Synthesis E.-K. Jung et al. Feature

Synthesis of Benzodioxane and Benzofuran Scaffolds Found in Neolignans via TMS Triflate Mediated Addition to 1,4-Benzodioxane Hemiacetals

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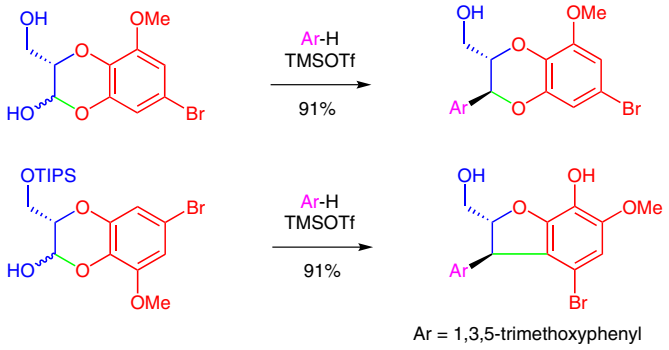

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Abstract This research reports the successful asymmetric synthesis of both a 9-hydroxy-5′-methoxy-1,4-benzodioxane framework and a highly functionalised benzofuran scaffold. Both synthetically desirable structures are the result of a Lewis acid catalysed addition of an aryl nucleophile to 1,4-benzodioxane hemiacetals and offer a route towards the synthesis of a number of naturally occurring neolignans.

Key words lignin, 1,4-benzodioxane, benzofuran, asymmetric synthesis, hemiacetal, oxonium, Mitsunobu reaction

1,4-Benzodioxane neolignans are a subclass of lignan natural products with notable biological activity.[1] Both naturally occurring compounds and their synthetic analogues have shown a range of activities, including hepaprotective,[2] neurotrophic,[3] antiproliferative,[4] antioxidant[5] and anti-angiogenic[6] properties, among many others.[7]

Previously, we have reported the synthesis of a number of 1,4-benzodioxane families, including the eusiderin family,[8] the isoamericanin family[9] and the rodgersinine family.[2] Of these, only the eusiderin family contains a 5′-methoxy group, while the isoamericanin family is the only family synthesised that contain the 9-hydroxy group. We wished to extend our synthesis to provide a 9-hydroxy-5′-methoxy-1,4-benzodioxane scaffold such as that shown in nitidanin (**1**),[10] its unnamed methyl analogue **2**,[11] jatrophasin D (**3**)[12] and excoecanol A (**4**)[13] (Figure 1).

We envisioned that this could be achieved by combining a substituted phenol **5** and chiral alcohol **6** in a Mitsunobu reaction to give ether **7**, which could be converted to the corresponding aldehyde for the addition of an appropriate aryl lithiate (Scheme 1). Cyclisation of **8** under acidic conditions, such as Amberlyst resins, would then provide the required 9-hydroxy-5′-methoxy-1,4-benzodioxane scaffold **9**.[9] We have previously shown that the aryl halide in similar substrates can undergo sidechain addition through a range of coupling procedures.[2,8,9]

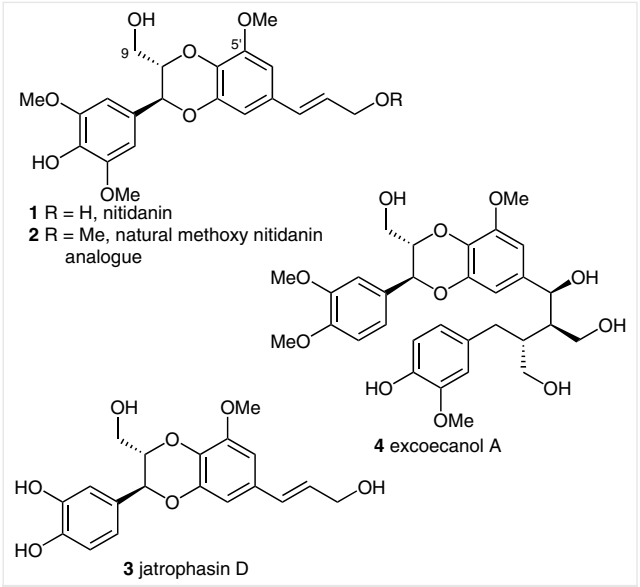


Figure 1 Structures of naturally occurring 9-hydroxy-5′-methoxy-1,4-benzodioxanes

We decided to synthesise the benzyl-protected variant, **10**, of phenol **5** that was previously used in the synthesis of the eusiderin family of compounds.[8] Phenol **10** was synthesised from *o*-vanillin (**11**) in 6 steps (Scheme 2). A four-step sequence from **11**, including bromination, MOM protection, and Dakin oxidation gave phenol **12**, which was then protected to give **13**. MOM deprotection of ether **13** gave **10** in 94% yield.

Phenol **10** then successfully underwent the Mitsunobu coupling with alcohol **6**,[9] giving ether **14** in good yield (Scheme 3). The PMB group in **14** was then removed using DDQ giving alcohol **15**, which was then oxidised to the corresponding aldehyde **16** using Dess–Martin periodinane. Unfortunately, the addition of numerous aryl lithiates to **16** was unsuccessful, with no desired addition product **17** or returned starting material was obtained.

We have previously shown the successful aryl lithiate addition to the demethoxy analogue of **16**,[9] which led us to the assumption that steric effects due to this additional group was the mitigating factor in this reaction. We wished to investigate if there could be a different outcome if the large TIPS group was absent. Therefore, PMB analogue **18** was prepared from the removal of the TIPS group of **14** to provide **19**, which was then oxidised to aldehyde **18** (Scheme 4). Unfortunately, no addition products **20** were obtained when a range of aryl lithiates were used.

It is proposed that the two *ortho* substituents on the aryl rings in combination with the β-alkoxy group, to the aldehyde, may contribute significantly to the perturbation of the lithiate addition, blocking nucleophilic addition to the aldehyde.

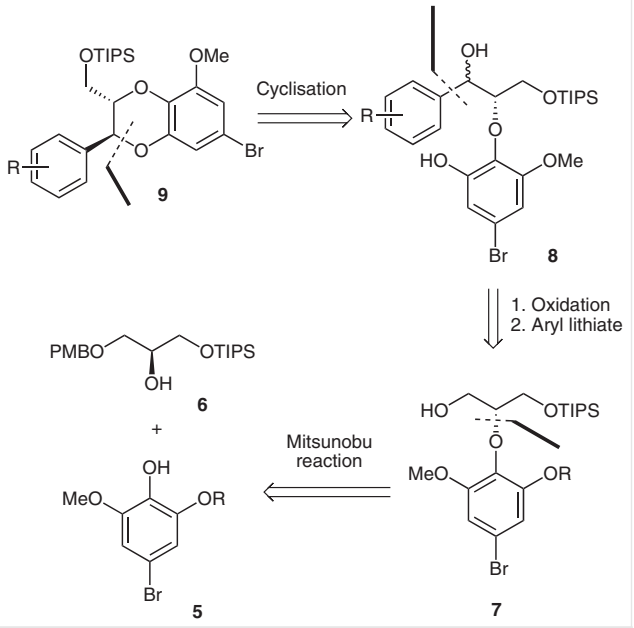
Recently, we have shown the successful generation of nitrogen analogues of 1,4-benzodioxanes through the acid-catalysed addition of electron-rich aryl groups to an *N*-acyliminium derived from benzomorpholine aminols.[14] The aryl additions to these benzomorpholine aminols was promoted under Brønsted acid conditions to give a variety of 3-arylbenzomorpholines as single diastereomers. Following the failure of the previous route involving aryl lithiate addition, we decided to attempt to adapt this chemistry to the synthesis of 9-hydroxy-5′-methoxy-1,4-benzodioxanes (Scheme 5).

Biographical sketches

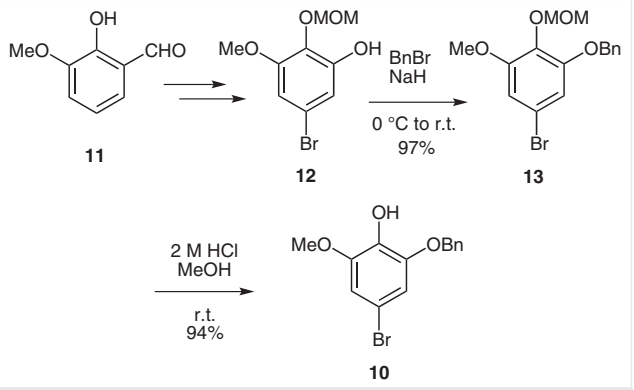
Eun-Kyung Jung was born in Seoul, South Korea. She graduated in 2011 from the University of Auckland with a B.Sc. degree in medicinal chemistry and then went on to graduate with a B.Sc. in medicinal chemistry (Honours, First Class) in 2012, followed by a Ph.D. in 2016 from the same university under the supervision of Assoc. Prof. David Barker, working on the development of synthetic methodology for the preparation of novel nitrogen-containing analogues of bioactive natural products, in particular lignan natural products.

Lisa I. Pilkington was born in Auckland, New Zealand. She graduated in 2010 from the University of Auckland with a B.A./B.Sc. conjoint degree majoring in chemistry, statistics, and german. Lisa then went on to graduate with a B.Sc. (Honours, First Class) in 2011, followed by a Ph.D. in 2015 from the same university under the supervision of Assoc. Prof. David Barker. After undertaking post-doctoral research with the Auckland Cancer Society Research Centre and the University of Auckland, she completed an M.Sc. degree at the University of Oxford in Applied Statistics. She is currently a post-doctoral research and teaching fellow at the School of Chemical Sciences, University of Auckland.

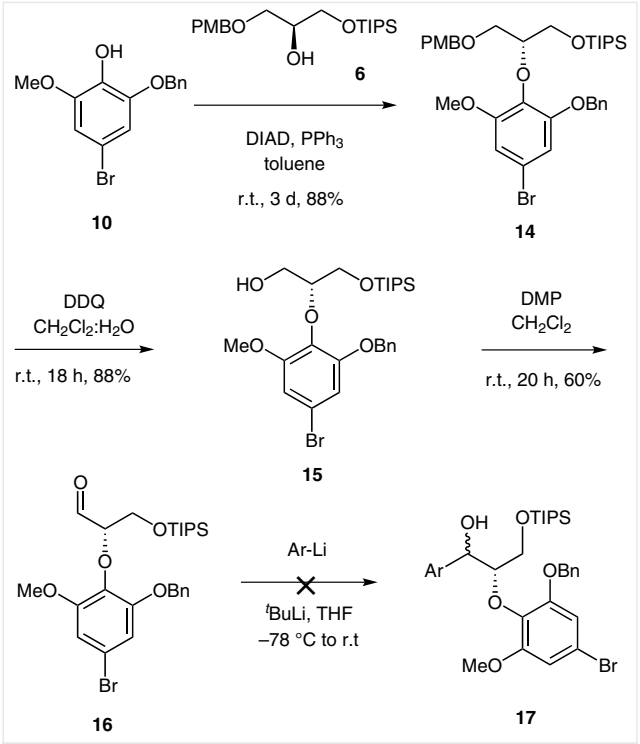
David Barker was born in Altrincham, UK. After moving to Australia, he graduated from the University of Sydney with a B.Sc. degree (Honours, First Class) and then completed his Ph.D. in 2002 at the same university. After post-doctoral research at the School of Medical Sciences at the University of New South Wales, he joined the University of Auckland as a lecturer. He is currently an Associate Professor in Organic and Medicinal Chemistry and he has a diverse range of synthetic interests including biologically active natural products, drug discovery, and development of novel polymeric scaffolds.



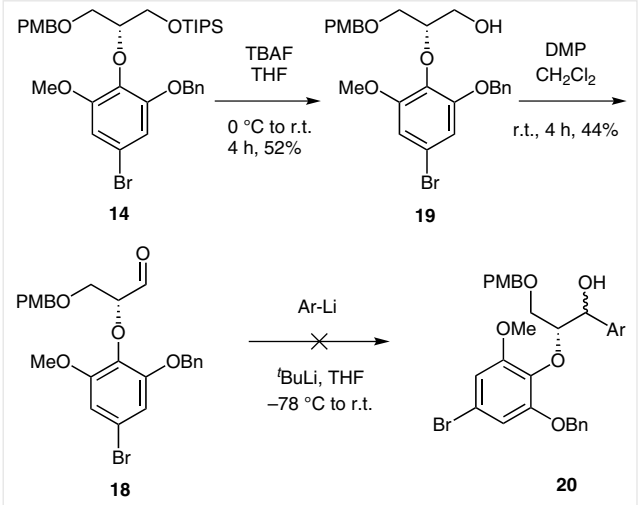
Scheme 1 Retrosynthetic analysis for 9-hydroxy-5′-methoxy-1,4-benzodioxanes



Scheme 2 Synthesis of phenol **10**



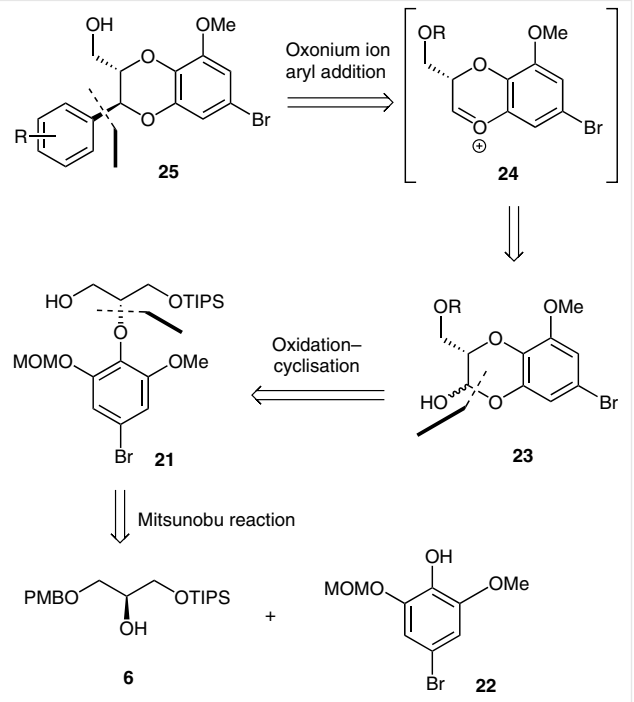
Scheme 3 Attempted synthesis of aryl addition product **17**



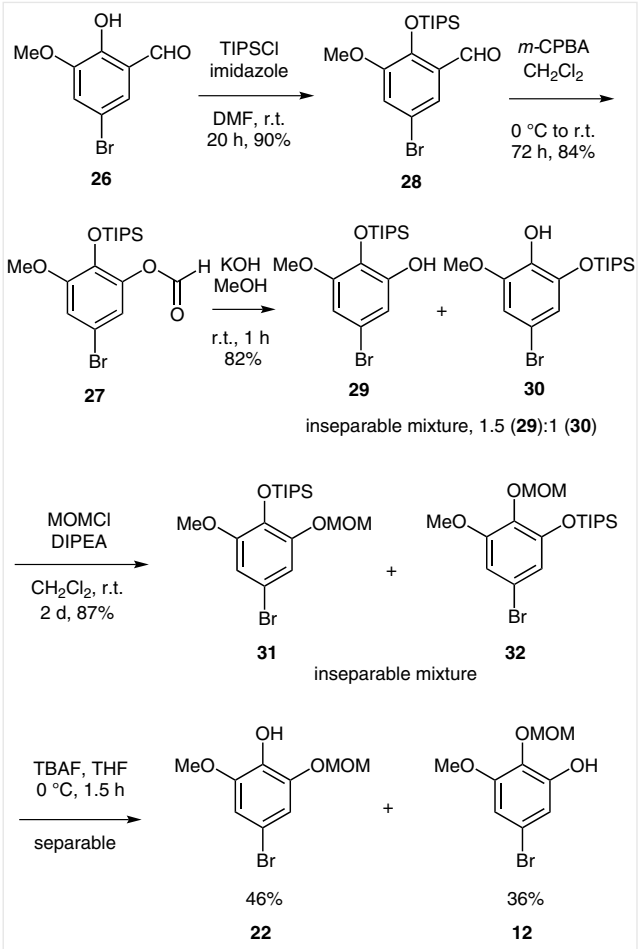
Scheme 4 Attempted synthesis of addition product **20**

Instead of using the relatively robust benzyl protecting group, we envisioned that this route would be improved by the use of an acid labile protecting group, such as MOM present in ether **21** (which would be generated by the Mitsunobu reaction of alcohol **6** and phenol **22**). We envisaged that **21** could undergo a one-pot oxidation and MOM deprotection along with intramolecular cyclisation in the acidic conditions generated during unbuffered DMP oxidations, to give benzodioxane hemiacetal **23**. The generated oxonium ion, **24**, could then undergo aryl addition to provide the desired 9-hydroxy-5′-methoxy-1,4-benzodioxane scaffold, **25**.

The first synthetic target was phenol **22** and we initially envisaged that this could be derived from phenol **26**, used previously in the synthesis of **10**. Using TIPS as a protecting group instead of MOM (which was required later in the synthesis), however, proved difficult as the hydrolysis of **27** in the second step of Dakin oxidation of **28** gave a mixture of regioisomeric phenols **29** and **30** (Scheme 6). This partial migration of the TIPS group occurs during the basic conditions required for hydrolysis and resulted in an inseparable 1:1.5 mixture of desired phenol **29** and unwanted **30**. The inseparable mixture of phenols was then MOM-protected, once again to give an inseparable mixture of ethers **31** and



Scheme 5 Alternative retrosynthetic analysis for 9-hydroxy-5′-methoxy-1,4-benzodioxanes



Scheme 6 Synthesis of phenols **12** and **22**

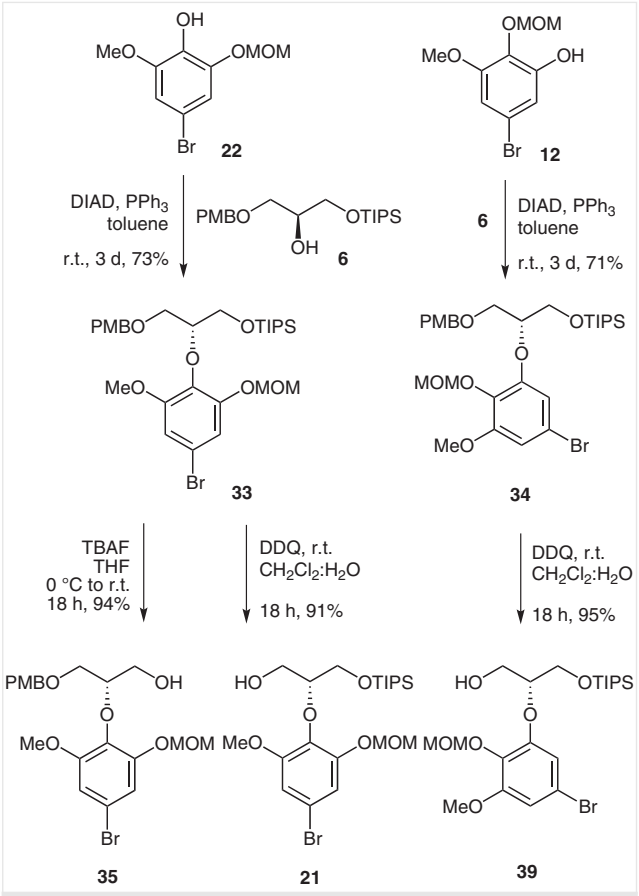
32. Fortunately, however, the removal of the TIPS ether from the mixture of **31**/**32** gave phenols **22** and **12**, which were easily separable by column chromatography, providing pure samples of each phenol.

As both phenols **12** and **22** were generated in substantial quantities, we decided to react both in tandem for the subsequent reactions with phenol **12** hopefully providing a regioisomer of the target benzodioxanes. Phenols **22** and **12** successfully underwent a Mitsunobu reaction with **6**, giving ethers **33** and **34**, respectively (Scheme 7). With the choice of removing either the TIPS or PMB protecting groups at this stage, we decided to first prepare the PMB-containing analogue, thus the TIPS protecting group of **33** was removed to give alcohol **35** in 94% yield.

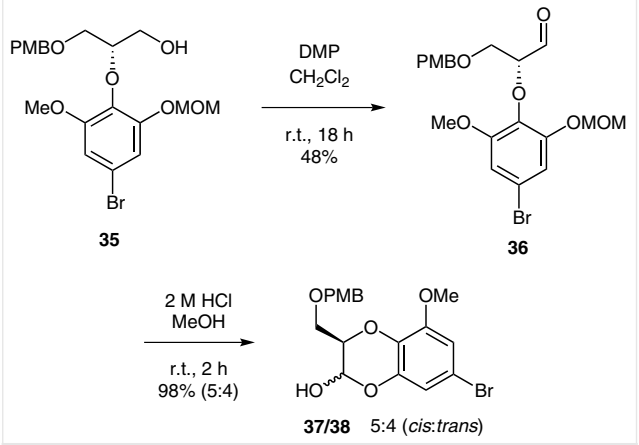
The next step in the synthesis was the generation of the benzodioxane hemiacetal, which we thought would be generated in a one-pot synthesis during DMP oxidation. Instead, however, when the reaction was conducted, only aldehyde **36** was isolated in moderate yield (Scheme 8). Fortunately, stirring aldehyde **36** in a mixture of aqueous acid and methanol gave the desired hemiacetal in 98% yield, as a 5:4 mixture of *cis*-**37** and *trans*-**38** isomers, respectively.

Having successfully generated the required hemiacetal, we next turned our attention to the addition of aryl groups to the 1,4-benzodioxane hemiacetal. Our previous work[14] showed that electron-rich aromatic donors gave the best yields in this reaction, thus 1,3,5-trimethoxybenzene was chosen to trial these reactions. Aryl addition to hemiacetal **37** was first attempted using sulfuric acid (8 equiv) in acetic acid, however the reaction only resulted in deprotection of the PMB group.[15] When other Brønsted[16] and Lewis acids were trialed in this transformation similar results were obtained with none of the desired arylbenzodioxane being formed. These results showed the additions to PMB ether-containing hemiacetals would not be suitable for this synthesis. Our attention then shifted to the TIPS analogues, thus the PMB groups were removed from ethers **33** and **34**, giving alcohols **21** and **39**, respectively (Scheme 7).

Interestingly, the generation of benzodioxane hemiacetals from **21** and **39** both proceeded during the oxidation reaction, as initially desired, with no additional acidic deprotection step required. After purification by column chromatography a mixture of MOM acetals (**40a**/**40b** from **39** and **41a**/**41b** from **21**) and hemiacetals (**42a**/**42b** from **39** and **43a**/**43b** from **21**) were isolated in separate fractions (Scheme 9). In both instances, more of the hemiacetals were produced (50% for **42a**/**b** vs. 24% for **40a**/**b**, 62% for **43a**/**b** vs. 37% for **41a**/**b**). Hemiacetals **42a**/**b** and **43a**/**b** were



Scheme 7 Mitsunobu reactions and deprotections of phenols **12** and **22**



Scheme 8 Synthesis of benzodioxane hemiacetals **37** and **38**

obtained in approximately 1:1 ratios of *cis* to *trans* isomers whilst for acetals **40a**/**b** and **41a**/**b** the *cis* isomer was the more predominantly formed isomer.

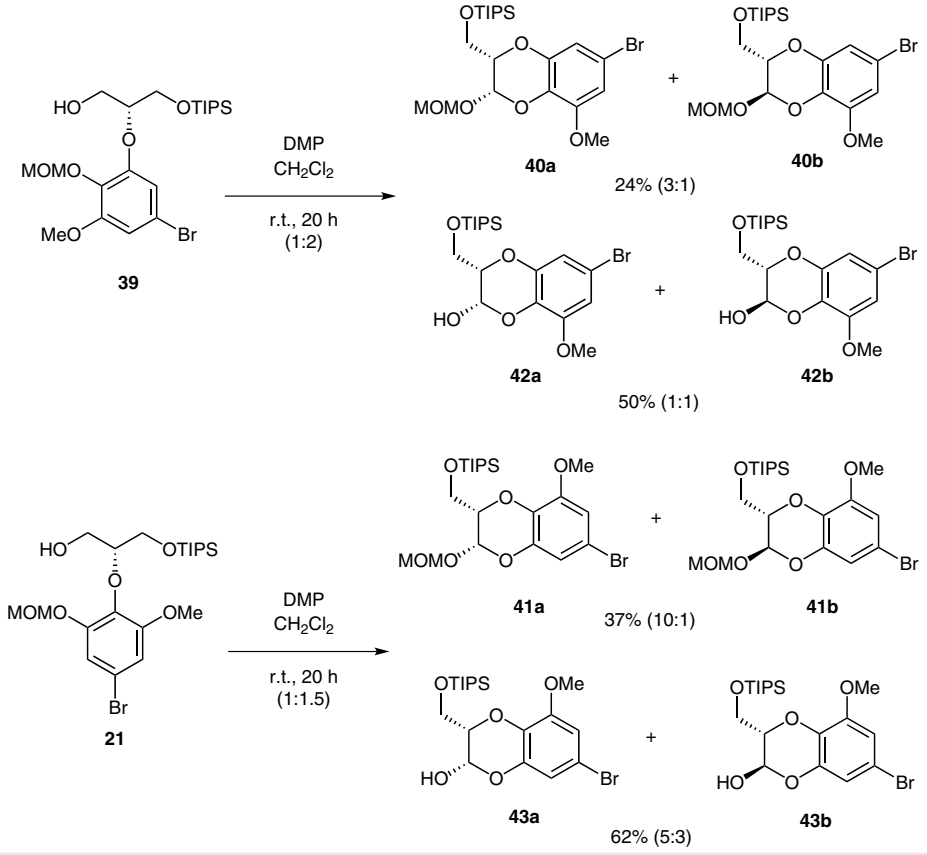
To convert the acetals and hemiacetals to the activated oxonium ion, a combination of TMSCl and $Zn(OTf)_2$ was employed, using a procedure reported by Susaki.[17] When the aryl addition reactions were attempted with acetals **40** and **41**, only starting material was returned. Unexpectedly, when the addition of trimethoxybenzene was attempted using TMSCl and $Zn(OTf)_2$ with hemiacetal **42**, instead of the expected 1,4-benzodioxane **44**, benzofuran **45** was produced as the sole product of the reaction in 56% yield (Scheme 10). The yield was further improved to 91% when TMSOTf was used.

One possible mechanism for the formation of benzofuran **45** from **42** is shown in Scheme 11. We purport that initially 3-aryl-1,4-benzodioxane **46** is formed via activation of the hemiacetal by TMSOTf and formation of the required oxonium ion **47**. However, electron donation from the methoxy substituents on the added aromatic ring and activation induces opening of the cyclic structure to give quinone methide **48**. At this point, the donation of electrons from the 3′-methoxy group results in attack from C-6′ onto the quinone methide and formation of a five-membered ring, with proton elimination from **49** giving the observed benzofuran **45**.

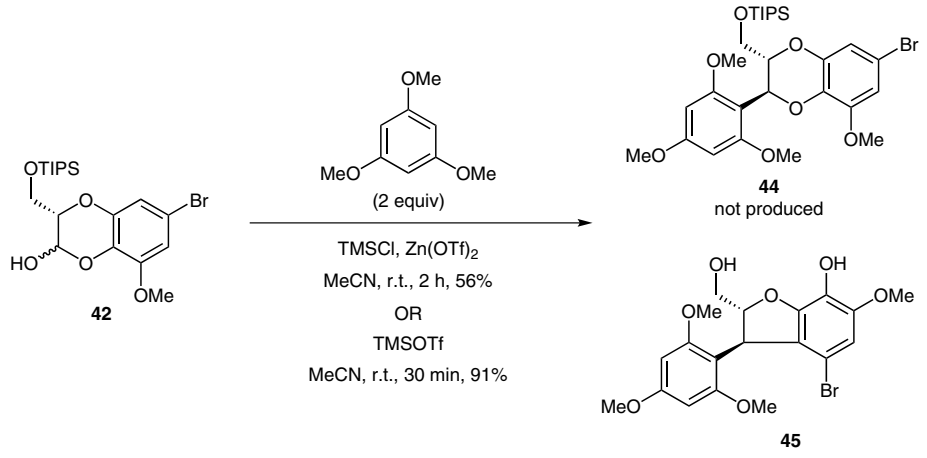
The substitution pattern on the aryl ring of hemiacetals **43**, however, is not favourable for such a rearrangement to occur as it would lead to a bridge-fused aromatic tricycle and therefore it was assumed that the hemiacetals **43** should provide aryl addition product **50**. Unfortunately, this was not the case – the reaction of **43** with 1,3,5-trimethoxybenzene only gave trace amounts of **50** when using 1.2 equivalents of TMSOTf and decomposition products when the equivalents of Lewis acid was increased (Table 1). When TMSCl and $Zn(OTf)_2$ were used to form TMSOTf in situ, only deprotected benzodioxane hemiacetal **51** was generated, in quantitative yield.

As the TIPS- and PMB-protected hemiacetals **37**, **42** and **43** were not successful in the aryl addition reactions, we decided to react the fully deprotected **51** in the aryl addition reaction. Pleasingly, **51** successfully underwent the aryl addition reaction with 1,3,5-trimethoxybenzene using TMSOTf, giving the desired 9-hydroxy-5′-methoxy-1,4-benzodioxane (**50**) as a single diastereoisomer in 91% yield (Scheme 12). The *trans* configuration in **50** was determined by analysis of the $J_{2,3}$ coupling constant with a 8.4 Hz value indicating a *trans* relationship between the two substituents. None of the *cis* isomer ($J_{2,3}$ ~2 Hz) was obtained showing that the reaction completely favours the more thermodynamically favoured product.[2,8]

When the corresponding reaction with syringol (**52**) was attempted, which would have provided the complete benzodioxane framework **53** for nitidanin (**1**), only a complex mixture was obtained. It is possible that the combination of alternative reactive sites on syringol **52** led to numerous reaction pathways. This result concurs with our findings in the synthesis of related benzomorpholines,[14]



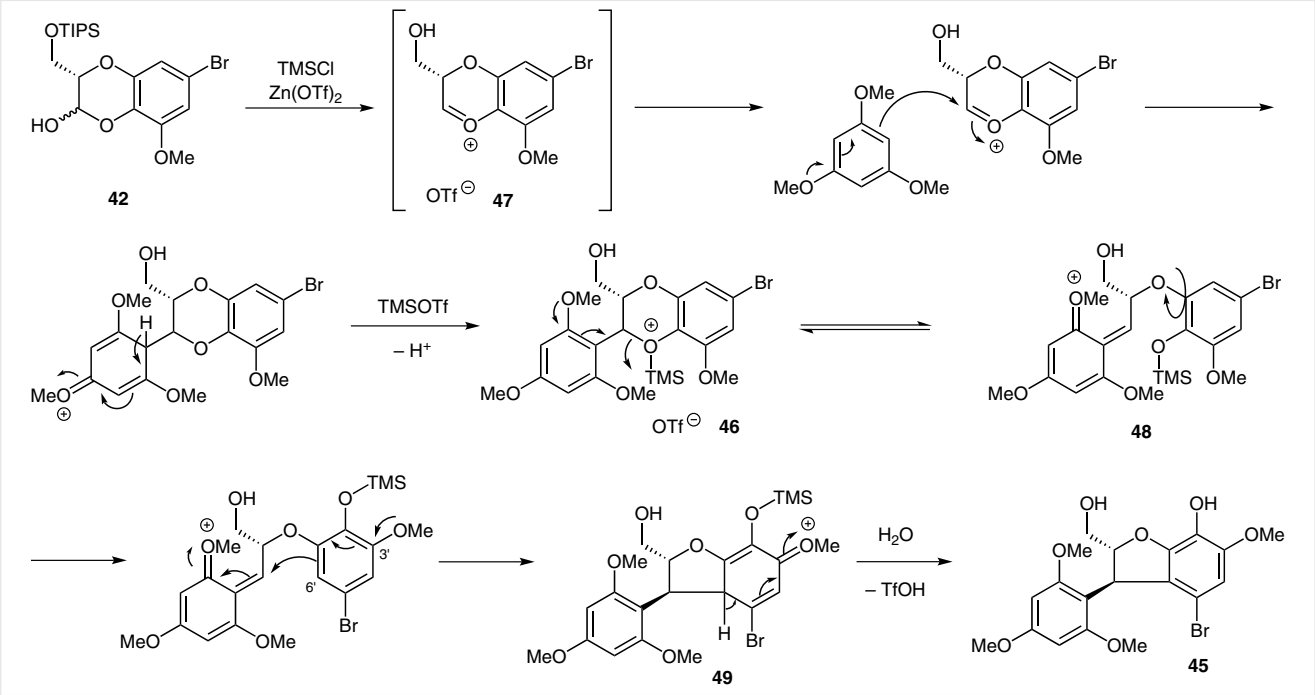
Scheme 9 Synthesis of 1,4-benzodioxane hemiacetals **42** and **43**



Scheme 10 Synthesis of benzofuran **45**

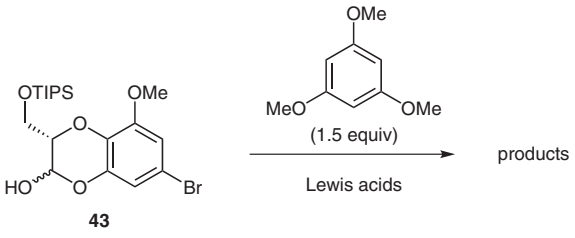
where electron-rich aromatics were shown to be best for the addition reaction, although this is an avenue for further ongoing investigation.

In summary, we have successfully enantioselectively synthesised the 9-hydroxy-5′-methoxy-1,4-benzodioxane framework that is present in a number of natural 1,4-benzodioxane neolignans. Our initial route, derived from our previous asymmetric syntheses of other, similar, 1,4-benzodioxanes, was unsuccessful due to the inability to add the additional aryl group through via the aryl lithiate. This issue was circumvented by the novel procedure adapted from our work on the synthesis of benzomorpholines –



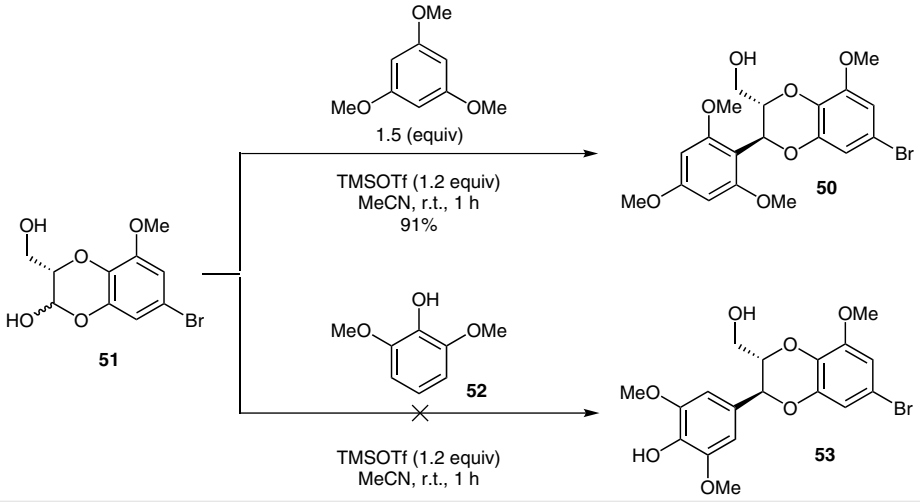
Scheme 11 Proposed mechanism for the generation of **45**

Table 1 Aryl Addition Reaction Outcomes to Benzodioxane Hemiacetals **43**



Lewis acid	Temp (°C)/time	Product
TMSCl (1.5 equiv)/$Zn(OTf)_2$ (0.5 equiv)	r.t., 2 h	**51** (quant)
TMSOTf (1.2 equiv)	r.t., 1 h	**50** trace
TMSOTf (4.0 equiv)	r.t., 0.5 h	decomposition

acid-catalysed addition of an aryl donor to an oxonium ion derived from a 1,4-benzodioxane hemiacetal, thereby achieving the desired framework. Additionally, the discovery of a novel way to produce benzofurans could allow for the synthesis of a number of natural products with this skeleton, such as magnolignan H.[18]



Scheme 12 Successful synthesis of the target 9-hydroxy-5′-methoxy-1,4-benzodioxane scaffold

All reactions were carried out under a N_2 atmosphere in anhydrous, freshly distilled solvents, unless otherwise noted. All NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer at ambient temperature. Chemical shifts are reported relative to the solvent peak of $CHCl_3$ (δ = 7.26 for ^1H and δ = 77.0 for ^{13}C). ^1H NMR data is reported as position (δ), relative integral, multiplicity (standard abbreviations), coupling constant (*J*, Hz), and the assignment of the atom. ^{13}C NMR data are reported as position (δ) and assignment of the atom. All NMR assignments were performed using HSQC and HMBC experiments. High-resolution mass spectroscopy (HRMS) was carried out by either chemical ionization (CI) or electrospray ionization (ESI) on a Micro-TOF-Q mass spectrometer. Unless noted, chemical reagents were used as purchased. Alcohol **6** was prepared using our reported method.[9] Optical rotations were measured at 20 °C on the sodium D line with a Rudolph Research Analytical Autopol IV automatic polarimeter.

5-Bromo-2-hydroxy-3-methoxybenzaldehyde (26)

To a solution of *o*-vanillin (**11**; 4.0 g, 0.026 mol) in AcOH (80 mL) at 0 °C was added NaOAc (2.37 g, 0.029 mol), followed by the dropwise addition of Br_2 (1.49 mL, 0.029 mol). The solution was stirred at r.t. for 30 min. H_2O (100 mL) was added and the aqueous mixture extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **26** (6.0 g, 98%) as a yellow solid; mp 119–123 °C (Lit.[19] mp 122–124 °C).

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.92 (3 H, s, OCH_3), 7.18 (1 H, d, *J* = 2.4 Hz, 4-H), 7.31 (1 H, d, *J* = 2.4 Hz, 6-H), 9.86 (1 H, s, CHO), 11.00 (1 H, s, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 111.1 (C-5), 120.8 (C-6), 121.3 (C-1), 126.1 (C-4), 149.3 (C-2), 150.9 (C-3), 195.4 (CHO).

The ^1H NMR and ^{13}C NMR data were in agreement with literature values.[19]

5-Bromo-3-methoxy-2-(methoxymethoxy)benzaldehyde

To phenol **26** (1.5 g, 6.49 mmol) in CH_2Cl_2 (50 mL) under an atmosphere of N_2 at r.t. was added DIPEA (4.53 mL, 25.97 mmol) followed by MOMCl (1.22 mL, 16.23 mmol) and the mixture was stirred at r.t. for 20 h. Sat. aq NH_4Cl (50 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (9:1 hexanes–EtOAc) to yield the title compound (1.65 g, 93%) as a white solid; mp 60–64 °C.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.55 (3 H, s, OCH_2OCH_3), 3.89 (3 H, s, OCH_3), 5.20 (2 H, s, OCH_2OCH_3), 7.23 (1 H, d, *J* = 2.4 Hz, 4-H), 7.54 (1 H, d, *J* = 2.4 Hz, 6-H), 10.38 (1 H, s, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 57.8 (OCH_2OCH_3), 99.2 (OCH_2OCH_3), 117.1 (C-5), 120.6 (C-4), 121.5 (C-6), 131.0 (C-1), 148.4 (C-2), 153.2 (C-3), 188.7 (CHO).

The ^1H NMR and ^{13}C NMR data were in agreement with literature values.[8]

5-Bromo-3-methoxy-2-(methoxymethoxy)phenol (12)

To a solution of 5-bromo-3-methoxy-2-(methoxymethoxy)benzaldehyde (1.65 g, 5.99 mmol) in CH_2Cl_2 (60 mL) under an atmosphere of N_2 at 0 °C was added *m*CPBA (3.11 g, 17.99 mol). The reaction mixture was stirred at 0 °C for 1 h and then left to warm to r.t. and stirred for 72 h. To the resulting suspension was added sat. aq $Na_2S_2O_3$ (60 mL) and the mixture extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with sat. aq Na_2CO_3 (50 mL), sat. aq NH_4Cl (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$) and the solvent removed in vacuo to give the crude formate ester, which was suspended in a solution of KOH (3.0 g) in MeOH (50 mL) and stirred at r.t. for 1 h. The resulting solution was added to aq 2 M HCl (50 mL) and extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with sat. aq Na_2CO_3 (40 mL) and brine (40 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (9:1 hexanes–EtOAc) to yield the title compound **12** (1.28 g, 86%) as a white solid; R_f = 0.63 (2:1 hexanes–EtOAc); mp 150–153 °C.

IR (film): 3441, 2970, 1738, 1609, 1501, 1449, 1425, 1365, 1214, 1154, 1107, 1070, 1001, 921, 852, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.57 (3 H, s, OCH_2OCH_3), 3.82 (3 H, s, OCH_3), 5.07 (2 H, s, OCH_2OCH_3), 6.60 (1 H, d, *J* = 2.4 Hz, 4-H), 6.79 (1 H, d, *J* = 2.4 Hz, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1 (OCH_2OCH_3), 57.5 (OCH_2OCH_3), 99.4 (OCH_2OCH_3), 107.6 (C-4), 112.7 (C-6), 117.1 (C-5), 133.2 (C-2), 150.5 (C-1), 152.7 (C-3).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_9H_{11}{}^{81}BrO_4Na$: 286.9713; found: 286.9718; *m*/*z* (M + Na^+) calcd for $C_9H_{11}{}^{79}BrO_4Na$: 284.9733; found: 284.9736.

1-(Benzyloxy)-5-bromo-3-methoxy-2-(methoxymethoxy)benzene (13)

To a stirred solution of NaH (60% w/w dispersion in mineral oil, 0.36 g, 9.12 mmol) in DMF (30 mL) under an atmosphere of N_2 at 0 °C was added a solution of phenol **12** (1.20 g, 4.56 mmol) in DMF (20 mL). The resulting mixture was stirred for 20 min before BnBr (0.65 mL, 5.47 mmol) was added and the mixture was allowed to warm to r.t. and then stirred for 3 d. Sat. aq NH_4Cl (50 mL) was added and the aqueous mixture extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **13** (1.54 g, 97%) as a colourless oil; R_f = 0.78 (2:1 hexanes–EtOAc).

IR (film): 3063, 3031, 2937, 2899, 1590, 1492, 1464, 1416, 1380, 1308, 1230, 1195, 1079, 1016, 925, 812, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.50 (3 H, s, OCH_2OCH_3), 3.78 (3 H, s, OCH_3), 5.01 (2 H, s, OCH_2OCH_3), 5.08 (2 H, br s, OCH_2Ph), 6.71 (1 H, d, *J* = 2.0 Hz, 6-H), 6.76 (1 H, d, *J* = 2.0 Hz, 4-H), 7.29–7.39 (5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1 (OCH_3), 57.0 (OCH_2OCH_3), 71.1 (OCH_2Ar), 98.0 (OCH_2OCH_3), 109.1 (C-6), 110.4 (C-4), 116.3 (C-5), 127.3, 128.0, 128.4 (ArCH), 134.3 (C-2), 136.2 (ArC), 153.0 (C-1), 154.0 (C-3).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{16}H_{17}{}^{81}BrO_4Na$: 377.0183; found: 377.0178; *m*/*z* (M + Na^+) calcd for $C_{16}H_{17}{}^{79}BrO_4Na$: 375.0202; found: 375.0197.

2-(Benzyloxy)-4-bromo-6-methoxyphenol (10)

To a solution of MOM ether **13** (1.55 g, 4.39 mmol) in MeOH (80 mL) was added aq 2 M HCl (14 mL) and the resultant mixture stirred at r.t. for 20 h. Aq 1 M NaOH was added until pH 5 and then the solution was extracted with EtOAc (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (9:1 hexanes–EtOAc) to give the title compound **10** (1.22 g, 94%) as an orange solid; mp 73–77 °C; R_f = 0.67 (2:1 hexanes–EtOAc).

IR (film): 3510, 3065, 3032, 2937, 2871, 1607, 1502, 1448, 1421, 1381, 3441, 2970, 1738, 1609, 1501, 1449, 1425, 1365, 1214, 1154, 1107, 1070, 1001, 921, 852, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.83 (3 H, s, OCH_3), 5.06 (2 H, s, OCH_2Ph), 5.76 (1 H, br s, OH), 6.72 (1 H, d, *J* = 2.2 Hz, 3-H), 6.78 (1 H, d, *J* = 2.2 Hz, 5-H), 7.34–7.42 (5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3 (OCH_3), 71.4 (OCH_2Ph), 108.8 (C-3), 110.1 (C-5), 110.7 (C-4), 127.6, 128.2, 128.5 (ArCH), 134.5 (C-1), 135.9 (ArC), 146.6 (C-1), 147.7 (C-3).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{14}H_{13}{}^{81}BrO_3Na$: 332.9920; found: 332.9913; *m*/*z* (M + Na^+) calcd for $C_{14}H_{13}{}^{79}BrO_3Na$: 330.9940; found: 330.9932;

(*R*)-{2-[2′-(Benzyloxy)-4-bromo-6-methoxyphenoxy]-3-[(4″-methoxybenzyl)oxy]propoxy}triisopropylsilane (14)

To a solution of alcohol **6**[9] (0.81 g, 2.20 mmol) in toluene (30 mL) under an atmosphere of N_2 was added PPh_3 (0.77 g, 2.91 mmol) and the resultant solution was stirred for 10 min. A solution of phenol **10** (0.45 g, 1.46 mmol) in toluene (20 mL) was then added dropwise and the mixture was stirred at 0 °C for 20 min. DIAD (0.57 mL, 2.91 mmol) was added and the solution was allowed to warm to r.t. and stirred for 3 days. Following this, the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 *n*-hexanes–EtOAc) to give the title compound **14** (0.81 g, 88%) as a yellow oil; R_f = 0.84 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +4.40 (*c* 0.25, $CHCl_3$).

IR (film): 2939, 2862, 1587, 1513, 1491, 1462, 1415, 1246, 1226, 1115, 1063, 1035, 881, 807, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.97–1.02 {21 H, m, $Si[CH(CH_3)_2]_3$}, 3.68 (1 H, dd, *J* = 10.4, 5.0 Hz, 3-H_a), 3.76 (3 H, s, 6′-OCH_3), 3.77 (1 H, dd, *J* = 10.4, 4.0 Hz, 3-H_b), 3.78 (3 H, s, 4″-OCH_3), 3.91 (1 H, dd, *J* = 10.4, 5.0 Hz, 1-H_a), 3.93 (1 H, dd, *J* = 10.4, 6.7 Hz, 1-H_b), 4.26–4.30 (1 H, m, 2-H), 4.37 (1 H, d, *J* = 11.6 Hz, OCH_aH_bAr), 4.42 (1 H, d, *J* = 11.6 Hz, OCH_aH_bAr), 4.99 (1 H, d, *J* = 11.6 Hz, OCH_aH_bPh), 5.03 (1 H, d, *J* = 11.6 Hz, OCH_aH_bPh), 6.69 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.75 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.81 (2 H, d, *J* = 8.6 Hz, 3″-H), 7.14 (2 H, d, *J* = 8.6 Hz, 2″-H), 7.28–7.41 (5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {$Si[CH(CH_3)_2]_3$}, 18.0 {$Si[CH(CH_3)_2]_3$}, 55.2 (4″-OCH_3), 56.2 (6′-OCH_3), 62.4 (C-1), 69.6 (C-3), 71.4 (OCH_2Ph), 72.9 (OCH_2Ar), 82.0 (C-2), 109.4 (C-5′), 110.9 (C-3′), 113.6 (C-3″), 115.6 (C-4′), 127.4, 127.9, 128.5 (ArCH), 129.1 (C-2″), 130.8 (C-1″), 136.6 (ArC), 136.7 (C-1′), 153.2 (C-2′), 154.3 (C-6′), 159.0 (C-4″).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{34}H_{47}{}^{81}BrO_6SiNa$: 683.2204; found 683.2223; *m*/*z* (M + Na^+) calcd for $C_{34}H_{47}{}^{79}BrO_6SiNa$: 681.2217; found: 681.2236.

(*R*)-2-[2-(Benzyloxy)-4-bromo-6-methoxyphenoxy]-3-[(triisopropylsilyl)oxy]propan-1-ol (15)

To a solution of ether **14** (0.43 g, 0.65 mmol) in a stirred suspension of CH_2Cl_2 (20 mL) and H_2O (20 mL) was added DDQ (0.19 g, 0.85 mmol) and the mixture stirred at r.t. for 18 h. The resulting solution was washed with portions of sat. aq $NaHCO_3$ until the washings were colourless. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (9:1 *n*-hexanes–EtOAc) to yield the title compound **15** (0.28 g, 88%) as a pale yellow oil; R_f = 0.79 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +9.50 (*c* 1.10, $CHCl_3$).

IR (film): 3526, 2942, 2866, 1590, 1491, 1464, 1417, 1225, 1116, 1026, 883 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.01–1.05 {21 H, m, $Si[CH(CH_3)_2]_3$}, 3.11 (1 H, t, *J* = 6.8 Hz, OH), 3.75 (2 H, dd, *J* = 6.6, 3.2 Hz, 1-H), 3.84 (3 H, s, 6′-OCH_3), 3.92 (1 H, d, *J* = 8.8 Hz, 3-H_a), 4.01 (1 H, d, *J* = 8.8 Hz, 3-H_b), 4.02–4.06 (1 H, m, 2-H), 5.04 (1 H, d, *J* = 11.6 Hz, OCH_aH_bPh), 5.07 (1 H, d, *J* = 11.6 Hz, OCH_aH_bPh), 6.74 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.81 (1 H, d, *J* = 2.0 Hz, 3′-H), 7.33–7.43 (5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {$Si[CH(CH_3)_2]_3$}, 17.9 {$Si[CH(CH_3)_2]_3$}, 56.3 (6′-OCH_3), 61.7 (C-1), 62.0 (C-3), 71.6 (OCH_2Ph), 83.8 (C-2), 109.3 (C-5′), 110.7 (C-3′), 116.4 (C-4′), 127.6, 128.4, 128.7 (ArCH), 135.6 (C-1′), 135.9 (ArC), 153.1 (C-2′), 154.0 (C-6′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{26}H_{39}{}^{81}BrO_5SiNa$: 563.1626; found: 563.1638; *m*/*z* (M + Na^+) calcd for $C_{26}H_{39}{}^{79}BrO_5SiNa$: 561.1642; found: 561.1658.

(*S*)-2-[2-(Benzyloxy)-4-bromo-6-methoxyphenoxy]-3-[(triisopropylsilyl)oxy]propanal (16)

To a stirred solution of alcohol **15** (0.14 g, 0.26 mmol) in CH_2Cl_2 (30 mL) was added DMP (0.22 g, 0.52 mmol) and the reaction mixture was left open to air and stirred at r.t. for 4 h. Sat. aq $Na_2S_2O_5$ (20 mL) was added followed by sat. aq $NaHCO_3$ (20 mL) and the mixture shaken until no further gas evolved. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **16** (0.081 g, 60%) as a pale yellow oil; R_f = 0.83 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ –7.80 (*c* 0.37, $CHCl_3$).

IR (film): 2941, 1865, 1733, 1591, 1492, 1462, 1461, 1381, 1307, 1223, 1117, 1061, 996, 881, 810, 736, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.99–1.05 {21 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.79 (3 H, s, 6′-OCH_3), 4.10–4.18 (3 H, m, 2-H, 3-H), 5.03 (2 H, br s, O*C*H_2Ph), 6.70 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.76 (1 H, d, *J* = 2.0 Hz, 3′-H), 7.32–7.39 (5 H, ArH), 9.87 (1 H, d, *J* = 2.4 Hz, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si[*C*H(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.1 (6′-OCH_3), 64.1 (C-3), 71.3 (O*C*H_2Ph), 87.4 (C-2), 109.2 (C-5′), 110.5 (C-3′), 116.6 (C-4′), 127.6, 128.3, 128.6 (ArCH), 136.0 (ArC), 136.3 (C-1′), 152.6 (C-2′), 153.6 (C-6′), 202.7 (C-1).

HRMS (ESI+): *m*/*z* (M + H^+) calcd for $C_{26}H_{38}{}^{81}BrO_5Si$: 539.1646; found: 539.1632; *m*/*z* (M + H^+) calcd for $C_{26}H_{38}{}^{79}BrO_5Si$: 537.1666; found: 537.1646.

(*S*)-2-[2-(Benzyloxy)-4-bromo-6-methoxyphenoxy]-3-[(4-methoxybenzyl)oxy]propan-1-ol (19)

To a stirred solution of the silyl ether **14** (0.14 g, 0.21 mmol) in THF (25 mL), at 0 °C was added 1 M TBAF in THF (0.85 mL, 0.85 mmol) dropwise and the mixture stirred for 18 h. Sat. aq $NaHCO_3$ (25 mL) was added and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (2:1 hexanes–EtOAc) to give the title compound **19** (0.052 g, 52%) as a yellow oil; R_f = 0.47 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ –13.04 (*c* 0.05, $CHCl_3$).

IR (film): 3524, 2922, 2854, 1713, 1611, 1588, 1512, 1490, 1448, 1416, 1247, 1221, 1112, 1031, 785, 752, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.07 (1 H, t, *J* = 6.8 Hz, OH), 3.68 (2 H, dd, *J* = 6.8, 3.0 Hz, 1-H), 3.73 (1 H, dd, *J* = 10.4, 5.2 Hz, 3-H_a), 3.78 (1 H, d, *J* = 10.4, 4.0 Hz, 3-H_b), 3.79 (3 H, s, 4″-OCH_3), 3.83 (3 H, s, 6′-OCH_3), 4.16–4.21 (1 H, m, 2-H), 4.40 (2 H, s, O*C*H_2Ar), 5.02 (1 H, d, *J* = 11.6 Hz, O*C*$H_a$$H_b$Ph), 5.06 (1 H, d, *J* = 11.6 Hz, OCH$_a$*H*$_b$Ph), 6.75 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.82 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.84 (2 H, d, *J* = 8.6 Hz, 3″-H), 7.18 (2 H, d, *J* = 8.6 Hz, 2″-H), 7.33–7.43 (5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (4″-OCH_3), 56.4 (6′-OCH_3), 62.2 (C-1), 69.1 (C-3), 71.6 (O*C*H_2Ph), 73.1 (O*C*H_2Ar), 82.1 (C-2), 109.6 (C-5′), 110.9 (C-3′), 116.4 (C-4′), 127.7, 128.4, 128.7 (ArCH), 135.5 (C-1′), 135.8 (ArC), 153.1 (C-2′), 154.0 (C-6′), 159.1 (C-4″).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{25}H_{27}{}^{81}BrO_6Na$: 527.0867; found: 527.0864; *m*/*z* (M + Na^+) calcd for $C_{25}H_{27}{}^{79}BrO_6Na$: 525.0883, found: 525.0879.

(*R*)-2-[2-(Benzyloxy)-4-bromo-6-methoxyphenoxy]-3-[(4-methoxybenzyl)oxy]propanal (18)

To a stirred solution of alcohol **19** (0.05 g, 0.10 mmol) in CH_2Cl_2 (15 mL) was added DMP (0.09 g, 0.20 mmol) and the reaction mixture was left open to air and stirred at r.t. for 4 h. Sat. aq $Na_2S_2O_5$ (15 mL) was added followed by sat. aq $NaHCO_3$ (15 mL) and the mixture shaken until no further gas evolved. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **18** (0.021 g, 44%) as a pale yellow oil; R_f = 0.67 (9:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +6.04 (*c* 0.27, $CHCl_3$).

IR (film): 2933, 2867, 1731, 1611, 1590, 1512, 1491, 1448, 1416, 1378, 1302, 1245, 1220, 1113, 1030, 811, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.64–3.75 (2 H, m, 3-H), 3.79 (3 H, s, 4″-OCH_3), 3.80 (3 H, s, 6′-OCH_3), 4.32 (1 H, td, *J* = 7.8, 2.0 Hz, 2-H), 4.36 (2 H, s, O*C*H_2Ar), 5.03 (2 H, s, O*C*H_2Ph), 6.72 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.79 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.83 (2 H, d, *J* = 8.6 Hz, 3″-H), 7.15 (2 H, d, *J* = 8.6 Hz, 2″-H), 7.33–7.43 (5 H, Ar-H), 9.89 (1 H, d, *J* = 2.0 Hz, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (4″-OCH_3), 56.2 (6′-OCH_3), 69.7 (C-3), 71.4 (OCH_2Ph), 73.2 (OCH_2Ar), 86.5 (C-2), 109.3 (C-5′), 110.6 (C-3′), 116.8 (C-4′), 127.5, 128.3, 128.6 (ArCH), 135.5 (C-1′), 136.0 (ArC), 152.7 (C-2′), 153.6 (C-6′), 159.1 (C-4″), 202.4 (C-1).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{25}H_{25}{}^{81}BrO_6Na$: 525.0710; found: 525.0745; *m*/*z* (M + Na^+) calcd for $C_{25}H_{25}{}^{79}BrO_6Na$: 523.0727; found: 523.0738.

5-Bromo-3-methoxy-2-[(triisopropylsilyl)oxy]benzaldehyde (28)

To a solution of phenol **26** (2.0 g, 8.66 mmol) and 1*H*-imidazole (1.18 g, 17.31 mmol) in DMF (50 mL) under an atmosphere of N_2 at r.t. was added TIPSCl (2.22 mL, 10.38 mmol) slowly, and the mixture stirred for 20 h. H_2O (50 mL) was added and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **28** (2.91 g, 90%) as a yellow oil; R_f = 0.93 (2:1 hexanes–EtOAc).

IR (film): 2941, 2863, 1738, 1682, 1573, 1481, 1465, 1321, 1261, 1246, 1191, 1076, 902, 836, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.05, 1.07, 1.09 {18 H, m, Si[CH(*C*H_3)$_2$]$_3$}, 1.25–1.31 {3 H, m, Si[*C*H(CH_3)$_2$]$_3$}, 3.83 (3 H, s, OCH_3), 7.11 (1 H, d, *J* = 2.0 Hz, 4-H), 7.50 (1 H, d, *J* = 2.4 Hz, 6-H), 10.45 (1 H, s, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 {Si[*C*H(CH_3)$_2$]$_3$}, 18.0 {Si[CH(CH_3)$_2$]$_3$}, 55.4 (OCH_3), 113.1 (C-5), 119.5 (C-4), 121.7 (C-6), 128.1 (C-1), 149.3 (C-2), 151.5 (C-3), 188.9 (CHO).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{17}H_{27}{}^{81}BrO_3SiNa$: 411.0786; found: 411.0784; *m*/*z* (M + Na^+) calcd for $C_{17}H_{27}{}^{79}BrO_3SiNa$: 409.0805; found: 409.0803.

4-Bromo-2-methoxy-6-[(triisopropylsilyl)oxy]phenol (30) and 5-Bromo-3-methoxy-2-[(triisopropylsilyl)oxy]phenol (29)

To a solution of aldehyde **28** (2.84 g, 7.33 mmol) in CH_2Cl_2 (70 mL) under an atmosphere of N_2 at 0 °C was added *m*CPBA (3.79 g, 21.99 mmol). The reaction mixture was stirred at 0 °C for 1 h and then left to warm to r.t. and stirred for 72 h. To the resulting suspension was added sat. aq $Na_2S_2O_3$ (70 mL) and the mixture extracted with EtOAc

(3 × 70 mL). The combined organic layers were washed with sat. aq Na_2CO_3 (60 mL), sat. aq NH_4Cl (60 mL) and brine (50 mL). The organic layer was then dried (Na_2SO_4) and the solvent removed in vacuo to give the crude formate ester **27**, which was suspended in a solution of KOH (3.3 g) in MeOH (60 mL) and stirred at r.t. for 1 h. The resulting solution was added to aq 2 M HCl (50 mL) and extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with sat. aq Na_2CO_3 (50 mL) and brine (50 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to give the title compounds **30** and **29** (2.2 g, 82%) as a 1:1.5 inseparable mixture; yellow oil; R_f = 0.93 (2:1 hexanes–EtOAc).

IR (film): 3531, 2945, 2867, 1738, 1603, 1498, 1449, 1421, 1365, 1312, 1230, 1209, 1106, 882, 802, 684 cm^{-1}.

30

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.05, 1.07, 1.10 {18 H, m, Si[CH(CH_3)$_2$]$_3$}, 1.24–1.32 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.77 (3 H, s, OCH_3), 5.62 (1 H, br s, OH), 6.56 (1 H, d, J = 2.0 Hz, 3-H), 6.75 (1 H, d, J = 2.4 Hz, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 {Si[CH(CH_3)$_2$]$_3$}, 18.0 {Si[CH(CH_3)$_2$]$_3$}, 55.3 (OCH_3), 107.1 (C-3), 111.3 (C-5), 138.3 (C-1), 143.9 (C-6), 148.1 (C-2).

29

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.05, 1.08, 1.12 {18 H, m, Si[CH(CH_3)$_2$]$_3$}, 1.24–1.32 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.86 (3 H, s, OCH_3), 5.37 (1 H, br s, OH), 6.67 (2 H, d, J = 2.0 Hz, 4-H, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 {Si[CH(CH_3)$_2$]$_3$}, 17.7 {Si[CH(CH_3)$_2$]$_3$}, 56.4 (OCH_3), 108.7 (C-4), 115.4 (C-6), 118.5 (C-5), 136.0 (C-2), 148.4 (C-1), 149.3 (C-3).

HRMS (ESI+): m/z ($M + Na^+$) calcd for $C_{16}H_{27}{}^{81}BrO_3SiNa$: 399.0786; found: 399.0781; m/z ($M + Na^+$) calcd for $C_{16}H_{27}{}^{79}BrO_3SiNa$: 397.0805; found: 397.0800.

[4-Bromo-2-methoxy-6-(methoxymethoxy)phenoxy]triisopropylsilane (31) and [5-Bromo-3-methoxy-2-(methoxymethoxy)phenoxy]triisopropylsilane (32)

To a mixture of phenol **29** and **30** (2.2 g, 5.86 mmol) in CH_2Cl_2 (60 mL) at r.t., under an atmosphere of N_2, was added DIPEA (3.45 mL, 23.44 mmol) followed by MOMCl (1.11 mL, 14.65 mmol) and the mixture was stirred at r.t. for 20 d. Sat. aq NH_4Cl (50 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to give the title compounds **31** and **32** (2.12 g, 87%) as a 1.2:1 inseparable mixture; yellow oil; R_f = 0.91 (2:1 hexanes–EtOAc).

IR: (film): 2944, 2867, 1738, 1586, 1500, 1463, 1449, 1416, 1316, 1218, 1158, 1116, 1075, 1012, 922, 883, 683 cm^{-1}.

31

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.07, 1.08, 1.11 {18 H, m, Si[CH(CH_3)$_2$]$_3$}, 1.22–1.27 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.57 (3 H, s, OCH_2OCH_3), 3.82 (3 H, s, OCH_3), 5.11 (2 H, s, OCH_2OCH_3), 6.67 (2 H, d, J = 2.0 Hz, 3-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.1 (OCH_3), 57.1 (OCH_2OCH_3), 98.2 (OCH_2OCH_3), 108.9 (C-3), 115.8 (C-4), 116.5 (C-5), 135.0 (C-1), 147.5 (C-6), 153.9 (C-2).

32

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.08, 1.09, 1.11 {18 H, m, Si[CH(CH_3)$_2$]$_3$}, 1.22–1.27 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.47 (3 H, s, OCH_2OCH_3), 3.76 (3 H, s, OCH_3), 4.86 (2 H, s, OCH_2OCH_3), 6.68 (1 H, d, J = 2.0 Hz, 4-H), 6.91 (1 H, d, J = 2.0 Hz, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 {Si[CH(CH_3)$_2$]$_3$}, 17.8 {Si[CH(CH_3)$_2$]$_3$}, 55.6 (OCH_3), 56.1 (OCH_2OCH_3), 95.2 (OCH_2OCH_3), 109.3 (C-4), 112.2 (C-6), 115.8 (C-5), 136.5 (C-2), 146.9 (C-1), 152.6 (C-3).

HRMS (ESI+): m/z ($M + Na^+$) calcd for $C_{18}H_{31}{}^{81}BrO_4SiNa$: 443.1049; found: 443.1066; m/z ($M + Na^+$) calcd for $C_{18}H_{31}{}^{79}BrO_4SiNa$: 441.1067; found: 441.1083.

4-Bromo-2-methoxy-6-(methoxymethoxy)phenol (22) and 5-Bromo-3-methoxy-2-(methoxymethoxy)phenol (12)

To a stirred solution of a mixture of silyl ethers **31** and **32** (2.10 g, 5.01 mmol) in THF (50 mL) at 0 °C was added 1 M TBAF in THF (20.02 mL, 20.02 mmol) dropwise and the mixture stirred for 2 h. Sat. aq $NaHCO_3$ (50 mL) was added and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (9:1 then 4:1 hexanes–EtOAc) to yield the title compound **22** (0.57 g, 46%) as a brown oil and the title compound **12** (0.46 g, 36%) as a yellow oil. **22**: R_f = 0.47 (2:1 hexanes–EtOAc); **12**: R_f = 0.63 (2:1 hexanes–EtOAc).

22

IR (film): 3441, 2970, 1738, 1609, 1501, 1449, 1425, 1365, 1214, 1154, 1107, 1070, 1001, 921, 852, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.51 (3H, s, OCH_2OCH_3), 3.86 (3 H, s, OCH_3), 5.18 (2 H, s, OCH_2OCH_3), 5.89 (1 H, br s, OH), 6.74 (1 H, d, J = 2.0 Hz, 3-H), 6.96 (1 H, s, J = 2.0 Hz, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3 (OCH_2OCH_3), 56.4 (OCH_3), 95.8 (OCH_2OCH_3), 109.5 (C-3), 110.7 (C-4), 112.9 (C-5), 135.2 (C-1), 145.1 (C-6), 147.9 (C-2).

HRMS (ESI+): m/z ($M + Na^+$) calcd for $C_9H_{11}{}^{81}BrO_4Na$: 286.9713; found: 286.9716; m/z ($M + Na^+$) calcd for $C_9H_{11}{}^{79}BrO_4Na$: 284.9733; found: 284.9729.

12

IR (film): 3441, 2970, 1738, 1609, 1501, 1449, 1425, 1365, 1214, 1154, 1107, 1070, 1001, 921, 852, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.57 (3 H, s, OCH_2OCH_3), 3.82 (3 H, s, OCH_3), 5.07 (2 H, s, OCH_2OCH_3), 6.60 (1 H, d, J = 2.0 Hz, 4-H), 6.79 (1 H, s, J = 2.0 Hz, 6-H), 6.84 (1 H, br s, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1 (OCH_3), 57.5 (OCH_2OCH_3), 99.4 (OCH_2OCH_3), 107.5 (C-4), 112.6 (C-6), 117.1 (C-5), 133.2 (C-2), 150.5 (C-1), 152.7 (C-3).

HRMS (ESI+): m/z ($M + Na^+$) calcd for $C_9H_{11}{}^{81}BrO_4Na$: 286.9713; found: 286.9718; m/z ($M + Na^+$) calcd for $C_9H_{11}{}^{79}BrO_4Na$: 284.9733; found: 284.9736.

(*R*)-{2-[4-Bromo-2-methoxy-6-(methoxymethoxy)phenoxy]-3-[(4-methoxybenzyl)oxy]propoxy}triisopropylsilane (33)

To a solution of alcohol **6** (0.59 g, 1.60 mmol) in toluene (25 mL) under an atmosphere of N_2 was added PPh_3 (0.56 g, 2.13 mmol) and the resultant solution was stirred for 10 min. A solution of phenol **22** (0.28 g, 1.06 mmol) in toluene (12 mL) was then added dropwise and the mixture was stirred at 0 °C for 20 min. DIAD (0.42 mL, 1.06 mmol) was added and the solution was allowed to warm to r.t. and stirred for 3 days. Following this, the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 *n*-hexanes–EtOAc) to give the title compound **33** (0.47 g, 73%) as a yellow oil; R_f = 0.64 (4:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +0.40 (*c* 0.25, $CHCl_3$).

IR (film): 2942, 2865, 1742, 1613, 1588, 1514, 1490, 1421, 1393, 1301, 1230, 1156, 1112, 1072, 1007, 911, 882, 815, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.03 {18 H, d, *J* = 4.8 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.05–1.08 {3 H, m, Si[CH(CH$_3$)$_2$]$_3$}, 3.45 (3 H, s, OCH$_2$OCH_3), 3.70 (1 H, dd, *J* = 10.4, 5.0 Hz, 3-H$_a$), 3.77 (3 H, s, 2′-OCH$_3$), 3.78 (3 H, s, 4″-OCH$_3$), 3.79 (1 H, dd, *J* = 10.4, 4.0 Hz, 3-H$_b$), 3.94 (1 H, dd, *J* = 10.4, 4.8 Hz, 1-H$_a$), 3.97 (1 H, dd, *J* = 10.4, 4.2 Hz, 1-H$_b$), 4.25–4.28 (1 H, m, 2-H), 4.45 (1 H, d, *J* = 11.6 Hz, OCH_aH$_b$Ar), 4.49 (1 H, d, *J* = 11.6 Hz, OCH$_a$H$_b$Ar), 5.10 (1 H, d, *J* = 6.8 Hz, OCH_aH$_b$CH$_3$), 5.12 (1 H, d, *J* = 6.8 Hz, OCH$_a$H$_b$CH$_3$), 6.73 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.84 (2 H, d, *J* = 8.4 Hz, 3″-H), 6.94 (1 H, d, *J* = 2.0 Hz, 5′-H), 7.19 (1 H, d, *J* = 8.4 Hz, 2″-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si[CH(CH$_3$)$_2$]$_3$}, 18.0 {Si[CH(CH_3)$_2$]$_3$}, 55.2 (2′-OCH$_3$), 56.1 (4″-OCH$_3$), 56.3 (OCH$_2$OCH$_3$), 62.5 (C-1), 69.5 (C-3), 72.9 (OCH$_2$Ar), 82.1 (C-2), 95.8 (OCH$_2$OCH$_3$), 110.1 (C-3′), 113.3 (C-5′), 113.6 (C-3″), 115.7 (C-4′), 129.1 (C-2″), 130.6 (C-1″), 136.8 (C-1′), 151.7 (C-6′), 154.2 (C-2′), 159.4 (C-4″).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{29}H_{45}{}^{81}BrO_7SiNa$: 637.1995; found: 637.1978; *m*/*z* (M + Na^+) calcd for $C_{29}H_{45}{}^{79}BrO_7SiNa$: 635.2010; found: 635.1993.

(*R*)-{2-[5-Bromo-3-methoxy-2-(methoxymethoxy)phenoxy]-3-[(4-methoxybenzyl)oxy]propoxy}triisopropylsilane (34)

To a solution of alcohol **6** (1.12 g, 3.02 mmol) in toluene (40 mL) under an atmosphere of N_2 was added PPh_3 (1.06 g, 4.03 mmol) and the resultant solution was stirred for 10 min. A solution of phenol **12** (0.53 g, 2.01 mmol) in toluene (20 mL) was then added dropwise and the mixture was stirred at 0 °C for 20 min. DIAD (0.79 mL, 4.03 mmol) was added and the solution was allowed to warm to r.t. and stirred for 3 days. Following this, the solvent was removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to give the title compound **34** (0.81 g, 71%) as a yellow oil; R_f = 0.55 (4:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +0.61 (*c* 0.83, $CHCl_3$).

IR (film): 2923, 2865, 1727, 1587, 1513, 1490, 1416, 1247, 1157, 1107, 1037, 1013, 881, 793, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.04 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.05–1.07 {3 H, m, Si[CH(CH$_3$)$_2$]$_3$}, 3.54 (3 H, s, OCH$_2$OCH_3), 3.66 (1 H, dd, *J* = 10.4, 5.0 Hz, 3-H$_a$), 3.74 (1 H, dd, *J* = 10.4, 4.4 Hz, 3-H$_b$), 3.80 (3 H, s, 4″-OCH$_3$), 3.82 (3 H, s, 3′-OCH$_3$), 3.89 (2 H, d, *J* = 5.4 Hz, 1-CH$_2$), 4.38–4.42 (1 H, m, 2-H), 4.47 (2 H, s, OCH_2Ar), 5.06 (1 H, d, *J* = 6.8 Hz, OCH_aH$_b$CH$_3$), 5.08 (1 H, d, *J* = 6.8 Hz, OCH$_a$H$_b$CH$_3$), 6.69 (1 H, d, *J* = 2.2 Hz, 4′-H), 6.86 (2 H, d, *J* = 8.8 Hz, 3″-H), 6.88 (1 H, d, *J* = 2.2 Hz, 6′-H), 7.23 (1 H, d, *J* = 8.8 Hz, 2″-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si(CH(CH$_3$)$_2$]$_3$}, 18.0 {Si[CH(CH_3)$_2$]$_3$}, 55.2 (4″-OCH$_3$), 56.2 (3′-OCH$_3$), 57.3 (OCH$_2$OCH$_3$), 62.6 (C-1), 68.9 (C-3), 73.2 (OCH$_2$Ar), 79.9 (C-2), 98.3 (OCH$_2$OCH$_3$), 109.3 (C-4′), 112.7 (C-6′), 113.8 (C-3″), 116.2 (C-5′), 129.3 (C-2″), 130.2 (C-1″), 135.3 (C-2′), 152.6 (C-1′), 154.2 (C-3′), 159.4 (C-4″).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{29}H_{45}{}^{81}BrO_7SiNa$: 637.1995; found: 637.1992; *m*/*z* (M + Na^+) calcd for $C_{29}H_{45}{}^{79}BrO_7SiNa$: 635.2010; found: 635.2008.

(*S*)-2-[4-Bromo-2-methoxy-6-(methoxymethoxy)phenoxy]-3-[(4-methoxybenzyl)oxy]propan-1-ol (35)

To a stirred solution of the silyl ether **33** (0.22 g, 0.35 mmol) in THF (30 mL) at 0 °C was added 1 M TBAF in THF (1.41 mL, 1.41 mmol) dropwise and the mixture stirred for 18 h. Sat. aq $NaHCO_3$ (30 mL) was added and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (2:1 hexanes–EtOAc) to give the title compound **35** (0.146 g, 94%) as a yellow oil; R_f = 0.37 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ –13.84 (*c* 0.22, $CHCl_3$).

IR (film): 3513, 2921, 2853, 1738, 1611, 1587, 1512, 1489, 1421, 1393, 1224, 1155, 1111, 1069, 1033, 998, 816, 783 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.14 (1 H, t, *J* = 6.8 Hz, OH), 3.46 (3 H, s, OCH$_2$OCH_3), 3.74 (2 H, dd, *J* = 6.2, 3.6 Hz, 1-CH$_2$), 3.78 (1 H, dd, *J* = 10.4, 6.4 Hz, 3-H$_a$), 3.80 (3 H, s, 4″-OCH$_3$), 3.81 (3 H, s, 2′-OCH$_3$), 3.83 (1 H, dd, *J* = 10.4, 5.2 Hz, 3-H$_b$), 4.15–4.21 (1 H, m, 2-H), 4.48 (1 H, d, *J* = 11.6 Hz, OCH_aH$_b$Ar), 4.53 (1 H, d, *J* = 11.6 Hz, OCH$_a$H$_b$Ar), 5.13 (1 H, d, *J* = 6.4 Hz, OCH_aH$_b$CH$_3$), 5.15 (1 H, d, *J* = 6.4 Hz, OCH$_a$H$_b$CH$_3$), 6.76 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.87 (2 H, d, *J* = 8.4 Hz, 3″-H), 6.96 (1 H, d, *J* = 2.0 Hz, 5′-H), 7.24 (1 H, d, *J* = 8.4 Hz, 2″-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (4″-OCH$_3$), 56.3 (2′-OCH$_3$), 56.5 (OCH$_2$OCH$_3$), 62.2 (C-1), 69.1 (C-3), 73.1 (OCH$_2$Ar), 82.2 (C-2), 95.6 (OCH$_2$OCH$_3$), 110.1 (C-3′), 112.9 (C-5′), 113.8 (C-3″), 116.5 (C-4′), 129.3 (C-2″), 130.4 (C-1″), 135.9 (C-1′), 151.6 (C-6′), 153.9 (C-2′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{20}H_{25}{}^{81}BrO_7Na$: 481.0658; found: 481.0659; *m*/*z* (M + Na^+) calcd for $C_{20}H_{25}{}^{79}BrO_7Na$: 479.0676; found: 479.0675.

(*R*)-2-[4-Bromo-2-methoxy-6-(methoxymethoxy)phenoxy]-3-[(4-methoxybenzyl)oxy]propanal (36)

To a stirred solution of alcohol **35** (0.073 g, 0.16 mmol) in CH_2Cl_2 (10 mL) was added DMP (0.10 g, 0.24 mmol) and the reaction mixture was left open to atmosphere and stirred at r.t. for 4 h. Sat. aq $Na_2S_2O_5$ (10 mL) was added followed by sat. aq $NaHCO_3$ (10 mL) and the mixture shaken until no further gas evolved. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 hexanes–EtOAc) to yield the title compound **36** (0.033 g, 48%) as a pale yellow oil; R_f = 0.72 (2:1 hexanes–EtOAc); $[\alpha]_D^{20}$ +9.82 (*c* 0.11, $CHCl_3$).

IR (film): 2960, 2921, 2852, 1712, 1597, 1514, 1496, 1419, 1361, 1258, 1220, 1151, 1068, 1016, 952, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.44 (3 H, s, OCH$_2$OCH_3), 3.79 (3 H, s, 2′-OCH$_3$), 3.80 (3 H, s, 4″-OCH$_3$), 3.84 (1 H, dd, *J* = 10.4, 5.2 Hz, 3-H$_a$), 3.88 (1 H, dd, *J* = 10.4, 6.4 Hz, 3-H$_b$), 4.32 (1 H, td, *J* = 8.2, 2.0 Hz, 2-H), 4.48 (1 H, d, *J* = 11.6 Hz, OCH_aH$_b$Ar), 4.53 (1 H, d, *J* = 11.6 Hz, OCH$_a$H$_b$Ar), 5.12 (2 H, s, OCH_2CH$_3$), 6.74 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.86 (2 H, d, *J* = 8.6 Hz, 3″-H), 6.96 (1 H, d, *J* = 2.0 Hz, 5′-H), 7.21 (1 H, d, *J* = 8.6 Hz, 2″-H), 9.94 (1 H, d, *J* = 2.0 Hz, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (4″-OCH$_3$), 56.1 (2′-OCH$_3$), 56.4 (OCH$_2$OCH$_3$), 69.5 (C-3), 73.2 (OCH$_2$Ar), 86.4 (C-2), 95.4 (OCH$_2$OCH$_3$), 109.9 (C-3′), 112.7 (C-5′), 113.7 (C-3″), 116.7 (C-4′), 129.2 (C-2″), 129.7 (C-1″), 136.5 (C-1′), 150.9 (C-6′), 153.3 (C-2′), 159.2 (C-4″), 202.2 (C-1).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{20}H_{23}{}^{81}BrO_7Na$: 479.0502; found: 479.0499; *m*/*z* (M + Na^+) calcd for $C_{20}H_{23}{}^{79}BrO_7Na$: 477.0519; found: 477.0516.

(2*R*,3*R*)-7-Bromo-5-methoxy-3-{[(4-methoxybenzyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (37) and (2*S*,3*R*)-7-Bromo-5-methoxy-3-{[(4-methoxybenzyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (38)

To a solution of aldehyde **36** (0.028 g, 0.061 mmol) in MeOH (6 mL) was added aq 2 M HCl (4 mL) and the resultant mixture stirred at r.t. for 3 h. Aq 1 M NaOH was added until pH 5 and then the solution was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (1:1 hexanes–EtOAc) to give the title compounds **37** and **38** (0.024 g, 98%) as a 5:4 inseparable mixture of diastereomers; yellow oil; R_f = 0.37 (2:1 hexanes–EtOAc).

IR (film): 3445, 2931, 2863, 1600, 1513, 1495, 1446, 1421, 1322, 1286, 1248, 1223, 1033, 908, 819, 730 cm^{-1}.

37

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.82 (2 H, d, *J* = 6.6 Hz, 9-CH_2), 3.84 (6 H, s, 4′-OCH_3, 5-OCH_3), 3.98 (1 H, d, *J* = 6.8 Hz, OH), 4.19–4.22 (1 H, m, 3-H), 4.52 (1 H, d, *J* = 11.2 Hz, O*CH*$_a$H$_b$Ar), 4.56 (1 H, d, *J* = 11.2 Hz, OCH$_a$*H*$_b$Ph), 5.53 (1 H, d, *J* = 7.0, 1.2 Hz, 2-H), 6.64 (1 H, d, *J* = 2.0 Hz, 6-H), 6.74 (1 H, d, *J* = 2.0 Hz, 8-H), 6.86 (2 H, d, *J* = 8.4 Hz, 3′-H), 7.26 (1 H, d, *J* = 8.4 Hz, 2′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4 (4′-OCH_3, 5-OCH_3), 67.5 (C-9), 73.4 (C-3), 73.6 (O*C*H$_2$Ar), 90.0 (C-2), 108.6 (C-6), 112.9 (C-7), 113.6 (C-8), 114.0 (C-3′), 129.5 (C-1′), 129.6 (C-2′), 130.7 (C-4a), 141.8 (C-8a), 149.2 (C-5), 159.6 (C-4′).

38

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.49 (1 H, d, *J* = 6.8 Hz, OH), 3.64 (1 H, dd, *J* = 10.4, 6.2 Hz, 9-H$_a$), 3.72 (1 H, dd, *J* = 10.4, 5.0 Hz, 9-H$_b$), 3.81 (6 H, s, 4′-OCH_3, 5-OCH_3), 4.19–4.22 (1 H, m, 3-H), 4.48 (1 H, d, *J* = 11.2 Hz, O*CH*$_a$H$_b$Ar), 4.52 (1 H, d, *J* = 11.2 Hz, OCH$_a$*H*$_b$Ph), 5.47 (1 H, d, *J* = 6.6, 3.6 Hz, 2-H), 6.64 (1 H, d, *J* = 2.0 Hz, 6-H), 6.71 (1 H, d, *J* = 2.0 Hz, 8-H), 6.85 (2 H, d, *J* = 8.4 Hz, 3′-H), 7.22 (1 H, d, *J* = 8.4 Hz, 2′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (4′-OCH_3, 5-OCH_3), 67.2 (C-9), 73.4 (O*C*H$_2$Ar), 74.2 (C-3), 89.6 (C-2), 108.7 (C-6), 113.2 (C-7), 113.4 (C-8), 113.9 (C-3′), 129.1 (C-1′), 129.4 (C-2′), 130.6 (C-4a), 141.7 (C-8a), 149.2 (C-5), 159.8 (C-4′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{18}H_{19}{}^{81}BrO_6Na$: 435.0239; found 435.0235; *m*/*z* (M + Na^+) calcd for $C_{18}H_{19}{}^{79}BrO_6Na$: 433.0257; found: 433.0254.

(*R*)-2-[4-Bromo-2-methoxy-6-(methoxymethoxy)phenoxy]-3-[(triisopropylsilyl)oxy]propan-1-ol (21)

To a solution of ether **33** (0.12 g, 0.20 mmol) in a stirred suspension of CH_2Cl_2 (10 mL) and H_2O (10 mL) was added DDQ (0.07 g, 0.29 mmol) and the mixture stirred at r.t. for 18 h. The resulting solution was washed with portions of sat. aq $NaHCO_3$ until the washings were colourless. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (14:1 hexanes–EtOAc) to yield the title compound **21** (0.08 g, 91%) as a yellow oil; R_f = 0.76 (2:1 hexanes–EtOAc); $[\alpha]_D{}^{20}$ +12.34 (*c* 0.15, $CHCl_3$).

IR (film): 3546, 2922, 2854, 1738, 1589, 1490, 1462, 1422, 1393, 1258, 1158, 1113, 1070, 1004, 882, 781, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.06 {18 H, d, *J* = 5.0 Hz, Si[CH(*CH*$_3$)$_2$]$_3$}, 1.08–1.11 {3 H, m, Si[*CH*(CH$_3$)$_2$]$_3$}, 3.20 (1 H, t, *J* = 6.6 Hz, OH), 3.49 (3 H, s, OCH_2OCH_3), 3.75 (2 H, dd, *J* = 6.6, 3.6 Hz, 1-H), 3.84 (3 H, s, 2′-OCH_3), 3.94–3.98 (1 H, m, 3-H$_a$), 4.04–4.09 (3 H, m, 3-H$_a$ and 2-H), 5.17 (2 H, s, OCH_2OCH_3), 6.77 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.98 (1 H, d, *J* = 2.0 Hz, 5′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si[*CH*(CH$_3$)$_2$]$_3$}, 17.9 {Si[CH(*CH*$_3$)$_2$]$_3$}, 56.2 (2′-OCH_3), 56.5 (OCH_2OCH_3), 61.7 (C-1), 62.1 (C-3), 83.7 (C-2), 95.5 (OCH_2OCH_3), 109.9 (C-3′), 112.7 (C-5′), 116.6 (C-4′), 135.9 (C-1′), 151.5 (C-6′), 153.9 (C-2′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{21}H_{37}{}^{81}BrO_6SiNa$: 517.1417; found: 517.1410; *m*/*z* (M + Na^+) calcd for $C_{21}H_{37}{}^{79}BrO_6SiNa$: 515.1435; found: 515.1428.

(*R*)-2-[5-Bromo-3-methoxy-2-(methoxymethoxy)phenoxy]-3-[(triisopropylsilyl)oxy]propan-1-ol (39)

To a solution of ether **34** (0.79 g, 1.29 mmol) in a stirred suspension of CH_2Cl_2 (30 mL) and H_2O (30 mL) was added DDQ (0.44 g, 1.93 mmol) and the mixture stirred at r.t. for 18 h. The resulting solution was washed with portions of sat. aq $NaHCO_3$ until the washings were colourless. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (9:1 *n*-hexanes–EtOAc) to yield the title compound **39** (0.60 g, 95%) as a yellow oil; R_f = 0.89 (2:1 hexanes–EtOAc); $[\alpha]_D{}^{20}$ +34.89 (*c* 0.28, $CHCl_3$).

IR (film): 3451, 2923, 2865, 1715, 1606, 1589, 1490, 1462, 1416, 1382, 1257, 1227, 1107, 962, 881, 789, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.06 {18 H, d, *J* = 5.2 Hz, Si[CH(*CH*$_3$)$_2$]$_3$}, 1.08–1.11 {3 H, m, Si[*CH*(CH$_3$)$_2$]$_3$}, 3.05 (1 H, t, *J* = 6.6 Hz, OH), 3.56 (3 H, s, OCH_2OCH_3), 3.77 (1 H, dd, *J* = 10.4, 5.4 Hz, 1-H$_a$), 3.82 (1 H, dd, *J* = 10.4, 4.0 Hz, 1-H$_b$), 3.82 (3 H, s, 3′-OCH_3), 3.89 (1 H, dd, *J* = 10.4, 6.0 Hz, 3-H$_a$), 3.95 (1 H, dd, *J* = 10.4, 5.4 Hz, 3-H$_b$), 4.28–4.31 (1 H, m, 2-H), 5.02 (1 H, d, *J* = 6.0 Hz, O*CH*$_a$H$_b$CH$_3$), 5.14 (1 H, d, *J* = 6.0 Hz, OCH$_a$*H*$_b$CH$_3$), 6.72 (1 H, d, *J* = 2.0 Hz, 4′-H), 6.93 (1 H, d, *J* = 2.0 Hz, 6′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 {Si[*CH*(CH$_3$)$_2$]$_3$}, 17.9 {Si[CH(*CH*$_3$)$_2$]$_3$}, 56.2 (3′-OCH_3), 57.3 (OCH_2OCH_3), 62.2 (C-1), 62.8 (C-3), 82.4 (C-2), 98.7 (OCH_2OCH_3), 109.7 (C-4′), 113.6 (C-5′), 116.5 (C-5′), 135.7 (C-2′), 152.6 (C-1′), 153.9 (C-3′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{21}H_{37}{}^{81}BrO_6SiNa$: 517.1417; found: 517.1414; *m*/*z* (M + Na^+) calcd for $C_{21}H_{37}{}^{79}BrNO_6SiNa$: 515.1435; found: 515.1431.

{[(2*S*,3*R*)-7-Bromo-5-methoxy-3-(methoxymethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl]methoxy}triisopropylsilane (40a) with {[(2*S*,3*S*)-7-Bromo-5-methoxy-3-(methoxymethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl]methoxy}triisopropylsilane (40b) and (2*S*,3*S*)-6-Bromo-8-methoxy-3-{[(triisopropylsilyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (42a) with (2*R*,3*S*)-6-Bromo-8-methoxy-3-{[(triisopropylsilyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (42b)

To a stirred solution of alcohol **39** (0.29 g, 0.59 mmol) in CH_2Cl_2 (30 mL) was added DMP (0.37 g, 0.88 mmol) and the mixture stirred at r.t. for 2 h. Sat. aq $Na_2S_2O_5$ (20 mL) was added followed by sat. aq $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (19:1 then 14:1 hexanes–EtOAc) to yield the title compounds **40a** and **40b** (0.063 g, 24%) as an inseparable 3:1 mixture of diastereomers;

yellow oil. In a separate fraction, the title compounds **42a** and **42b** (0.13 g, 50%) were obtained as an inseparable 1:1 mixture of diastereomers; yellow oil; **40**: R_f = 0.95 (1:2 hexanes–EtOAc); **42**: R_f = 0.78 (1:2 hexanes–EtOAc).

40a

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.04 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.08–1.11 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.39 (3 H, s, OCH_2OCH_3), 3.83 (3 H, s, 8-OCH_3), 3.84 (1 H, dd, *J* = 10.4, 6.0 Hz, 9-H_a), 3.89 (1 H, dd, *J* = 10.4, 5.2 Hz, 9-H_b), 4.19–4.22 (1 H, m, 2-H), 4.65 (1 H, d, *J* = 6.2 Hz, $OCH_aH_bCH_3$), 5.08 (1 H, d, *J* = 6.2 Hz, $OCH_aH_bCH_3$), 5.62 (1 H, d, *J* = 2.4 Hz, 3-H), 6.62 (1 H, d, *J* = 2.2 Hz, 6-H), 6.70 (1 H, d, *J* = 2.2 Hz, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si(CH[CH_3)$_2$]$_3$}, 56.1 (OCH_2OCH_3), 56.4 (8-OCH_3), 61.5 (C-9), 75.4 (C-2), 89.7 (C-3), 93.6 (OCH_2OCH_3), 108.1 (C-6), 112.8 (C-8), 112.9 (C-7), 129.0 (C-4a), 143.5 (C-8a), 149.8 (C-8).

40b

IR (film): 2943, 2866, 1724, 1600, 1496, 1446, 1421, 1219, 1155, 1113, 1035, 987, 882, 811, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.07 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.08–1.11 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.37 (3 H, s, OCH_2OCH_3), 3.84 (3 H, s, 8-OCH_3), 3.98 (1 H, dd, *J* = 9.8, 8.0 Hz, 9-H_a), 4.04 (1 H, dd, *J* = 9.8, 5.4 Hz, 9-H_b), 4.12–4.15 (1 H, m, 2-H), 4.63 (1 H, d, *J* = 6.8 Hz, $OCH_aH_bCH_3$), 5.06 (1 H, d, *J* = 6.8 Hz, $OCH_aH_bCH_3$), 5.68 (1 H, d, *J* = 1.2 Hz, 3-H), 6.64 (1 H, d, *J* = 2.2 Hz, 6-H), 6.71 (1 H, d, *J* = 2.2 Hz, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.2 (OCH_2OCH_3), 56.4 (8-OCH_3), 61.8 (C-9), 74.9 (C-2), 89.9 (C-3), 93.5 (OCH_2OCH_3), 108.5 (C-6), 112.9 (C-7), 113.2 (C-8), 129.5 (C-4a), 143.5 (C-8a), 149.9 (C-8).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{21}H_{35}{}^{81}BrO_6SiNa$: 515.1261; found: 515.1256; *m*/*z* (M + Na^+) calcd for $C_{21}H_{35}{}^{79}BrO_6SiNa$: 513.1278, found: 513.1274.

42a

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.08 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.09–1.12 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.85 (3 H, s, 8-OCH_3), 4.03–4.08 (1 H, m, 3-H), 4.09 (2 H, d, *J* = 6.4 Hz, 9-CH_2), 4.26 (1 H, d, *J* = 5.6 Hz, OH), 5.70 (1 H, d, *J* = 5.4 Hz, 2-H), 6.65 (1 H, d, *J* = 2.2 Hz, 7-H), 6.72 (1 H, d, *J* = 2.2 Hz, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.3 (8-OCH_3), 62.0 (C-9), 73.8 (C-3), 89.8 (C-2), 108.6 (C-7), 112.8 (C-5), 113.6 (C-6), 129.5 (C-8a), 143.8 (C-4a), 149.8 (C-8).

42b

IR: (film): 3476, 2942, 2865, 2891, 1600, 1494, 1446, 1462, 1446, 1442, 1285, 1219, 1208, 1107, 1063, 960, 880, 802, 681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.04 {18 H, d, *J* = 5.2 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.09–1.13 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.38 (1 H, d, *J* = 5.6 Hz, OH), 3.85 (3 H, s, 8-OCH_3), 3.88 (1 H, dd, *J* = 10.4, 6.2 Hz, 9-H_a), 3.95 (1 H, dd, *J* = 10.4, 4.8 Hz, 9-H_b), 4.03–4.08 (1 H, m, 3-H), 5.59 (1 H, dd, *J* = 6.6, 3.6 Hz, 2-H), 6.63 (1 H, d, *J* = 2.2 Hz, 7-H), 6.73 (1 H, d, *J* = 2.0 Hz, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 {Si[CH(CH_3)$_2$]$_3$}, 17.8 {Si[CH(CH_3)$_2$]$_3$}, 56.4 (8-OCH_3), 61.6 (C-9), 75.6 (C-3), 89.3 (C-2), 108.2 (C-7), 112.9 (C-5), 113.7 (C-6), 129.4 (C-8a), 143.2 (C-4a), 149.5 (C-8).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{19}H_{31}{}^{81}BrO_5SiNa$: 471.0998; found: 471.1012; *m*/*z* (M + Na^+) calcd for $C_{19}H_{31}{}^{79}BrO_5SiNa$: 469.1016; found: 469.1028.

{[(2*S*)-6-Bromo-8-methoxy-3-(methoxymethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl]methoxy}triisopropylsilane (41a/b), (2*S*,3*S*)-7-Bromo-5-methoxy-3-{[(triisopropylsilyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (43a) and (2*R*,3*S*)-7-Bromo-5-methoxy-3-{[(triisopropylsilyl)oxy]methyl}-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (43b)

To a stirred solution of alcohol **21** (0.08 g, 0.16 mmol) in CH_2Cl_2 (15 mL) was added DMP (0.11 g, 0.24 mmol) and the mixture stirred at r.t. for 2 h. Sat. aq $Na_2S_2O_5$ (10 mL) was added followed by sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (14:1 then 9:1 hexanes–EtOAc) to yield the title compound **41a**/**b** (0.03 g, 37%) as a yellow oil, and in a separate fraction, the title compounds **43a** and **43b** (0.044 g, 62%) as an inseparable 5:3 mixture of diastereomers; yellow oil. **41**: R_f = 0.94 (1:2 hexanes–EtOAc); **43**: R_f = 0.88 (1:2 hexanes–EtOAc).

41a/b

IR: (film): 2943, 2866, 1725, 1600, 1497, 1463, 1420, 1285, 1217, 1123, 1036, 983, 946, 882, 812, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.04 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.05–1.08 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.39 (3 H, s, OCH_2OCH_3), 3.79 (1 H, dd, *J* = 10.0, 8.8 Hz, 9-H_a), 3.84 (3 H, s, 8-OCH_3), 3.99 (1 H, dd, *J* = 10.0, 4.6 Hz, 9-H_b), 4.29–4.33 (1 H, m, 2-H), 4.63 (1 H, d, *J* = 6.2 Hz, $OCH_aH_bCH_3$), 5.03 (1 H, d, *J* = 6.2 Hz, $OCH_aH_bCH_3$), 5.63 (1 H, d, *J* = 2.0 Hz, 3-H), 6.65 (1 H, d, *J* = 2.2 Hz, 6-H), 6.73 (1 H, d, *J* = 2.2 Hz, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.1 (OCH_2OCH_3), 56.3 (8-OCH_3), 61.2 (C-9), 74.8 (C-2), 89.6 (C-3), 93.4 (OCH_2OCH_3), 108.8 (C-6), 112.1 (C-7), 113.6 (C-8), 131.4 (C-8a), 141.6 (C-4a), 149.1 (C-8).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{21}H_{35}{}^{81}BrO_6SiNa$: 515.1261; found: 515.1264; *m*/*z* (M + Na^+) calcd for $C_{21}H_{35}{}^{79}BrO_6SiNa$: 513.1278; found: 513.1277.

43a

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.07 {18 H, d, *J* = 5.6 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.09–1.13 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.84 (3 H, s, 5-OCH_3), 4.11 (2 H, d, *J* = 5.4 Hz, 9-CH_2), 4.16–4.21 (1 H, m, 3-H), 4.34 (1 H, d, *J* = 7.6 Hz, OH), 5.59 (1 H, dd, *J* = 7.6, 1.1 Hz, 2-H), 6.65 (1 H, d, *J* = 2.2 Hz, 6-H), 6.76 (1 H, d, *J* = 2.2 Hz, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 {Si[CH(CH_3)$_2$]$_3$}, 17.9 {Si[CH(CH_3)$_2$]$_3$}, 56.4 (5-OCH_3), 61.7 (C-9), 73.1 (C-3), 90.4 (C-2), 108.6 (C-6), 113.0 (C-7), 113.6 (C-8), 131.4 (C-4a), 142.0 (C-8a), 149.2 (C-5).

43b

IR (film): 3481, 2943, 2866, 1600, 1498, 1463, 1446, 1421, 1320, 1285, 1222, 1098, 1062, 986, 882, 810, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.04 {18 H, d, *J* = 5.2 Hz, Si[CH(CH_3)$_2$]$_3$}, 1.09–1.13 {3 H, m, Si[CH(CH_3)$_2$]$_3$}, 3.62 (1 H, d, *J* = 6.4 Hz, OH), 3.82 (1 H, dd, *J* = 10.4, 7.6 Hz, 9-H_a), 3.84 (3 H, s, 5-OCH_3), 3.99 (1 H, dd, *J* = 10.4, 5.0 Hz, 9-H_b), 4.19–4.22 (1 H, m, 3-H), 5.57 (1 H, dd, *J* = 6.6, 3.6 Hz, 2-H), 6.65 (1 H, d, *J* = 2.0 Hz, 6-H), 6.74 (1 H, d, *J* = 2.0 Hz, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 {Si[$CH(CH_3)_2$]$_3$}, 17.8 {Si[$CH(CH_3)_2$]$_3$}, 56.4 (5-OCH_3), 61.5 (C-9), 74.9 (C-3), 89.4 (C-2), 108.7 (C-6), 112.7 (C-7), 113.7 (C-8), 130.8 (C-4a), 141.5 (C-8a), 149.1 (C-5).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{19}H_{31}{}^{81}BrO_5SiNa$: 471.0998; found: 471.0985; *m*/*z* (M + Na^+) calcd for $C_{19}H_{31}{}^{79}BrO_5SiNa$: 469.1016; found: 469.1003.

(2*R*,3*R*)-4-Bromo-2-(hydroxymethyl)-6-methoxy-3-(2′,4′,6′-trimethoxyphenyl)-2,3-dihydrobenzofuran-7-ol (45)

To a solution of hemiacetal **42** (0.038 g, 0.085 mmol) in MeCN (6 mL) was added 1,3,5-trimethoxybenzene (0.03 g, 0.169 mmol) and the resultant mixture stirred at r.t. for 5 min. TMSOTf (0.017 mL, 0.093 mmol) was then added and the resultant solution was stirred at r.t. for 1 h. The resulting solution was washed with H_2O (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (1:2 hexanes–EtOAc) to give the title compound **45** (0.031 g, 91%) as a brown oil; R_f = 0.44 (1:2 hexanes–EtOAc); $[\alpha]_D^{20}$ –79.79 (*c* 0.39, $CHCl_3$).

IR (film): 3459, 2938, 1736, 1592, 1496, 1454, 1356, 1226, 1205, 1152, 1116, 818, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.51 (3 H, s, 6′-OCH_3), 3.78 (1 H, dd, *J* = 12.2, 5.4 Hz, 8-H_a), 3.80 (3 H, s, 4′-OCH_3), 3.83 (3 H, s, 6-OCH_3), 3.86 (3 H, s, 2′-OCH_3), 3.88 (1 H, dd, *J* = 12.2, 3.2 Hz, 8-H_b), 4.89 (1 H, ddd, *J* = 8.0, 5.4, 3.2 Hz, 2-H), 4.98 (1 H, d, *J* = 8.0 Hz, 3-H), 6.08 (1 H, d, *J* = 2.0 Hz, 5′-H), 6.16 (1 H, d, *J* = 2.0 Hz, 3′-H), 6.43 (1 H, s, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.4 (C-3), 55.3 (4′-OCH_3), 55.9 (6′-OCH_3), 56.2 (2′-OCH_3), 56.5 (6-OCH_3), 64.6 (C-8), 90.6 (C-3′), 90.7 (C-2), 91.5 (C-5′), 106.8 (C-4), 108.7 (C-1′), 125.2 (C-3a), 129.0 (C-7), 147.2 (C-7a), 147.4 (C-6), 158.9 (C-2′), 159.8 (C-6′), 160.6 (C-4′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{19}H_{21}{}^{81}BrO_7Na$: 465.0345; found: 465.0342; *m*/*z* (M + Na^+) calcd for $C_{19}H_{21}{}^{79}BrO_7Na$: 463.0363, found: 463.0362.

(2*S*,3*S*)-7-Bromo-3-(hydroxymethyl)-5-methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (51a) and (2*R*,3*S*)-7-Bromo-3-(hydroxymethyl)-5-methoxy-2,3-dihydrobenzo[*b*][1,4]dioxin-2-ol (51b)

To a solution of hemiacetal **43** (0.025 g, 0.056 mmol) in MeCN (5 mL) was added 1,3,5-trimethoxybenzene (0.019 g, 0.11 mmol) and the resultant mixture stirred at r.t. for 5 min. $Zn(OTf)_2$ (0.010 g, 0.028 mmol) and TMSCl (0.011 mL, 0.084 mmol) were then added and the resultant solution was stirred at r.t. for 1.5 h. The resulting solution was washed with H_2O (5 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (1:2 hexanes–EtOAc) to give the title compound **51a** and **51b** (0.016 g, quant) as a 1:1 inseparable mixture of diastereomers; yellow oil; R_f = 0.32 (1:2 hexanes–EtOAc).

IR (film): 3473, 3339, 2940, 1738, 1601, 1498, 1421, 1285, 1209, 1127, 961, 812 cm^{-1}.

51a

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.82 (3 H, s, 5-OCH_3), 3.84–3.87 (2 H, m, 9-CH_2), 3.94–3.98 (1 H, m, 3-H), 5.52 (1 H, d, *J* = 1.0 Hz, 2-H), 6.66 (1 H, d, *J* = 2.2 Hz, 8-H), 6.71 (1 H, d, *J* = 2.2 Hz, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.0 (5-OCH_3), 62.0 (C-9), 77.3 (C-3), 90.2 (C-2), 109.6 (C-6), 113.7 (C-7), 114.1 (C-8), 133.7 (C-4a), 143.7 (C-8a), 150.7 (C-5).

51b

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.78–3.81 (2 H, m, 9-CH_2), 3.82 (3 H, s, 5-OCH_3), 3.84–3.87 (1 H, m, 3-H), 5.31 (1 H, d, *J* = 4.6 Hz, 2-H), 6.66 (1 H, d, *J* = 2.0 Hz, 8-H), 6.74 (1 H, d, *J* = 2.0 Hz, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.0 (5-OCH_3), 61.4 (C-9), 78.1 (C-3), 91.1 (C-2), 109.6 (C-6), 113.7 (C-7), 114.5 (C-8), 133.0 (C-4a), 144.3 (C-8a), 150.9 (C-5).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{10}H_{11}{}^{81}BrO_5Na$: 314.9663; found: 314.9666; *m*/*z* (M + Na^+): $C_{10}H_{11}{}^{79}BrO_5Na$: 312.9682; found: 312.9684.

[(2*S*,3*S*)-6-Bromo-8-methoxy-3-(2′,4′,6′-trimethoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl]methanol (50)

To a solution of hemiacetal **51** (0.025 g, 0.056 mmol) in MeCN (6 mL) was added 1,3,5-trimethoxybenzene (0.022 g, 0.128 mmol) and the resultant mixture stirred at r.t. for 5 min. TMSOTf (0.019 mL, 0.103 mmol) was then added and the resultant solution was stirred at r.t. for 1 h. The resulting solution was washed with H_2O (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (1:2 hexanes–EtOAc) to give the title compound **50** (0.030 g, 91%) as a yellow oil; R_f = 0.63 (1:2 hexanes–EtOAc); $[\alpha]_D^{20}$ –119.05 (*c* 0.09, $CHCl_3$).

IR (film): 3416, 2940, 1594, 1495, 1465, 1420, 1222, 1207, 1152, 1121, 812, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.63 (1 H, dd, *J* = 12.2, 5.0 Hz, 9-H_a), 3.79 (6 H, s, 2′-OCH_3, 6′-OCH_3), 3.82 (1 H, dd, *J* = 12.2, 3.0 Hz, 9-H_b), 3.83 (3 H, s, 4′-OCH_3), 3.87 (3 H, s, 8-OCH_3), 4.81 (1 H, ddd, *J* = 8.4, 5.0, 3.0 Hz, 2-H), 5.54 (1 H, d, *J* = 8.4 Hz, 3-H), 6.16 (2 H, s, 3′-H, 5′-H), 6.62 (1 H, d, *J* = 2.0 Hz, 7-H), 6.74 (1 H, d, *J* = 2.0 Hz, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4 (4′-OCH_3), 56.1 (2′-OCH_3, 6′-OCH_3), 56.3 (8-OCH_3), 62.3 (C-9), 70.1 (C-3), 75.5 (C-2), 91.4 (C-3′, 5′), 104.1 (C-1′), 107.4 (C-7), 112.1 (C-6), 113.2 (C-5), 132.7 (C-8a), 145.7 (C-4a), 149.5 (C-8), 160.2 (C-2′, C-6′), 162.4 (C-4′).

HRMS (ESI+): *m*/*z* (M + Na^+) calcd for $C_{19}H_{21}{}^{81}BrO_7Na$: 465.0345; found: 465.0331; *m*/*z* (M + Na^+) calcd for $C_{19}H_{21}{}^{79}BrO_7Na$: 463.0363; found: 463.0345.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588939.

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