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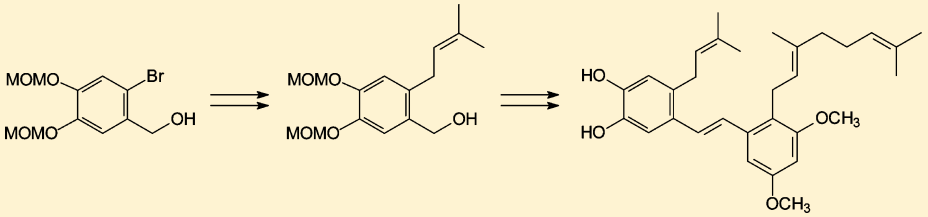
Selective Prenylation of Protected Phenols for Synthesis of Pawhuskin A Analogues

Kevyn D. Gardner and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294, United States

Supporting Information



ABSTRACT: Pawhuskin A is a prenylated stilbene that functions as an antagonist of the kappa opioid receptor. Analogues of this natural product bearing different placements of the prenyl group in the A-ring have shown selectivity for either the kappa or the delta receptors subtypes. This differential activity has drawn attention to regiospecific preparation of the C-2, C-5, and C-6 prenylated A-ring regioisomers. Through halogen metal exchange, advanced intermediates representing each of these regioisomers have been prepared, and the new C-6 intermediate has been converted to a new analogue of the natural stilbene.

INTRODUCTION

The linear intermediates of isoprenoid metabolism often are appended to aromatic compounds to generate meroterpenoids,[1] products of mixed biogenetic origin. Various enzymes mediate these additions, but in general they display exquisite regiocontrol. As just one example, biosynthetic studies have indicated that farnesylation of 3,4-dihydroxybenzoic acid occurs at C-5 in the basidiomycete *Chroogomphus rutilus* to afford compound **1**, while geranylgeranylation occurs at C-2 in *Suillus bovines* to give compound **2** (Figure 1).[2] It can be challenging for the synthetic chemist to accomplish this regiocontrol, and with unsymmetrical stilbenes where both aromatic rings can be viewed as *C*-prenylated phenols the challenges only grow. Of particular interest to us, both the schweinfurthins[3] (e.g., **3** and **4**) and the pawhuskins[4] (e.g., **5**) display different oxygenation patterns on the aromatic core and both rings bear isoprenoid substituents.

The prominence of prenylated compounds in nature, together with the significant biological activity that they often display, has generated substantial interest in development of applicable synthetic methodology. Even so, selective addition of a prenyl chain in a complicated system still can prove to be difficult.[5] Approaches that have been explored include Claisen rearrangements,[6−8] olefin cross metathesis,[8,9] and Suzuki reactions.[10,11] All of these strategies have limitations and may require a specific adjacent functional group, regiocontrolled installation of a precursor such as an allyl group, and/or a particular skeletal motif.

During the course of our syntheses of schweinfurthin A[12] and B,[13] we relied upon a halogen metal exchange reaction for introduction of the geranyl chain used to generate the A- and B-rings, while directed ortho metalation (DoM) was employed to introduce the isoprenoid substituent on a precursor to the D-ring.[14] More recently, we have become interested in the pawhuskins, which have different placements of the isoprenoid substituent in both the catechol and the resorcinol rings and which were reported to demonstrate activity toward an opioid

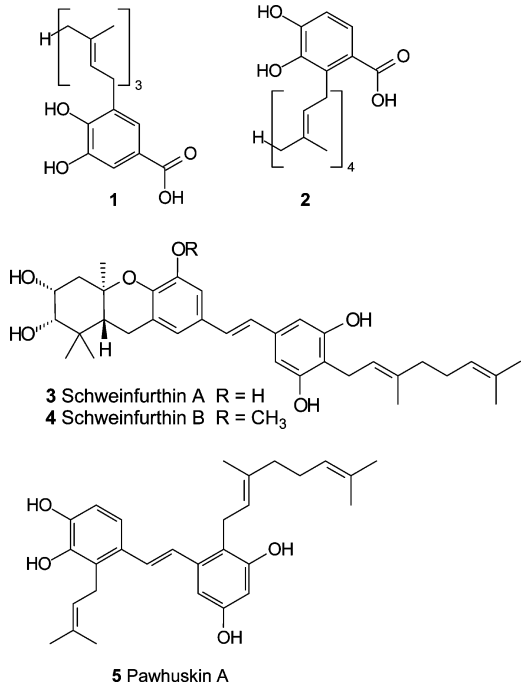


Figure 1. Selected examples of *C*-prenylated phenols.

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receptor in an *ex vivo* tissue preparation.[4] The synthesis of pawhuskin A[15] and some methylated analogues[16,17] allowed more detailed bioassays and identified these compounds as functional antagonists in cell lines transfected with individual human receptor subtypes. However, while both the natural product **5** and the analogue **6** (Figure 2) have greater affinity

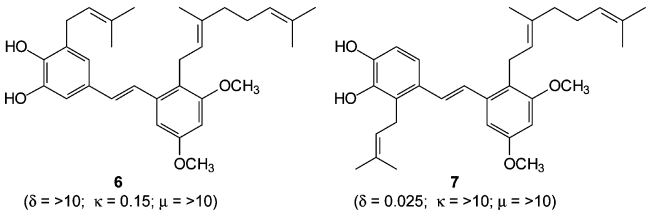
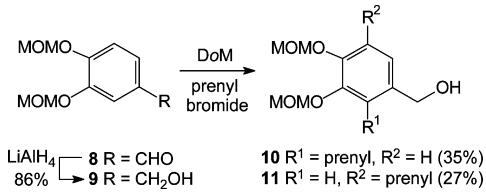


Figure 2. Pawhuskin analogues with apparent affinity as antagonists at the opioid receptors (μM).[16,17]

for the kappa opioid receptor, the isomeric compound **7** recently has been found to be a selective antagonist of the delta opioid receptor.[17] Given the growing interest in non-nitrogenous compounds as opioid receptor ligands[18−20] and the observation that simple modification of the prenyl group placement in compounds **6** and **7** significantly altered the opioid receptor selectivity, strategies that could deliver prenylated aromatic compounds with regiospecificity became a priority.

Analogues **6** and **7** originally were synthesized from MOM-protected 3,4-dihydroxybenzaldehyde (**8**) utilizing a DoM approach (Scheme 1). After reduction of the aldehyde to the

Scheme 1. Prenylation of a Benzyl Alcohol via Directed Ortho Metalation[17,21]

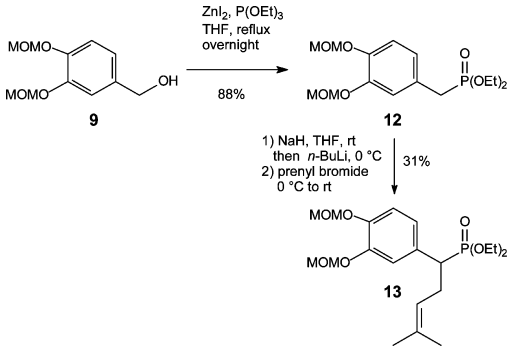


benzyl alcohol, metalation and reaction with prenyl bromide gave both the 2- and the 5-substituted isomers (**10** and **11**) in low to modest yields under all of the conditions examined.[17,21] While this strategy allowed synthesis of several target compounds, formation of both isomers limits the yield of either and complete separation of the alcohols **10** and **11** has become more critical given the different biological activity of the stilbenes prepared from them. Furthermore, observation of significant activity in both the 2- and the 5-substituted compounds piqued our interest in preparation of compounds in the C-6 prenylated series, the remaining A-ring regioisomer. Herein is described the exploration of alternative methods to the C-2 and C-5 isomers as well as a parallel approach for preparation of the C-6-substituted compounds. Synthesis of the C-6 alcohol ultimately allowed preparation of a new pawhuskin regioisomer which will be examined for its opioid-like activity.

RESULTS AND DISCUSSION

Because a DoM approach with alcohol **9** did allow prenylation, albeit affording a mixture of regioisomers, the feasibility of a dianion strategy with a different substrate was examined. First, the benzylic alcohol **9** was treated with zinc iodide and triethyl phosphite,[22,23] which gave phosphonate **12** in a single step with a yield comparable to the more traditional Arbuzov sequence[24] (Scheme 2). Upon exposure of phosphonate **12** to NaH,

Scheme 2. Synthesis and Prenylation of Phosphonate 12

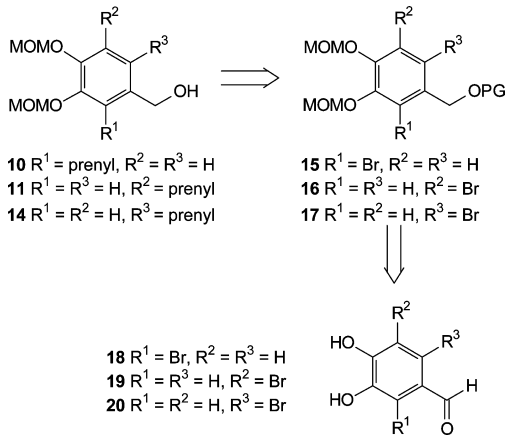


followed by treatment with *n*-BuLi,[25] reaction with prenyl bromide provided the undesired isomer **13** as the major product (31%), along with small amounts of both the C-2 and the C-5 prenylated compounds. Use of LiHMDS instead of NaH did not provide a better outcome. Instead, based on the ^{31}P NMR spectrum of the reaction mixture it was clear that the major product again was the result of prenylation at the α-position.

Numerous aromatic alkylations have been accomplished through halogenated precursors,[26−28] and so the next approach was to consider formation of the three prenylated regiosomers through the corresponding bromide intermediates. While cross-coupling reactions might allow introduction of the prenyl substituent,[29−31] an sp^2−sp^3 coupling can be challenging and a set of conditions more parallel to the DoM route could be based on halogen metal exchange reactions. From either perspective, a retrosynthetic analysis of the three alcohols **10**, **11**, and **14** suggested that they could arise from protected intermediates **15**−**17**, which in turn might be derived from the three commercially available bromobenzaldehydes (**18**−**20**, Scheme 3). All three of the bromides **18**,[32,33] **19**,[26,34] and **20**[35,36] also can be readily prepared.

In the synthetic direction, the bromides **18**−**20** were treated with MOMCl, followed by aldehyde reduction under standard conditions (Scheme 4) to provide the desired benzylic alcohol intermediates **21**−**23** in high yields.

Scheme 3. Alternative Strategy Parallel to a DoM Sequence



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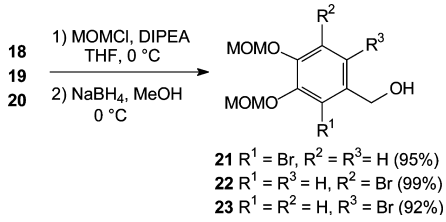
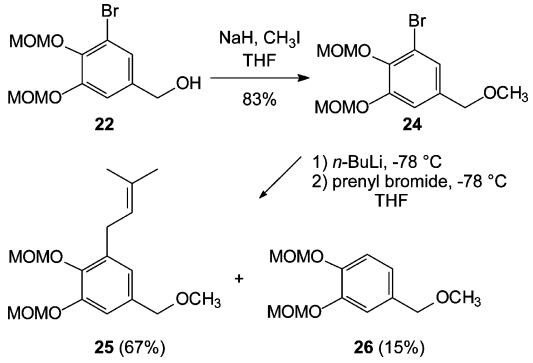
Scheme 4. Synthesis of Aryl Bromide Isomers 21−23



Compound **22** was readily available from the relatively inexpensive 5-bromovanillin, and therefore, this isomer was used to explore halogen metal exchange conditions[37] in the presence of different alcohol protecting groups. A benzyl methyl ether (**24**) was utilized first because that group has proven so useful in syntheses of schweinfurthins[13,38] and other hexahydroxanthenes[39] (Scheme 5). With the methyl ether **24** it

Scheme 5. Solvent Impact on Prenylation of the 5-Bromo Isomer

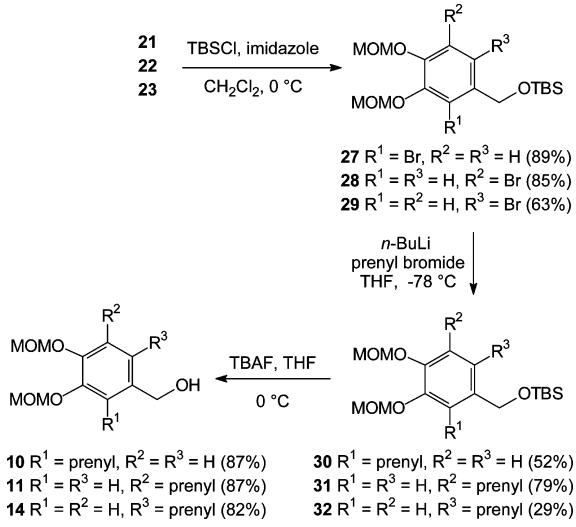


was determined that treatment with *n*-BuLi followed by prenyl bromide in Et_2O provided the desired prenyl compound **25** but in only modest yield, while the debrominated starting material **26** was the major product. Fortunately simple modification of the reaction conditions to use of THF as the solvent gave compound **25** in 67% yield and the undesired **26** in only 15% yield.

It would be attractive to take advantage of the small methyl group as the protecting group, and this strategy was successful in our earlier work when there were no prenyl groups present at the time of deprotection.[13,38,39] However, in this case, attempted use of DDQ to cleave the benzyl methyl ether did not give any significant amount of the desired aldehyde under standard conditions.[13,40,41] Therefore, other protecting groups were explored.

The halogen metal exchange protocol was successfully conducted on a TBS-protected 5-bromovanillin derivative, followed by alkylation with geranyl bromide, during synthesis of schweinfurthin intermediates.[26] Therefore, one might assume that it would be reasonable to employ a TBS group with all three isomeric aryl bromides (Scheme 6). Introduction of the TBS group was accomplished under standard conditions in all three cases, providing the desired silyl compounds **27−29** in acceptable yields. Upon treatment with *n*-BuLi and prenyl bromide, the C-5 isomer was alkylated smoothly while the C-2 and C-6 isomers gave more modest yields. Nevertheless, all three isomers were prenylated regiospecifically, and deprotection of the silyl compounds was possible in high yield. The overall sequence provided the desired alcohol isomers **10**, **11**,

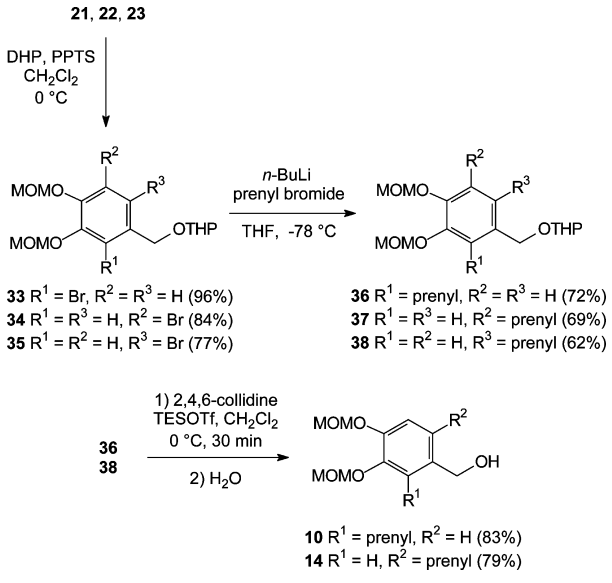
Scheme 6. Halogen Metal Exchange Sequence with TBS Ethers 27−29



and **14** in overall yields of 38%, 58%, and 14%, respectively, over 5 steps. Thus, this reaction sequence gave the known products **10** and **11** in yields higher than those obtained from the DoM sequence (vide supra),[15,17,21] avoids the need for purification of the isomers, and also gives access to the new C-6 isomer **14** in a modest overall yield.

In the series of TBS ethers, there may be several reasons why the C-2 and C-6 isomers are lower yielding in the alkylation reaction than the corresponding C-5 isomer, including steric effects and the possibility of a retro-Brook rearrangement as a competing side reaction.[42] To avoid the possibility of a silyl rearrangement, use of a parallel sequence with THP ethers was examined (Scheme 7). Protection to the corresponding THP intermediates **33−35** proved to be straightforward. Treatment of the C-2, C-5, and C-6 isomers with *n*-BuLi and prenyl bromide gave the desired products **36−38** in reasonable yields. Selective hydrolysis of the THP acetal in the presence of two MOM acetals proved somewhat challenging. Attempted

Scheme 7. Halogen Metal Exchange Reactions with THP Ethers 33−35



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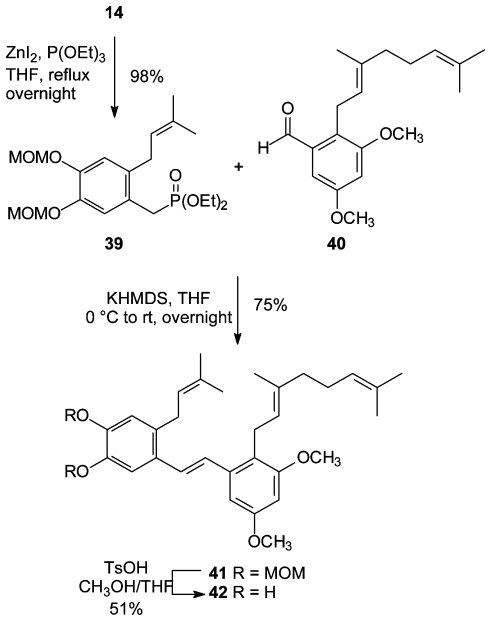
hydrolysis by treatment with TsOH in methanol gave the desired products **10** and **14** in low yields, accompanied by products of MOM hydrolysis. Fortunately, reaction with collidine and TESOTf cleanly afforded the benzylic alcohols **10** (83%) and **14** (79%) while preserving the MOM-protected phenols.[43] Thus, the overall yields of the known C-2 compound **10** and new C-6 isomer **14** were 55% and 35%, respectively, for the 5-step sequences from the corresponding benzaldehydes **18** and **20**. The C-5 isomer already had been obtained in a comparable yield (58%) via the TBS-protected sequence, so the THP derivative was not carried through the hydrolysis step.

Through the halogen metal exchange approach, the formation of the desired alcohol **14** was accomplished in a reasonable yield and in sufficient quantity to complete the synthesis of the new pawhuskin analogue **42** (Scheme 8).

Scheme 8. Preparation of a C-6 Analogue of Pawhuskin A



Treatment of alcohol **14** with triethyl phosphite and zinc iodide[22,23] gave the desired phosphonate **39** in excellent yield. Condensation of phosphonate **38** with the known aldehyde **40**[15−17,21] under standard HWE conditions provided the stilbene **41** in 75% yield, with no apparent steric impact of the prenyl group ortho to the phosphonate. Final hydrolysis of the MOM protecting groups afforded the new pawhuskin analogue **42**.

Full characterization of the biological activity of compound **42** has not yet been completed. However, preliminary studies with a FLIPR assay of Ca^{2+} mobilization[44] in kappa opioid receptor expressing CHO cells suggest that this compound has modest activity as either an antagonist or a negative allosteric modulator when compared to the known kappa agonist U50,488.[45] A more thorough profile of its activity and selectivity for the various opioid receptors is underway and will be reported in due course.

In conclusion, all three prenylated regioisomers of the 3,4-dihydroxybenzaldehyde derivatives were synthesized through a halogen metal exchange sequence. Both the C-2 and the C-5 regioisomers now have been formed selectively and in higher yields than the original DoM route, despite the additional steps. The halogen metal exchange strategy in the presence of a TBS ether works best for preparation of the C-5 isomer, whereas the C-2 and C-6 isomers are best prepared via intermediates with a THP protecting group. The C-6 regioisomer has been prepared for the first time and used to generate the new pawhuskin analogue **42**. This stilbene has been synthesized as a single isomer in 13% yield over 8 steps through the halogen metal exchange approach. With the new C-6 analogue **42** now in hand, additional bioassays with the various opioid receptors will be pursued and results of those assays will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Both tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium and benzophenone, whereas methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. The ZnI_2 was oven dried overnight, and solutions of *n*-BuLi were purchased from a commercial source and titrated with diphenylacetic acid prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with a magnetic stir bar. NMR spectra were obtained at 300 or 500 MHz for ^{1}H, 75 or 125 MHz for ^{13}C NMR, and 121 or 202 MHz for ^{31}P in $CDCl_3$ with $(CH_3)_4Si$ (^{1}H, 0.00 ppm) or $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C NMR; 77.0 ppm) as the internal standard. High-resolution mass spectra were obtained by GC-TOF. Silica gel (60 Å, 0.040−0.063 mm) was used for flash column chromatography.

*Diethyl 3,4-bis(methoxymethoxy)benzylphosphonate (**12**).* Treatment of benzylic alcohol **9** (165 mg, 0.72 mmol) in THF (15 mL) with ZnI_2 (374 mg, 1.2 mmol) was followed by $P(OEt)_3$ (0.3 mL, 1.7 mmol). The reaction was heated at reflux overnight before the heat source was removed, and the reaction mixture was concentrated in vacuo. The residual oil was diluted with EtOAc and washed with 2 M NaOH, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to provide phosphonate **12** (221 mg, 88%) as a clear oil, with a ^{1}H NMR spectrum that matched closely to known data.[24]

*Diethyl (1-(3,4-bis(methoxymethoxy)phenyl)-4-methylpent-3-en-1-yl)phosphonate (**13**).* To a stirred suspension of NaH (60% dispersion in mineral oil, washed with hexanes, 38 mg, 0.94 mmol) in THF (0.34 mL), phosphonate **12** (322 mg, 0.92 mmol) in THF was added at room temperature. After 1 h, the reaction mixture was placed in an ice bath, followed by dropwise addition of *n*-BuLi (2.44 M in hexanes, 0.42 mL, 1.03 mmol). After 20 min, prenyl bromide (0.13 mL, 1.13 mmol) was added and the ice bath was removed. After an additional hour, the reaction mixture was quenched by addition of 2 N HCl. The aqueous layer was extracted with $CHCl_3$, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification via flash column chromatography (0.25−1% EtOH in CH_2Cl_2) afforded the new prenyl compound **13** (119 mg, 31%) as a pale green oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.08 (m, 2H), 6.92 (dt, J = 8.5, 2.2 Hz, 1H), 5.25−5.20 (m, 4H), 4.96 (t, J = 6.6 Hz, 1H), 4.13−3.74 (m, 4H), 3.52 (s, 3H), 3.51 (s, 3H), 2.94 (ddd, J_{HP} = 21.3 Hz, J = 11.0, 4.0 Hz, 1H), 2.77 (m, 1H), 2.59 (m, 1H), 1.60 (s, 3H), 1.56 (d, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8 (d, J_{CP} = 2.6 Hz), 146.3 (d, J_{CP} = 3.4 Hz), 133.2 (d, J_{CP} = 1.6 Hz), 130.3 (d, J_{CP} = 6.7 Hz), 123.3 (d, J_{CP} = 7.1 Hz), 121.3 (d, J_{CP} = 15.6 Hz), 118.0 (d, J_{CP} = 6.8 Hz), 116.4 (d, J_{CP} = 2.6 Hz), 95.5, 95.4, 62.2 (d, J_{CP} = 6.9 Hz), 61.6 (d, J_{CP} = 7.2 Hz), 56.1, 56.0, 44.2 (d, J_{CP} = 135.5 Hz), 28.4 (d, J_{CP} = 2.6 Hz), 25.5, 17.7, 16.3 (d, J_{CP} = 5.9 Hz), 16.2 (d, J_{CP} = 5.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.7; and HRMS (EI$^+$) m/z calcd for $C_{20}H_{33}O_7P$ (M^+) 416.1964, found 416.1967.

General Procedure for MOM Protection. Treatment of the diphenol in THF with DIPEA at 0 °C was followed by addition of MOMCl in small portions. The reaction was allowed to warm over time, and the resulting solution was quenched by addition of saturated

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NH_4Cl and extracted with EtOAc.[26,46] The combined organic layers were washed with 1 M NaOH and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo to give the desired bis(methoxymethoxy) compound.

*(2-Bromo-3,4-bis(methoxymethoxy)phenyl)methanol (**21**).* Diphenol **18** (2.12 g, 9.8 mmol) in THF (40 mL) and CH_2Cl_2 was treated with DIPEA (5.6 mL, 32.2 mmol) and MOMCl (2.8 mL, 36.9 mmol) under standard MOM protection conditions. After the reaction was stirred for 5 h, standard workup gave 2-bromo-3,4-bis-(methoxymethoxy)benzaldehyde as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (d, J = 0.6 Hz, 1H), 7.56 (d, J = 5.4 Hz, 1H), 7.09 (d, J = 5.1 Hz, 1H), 5.10 (s, 2H), 5.19 (s, 2H), 3.57 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 155.6, 143.6, 128.0, 126.0, 122.9, 114.1, 98.6, 94.6, 57.8, 56.3; HRMS (EI$^+$) m/z calcd for $C_{11}H_{13}BrO_5$ (M^+) 303.9946, found 303.9959.

Under standard aldehyde reduction conditions,[26,46] 2-bromo-3,4-bis(methoxymethoxy)benzaldehyde in MeOH (100 mL) was treated with $NaBH_4$ (0.419 g, 11.1 mmol) and the reaction was allowed to warm overnight. Standard workup provided benzyl alcohol **21** (2.84 g, 95% over 2 steps) as a white solid: mp 57−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 4.66 (br s, 2H), 3.67 (s, 3H), 3.49 (s, 3H), 2.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 144.0, 134.5, 124.1, 118.2, 115.3, 98.8, 95.2, 64.8, 57.9, 56.2; HRMS (EI$^+$) m/z calcd for $C_{11}H_{15}BrO_5$ (M^+) 306.0103, found 306.0091.

*(3-Bromo-4,5-bis(methoxymethoxy)phenyl)methanol (**22**).* Compound **19** (2.51 g, 11.6 mmol) in THF (50 mL) was treated with DIPEA (6.8 mL, 39.0 mmol) and MOMCl (2.7 mL, 35.6 mmol) under standard conditions. Following the usual workup, the resulting orange oil was diluted with MeOH (115 mL) and treated with $NaBH_4$ (0.497 g, 13.1 mmol) under standard conditions. The reaction was allowed to warm to rt over 1 day, and standard workup gave benzyl alcohol **22** (3.50 g, 99% over 2 steps) as an orange oil. The ^{1}H NMR spectrum closely matches the reported literature.[14,46]

*(2-Bromo-4,5-bis(methoxymethoxy)phenyl)methanol (**23**).* Diphenol **20** (2.37 g, 10.9 mmol) in THF (44 mL) was treated with DIPEA (6.4 mL, 36.7 mmol) and MOMCl (2.5 mL, 32.9 mmol) under standard conditions. After warming to rt overnight, the usual workup gave 2-bromo-4,5-bis(methoxymethoxy)benzaldehyde as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.69 (s, 1H), 7.41 (s, 1H), 5.32 (s, 2H), 5.27 (s, 2H), 3.53 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 152.7, 146.6, 127.6, 120.9, 119.8, 116.2, 95.3, 95.1, 56.6, 56.4; HRMS (EI$^+$) m/z calcd for $C_{11}H_{13}BrO_5$ (M^+) 303.9946, found 303.9950.

Under standard conditions aldehyde 2-bromo-4,5-bis-(methoxymethoxy)benzaldehyde in MeOH (110 mL) was treated with $NaBH_4$ (0.47 g, 12.3 mmol), and the reaction was allowed to warm to rt over 1 day. The resulting solution was quenched by addition of H_2O and brine and concentrated in vacuo. The aqueous layer was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo to afford benzylic alcohol **23** (3.10 g, 92% over 2 steps) as a tan solid: mp 51−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.29 (s, 1H), 5.23 (s, 2H), 5.22 (s, 2H), 4.67 (d, J = 6.3 Hz, 2H), 3.51 (s, 6H), 1.93 (t, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 146.7, 133.7, 120.6, 117.0, 114.3, 95.5, 95.4, 64.7, 56.3 (2C); HRMS (EI$^+$) m/z calcd for $C_{11}H_{15}BrO_5$ (M^+) 306.0103, found 306.0114.

*1-Bromo-2,3-bis(methoxymethoxy)-5-(methoxymethyl)benzene (**24**).* Treatment of benzylic alcohol **22** (1.01 g, 3.3 mmol) in THF (12 mL) with NaH (60% dispersion in mineral oil, 162 mg, 4.0 mmol) at 0 °C was followed by addition of CH_3I (0.3 mL, 4.8 mmol). After stirring for 5 h, NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol) and CH_3I (0.2 mL, 3.2 mmol) were added and the reaction was allowed to continue stirring while it warmed to rt overnight. The reaction was quenched by addition of saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The resulting oil was diluted with EtOAc and filtered. Final purification via flash column chromatography (15% EtOAc in hexanes) provided the desired methyl ether **24** (0.88 g, 83%) as a clear oil with an NMR spectrum that closely matches the reported literature.[38]

*1,2-Bis(methoxymethoxy)-5-(methoxymethyl)-3-(3-methylbut-2-en-1-yl)benzene (**25**) and 1,2-bis(methoxymethoxy)-4-(methoxymethyl)benzene (**26**).* To a solution of methyl ether **24** (313 mg, 0.97 mmol) in THF (1 mL) in a dry ice/acetone bath was added n-BuLi (2.50 M in hexanes, 0.4 mL, 1.0 mmol). After 8 min, prenyl bromide (0.15 mL, 1.1 mmol) in THF (1.5 mL) was slowly added. The bath was allowed to warm to just above 0 °C over 2 h, before the reaction was quenched by addition of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Further purification via flash column chromatography (5% EtOAc in hexanes) afforded the prenyl compound **25** (202 mg, 67%) as a clear oil and compound **26** (36 mg, 15%) as a clear oil. For compound **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 1.0 Hz, 1H), 5.26 (m, 1H), 5.19 (s, 2H), 5.10 (s, 2H), 4.35 (s, 2H), 3.59 (s, 3H), 3.50 (s, 3H), 3.41 (d, J = 7.0 Hz, 2H), 3.38 (s, 3H), 1.74 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 144.2, 135.9, 134.2, 132.5, 122.6, 122.4, 113.6, 99.0, 95.1, 74.5, 58.1, 57.4, 56.2, 28.5, 25.7, 17.8; HRMS (EI$^+$) m/z calcd for $C_{17}H_{26}O_5$ (M^+) 310.1780, found 310.1776. For compound **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 8.3, 1.8 Hz, 1H), 5.23 (s, 2H), 5.21 (s, 2H), 4.36 (s, 2H), 3.51 (s, 3H), 3.50 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 146.6, 132.5, 121.7, 116.5, 116.2, 95.3, 95.2, 74.1, 57.7, 55.9, 55.9.[47]

*((2-Bromo-3,4-bis(methoxymethoxy)benzyl)oxy)(tert-butyl)-dimethylsilane (**27**).* Treatment of benzyl alcohol **21** (1.42 g, 4.6 mmol) in CH_2Cl_2 (19 mL) with TBSCl (0.927 g, 6.2 mmol) and imidazole (0.964 g, 14.2 mmol) under standard conditions[26] for 2 h followed by workup gave the silyl compound **27** (1.74 g, 89%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 4.69 (s, 2H), 3.67 (s, 3H), 3.50 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 143.7, 135.0, 122.7, 116.6, 115.5, 98.9, 95.4, 64.5, 58.0, 56.2, 25.9 (3C), 18.4, −5.4 (2C); HRMS (EI$^+$) m/z calcd for $C_{13}H_{20}BrO_5Si$ (M^+) 363.0263, found 363.0253.

*((3-Bromo-4,5-bis(methoxymethoxy)benzyl)oxy)(tert-butyl)-dimethylsilane (**28**).* Under standard conditions benzyl alcohol **22** (1.05 g, 3.4 mmol) in CH_2Cl_2 (14 mL) was treated with TBSCl (0.729 g, 4.8 mmol) and imidazole (0.712 g, 10.5 mmol). After 2 h, the usual workup provided silyl compound **28** (1.23 g, 85%) as a clear oil, and the ^{1}H NMR spectrum matched known data.[46,48]

*((2-Bromo-4,5-bis(methoxymethoxy)benzyl)oxy)(tert-butyl)-dimethylsilane (**29**).* Under standard conditions, benzyl alcohol **23** (427 mg, 1.4 mmol) in CH_2Cl_2 (6 mL) was treated with TBSCl (280 mg, 1.9 mmol) and imidazole (292 mg, 4.3 mmol). After 1 h, workup afforded silyl ether **29** (369 mg, 63%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.31 (s, 1H), 5.21 (s, 2H), 5.19 (s, 2H), 4.66 (d, J = 0.9 Hz, 2H), 3.50 (s, 3H), 3.49 (s, 3H), 0.97 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 146.4, 134.3, 120.2, 116.0, 112.2, 95.5, 95.4, 64.0, 56.0, 55.9, 25.7 (3C), 18.1, −5.5 (2C); HRMS (EI$^+$) m/z calcd for $C_{17}H_{29}BrO_5Si$ (M^+) 420.0968, found 420.0950.

*((3,4-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)benzyl)oxy) tert-butyl)dimethylsilane (**30**).* To a stirred solution of silyl compound **27** (1.65 g, 3.9 mmol) in THF (8 mL) in a dry ice/acetone bath, n-BuLi (2.5 M in hexanes, 1.6 mL, 4.0 mmol) was added slowly. After 14 min, prenyl bromide (0.6 mL, 5.0 mmol) in THF (2 mL) was added slowly. The bath was allowed to warm to 5 °C over 3 h before the reaction was quenched by addition of H_2O and extracted with EtOAc, and the organic layer was washed with brine. The combined organic phases were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. Further purification via flash column chromatography (2% EtOAc in hexanes) gave prenyl compound **30** (0.831 g, 52%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 5.17 (s, 2H), 5.09−5.06 (m, 3H), 4.64 (s, 2H), 3.58 (s, 3H), 3.49 (s, 3H), 3.42 (d, J = 6.5 Hz, 2H), 1.76 (s, 3H), 1.67 (d, J = 1.0 Hz, 3H), 0.93 (s, 9H), 0.07 (s,

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6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 144.6, 134.1, 133.0, 131.3, 122.9, 122.7, 113.8, 99.2, 95.2, 62.5, 57.4, 56.1, 25.9 (3C), 25.6, 25.1, 18.4, 17.9, −5.3 (2C); HRMS (EI$^+$) m/z calcd for $C_{22}H_{38}O_5Si$ (M^+) 410.2489, found 410.2486.

*((3,4-Bis(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)benzyl)oxy)(tert-butyl)dimethysilane (**31**).* To a solution of bromide **28** (2.41 g, 5.7 mmol) in THF (10 mL) in a dry ice/acetone bath was slowly added *n*-BuLi (2.50 M in hexanes, 2.5 mL, 6.3 mmol). After 12 min, prenyl bromide (0.87 mL, 7.5 mmol) in THF (4 mL) was added over 5 min. The bath was allowed to warm to 13 °C over 4 h before the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification via flash column chromatography (0.5% to 2% EtOAc in hexanes) afforded prenyl compound **31** (1.86 g, 79%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 1.8 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 5.31 (m, 1H), 5.17 (s, 2H), 5.09 (s, 2H), 4.65 (s, 2H), 3.59 (s, 3H), 3.49 (s, 3H), 3.40 (d, J = 7.5 Hz, 2H), 1.74 (d, J = 0.9 Hz, 3H), 1.71 (s, 3H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 143.4, 137.4, 135.6, 132.5, 122.7, 120.4, 112.0, 99.1, 95.2, 64.6, 57.4, 56.0, 28.5, 25.9 (3C), 25.7, 18.3, 17.8, −5.3 (2C); HRMS (EI$^+$) m/z calcd for $C_{22}H_{38}O_5Si$ (M^+) 410.2489, found 410.2488.

*((4,5-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)benzyl)oxy)(tert-butyl)dimethylsilane (**32**).* To a stirred solution of bromide **29** (350 mg, 0.83 mmol) in THF (1 mL) in a dry ice/acetone bath, *n*-BuLi (2.5 M in hexanes, 0.34 mL, 0.85 mmol) was added slowly. After 11 min, prenyl bromide (0.14 mL, 1.2 mmol) in THF (1.1 mL) was added slowly. The bath was allowed to warm to 6 °C over 4 h before the reaction was quenched by addition of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification via flash column chromatography (1−2% EtOAc in hexanes) provided the desired prenyl compound **32** (97 mg, 29%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.97 (s, 1H), 5.25−5.22 (m, 5H), 4.68 (s, 2H), 3.54 (s, 3H), 3.53 (s, 3H), 3.25 (d, J = 7.0 Hz, 2H), 1.75 (s, 3H), 1.74 (s, 3H), 0.97 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 145.4, 133.4, 132.6, 132.3, 122.7, 117.9, 116.1, 95.7, 95.7, 62.3, 56.1, 55.9, 30.7, 25.9 (3C), 25.6, 18.3, 17.8, −5.4 (2C); HRMS (EI$^+$) m/z calcd for $C_{22}H_{38}O_5Si$ (M^+) 410.2489, found 410.2467.

*(3,4-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)phenyl)methanol (**10**).* Silyl compound **30** (0.824 g, 2.0 mmol) in THF (68 mL) was treated with TBAF (1.0 M in THF, 2.2 mL, 2.2 mmol) under standard conditions.[26] After 3 h, the usual workup followed by flash column chromatography (10−12% EtOAc in hexanes) afforded benzyl alcohol **10** (0.517 g, 87%) as a cloudy white oil.[15,17,21]

*(3,4-Bis(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)phenyl)methanol (**11**).* Silyl compound **31** (897 mg, 2.2 mmol) in THF (70 mL) was treated with TBAF (1.0 M in THF, 2.4 mL, 2.4 mmol) under standard conditions for 1 h. The usual workup followed by further purification via flash column chromatography (10−15% EtOAc in hexanes) afforded benzylic alcohol **11** (565 mg, 87%) as a yellow oil.[16,21]

*(4,5-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)phenyl)methanol (**14**).* Silyl compound **32** (95 mg, 0.23 mmol) in THF (7.8 mL) was treated with TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol) under standard conditions. After 2 h, standard workup followed by purification via flash column chromatography (12% EtOAc in hexanes) provided benzyl alcohol **14** (56 mg, 82%) as a cloudy white oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.99 (s, 1H), 5.24−5.19 (m, 5H), 4.60 (s, 2H), 3.51 (s, 3H), 3.51 (s, 3H), 3.33 (d, J = 6.9 Hz, 2H), 1.83−1.72 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 145.3, 134.2, 132.8, 132.6, 123.2, 118.2, 117.3, 95.5 (2C), 62.8, 56.1 (2C), 31.0, 25.6, 17.9; HRMS (EI$^+$) m/z calcd for $C_{16}H_{24}O_5$ (M^+) 296.1624, found 296.1622.

*2-((2-Bromo-3,4-bis(methoxymethoxy)benzyl)oxy)tetrahydro-2H-pyran (**33**).* Treatment of benzyl alcohol **21** (1.42 g, 4.6 mmol) in CH_2Cl_2 (19 mL) with DHP (0.65 mL, 7.2 mmol) and PPTS (121 mg, 0.48 mmol) under standard conditions[49] was allowed to proceed for 6 h. The usual workup was followed by final purification via flash column chromatography (4−5% EtOAc in hexanes) to provide acetal **33** (1.74 g, 96%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 4.80−4.74 (m, 2H), 4.54 (d, J = 12.9 Hz, 1H), 3.92 (m, 1H), 3.67 (s, 3H), 3.56 (m, 1H), 3.48 (s, 3H), 1.95−1.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 144.0, 132.3, 124.4, 118.6, 115.1, 98.7, 98.1, 95.1, 68.4, 62.0, 57.8, 56.1, 30.4, 25.3, 19.2; HRMS (EI$^+$) m/z calcd for $C_{16}H_{23}BrO_6$ (M^+) 390.0678, found 390.0701.

*2-((3-Bromo-4,5-bis(methoxymethoxy)benzyl)oxy)tetrahydro-2H-pyran (**34**).* Treatment of benzyl alcohol **22** (1.05 g, 3.4 mmol) in CH_2Cl_2 (12 mL) with DHP (0.6 mL, 6.6 mmol) and PPTS (92 mg, 0.4 mmol) under standard conditions was allowed to proceed for 6 h. After workup, final purification via flash column chromatography (4% EtOAc in hexanes) gave the desired acetal **34** (1.13 g, 84%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 2.1 Hz, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 4.70−4.66 (m, 2H), 4.40 (d, J = 12.3 Hz, 1H), 3.89 (m, 1H), 3.66 (s, 3H), 3.54 (m, 1H), 3.49 (s, 3H), 1.90−1.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 143.3, 135.7, 125.5, 117.6, 115.2, 98.7, 97.7, 95.2, 67.7, 62.1, 57.8, 56.3, 30.4, 25.3, 19.2; HRMS (EI$^+$) m/z calcd for $C_{16}H_{23}BrO_6$ (M^+) 390.0678, found 390.0687.

*2-((2-Bromo-4,5-bis(methoxymethoxy)benzyl)oxy)tetrahydro-2H-pyran (**35**).* Treatment of benzyl alcohol **23** (1.13 g, 3.7 mmol) in CH_2Cl_2 (15 mL) with DHP (0.70 mL, 7.7 mmol) and PPTS (95 mg, 0.38 mmol) under standard conditions was allowed to proceed for 5 h. The usual workup was followed by final purification via flash column chromatography (5% EtOAc in hexanes) to afford the new acetal **35** (1.10 g, 77%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.22 (s, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 4.66−4.61 (m, 2H), 4.40 (d, J = 12.9 Hz, 1H), 3.83 (m, 1H), 3.49−3.40 (m, 7H), 1.86−1.42 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 146.3, 131.4, 120.4, 117.5, 114.5, 98.0, 95.3, 95.3, 68.0, 61.9, 56.0, 55.9, 30.2, 25.2, 19.1; HRMS (EI$^+$) m/z calcd for $C_{16}H_{23}BrO_6$ (M^+) 390.0678, found 390.0680.

*2-((3,4-Bis(methoxymethoxy)-2-(3-methylbuten-2-en-1-yl)benzyl)oxy)tetrahydro-2H-pyran (**36**).* *n*-BuLi (2.5 M in hexanes, 3.8 mL, 9.5 mmol) was added slowly to a stirred solution of bromide **33** (3.53 g, 9.0 mmol) in THF (20 mL) in a dry ice/acetone bath. After 9 min, prenyl bromide (1.5 mL, 13.0 mmol) in THF (3.5 mL) was added and the bath was allowed to warm to 4 °C over 3 h before the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc, and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo followed by purification of the resulting oil via flash column chromatography (5% EtOAc in hexanes) to give the prenyl compound **36** (2.47 g, 72%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 5.18 (s, 2H), 5.11 (m, 1H), 5.09 (s, 2H), 4.71 (d, J = 12.0 Hz, 1H), 4.67 (t, J = 3.5 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 3.91 (m, 1H), 3.59 (s, 3H), 3.56−3.49 (m, 6H), 1.85 (m, 1H), 1.77 (s, 3H), 1.74−1.58 (m, 6H), 1.55−1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 144.9, 135.2, 131.2, 130.9, 125.4, 123.2, 113.7, 99.1, 97.8, 95.1, 66.7, 62.0, 57.4, 56.1, 30.6, 25.6, 25.5 (2C), 19.3, 18.0; HRMS (EI$^+$) m/z calcd for $C_{21}H_{32}O_6$ (M^+) 380.2199, found 380.2175.

*2-((3,4-Bis(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)benzyl)oxy)tetrahydro-2H-pyran (**37**).* To a solution of bromide **34** (1.12 g, 2.9 mmol) in THF (5 mL) in a dry ice/acetone bath was slowly added *n*-BuLi (2.34 M in hexanes, 1.3 mL, 3.0 mmol). After 10 min, prenyl bromide (0.45 mL, 3.9 mmol) in THF (2 mL) was added over 2 min. The bath was allowed to warm to 12 °C over 4 h before the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification via flash column chromatography (5% EtOAc in hexanes) afforded prenyl compound **37** (0.74 g, 69%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 1.5 Hz, 1H), 5.31 (m, 1H), 5.18 (d, J = 0.5 Hz, 2H), 5.09 (s, 2H), 4.70−4.68 (m, 2H), 4.41 (d, J = 12.0 Hz, 1H), 3.92 (m,

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1H), 3.59 (s, 3H), 3.54 (m, 1H), 3.50 (s, 3H), 3.40 (d, J = 7.5 Hz, 2H), 1.86 (m, 1H), 1.77−1.71 (m, 7H), 1.66−1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 144.1, 135.8, 134.2, 132.5, 122.6, 122.5, 113.8, 99.0, 97.7, 95.2, 68.7, 62.2, 57.4, 56.1, 30.5, 28.5, 25.7, 25.4, 19.4, 17.8; HRMS (EI$^+$) m/z calcd for $C_{21}H_{32}O_6$ (M^+) 380.2199, found 380.2182.

*2-((4,5-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)benzyl)-oxy)tetrahydro-2H-pyran (**38**).* To a stirred solution of bromide **35** (1.10 g, 2.8 mmol) in THF (5.0 mL) in a dry ice/acetone bath was slowly added *n*-BuLi (2.5 M in hexanes, 1.2 mL, 3.0 mmol). After 11 min, prenyl bromide (0.5 mL, 4.3 mmol) in THF (2.0 mL) was added over 1 min. The bath was allowed to warm to 11 °C for 5 h before the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc, and the organic layer was washed with brine. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. Final purification via flash column chromatography (5% EtOAc in hexanes) gave the new prenyl compound **38** (0.67 g, 62%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.98 (s, 1H), 5.26−5.18 (m, 5H), 4.74−4.67 (m, 2H), 4.42 (d, J = 11.4 Hz, 1H), 3.92 (m, 1H), 3.58−3.50 (m, 7H), 3.32 (d, J = 6.9 Hz, 2H), 1.93−1.50 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 145.0, 134.7, 132.0, 129.9, 122.9, 118.1, 117.8, 97.7, 95.5, 95.4, 66.4, 61.9, 55.9, 55.9, 30.7, 30.4, 25.5, 25.3, 19.2, 17.7; HRMS (EI$^+$) m/z calcd for $C_{21}H_{32}O_6$ (M^+) 380.2199, found 380.2177.

General Procedure for Deprotection of THP acetals with 2,4,6-collidine and TESOTf. Treatment of the acetal in CH_2Cl_2 at 0 °C with 2,4,6-collidine was followed by addition of TESOTf. After 30 min the clear reaction solution was quenched by addition of H_2O, and the reaction was allowed to stir for 10 min, resulting in a cloudy white mixture. The organic layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, the filtrate was concentrated in vacuo, and the resulting oil was purified by flash column chromatography.[43]

*(3,4-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)phenyl)-methanol (**10**).* Acetal **36** (0.50 g, 1.3 mmol) in CH_2Cl_2 (13.2 mL) was treated with 2,4,6-collidine (0.54 mL, 4.1 mmol) and TESOTf (0.60 mL, 2.7 mmol) under standard conditions. Further purification via flash column chromatography (15% EtOAc and 1% TEA in hexanes) provided the desired benzylic alcohol **10** (325 mg, 83%) as a yellow oil.

*(4,5-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)phenyl)-methanol (**14**).* Acetal **38** (270 mg, 0.71 mmol) in CH_2Cl_2 (7.0 mL) was treated with 2,4,6-collidine (0.29 mL, 2.2 mmol) and TESOTf (0.32 mL, 1.4 mmol) under standard conditions. Final purification via flash column chromatography (15−18% EtOAc in hexanes) afforded benzylic alcohol **14** (166 mg, 79%) as a pale yellow oil.

*Diethyl 4,5-bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)-benzylphosphonate (**39**).* To a stirred mixture of oven-dried ZnI_2 (84 mg, 0.26 mmol) and $P(OEt)_3$ (0.06 mL, 0.34 mmol) was added benzylic alcohol **14** (41 mg, 0.14 mmol) in THF (3 mL). The reaction was heated at reflux overnight before the heat source was removed, and the solution was concentrated in vacuo. The resulting oil was washed with 2 M NaOH, and the organic layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to provide phosphonate **39** (57 mg, 98%) as a pale orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 3.0 Hz, 1H), 7.00 (s, 1H), 5.19 (s, 5H), 4.05−4.00 (m, 4H), 3.51−3.50 (m, 6H), 3.36 (d, J = 7.0 Hz, 2H), 3.10 (d, J_{HP} = 21.0 Hz, 2H), 1.73, (s, 6H), 1.26 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2 (d, J_{CP} = 4.0 Hz), 145.2 (d, J_{CP} = 3.8 Hz), 134.9 (d, J_{CP} = 7.3 Hz), 132.6, 123.7 (d, J_{CP} = 9.4 Hz), 122.7 (d, J_{CP} = 0.9 Hz), 119.5 (d, J_{CP} = 5.1 Hz), 118.1 (d, J_{CP} = 3.3 Hz), 95.6 (2C), 61.8 (d, J_{CP} = 6.8 Hz, 2C), 56.1, 56.1, 31.5 (d, J_{CP} = 1.3 Hz), 30.0 (d, J_{CP} = 138.1 Hz), 25.6, 17.9, 16.4, 16.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.8; HRMS (EI$^+$) m/z calcd for $C_{20}H_{33}O_7P$ (M^+) 416.1964, found 416.1988.

*1-((E)-4,5-Bis(methoxymethoxy-2-(3-methylbut-2-en-1-yl)styryl)-2-(E)-3,7-dimethylocta-2,6-dien-1-yl)-3,5-dimethoxybenzene (**41**).* To a solution of KHMDS (1.0 M in THF, 0.32 mL, 0.32 mmol) at 0 °C was added phosphonate **39** (41 mg, 0.10 mmol) and aldehyde **40** (19 mg, 0.06 mmol) in THF (1.3 mL). The reaction was allowed to warm to rt overnight before it was quenched by addition of saturated NH_4Cl and the organic layer was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Further purification via flash column chromatography (2% EtOAc in hexanes) afforded stilbene **41** (27 mg, 75%) as a cloudy white oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.11 (s, 2H), 6.97 (s, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 5.23 (s, 5H), 5.12 (m, 1H), 5.05 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.53 (s, 6H), 3.42 (d, J = 6.5 Hz, 2H), 3.38 (d, J = 7.0 Hz, 2H), 2.03 (m, 2H), 1.95 (m, 2H), 1.78 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.61 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.4, 147.0, 145.7, 138.3, 134.4, 134.3, 132.1, 121.2, 130.7, 127.7, 127.3, 124.4, 123.4, 123.2, 121.3, 117.8, 114.5, 101.9, 98.0, 95.8, 95.5, 56.2, 56.2, 55.7, 55.3, 39.7, 32.0, 26.8, 25.7, 25.6, 24.4, 18.0, 17.6, 16.3; HRMS (EI$^+$) m/z calcd for $C_{35}H_{48}O_6$ (M^+) 564.3451, found 564.3427.

*4-((E)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-3,5-dimethoxystyr-yl)-5-(3-methylbut-2-en-1-yl)benzene-1,2-diol (**42**).* Bis-(methoxymethoxy) acetal **41** (27 mg, 0.05 mmol) in MeOH (4 mL) and THF (0.8 mL) was treated with TsOH (40 mg, 0.21 mmol) at rt, and the reaction was allowed to stir overnight before it was quenched by addition of saturated $NaHCO_3$. The organic layer was extracted with EtOAc, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification via preparative TLC (25% EtOAc in hexanes, run twice) provided the desired analogue **42** (11 mg, 51%) as a gel-like orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.09 (m, 2H), 7.06 (d, J = 16.0 Hz, 1H), 6.71−6.69 (m, 2H), 6.41 (d, J = 2.5 Hz, 1H), 5.25−5.20 (m, 2H), 5.12 (m, 1H), 5.07−5.05 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.42 (d, J = 7.0 Hz, 2H), 3.34 (d, J = 6.5 Hz, 2H), 2.05 (m, 2H), 1.97 (m, 2H), 1.78 (s, 3H), 1.73 (s, 6H), 1.62 (d, J = 0.5 Hz, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 158.5, 143.3, 141.7, 138.4, 134.6, 133.0, 132.2, 131.3, 129.4, 127.5, 126.7, 124.4, 123.5, 123.2, 121.2, 116.2, 112.7, 101.9, 97.9, 55.7, 55.3, 39.7, 31.4, 26.8, 25.7, 25.6, 24.4, 17.9, 17.6, 16.3; HRMS (EI$^+$) m/z calcd for $C_{31}H_{40}O_4$ (M^+) 476.2927, found 476.2917.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02756.

^{1}H and ^{13}C NMR spectra of compounds **13**, **14**, **21**, **23**, **25**−**27**, **29**−**39**, **41**, and **42**, and the ^{1}H NMR spectra of compounds **10** and **11** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david-wiemer@uiowa.edu

Notes

The authors declare no competing financial interests.

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