aldol reaction. Preservation of the rotational symmetry of the aromatic nucleus was found to be essential to circumvent problems associated with regioselective halogenation. Hydrogen-bonding between the phthalide carbonyl and the *peri* phenol was exploited to direct the regiochemistry of spiroketal formation. The overall approach should be scalable and amenable to the construction of analogues and the remaining members of this family of natural products.

Experimental Section

General Procedures

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 and MeOH were freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230-400 mesh) was used for flash column chromatography. Preparatory TLC was carried out on 500 μm, 20 × 20 cm silica gel thin layer chromatography plates. NMR spectra were recorded at room temperature in $CDCl_3$, CD_3OD, $(CD_3)_3CO$, C_6D_6 or $(CD_3)SO$ solutions on either a spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, *J*, are in hertz (Hz). Multiplicities are reported as “s” (singlet), “br s” (broad singlet), “d” (doublet),

"dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet) and "m" (multiplet). Where distinct from those due to the major rotamer, resonances due to minor rotamers are denoted by an asterix. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded as a thin film on a composite of zinc selenide and diamond crystal on a FT-IR system transform spectrometer. Melting points are uncorrected. High-resolution mass spectra (HRMS) were obtained using a spectrometer operating at a nominal accelerating voltage of 70 eV or on a TOF-Q mass spectrometer.

Methyl-4-(benzyloxy)-2-hydroxy-6-methoxybenzoate

To a stirred solution of methyl-4-(benzyloxy)-2,6-dihydroxybenzoate (4.4 g, 16 mmol), PPh_3 (4.3 g, 16 mmol) and MeOH (0.98 mL, 24 mmol) in THF (120 mL) at 0 °C was added DIAD (3.2 mL, 16 mmol) dropwise. The solution was allowed to warm to room temperature, stirred for 2 h and quenched with sat. aq. NH_4Cl (40 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 8:1) afforded the *title compound* (3.0 g, 10 mmol, 63%) as a colourless solid; m.p. 116-117 °C (lit., 106 °C)[54]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.03 (1H, s, OH), 7.44-7.35 (5H, m, Ar-H), 6.20 (1H, d, J = 2.4 Hz, Ar-H), 6.06 (1H, d, J = 2.4 Hz, Ar-H), 5.06 (2H, s, CH_2), 3.92 (3H, s, CH_3), 3.82 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C=O), 165.9 (C), 164.5 (C), 162.2 (C), 136.0 (C), 128.7 (Ar-CH × 2), 128.3 (Ar-CH), 127.7 (Ar-CH × 2), 96.8 (C), 94.4 (Ar-CH), 92.2 (Ar-CH), 70.2 (CH_2), 56.1 (CH_3), 52.2 (CH_3). The spectroscopic data were in agreement with that reported in the literature.[54]

(*E*)-methyl 4-(benzyloxy)-6-methoxy-2-(prop-1-en-1-yl)benzoate 19

To a solution of methyl 4-(benzyloxy)-2-methoxy-6(((trifluoromethyl)sulfonyl)oxy)-benzoate **17** (1.9 g, 4.5 mmol) and LiCl (0.58 g, 14 mmol) in degassed THF (8 mL) was added $Pd(PPh_3)_4$ (0.26 g, 0.2 mmol) and allyltributylstannane (1.6 mL, 5.1 mmol). The reaction mixture was heated to 80 °C, stirred for 48 h and then allowed to cool to room temperature. THF (40 mL) and ^{t}BuOK (1.5 g, 13 mmol) were added and the reaction mixture heated to 45 °C with stirring for 8 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL). The layers were separated and the combined organic extracts washed successively with aq. NH_3 (25% v/v, 25 mL), aq. HCl (1 M, 25 mL) and sat. aq. $NaHCO_3$ (25 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the *title compound* **19** (1.2 g, 3.8 mmol, 84%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.31 (5H, m, Ar-H), 6.67 (1H, d, J = 2.0 Hz, Ar-H), 6.42 (1H, d, J = 2.0 Hz, Ar-H), 6.36 (1H, dd, J = 15.6, 1.6 Hz, CH), 6.18 (1H, dq, J = 15.6, 6.5 Hz, CH), 5.10 (2H, s, CH_2), 3.89 (3H, s, CH_3), 3.76 (3H, s, CH_3), 1.85 (3H, dd, J = 6.5, 1.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C=O), 160.3 (C), 157.8 (C), 137.7 (C), 136.4 (C), 129.0 (CH), 128.4 (Ar-CH × 2), 127.9 (CH), 127.5 (Ar-CH), 127.3 (Ar-CH × 2), 115.3 (C), 102.4 (Ar-CH), 97.9 (Ar-CH), 69.9 (CH_2), 55.7 (CH_3), 52.0 (CH_3), 18.5 (CH_3); IR (film) ν_{max} 2950, 1724, 1599, 1427, 1260, 1155, 1097, 1039, 961, 700 cm^{-1}; HRMS (ESI+) for $C_{19}H_{20}O_4$ $[M+Na]^+$ requires 335.1254 found 335.1240.

5-(benzyloxy)-3-(1-hydroxyethyl)-7-methoxyisobenzofuran-1(3*H*)-one 20

To a solution of (*E*)-methyl 4-(benzyloxy)-2-methoxy-6-(prop-1-en-1-yl)benzoate **19** (370 mg, 1.2 mmol) in acetone- H_2O (1:1, 9.5 mL) was added NMO (150 mg, 1.3 mmol) and OsO_4 (2.5% w/w in ^{t}BuOH, 0.31 mL, 0.024 mmol) and the resultant mixture stirred at room

temperature for 16 h. The reaction mixture was diluted with EtOAc (30 mL), the layers separated and the organic layer washed successively with sat. aq. $Na_2S_2O_4$ (5 mL), H_2O (5 mL) and brine (5 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the *title compound* **20** (310 mg, 0.98 mmol, 82%) as a white solid; m.p. 75-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.31 (5H, m, Ar-H), 6.64 (1H, s, Ar-H), 6.47 (1H, s, Ar-H), 5.19 (1H, d, J = 4.0 Hz, CH), 5.08 (2H, ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 11.5 Hz, CH_2), 4.15-4.13 (1H, m, CH), 3.85 (3H, s, CH_3), 2.65 (1H, br s, OH), 1.23 (3H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (C=O), 165.6 (C), 159.4 (C), 151.9 (C), 135.5 (C), 128.6 (Ar-CH × 2), 128.3 (Ar-CH), 127.5 (Ar-CH × 2), 107.3 (C), 99.7 (Ar-CH), 99.3 (Ar-CH), 82.5 (CH), 70.6 (CH_2), 68.2 (CH), 55.8 (CH_3), 18.1 (CH_3); IR (film) ν_{max} 3452, 2935, 1716, 1603, 1347, 1317, 1213, 1161, 1064, 762, 689 cm^{-1}; HRMS (ESI+) for $C_{18}H_{18}O_5$ $[M+Na]^+$ requires 337.1046 found 337.1060.

5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3*H*)-one 12

To a stirred solution of 5-(benzyloxy)-3-(1-hydroxyethyl)-7-methoxyisobenzofuran-1(3H)-one **20** (250 mg, 0.80 mmol) and DIPEA (1.1 mL, 6.4 mmol) in THF (7 mL) at 0 ºC was added EOMCl (0.75 mL, 8.0 mmol). The resultant solution was allowed to warm to room temperature and stirred for 48 h. The reaction was quenched with sat. aq. $NaHCO_3$ (7 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the *title compound* **12** (290 mg, 0.77 mmol, 96%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (5H, m, Ar-H), 6.65 (1H, s, Ar-H), 6.48 (1H, s, Ar-H), 5.27 (1H, d, J = 3.6 Hz, CH), 5.10 (2H, s, CH_2), 4.63 (2H, ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 7.0 Hz, CH_2), 4.18-4.14 (1H, m, CH), 3.87 (3H, s, CH_3), 3.48-3.39 (2H, m, CH_2),

1.12 (3H, t, J = 6.8 Hz, CH_3), 1.01 (3H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (C=O), 165.3 (C), 159.3 (C), 151.8 (C), 135.5 (C), 128.5 (Ar-CH × 2), 128.2 (Ar-CH), 127.4 (Ar-CH × 2), 107.6 (C), 99.7 (Ar-CH), 99.5 (Ar-CH), 93.8 (CH_2), 80.5 (CH), 72.4 (CH), 70.5 (CH_2), 63.3 (CH_2), 55.8 (CH_3), 14.8 (CH_3), 14.7 (CH_3); IR (film) ν_{max} 2976, 2934, 1756, 1604, 1450, 1326, 1211, 1157, 1019, 840 cm^{-1}; HRMS (ESI+) for $C_{21}H_{24}O_6$ $[M+Na]^+$ requires 395.1465 found 395.1467.

5-(benzyloxy)-3-(1-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3*H*)-one 13

To a stirred solution of phthalide **20** (100 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) at −78 °C under nitrogen was added 2,6-lutidine (0.15 mL, 1.3 mmol) and *tert*-butyldimethylsilyl triflate (0.20 mL, 0.95 mmol). The resultant solution was stirred at −78 °C for 4 h, and then quenched by the addition of sat. aq. $NaHCO_3$ (2 mL). Upon warming to room temperature, the layers were separated, and the aqueous layer further extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* **13** (140 mg, 0.32 mmol, 100%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (5H, m, Ar-H), 6.68 (1H, d, J = 2.0 Hz, Ar-H), 6.49 (1H, d, J = 2.0 Hz, Ar-H), 5.15 (1H, d, J = 3.7 Hz, CH), 5.09 (2H, s, CH_2), 4.25-4.18 (1H, m, CH), 3.87 (3H, s, CH_3), 0.96 (3H, d, J = 6.6 Hz, CH_3), 0.82 (9H, s, CH_3), 0.04 (3H, s, CH_3), −0.02 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2 (C=O), 165.3 (C), 159.4 (C), 152.2 (C), 135.7 (C), 128.7 (Ar-CH × 2), 128.3 (Ar-CH), 127.4 (Ar-CH × 2), 108.0 (C), 99.9 (Ar-CH), 99.5 (Ar-CH), 81.6 (CH), 70.4 (CH_2), 68.2 (CH), 55.8 (CH_3), 25.5 (CH_3 × 3), 17.8 (C), 17.6 (CH_3), −4.6 (CH_3), −5.1 (CH_3); IR (film) ν_{max} 2953, 2929, 2856, 1755, 1602, 1471, 1322, 1210, 1154, 1021, 957, 833, 732 cm^{-1}; HRMS (ESI+) for $C_{24}H_{32}O_5Si$ $[M+Na]^+$ requires 451.1911, found 451.1897.

3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one 14

To a stirred solution of 5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one **12** (110 mg, 0.29 mmol) in MeOH (6 mL) was added Pd/C (11 mg, 10% w/w) and stirred under H_2 at room temperature for 24 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* **14** (74 mg, 0.26 mmol, 89%) as a colourless solid; m.p. 134-137 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (1H, br s, OH), 6.63 (1H, s, Ar-H), 6.49 (1H, s, Ar-H), 5.31 (1H, d, J = 3.6 Hz, CH), 4.66 (2H, ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 7.0 Hz, CH_2), 4.20-4.17 (1H, m, CH), 3.88 (3H, s, CH_3), 3.50-3.44 (2H, m, CH_2), 1.15 (3H, t, J = 7.2 Hz, CH_3), 1.10 (3H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C=O), 164.4 (C), 159.9 (C), 152.0 (C), 106.5 (C), 101.9 (Ar-CH), 99.5 (Ar-CH), 94.0 (CH_2), 81.3 (CH), 72.5 (CH_2), 63.6 (CH), 55.8 (CH_3), 15.1 (CH_3), 14.9 (CH_3); IR (film) ν_{max} 3274, 2976, 2927, 1708, 1599, 1439, 1169, 966, 845, 689 cm^{-1}; HRMS (ESI+) for $C_{14}H_{18}O_6$ $[M+Na]^+$ requires 305.0996 found 305.0997.

(*E*)-methyl 4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate 21

To a stirred solution of alkene **19** (100 mg, 0.32 mmol) in CH_2Cl_2 (1.6 mL) under argon at −78 °C was added BBr_3 (1M in CH_2Cl_2, 1.6 mL) over 20 min. The solution was strirred at −78 °C for a further 20 min and then quenched by the addition of H_2O (1 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the *title compound* **21** (67 mg, 0.28 mmol, 87%); m.p. 117-119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.63 (1H, s, OH), 6.92 (1H, dq, J = 15.5, 1.8 Hz, CH), 6.40 (1H, d, J = 2.5 Hz, Ar-H), 6.33 (1H, s, J = 2.5 Hz, Ar-H), 5.93 (1H, dq, J = 15.5, 6.5 Hz, CH), 5.63 (1H, s, OH), 3.92 (3H, s, CH_3), 1.87 (3H, dd, J = 6.5, 1.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8

(C=O), 164.6 (C), 160.5 (C), 144.4 (C), 131.8 (CH), 128.3 (CH), 108.4 (Ar-CH), 104.2 (C), 102.2 (Ar-CH), 52.2 (CH_3), 18.7 (CH_3); IR (film) ν_{max} 3342, 1911, 1644, 1577, 1325, 1267, 1178, 1018, 832, 690 cm^{-1}; HRMS (ESI+) for $C_{11}H_{12}O_4$ $[M+Na]^+$ requires 231.0628 found 231.0631.

(*E*)-methyl 4-(benzyloxy)-6-hydroxy-2-(prop-1-en-1-yl)benzoate 22

A stirred suspension of alkene **21** (42 mg, 0.19 mmol), K_2CO_3 (27 mg, 0.19 mmol) and benzyl bromide (27 μL, 0.23 mmol) in acetone (1.0 mL) was heated under reflux for 16 h. The reaction mixture was allowed to cool to room temperature, H_2O (2.0 mL) added and the resultant solution extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* **22** (41 mg, 0.14 mmol, 68%) as a colourless solid; m.p. 82-85 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.63 (1H, s, OH), 7.39-7.27 (5H, m, Ar-H), 6.92 (1H, dq, J = 15.4, 1.6 Hz, CH), 6.53 (1H, d, J = 2.5 Hz, Ar-H), 6.42 (1H, d, J = 2.5 Hz, Ar-H), 5.91 (1H, dq, J = 15.4, 6.5 Hz, CH), 4.99 (2H, s, CH_2), 3.86 (3H, s, CH_3), 1.85 (3H, dd, J = 6.5, 1.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C=O), 164.9 (C), 163.1 (C), 143.5 (C), 136.2 (C), 132.0 (CH), 128.6 (Ar-CH × 2), 128.1 (Ar-CH), 127.7 (CH), 127.5 (Ar-CH × 2), 108.5 (Ar-CH), 103.8 (C), 100.6 (Ar-CH), 69.9 (CH_2), 51.9 (CH_3), 18.6 (CH_3); IR (film) ν_{max} 2916, 1646, 1607, 1568, 1430, 1328, 1252, 1168, 1029, 962, 731, 692 cm^{-1}; HRMS (ESI+) for $C_{18}H_{18}O_4$ $[M+Na]^+$ requires 321.1097 found 321.1099.

5-(benzyloxy)-4-bromo-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3*H*)-one 23a

To a stirred solution of 5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one **12** (60 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) at 0 ºC was added *N*-bromosuccinimide (32 mg, 0.18 mmol) in three portions over 30 min. The resultant

mixture was allowed to warm to room temperature and stirred for 16 h and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the *title compound* **23a** (68 mg, 0.15 mmol, 93%) as a colourless solid; m.p. 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.34 (5H, m, Ar-H), 6.51 (1H, s, Ar-H), 5.24 (2H, s, CH_2), 5.17 (1H, s, CH), 4.72 (1H, q, J = 6.2 Hz, CH) 4.44 (1H, d, J = 7.2 Hz, CH_2), 4.28 (1H, d, J = 7.2 Hz, CH_2), 3.91 (3H, s, CH_3), 3.20 (1H, m, CH_2), 2.99 (1H, m, CH_2), 1.45 (3H, d, J = 6.4 Hz, CH_3), 1.01 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4 (C=O), 160.7 (C), 158.7 (C), 150.0 (C), 135.2 (C), 128.7 (Ar-CH × 2), 128.4 (Ar-CH), 127.0 (Ar-CH × 2), 109.4 (C), 97.7 (Ar-CH), 96.0 (C), 93.0 (CH_2), 83.2 (CH), 71.5 (CH_2), 68.8 (CH), 63.0 (CH_2), 56.2 (CH_3), 17.4 (CH_3), 14.8 (CH_3); IR (film) ν_{max} 2976, 1760, 1601, 1358, 1202, 1183, 1028, 985 cm^{-1}; HRMS (ESI+) for $C_{21}H_{23}O_6Br$ $[M+Na]^+$ requires 473.0570 found 473.0562.

5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-4-iodo-7-methoxyisobenzofuran-1(3*H*)-one 23b

To a stirred solution of 5-(benzyloxy)-3-(1-(ethoxymethoxy)ethyl)-7-methoxyisobenzofuran-1(3H)-one **12** (60 mg, 0.16 mmol) and silver trifluoracetate (53 mg, 0.24 mmol) in CH_2Cl_2 (3.2 mL) was added I_2 (61 mg, 0.24 mmol) in CH_2Cl_2 (1.7 mL) dropwise over 30 min. The reaction mixture was stirred at room temperature for 30 min, then filtered through Celite®. Sat. aq. $Na_2S_2O_3$ (1 mL) and NaOH (1M, 1 mL) were added to the filtrate with stirring. The layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromtography (hexanes/EtOAc 2:1) afforded the *title compound* **23b** (77 mg, 0.15 mmol, 96%) as a colourless solid; m.p. 146-148 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.32 (5H, m, Ar-H), 6.45 (1H, s, Ar-H), 5.24 (2H, s, CH_2), 5.06 (1H, d, J = 1.0 Hz, CH),

4.82 (1H, qd, J = 6.5 Hz, 1.0 Hz, CH), 4.43 (1H, d, J = 7.6 Hz, CH_2), 4.25 (1H, d, J = 7.6 Hz, CH_2), 3.94 (3H, s, CH_3), 3.20-3.16 (1H, m, CH_2), 2.97-2.93 (1H, m, CH_2), 1.47 (3H, d, J = 6.5 Hz, CH_3), 1.00 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6 (C=O), 162.8 (C), 159.9 (C), 153.9 (C), 135.3 (C), 128.8 (Ar-CH × 2), 128.4 (Ar-CH), 127.0 (Ar-CH × 2), 110.3 (C), 97.0 (Ar-CH), 96.8 (CH_2), 84.9 (CH), 71.6 (CH_2), 68.8 (C), 68.7 (CH), 63.0 (CH_2), 56.2 (CH_3), 17.4 (CH_3), 14.9 (CH_3); IR (film) ν_{max} 2969, 2928, 1744, 1592, 1439, 1241, 1199, 1181, 1021, 974, 844, 743 cm^{-1}; HRMS (ESI+) for $C_{21}H_{23}O_6I$ $[M+Na]^+$ requires 521.0432 found 521.0427.

5-(benzyloxy)-4-bromo-3-(1-((tert-butyldimethylsilyl)oxy)ethyl)-7-methoxyisobenzofuran-1(3*H*)-one 23c

To a stirred solution of phthalide **13** (35 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added *N*-bromosuccinimide (16 mg, 0.090 mmol) portionwise over 30 min. The resultant solution was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched by the addition of H_2O (1 mL) and the layers separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 3 mL), the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the *title compound* **23c** (38 mg, 0.075 mmol, 93%) as a colourless solid; m.p. 150.3-153.7 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.34 (5H, m, Ar-H), 6.48 (1H, s, Ar-H), 5.26 (2H, ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 12.2 Hz, CH_2), 5.14 (1H, d, J = 1.0 Hz, CH), 4.72 (1H, qd, J = 6.4, 1.0 Hz, CH), 3.89 (3H, s, CH_3), 1.44 (3H, d, J = 6.4 Hz, CH_3), 0.57 (9H, s, CH_3), −0.06 (3H, s, CH_3), −0.39 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C=O), 160.8 (C), 158.9 (C), 150.7 (C), 135.5 (C), 128.9 (Ar-CH × 2), 128.5 (Ar-CH), 127.1 (Ar-CH × 2), 110.1 (C), 98.1 (Ar-CH), 96.3 (C), 84.1 (CH), 71.7 (CH_2), 65.7 (CH), 56.5 (CH_3), 25.4 (CH_3 × 3), 21.2 (CH_3), 17.6 (C), −4.3 (CH_3), −5.6 (CH_3); IR (film) ν_{max} 2954, 2929, 2856, 1751,

1600, 1441, 1361, 1203, 1047, 956, 835, 775, 728 cm^{-1}; HRMS (ESI+) for $BrC_{24}H_{31}O_5Si$ $[M+Na]^+$ requires 529.1016 found 529.1014.

5-(benzyloxy)-3-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-7-methoxyisobenzofuran-1(3*H*)-one 23d

To a stirred solution of phthalide **13** (25 mg, 0.058 mmol) and silver trifluoroacetate (19 mg, 0.088 mmol) in CH_2Cl_2 (1.2 mL) was added a solution of I_2 (22 mg, 0.088 mmol) in CH_2Cl_2 (0.6 mL) over 30 min. The resultant suspension was stirred at room temperature for 3 h and then filtered through Celite®. Excess I_2 was scavenged by the addition of sat. aq. $Na_2S_2O_3$ (0.5 mL). The layers were separated and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* **23d** (29 mg, 0.052 mmol, 90%) as a colourless solid; m.p. 170.0-173.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.35 (5H, m, Ar-H), 6.43 (1H, s, Ar-H), 5.26 (2H, ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 12.3 Hz, CH_2), 5.02 (1H, s, CH), 4.79 (1H, q, J = 6.5 Hz, CH), 3.90 (3H, s, CH_3), 1.45 (3H, d, J = 6.5 Hz, CH_3), 0.57 (9H, s, CH_3), −0.06 (3H, s, CH_3), −0.41 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 (C=O), 162.8 (C), 160.1 (C), 154.5 (C), 135.5 (C), 128.9 (Ar-CH × 2), 128.5 (Ar-CH), 127.1 (Ar-CH × 2), 111.0 (C), 97.3 (Ar-CH), 85.7 (CH), 71.8 (CH_2), 69.1 (C), 65.6 (CH), 56.5 (CH_3), 25.4 (CH_3 × 3), 21.1 (CH_3), 17.6 (C), -4.3 (CH_3), -5.4 (CH_3); IR (film) ν_{max} 2928, 2855, 1760, 1594, 1358, 1180, 1043, 957, 837, 776 cm^{-1}; HRMS (ESI+) for $C_{24}H_{31}IO_5Si$ $[M+H]^+$ requires 555.1058 found 555.1058.

4-bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one 23e and 4,6-dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one 24e

To a stirred solution of 3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one **14** (30 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL) at 0 ºC was added *N*-bromosuccinimide (21 mg, 0.12 mmol) in 3 portions over 30 min. The reaction mixture was allowed to warm to room temperature, stirred for 24 h and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the *title compounds* **23e** (24 mg, 0.07 mmol, 62%) and **24e** (7 mg, 0.02 mmol, 15%) as colourless solids.

4-bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one 23e

Contains 14% starting material and *N*-hydroxysuccinimide by NMR.

m.p. 145-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (1H, s, Ar-H), 5.19 (1H, d, J = 1.0 Hz, CH), 4.70-4.66 (1H, m, CH), 4.49 (1H, d, J = 7.5 Hz, CH_2), 4.32 (1H, d, J = 7.5 Hz, CH_2), 3.92 (3H, s, CH_3), 3.27-3.19 (1H, m, CH_2), 3.07-2.99 (1H, m, CH_2), 1.47 (3H, d, J = 6.5 Hz, CH_3), 1.04 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5 (C=O), 168.1 (Ar-C), 159.7 (Ar-C), 159.2 (Ar-C), 150.3 (Ar-C), 109.7 (Ar-C) 100.2 (Ar-CH), 93.2 (CH_2), 83.3 (CH), 69.0 (CH), 63.4 (CH_2), 56.4 (CH_3), 17.6 (CH_3), 15.0 (CH_3); IR (film) ν_{max} 3171, 1975, 2932, 1709, 1594, 1360, 1211, 1070, 976, 836 cm^{-1}; HRMS (ESI+) for $BrC_{14}H_{17}O_6$ $[M+Na]^+$ requires 383.0101 found 383.0102.

4,6-dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one 24e

m.p. 118-121 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (1H, d, J = 1.6 Hz, CH), 4.69 (1H, qd, J = 6.4, 1.6 Hz, CH), 4.50 (1H, d, J = 7.0 Hz, CH_2), 4.32 (1H, d, J = 7.0 Hz, CH_2), 4.18 (3H,

s, CH_3), 3.27-3.20 (1H, m, CH_2), 3.02-2.95 (1H, m, CH_2), 1.49 (3H, d, J = 6.4 Hz, CH_3), 1.03 (3H, t, J = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2 (C=O), 156.3 (C), 155.1 (C), 148.8 (C), 113.4 (C), 106.4 (C), 97.3 (C), 93.3 (CH_2), 83.5 (CH), 69.1 (CH_2), 63.5 (CH_3), 63.3 (CH), 17.6 (CH_3), 15.0 (CH_3); IR (film) ν_{max} 3223, 2927, 1732, 1586, 1364, 1159, 1089, 1017, 772 cm^{-1}; HRMS (ESI+) for $Br_2C_{14}H_{16}O_6$ $[M+Na]^+$ requires 460.9206 found 460.9198.

3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-4-iodo-7-methoxyisobenzofuran-1(3*H*)-one 23f and 3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-4,6-diiodo-7-methoxyisobenzofuran-1(3*H*)-one 24f

To a stirred solution of 3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one **14** (37 mg, 0.13 mmol) and silver trifluoroacetate (43 mg, 0.19 mmol) in CH_2Cl_2 (2.6 mL) was added I_2 (29 mg, 0.19 mmol), in CH_2Cl_2 (1.5 mL) over 30 min. The reaction mixture was stirred at room temperature for 16 h and filtered through Celite®. Sat. aq. $Na_2S_2O_3$ (1.0 mL) was added to the filtrate. The layers were separated, the aqueous layer further extracted with CH_2Cl_2 (2 × 3 mL), the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the *title compounds* **23f** (29.5 mg, 0.070 mmol, 56%) and **24f** (14.3 mg, 0.030 mmol, 20%) as colourless solids.

3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-4-iodo-7-methoxyisobenzofuran-1(3*H*)-one 23f

Contains 15% starting material by NMR.

m.p. 149-151 ºC (Some trace material did not melt until 169 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (1H, s, Ar-H), 5.08 (1H, d, J = 1.0 Hz, CH), 4.78 (1H, qd, J = 6.6 Hz, 1.0 Hz, CH), 4.47 (1H, d, J = 7.2 Hz, CH_2), 4.28 (1H, d, J = 7.2 Hz, CH_2), 3.91 (3H, s, CH_3), 3.22-3.18 (1H, m, CH_2), 3.00-2.97 (1H, m, CH_2), 1.47 (1H, d, J = 6.6 Hz, CH_3), 1.03 (3H, t, J

= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C=O), 162.3 (C), 160.1 (C), 154.1 (C), 109.9 (C), 99.2 (Ar-CH), 93.0 (CH_2), 85.1 (CH), 68.5 (CH), 67.1 (C), 63.3 (CH_2), 56.2 (CH_3), 17.4 (CH_3), 15.0 (CH_3); IR (film) ν_{max} 3172, 2975, 2926, 1708, 1586, 1447, 1362, 1212, 1070, 980, 834, 732 cm^{-1}; HRMS (ESI+) for $C_{14}H_{17}IO_6$ $[M+Na]^+$ requires 430.9962 found 430.9966.

3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-4,6-diiodo-7-methoxyisobenzofuran-1(3*H*)-one 24f

m.p. 119-121 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (1H, d, J = 1.5 Hz, CH), 4.77 (1H, qd, J = 6.5, 1.5 Hz, CH), 4.48 (1H, d, J = 7.5 Hz, CH_2), 4.29 (1H, d, J = 7.5 Hz, CH_2), 4.17 (3H, s, CH_3), 3.24-3.16 (1H, m, CH_2), 2.96-2.88 (1H, m, CH_2), 1.51 (3H, d, J = 6.5 Hz, CH_3), 1.02 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C=O), 159.7 (C), 159.3 (C), 154.4 (C), 113.2 (C), 93.3 (CH_2), 91.0 (C), 85.3 (CH), 83.0 (C), 68.9 (CH), 63.5 (CH_2), 63.3 (CH_3), 17.6 (CH_3), 15.1 (CH_3); IR (film) ν_{max} 3365, 2983, 2928, 1748, 1574, 1401, 1170, 1068, 1012, 730 cm^{-1}; HRMS (ESI+) for $C_{14}H_{16}I_2O_6$ $[M+Na]^+$ requires 556.8928 found 556.8932.

(*E*)-methyl 4-(benzyloxy)-3-bromo-6-methoxy-2-(prop-1-en-1-yl)benzoate 23g

To a stirred solution of **19** (50 mg, 0.16 mmol) in CH_2Cl_2 at 0 °C was added *N*-bromosuccinimide (31 mg, 0.18 mmol) in three portions over 30 min. The reaction mixture was stirred at 0 °C for 3 h and stored at 0 °C overnight. The solution was allowed to warm to room temperature and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the *title compound* **23g** as a colourless solid; m.p. 89-91 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.29 (5H, m, Ar-H), 6.47 (1H, d, J = 16.0 Hz, CH), 6.41 (1H, s, Ar-H), 5.86 (1H, dq, J = 16.0, 6.4 Hz, CH), 5.16 (2H, s, CH_2), 3.80 (3H, s, CH_3), 3.74

(3H, s, CH_3), 1.85 (1H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C=O), 156.1 (C), 156.3 (C), 138.5 (C), 136.1 (C), 131.8 (CH), 128.8 (CH), 128.7 (Ar-CH × 2), 128.1 (Ar-CH), 127.0 (Ar-CH × 2), 117.2 (C), 104.8 (C), 96.8 (Ar-CH), 71.2 (CH_2), 56.1 (CH_3), 52.3 (CH_3), 18.8 (CH_3); IR (film) ν_{max} 2947, 1729, 1585, 1570, 1336, 1218, 1202, 1067, 974, 738 cm^{-1}; HRMS (ESI+) for $BrC_{19}H_{19}O_4$ $[M+Na]^+$ requires 413.0359 found 413.0361.

(*E*)-methyl 3,5-dibromo-4,6-dihydroxy-2-(prop-1-en-1-yl)benzoate 24h

To a stirred solution of alkene **21** (30 mg, 0.14 mmol) in toluene (1.3 mL) at 0 °C under nitrogen was added *N*-bromosuccinimide (28 mg, 0.16 mmol) in three portions over 30 min. The resultant mixture was stirred at room temperature for 16 h and then concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 10:1 to 5:1) afforded the *title compound* **24h** (30 mg, 0.088 mmol, 56%) as a colourless solid; m.p. 93-96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (1H, dq, J = 16.0, 2.0 Hz, CH), 5.55 (1H, dq, J = 16.0, 6.6 Hz, CH), 3.90 (3H, s, CH_3), 1.89 (3H, dd, J = 6.6, 2.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C=O), 158.8 (C), 153.9 (C), 141.6 (C), 131.4 (CH), 129.5 (CH), 107.4 (C), 103.8 (C), 97.2 (C), 52.7 (CH_3), 18.4 (CH_3); IR (film) ν_{max} 3412, 2956, 2853, 1637, 1580, 1395, 1318, 1243, 952, 795 cm^{-1}; HRMS (ESI+) for $Br_2C_{11}H_{10}O_4$ $[M+Na]^+$ requires 386.8838 found 386.8837.

2-Bromo-1,3-bis(ethoxymethoxy)benzene 27

To a stirred solution of 2-bromoresorcinol **25**[33] (2.0 g, 11 mmol) and diisopropylethylamine (11 mL, 64 mmol) in CH_2Cl_2 (13 mL) at 0 °C was added chloromethylethyl ether (3 mL, 32 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by flash chromatography (hexanes/EtOAc 10:1) afforded the *title compound* **27** (3.2 g, 11 mmol, 99%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (1H, t, J = 8.4 Hz, Ar-H), 6.84 (2H, d, J = 8.4 Hz, Ar-H), 5.28 (4H, s, CH_2), 3.77 (4H, q, J = 6.8 Hz, CH_2), 1.22 (6H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2 (Ar-C × 2), 128.2 (Ar-CH), 109.4 (Ar-CH × 2), 103.8 (C), 93.9 (CH_2 × 2), 64.7 (CH_2 × 2), 15.1 (CH_3 × 2); IR (film) ν_{max} 2977, 2902, 1593, 1466, 1242, 1028, 890, 771 cm^{-1}; HRMS (ESI+) for $BrC_{12}H_{17}O_4$ $[M+Na]^+$ requires 327.0202 found 327.0211.

2-Iodo-1,3-bis(ethoxymethoxy)benzene 28

To a stirred solution of 2-iodoresorcinol **26**[34] (0.77 g, 3.3 mmol) and diisopropylethylamine (3.4 mL, 20 mmol) in CH_2Cl_2 (5.2 mL) at 0 °C was added chloromethylethyl ether (0.91 mL, 9.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of H_2O (10mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes-EtOAc 10:1) afforded the *title compound* **28** (1.0 g, 2.9 mmol, 89%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (1H, t, J = 8.0 Hz, Ar-H), 6.76 (2H, d, J = 8.0 Hz, Ar-H), 5.28 (4H, s, CH_2), 3.76 (4H, q, J = 7.2 Hz, CH_2), 1.22 (6H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6 (Ar-C × 2), 129.7 (Ar-CH), 108.5 (Ar-CH × 2), 93.8 (CH_2 × 2), 80.7 (C), 64.7 (CH_2 × 2), 15.1 (CH_3 × 2); IR (film) ν_{max} 2976, 2902, 1587, 1461, 1240, 1115, 1034, 888, 771cm^{-1}; HRMS (ESI+) for $C_{12}H_{17}IO_4$ $[M+Na]^+$ requires 375.0064 found 375.0071.

(*S*)-3-(2,6-bis(ethoxymethoxy)phenyl)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpropanamide 29

A flask was charged with trifluoroborate **10** (400 mg, 1.2 mmol), bromide **27** (390 mg, 1.3 mmol), $Pd(OAc)_2$ (13.0 mg, 0.06 mmol, 10 mol %), RuPhos (55 mg, 0.12 mmol, 20 mol %) and K_2CO_3 (490 mg, 3.5 mmol) and purged with N_2 three times. A degassed mixture of toluene (4 mL) and H_2O (1 mL) was then added. The reaction mixture was heated at 85 °C with stirring for 1.5 h and then allowed to cool to room temperature. A solution of pH 7 buffer (2 mL), prepared from $NaHPO_4$ (1.7 g) and $NaH_2PO_4 \cdot 2H_2O$ (1.2 g) in H_2O (50 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes-EtOAc 4:1 to 1:1) afforded the title compound **29** (330 mg, 0.72 mmol, 60%) as a colourless oil; $[\alpha]_D^{25}$ = −26.4 (c 0.73 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 5:1 rotamer ratio, asterisk denotes minor rotamer peaks): δ 7.36-7.22 (5H, m, Ar-H × 5), 7.15-7.08 (1H, m, Ar-H), 6.85* (2H, d, *J* = 8.4 Hz, Ar-H), 6.78 (2H, d, *J* = 8.4 Hz, Ar-H), 5.20 (4H, s, CH_2), 4.84 (1H, br s, OH), 4.65-4.61 (1H, m, CH), 4.55* (1H, d, *J* = 8.2 Hz, CH), 4.32-4.30 (1H, m, CH), 4.20-4.15* (1H, m, CH), 3.72-3.66 (4H, m, CH_2), 3.30-3.26* (1H, m, CH), 3.15-2.99* (2H, m, CH_2), 3.04-2.99 (1H, m, CH), 2.92-2.86 (1H, m, CH_2 + NCH_3*), 2.82 (3H, s, NCH_3), 2.67 (1H, dd, *J* = 12.8, 4.6 Hz, CH_2), 1.23-1.17 (6H, m, CH_3), 1.14 (3H, d, *J* = 7.0 Hz, CH_3), 1.03 (3H, d, *J* = 6.6 Hz, CH_3), 0.96* (3H, d, *J* = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5 (C=O), 178.3* (C=O), 156.9* (C), 156.7 (C), 142.9 (C), 141.2* (C), 128.7* (Ar-CH × 2), 128.4 (Ar-CH × 2), 127.6 (Ar-CH), 127.5 (Ar-CH), 127.3* (Ar-CH × 2), 126.4 (Ar-CH × 2), 118.3* (C), 117.7 (C), 107.9* (Ar-CH × 2), 107.6 (Ar-CH × 2), 93.4* (CH_2 × 2), 93.3 (CH_2 × 2), 76.8 (CH), 75.4* (CH), 64.5 (CH_2 × 2), 60.1 (CH), 58.2* (CH), 36.3 (CH), 35.5* (CH), 33.5 (CH_3), 27.5 (CH_2), 26.8* (CH_2), 17.0* (CH_3), 16.1 (CH_3), 15.4* (CH_3), 15.2 (CH_3 × 2), 14.6

(CH_3); IR (film) ν_{max} 3379, 2951, 1614, 1469, 1251, 1073, 1029, 703 cm^{-1}; HRMS (ESI+) for $C_{26}H_{37}NO_6$ $[M+Na]^+$ requires 482.2513 found 482.2519.

(*S*)-4-(2,6-bis(ethoxymethoxy)phenyl)-3-methylbutan-2-one 32

To a stirred solution of **29** (100 mg, 0.22 mmol) in Et_2O (2.2 mL) at -78 °C was added MeLi (0.5 M in Et_2O, 1.1 mL, 0.55 mmol). The resultant suspension was warmed to 0 °C and stirred for 15 min. Excess MeLi was scavenged by the addition of diisopropylamine (0.25 mL, 1.8 mmol) and the reaction mixture stirred for a futher 15 minutes at 0 °C. A solution of acetic acid (0.25 mL) in Et_2O (1.5 mL) was added, followed by H_2O (10 mL). The reaction mixture was extracted with Et_2O (3 × 10 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 7:1) afforded the *title compound* **32** (59 mg, 0.19 mmol, 88%) as a colourless oil; $[\alpha]_D^{25}$ = +45.9 (c 1.07 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (1H, t, J = 8.4 Hz, Ar-H), 6.79 (2H, d, J = 8.4 Hz, Ar-H), 5.21 (4H, s, CH_2), 3.71 (4H, q, J = 7.2 Hz, CH_2), 2.88 (1H, dd, J = 12.0, 5.0 Hz, CH_2), 2.83-2.75 (1H, m, CH), 2.72 (1H, dd, J = 12.0, 8.4 Hz, CH_2), 2.14 (3H, s, CH_3), 1.17 (6H, t, J = 7.2 Hz, CH_3), 0.96 (3H, d, J = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.9 (C=O), 156.6 (Ar-C × 2), 127.6 (Ar-CH), 117.8 (C), 107.7 (Ar-CH x2), 93.4 (CH_2 × 2), 64.5 (CH_2 × 2), 47.0 (CH), 28.4 (CH_3), 26.7 (CH_2), 15.7 (CH_2), 15.3 (CH_3 × 2); IR (film) ν_{max} 2976, 2931, 1711, 1594, 1467, 1251, 1097, 1030 cm^{-1}; HRMS (ESI+) for $C_{17}H_{26}O_5$ $[M+Na]^+$ requires 333.1672 found 333.1684.

(2*S*,5*R*,7*S*)-1-(2,6-bis(ethoxymethoxy)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one 34

To a stirred solution of ketone **32** (160 mg, 0.51 mmol) and triethylamine (0.21 mL, 1.5 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C was added trimethylsilyl triflate (0.14 mL, 0.76 mmol) dropwise. The resultant mixture was stirred for 30 minutes then quenched by addition of sat.

aq. NH_4Cl (3 mL). The layers were separated, and the aqueous layer further extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude silyl enol ether was azeotropically dried with toluene and used directly in the next step without further purification.

Boron trifluoride diethyl etherate (0.16 mL, 1.2 mmol) was added to a solution of aldehyde **33** (130 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) at −78 °C and the resultant solution stirred for 2 minutes. A solution of silyl enol ether prepared above in CH_2Cl_2 (2 mL) was added dropwise. The resultant solution was stirred at −78 °C for 90 minutes and quenched by the addition of sat. aq. $NaHCO_3$ (5 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 4:1 to 1:1) afforded the *title compound* **34** (220 mg, 0.42 mmol, 82%) as a colourless oil; $[\alpha]_D^{25}$ +39.5 (c 0.74 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (2H, m, Ar-H), 7.10 (1H, t, J = 8.4 Hz, Ar-H), 6.88-6.85 (2H, m, Ar-H), 6.78 (2H, d, J = 8.4 Hz, Ar-H), 5.22-5.19 (4H, m, CH_2), 4.55 (1H, d, J = 11.0 Hz, CH_2), 4.38 (1H, d, J = 11.0 Hz, CH_2), 4.37-4.29 (1H, m, CH), 3.87-3.82 (1H, m, CH), 3.79 (3H, s, CH_3), 3.70 (4H, q, J = 6.9 Hz, CH_2), 3.42 (1H, br s, OH), 2.94-2.90 (1H, m, CH_2), 2.87-2.82 (1H, m, CH), 2.79-2.74 (1H, m, CH_2), 2.67-2.53 (2H, m, CH_2), 1.64-1.50 (2H, m, CH_2), 1.22 (3H, d, J = 6.2 Hz, CH_3) 1.22 (6H, t, J = 6.9 Hz, CH_3), 1.01 (3H, d, J = 6.7 Hz, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.8 (C=O), 159.3 (C), 156.5 (Ar-C × 2), 130.9 (C), 129.5 (Ar-CH × 2), 127.7 (Ar-CH), 117.6 (C), 113.9 (Ar-CH × 2), 107.6 (Ar-CH × 2), 93.4 (CH_2 × 2), 71.9 (CH), 70.7 (CH_2), 64.9 (CH), 64.5 (CH_2 × 2), 55.4 (CH_3), 48.0 (CH_2), 46.6 (CH), 43.7 (CH_2), 26.5 (CH_2), 19.9 (CH_3), 15.5 (CH_3), 15.2 (CH_3 × 2); IR (film) ν_{max} 3489, 2971, 2926, 1704, 1594, 1514, 1469, 1248, 1151, 1095, 1032, 821 cm^{-1}; HRMS (ESI+) for $C_{29}H_{42}NaO_8$ $[M+Na]^+$ requires 541.2772 found 541.2754.

(4*R*,6*S*)-2-((*S*)-1-(2,6-bis(ethoxymethoxy)phenyl)propan-2-yl)-2-methoxy-6-methyltetrahydro-2*H*-pyran-4-ol 35

A mixture of aldol **34** (100 mg, 0.20 mmol) and palladium hydroxide on carbon (80 mg) in MeOH (44 mL) under hydrogen was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo* to give the *title compound* **35** (77 mg, 0.19 mmol, 95%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.04 (1H, m, Ar-H), 6.79-6.75 (2H, m, Ar-H), 4.21 (4H, s, CH_2), 4.15-4.07 (1H, m, CH), 3.78-3.66 (5H, m, CH and CH_2), 3.12* (3H, s, CH_3), 3.08 (3H, s, CH_3), 2.95-2.89 (1H, m, CH_2), 2.59-2.51 (1H, m, CH_2), 2.35-2.26 (1H, m, CH), 2.24-2.19* (1H, m, CH), 2.04-1.97 (1H, m, CH_2) 1.96-1.91 (1H, m, CH_2), 1.87-1.80* (1H, m, CH), 1.48-1.43 (1H, m, CH_2), 1.23 (6H, t, J = 7.0 Hz, CH_3), 1.17 (3H, d, J = 6.3 Hz, CH_3), 1.15-1.09 (1H, m, CH_2), 1.11* (3H, d, J = 5.9 Hz, CH_3), 0.76 (3H, d, J = 7.0 Hz, CH_3), 0.73* (3H, d, J = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7* (C), 156.6 (C), 126.9 (Ar-CH), 126.7* (Ar-CH), 120.5* (C), 120.2 (C), 107.9* (Ar-CH × 2), 107.8 (Ar-CH × 2), 103.8 (C), 101.9* (C), 93.5* (CH_2 × 2), 93.4 (CH_2 × 2), 66.1* (CH), 65.5 (CH), 65.0 (CH), 64.3 (CH_2 × 2), 46.4 (CH_3), 42.6 (CH_2), 37.4 (CH), 36.8 (CH), 36.5 (CH_2), 32.9* (CH_2), 25.4 (CH_2), 22.1* (CH_3), 21.6 (CH_3), 15.3 (CH_3 × 2), 13.3 (CH_3); IR (film) ν_{max} 2971, 2933, 1594, 1469, 1381, 1251, 1151, 1095, 1079, 1034, 922, 779 cm^{-1}; HRMS (ESI+) for $C_{22}H_{36}NaO_7$ $[M+Na]^+$ requires 435.2353 found 435.2344. The optical rotation of **X** was not measured because the sample was not diastereomerically pure.

4-triisopropylsilyloxy-(4*R*,6*S*)-2-((*S*)-1-(2,6-bis(ethoxymethoxy)phenyl)propan-2-yl)-2-methoxy-6-methyltetrahydro-2*H*-pyran 36

To a stirred solution of methoxy acetal **35** (10 mg, 0.024 mmol) and 2,6-lutidine (7 μL, 0.061 mmol) in CH_2Cl_2 (0.5 mL) at −78 ° C under nitrogen was added triisopropyl triflate (8 μL, 0.029 mmol). The resultant solution was stirred at −78 °C for 1 h then quenched by the

addition of sat. aq. $NaHCO_3$ (1 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 40:1 with 0.25% v/v NEt_3) afforded the *title compound* **36** (9.6 mg, 0.017 mmol, 70%) as a colourless oil; $[\alpha]_D^{25}$ −9.3 (c 0.74 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (1H, t, J = 8.3 Hz, Ar-H), 6.77 (2H, d, J = 8.3 Hz, Ar-H), 5.22 (4H, s, CH_2), 4.23-4.14 (1H, m, CH), 3.79-3.71 (4H, m, CH_2), 3.69-3.61 (1H, m, CH), 3.07 (3H, s, CH_3), 2.92 (1H, dd, J = 12.4, 3.6 Hz, CH_2), 2.57 (1H, dd, J = 12.4, 10.8 Hz, CH_2), 2.32-2.23 (1H, m, CH), 1.96 (1H, ddd, J = 12.7, 4.7, 1.7 Hz, CH_2), 1.90-1.86 (1H, m, CH_2), 1.47 (1H, dd, J = 12.7, 10.6 Hz, CH_2), 1.24 (3H, t, J = 7.0 Hz, CH_3), 1.24-1.17 (1H, m, CH_2), 1.16 (3H, d, J = 6.2 Hz, CH_3), 1.09 (21H, s, CH_3), 0.75 (3H, d, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (C), 126.8 (Ar-CH), 120.6 (C), 107.9 (Ar-CH × 2), 103.8 (C), 93.4 (CH_2 × 2), 66.1 (CH), 64.9 (CH), 64.3 (CH_2), 46.4 (CH_2), 43.3 (CH_2), 37.1 (CH_2), 36.9 (CH), 25.4 (CH_2), 21.7 (CH_3), 18.3 (CH_3 × 6), 15.3 (CH_3 × 2), 13.4 (CH_3), 12.5 (CH × 3); IR (film) ν_{max} 2939, 2867, 1731, 1594, 1467, 1384, 1154, 1095, 1037, 850, 681 cm^{-1}; HRMS (ESI+) for $C_{31}H_{56}NaO_7Si$ $[M+Na]^+$ requires 591.3688 found 591.3686.

(2*S*,5*R*,7*S*)-1-(2,6-bis((benzyloxy)methoxy)-4-((*E*)-prop-1-en-1-yl)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one 45

To a stirred solution of methyl ketone **44** (26 mg, 0.055 mmol), triethylamine (23 μL, 0.17 mmol) and *N*,*N*-dimethylaminopyridine (1 mg, 8.2 μmol) in CH_2Cl_2 (0.5 mL) at 0° C under nitrogen was added trimethylsilyl triflate (15 μL, 0.083 mmol). The resultant solution was stirred for 10 minutes, and then quenched by the addition of sat. aq. NH_4Cl (2 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 × 5 mL). The combined

organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude silyl enol ether was dried by azeotropic distillation with toluene and used directly in the next step without further purification.

Boron trifluoride diethyl etherate (21 μL, 0.17 mmol) was added to a solution of aldehyde **33** (17 mg, 0.083 mmol) in CH_2Cl_2 (1.4 mL) at -78 °C and the resultant solution stirred for 2 minutes. A solution of silyl enol ether prepared above in CH_2Cl_2 (0.6 mL) was added dropwise. The resultant solution was stirred at -78 °C for 3 h and quenched by the addition of sat. aq. $NaHCO_3$ (1 mL). Upon warming to room temperature, the layers were separated and the aqueous layer further extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 4:1) afforded the *title compound* **45** (22 mg, 0.032 mmol, 58%) as a colourless oil; $[\alpha]_D^{25}$ = +44.8 (c 0.58 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.24 (12H, m, Ar-H), 6.86-6.84 (4H, m, Ar-H), 6.32 (1H, dq, J = 15.7, 1.3 Hz, CH), 6.18 (1H, dq, J = 15.7, 6.3 Hz, CH), 5.28 (4H, s, CH_2), 4.70 (4H, s, CH_2), 4.52 (1H, d, J = 11.1 Hz, CH_2), 4.36 (1H, d, J = 11.1 Hz, CH_2), 4.36-4.29 (1H, m, CH), 3.85-3.80 (1H, m, CH), 3.76 (3H, s, CH_3), 3.42 (1H, br s, OH), 2.92 (1H, dd, J = 11.8, 4.4 Hz, CH_2), 2.84-2.72 (2H, m, CH and CH_2), 2.64-2.53 (2H, m, CH_2), 1.84 (3H, dd, J = 6.7, 1.3 Hz, CH_3), 1.63-1.49 (2H, m, CH_2), 1.21 (3H, d, J = 6.1 Hz, CH_3), 1.02 (3H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.7 (C=O), 159.3 (C), 156.4 (C), 138.0 (C), 137.4 (C), 131.0 (CH), 130.9 (C), 129.5 (Ar-CH × 2), 128.6 (Ar-CH × 4), 128.1 (Ar-CH × 4), 128.0 (Ar-CH × 2), 126.1 (CH), 116.3 (C), 113.9 (Ar-CH × 2), 105.5 (Ar-CH × 2), 92.5 (CH_2 × 2), 71.9 (CH), 70.6 (CH_2), 70.3 (CH_2 × 2), 64.9 (CH), 55.3 (CH_3), 48.0 (CH_2), 46.7 (CH), 43.6 (CH_2), 26.1 (CH_2), 19.9 (CH_3), 18.4 (CH_3), 15.5 (CH_3); IR (film) ν_{max} 3511, 2923, 1704, 1609, 1512, 1455, 1377, 1247, 1037, 930, 742, 699 cm^{-1}; HRMS (ESI+) for $C_{42}H_{50}NaO_8$ $[M+Na]^+$ requires 705.3398 found 705.3395.

(2*S*,5*R*,7*S*)-1-(2,6-bis((benzyloxy)methoxy)-4-((1*S*,2*S*)-1,2-dihydroxypropyl)phenyl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyloctan-3-one 46

A solution of $K_2OsO_2(OH)_4$ (0.08 mg, 0.2 μmol), $(DHQ)_2PHAL$ (0.9 mg, 1.2 μmol) $K_3Fe(CN)_6$ (110 mg, 0.34 mmol), K_2CO_3 (47 mg, 0.34 mmol) and $MeSO_2NH_2$ (11 mg, 0.11 mmol) in *t*-BuOH (1.1 mL) and H_2O (0.55 mL) was added to alkene **45** (78 mg, 0.11 mmol) at 0 °C with stirring. The resultant mixture was stirred at 0 °C for 16 h. Sat. aq. Na_2SO_3 (1 mL) was added and the reaction mixture stirred for a further 30 minutes at room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the *title compound* **46** (72 mg, 0.10 mmol, 91%) as a colourless oil; $[\alpha]_D^{25} = -12.1$ (c 0.70 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (12H, m, Ar-H), 6.88-6.86 (4H, m, Ar-H), 5.30 (4H, ABq, $\Delta\delta_{AB} = 0.02$, $J_{AB} = 7.0$ Hz, CH_2), 4.71 (4H, ABq, $\Delta\delta_{AB} = 0.02$, $J_{AB} = 11.9$ Hz, CH_2), 4.55 (1H, d, $J = 11.1$ Hz, CH_2), 4.38 (1H, d, $J = 11.1$ Hz, CH_2), 4.34-4.26 (2H, m, CH × 2), 3.86-3.75 (2H, m, CH × 2), 3.78 (3H, s, CH_3), 3.42 (1H, br s, OH), 3.04 (1H, br s, OH), 2.94 (1H, d, $J = 11.9, 4.7$ Hz, CH_2), 2.88-2.71 (3H, m, CH, CH_2 and OH), 2.58 (2H, m, CH_2), 1.63-1.41 (2H, m, CH_2), 1.22 (3H, d, $J = 6.2$ Hz, CH_3), 1.07 (3H, d, $J = 6.3$ Hz, CH_3), 1.04 (3H, d, $J = 6.6$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6 (C=O), 159.3 (C), 156.2 (C), 141.4 (C), 137.3 (C), 130.8 (C), 129.5 (Ar-CH × 2), 128.6 (Ar-CH × 4), 128.0 (Ar-CH × 6), 117.2 (C), 113.9 (Ar-CH × 2), 106.3 (Ar-CH × 2), 92.5 (CH_2 × 2), 79.4 (CH), 72.1 (CH), 71.9 (CH), 70.6 (CH_2), 70.3 (CH_2 × 2), 64.8 (CH), 55.3 (CH_3), 48.1 (CH_2), 46.4 (CH), 43.5 (CH_2), 26.5 (CH_2), 19.8 (CH_3), 18.9 (CH_3), 15.7 (CH_3); IR (film) ν_{max} 3396, 2967, 2923, 1701, 1611, 1586, 1513, 1330, 1247, 1154, 1035, 1026, 819, 742, 699 cm^{-1}; HRMS (ESI+) for $C_{42}H_{52}NaO_{10}$ $[M+Na]^+$ requires 739.3453 found 739.3442.

(2*R*,3*S*,4'*R*,6'*S*)-7-((1*S*,2*S*)-1,2-dihydroxypropyl)-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol 47

A mixture of ketone **46** (35 mg, 0.049 mmol) and Pd/C (10% wt., 50 mg) in EtOAc (2 mL) was stirred under an atmosphere of H_2 at room temperature for 3 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 1:4) gave the *title compound* **47** (9 mg, 0.027 mmol, 55%) as a colourless oil. $[\alpha]_D^{25} = -12.1$ (c 0.70 in MeOH); ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.12 (1H, br s, OH), 6.47 (1H, d, J = 1.4 Hz, Ar-H), 6.31 (1H, d, J = 1.4 Hz, Ar-H), 4.30-4.24 (1H, m, CH), 4.16 (1H, br s, OH), 4.12 (1H, d, J = 7.0 Hz, CH), 3.86-3.81 (2H, m, CH and OH), 3.68-3.65 (2H, m, CH and OH), 2.63 (1H, dd, J = 16.5, 5.8 Hz, CH_2), 2.36 (1H, dd, J = 16.5, 12.0 Hz, CH_2), 2.04-1.94 (2H, m, CH_2), 1.92-1.84 (1H, m, CH), 1.61 (1H, dd, J = 12.5, 11.1 Hz, CH_2), 1.15-1.07 (1H, m, CH_2), 1.10 (3H, d, J = 6.7 Hz, CH_3), 1.02 (3H, d, J = 6.2 Hz, CH_3), 0.95 (3H, d, J = 6.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (C), 142.4 (C) 110.6 (C), 107.7 (CH), 106.9 (C), 106.3 (CH), 101.2 (C), 79.8 (CH), 72.5 (CH), 66.5 (CH), 64.4 (CH), 43.7 (CH_2), 41.2 (CH_2), 35.2 (CH), 25.3 (CH_2), 21.8 (CH_3), 19.4 (CH_3), 16.4 (CH_3); IR (film) ν_{max} 3345, 2970, 2928, 1626, 1594, 1435, 1378, 1141, 1062, 1030, 993, 912, 799 cm^{-1}; HRMS (ESI+) for $C_{18}H_{26}NaO_6$ $[M+Na]^+$ requires 361.1622 found 361.1632.

(2*R*,3*S*,4'*R*,6'*S*)-7-((1*S*,2*S*)-1,2-dihydroxypropyl)-6-iodo-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol 48 and (2*R*,3*S*,4'*R*,6'*S*)-7-((1*S*,2*S*)-1,2-dihydroxypropyl)-8-iodo-3,6'-dimethyl-3',4',5',6'-tetrahydrospiro[chroman-2,2'-pyran]-4',5-diol 49

To a stirred solution of spiroketal **47** (10 mg, 0.030 mmol) in DMF (0.5 mL) at −40 °C was added *N*-iodosuccinimide (7 mg, 0.030 mmol) and the reaction mixture stirred for 24 h. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (1 mL) and allowed to warm to

room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 2:1) afforded the *title compounds* **48** and **49** (8.4 mg, 0.018 mmol, 60%) as an inseparable mixture. For this reason the ^{1}H NMR spectrum could not be fully assigned. The regioisomeric mixture was employed in subsequent reactions; HRMS (ESI+) for $C_{18}H_{25}INaO_6$ $[M+Na]^+$ requires 487.0588 found 487.0597.

(*S*)-4-(2,6-bis((benzyloxy)methoxy)-4-((1*S*,2*S*)-1,2-dihydroxypropyl)phenyl)-3-methylbutan-2-one 50

To a stirred solution of $K_2OsO_2(OH)_4$ (1 mg, 0.003 mmol), $(DHQ)_2PHAL$ (10 mg, 0.013 mmol), $K_3Fe(CN)_6$ (250 mg, 0.76 mmol), K_2CO_3 (105 mg, 0.76 mmol) and $MeSO_2NH_2$ (24 mg, 0.25 mmol) in ^{t}BuOH/water (1:1, 2.5 mL) was added **44** (120 mg, 0.25 mmol) and the reaction mixture stirred at room temperature for 18 hours. Sat. aq. $Na_2S_2O_3$ (1 mL) was added and the reaction mixture stirred for 30 minutes. The reaction mixture was extracted with EtOAc (3 × 2 mL), the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexanes/EtOAc 1:1) afforded the *title compound* **50** (104 mg, 0.20 mmol, 84%) as a colourless oil; $[\alpha]_D^{25}$ = +35.0 (c 0.3 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, contains less than 10% wt. $MeSO_2NH_2$): δ 7.35-7.32 (10H, m, Ar-H), 6.88 (2H, s, Ar-H), 5.32 (4H, s, CH_2), 4.72 (4H, s, CH_2), 4.31 (1H, d, J = 7.0 Hz, CH), 3.86-3.80 (1H, m, CH), 2.98-2.94 (1H, m, CH_2), 2.86-2.74 (2H, m, CH and CH_2), 2.15 (3H, s, CH_3), 1.08 (3H, d, J = 6.3 Hz, CH_3), 1.05 (3H, d, J = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.9 (C=O), 156.3 (C), 141.2 (C), 137.2 (C), 128.6 (4 × Ar-CH), 128.0 (Ar-CH × 6), 117.5 (C), 106.2 (Ar-CH × 2), 92.5 (2 × CH_2), 79.5 (CH), 72.2 (CH), 70.3 (2 × CH_2), 46.9 (CH), 28.3 (CH_3), 26.7 (CH_2), 19.0 (CH_3), 15.7 (CH_3); IR (film) ν_{max} 3416, 2977,

2935, 1706, 1588, 1459, 1130, 1043, 739, 701 cm^{-1}; HRMS (ESI+) for $C_{30}H_{36}NaO_7$ $[M+Na]^+$ requires 531.2353 found 531.2356.

(*S*)-4-(2,6-bis((benzyloxy)methoxy)-4-((1*S*,2*S*)-1,2-dihydroxypropyl)-3-iodophenyl)-3-methylbutan-2-one 51

To a stirred solution of ketone **50** (104 mg, 0.20 mmol) and silver trifluoroacetate (47 mg, 0.21 mmol) in $CHCl_3$ (4 mL) at 0 °C was added I_2 (55 mg, 0.21 mmol) in $CHCl_3$ (2 mL) portionwise over 30 minutes. The reaction mixture was stirred at room temperature for 1 hour, quenched with sat. aq. $Na_2S_2O_3$ (0.5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* **51** (93 mg, 0.15 mmol, 72%) as a colourless oil; $[\alpha]_D^{25}$ = +16.7 (c 0.27 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (10H, m, Ar-H), 7.13 (1H, s, Ar-H), 5.29 (2H, ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 6.9 Hz, CH_2), 5.16 (2H, ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 5.9 Hz, CH_2), 4.88 (2H, ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 11.8 Hz, CH_2), 4.83 (1H, d, J = 5.1 Hz, CH), 4.69 (2H, s, CH_2), 3.93-3.87 (1H, m, CH), 3.14 (1H, br s, OH), 3.08-3.03 (1H, m, CH_2), 2.91-2.85 (2H, m, CH and CH_2), 2.53 (1H, br s, OH), 2.09 (3H, s, CH_3), 1.21 (3H, d, J = 6.5 Hz, CH_3), 1.02 (3H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4 (C=O), 156.9 (C), 156.7 (C), 144.0 (C), 137.2 (C), 137.1 (C), 128.6 (4 × Ar-CH), 128.1 (Ar-CH × 2), 128.0 (4 × Ar-CH), 124.1 (C), 110.2 (Ar-CH), 98.6 (CH_2), 92.5 (CH_2), 88.6 (C), 81.0 (CH), 72.1 (CH_2), 71.6 (CH), 70.5 (CH_2), 46.9 (CH), 28.3 (CH_2), 28.1 (CH_3), 19.4 (CH_3), 16.0 (CH_3); IR (film) ν_{max} 3423, 2935, 1708, 1590, 1455, 1373, 1158, 1082, 1031, 1000, 742 cm^{-1}; HRMS (ESI+) for $C_{30}H_{35}IKO_7$ $[M+K]^+$ requires 673.1059 found 673.1063.

(*S*)-5,7-bis((benzyloxy)methoxy)-3-((*S*)-1-hydroxyethyl)-6-((*S*)-2-methyl-3-oxobutyl)isobenzofuran-1(3H)-one 52

A stirred solution of iodide **51** (45 mg, 0.07 mmol), $Pd(PPh_3)_4$ (40 mg, 0.03 mmol) and diisopropylethylamine (25 μL, 0.14 mmol) in degassed DMF (0.5 mL) was placed under a CO atmosphere (1 atm) using a balloon and heated at 100 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and brine (3 mL) added. The layers were separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 2:1 to 1:1) afforded the *title compound* **52** (33 mg, 0.06 mmol, 75%, 10% remaining starting material, inseparable by chromatography) as a pale yellow oil; $[\alpha]_D^{25}$ = +42.0 (c 0.35 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.28 (10H, m, Ar-H), 7.05 (1H, s, Ar-H), 5.53 (2H, s, CH_2), 5.37 (2H, ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 7.0 Hz, CH_2), 5.18 (1H, d, J = 4.0 Hz, CH), 4.82 (2H, s, CH_2), 4.62 (2H, ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 11.8 Hz, CH_2), 4.12-4.08 (1H, m, CH), 3.08-3.03 (1H, m, CH_2), 2.93-2.85 (2H, m, CH and CH_2), 2.14 (3H, s, CH_3), 1.89 (1H, d, J = 6.0 Hz, OH), 1.34 (3H, d, J = 6.5 Hz, CH_3), 1.05 (3H, d, J = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.1 (C=O), 168.3 (C), 161.9 (C), 156.0 (C), 149.1 (C), 137.2 (C), 136.7 (C), 128.7 (Ar-CH × 2), 128.6 (Ar-CH × 2), 128.4 (Ar-CH), 128.2 (Ar-CH × 2), 128.1 (Ar-CH), 128.0 (Ar-CH × 2), 123.5 (C), 110.9 (C), 103.0 (Ar-CH), 99.5 (CH_2), 92.6 (CH_2), 83.1 (CH), 72.1 (CH_2), 71.0 (CH_2), 68.9 (CH), 46.8 (CH), 28.3 (CH_3), 26.9 (CH_2), 19.0 (CH_3), 15.9 (CH_3); IR (film) ν_{max} 3436, 2933, 1753, 1708, 1604, 1453, 1228, 1089, 1029, 921, 742, 699 cm^{-1}; HRMS (ESI+) for $C_{31}H_{34}NaO_8$ $[M+Na]^+$ requires 557.2146 found 557.2133.

(*S*)-5,7-bis((benzyloxy)methoxy)-6-((2*S*,5*R*,7*S*)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyl-3-oxooctyl)-3-((*S*)-1-hydroxyethyl)isobenzofuran-1(3*H*)-one 55

To a stirred solution of ketone **52** (20 mg, 0.037 mmol), triethylamine (26 μL, 0.19 mmol) and DMAP (5 mg, 0.041 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added TMSOTf (20 μL, 0.11 mmol). The reaction mixture was stirred for 15 minutes, and then quenched with sat. aq. NH_4Cl (1 mL). The layers were separated, and the aqueous layer extracted with Et_2O (2 × 1 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and then azeotropically dried with toluene to give crude enol ether **54** which was used without further purification.

To a stirred solution of aldehyde **33** (28 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at -78 °C was added $BF_3{\cdot}OEt_2$ (20 μL, 0.14 mmol) and the solution stirred for 3 minutes. A solution of the crude silyl enol ether **54** in CH_2Cl_2 (1 mL) was added dropwise and the reaction mixture stirred at -78 °C for 1.5 h. Sat. aq. $NaHCO_3$ (1 mL) was added and the reaction mixture allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude aldol product.

The crude aldol product was dissolved in MeOH (1 mL), sat. aq. K_2CO_3 (0.1 mL) added and the reaction mixture stirred at room temperature for 15 minutes. $MgSO_4$ was added and the reaction mixture filtered, then concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc 2:1 to 1:1) afforded the *title compound* **55** (18 mg, 0.024 mmol, 65% over 3 steps) as a colourless oil; $[\alpha]_D^{25}$ = +40.3 (c 0.37 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (12H, m, Ar-H), 7.02 (1H, s, Ar-H), 6.87-6.84 (2H, m, Ar-H), 5.54 (2H, s, CH_2), 5.37 (2H, ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 7.2 Hz, CH_2), 5.17 (1H, d, J = 3.5 Hz, CH), 4.82 (2H, ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 12.0 Hz, CH_2), 4.72 (2H, ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 11.8 Hz, CH_2),

4.54-4.52 (1H, m, CH_2), 4.37-4.34 (1H, m, CH_2), 4.33-4.27 (1H, m, CH), 4.11-4.07 (1H, m, CH), 3.82-3.78 (4H, m, CH and CH_3), 3.27 (1H, d, J = 3.0 Hz, OH), 3.08-3.01 (1H, m, CH_2), 2.93-2.85 (2H, m, CH and CH_2), 2.57 (1H, dd, J = 17.5, 14.0 Hz, CH_2), 2.46 (1H, dd, J = 17.5, 8.5 Hz, CH_2), 1.97 (1H, br s, OH), 1.58-1.46 (2H, m, CH_2), 1.35 (3H, d, J = 6.5 Hz, CH_3), 1.20 (3H, d, J = 6.2 Hz, CH_3), 1.04 (3H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9 (C=O), 168.3 (C), 161.8 (C), 159.3 (C), 156.0 (C), 149.3 (C), 137.2 (C), 136.8 (C), 130.9 (C), 129.4 (Ar-CH × 2), 128.6 (Ar-CH × 2), 128.5 (Ar-CH × 2), 128.2 (Ar-CH), 128.0 (Ar-CH × 2), 127.9 (Ar-CH), 127.8 (Ar-CH × 2), 123.2 (C), 113.8 (Ar-CH × 2), 110.9 (C), 103.0 (Ar-CH), 99.5 (CH_2), 92.7 (CH_2), 83.1 (CH), 71.9 (CH_2), 71.8 (CH), 70.9 (CH_2), 70.4 (CH_2), 68.6 (CH), 64.7 (CH), 55.4 (CH_3), 48.5 (CH_2), 46.2 (CH), 43.4 (CH_2), 27.0 (CH_2), 19.8 (CH_3), 19.1 (CH_3), 15.9 (CH_3); IR (film) ν_{max} 3465, 2930, 1755, 1608, 1514, 1455, 1249, 1035, 743, 699 cm^{-1}; HRMS (ESI+) for $C_{43}H_{50}NaO_{11}$ $[M+Na]^+$ requires 765.3245 found 765.3260.

Acknowledgements

The authors would like to thank the University of Auckland for the award of an Auckland Doctoral Scholarship to PAH. We also thank Prof. G. Molander and Inji Shin for helpful discussions.

Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds **S1**, **12-14**, **19-24**, **27-29**, **32**, **34-36**, **44-49**, **50-52**, **55**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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