A Pinacol Rearrangement/Oxidation Synthetic Route to Hydroxyphenstatin[1]

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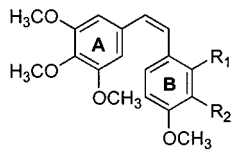
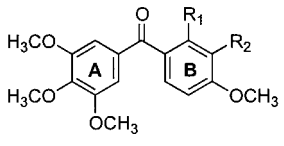
In an attempt to develop biologically active compounds from the inactive trans isomer (**3a**) of stilbene **1a**, after asymmetric dihydroxylation to optically pure (*R,R*)-diol **8** the unexpected racemic diphenylacetaldehyde (**9**) was generated via a Pinacol rearrangement. Several derivatives of diphenylacetaldehyde **9** were synthesized (**11**−**15**) and reported. Further reaction of aldehyde **9** during desilylation through autoxidative decarbonylation afforded benzophenone **2b**, designated hydroxyphenstatin, a potent antitumor and antimitotic agent. Hydroxyphenstatin showed potent inhibition of the tubulin assembly (IC_{50} 0.82 μM) and exhibited an ED_{50} of 2.5 μg/mL against the P388 lymphocytic leukemia cell line.

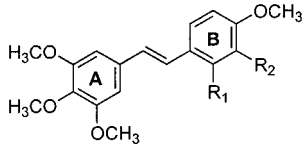
Two of the most promising biologically active lead compounds that we isolated from the African willow tree *Combretum caffrum* Kuntze (Combretaceae) are combretastatins A-1 (**1a**)[2a] and A-4 (**1b**),[2b] reported in 1987 and 1989, respectively. Both stilbenes structurally resemble the antimitotic and cytotoxic agents colchicine[4,6] and podophyllotoxin.[5,6] Monophenol **1b** is a potent inhibitor of microtubule assembly[3] (IC_{50} 2−3 μM) and of a broad range of cancer cell lines,[3e] e.g., IC_{50} 0.002 μg/mL against the murine L1210 leukemia.[2,3a] Diphenol **1a** has shown similar inhibition of microtubule assembly (IC_{50} 2−3 μM), although it has proved to be less active against the murine L1210 leukemia cell line (0.2 μg/mL)[2a,3a] and other cancer cell lines. However, combretastatin A-1 (**1a**) was found to be more potent than combretastatin A-4 (**1b**) in its ability to increase intracellular daunorubicin concentrations in multidrug-resistant cancer cell lines.[7] Most importantly, the strong tubulin-binding *cis*-stilbenes **1a** and **1b** elicit irreversible vascular shutdown selectively within solid tumors.[8a] The degree of reduction ranged from 50% with diphenol **1a** to 70% with monophenol **1b**,[8a] while the combretastatin A-4 prodrug (**1c**)[8a] induces complete vascular shutdown within cancer microvascular systems at doses one-tenth of the maximum tolerated dose.[8b] Since tumor growth relies on the development of new blood vessels, or angiogenesis, cancer-specific antiangiogenic drugs such as the combretastatin derivatives discussed above are an attractive way to approach the cancer problem.[8c,d]



1a, R_1=R_2=OH
combretastatin A-1
b, R_1=H, R_2=OH
combretastatin A-4
c, R_1=H, R_2=OP(O)(ONa)$_2$
combretastatin A-4 prodrug
d, R_1=R_2=OP(O)(ONa)$_2$
combretastatin A-1 prodrug



2a, R_1=H, R_2=OH
phenstatin
b, R_1=R_2=OH
hydroxyphenstatin
c, R_1=H, R_2=OP(O)(ONa)$_2$
phenstatin prodrug
d, R_1=R_2=OP(O)(ONa)$_2$
hydroxyphenstatin prodrug



3a, R_1=R_2=OH
(*E*)-combretastatin A-1
b, R_1=H, R_2=OH
(*E*)-combretastatin A-4

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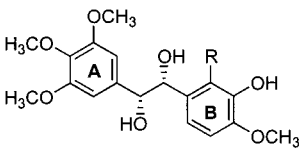
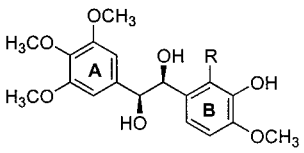
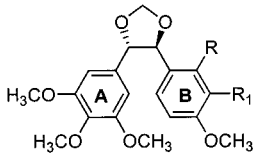
An SAR investigation of potential cancer antiangiogenic agents based on the combretastatin A-series of structural leads has continued to be of high priority in our research directed at the discovery of new anticancer drugs. Our previous SAR analyses of the combretastatins have indicated that the *cis*-stilbene geometry is the most important factor for the inhibition of cancer cell growth.[2] With the corresponding (*E*)-stilbenes, the cancer cell growth inhibitory and antitubulin activity drops sharply from that exhibited by the corresponding (*Z*)-isomers.[9,10] Recently, the water-soluble phosphate derivative of combretastatin A-1 (**1d**) was synthesized and found to have improved therapeutic potential, as was earlier shown for combretastatin A-4 (**1b**) and its prodrug (**1c**).[11] These prodrugs are now undergoing preclinical and clinical development, respectively. As part of the overall SAR study, benzophenones **2a** and **2b**, designated phenstatin[12a] and hydroxyphenstatin,[12b] respectively, were synthesized by our group. These benzophenones were also found to display strong anticancer and antimitotic activity. The sp^2-hybridized carbonyl group keeps the two aryl rings in a quasi "cis" orientation, which appears to be necessary for significant biological activity. These experiments also showed that the two-carbon ethene unit can be replaced by a one-carbon ketone, with retention of activity. Furthermore, the corresponding phosphate prodrugs **2c** and **2d** again showed strong anticancer activity.[12a,b] Other extensions of these SAR studies led to the synthesis and biological evaluation of the (*S*,*S*) and (*R*,*R*)-diols, **4a**−**5b**.[9] Diols **4a**−**5b**, synthesized from the essentially inactive trans isomers **3a** and **3b** employing the Sharpless asymmetric dihydroxylation technique,[9] showed reduced cancer cell line inhibitory activity when compared to their parent *cis*-stilbenes. Interestingly, (*S*,*S*)-derivatives **5a** and **5b** exhibited greater overall biological activity (tubulin binding and cancer cell line) when compared to their (*R*,*R*)-enantiomers, thus indicating a favored conformation for activity.



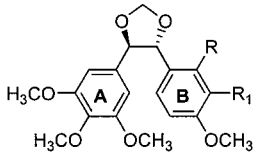
4a, R=H
(*R*,*R*)-combretastatin A-4 diol
b, R=OH
(*R*,*R*)-combretastatin A-1 diol



5a, R=H
(*S*,*S*)-combretastatin A-4 diol
b, R=OH
(*S*,*S*)-combretastatin A-1 diol



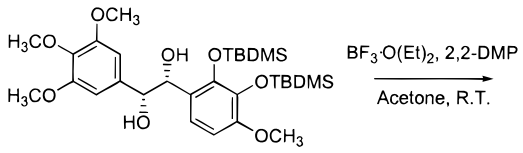
(*S*,*S*)-**6a**, R=R$_1$=OH
(*S*,*S*)- **b**, R=R$_1$=OP(O)(ONa)$_2$



(*R*,*R*)-**7**, R=R$_1$=OH

To further examine structural requirements involving the ethylene cis-bridging of the combretastatin A-series for potent anticancer activity, we have synthesized and evaluated the 1,3-dioxolanes (*S*,*S*)-**6a** (designated dioxostatin), its prodrug (*S*,*S*)-**6b** and (*R*,*R*)-**7**.[9c] The results again illustrated the importance of the hydroxyl group in the 2-position of the B ring for tubulin binding[9] and of the *cis*-diaryl relationship for cancer cell growth inhibition. Dioxostatin (**6a**) was found to be a most potent inhibitor of microtubule assembly at the colchicine site.[9c]

During the preparation of other conformationally restricted combretastatin A-series SAR probes, (*R*,*R*)-diol **8** was allowed to react with 2,2-dimethoxypropane in the presence of boron trifluoride etherate (at room temperature) in an attempt to synthesize the acetonide derivative. Mass spectral analysis of the major isolated product indicated the loss of 18 (H_2O) from the molecular weight of (*R*,*R*)-diol **8**. An aldehyde carbonyl peak at 1726 cm^{-1} was recorded in the IR spectrum, and the ^1H NMR signal at 9.84 ppm further established the presence of an aldehyde group. The product was then presumed to arise from a pinacol rearrangement (**8**→**9**) and its structure was confirmed by an X-ray crystallographic structure determination.



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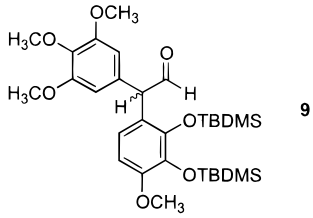

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The X-ray structure determination also helped to resolve the question as to whether the diphenylacetaldhyde product (**9**) had retained chirality during the pinacol rearrangement or had been converted to a racemic mixture. The former would be the expected outcome of a concerted type of reaction with inversion of stereochemistry at the carbon atom bearing the hydroxyl leaving group (i.e., C7 in Figure 1), whereas formation of a free, stable carbonium ion intermediate at C7 would result in the loss of chirality at this atom.

Initially, assignment of the correct space group could not be readily ascertained; the structure solution and refinement of aldehyde **9** could be accomplished in both the *P*1 and $P\bar{1}$ space groups and the final *R* value was nearly identical in both cases. However, in the case of

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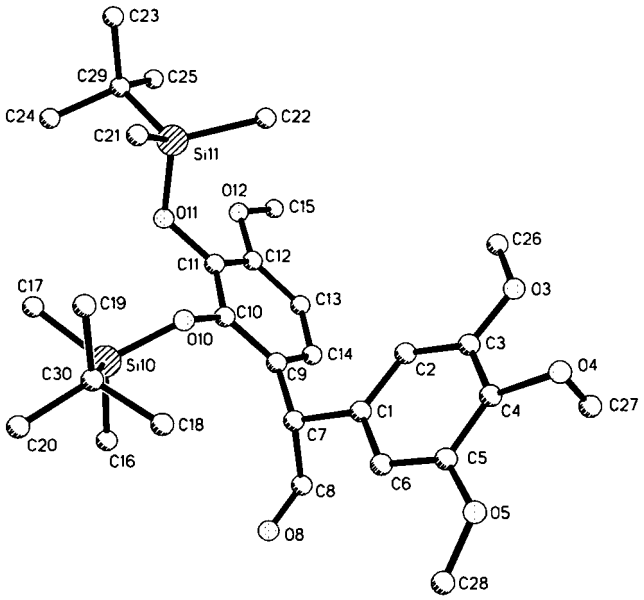
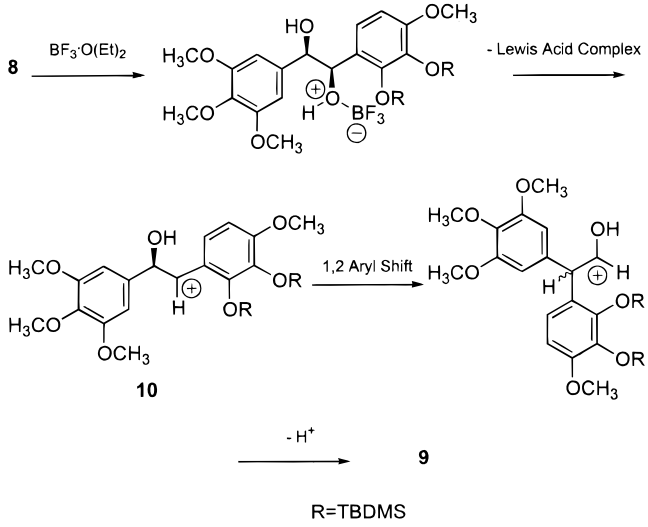


Figure 1. Computer-generated perspective of one enantiomer of (±)-diphenylacetaldehyde derivative (**9**) (H atoms and disorder not shown).

the P1 space group, SHELXL[17] refinement suggested that the data was twinned and that the structure should be treated as a racemic twin, present in the approximate ratio of 1:1. Since these conditions are the same as those met by assuming that the crystal is really a racemic mixture of the same molecule in the $P\bar{1}$ space group, the latter was chosen as being the correct space group assignment. A final conventional residual index R_1 of 0.113 was obtained for the refinement of aldehyde **9** in $P\bar{1}$ space group. The rather poor *R* value obtained, even for an ambient temperature (26 °C) data collection, could be attributed in part to the obvious disorder exhibited by the OMe groups, as well as the higher than average residual electron density (+0.73 e/Å^3 and −0.75 e/Å^3) still remaining in the final refinement model. The major proportion of this residual density, however, could be attributed to the Si atoms themselves (e.g., bond distances of ≤1.0 Å to Si atoms), indicating that other, unaccounted for atoms (such as solvent) were not present.

The unit cell of the X-ray structure was determined to contain a 1:1 ratio of the two enantiomers of the aldehyde, one enantiomer of which is shown in Figure 1. The presence of a racemic mixture implies that all optical activity was lost in the pinacol reaction, presumably owing to the formation of a carbonium ion intermediate leading to aldehyde **9**. Such a conclusion was supported by the fact that no measurable optical rotation could be observed for a solution of the pinacol reaction product in chloroform [the rotation of the optically active starting material, (*R*,*R*)-diol **8**, was +46° (*c* 1.24, $CHCl_3$)][9b] again suggesting that a 1:1 enantiomeric ratio (racemic mixture) had been formed in the pinacol reaction.

Scheme 1



Optimization of the pinacol rearrangement[13] was accomplished through the use of two equivalents of the Lewis acid in tetrahydrofuran to afford racemic aldehyde **9**, in 68% yield. While stereospecific 1,2-rearrangements for pinacol type reactions using carefully controlled conditions with a Lewis acid have been reported,[14] under the present reaction conditions (Scheme 1) the 1,2-aryl shift occurs equally above and below the plane of carbocation **10**, thus generating racemic aldehyde **9**.

Diphenylacetaldehyde **9** was converted to the crystalline derivatives shown in Scheme 2. (*E*)- and (*Z*)-oximes **11** and **12** (~3:1) were both obtained owing to the sterically small oxime hydroxyl group. However, (*Z*)-oxime **12** proved to be unstable upon isolation and was readily converted to the (*E*)-isomer during crystallization. Thiosemicarbazone **13**, 2,4-dinitrophenylhydrazone **14**, and semicarbazone **15** were all isolated as their (*E*)-isomers in good yield. Attempts at cleavage of the silyl protecting group from derivatives **11**−**15** afforded mixtures[15] and were not further pursued. However, upon desilylation of diphenylacetaldehyde **9** using tetrabutylammonium fluoride (TBAF) another unexpected reaction occurred. Benzophenone **2b** was consistently obtained in yields greater than 45%. Loss of the aldehyde group was established by NMR analyses. Mass spectral analysis indicated that a CH_2 unit had been lost in addition to the silyl groups, and a conjugated carbonyl absorption at 1631 cm^{-1} was seen in the IR spectrum. In addition, the physical properties exhibited by this new product led us to believe that it was identical to that of a compound previously prepared in our laboratories,[12b] designated hydroxyphenstatin. We anticipated that confirmation of its identity could most readily be accomplished by the simple comparison of cell parameters of the new product with those of the previously prepared, authentic sample of hydroxyphenstatin (for which a complete X-ray crystal structure determination had already been performed). Since both samples had been crystallized from the same solvent (CH_3OH), it was assumed they would adopt the same crystalline habit and have identical cell parameters. Surprisingly, this was not the case. Instead, the newly prepared hydroxyphenstatin **2b** crystallized in space group *Pbca*, assuming nearly twice the cell volume as

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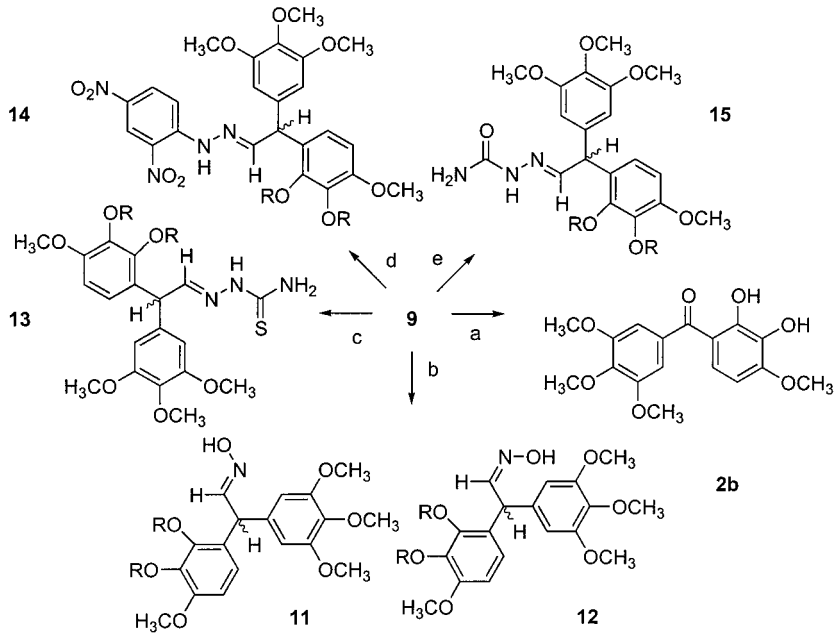
Scheme 2[a]



[a]**Reagents**: (a) TBAF, THF; (b) $HONH_2 \cdot HCl$, $NaOC(O)CH_3$, CH_3OH/H_2O; (c) $H_2NC(S)NHNH_2$, CH_3OH/H_2O; (d) $(NO_2)_2C_6H_5NH_2$, H_2SO_4, CH_3OH; (e) $H_2NC(O)NHNH_2 \cdot HCl$, $NaOC(O)CH_3$, CH_3OH/H_2O.

that noted for the previously prepared, authentic sample of hydroxyphenstatin, which had crystallized in space group Pc from the same solvent. Since such a phenomenon is an extremely unusual event, complete data collection and structure solution was required on the new sample of hydroxyphenstatin, to positively confirm its identity. An X-ray structural model of the results is shown in Figure 2a, along with a comparative view of the previously obtained hydroxyphenstatin X-ray structural results in Figure 2b. Comparison of parts a and b of Figure 2 shows the slight conformational differences assumed by the *p*-*O*-methyl substituent in the trimethoxybenzene rings of the two structures, thus explaining the difference in crystalline habit adopted by each of these two different crystallization specimens of hydroxyphenstatin **2b**.

Authentication of the new compound as hydroxyphenstatin confirmed that a base-catalyzed autoxidative decarbonylation (Scheme 3) had occurred. This is analogous to the reaction of diphenylacetaldehyde to yield benzophenone, as reported in the literature.[16] Initiation of the chain reaction leading to ketone **2b** would appear to begin with formation of free radical **16**. The conjugation to the two aryl rings and carbonyl group would allow favorable delocalization and hence stabilization of the radical. Propagation of radical **16** through reaction with molecular oxygen would then afford radical **17**. Although this reaction was performed under argon and anhydrous conditions, one can assume the tetrahydrofuran solvent was the source of oxygen owing to the solubility of oxygen in tetrahydrofuran and peroxide formation. Radical propagation would continue when radical **17** abstracts a hydrogen from another molecule of diphenylacetaldehyde **9**, to yield radical **16** and hydroperoxide **18**. Finally, termination of radical propagation would occur when hydroperoxide **18** reacts with a fluoride ion (from 2.2 equivalents of TBAF) at the carbonyl carbon on aldehyde **18**, thereby eliminating formyl fluoride.[17]

In summary, *trans*-stilbene **3a** was converted (overall 33% yield) into the strong cancer cell growth inhibitory and antimitotic agent hydroxyphenstatin, **2b**, via a pinacol rearrangement and base-catalyzed autooxidative decarbonylation sequence.

Experimental Section

General Experimental Procedures. Methanol (CH_3OH), ethyl acetate (EtOAc), hexane, and dichloromethane (DCM) were distilled prior to use. TBAF refers to tetrabutylammonium fluoride. Thiosemicarbazide and sodium chloride were purchased from the Fisher-Acros Chemical Co., sodium hydroxide was purchased from VWR Scientific, hydroxylamine hydrochloride was purchased from the Eastman Chemical Co., 2,4-dinitrophenylhydrazine, semicarbazide hydrochloride, and hydrochloric acid were purchased from the J. T. Baker Chemical Co., anhydrous sodium acetate was purchased from the Mallinckrodt Chemical Co., and all other reagents were purchased from the Sigma-Aldrich Chemical Co. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. Column chromatography was performed using either flash silica (230−400 mesh ASTM) or gravity silica (70−230 mesh ASTM) from E. Merck. Analtech silica gel GHLF plates were used for TLC. All compounds were visible with fluorescent short-wave light (254 nm).

Melting points are uncorrected. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN.

(±)-2-(2′,3′-Di[(*tert*-butyldimethylsilyl)oxy]-4′-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acetaldehyde (9). Initial Synthesis. $BF_3 \cdot OEt_2$ (0.10 mL; 0.81 mmol; 4 equiv) was added dropwise to a stirred solution of (*R*,*R*)-diol **8** (0.11 g; 0.18 mmol) and 2,2-DMP (0.19 mL; 1.5 mmol; 8 equiv) in acetone (2 mL) under argon at room temperature. After 1 h, saturated $NaHCO_3$ (aq) was added to the mixture before extraction with DCM (4 × 5 mL) and drying of the combined

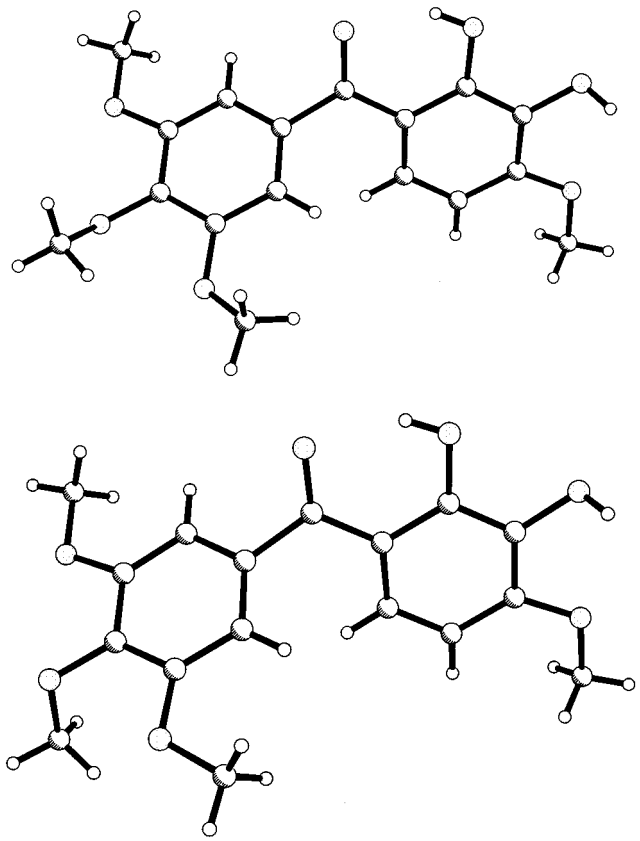


Figure 2. (a) X-ray crystal structure conformation of hydroxyphenstatin **2b**, showing contents in an asymmetric unit of the cell, for space group *Pbca*. (b) X-ray crystal structure conformation of hydroxyphenstatin **2b**, showing one of the two independent molecules present in an asymmetric unit of the cell, for space group *Pc*.

organics. Evaporation of the solvent in vacuo afforded a light brown oil, which was subject to flash column chromatography (15:1 hexanes−EtOAc) to generate a clear oil that crystallized from CH_3OH as a colorless solid (0.040 g; 39%): mp 103−104 °C; R_f 0.15 (10:1, hexanes−EtOAc); EIMS *m*/*z* 576 (M^+, 20%); IR (film) ν_{max} 1726 cm^{-1} [HC(O)R]; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.16 (6H, s), 0.96 (9H, s), 1.03 (9H, s), 3.77 (6H, s), 3.78 (3H, s), 3.84 (3H, s), 5.24 (1H, d, J = 1.8 Hz), 6.34 (2H, s), 6.56 (1H, d, J = 8.1 Hz), 6.64 (1H, d, J = 8.7 Hz), 9.84 (1H, d, J = 1.5 Hz). Anal. Calcd for $C_{30}H_{48}O_7Si_2$: C, 62.46; H, 8.39. Found: C, 62.14; H, 8.61. **Optimized Synthesis.** $BF_3{\cdot}OEt_2$ (0.82 mL; 6.7 mmol; 2 equiv) was added dropwise to a stirred solution of (*R*,*R*)-diol **8** and (1*S*,2*S*)-1-[2′,3′-di[(*tert*-butyldimethylsilyl)oxy]-4′methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethane-1,2-diol (2.1 g; 3.3 mmol) in anhydrous THF (20 mL) under argon at room temperature. After 1 h, saturated $NaHCO_3$ (aq) was added to the mixture before extraction with EtOAc (4 × 15 mL) and drying of the combined organics. Evaporation of the solvent in vacuo afforded a light brown oil, which was subjected to flash column chromatography (15:1 hexanes−EtOAc) to generate a clear oil that crystallized from CH_3OH as a colorless solid (1.3 g; 68%) that was spectroscopically identical to product afforded from the above procedure.

X-ray Crystal Structure Determination. Diphenylacetaldehyde Silyl derivative 9. Very large, colorless crystals of this compound were obtained from hexane solution. A crystalline specimen, with approximate dimensions of 0.42 × 0.40 × 0.10 mm, was obtained by cleavage from a larger crystal and mounted on the tip of a glass fiber with Super Glue. Data collection was performed at 26 ± 1° for a triclinic system, with all reflections corresponding to slightly more than a complete hemisphere ($2\theta \leq 130°$) being measured using an $\omega/2\theta$ scan technique. Subsequent statistical analysis of the complete reflection data set using the XPREP[18] program indicated the space group was either $P1$ or $P\bar{1}$. Subsequent structure refinements allowed the final correct assignment of the space group as $P\bar{1}$. Crystal data: $C_{30}H_{48}O_7Si_2$, a = 7.787(2) Å, b = 11.379(2) Å, c = 19.791(4) Å, α = 94.43(3)°, β = 100.55(3)°, γ = 98.95(3)°, V = 1693.0(6) $Å^3$, λ (Cu Kα) = 1.541 78 Å, ρ_c = 1.132 g cm^{-3} for Z = 2 and FW = 576.86, F(000) = 624. After Lorentz and polarization corrections, merging of equivalent reflections and rejection of systematic absences, 5594 unique reflections (R(int) = 0.0417) remained, of which 4292 were considered observed ($I_o > 2\sigma(I_o)$) and were used in the subsequent structure solution and refinement. Linear and anisotropic decay corrections were applied to the intensity data as well as an empirical absorption correction (based on a series of psi-scans).[19] Structure determination was accomplished with SHELXS.[18] All non-hydrogen atoms for **9** were located using the default settings of that program. The remaining hydrogen atom coordinates were calculated at optimum positions using the SHELXTL[18] software suite . The latter atoms were assigned thermal parameters equal to either 1.2 or 1.5 (depending upon chemical type) of the Uiso value of the atom to which they were attached and then both coordinates and thermal values were forced to ride that atom during final cycles of refinement. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process with SHELXL.[18] Disorder was noted for several of the methoxyl groups, with splitting occurring for the O3, O4, C26, and C27 atoms. During final anisotropic refinement, these atoms were treated as if they were each residing over two, separate, half-occupied sites. The final standard residual R_1 value for the model shown in Figure 1 was 0.1126 (for observed data) and 0.1291 (for all data). The corresponding Sheldrick R values were wR_2 of 0.2973 and 0.3182, respectively. The difference Fourier map exhibited some residual electron density; the largest difference peak and hole being +0.727 and −0.752 e/$Å^3$, respectively. However, nearly all of this residual density sites were proximate (~1.0 Å) to, and attributed to, the Si atoms. The unit cell was found to contain two molecules of the parent molecule, related as enantiomeric mirror images. As a consequence, the diphenylacetaldehyde derivative **9** existed as a racemic mixture.

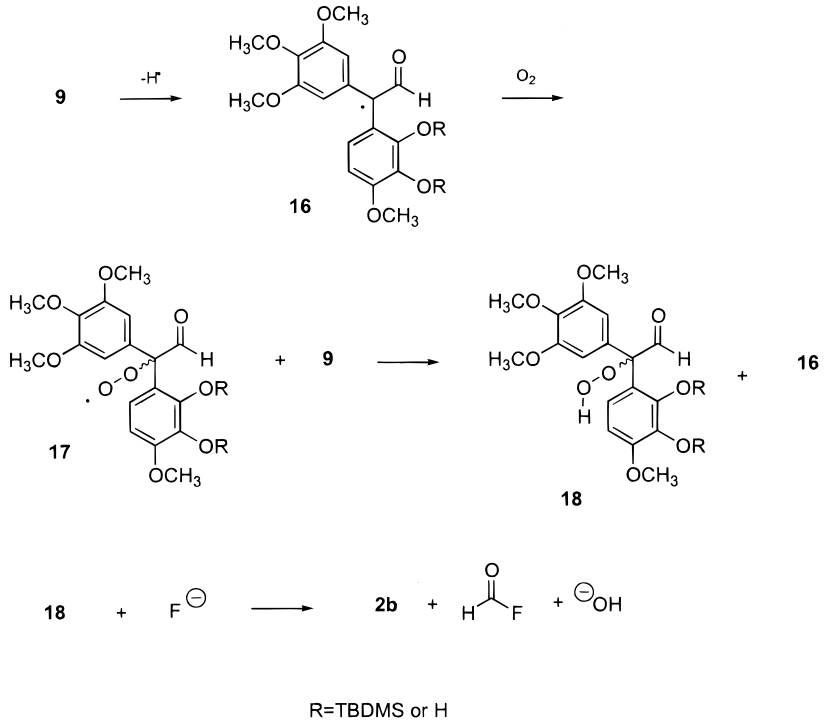
2′,3′-Dihydroxy-3,4,4′,5-tetramethoxybenzophenone (Hydroxyphenstatin) (2b). TBAF (0.88 mL; 0.88 mmol; 2.2 equiv; 1 M in THF solution) was added to a stirred solution of diphenylacetaldehyde **9** (0.23 g; 0.40 mmol) in anhydrous THF (5 mL) under argon. After 20 min, ice-cold 2 N HCl was added, and the product was extracted with EtOAc (4 × 25 mL). The combined extract was washed with saturated NaCl (aq) and dried. Evaporation of the solvents in vacuo resulted in a light brown oil, which was subjected to column chromatography (50:50:1 hexane/EtOAc/AcOH) to afford a yellow oil that was recrystallized from CH_3OH as a yellow solid (65 mg; 49%): mp 178−179 °C; R_f 0.69 (hexanes−EtOAc−AcOH, 50:50:1); EIMS *m*/*z* 334 (M^+, 40%); IR (film) ν_{max} 1631 cm^{-1} [ArC(O)Ar]; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (6H, s), 3.94 (3H, s), 3.99 (3H, s), 5.56 (1H, s), 6.51 (1H, d, J = 9.0 Hz), 6.92 (2H, s), 7.26 (1H, d, J = 9.3 Hz), 12.22 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.59, 152.92, 152.09, 150.93, 141.33, 133.66, 133.12, 125.59, 114.02, 106.79, 102.55, 60.98, 56.32, 56.24. Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.08; H, 5.43. Found: C, 61.00; H, 5.54.

X-ray Crystal Structure Determination. Hydroxyphenstatin, 2b. Colorless crystals of this compound were obtained from methanol solution. A specimen, with approximate dimensions of 0.54 × 0.44 × 0.18 mm, was mounted on the tip of a glass fiber with Super Glue. Data collection was performed at

(18) SHELXTL, Version 5.101, **1998**, an integrated software system for the determination of crystal structures from diffraction data, Bruker Analytical X-ray Systems, Inc., Madison, WI 53719. This package includes, among others: XPREP, an automatic space group determination program; XS, the Bruker SHELXS module for the solution of X-ray crystal structures from diffraction data; XL, the Bruker SHELXL module for structure refinement; XP, the Bruker interactive graphics display module for crystal structures.

(19) North, A. C.; Phillips, D. C.; Mathews, F. S. *Acta Crystallogr.* **1968**, *A24*, 351−359.

Scheme 3



23 ± 1° for an orthorhombic system, with all reflections corresponding to slightly more than a octant of data ($2\theta \leq 130°$) being measured using an $\omega/2\theta$ scan technique. Subsequent statistical analysis of the complete reflection data set using the XPREP[18] program indicated the space group was *Pbca*. Crystal data: $C_{17}H_{18}O_7$, $a = 10.807(2)$ Å, $b = 14.630(3)$ Å, $c = 19.876(4)$ Å, $V = 3142.5(11)$ Å^3, λ (Cu Kα) = 1.541 78 Å, $\rho_c = 1.413$ g cm^{-3} for $Z = 8$ and FW = 334.31, $F(000) = 1408$. After Lorentz and polarization corrections, merging of equivalent reflections and rejection of systematic absences, 2650 unique reflections (R(int) = 0.0339) remained, of which 2381 were considered observed ($I_o > 2\sigma(I_o)$) and were used in the subsequent structure solution and refinement. Linear and anisotropic decay corrections were applied to the intensity data as well as an empirical absorption correction (based on a series of psi-scans).[19] Structure determination was accomplished with SHELXS.[18] All non-hydrogen atoms for **2b** were located using the default settings of that program. The remaining hydrogen atom coordinates were calculated at optimum positions using the SHELXTL[18] software suite. The latter atoms were assigned thermal parameters equal to either 1.2 or 1.5 (depending upon chemical type) of the U_{iso} value of the atom to which they were attached and then both coordinates and thermal values were forced to ride that atom during final cycles of refinement. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process with SHELXL.[18] The final standard residual R_1 value for the model shown in Figure 2a was 0.0738 (for observed data) and 0.0783 (for all data). The corresponding Sheldrick R values were wR_2 of 0.1836 and 0.1891, respectively. The largest difference peak and hole in the final difference Fourier map were +0.551 and −0.377 e/Å^3, respectively. All bond distances and angles were within generally accepted limits.

Oximes 11 and 12. Aldehyde **9** (0.50 g; 0.87 mmol) was added to a mixture of hydroxylamine hydrochloride (1.0 g; 42 mmol; 48 equiv) and sodium acetate (2.0 g, 25 mmol; 28 equiv) in H_2O (10 mL) and CH_3OH (20 mL). The mixture was heated for 30 min and stirred for an additional 6 h before being absorbed onto silica gel and subjected to flash column chromatography (10:1 hexanes−EtOAc) to afford two products as clear oils that each crystallized from H_2O−CH_3OH as a colorless crystalline solid. Compound **11** [(*E*)-oxime, 0.31 g; 60%]: mp 171−172 °C; R_f 0.77 (7:3, hexanes−EtOAc); EIMS *m*/*z* 591 (M$^+$, 10); IR (film) ν_{max} 3450 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.13 (6H, s), 0.17 (3H, s), 0.95 (9H, s), 1.01 (9H, s), 3.74 (6H, s), 3.77 (3H, s), 3.82 (3H, s), 5.23 (1H, d, $J = 6.6$ Hz), 6.32 (2H, s), 6.53 (1H, d, $J = 8.7$ Hz), 6.69 (1H, d, $J = 8.1$ Hz), 7.66 (1H, s), 7.74 (1H, d, $J = 6.6$ Hz). Anal. Calcd for $C_{30}H_{49}O_7Si_2N$: C, 60.88; H, 8.35; N, 2.37. Found: C, 61.16; H, 8.44; N, 2.36. Compound **12** [(*Z*)-oxime, 87 mg; 17%): mp 162−163 °C; R_f 0.54 (7:3, hexanes−EtOAc); EIMS *m*/*z* 591 (M$^+$, 10); IR (film) ν_{max} 3439 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.09 (6H, s), 0.15 (3H, s), 0.20 (3H, s), 0.96 (9H, s), 1.02 (9H, s), 3.74 (6H, s), 3.76 (3H, s), 3.80 (3H, s), 5.85 (1H, d, $J = 6.6$ Hz), 6.36 (2H, s), 6.53 (1H, d, $J = 8.7$ Hz), 6.71 (1H, d, $J = 8.1$ Hz), 7.13 (1H, d, $J = 7.2$ Hz), 8.04 (1H, brs). Anal. Calcd for $C_{30}H_{49}O_7Si_2N.^1/_2H_2O$: C, 59.97; H, 8.39; N, 2.33. Found: C, 60.09; H, 8.30; N, 2.40.

Thiosemicarbazone 13. Aldehyde **9** (0.10 g; 0.17 mmol) was added to a solution of thiosemicarbazide (16 mg; 0.18 mmol; 1 equiv) in H_2O (2 mL) and CH_3OH (3 mL). The mixture was heated for 15 min and stirred for an additional 6 h before the reaction mixture was concentrated in vacuo and the product recrystallized from H_2O−CH_3OH to afford a colorless solid (91 mg; 81%): mp 160−161 °C; R_f 0.33 (7:3, hexanes−EtOAc); EIMS *m*/*z* 649 (M$^+$, 10); IR (film) ν_{max} 1452 cm^{-1} [C=S]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.16 (3H, s), 0.16 (3H, s), 0.95 (9H, s), 1.02 (9H, s), 3.76 (6H, s), 3.77 (3H, s), 3.83 (3H, s), 5.26 (1H, d, $J = 6.3$ Hz), 6.14 (1H, brs), 6.29 (2H, s), 6.51 (1H, d, $J = 8.7$ Hz), 6.57 (1H, d, $J = 9.0$ Hz), 6.91 (1H, brs), 7.41 (1H, d, $J = 6.0$ Hz), 8.91 (1H, brs). Anal. Calcd. for $C_{31}H_{51}O_6Si_2N_3S$: C, 57.28; H, 7.91; N, 6.46. Found: C, 57.55; H, 8.02; N, 6.40.

2,4-Dinitrophenylhydrazone 14. Aldehyde **9** (99 mg; 0.17 mmol) was added to a solution of 2,4-dinitrophenylhydrazine (35 mg; 0.17 mmol; 1 equiv) in CH_3OH (5 mL) and concentrated HCl (0.50 mL), that had been previously heated and filtered. The mixture was stirred for 6 h before the reaction mixture was concentrated in vacuo and the product recrystallized from EtOH to afford a yellow crystalline solid (69 mg; 54%): mp 190−191 °C; R_f 0.71 (7:3, hexanes−EtOAc); EIMS *m*/*z* 757 (M$^+$, 5); IR (film) ν_{max} 1504 cm^{-1} (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.14 (3H, s), 0.21 (6H, s), 0.96 (9H, s), 1.08 (9H, s), 3.78 (6H, s), 3.80 (3H, s), 3.85 (3H, s), 5.24 (1H, d, $J = 6.5$ Hz), 6.38 (2H, s), 6.58 (1H, d, $J = 9.0$ Hz),

6.71 (1H, d, $J = 8.5$ Hz), 7.80 (1H, d, $J = 6.5$ Hz), 7.84 (1H, d, $J = 9.0$ Hz), 8.29 (1H, d, $J = 9.5$ Hz), 9.12 (1H, s), 11.13 (1H, s). Anal. Calcd for $C_{36}H_{52}O_{10}Si_2N_4$: C, 57.12; H, 6.92; N, 7.40. Found: C, 56.85; H, 6.95; N, 7.25.

Semicarbazone 15. Aldehyde **9** (0.50 g; 0.88 mmol) was added to a mixture of semicarbazide hydrochloride (1.1 g; 9.7 mmol; 11 equiv) and sodium acetate (1.5 g, 18 mmol; 21 equiv) in H_2O (10 mL) and CH_3OH (10 mL). The mixture was heated for 15 min and stirred for an additional 30 min before the reaction mixture was absorbed onto silica gel and subjected to flash column chromatography (1:1 EtOAc−hexane) to afford a clear oil that crystallized from H_2O-CH_3OH as a colorless crystalline solid (442 mg; 79%): mp 145−146 °C; R_f 0.09 (1:1, hexanes−EtOAc); EIMS m/z 633 (M^+, 10); IR (film) ν_{max} 1691 cm^{-1} [C(O)NH_2]; ^1H NMR (300 MHz, CD_3OD) δ 0.11 (3H, s), 0.18 (3H, s), 0.21 (3H, s), 0.25 (3H, s), 1.00 (9H, s), 1.09 (9H, s), 3.76 (6H, s), 3.77 (3H, s), 3.81 (3H, s), 5.27 (1H, d, $J = 6.6$ Hz), 6.42 (2H, s), 6.70 (1H, d, $J = 8.7$ Hz), 6.77 (1H, d, $J = 8.7$ Hz), 7.61 (1H, d, $J = 7.2$ Hz). Anal. Calcd for $C_{31}H_{51}O_7Si_2N_3$: C, 58.73; H, 8.10; N, 6.62. Found: C, 58.64; H, 8.27; N, 6.66.

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Supporting Information Available: Tables of crystallographic data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters are available for structures **9** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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