Development of Synthetic Methodology Suitable for the Radiosynthesis of Combretastatin A-1 (CA1) and Its Corresponding Prodrug CA1P†

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Synthetic methodology has been established suitable for the preparation of combretastatin A-1 (CA1) and its corresponding phosphate prodrug salt (CA1P) in high specific activity radiolabeled form. Judicious selection of appropriate phenolic protecting groups to distinguish positions on the A-ring from the B-ring of the stilbenoid was paramount for the success of this project. Methylation of the C-4′ phenolic moiety by removal of the *tert*-butyldimethylsilyl protecting group in the presence of methyl iodide was accomplished in excellent yield without significant *Z* to *E* isomerization. This step (carried out with ^{12}C-methyl iodide as proof of concept in this study) represents the process in which a ^{14}C radioisotope could be incorporated in an actual radiosynthesis. CA1 is a natural product isolated from the African bush willow tree (*Combretum caffrum*) that has important medicinal value due, in part, to its ability to inhibit tubulin assembly. As a prodrug, CA1P (OXi4503) is in human clinical trials as a vascular disrupting agent.

Combretastatin A-1 phosphate (CA1P, also known as OXi4503)[1,2] and combretastatin A-4 phosphate (CA4P, also known as Zybrestat)[1,3] are well-known small-molecule vascular disrupting agents (VDAs), which, along with several other agents, are currently in human clinical studies for the treatment of cancer (Figure 1). The combretastatins were originally isolated from the African bush willow tree *Combretum caffrum* Kuntze (Combretaceae) by Pettit and co-workers.[4,5] Both CA1P and CA4P are known to undergo enzymatic dephosphorylation and subsequently function by selectively disrupting the tubulin−microtubule protein system in the endothelial cells lining the inner walls of the tumor vasculature. The resulting endothelial cell morphology changes along with several cell signaling pathways cause rapid blood flow shutdown and ultimately leads to necrosis in solid tumors.[6−8] Although the mechanism of action of both CA1P and CA4P has been extensively studied by numerous researchers, the specific mechanisms responsible for the selective disruption of tumor vasculature are not known completely.[9,10] In addition, in a preclinical study carried out by Hill and co-workers,[11] CA1P demonstrated higher vascular disrupting and antitumor activity when compared to CA4P.[11−13] The increase in efficacy of CA1P as a VDA, though not clearly known, is attributed to the presence of an additional hydroxy substituent, which may result in the formation of a highly reactive *ortho*-quinone through oxidative metabolism.[14] These reactive metabolites are believed to exhibit additional cytotoxic effects. Availability of high specific activity radiolabeled CA1P would facilitate additional pharmacological studies with the aim of further elucidation of the biological mechanisms utilized by this promising new VDA. Accordingly, an important goal has become the discovery and development of synthetic methodology suitable for the incorporation of an appropriate radioisotope into CA1P in a metabolically stable position. ^{32}P was ruled out as a potential radiotracer in the synthesis of radiolabeled CA1P since the phosphate groups on CA1P are cleaved *in vivo* by phosphatase enzymes. ^{14}C was chosen as a radiotracer due to its high sensitivity and longer half-life period.[15] The easily replaceable methoxy group at the 4-position in the 3,4,5-trimethoxyphenyl unit (A-ring, Figure 1) was chosen as the location to incorporate a ^{14}C-methoxy moiety in the CA1P radiosynthesis.

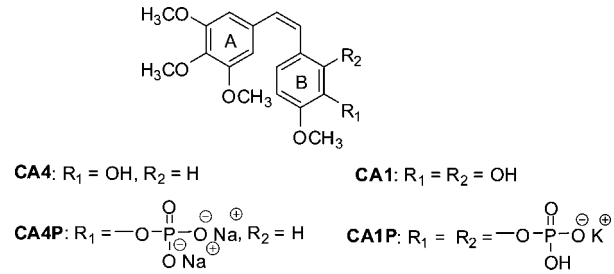

Figure 1. CA4, CA1, and their corresponding prodrugs CA4P and CA1P.

In this paper, we discuss the synthetic methodology requisite for the preparation of CA1 and CA1P in high specific activity radiolabeled form.[16] Briefly, this involved initial preparation of an appropriately protected CA1 analogue (referred to as "cold precursor"), followed by synthetic elaboration of this cold precursor to CA1 and CA1P through methodology capable of ultimately incorporating a ^{14}C-radioisotope. All of the reactions reported herein have been performed using ^{12}C instead of ^{14}C. The actual radiosynthesis of CA1 and CA1P using this methodology has been accomplished and will be reported in due course.[17] In addition, alternative routes explored for incorporation of a radioisotope in CA1 and CA1P are also discussed.

Results and Discussion

The synthesis of cold precursor **1** (Scheme 1) was facilitated by a Wittig reaction utilizing methodology reminiscent of the synthesis of many previously reported combretastatins.[4,18,19] In order to selectively incorporate the radiolabel in the center (C-4) methoxy of the A-ring, it was paramount to distinguish this methoxy position (from the other methoxy and phenolic moieties in CA1) through a strategic protecting group strategy. This was accomplished by using isopropyl protection on the B-ring phenolic positions[20] and *tert*-butyldimethylsilyl (TBS) protection on the A-ring phenol[21] of the corresponding pre-Wittig aldehydes, as described in Scheme 1.[22]

† Dedicated to Dr. David G. I. Kingston of Virginia Polytechnic Institute and State University for his pioneering work on bioactive natural products.

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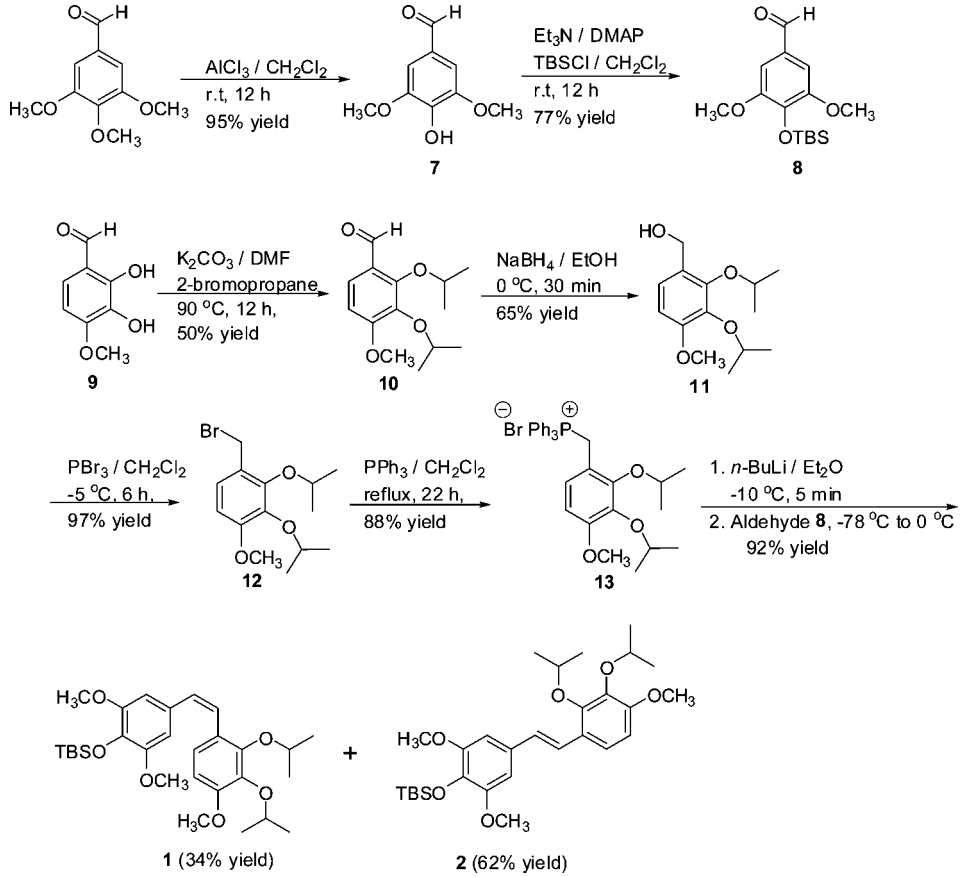
Scheme 1. Synthesis of Cold Precursors **1** and **2**



The diisopropyl protected aldehyde **10** was converted to its corresponding phosphonium bromide salt **13** in good yield (Scheme 1) following standard procedures.[18] *Z*-Cold precursor **1** was prepared through a Wittig reaction between **13** and aldehyde **8**, followed by separation of the *Z*- and *E*-isomers by careful gravity column chromatography. Cold precursor **1** was successfully converted to CA1 and subsequently CA1P with incorporation of ^{12}C (as proof of concept) rather than with ^{14}C necessary for the actual radiosynthesis (Scheme 2). Selective methylation on the A-ring was accomplished by treatment of cold precursor **1** with methyl iodide in the presence of tetrabutylammonium fluoride (TBAF).

An initial strategy to carry out a stepwise deprotection of the TBS group (Scheme 3) followed by methylation of the resultant phenol **14a** was unsuccessful due to consistent conversion to the *E*-stilbene **14b**.

The *Z* to *E* double-bond isomerization was most likely facilitated by resonance stabilization of the initial anion formed from removal of the TBS group (Figure 2).

To overcome this problem, deprotection of the TBS group in cold precursor **1** was carried out using TBAF in the presence of methyl iodide (4 equiv), resulting in the methylated *Z*-isomer **15** in high yield (Scheme 2).

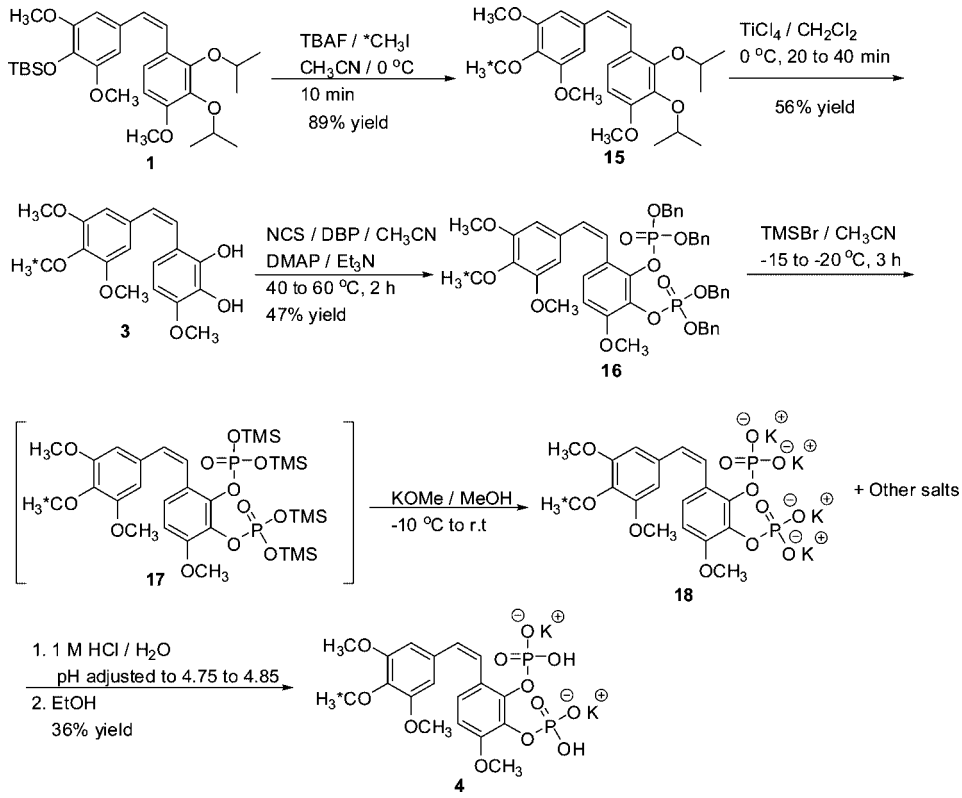
Deprotection of the isopropyl groups in stilbene **15** afforded CA1 (**3**) in moderate yield, which was then converted to its corresponding tetrabenzylphosphate derivative **16**.[18,23] The purity of the $TiCl_4$ used greatly affected both reaction time and product yield. Utilizing a new, not previously opened, highly pure bottle of $TiCl_4$ (99.999%), the reaction was complete within 20 to 40 min and CA1 (**3**) was obtained in good yield without isomerization. It is important to note that the CA1 obtained after the deprotection of the isopropyl groups was purified using silica gel capped with Florisil, to remove the potential titanium impurities. When CA1 purified chromatographically without Florisil was used in the synthesis of salt **4**, significant (50−90%) isomerization (*Z* to *E*) was observed.

Importantly, while the synthetic methodology described in Scheme 2 utilized 4 molar equiv of methyl iodide, the actual radiosynthesis employed only 1 equiv of methyl iodide in order to maximize cost effectiveness, while minimizing the amount of radioactive waste produced. Use of 1 equiv of ^{14}C-methyl iodide yielded ^{14}C-labeled stilbene **15** in a 75% yield in the actual radiosynthesis.[17]

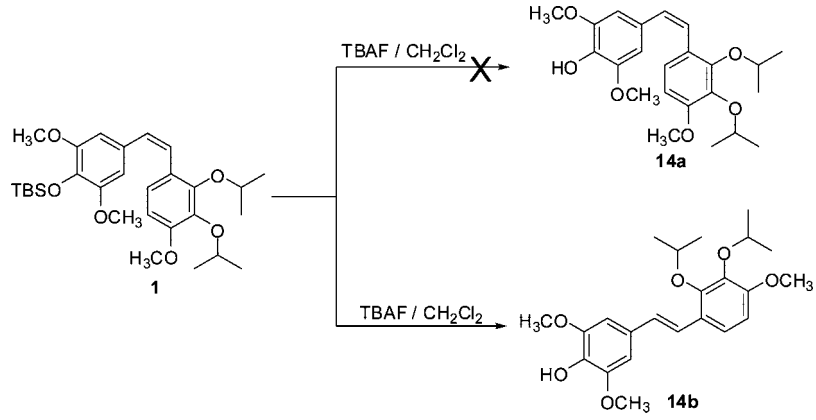
Debenzylation of stilbene **16** using TMSBr resulted in the tetra-TMS-phosphate ester **17**, which was quenched into a solution of excess KOMe in MeOH to afford tetrapotassium salt **18** along with other mono-, di-, and tripotassium-substituted salts. This mixture of salts was then dissolved in water, and the resultant aqueous solution was carefully adjusted to a pH of 4.75 to 4.85 using 1 M HCl, followed by precipitation of the salt CA1P (**4**) with EtOH.[23] Careful spectrometric characterization of the desired dipotassium salt **4** revealed the anticipated ^1H, ^{13}C, and ^{31}P NMR patterns. However, on certain occasions, the phosphorus peaks of compound **4** were not detectable by ^{31}P NMR analysis. This interesting and unanticipated result was ultimately attributed to the plausible presence of trace amounts of paramagnetic metals, most likely iron, resulting, in these cases, from the use of oven-dried reusable stainless steel syringe needles to transfer reagents. To confirm this hypothesis, minute amounts of (ethylenedinitrilo)tetraacetic acid (disodium salt dihydrate) were added to the solution containing the sample, and the resulting mixture was filtered and reanalyzed by NMR, resulting in observation of two phosphorus peaks, pertaining to the two phosphorus atoms in compound **4**.[24]

Two alternative methods were also evaluated as potential methodologies suitable for the preparation of radiolabeled CA1 (**3**) and its corresponding prodrug CA1P (**4**). One such method involved the synthesis of cold precursor **5**, in which the two protecting functionalities were switched between the A-ring and B-ring (Scheme 4). However, attempts to deprotect the isopropyl group and methylate the resultant phenoxide ion *in situ* to obtain *Z*-stilbene

Scheme 2. Synthesis of CA1 (**3**) and CA1P (**4**) Utilizing Methodology Suitable for Isotope Incorporation (* indicates the position where ^{14}C-CH_3 would be incorporated in the actual radiosynthesis)[17]



Scheme 3. Isomerization upon Deprotection of TBS Group



24 were unsuccessful, as evidenced by multiple product formation observed in the ^1H NMR spectra.

Another alternative methodology suitable for the incorporation of a radioisotope into CA1 (**3**) began with commercially available syringaldehyde (Scheme 5). In this protocol, methylation (^{12}C in this case) took place in the first synthetic step of the sequence, resulting in compound **25** (Scheme 5). Di-TBS protected *Z*-stilbene **24** was obtained via a Wittig reaction between phosphonium bromide **23** and aldehyde **25**. Removal of the two TBS groups yielded CA1 (**3**) in excellent yield,[4,18] which was successfully converted to its corresponding prodrug, CA1P (**4**), following methodology as described in Scheme 2.

Conclusions

Three different synthetic approaches were evaluated in order to establish a protocol suitable for an efficient and safe radiosynthesis of CA1 (**3**) and CA1P (**4**). The initial methodology described in this paper (Schemes 1 and 2), namely, concomitant deprotection and methylation of the suitably functionalized cold precursor **1**, followed by salt formation, proved to be extremely robust, giving acceptable reaction yields and the absence of the potentially troublesome *Z* to *E* double-bond isomerization. This methodology (described herein with ^{12}C) has been successfully utilized by others for the radiosynthesis of CA1 and CA1P containing ^{14}C.[17] The alternative methodology with juxtaposed protecting groups on the A-ring and B-ring was unsuccessful (Scheme 4). While the methodology described beginning with syringaldehyde (Scheme 5) was successful and ultimately resulted in conversion to CA1 and CA1P, it is less desirable to incorporate an actual radioisotope at such an early stage in the synthetic sequence.

Experimental Section

General Experiemental Procedures. Reactions were performed under an inert atmosphere using nitrogen gas unless specified differently. Chemical reagents used in the synthetic procedures were obtained from various chemical suppliers (Sigma Aldrich, Acros Chemical Co., Alfa Aesar, Fisher Scientific, EMD Chemicals, and VWR). Silica gel (200−400 mesh, 60 Å), used for column chromatography, was obtained from either Silicycle Inc. or VWR. TLC plates (precoated glass plates

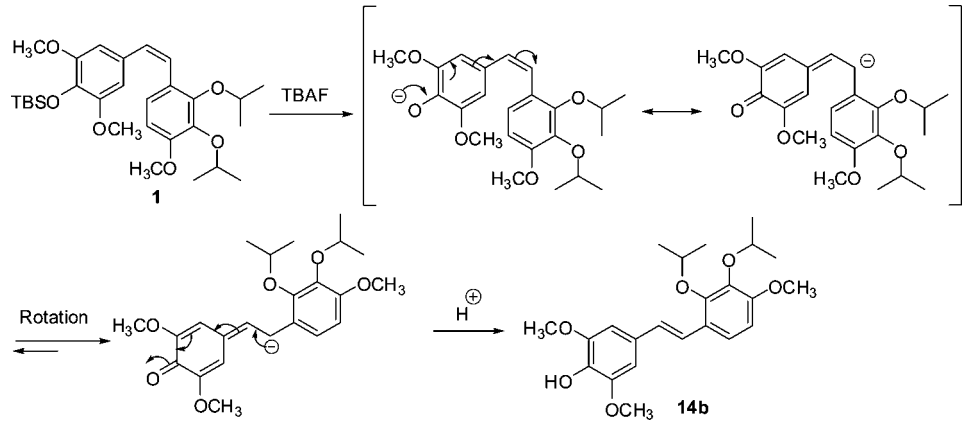
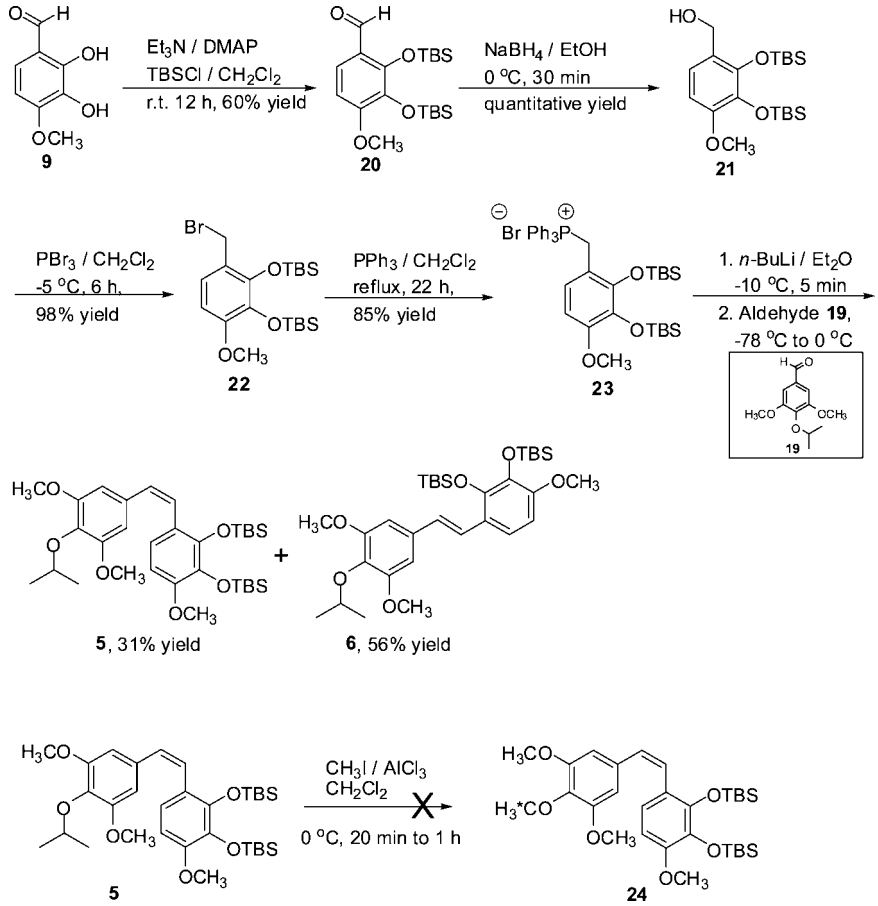


Figure 2. Plausible mechanism for isomerization to form stilbene **14b**.

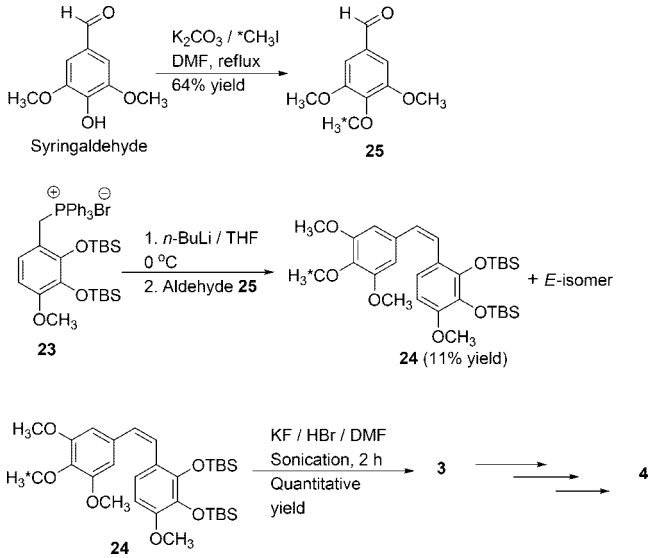
Scheme 4. Synthesis of Alternative Cold Precursor **5** (* indicates the position where ^{14}C -CH_3 would be incorporated in the actual radiosynthesis)[17]



with silica gel 60 F254, 0.25 mm thickness, EMD chemicals, VWR) were used to monitor reactions. Intermediates and products synthesized were characterized on the basis of ^1H NMR (Bruker DPX operating at 300 MHz or Varian operating at 500 MHz), ^{13}C NMR (Bruker DPX operating at 75 MHz or Varian operating at 125 MHz), and ^{31}P NMR (Bruker DPX operating at 121 MHz or Varian operating at 202 MHz). All the chemical shifts are expressed in ppm (δ), coupling constants (*J*) are presented in Hz, and peak patterns are reported as broad (br), singlets (s), doublets (d), triplets (t), quartets (q), septets (sept), and multiplets (m). Elemental analysis was performed by Atlantic Microlab, Norcross, GA. High-resolution mass spectra (HREIMS), unit resolution gas chromatography mass spectra (EIMS), and unit resolution mass spectra (ESIMS) were obtained on a VG Prospec Micromass spectrometer, a Thermo Scientific DSQ II, and a Thermo Finnigan LCQ Classic, respectively, in the Baylor University Mass Spectrometry Core Facility. Purity of the compounds was further analyzed using a Hewlett-Packard HP Series 1050 HPLC system with UV detection and a Supelco Discovery C_{18} HPLC column (12.5 cm × 4.6 mm, 5 μm, T = 25 °C; eluents, solvent A, 25 mM tetrabutylammonium bromide (TBAB) with 0.1% trifluoroacetic acid (TFA) in water, solvent B, 25 mM TBAB with 0.08% TFA in water/acetonitrile (2/8 v/v); gradient, 80% A/20% B → 5% A/95% B over 0 to 45 min; flow rate 0.7 mL/min; injection volume 25 μL; monitored at 264 nm wavelength).

4-Hydroxy-3,5-dimethoxybenzaldehyde (7).[25] 3,4,5-Trimethoxybenzaldehyde (11.99 g, 61.16 mmol) was dissolved in dry CH_2Cl_2 (200 mL) at rt under nitrogen. Anhydrous $AlCl_3$ (16.31 g, 122.3 mmol) was added, and the reaction mixture stirred for 12 h. The reaction was quenched with H_2O (100 mL), the organic phase separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. Aldehyde **6** (10.58 g, 58.08 mmol, 95% yield) was obtained as a white powder, R_f 0.46 (70:30 hexanes−EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (1H, s, C-1 C*H*O), 7.16 (2H, s, H-2, H-6), 6.09 (1H, s, C-4 O*H*), 3.97 (6H, s,

Scheme 5. Alternative Protocol Suitable for the Incorporation of ^{14}C-methyl in CA1 (**3**) (* indicates the position where ^{14}C -CH_3 would be incorporated in the actual radiosynthesis)[17]



C-3, C-5 O*C*H_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.7 (C, C-1 *C*HO), 147.3 (C, C-3, C-5), 140.8 (C, C-4), 128.4 (C, C-1), 106.7 (CH, C-2, C-6), 56.5 (CH_3, C-3, C-5 O*C*H_3); HREIMS *m*/*z* 182.0577 (calcd for $C_9H_{10}O_4$, 182.0579).

4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethoxybenzaldehyde (8).[21] To a well-stirred solution of aldehyde **7** (10.62 g, 58.29 mmol) in anhydrous CH_2Cl_2 (150 mL) at 0 °C were added Et_3N (12.15 mL, 87.12 mmol) and *N,N*-dimethylaminopyridine (DMAP) (14.0 mg, 1.20 mmol) under nitrogen. The reaction mixture was stirred for 10 min followed by the addition of *tert*-butyldimethylsilyl chloride (TBSCl) (13.18 g, 87.45 mmol) in portions. The reaction mixture was stirred for 12 h followed by the addition of H_2O (100 mL). The organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 400 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude off-white solid was recrystallized with absolute EtOH to obtain TBS protected aldehyde **8** (13.20 g, 44.53 mmol, 77% yield) as pale yellow crystals, R_f 0.57 (70:30 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.82 (1H, s, C-1 C*H*O), 7.10 (2H, s, H-2, H-6), 3.87 (6H, s, C-3, C-5 O*C*H_3), 1.01 (9H, s, C-4 OSi(CH_3)$_2$C(*C*H_3)$_3$), 0.16 (6H, s, C-4 OSi(*C*H_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.0 (C, C-1 *C*HO), 151.9 (C, C-3, C-5), 140.6 (C, C-4), 129.3 (C, C-1), 106.7 (CH, C-2, C-6), 55.8 (CH_3, C-3, C-5 O*C*H_3), 25.6 (CH_3, C-4 OSi(CH_3)$_2$C(*C*H_3)$_3$), 18.8 (C, C-4 OSi(CH_3)$_2$*C*(CH_3)$_3$), −4.6 (CH_3, C-4 OSi(*C*H_3)$_2$C(CH_3)$_3$); HREIMS *m*/*z* 296.1443 (calcd for $C_{15}H_{24}O_4Si$, 296.1444).

Note: Compound **7** is commercially available as syringaldehyde. Conversion of synthesized **7** or commercially available syringaldehyde to silyl ether **8** proceeded in an analogous fashion.

2,3-Di[(isopropyl)oxy]-4-methoxybenzaldehyde (10).[20] 2,3-Dihydroxy-4-methoxybenzaldehyde[18] (12.12 g, 72.07 mmol) was dissolved in anhydrous DMF (100 mL). Anhydrous K_2CO_3 (21.20 g, 214.0 mmol) and 2-bromopropane (37.80 mL, 214.0 mmol) were added, and the reaction mixture was stirred at 90 °C for 12 h. H_2O (100 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic phases were washed with H_2O followed by brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5:95 EtOAc−hexanes) to afford aldehyde **10** (9.80 g, 38.8 mmol, 51% yield) as a yellow oil, R_f 0.38 (70:30 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.28 (1H, s, C-1 C*H*O), 7.62 (1H, d, J = 8.8 Hz, H-6), 6.75 (1H, d, J = 8.8 Hz, H-5), 4.82 (1H, sept, J = 6.1 Hz, C-2 O*C*H(CH_3)$_2$), 4.45 (1H, sept, J = 6.1 Hz, C-3 O*C*H(CH_3)$_2$), 3.91 (3H, s, C-4 O*C*H_3), 1.30 (12H, d, J = 6.1 Hz, C-2, C-3 OCH(*C*H_3)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6 (C, C-1 *C*HO), 159.8 (C, C-4), 155.4 (C, C-2), 139.8 (C, C-3), 124.9 (CH, C-6), 123.5 (C, C-1), 107.2 (CH, C-5), 75.9 (CH, C-3, O*C*H(CH_3)$_2$), 75.4 (CH, C-2 O*C*H(CH_3)$_2$), 56.0 (CH_3, C-4 O*C*H_3), 22.4 (CH_3, C-3 OCH(*C*H_3)$_2$), 22.0 (CH_3, C-2 OCH(*C*H_3)$_2$); HREIMS *m*/*z* 252.1368 (calcd for $C_{14}H_{20}O_4$, 252.1368).

2,3-Di[(isopropyl)oxy]-4-methoxybenzyl Alcohol (11). $NaBH_4$ (2.378 g, 62.88 mmol) was added in portions to a stirred solution of aldehyde **10** (15.81 g, 62.66 mmol) in anhydrous EtOH (100 mL) at 0 °C. The reaction mixture was stirred for 30 min and quenched with H_2O (100 mL) cautiously. Organic solvent was removed *in vacuo*, and the aqueous phases were extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was subjected to flash column chromatography (silica gel, 10:90 EtOAc−hexanes) to afford benzyl alcohol **11** (10.30 g, 40.50 mmol, 65% yield) as a colorless oil, R_f 0.33 (70:30 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (1H, d, J = 8.5 Hz, H-6), 6.61 (1H, d, J = 8.5 Hz, H-5), 4.86 (1H, sept, J = 6.0 Hz, C-2, O*C*H(CH_3)$_2$), 4.61 (2H, d, J = 6.0 Hz, C-1 C*H*$_2$OH), 4.40 (1H, sept, J = 6.0 Hz, C-3 O*C*H(CH_3)$_2$), 3.82 (3H, s, C-4 O*C*H_3), 2.53 (1H, t, J = 6.5 Hz, C-1 CH$_2$O*H*), 1.27 (6H, d, J = 6.0 Hz, C-3 OCH(*C*H_3)$_2$), 1.26 (6H, d, J = 6.0 Hz, C-2 OCH(*C*H_3)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0 (C, C-4), 149.9 (C, C-2), 139.8 (C, C-3), 127.8 (CH, C-6), 122.8 (C, C-1), 106.5 (CH, C-5), 74.9 (CH, C-3 O*C*H(CH_3)$_2$), 74.3 (CH, C-2 O*C*H(CH_3)$_2$), 62.1 (CH_2, C-1 *C*H$_2$OH), 55.7 (CH_3, C-4, O*C*H_3), 22.5 (CH_3, C-3 OCH(*C*H_3)$_2$), 22.4 (CH_3, C-2 OCH(*C*H_3)$_2$); HREIMS *m*/*z* 254.1514 (calcd for $C_{14}H_{22}O_4$, 254.1518).

2,3-Di[(isopropyl)oxy]-4-methoxybenzyl Bromide (12). To a well-stirred solution of alcohol **11** (10.30 g, 40.50 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C under nitrogen was added PBr_3 (3.10 mL, 40.5 mmol). The reaction mixture was stirred for 6 h at 0 °C. H_2O (100 mL) was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. Benzyl bromide **12** (12.50 g, 39.40 mmol, 97% yield) was obtained as a pale yellow oil and needed no further purification, R_f 0.70 (60:40 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (1H, d, J = 8.5 Hz, H-6), 6.63 (1H, d, J = 8.5 Hz, H-5), 4.87 (1H, sept, J = 6.0 Hz, C-2 O*C*H(CH_3)$_2$), 4.58 (2H, s, C-1 C*H*$_2$Br), 4.40 (1H, sept, J = 6.0 Hz, C-3 O*C*H(CH_3)$_2$), 3.83 (3H, s, C-4 O*C*H_3), 1.29 (6H, d, J = 6.0 Hz, C-3 OCH(*C*H_3)$_2$), 1.28 (6H, d, J = 6.0 Hz, C-2 OCH(*C*H_3)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8 (C, C-4), 150.1 (C, C-2), 139.8 (C, C-3), 125.5 (CH, C-6), 124.7 (C, C-1), 107.0 (CH, C-5), 75.1 (CH, C-3 O*C*H(CH_3)$_2$), 74.4 (CH, C-2 O*C*H(CH_3)$_2$), 55.9 (CH_3, C-4 O*C*H_3), 29.7 (CH_2, C-1 *C*H$_2$Br), 22.6 (CH_3, C-3 OCH(*C*H_3)$_2$), 22.4 (CH_3, C-2 OCH(*C*H_3)$_2$); EIMS *m*/*z* (317, M^+).

2,3-Di[(isopropyl)oxy]-4-(methoxybenzyl)triphenylphosphonium Bromide (13). A mixture of bromide **12** (12.50 g, 39.40 mmol) and PPh_3 (11.40 g, 43.40 mmol) in dry CH_2Cl_2 (200 mL) was refluxed for 22 h under N_2. Solvent was removed to afford an off-white solid. Et_2O was added, and the solid was filtered, washed with Et_2O, and dried under high vacuum to obtain the phosphonium salt **13** (20.01 g, 34.59 mmol, 88% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (9H, m, C-1 CH$_2$P(C$_6$*H*$_5$)$_3$), 7.64 (6H, m, CH$_2$P(C$_6$*H*$_5$)$_3$), 7.09 (1H, dd, J = 8.5 Hz, 3.0 Hz, H-6), 6.50 (1H, d, J = 8.5 Hz, H-5), 5.19 (2H, d, J_{H-P} = 14.0 Hz, C-1 C*H*$_2$P(C$_6$H$_5$)$_3$), 4.72 (1H, sept, J = 6.0 Hz, C-2 O*C*H(CH_3)$_2$), 3.97 (1H, sept, J = 6.0 Hz, C-3 O*C*H(CH_3)$_2$), 3.76 (3H, s, C-4 O*C*H_3), 1.11 (6H, d, J = 6.0 Hz, C-3 OCH(*C*H_3)$_2$), 1.10 (6H, d, J = 6.5 Hz, C-2 OCH(*C*H_3)$_2$); ^{31}P NMR ($CDCl_3$, 202 MHz) δ 21.9; ESIMS *m*/*z* 499 (100, M^{+1}), 237 (15), 194 (25), 153 (25).

(*Z*)/(*E*)-1-[3′,5′-Dimethoxy-4′-[(*tert*-butyldimethylsilyl)oxy]phenyl]-2-[2″,3″-di[(isopropyl)oxy]-4″-methoxyphenyl]ethene (1 and 2, respectively). *n*-BuLi (2.0 M in hexanes, 19.20 mL, 38.30 mmol) was added dropwise to a well-stirred solution of Wittig salt **13** (20.01 g, 34.54 mmol) in anhydrous THF (250 mL) at −10 °C. The reaction mixture was then cooled to −78 °C, and aldehyde **8** (9.30 g, 31.4 mmol) dissolved in anhydrous THF (30 mL) was added dropwise. The reaction was stirred until the temperature gradually rose to 0 °C. The reaction was quenched by careful addition of H_2O (100 mL) followed by removal of THF *in vacuo*. The aqueous phase was extracted with Et_2O (3 × 200 mL), and the combined organic phases were washed with brine. After drying with Na_2SO_4, the solvents were removed under reduced pressure and the crude product obtained was subjected to gravity column chromatography (silica gel, EtOAc−hexanes, gradient 0.5:99.5 to 2:98) to obtain the *Z*-isomer **1** (5.53 g, 10.70 mmol, 34% yield), as an off-white oil, which crystallized upon cooling to −20 °C, and the *E*-isomer **2** (10.0 g, 19.35 mmol, 62% yield), as a pale yellow oil, $R_{f(Z\text{-isomer})}$ 0.45, $R_{f(E\text{-isomer})}$ 0.33 (90:10 hexanes−EtOAc); *Z*-isomer **1**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90 (1H, d, J = 8.5 Hz, H-6″), 6.57

(1H, d, J = 12.0 Hz, H-5″), 6.45 (3H, m, H-2′, H-6′, H-2), 6.43 (1H, d, J = 12.0 Hz, H-1), 4.68 (1H, sept, J = 6.5 Hz, C-2″ OC*H*(CH_3)$_2$), 4.42 (1H, sept, J = 6.5 Hz, C-3″ OC*H*(CH_3)$_2$), 3.78 (3H, s, C-4″ OCH_3), 3.58 (6H, s, C-3′, C-5′ OCH_3), 1.29 (6H, d, J = 6.5 Hz, C-2″ OCH-(CH_3)$_2$), 1.28 (6H, J = 6.5 Hz, C-3″ OCH(CH_3)$_2$), 0.99 (9H, s, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$), 0.11 (6H, s, OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6 (C, C-4″), 151.1 (C, C-3′, C-5′), 150.4 (C, C-2″), 140.3 (C, C-3″), 133.3 (C,C-1′), 129.8 (C, C-4′), 129.2 (CH, C-1), 125.6 (CH, C-2), 125.4 (CH, C-6″), 124.8 (C, C-1″), 106.3 (CH, C-5″), 106.1 (CH, C-2′, C-6′), 75.1 (CH, C-3″ OC*H*(CH_3)$_2$), 74.8 (CH, C-2″ OC*H*(CH_3)$_2$), 55.8 (CH_3, C-4″ OCH_3), 55.4 (CH_3, C-3′, C-5′ OCH_3), 25.8 (CH_3, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$), 22.5 (CH_3, C-2″ OCH-(CH_3)$_2$), 22.4 (CH_3, C-3″ OCH(CH_3)$_2$), 18.7 (C, C-4′ OSi(CH_3)$_2$C-(CH_3)$_3$), −4.7 (CH_3, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$); HREIMS m/z 516.2936 (calcd for $C_{29}H_{44}O_6Si$, 516.2907); *E*-isomer **2**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (1H, d, J = 8.6 Hz, H-6″), 7.27 (1H, d, J = 16.5 Hz, H-2), 6.87 (1H, d, J = 16.5 Hz, H-1), 6.71 (2H, s, H-2′, H-6′), 6.68 (1H, d, J = 8.8 Hz, H-5″), 4.60 (1H, sept, J = 6.0 Hz, C-2″ OC*H*(CH_3)$_2$), 4.46 (1H, sept, J = 6.0 Hz, C-3″ OC*H*(CH_3)$_2$), 3.85 (3H, s, C-4″ OCH_3), 3.83 (6H, s, C-3′, C-5′ OCH_3), 1.30 (12H, d, J = 6.0 Hz, C-2″, C-3″ OCH(CH_3)$_2$), 1.02 (9H, s, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$), 0.14 (6H, s, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7 (C, C-4″), 151.7 (C, C-3′, C-5′), 150.0 (C, C-2″), 140.4 (C, C-3″), 134.1 (C, C-1′), 131.0 (C, C-4′), 127.3 (CH, C-1), 125.8 (CH, C-2), 122.4 (CH, C-6″), 119.8 (C, C-1″), 107.3 (C, C-5″), 103.6 (CH, C-2′, C-6′), 75.5 (CH, C-2″ OC*H*(CH_3)$_2$), 75.1 (CH, C-3″ OC*H*(CH_3)$_2$), 55.9 (CH_3, C-4″ OCH_3), 55.7 (CH_3, C-3′, C-5′ OCH_3), 25.8 (CH_3, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$), 22.6 (CH_3, C-2″ OCH(CH_3)$_2$), 22.5 (CH_3, C-3″ OCH(CH_3)$_2$), 18.7 (C, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$), −4.6 (CH_3, C-4′ OSi(CH_3)$_2$C(CH_3)$_3$); HREIMS m/z 516.2893 (calcd for $C_{29}H_{44}O_6Si$, 516.2907).

(*Z*)-1-[3′,4′,5′-Trimethoxyphenyl]-2-[2″,3″-di[(isopropyl)oxy]-4″-methoxyphenyl]ethene (15). The *Z*-isomer of cold CA1 precursor **1** (1.40 g, 2.71 mmol) was dissolved in anhydrous CH_3CN (20 mL), and the solution was cooled to 0 °C. CH_3I (0.67 mL, 10.8 mmol) was added and the reaction mixture stirred for 10 min at 0 °C. To this solution was added tetrabutylammonium fluoride (TBAF) (2.98 mL, 2.98 mmol), and the resultant deep yellow colored reaction mixture was stirred for 10 min at 0 °C. H_2O (10 mL) was added, and the product was extracted in EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. White crystals of tetrabutylammonium hydroxide byproduct precipitated. These crystals were filtered and washed with additional ethyl acetate. The combined filtrates were then evaporated under reduced pressure to obtain the crude product, which was subjected to flash column chromatography (silica gel, 4:96 EtOAc−hexanes) to afford product **15** (1.01 g, 2.42 mmol, 89% yield) as a colorless oil, R_f 0.26 (90:10 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (1H, d, J = 8.6 Hz, H-6″), 6.64 (1H, d, J = 12.3 Hz, H-2), 6.49 (3H, m, H-2′, H-6′, H-5″), 6.43 (1H, d, J = 12.3 Hz, H-1), 4.70 (1H, sept, J = 6.2 Hz, C-2″ OC*H*(CH_3)$_2$), 4.43 (1H, sept, J = 6.2 Hz, C-3″ OC*H*(CH_3)$_2$), 3.82 (3H, s, C-4″ OCH_3), 3.79 (3H, s, C-4′ OCH_3), 3.64 (6H, s, C-3′, C-5′ OCH_3), 1.29 (12H, d, J = 6.2 Hz, C-2″, C-3″ OCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7 (C, C-4″), 152.6 (C, C-3′, C-5′), 150.3 (C, C-2″), 140.3 (C, C-4′), 136.8 (C, C-3″), 132.8 (C, C-1′), 128.7 (CH, C-1), 126.6 (CH, C-2), 125.1 (C, C-1″), 124.7 (CH, C-6″), 106.4 (CH, C-5″), 106.0 (C, C-2′, C-6′), 75.0 (CH, C-2″ OC*H*(CH_3)$_2$), 74.8 (CH, C-3″ OC*H*(CH_3)$_2$), 60.8 (CH_3, C-4′ OCH_3), 55.8 (CH_3, C-4″ OCH_3), 55.7(CH_3, C-3′, C-5′ OCH_3), 22.5 (CH_3, C-2″ OCH(CH_3)$_2$), 22.4 (CH_3, C-3″ OCH(CH_3)$_2$); *anal*. C 69.25%, H 7.78%, calcd for $C_{24}H_{32}O_6$, C 69.21%, H 7.74%; HPLC retention time 19.73 min.

(*Z*)-1-[3′,4′,5′-Trimethoxyphenyl]-2-[2″,3″-dihydroxy-4″-methoxyphenyl]ethene (*Z*-CA1, 3).[4,18] The *Z*-isomer **15** (1.01 g, 2.42 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL), and the solution cooled to 0 °C. $TiCl_4$ (1.16 mL, 10.06 mmol) was added to the reaction mixture, and the dark brown colored reaction mixture was stirred for 40 min at 0 °C. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were rinsed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification using flash chromatography (silica gel capped with Florisil, 40:60 EtOAc−hexanes) afforded pure *Z*-CA1 **3** as a pale yellow oil, which was crystallized with hexanes−EtOAc (50:50), yielding *Z*-CA1 **3** (0.36 g, 1.08 mmol, 45% yield) as tan-colored crystals, R_f 0.15 (EtOAc−hexanes, 40:60); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (1H, d, J = 8.6 Hz, H-6″), 6.59 (1H, d, J = 12.2 Hz, H-2), 6.54 (3H, m, H-1, H-2′, H-6′), 6.38 (1H, d, J = 8.8 Hz, H-5″), 5.40 (2H, s, C-2″, C-3″ O*H*), 3.86 (3H, s, C-4″ OCH_3), 3.83 (3H, s, C-4′ OCH_3), 3.67 (6H, s, C-3′, C-5′ OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.8 (C, C-3′, C-5′), 146.3 (C, C-4″), 141.6 (C, C-2″), 137.3 (C, C-4′), 132.6 (C, C-3″), 132.5 (C, C-1′), 130.3 (CH, C-1), 124.0 (CH, C-2), 120.3 (CH, C-6″), 117.8 (C, C-1″), 105.9 (CH, C-2′, C-6′), 102.9 (C, C-5′), 60.9 (CH_3, C-4′ OCH_3), 56.2 (CH_3, C-4″ OCH_3), 55.8 (CH_3, C-3′, C-5′ OCH_3); HPLC retention time 21.39 min.

(*Z*)-1-[3′,4′,5′-Trimethoxyphenyl]-2-[2″,3″-di[([bis[(benzyl)oxy-]]phosphoryl)oxy]-4″-methoxyphenyl]ethene (16).[18,23] *N*-Chlorosuccinimide (0.430 g, 3.24 mmol) was dissolved in anhydrous CH_3CN (10 mL). The reaction mixture was then heated to 40 °C and stirred at this temperature for 5 min. The heat source was removed, and dibenzyl phosphite (DBP) (0.71 mL, 3.24 mmol) was added dropwise. The reaction mixture was then stirred for 3 h at rt.

In a separate 100 mL dry round-bottom flask, equipped with a stir bar, was charged CA1 (**3**) (360 mg, 1.080 mmol) followed by anhydrous CH_3CN (10 mL) and DMAP (13 mg, 0.10 mmol). The temperature of the reaction mixture was maintained between 10 and 20 °C, and anhydrous Et_3N (0.45 mL, 3.24 mmol) was added. The reaction mixture was then cooled to 0 °C, and the dibenzyl chlorophosphate solution was added slowly over a period of 5 to 10 min. The brown-colored reaction mixture was then warmed to rt and stirred for 16 h. The solvent was evaporated completely under reduced pressure using a rotary evaporator, followed by the addition of toluene (∼15 mL). The solvent (toluene) was evaporated under reduced pressure, and additional toluene (15 mL) was added. The precipitated succinimide byproduct was filtered and washed with more toluene. The combined filtrates were washed with 0.5 M KH_2PO_4 (2 × 10 mL), followed by 0.5 M NaOH (2 × 5 mL), and finally with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude reaction mixture was purified by flash column chromatography (silica gel, 40:60 EtOAc−hexanes) to obtain the tetrabenzyl phosphate derivative of CA1 **16** (0.39 g, 0.46 mmol, 42% yield) as an off-white oil, R_f 0.22 (EtOAc−hexanes, 50:50); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (20H, m, C-2″, C-3″ OP(O)(OC$H_2C_6H_5$)$_2$), 7.00 (1H, d, J = 8.7 Hz, H-6″), 6.67 (1H, d, J = 8.5 Hz, H-5″), 6.64 (1H, d, J = 12.0 Hz, H-2), 6.51 (1H, d, J = 12.0 Hz, H-1), 6.46 (2H, s, H-2′, H-6′), 5.09 (8H, m, C-2″, C-3″ OP(O)(OC$H_2C_6H_5$)$_2$), 3.79 (3H, s, C-4″ OCH_3), 3.76 (3H, s, C-4′ OCH_3), 3.62 (6H, s, C-3′, C-5′ OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.8 (C, C-3′, C-5′), 151.6 (C, C-4″), 137.2 (C, C-2″), 135.9, 135.8 (C, C-2″, C-3″ OP(O)(OC$H_2C_6H_5$)$_2$), 135.7 (C, C-4′), 135.6 (C, C-3″), 132.0 (C, C-1′), 131.6 (CH, C-1), 128.4, 128.3, 128.0, 127.8 (CH, C-2″, C-3″ OP(O)(OC$H_2C_6H_5$)$_2$), 126.9 (CH, C-2), 124.6 (CH, C-6″), 124.4 (C, C-1″), 109.3 (CH, C-5″), 106.2 (CH, C-2′, C-6′), 70.0, 69.9, 69.8, 69.6 (CH_2, C-2″, C-3″ OP(O)(O*C*$H_2C_6H_5$)$_2$), 60.8 (CH_3, C-4′ OCH_3), 56.4 (CH_3, C-4″ OCH_3), 55.9 (CH_3, C-3′, C-5′ OCH_3); ^{31}P NMR ($CDCl_3$, 122 MHz) δ −5.3, −5.4; HPLC retention time 38.13 min.

(*Z*)-1-[3′,4′,5′-Trimethoxyphenyl]-2-[2″,3″-di[(monopotassium)-phosphate]-4″-methoxyphenyl]ethene (4).[23] The tetrabenzyl phosphate derivative of CA1 **16** (0.32 g, 0.38 mmol) was dissolved in anhydrous CH_3CN (10 mL), and the reaction contents were cooled to −10 °C. Trimethlysilyl bromide (TMSBr) (freshly distilled over CaH, 0.25 mL, 1.89 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred for 1.5 h at −10 °C to afford the tetra-TMS-phosphate ester derivative of CA1, which was added dropwise to a well-stirred solution of KOMe (260 mg, 3.78 mmol) in dry MeOH (4.5 mL) at −10 °C. The reaction mixture was gradually allowed to reach rt and then stirred for additional 15 min at rt. The solvents were evaporated under reduced pressure (the temperature of the H_2O bath was maintained below 35 °C) to obtain a dry off-white-colored powder, which was dissolved in deionized H_2O (2 mL). The pH of the resultant solution was then carefully titrated to 4.75 to 4.85 using 1 M HCl (subsequently switched to 0.1 M HCl once the pH of the reaction mixture reached ∼5.5) with good stirring. The reaction mixture was then filtered, and to the filtrate was added anhydrous EtOH (7 mL). CA1P **4** precipitated out as a white solid. The reaction mixture was stirred for 5 min. The solid separated was filtered, washed with anhydrous EtOH (2−4 mL), and dried (filter funnel, 15 to 20 min) to yield CA1P **4** (0.10 g, 0.16 mmol, 45% yield): ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (1H, d, J = 8.7 Hz, H-6″), 6.74 (1H, d, J = 11.9 Hz, H-2), 6.68 (1H, d, J = 8.7 Hz, H-5″), 6.67 (2H, s, H-2′, H-6′), 6.64 (1H, d, J = 11.9 Hz, H-1), 3.83 (3H, s, C-4″ OCH_3), 3.74 (3H, s, C-4′

OCH_3), 3.68 (6H, s, C-3′, C-5′ OCH_3); ^{13}C NMR (D_2O, 75 MHz) δ 152.0 (C, C-3′, C-5′), 151.7 (C, C-4″), 143.5 (C, C-2″), 135.6 (C, C-4′), 134.3 (C, C-3″), 133.7 (C, C-1′), 129.9 (CH, C-1), 126.0 (CH, C-2), 125.1 (CH, C-6″), 124.0 (C, C-1″), 108.2 (CH, C-5″), 106.6 (CH, C-2′, C-6′), 60.8 (CH_3, C-4′ OCH_3), 56.1 (CH_3, C-4″ OCH_3), 55.9 (CH_3, C-3′, C-5′ OCH_3); ^{31}P NMR (D_2O, 122 MHz) δ −3.0, −3.7; ESIMS *m*/*z* 491 (100, M^{-1}), 393 (40), 363 (15); HPLC retention time 17.29 min.

3,5-Dimethoxy-4-[(isopropyl)oxy]benzaldehyde (19).[26] Commercially available syringaldehyde (5.32 g, 29.2 mmol) was dissolved in anhydrous DMF (100 mL). Anhydrous K_2CO_3 (8.07 g, 58.4 mmol) and 2-bromopropane (5.48 mL, 58.4 mmol) were added, and the reaction mixture was stirred at 90 °C for 12 h followed by the addition of H_2O (100 mL). The resultant solution was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phases were washed with H_2O, followed by brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5:95 EtOAc−hexanes) to afford aldehyde **19** (6.51 g, 29.03 mmol, 99% yield) as a yellow oil, R_f 0.48 (EtOAc−hexanes, 40:60); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (1H, s, C-1 C*H*O), 7.13 (2H, s, H-2, H-6), 4.54 (1H, sept, J = 6.0 Hz, C-4 OC*H*(CH_3)$_2$), 3.90 (6H, s, C-3, C-5 OCH_3), 1.32 (6H, d, J = 6.0 Hz, C-4 OCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.0 (CH, C-1 *C*HO), 154.2 (C, C-3, C-5), 141.9 (C, C-4), 131.5 (C, C-1), 106.6 (CH, C-2, C-6), 75.8 (CH, C-4 O*C*H(CH_3)$_2$), 56.1 (CH_3, C-3, C-5 OCH_3), 22.4 (CH_3, C-4 OCH(*C*H_3)$_2$); HREIMS *m*/*z* 224.1055 (calcd for $C_{12}H_{16}O_4$, 224.1049).

2,3-Di[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde (20).[18] To a well-stirred solution of 2,3-dihydroxy-4-methoxybenzaldehyde **9**[18] (4.99 g, 29.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was added successively triethylamine (12.4 mL) and DMAP (0.91 g, 7.43 mmol). The mixture was stirred for 10 min, followed by the addition of TBSCl (10.71 g, 71.32 mmol) in portions. The reaction mixture was stirred for 12 h at rt, followed by the addition of H_2O (100 mL), and the product was extracted in CH_2Cl_2 (2 × 250 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Filtration followed by removal of solvent under reduced pressure gave a tan-colored solid. The solid was recrystallized with MeOH to afford the product **20** (7.07 g, 17.8 mmol, 60% yield) as pale yellow crystals, R_f 0.47 (EtOAc−hexanes, 15:85); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.22 (1H, s, C-1 C*H*O), 7.48 (1H, d, J = 9.0 Hz, H-6), 6.63 (1H, d, J = 8.5 Hz, H-5), 3.84 (3H, s, C-4 OCH_3), 1.04 (9H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 1.0 (9H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$), 0.14 (12H, s, C-2, C-3 OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (CH, C-1 *C*HO), 157.5 (C, C-4), 151.0 (C, C-2), 136.8 (C, C-3), 123.4 (CH, C-6), 121.4 (C, C-1), 105.4 (CH, C-5), 55.2 (CH_3, C-4 O*C*H_3), 26.2 (CH_3, C-2 OSi(CH_3)$_2$C(*C*H_3)$_3$), 26.0 (CH_3, C-3 OSi(CH_3)$_2$C(*C*H_3)$_3$), 18.7 (C, C-2 OSi(CH_3)$_2$*C*(CH_3)$_3$), 18.6 (C, C-3 OSi(CH_3)$_2$*C*(CH_3)$_3$), −3.84 (CH_3, C-2, C-3 OSi(*C*H_3)$_2$C(CH_3)$_3$).

2,3-Di[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzyl Alcohol (21). To a stirred solution of aldehyde **20** (5.30 g, 13.4 mmol) in anhydrous EtOH (50 mL) at 0 °C was added $NaBH_4$ (0.50 g, 13.4 mmol) in portions. The reaction mixture was stirred for 30 min and terminated by cautious addition of H_2O (100 mL). Solvents were removed *in vacuo*, and the aqueous phases were extracted with EtOAc (3 × 150 mL). Combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The organic solvents were evaporated to dryness, and the crude product was crystallized with absolute EtOH to afford product **21** as off-white crystals (5.30 g, 13.3 mmol, quantitative yield), R_f 0.49 (EtOAc−hexanes, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (1H, d, J = 8.5 Hz, H-6), 6.51 (1H, d, J = 8.0 Hz, H-5), 4.60 (2H, d, J = 5.5 Hz, C-1 CH_2OH), 3.76 (3H, s, C-4 OCH_3), 1.84 (1H, t, J = 5.5 Hz, C-1 CH$_2$O*H*), 1.04 (9H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 0.98 (9H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$), 0.14 (6H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 0.10 (6H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9 (C, C-4), 145.2 (C, C-2), 136.8 (C, C-3), 126.2 (C, C-1), 120.6 (CH, C-6), 104.8 (CH, C-5), 61.6 (CH_2, C-1 *C*H$_2$OH), 54.9 (CH_3, C-4 O*C*H_3), 26.16 (CH_3, C-2 OSi(CH_3)$_2$C(*C*H_3)$_3$), 26.15 (CH_3, C-3 OSi(CH_3)$_2$C(*C*H_3)$_3$), 18.8 (C, C-2 OSi(CH_3)$_2$*C*(CH_3)$_3$), 18.4 (C, C-3 OSi(CH_3)$_2$*C*(CH_3)$_3$), −3.6 (CH_3, C-2 OSi(*C*H_3)$_2$C(CH_3)$_3$), −3.8 (CH_3, C-3 OSi(*C*H_3)$_2$C(CH_3)$_3$); HREIMS *m*/*z* 398.2303 (calcd for $C_{20}H_{38}O_4Si_2$, 398.6843).

2,3-Di[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzyl Bromide (22). To a well-stirred solution of alcohol **21** (5.30 g, 13.4 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added PBr_3 (1.26 mL, 13.4 mmol). The reaction mixture was stirred for 6 h at 0 °C, followed by the addition of H_2O (100 mL). The organic layers were separated, and the aqueous phases were extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Benzyl bromide **22** (6.03 g, 13.06 mmol, 98% yield) was obtained as a tan-colored solid, which needed no further purification, R_f 0.70 (EtOAc−hexanes, 40:60); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (1H, d, J = 8.5 Hz, H-6), 6.50 (1H, d, J = 8.6 Hz, H-5), 4.53 (2H, s, C-1 CH_2Br), 3.76 (3H, s, C-4 OCH_3), 1.07 (9H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 0.98 (9H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$), 0.14 (6H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 0.11 (6H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7 (C, C-4), 145.8 (C, C-2), 137.0 (C, C-3), 123.1 (CH, C-6), 122.9 (C, C-1), 105.0 (CH, C-5), 55.0 (CH_3, C-4 OCH_3), 30.8 (CH_2, C-1 *C*H$_2$Br), 26.2 (CH_3, C-2 OSi(CH_3)$_2$C(*C*H_3)$_3$), 26.1 (CH_3, C-3 OSi(CH_3)$_2$C(*C*H_3)$_3$), 18.7 (C, C-2 OSi(CH_3)$_2$*C*(CH_3)$_3$), 18.6 (C, C-3 OSi(CH_3)$_2$*C*(CH_3)$_3$), −3.6 (CH_3, C-2 OSi(*C*H_3)$_2$C(CH_3)$_3$), −3.8 (CH_3, C-3 OSi(*C*H_3)$_2$C(CH_3)$_3$).

2,3-Di[(*tert*-butyldimethylsilyl)oxy]-4-(methoxybenzyl)triphenylphosphonium Bromide (23). A mixture of bromide **22** (6.03 g, 13.1 mmol) and PPh_3 (3.77 g, 14.4 mmol) in dry CH_2Cl_2 (100 mL) was heated at reflux for 22 h. Solvent was removed under reduced pressure to afford an off-white solid. Et_2O (200 mL) was added to the solid, and the resultant slurry was stirred for 1 h. The solid was filtered and washed with Et_2O to obtain phosphonium bromide salt **23** (8.04 g, 11.1 mmol, 85% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (9H, m, C-1 CH$_2$P(C$_6$*H*$_5$)$_3$), 7.47 (6H, m, C-1 CH$_2$P(C$_6$*H*$_5$)$_3$), 6.68 (1H, dt, J_{H-H} = 9.0 Hz, J_{H-P} = 2.5 Hz, H-6), 6.32 (1H, d, J = 9.0 Hz, H-5), 5.21 (2H, dd, J_{H-P} = 14.0 Hz, J_{H-H} = 2.5 Hz, C-1 CH_2P(C$_6$H$_5$)$_3$), 3.68 (3H, s, C-4 OCH_3), 0.97 (9H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), 0.84 (9H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$), 0.15 (6H, s, C-2 OSi(CH_3)$_2$C(CH_3)$_3$), −0.02 (6H, s, C-3 OSi(CH_3)$_2$C(CH_3)$_3$); ^{31}P NMR ($CDCl_3$, 122 MHz) δ 21.3; ESIMS *m*/*z* 643 (100, M^{+1}).

(*Z*)/(*E*)-1-[3′,5′-Dimethoxy-4′-[(isopropyl)oxy]phenyl]-2-[(2″,3″-di[(*tert*-butylsilyl)oxy]-4″-methoxy)phenyl]ethene (5 and 6). *n*-BuLi (2.0 M in hexanes, 5.56 mL, 11.1 mmol) was added dropwise to a well-stirred solution of Wittig salt **23** (8.04 g, 11.10 mmol) in anhydrous THF (150 mL) at −10 °C. The reaction mixture was then cooled to −78 °C, and aldehyde **19** (2.73 g, 12.20 mmol) dissolved in anhydrous THF (20 mL) was added dropwise. The reaction mixture was stirred until the temperature gradually reached 0 °C. The reaction was terminated by careful addition of H_2O (100 mL) followed by removal of THF *in vacuo*. The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was crystallized with absolute EtOH. The *Z*-isomer **5** (1.99 g, 3.39 mmol, 31% yield) was obtained as a white solid, after filtration and washing with ice-cold EtOH. The filtrates were evaporated, and the pale yellow solid was crystallized with absolute EtOH and EtOAc to afford *E*-isomer **6** as off-white crystals (3.68 g, 6.23 mmol, 56% yield), $R_{f(Z\text{-isomer})}$ 0.48, $R_{f(E\text{-isomer})}$ 0.31 (90:10 hexanes−EtOAc); *Z*-isomer **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (1H, d, J = 8.6 Hz, H-6″), 6.60 (2H, s, H-2′, H-6′), 6.57 (1H, d, J = 12.2 Hz, H-2), 6.35 (2H, m, H-1, H-5″), 4.33 (1H, sept, J = 6.1 Hz, C-4′ OC*H*(CH_3)$_2$), 3.73 (3H, s, C-4″ OCH_3), 3.64 (6H, s, C-3′ C-5′ OCH_3), 1.28 (6H, d, J = 6.1 Hz, C-4′ OCH(CH_3)$_2$), 1.03 (9H, s, C-2″ OSi(CH_3)$_2$C(CH_3)$_3$), 1.00 (9H, s, C-3″ OSi(CH_3)$_2$C(CH_3)$_3$), 0.19 (6H, s, C-2″ OSi(CH_3)$_2$C(CH_3)$_3$), 0.10 (6H, s, C-3″ OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3 (C, C-3′, C-5′), 151.6 (C, C-4″), 146.2 (C, C-2″), 136.7 (C, C-3″), 135.1 (C, C-4′), 132.4 (C, C-1′), 127.8 (C, C-1), 127.0 (C, C-2), 123.3 (CH, C-6″), 122.2 (C, C-1″), 105.9 (CH, C-2′, C-6′), 104.1 (CH, C-5″), 75.2 (CH, C-4′ O*C*H(CH_3)$_2$), 55.8 (CH_3, C-3′, C-5′ O*C*H_3), 54.9 (CH_3, C-4″ O*C*H_3), 26.4 (CH_3, C-2″ OSi(CH_3)$_2$C(*C*H_3)$_3$), 26.1 (CH_3, C-3″ OSi(CH_3)$_2$C(*C*H_3)$_3$), 22.5 (CH_3, C-4′ OCH(*C*H_3)$_2$), 18.7 (C, C-2″ OSi(CH_3)$_2$*C*(CH_3)$_3$), 18.6 (C, C-3″ OSi(CH_3)$_2$*C*(CH_3)$_3$), −3.2 (CH_3, C-2″ OSi(CH_3)$_2$C(*C*H_3)$_3$), −3.9 (CH_3, C-3″ OSi(CH_3)$_2$C(*C*H_3)$_3$); HREIMS *m*/*z* 588.3299 (calcd for $C_{32}H_{52}O_6Si_2$, 588.3302); *E*-isomer **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (1H, d, J = 16.4 Hz, H-2), 7.19 (1H, d, J = 8.7 Hz, H-6″), 6.81 (1H, d, J = 16.4 Hz, H-1), 6.70 (2H, s, H-2′, H-6′), 6.55 (1H, d, J = 8.7 Hz, H-5″), 4.36 (1H, sept, J = 6.2 Hz, C-4′ OC*H*(CH_3)$_2$), 3.85 (6H, s, C-3′, C-5′ OCH_3), 3.79 (3H, s, C-4″ OCH_3), 1.31 (6H, d, J = 6.2 Hz, C-4′ OCH(CH_3)$_2$), 1.09 (9H, s, C-2″ OSi(CH_3)$_2$C(CH_3)$_3$), 1.00 (9H, s, C-3″ OSi(CH_3)$_2$C(CH_3)$_3$), 0.13 (6H, s, C-2″ OSi(CH_3)$_2$C(CH_3)$_3$), 0.12 (6H, s, C-3″ OSi(CH_3)$_2$C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9 (C, C-3′, C-5′), 151.8 (C, C-4″), 145.5 (C, C-2″), 137.0 (C, C-3″), 135.6 (C, C-4′), 133.4 (C, C-1′),

126.2 (CH, C-6″), 123.9 (CH, C-1), 123.8 (CH, C-2), 117.3 (C, C-1″), 105.2 (CH, C-2′, C-6′), 103.2 (CH, C-5″), 75.4 (CH, C-4′ O*C*H$(CH_3)_2$), 55.9 (CH_3, C-3′, C-5′ O*C*H$_3$), 55.0 (CH_3, C-2″ O*C*H$_3$), 26.5 (CH_3, C-2″ OSi$(CH_3)_2$C(*C*H$_3)_3$), 26.1 (CH_3, C-3″ OSi$(CH_3)_2$C(*C*H$_3)_3$), 22.5 (CH_3, C-4′ OCH(*C*H$_3)_2$), 18.8 (C, C-2″ OSi$(CH_3)_2$*C*(CH$_3)_3$), 18.7 (C, C-3″ OSi$(CH_3)_2$*C*(CH$_3)_3$), −3.5 (CH_3, C-2″ OSi(*C*H$_3)_2$C(CH$_3)_3$), −3.8 (CH_3, C-3″ OSi(*C*H$_3)_2$C(CH$_3)_3$); HREIMS *m*/*z* 588.3306 (calcd for $C_{32}H_{52}O_6Si_2$, 588.3302).

3,4,5-Trimethoxybenzaldehyde (25). 4-Hydroxy-3,5-dimethoxybenzaldehyde (4.77 g, 26.2 mmol) was dissolved in anhydrous DMF (50 mL). To this was added anhydrous potassium carbonate (7.24 g, 52.4 mmol) and ^{12}C-methyl iodide (3.26 mL, 52.4 mmol). The reaction was allowed to reflux for 16 h, after which water (60 mL) was added. The products were extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with copious amounts of water to remove residual DMF, followed by brine, dried with Na_2SO_4, filtered, and condensed *in vacuo*. The resultant solid was recrystallized with hexanes and EtOAc to afford aldehyde **24** as white crystals (3.31 g, 16.82 mmol, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.87 (1H, s, C-1 C*H*O), 7.13 (2H, s, C-2, C-6), 3.94 (3H, s, C-4 OC*H*$_3$), 3.93 (6H, s, C-3, C-5 OC*H*$_3$).

(*Z*)-1-[3′,4′,5′-Trimethoxyphenyl]-2-[2″,3″-di(*tert*-butyldimethylsilyl)oxy]-4″-methoxy]ethene (24).[18] To a well-stirred solution of phosphonium bromide **23** (12.18 g, 16.80 mmol) in dry THF (100 mL) was added *n*-BuLi (6.7 mL, 15.3 mmol) at 0 °C, and the reaction mixture was stirred for 10 min. Aldehyde **25** (3.00 g, 15.3 mmol) dissolved in dry THF (10 mL) was added, and the reaction mixture was stirred for 2 h. H_2O (100 mL) was added, and the THF was removed *in vacuo*. The aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to flash column chromatography to afford *Z*-isomer **24** (1.04 g, 1.85 mmol, 1.78 mmol, 11% yield) as a white solid: R_f 0.24 (60:40 EtOAc−hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (1H, d, J = 8.63 Hz, H-6″), 6.62 (2H, s, H-2′, H-6′), 6.59 (1H, d, J = 12.4 Hz, H-2), 6.36 (2H, m, H-1, H-5″), 3.83 (3H, s, C-4″ OC*H*$_3$), 3.73 (3H, s, C-4′ OC*H*$_3$), 3.67 (6H, s, C-3′, C-5′ OC*H*$_3$), 1.04 (9H, s, C-2″ OSi$(CH_3)_2$C(C*H*$_3)_3$), 1.00 (9H, s, C-3″ OSi$(CH_3)_2$C(C*H*$_3)_3$), 0.19 (6H, s, C-2″ OSi(C*H*$_3)_2$C$(CH_3)_3$), 0.11 (6H, s, C-3″ OSi(C*H*$_3)_2$C$(CH_3)_3$).

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Supporting Information Available: Stilbenoid structure elucidating the molecular numbering scheme utilized. This material is available free of charge via the Internet at http://pubs.acs.org.

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