

An Efficient Synthetic Strategy for Obtaining 4-Methoxy Carbon Isotope Labeled Combretastatin A-4 Phosphate and Other Z-Combretastatins^{1,1}

George R. Pettit,^{*,†} Mathew D. Minardi,[†] Fiona Hogan,[†] and Pat M. Price[‡]

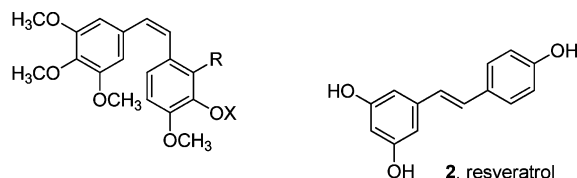
Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, P.O. Box 871604, Tempe, Arizona 85287-1604, and University of Manchester, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, United Kingdom

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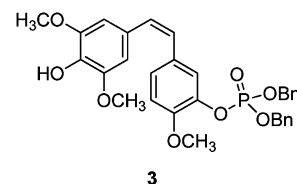
Human cancer and other clinical trials under development employing combretastatin A-4 phosphate (**1b**, CA4P) should benefit from the availability of a [¹¹C]-labeled derivative for positron emission tomography (PET). In order to obtain a suitable precursor for addition of a [¹¹C]methyl group at the penultimate step, several new synthetic pathways to CA4P were evaluated. Geometrical isomerization (*Z* to *E*) proved to be a challenge, but it was overcome by development of a new CA4P synthesis suitable for 4-methoxy isotope labeling.

In 1987, we reported¹ the isolation, structure, and synthesis of combretastatin A-1 (**1c**, CA1) from the subtropical tree *Combretum caffrum* (Eckl. and Zeyh.) Kuntze (Combretaceae)^{1b} collected in southern Africa, and two years later combretastatin A-4 (**1a**, CA4) from the same source was isolated and synthesized.² Subsequently, both CA1 and CA4 were converted to phosphate prodrugs (**1d**, CA1P,³ and **1b**, CA4P⁴) and developed⁵ to human cancer clinical trials.⁶ CA1P and CA4P are presently in phase I/II and III cancer trials, respectively, and CA4P is also in phase II human macular degeneration (leading cause of blindness)⁷ clinical trials. The potential of CA4P in treating other eye diseases such as diabetic retinopathy^{7d} and retinoblastoma^{7b,e} is also being developed. Presently, CA4P (aka Zybrestat) followed by CA1P is the lead among cancer vasculature disrupting drugs.^{8a–c} A large number of other potentially important recent observations concerning medical applications of the leading combretastatins include evidence that CA4P is antiangiogenic,^{8f} increases aberrant organization of metaphase chromosomes in non-small cell lung cancer cells,^{8g} inhibits gastric cancer cell metastasis,^{8h} and improves glucose tolerance in diabetic mice, which in turn suggests a possible new approach to treatment of type 2 diabetes.⁸ⁱ The latter evidence provides another mechanistic parallel to resveratrol (**2**)^{8j} and suggests many other avenues for research from cancer prevention^{8k} to longevity.^{8k}

By 2000, positron emission tomography (PET) was already well established as a noninvasive technique for biomedical imaging, and its potential for necessary applications in preclinical and clinical research employing the lead combretastatins, particularly CA4P, was clearly evident. To follow is both a brief outline of the radiolabeling rationale and a practical synthetic route to employ as a model for later introduction of a [¹¹C]-isotope into CA4/CA4P. A [¹¹C]methyl group was selected as the most efficient method, which required completion of an appropriate new synthesis of CA4 and now remains a most practical option. Meanwhile, a variety of other new syntheses of CA4^{9a,b} and its analogues^{9c–g} have been reported, as well as syntheses of CA1P radiolabeled with a [¹⁴C]methyl group in high specific activity^{10a} and [¹¹C]methyl derivatives^{10b} of resveratrol (**2**), augmented by other structural modifications^{8j} of this increasingly important naturally occurring stilbene.^{8h}



- 1a**, R = X = H, CA4
b, R = H, X = P(O)(ONa)₂, CA4P
c, R = OH, X = H, CA1
d, R = OP(O)(ONa)₂, X = P(O)(ONa)₂, CA1P



Results and Discussion

When we began this research in 2001, the knowledge of CA4 *in vivo* metabolism left some uncertainties as to whether [¹¹C]-CA4 was an appropriate target. That has in the interim been resolved. Very recently, it has been confirmed that CA4 is transformed in rat and human liver fractions to a glucuronide metabolite.¹¹ In the rat, with an approximate therapeutic dose, CA4 is metabolized to both the glucuronide and a previously undetected sulfate derivative at the 4'-phenol position.¹¹ One or both of these relatively long-lived (compared to the 20.1 min half-life of [¹¹C]) modifications would be useful for measurement of radiation (dosimetry) in the study of absorption, distribution, metabolism, and elimination (pharmacokinetics) of CA4P as part of current human trials. In turn, that would allow a better knowledge of the distribution of CA4 between neoplastic and normal tissue as well as the relative binding potential/effective blockade vs dose. Those early objectives required a synthesis of CA4P that would allow a short reaction path and high-yield penultimate step for obtaining [¹¹C]-CA4P.

Substitution of a CA4P A-ring methyl group with a [¹¹C]methyl seemed to offer the fewest difficulties^{10b} and would also utilize some of the synthetic procedures we previously developed for synthesizing combretastatin A-3, the 3-desmethyl derivative of CA4.¹² When an approach based on the 3-hydroxy-4,5-dimethoxyphenyl A-ring of combretastatin A-3 was discontinued owing to geometrical isomerization problems at the stilbene stage, attention was next focused on a 3,5-dimethoxy-4-hydroxyphenyl A-ring precursor that would lead to phenol **3** and allow methylation without *cis/trans* isomerism. The first such attempt to synthesize phenol **3**

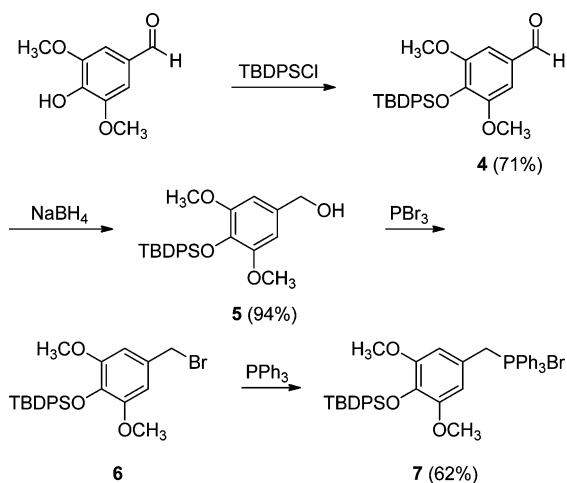
¹ Dedicated to the late Dr. John W. Daly of NIDDK, NIH, Bethesda, Maryland, and to the late Dr. Richard E. Moore of the University of Hawaii at Manoa for their pioneering work on bioactive natural products.

* To whom correspondence should be addressed. Tel: 480 965-3351. Fax: 480 965-2747. E-mail: bpettit@asu.edu.

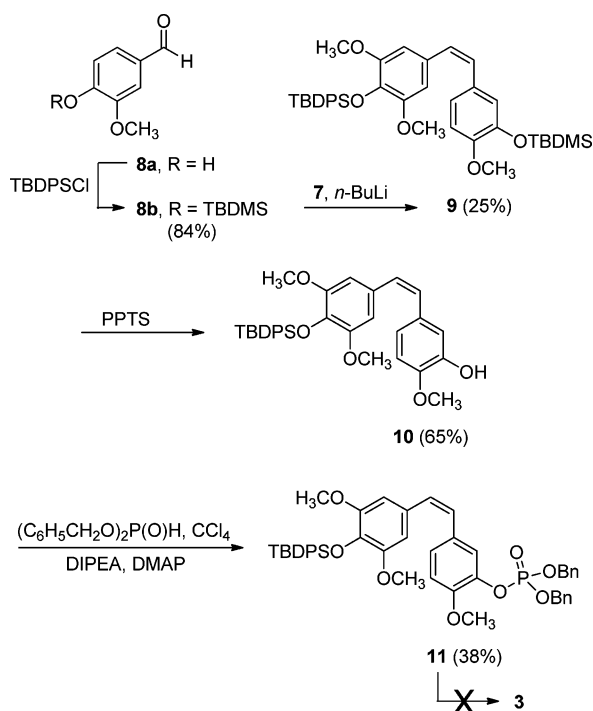
[†] Arizona State University.

[‡] University of Manchester.

Scheme 1



Scheme 2

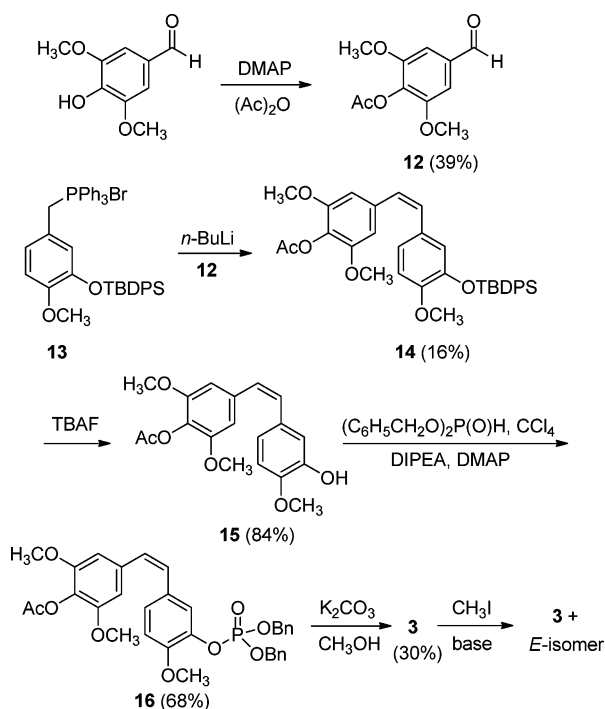


began with silyl protection of 3,5-dimethoxy-4-hydroxybenzaldehyde using *tert*-butyldiphenylsilyl chloride (TBDPSCI), which gave a 71% yield of silyl ether **4** (Scheme 1). The benzaldehyde (**4**) was reduced with NaBH_4 to afford benzyl alcohol **5** (94%), which was then converted to benzyl bromide **6**, and subsequent treatment with triphenylphosphine led to Wittig salt **7** (62%).

Synthesis of the B-ring was begun (Scheme 2) by protection of isovanillin (**8a**) with the *tert*-butyldimethylsilyl (TBDMS) group (**8b**, 84%) as previously reported.^{12a} The Wittig coupling of the A- and B-rings was accomplished by the treatment of phosphonium bromide **7** with *n*-butyllithium followed by addition of aldehyde **8b** to afford stilbene **9** in 25% yield. Disilyl ether **9** was then selectively deprotected with pyridinium *p*-toluenesulfonate (PPTS) in ethanol to afford 3'-phenol **10** in 65% yield. Stilbene **10** was phosphorylated with dibenzylphosphite to afford the phosphate ester (**11**, 38%).^{4,12b,13} Subsequently, the desilylation of phosphorylated stilbene **11** to obtain 4-phenol **3** was attempted, but all efforts failed owing to concomitant cleavage of the phosphate ester.

Since removal of the silyl protecting group was causing difficulty, a different protecting group such as acetate was needed in order to eventually obtain phenol **3**. Because an acetate group is labile under

Scheme 3

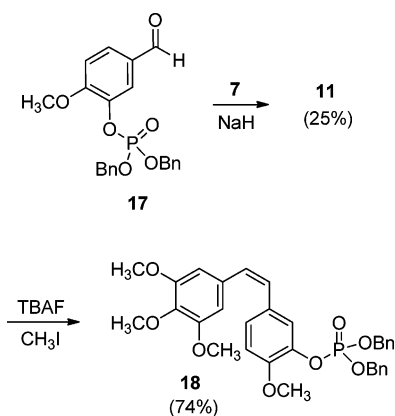


the basic conditions required for a Wittig condensation, it had to be on the A-ring aldehyde unit rather than on the phosphonium salt moiety (ring B). The new A-ring was prepared by the acetylation of 3,5-dimethoxy-4-hydroxybenzaldehyde to give **12** (Scheme 3). The Wittig olefin reaction was accomplished by treatment of phosphonium salt **13**^{12b} with *n*-butyllithium followed by the addition of aldehyde **12** to produce stilbene **14** (16%). Desilylation with tetrabutylammonium fluoride (TBAF) afforded 3'-phenol **15** (84%). The phenol group was phosphorylated^{4,12b,13} with dibenzylphosphite to produce phosphate ester **16** (68%), and deacetylation by treatment with 5% potassium carbonate in methanol afforded 4-phenol **3**, albeit in moderate yields (30%; 2.4% overall yield from **13**) owing to partial isomerization to the corresponding *trans*-stilbene.

Once the necessary precursor of combretastatin A-4 prodrug was in hand, a suitable methylation procedure was needed that could be easily employed to produce [¹¹C]combretastatin A-4 phosphate prodrug. A selection of procedures for the methylation of 4-phenol **3** were attempted using CH_3I , as this would be a choice methylating agent for producing a [¹¹C]-methylated derivative. However, all attempts to methylate the phenol (**3**) with CH_3I resulted in *cis/trans* isomerization.^{10a} Therefore, a new approach that would avoid isomerization by way of direct conversion of the silyl ether to a methyl ether was examined.

In a new route to **11** (Scheme 4), Wittig salt **7** was treated with NaH and aldehyde **17**, which was prepared directly from isovanillin (**8a**) in 85% yield. Desilylation of the product, stilbene **11**, with concurrent methylation that could be used to efficiently obtain [¹¹C]combretastatin A-4 was first explored by modification of an existing procedure, in which a TBDMS ether can be converted into a benzyl ether by use of KF and benzyl bromide in tetrahydrofuran. An attempt to apply this method using KF and CH_3I to convert the TBDPS ether directly to a methyl ether did not succeed. However, the approach was successful when TBAF and CH_3I were used and led to combretastatin A-4 3'-dibenzylphosphate (**18**). That result completed a very useful synthetic approach that can now be employed to obtain 4-methoxy isotope-labeled combretastatins and related stilbenes.

Scheme 4



Experimental Section

General Experimental Procedures. Abbreviations: TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; DIPEA, diisopropylethylamine; LAH, lithium aluminum hydride; DMAP, dimethylaminopyridine; TBAF, tetrabutylammonium fluoride; DMF, *N,N*-dimethylformamide; THF, tetrahydrofuran; DCM, dichloromethane; TLC, thin-layer chromatography. All solvents (ether refers to diethyl ether) used in chemical reactions were redistilled and dried. Other reagents were purchased from Sigma-Aldrich Chemical Co., Lancaster-Clariant, or Fisher-ACROS Chemical Co. Solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate unless otherwise noted. Gravity column chromatography (CC) was performed using silica gel (70–230 mesh) from VWR Scientific. All melting points were determined with an Electrochemical digital melting point apparatus, model IA 9200, and are uncorrected. NMR spectra were recorded using a Varian Gemini 300 or a Varian Unity 400 instrument. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane as an internal standard. High-resolution FAB mass spectra were obtained on a Kratos MS-50 (Midwest Center for Mass Spectrometry, University of Nebraska–Lincoln). Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN.

4-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethoxybenzaldehyde (4). To a solution of imidazole (7.5 g, 109 mmol), 3,5-dimethoxy-4-hydroxybenzaldehyde (10 g, 55 mmol), and DMF (100 mL) was added TBDPSCl² (16 mL, 60 mmol). After stirring 16 h, the reaction was terminated by the addition of water and extracted with hexane–EtOAc (1:1, 3 \times 75 mL). The extract was washed with brine, and following removal of solvent, the residue was separated by flash chromatography (9:1, hexane–EtOAc) to afford aldehyde **4** as a clear oil (16.25 g, 71%): bp 202–204 °C (0.01 mmHg); ¹H NMR (CDCl₃, 300 MHz) δ 1.12 (s, 9H), 3.51 (s, 6H), 6.98 (s, 2H), 7.36 (m, 6H), 7.68 (d, *J* = 8.1 Hz, 4H), 9.76 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 26.62, 55.23, 106.51, 127.15, 127.66, 129.32, 129.55, 133.82, 134.78, 134.97, 140.43, 151.33, 191.01; *anal.* C 71.17%, H 6.90%, calcd for C₂₅H₂₈O₄Si, C 71.39%, H 6.71%.

4-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethoxybenzyl Alcohol (5). Benzaldehyde **4** (5.3 g, 12.6 mmol) was dissolved in ethanol (100 mL), and NaBH₄ (0.6 g, 15.1 mmol) was added. After stirring 3 h, the reaction mixture was acidified with dilute HCl (1 N) and extracted with EtOAc. After solvent removal in vacuo, the resulting oil was purified by CC (7:3 hexane–EtOAc) to afford alcohol **5** (5.01 g, 94%) as a clear oil: bp 218 °C (0.01 mmHg); IR ν_{max} 1134, 1242, 1340, 1427, 1462, 1512, 1593, 2859, 2936, 3420 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.091 (s, 9H), 1.99 (bs, 1H), 3.41 (s, 6H), 4.48 (s, 2H), 6.39 (s, 2H), 7.31 (m, 6H), 7.69 (d, *J* = 7.8 Hz, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 20.05, 26.52, 26.73, 55.13, 65.51, 103.77, 126.96, 127.61, 129.01, 133.36, 133.62, 134.55, 134.76, 135.12, 150.86; *anal.* C 71.22%, H 7.08%, calcd for C₂₅H₃₀O₄Si, C 71.05%, H 7.16%.

4-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethoxybenzyl Bromide (6). To a solution of benzyl alcohol **5** (5 g, 12 mmol) in DCM (100 mL) was added PBr₃ (1 M in DCM, 6 mL, 6 mmol). After stirring 18 h, the reaction was terminated by the addition of NaHCO₃ (10%, 25 mL), and the aqueous phase was extracted with DCM. The combined extract was washed with cold water. Removal of solvent yielded a brown oil (**6**) that was not further purified.

4-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethoxybenzyltriphenylphosphonium Bromide (7). Benzyl bromide **6** (5.5 g) was dissolved in toluene (200 mL), and triphenylphosphine (3.5 g, 13 mmol) was added. The solution was heated at reflux for 1 h, cooled to rt, and allowed to stir an additional 2 h. The resulting precipitate was collected and triturated with ether to afford bromide **7** (5.5 g) as a colorless, amorphous solid (62% over 2 steps): mp 152–153 °C (CH₃OH); ¹H NMR (CD₃OD, 300 MHz) δ 1.061 (s, 9H), 3.11 (s, 6H), 4.88 (d, *J*_{PCH} = 14.4 Hz, 2H), 6.08 (s, 1H), 6.09 (s, 1H), 7.28 (m, 6H), 7.65 (m, 20H), 7.85 (m, 4H); ¹³C NMR (CD₃OD, 75 MHz) δ 20.83, 27.28, 30.98, 31.60, 55.55, 109.14, 109.22, 118.54, 119.67, 120.35, 120.48, 128.11, 129.20, 129.90, 130.55, 131.14, 131.30, 134.95, 135.44, 135.57, 136.35, 152.35, 152.40; *anal.* C 68.62%, H 6.11%, calcd for C₄₃H₄₄BrO₃PSi, C 69.07%, H 5.93%.

4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (8b). A solution of isovanillin (**8a**, 20 g, 131 mmol) in DCM (400 mL) and DIPEA (25 mL, 145 mmol) was stirred for 10 min, and TBDMSCl (22 g, 145 mmol) was added. After stirring 16 h, the reaction was terminated by the addition of water (50 mL). The organic phase was separated and washed with NaOH (5%, 50 mL) followed by brine. The solvent was removed to provide an orange-brown oil, which was separated by vacuum distillation to afford a colorless oil (29.3 g, 84%): bp 140–142 °C (0.01 mmHg); ¹H NMR (CD₃OD, 300 MHz) δ 0.13 (s, 6H), 0.96 (s, 9H), 3.84 (s, 3H), 6.91 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.43 (dd, *J* = 2.1, 8.1 Hz, 1H), 9.77 (s, 1H).

3'-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-3,4',5-trimethoxy-(*Z*)-stilbene (9). Phosphonium bromide **7** (5 g, 6.7 mmol) was dissolved in THF (100 mL) and cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 2.7 mL, 6.7 mmol) was added, followed after 1 h by aldehyde **8b** (1.95 g, 7.4 mmol) over 5 min. After stirring for 16 h, the reaction was terminated by the addition of water, and the mixture was extracted with EtOAc. The solvent was removed from the organic phase, and the residue was separated by CC to afford a clear oil (**9**, 0.5 g, 25%): bp (dec) 94–96 °C (0.01 mmHg); ¹H NMR (CD₃OD, 300 MHz) δ 0.15 (s, 6H), 1.02 (s, 9H), 1.15 (s, 9H), 3.32 (s, 6H), 3.79 (s, 3H), 6.41 (s, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.82 (s, 1H), 6.85 (s, 1H), 7.04 (s, 1H), 7.37 (m, 10H), 7.75 (m, 4H); ¹³C NMR (CD₃OD, 75 MHz) δ –4.81, 18.31, 20.05, 25.64, 26.73, 30.27, 30.79, 34.16, 54.92, 55.38, 100.61, 105.79, 111.56, 121.45, 122.56, 125.46, 126.91, 128.57, 128.96, 129.16, 129.73, 130.36, 133.47, 134.55, 135.12, 144.57, 149.95, 150.47; *anal.* C 71.19%, H 7.74%, calcd for C₃₉H₅₀O₅Si₂, C 71.52%, H 7.69%.

4-(*tert*-Butyldiphenylsilyloxy)-3'-hydroxy-3,4',5-trimethoxy-(*Z*)-stilbene (10). Stilbene **9** (0.34 g, 0.5 mmol) and PPTS (12 mg, 0.05 mmol) were dissolved in ethanol (25 mL). The mixture was heated to 60 °C and allowed to stir for 100 h. Ethanol was removed, and the residue was separated by CC (9:1 hexane–EtOAc) to yield stilbene **10** (0.18 g, 65%): mp 86–87 °C; ¹H NMR (CD₃OD, 300 MHz) δ 1.089 (s, 9H), 3.28 (s, 6H), 3.84 (s, 3H), 5.46 (s, 1H), 6.36 (s, 2H), 6.65 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.33 (m, 10H), 7.70 (m, 4H); ¹³C NMR (CD₃OD, 75 MHz) δ 19.99, 26.67, 29.10, 30.76, 54.94, 55.79, 105.78, 110.21, 115.06, 120.93, 126.88, 128.44, 128.96, 129.24, 129.68, 130.69, 133.46, 134.39, 135.12, 145.14, 145.60, 150.50; *anal.* C 72.98%, H 6.53%, calcd for C₃₃H₃₆O₅Si, C 73.30%, H 6.71%.

3'-*O*-Bis(benzyl)phosphoryl-4-(*tert*-butyldiphenylsilyloxy)-3,4',5-trimethoxy-(*Z*)-stilbene (11). From Phenol **10**. Method A. To a solution of 3'-phenol **10** (0.18 g, 0.33 mmol) in acetonitrile (10 mL) that was cooled to –10 °C was added CCl₄ (0.32 mL, 3.3 mmol). The mixture was stirred for 10 min before the addition of DIPEA (0.12 mL, 0.68 mmol) and DMAP (4 mg, 0.033 mmol), and after 1 min dibenzylphosphite (0.11 mL, 0.49 mmol)⁴ was added (dropwise over 5 min). The reaction mixture was stirred for 3 h at –10 °C, treated with KH₂PO₄ (20 mL, 0.5 M), stirred for 10 min, and then extracted with EtOAc. Removal of solvent and separation by CC (1:1 hexane–EtOAc) afforded phosphite **11** (0.10 g, 38%): bp (dec) 148 °C (0.01 mmHg); ¹H NMR (CDCl₃, 300 MHz) δ 3.64 (s, 6H), 3.76 (s, 3H), 5.11 (s, 2H), 5.14 (s, 2H), 6.44 (d, *J* = 2.1 Hz, 2H), 6.50 (s, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.12 (m, 1H), 7.32 (s, 10H); *anal.* C 70.22%, H 6.31%, calcd for C₄₇H₄₉O₈PSi, C 70.48%, H 6.17%.

4-Acetoxy-3,5-dimethoxybenzaldehyde (12). A solution prepared from 3,5-dimethoxy-4-hydroxybenzaldehyde (5 g, 27 mmol) and DMAP (0.34 g, 2.7 mmol) in pyridine (50 mL) and acetic anhydride (8 mL, 81 mmol) was stirred for 16 h. Reaction was terminated by the addition of water (100 mL) followed by extraction with EtOAc, washing of the

organic phase with HCl (1 N), and removal of solvent. The residue was purified by CC (7:3 hexane–EtOAc) to give **12** (2.4 g) as a colorless solid that crystallized from EtOAc–hexane: mp 116–117 °C; ¹H NMR (CD₃OD) δ 2.36 (s, 3H), 3.90 (s, 6H), 7.15 (s, 2H), 9.91 (s, 1H).

4-Acetoxy-3'-(tert-butyl)diphenylsilyloxy)-3,4',5-trimethoxy-(Z)-stilbene (14). Phosphonium bromide **13** (7.7 g, 1.07 mmol)^{12b} in THF (50 mL) was cooled to –78 °C, and *n*-BuLi (2.5 M in hexane, 3.9 mL) was added. The mixture was stirred for 1 h, aldehyde **12** (2 g, 8.9 mmol) was added in four portions (over 5 min), and the resulting mixture was allowed to warm to rt and stirred an additional 3 h. Water (100 mL) was added, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over sodium sulfate. After removal of solvents, the resulting oil was separated by CC (9:1 hexane–EtOAc) to yield stilbene **14** (0.81 g, 16%): mp 81–82 °C (hexane–acetone); ¹H NMR (CD₃OD, 300 MHz) δ 1.09 (s, 9H), 2.32 (s, 3H), 3.47 (s, 3H), 3.61 (s, 6H), 6.32 (d, *J* = 1.2 Hz, 2H), 6.47 (s, 2H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 2.4, 8.1 Hz, 1H); *anal.* C 71.87%, H 6.42%, calcd for C₃₅H₃₈O₆Si, C 72.14%, H 6.57%.

4-Acetoxy-3'-hydroxy-3,4',5-trimethoxy-(Z)-stilbene (15). To a solution of stilbene **14** (0.81 g, 1.4 mmol) in THF (30 mL) was added TBAF (1 M in THF, 1.5 mL), stirring was continued for 2 h, 50 mL of 1 N HCl was added, and the mixture was extracted with EtOAc. The solvent was removed from the organic phase, and the residue was separated by CC (7:3 hexane–EtOAc) to give stilbene **15** as a colorless oil (0.40 g, 84%): bp (dec) 110–112 °C (0.01 mmHg) ¹H NMR (CD₃OD, 300 MHz) δ 2.32 (s, 3H), 3.66 (s, 6H), 3.86 (s, 3H), 5.60 (s, 1H), 6.42 (d, *J* = 12 Hz, 1H), 6.50 (d, *J* = 12 Hz, 1H), 6.55 (s, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.79 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H); ¹³C NMR (CD₃OD, 75 MHz) δ 20.53, 55.95, 56.02, 105.61, 110.27, 115.01, 121.04, 127.57, 128.74, 130.07, 130.26, 135.37, 145.15, 145.74, 151.64, 168.64; *anal.* C 66.33%, H 5.80%, calcd for C₁₉H₂₀O₆, C 66.27%, H 5.85%.

4-Acetoxy-3'-O-bis(benzyl)phosphoryl-3,4',5-trimethoxy-(Z)-stilbene (16). To a solution of 3'-phenol **15** (0.55 g, 1.6 mmol) in acetonitrile (10 mL) that was cooled to –10 °C was added CCl₄ (1.5 mL, 15.8 mmol). The mixture was stirred for 10 min before the addition of DIPEA (0.56 mL, 3.25 mmol) and DMAP (20 mg, 0.15 mmol). After 1 min, dibenzylphosphite (0.525 mL, 2.4 mmol) was added (dropwise over 5 min). The reaction mixture was stirred an additional 3 h at –10 °C, treated with KH₂PO₄ (20 mL, 0.5 M), stirred for a further 10 min, and then extracted with EtOAc. The solvent was removed from the organic phase, and the residue was separated by CC (3:2 hexane–EtOAc) to yield phosphate **16** (0.65 g, 68%): mp 82–83 °C; ¹H NMR (CDCl₃, 300 MHz) δ 3.64 (s, 6H), 3.76 (s, 3H), 5.11 (s, 2H), 5.14 (s, 2H), 6.44 (d, *J* = 2.1 Hz, 2H), 6.50 (s, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.12 (m, 1H), 7.32 (s, 10H); *anal.* C 66.82%, H 5.79%, calcd for C₃₃H₃₃O₉P, C 66.57%, H 5.50%.

3'-O-Bis(benzyl)phosphoryl-4-hydroxy-3,4',5-trimethoxy-(Z)-stilbene (3). To a solution of stilbene **16** (0.60 g, 0.1 mmol) in CH₃OH (10 mL) was added K₂CO₃ (5 mL, 5% in 1:1 CH₃OH–H₂O). After stirring for 1 h, the reaction was terminated by the addition of HCl (1 N, until pH ~7) and extracted with EtOAc. Solvent was removed (in vacuo) from the organic phase, and the residue was separated by CC (3:2 hexane–EtOAc) to afford stilbene **3** as a yellow oil (0.18 g, 30%): bp (dec) 53–55 °C (0.01 mm); ¹H NMR (CDCl₃, 300 MHz) δ 3.80 (s, 3H), 3.94 (s, 6H), 5.18 (s, 2H), 5.20 (s, 2H), 5.6 (bs, 1H), 6.70 (s, 2H), 6.81 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.33 (m, 10H); *anal.* C 65.93%, H 5.82%, calcd for C₃₁H₃₁O₈P, C 66.19%, H 5.55%.

3-O-Bis(benzyl)phosphoryl-4-methoxybenzaldehyde (17). Isovanillin (5 g, 32 mmol) was phosphorylated using DIPEA (1.7 mL, 67 mmol), DMAP (0.40 g, 3.2 mmol), dibenzylphosphite (10.6 mL, 48 mmol), acetonitrile (200 mL), and CCl₄ (30 mL, 320 mmol) as described above (see **16**). Removal of solvent (in vacuo) and separation by CC (1:1 hexane–EtOAc) afforded phosphate **17** (11.2 g, 85%) as a colorless solid: mp 68–69 °C (from hexane–EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 3.85 (s, 3H), 5.18 (d, *J* = 9.3 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 10H), 7.62 (s, 1H), 7.77 (m, 1H), 9.75 (s, 1H).

4-(tert-Butyldiphenylsilyloxy)-3'-O-bis(benzyl)phosphoryl-3,4',5-trimethoxy-(Z)-stilbene (11). From Salt 7. Method B. To a suspension of Wittig salt **7** (7.6 g, 10 mmol) in toluene (500 mL, freshly distilled) was added NaH (0.53 g, 13 mmol) with stirring (1 h). The solution

was cooled to 0 °C before the addition of aldehyde **17** (4.13 g, 10 mmol). Stirring was continued at 0 °C for 6 h and at rt for 16 h before the addition of water (100 mL) and extraction with EtOAc. After removal of solvent (in vacuo) from the organic phase, the oil was separated by CC (7:3 hexane–EtOAc), affording stilbene **11** (2.1 g, 25%) as a colorless oil.

3'-O-Bis(benzyl)phosphoryl-combretastatin A-4 (18). To a solution of Na₂S₂O₃ (20 mg, 0.125 mmol), TBAF (125 μL, 1 M in THF), and CH₃I (80 μL, 1.25 mmol) in THF (1 mL) was added stilbene **11** (0.10 g, 0.125 mmol), and the mixture was stirred for 1 h at rt. The reaction was terminated by the addition of water (5 mL), and the mixture was extracted with DCM. The solvent was removed (in vacuo) from the organic phase, and the residue was separated by CC (3:2 hexane–EtOAc) to yield stilbene **18**⁴ (51 mg, 74%): mp 73 °C; (lit⁴ mp 73 °C); ¹H NMR (CDCl₃, 300 MHz) δ 3.67 (s, 6H), 3.77 (s, 3H), 3.80 (s, 3H), 5.12 (s, 2H), 5.14 (s, 2H), 6.40 (d, *J* = 12 Hz, 1H), 6.45 (d, *J* = 12 Hz, 1H), 6.48 (s, 2H), 6.78 (d, *J* = 9 Hz, 1H), 7.06 (dd, *J* = 1.8, 9 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.30 (s, 10H).

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