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Total Synthesis of Virgatolide B via Exploitation of Intramolecular Hydrogen Bonding

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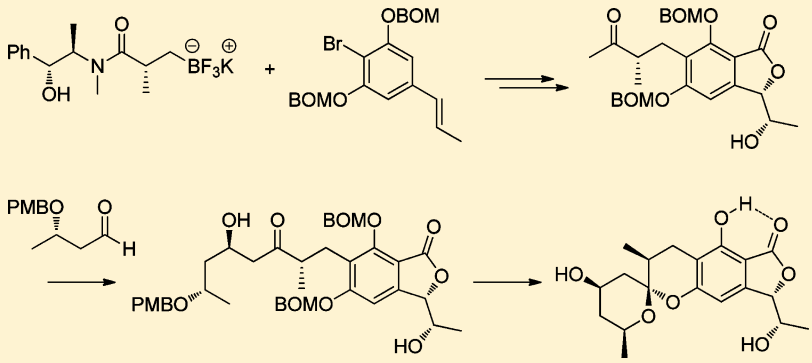
Supporting Information



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 spiroketalization 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 toward 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** were unambiguously secured by X-ray crystallography, and the absolute stereochemistry was 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 those of **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 among 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

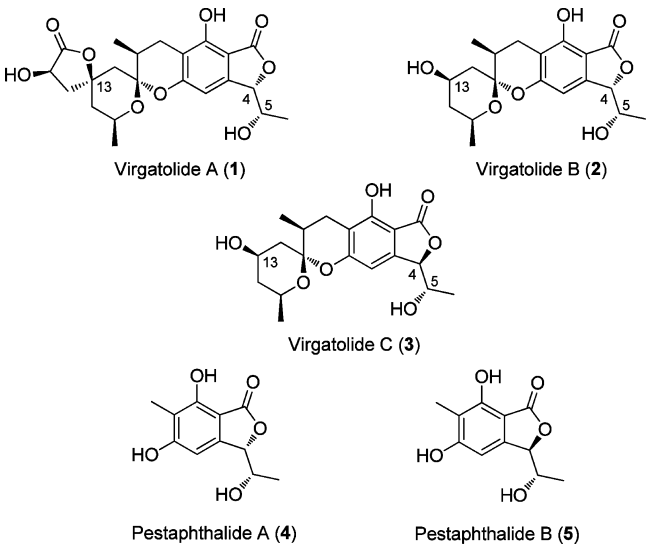


Figure 1. Virgatolides A–C (**1**–**3**) and pestaphthalides A (**4**) and B (**5**).

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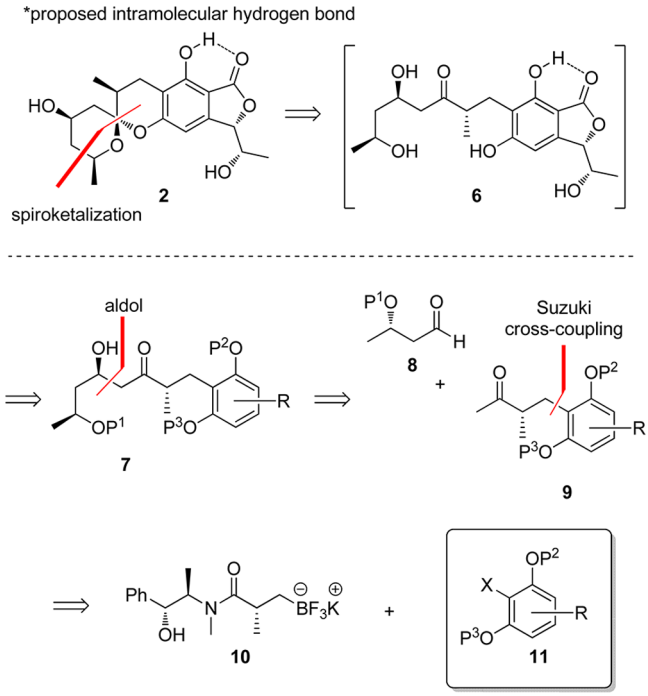
stereochemical assignments of **1**−**3** captured our interest, and we were thus inspired to develop a synthetic approach to the virgatolides. We herein report the full details of this synthetic undertaking.[9]

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)



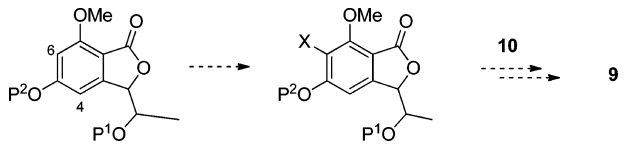
Retrosynthetically, disconnection of the spiroketal ring system in virgatolide B (**2**) provides ketone **6**. It was postulated that intramolecular hydrogen bonding between the phthalide carbonyl and the neighboring phenol would result in an energetic differential between **2** and the spiroketal regioisomer formed upon spirocyclization of the alternate phenolic oxygen. We hypothesized that this would favor formation of **2** via acid-catalyzed 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 carbonyl compounds.[21−24] Each of these methods suffer from nontrivial 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 focused 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).

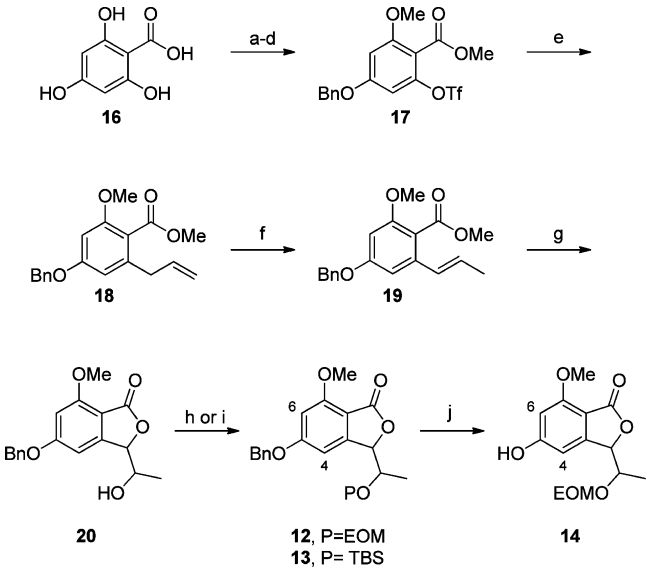
Scheme 2. Proposed Coupling of Halo-Phthalide 15 with 10



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 the 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

Scheme 3. Synthesis of Phthalides 12−14[a]



[a]Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, room temperature, 16 h, 56%; (b) BnBr, K_2CO_3, NaI, acetone, reflux, 3 h, 62%; (c) DIAD, PPh_3, MeOH, THF, room temperature, 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), room temperature, 16 h, 90%; (h) EOMCl, DIPEA, DMAP, CH_2Cl_2, room temperature, 48 h, quantitative; (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 4 h, quantitative; (j) H_2, Pd/C, MeOH, room temperature, 24 h, 89%.

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the triflate provided **17** in moderate yield over four steps. Stille cross-coupling with allyltributyltin and base-mediated isomerization to the thermodynamically favored (*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-catalyzed *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**.

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 on the basis of 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 toward halogenation at C-4 which would likely be difficult to overturn.

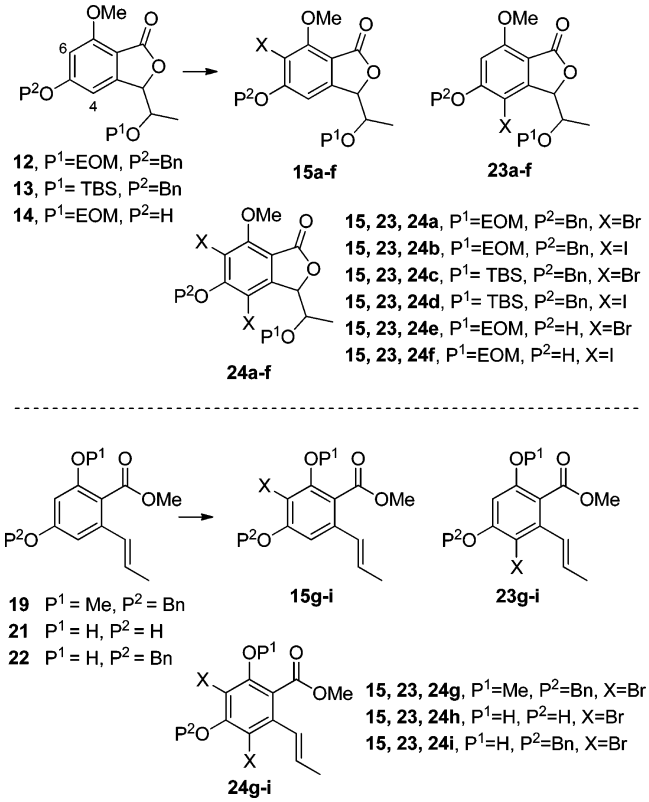
Use of a Simplified Halide Coupling Partner for the Suzuki Coupling. Following unsuccessful efforts to achieve the synthesis of compounds **15a**−**i**, we noted that use of a simpler, rotationally symmetric halide coupling partner would remove the requirement for regioselective functionalization of the aromatic nucleus. The required functionalization was envisioned to be possible via iridium-catalyzed CH borylation at a later stage.[12,30−32] We therefore now focused our attention 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 oxidized amide **30** were also obtained. Amide **30** coeluted 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).

Pleased with the successful union of **10** and **27**, we now sought to investigate the construction of the spiroketal core prior to further functionalization of the aromatic ring. Treatment of amide **29** with methyllithium generated methyl ketone **32** in good yield (Scheme 4).[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 the union of ketone **32** with aldehyde **33** provided aldol products only with moderate diastereoselectivity (dr ≈ 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

Table 1. Attempted Synthesis of 15a−i



			yield (%)		
entry	substrate	method[a]	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	three-component mixture		

[a]Methods: (A) NBS, CH_2Cl_2, 0 °C to room temperature; (B) I_2, AgO_2CF_3, CH_2Cl_2, 0 °C to room temperature. [b]The remaining material was isolated as an inseparable mixture of **21** and monobrominated species.

yield. The stereochemistry of the newly generated chiral center was not assigned at this stage, since cyclization would allow assignment of the configuration by NOESY analysis. With the carbon framework required for the spiroketal core in place, the key spirocyclization process was now investigated to ascertain whether the desired spiroketalization would be possible on a more advanced intermediate.

The PMB group in aldol product **34** was removed first, allowing formation of a cyclic acetal that would hopefully minimize the propensity for acid-catalyzed 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 spirocyclization of **35** and TIPS ether **36** (Scheme 5). Unfortunately, treatment of **35** and **36** with

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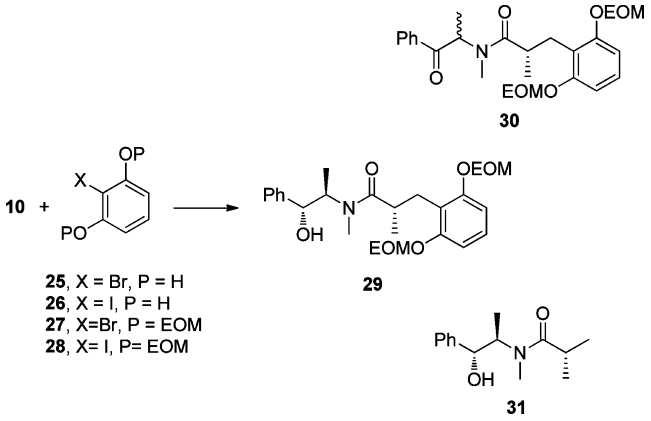
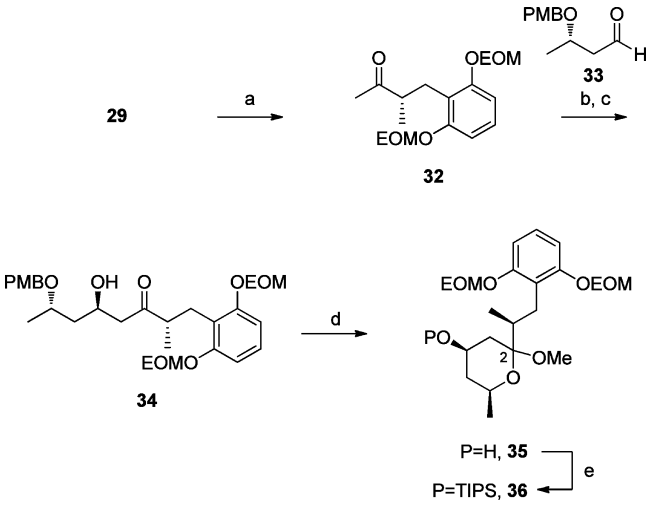
Table 2. Suzuki Cross-Coupling of 10 and Aryl Halides 25–28



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		

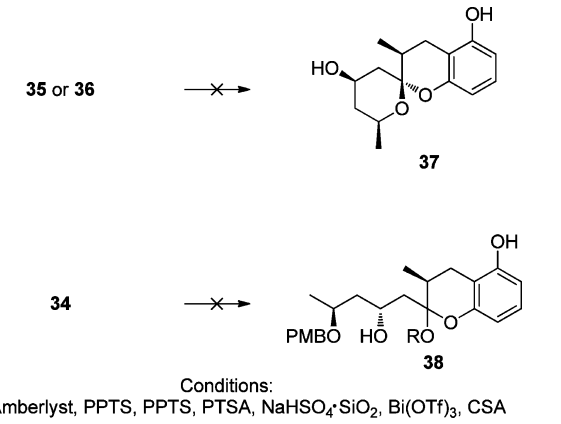
Scheme 4. Synthesis of Acetals 35 and 36[a]



[a]Reagents and conditions: (a) MeLi, Et_2O, −78 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 addition of silyl enol ether, 1.5 h, 82% over two steps; (d) H_2, $Pd(OH)_2/C$, MeOH, room temperature, 1 h, 90%; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 40 min, 75%.

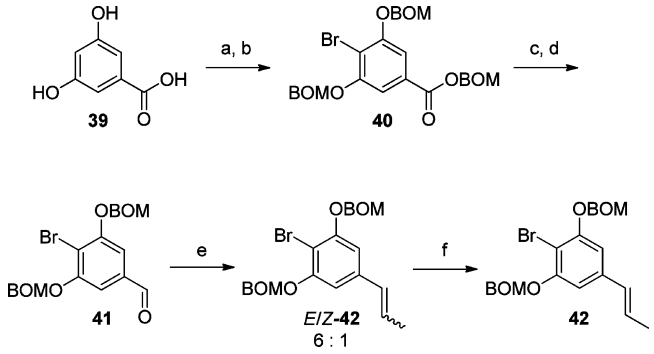
$NaHSO_4{\cdot}SiO_2$,[39] PPTS,[40] HCl, CSA, Amberlyst-15,[41] or $Bi(OTf)_3$[42] all failed to effect formation of spiroketal **37**. NMR analysis revealed the formation of complex product mixtures containing olefinic resonances, presumably resulting from acid-catalyzed elimination. Reactions in methanol generated methylated byproducts likely formed via elimination and subsequent addition of a solvent molecule. Since 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-catalyzed 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[a]



[a]Reagents and conditions: (a) Br_2, 20% aqueous HCl, reflux, 2 h, 99%; (b) BOMCl, DIPEA, CH_2Cl_2, room temperature, 16 h, 87%: (c) DIBAL-H, CH_2Cl_2, −78 to 0 °C, 20 min, 95%; (d) $SO_3{\cdot}py$, DIPEA, DMSO, 0 °C, 15 min, quantitative; (e) ethyltriphenylphosphonium iodide, KO^tBu, 18-crown-6, CH_2Cl_2, room temperature, 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 a smooth Wittig reaction with ethyltriphenylphosphonium iodide, affording (*E*/*Z*)-alkene **42** as an inseparable 6/1 mixture of

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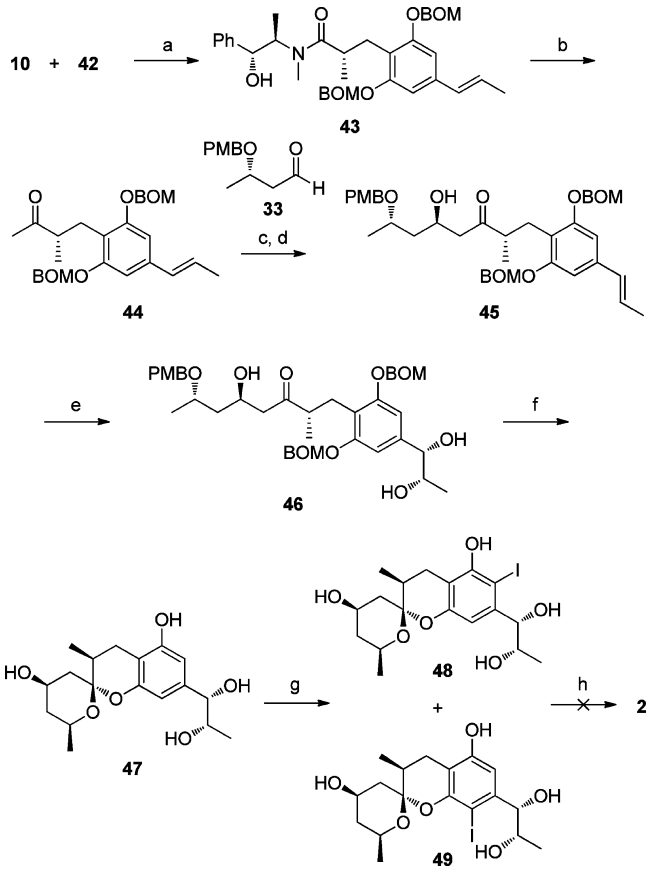
isomers. Isomerization to **42** was readily achieved by subjecting the mixture to ruthenium(II) catalysis in refluxing toluene.[45]

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 a 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.

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



[a]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 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 addition of 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, room temperature, 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 room temperature, 3 or 24 h.

Pleasingly, the BOM groups were readily removed by hydrogenolysis, allowing successful formation of spiroketal **47** following global deprotection. Now that the spiroketal core of the virgatolide skeleton was successfully formed, all that remained was to complete the installation of the phthalide moiety. Iodination of **47** was nonselective, 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-catalyzed equilibration. Disappointingly, however, attempted carbonylation of **48**/**49** to give **2** resulted only in protodehalogenation, regenerating spiroketal **47** and 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, reordering the sequence of synthetic events. Critically, it was noted that carbonylation of the rotationally symmetric aromatic nucleus prior to spiroketalization would avoid the requirement to effect regioselective functionalization 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 spiroketalization.

We therefore focused our attention next on the 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 spirocyclization precursor **55**.

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 monoiodination of the aromatic ring afforded iodide **51**, with only traces of the easily separable diiodinated product being formed. The formation of a single diastereoisomer in the asymmetric dihydroxylation was confirmed by subjecting a sample of **44** to nonselective 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 center. Carbonylation of homochiral iodide **51** with concomitant intramolecular alkoxylation[48−53] afforded phthalide **52** in 75% yield. Gratifyingly, the cyclization 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 spirocyclization step. Spectroscopic data (^1H 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

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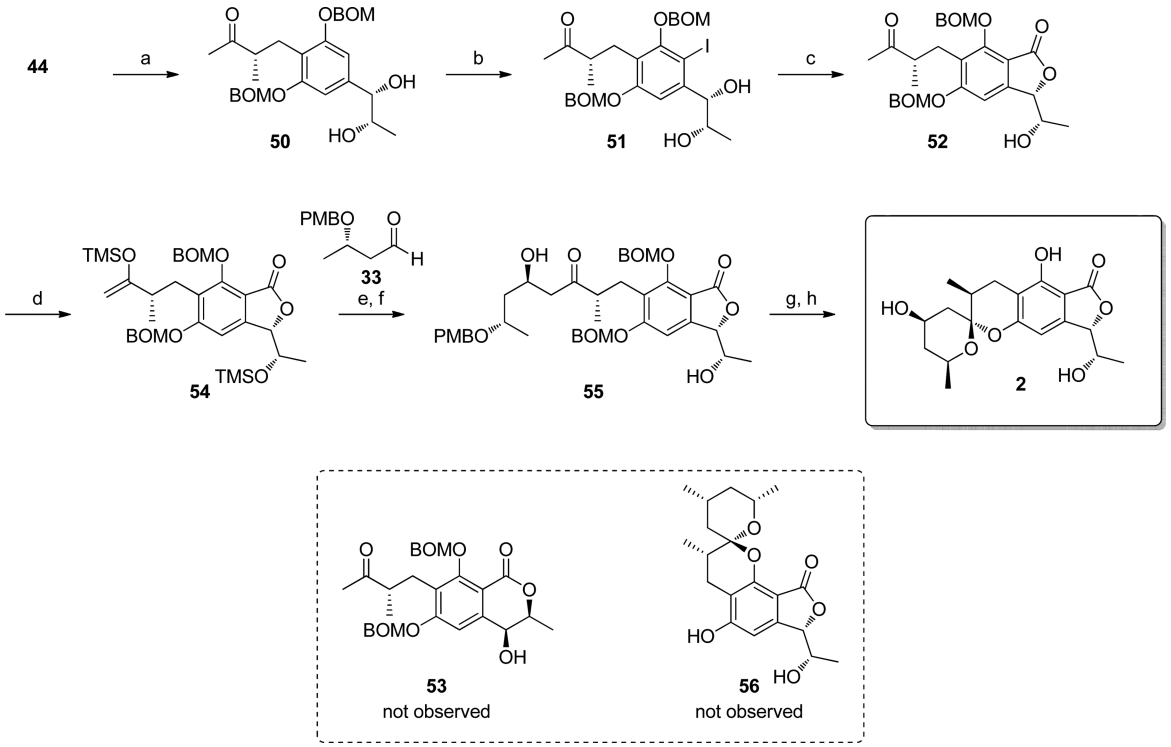
Scheme 8. Synthesis of Virgatolide B (2)[a]



[a]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 room temperature, 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) saturated aqueous K_2CO_3 (5 drops), MeOH, room temperature, 30 min, 65% over three steps; (g) H_2, Pd/C, EtOAc, room temperature, 3 h; (h) CSA, CH_2Cl_2, 16 h, 55% over two steps.

of the optical rotation values ($[\alpha]_D^{25}$ = +19.1° (*c* 0.25 in MeOH); lit. $[\alpha]_D^{25}$ = +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-step 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 the 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 asterisk. ^{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 thin films 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 warmed to room temperature, stirred for 2 h, and quenched with saturated aqueous 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 colorless solid: mp 116–117 °C (lit.[54] mp 106 °C); ^{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=

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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 those 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) were 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 cooled to room temperature. THF (40 mL) and ^{t}BuOK (1.5 g, 13 mmol) were added, and the reaction mixture was 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 aqueous NH_3 (25% v/v, 25 mL), aqueous HCl (1 M, 25 mL), and saturated aqueous $NaHCO_3$ (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 colorless 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+) calcd for $C_{19}H_{20}O_4$ $[M + Na]^+$ 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) were 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 was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (30 mL), the layers were separated, and the organic layer was washed successively with saturated aqueous $Na_2S_2O_4$ (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: mp 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+) calcd for $C_{18}H_{18}O_5$ $[M + Na]^+$ 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(3*H*)-one (**20**; 250 mg, 0.80 mmol) and DIPEA (1.1 mL, 6.4 mmol) in THF (7 mL) at 0 °C was added EOMCl (0.75 mL, 8.0 mmol). The resultant solution was warmed to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (7 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were 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 colorless 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+) calcd for $C_{21}H_{24}O_6$ $[M + Na]^+$ 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 were 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 saturated aqueous $NaHCO_3$ (2 mL). After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was 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 colorless 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+) calcd for $C_{24}H_{32}O_5Si$ $[M + Na]^+$ 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(3*H*)-one (**12**; 110 mg, 0.29 mmol) in MeOH (6 mL) was added Pd/C (11 mg, 10% w/w), and the mixture was 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 colorless solid: mp 134−137 °C; ^{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+) calcd for $C_{14}H_{18}O_6$ $[M + Na]^+$ 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 (1 M in CH_2Cl_2, 1.6 mL) over 20 min. The solution was stirred at −78 °C for a further 20 min and then quenched by the addition of H_2O (1 mL). After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was 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%): mp 117−119 °C; ^{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+) calcd for $C_{11}H_{12}O_4$ $[M + Na]^+$ 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

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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 cooled to room temperature, H_2O (2.0 mL) was added, and the resultant solution was 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 colorless solid: mp 82−85 °C; ^{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+) calcd for $C_{18}H_{18}O_4$ $[M + Na]^+$ 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(3*H*)-one (**12**; 60 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added *N*-bromosuccinimide (32 mg, 0.18 mmol) in three portions over 30 min. The resultant mixture was warmed 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 colorless solid: mp 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+) calcd for $C_{21}H_{23}O_6Br$ $[M + Na]^+$ 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(3*H*)-one (**12**; 60 mg, 0.16 mmol) and silver trifluoroacetate (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 and then filtered through Celite. Saturated aqueous $Na_2S_2O_3$ (1 mL) and NaOH (1 M, 1 mL) were added to the filtrate with stirring. The layers were separated, and the aqueous layer was 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 colorless solid: mp 146−148 °C; ^{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+) calcd for $C_{21}H_{23}O_6I$ $[M + Na]^+$ 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 warmed to room temperature and stirred for 18 h. The reaction was quenched by the addition of H_2O (1 mL), and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were 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 colorless solid: mp 150.3−153.7 °C; ^{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+) calcd for $BrC_{24}H_{31}O_5Si$ $[M + Na]^+$ 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 saturated aqueous $Na_2S_2O_3$ (0.5 mL). The layers were separated, and the aqueous layer was 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 colorless solid: mp 170.0−173.0 °C; ^{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+) calcd for $C_{24}H_{31}IO_5Si$ $[M + H]^+$ 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 °C was added *N*-bromosuccinimide (21 mg, 0.12 mmol) in three portions over 30 min. The reaction mixture was warmed 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 colorless solids.

*4-Bromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one (**23e**):* contains 14% starting material and *N*-hydroxysuccinimide by NMR: mp 145−150 °C; ^{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+) calcd for $BrC_{14}H_{17}O_6$ $[M + Na]^+$ 383.0101, found 383.0102.

*4,6-Dibromo-3-(1-(ethoxymethoxy)ethyl)-5-hydroxy-7-methoxyisobenzofuran-1(3H)-one (**24e**):* mp 118−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, d, *J* = 1.6 Hz, CH), 4.69 (1H, qd, *J* = 6.4,

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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+) calcd for $Br_2C_{14}H_{16}O_6$ [M + Na]$^+$ 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(3*H*)-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. Saturated aqueous $Na_2S_2O_3$ (1.0 mL) was added to the filtrate. The layers were separated, the aqueous layer was further extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic extracts were 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 colorless solids.

*3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-4-iodo-7-methoxyisobenzofuran-1(3H)-one (**23f**):* contains 15% starting material by NMR; mp 149−151 °C (some trace material did not melt until 169 °C); ^{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+) calcd for $C_{14}H_{17}IO_6$ [M + Na]$^+$ 430.9962, found 430.9966.

*3-(1-(Ethoxymethoxy)ethyl)-5-hydroxy-4,6-diiodo-7-methoxyisobenzofuran-1(3H)-one (**24f**):* mp 119−121 °C; ^{1}H 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+) calcd for $C_{14}H_{16}I_2O_6$ [M + Na]$^+$ 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 warmed to room temperature and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 5/1) afforded the title compound **23g** as a colorless solid: mp 89−91 °C; ^{1}H 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+) calcd for $BrC_{19}H_{19}O_4$ [M + Na]$^+$ 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 colorless solid: mp 93−96 °C; ^{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+) calcd for $Br_2C_{11}H_{10}O_4$ [M + Na]$^+$ 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 chloromethyl ethyl ether (3 mL, 32 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture 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 colorless 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+) calcd for $BrC_{12}H_{17}O_4$ [M + Na]$^+$ 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 chloromethyl ethyl ether (0.91 mL, 9.8 mmol). The reaction mixture was warmed 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 **28** (1.0 g, 2.9 mmol, 89%) as a colorless 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, 771 cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_{17}IO_4$ [M + Na]$^+$ 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 cooled to room temperature. A solution of pH 7 buffer (2 mL), prepared from $NaHPO_4$ (1.7 g) and NaH_2PO_4·$2H_2O$ (1.2 g) in H_2O (50 mL), was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were 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 colorless 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,

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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+) calcd for $C_{26}H_{37}NO_6$ [M + Na]$^+$ 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 was stirred for a further 15 min 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), and the combined organic extracts were 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 colorless 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+) calcd for $C_{17}H_{26}O_5$ [M + Na]$^+$ 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 min and then quenched by addition of saturated aqueous NH_4Cl (3 mL). The layers were separated, and the aqueous layer was 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 was stirred for 2 min. 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 min and quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was 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 colorless 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+) calcd for $C_{29}H_{42}NaO_8$ [M + Na]$^+$ 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 colorless 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+) calcd for $C_{22}H_{36}NaO_7$ [M + Na]$^+$ 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 and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was further extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (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 colorless 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+) calcd for $C_{31}H_{56}NaO_7Si$ [M + Na]$^+$ 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 min and then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4

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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 was stirred for 2 min. 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 saturated aqueous $NaHCO_3$ (1 mL). After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was 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 colorless 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 ($CH_{2\times}$ 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+) calcd for $C_{42}H_{50}NaO_8$ $[M + Na]^+$ 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. Saturated aqueous Na_2SO_3 (1 mL) was added, and the reaction mixture was stirred for a further 30 min at room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were 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 colorless 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+) calcd for $C_{42}H_{52}NaO_{10}$ $[M + Na]^+$ 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 colorless 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+) calcd for $C_{18}H_{26}NaO_6$ $[M + Na]^+$ 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 was stirred for 24 h. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and warmed to room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were 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+) calcd for $C_{18}H_{25}INaO_6$ $[M + Na]^+$ 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 was stirred at room temperature for 18 h. Saturated aqueous $Na_2S_2O_3$ (1 mL) was added and the reaction mixture was stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were 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 colorless 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+) calcd for $C_{30}H_{36}NaO_7$ $[M + Na]^+$ 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 min. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ (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 colorless oil: $[\alpha]_D^{25}$ = +16.7° (*c* 0.27 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ

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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+) calcd for $C_{30}H_{35}IKO_7$ $[M+K]^+$ 673.1059, found 673.1063.

(*S*)-5,7-Bis((benzyloxy)methoxy)-3-((*S*)-1-hydroxyethyl)-6-((*S*)-2-methyl-3-oxobutyl)isobenzofuran-1(3*H*)-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 to 100 °C for 24 h. The reaction mixture was cooled to room temperature, and brine (3 mL) was added. The layers were separated, and the aqueous layer was 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+) calcd for $C_{31}H_{34}NaO_8$ $[M + Na]^+$ 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 min and then quenched with saturated aqueous NH_4Cl (1 mL). The layers were separated, and the aqueous layer was 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 the 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 was stirred for 3 min. A solution of the crude silyl enol ether **54** in CH_2Cl_2 (1 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 1.5 h. Saturated aqueous $NaHCO_3$ (1 mL) was added, and the reaction mixture was warmed to room temperature. The layers were separated, and the aqueous layer was 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), saturated aqueous K_2CO_3 (0.1 mL) was added, and the reaction mixture stirred at room temperature for 15 min. $MgSO_4$ 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 three steps) as a colorless 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+) calcd for $C_{43}H_{50}NaO_{11}$ $[M + Na]^+$ 765.3245, found 765.3260.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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