# Synthesis and biological evaluation of boronic acid-containing phenstatin analogues

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**Dedicated to Professor Keith Smith on the occasion of his 65th anniversary**

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**Abstract**

A series of boronic acid-containing benzophenones was synthesized by introducing a boronic acid as an acceptor-type functional group into the aromatic ring B of the phenstatin skeleton. Among the compounds synthesized, **4c** in which a hydroxyl group on the aromatic ring B of the phenstatin was replaced by a boronic acid, exhibited significant cell growth inhibition and the $GI_{50}$ values toward B-16 and 1-87 cell lines are 0.013 μM and 0.087 μM, respectively.

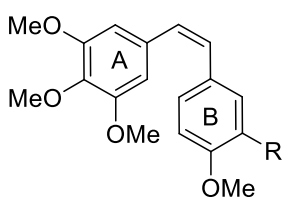
**Keywords:** Boronic acid, phenstatin, cell growth inhibition, benzophenone

## Introduction

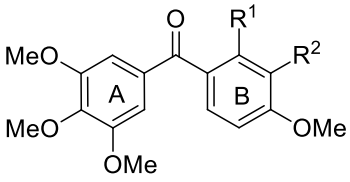
Combretastatin A-4 (**1a**) was isolated by Pettit and coworkers from the stem wood of the South African tree *Combretum caffrum* in 1982.[1] This compound is one of the most potent antimitotic agents and exhibits potent cytotoxicity against a wide variety of human cancer cells including multidrug resistant cancer cell lines.[2] Phenstatin (**2a**) is a synthetic tubulin assembly inhibitor developed by the same research group in 1998.[3] This compound is a benzophenone-type molecule and the functional groups on the two phenyl rings are similar to combretastatin A-4.[4] Based on the structures of both lead compounds, various benzophenone derivatives have been developed including aminobenzophenones (**2b**-**c**)[5,6] and *iso*combretastatin A (**3**).[7] These analogues have a donor-type functional group, as a common feature, substituted on the aromatic ring B (Figure 1). We are interested in introducing boronic acid as an acceptor-type functional group into the aromatic ring B in the phenstatin skeleton.

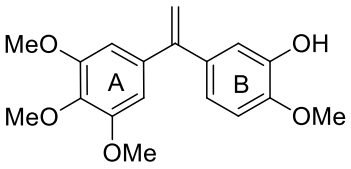
A boron atom has a vacant orbital and interconverts with ease between the neutral $sp^2$ and the anionic $sp^3$ hybridization states, which generates a new stable interaction between a boron atom and a donor molecule through a covalent bond.[8] Therefore, it is expected that the boron atoms introduced into biologically active molecular frameworks would interact with a target protein not only through hydrogen bonds but also through covalent bonds, and this interaction might produce a potent biological activity.[9]




**1a:** R = OH, combretastatin A-4
**1b:** R = $NH_2$, AVE-8063
**1c:** R = NH-Ser HCl salt, AVE-8062
**1d:** R = $B(OH)_2$



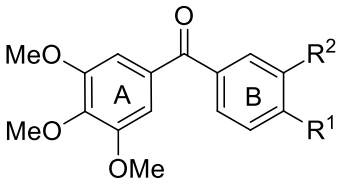

**2a:** $R^1$ = H, $R^2$ = OH, phenstatin
**2b:** $R^1$ = $NH_2$, $R^2$ = H, 2-aminobenzophenone
**2c:** $R^1$ = H, $R^2$ = $NH_2$, 3-aminobenzophenone




**3:** *iso*combretastatin A-4

**Figure 1.** Structures of combretastatin and phenstatin derivatives **1**-**3**.

Our strategy for the design of boron compounds is based on the properties that make them different from conventional biologically active compounds.[10-15] Previously, we reported the synthesis of boronic acid-containing combretastatin A-4 analogue **1d**.[11,16] Herein, we report the synthesis and biological evaluation of boronic acid-containing phenstatin analogues (Figure 2).




**4a:** $R^1$ = $B(OH)_2$, $R^2$ = H
**4b:** $R^1$ = H, $R^2$ = $B(OH)_2$
**4c:** $R^1$ = OMe, $R^2$ = $B(OH)_2$

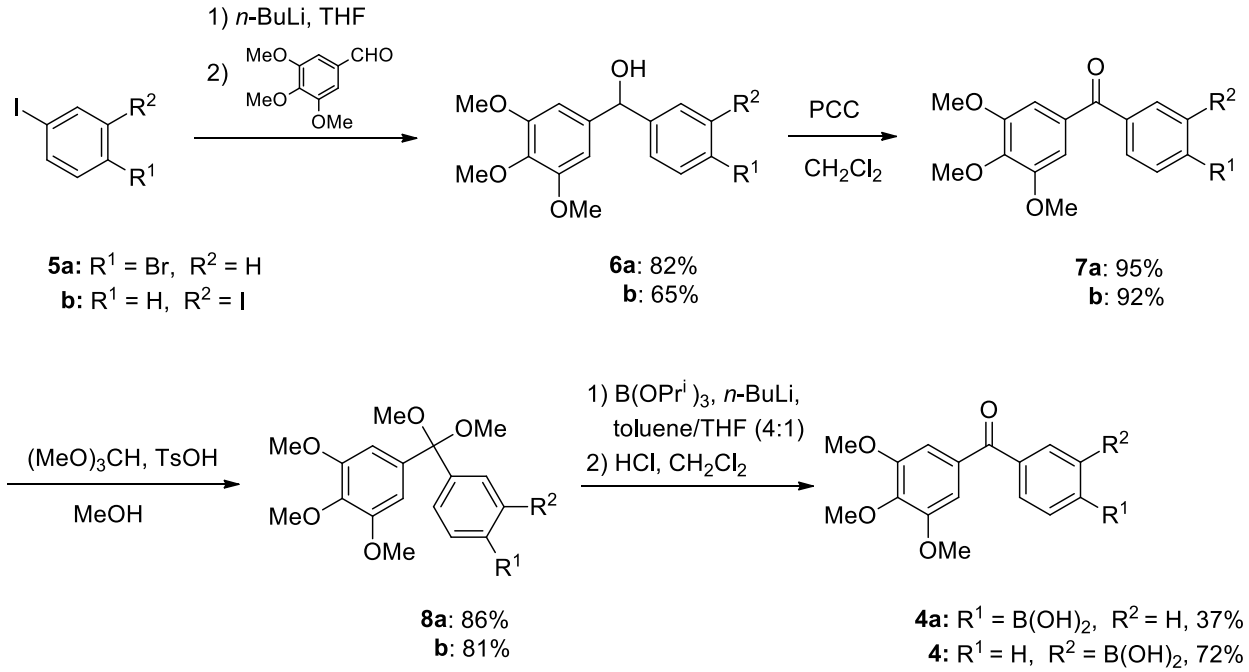
**Figure 2.** Design of boronic acid containing phenstatin analogues **4**.

## Results and Discussion

The boronic acid-containing phenstatin analogues **4a** and **4b** were synthesized from 3,4,5-trimethoxybenzaldehyde and dihalobenzenes as shown in Scheme 1. The reaction of 1-bromo-4-iodobenzene **5a** with *n*-butyllithium in THF generated the 4-bromophenyllithium, which reacted with 3,4,5-trimethoxybenzaldehyde to give the corresponding carbinol **6a** in 82% yield.[17] In a

similar manner, carbinol **6b** was obtained from 1,3-diiodobenzene **5b** in 65% yield. The carbinols **6a** and **6b** were converted into the corresponding ketones **7a**[17] and **7b** using pyridinium chlorochromate (PCC) as an oxidizing agent and the ketal protection of the carbonyl groups was performed by treating with triomethyl orthoformate in methanol under acidic conditions to give **8a** and **8b** in 86% and 81% yields, respectively. Treatment of the ketals **8a** and **8b** with *n*-butyllithium and triisopropyl borate at -78 ºC, followed by acidic hydrolysis, afforded the boronic acid-containing phenstatin analogues **4a** and **4b** in 37% and 72% yields in two steps, respectively.



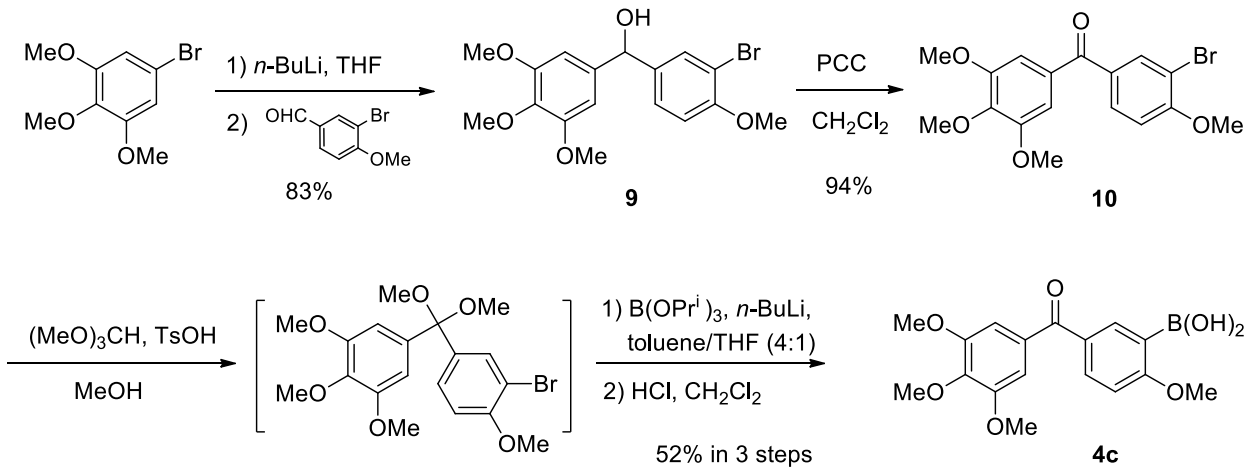

**Scheme 1.** Synthesis of boronic acid-containing phenstatin analogues **4a** and **4b**.

We also synthesized boronic acid-containing phenstatin analogue **4c** (Scheme 2). The reaction of 5-bromo-1,2,3-trimethoxybenzene with *n*-butyllithium in THF generated the corresponding aryllithium, which reacted with 3-bromo-4-methoxybenzaldehyde to give the carbinol **9** in 83% yield. The carbinol **9** underwent oxidation by treatment with PCC to give the corresponding ketone **10** in 94% yield. Protection of the carbonyl group in ketone **10** followed by introduction of boronic acid using *n*-butyllithium and triisopropyl borate at -78 ºC and deprotection of the ketal group under acidic conditions gave phenstatin analogue **4c** in 52% yield in three steps.

We next examined inhibition of cell growth by the boronic acid analogues using B16 and 1-87 cell lines. The results are summarized in Table 1. The benzophenones **4a** and **4b** exhibited 50% inhibition of cell growth at 0.85 μM and 0.37 μM concentrations toward B16 cells and at 3.1 μM and 1.9 μM concentrations toward 1-87 cells, respectively. The benzophenone **4c**, which

has a boronic acid group at the *meta* position and a methoxy group at the *para* position, exhibited higher inhibition of cell growth against both cell lines and the $GI_{50}$ values of **4c** toward B16 and 1-87 cells are 0.013 μM and 0.087 μM, respectively. The boronic acid-containing combretastatin A-4 analogue **1d**, which was previously synthesized as a tubulin polymerization inhibitor in our group[11] as well as Brown's group, independently,[16] was more potent in cell growth inhibition. In all cases, B16 cells are more sensitive toward the synthesized boronic acids than 1-87 cells. ClogP (partition coefficient of a compound between octanol/water speculated by structure-based speculated program) values of each compound are also shown in Table 1. According to the ClogP values, one of the low inhibitory potency of **4a** and **4b** toward cell growth may be due to higher hydrophilicity, which could prevent the compounds from crossing the cell membrane.




**Scheme 2.** Synthesis of boronic acid-containing phenstatin analogue **4c**.

**Table 1.** Cell growth inhibition of boronic acid containing phenstatin analogues [a]

| compound | $GI_{50}$ /μM | | Clog P [d] |
|---|---|---|---|
| | B16 cell [b] | 1-87 cell [c] | |
| **4a** | 0.85 | 3.1 | 0.989 |
| **4b** | 0.37 | 1.9 | 0.989 |
| **4c** | 0.013 | 0.087 | 2.06 |
| **1d** | 0.0062 | 0.013 | 3.50 |

[a] The compounds were assayed at least three times and the $GI_{50}$ values reported here are mean of an average of three experiments. [b] Mouse B-16 melanoma cell line. [c] Human lung carcinoma 1-87 cell line. [d] Clog P values were speculated by using structure-based calculation program, ChemBioDraw Ultra ver. 12, PerkinElmer Inc.

We also examined the effects of the boronic acid-containing phenstatin analogues **4a-c** on *in vitro* polymerization of tubulin. The tubulin was purified from porcine brains according to the Shelanski protocol[18] with modification.[19] Although it was reported that phenstatin significantly inhibits tubulin polymerization *in vitro* with an $IC_{50}$ value of 1.1 μM, the boronic acid containing phenstatin analogues **4a-c** did not exhibited inhibition potency even at 100 μM. These results indicate that the current boronic acid containing phenstatin analogues, especially compound **4c**, possess significant inhibitory activity toward cell growth without interacting microtubule system.

## Conclusions

We succeeded in synthesizing the boronic acid-containing phenstatin analogues **4a**-**4c**. The lithiation of the aromatic ring B of the phenstatin with *n*-butyllithium is essential for introduction of a boronic acid moiety in the molecules. Among the boronic acid-containing phenstatin analogues synthesized, compound **4c**, in which a hydroxyl group on the aromatic ring B of the phenstatin was replaced by a boronic acid, exhibited significant cell growth inhibition. Since the current synthesized compounds **4a**-**4c** did not show any inhibition potency toward tubulin polymerization process *in vitro*, they are considered to inhibit cell growth by different mechanisms other than inhibition of the microtubule system.

## Experimental Section

**General.** $^1$H NMR and $^{13}$C NMR spectra were measured on a JEOL JNM-AL 300 (300 MHz) or VARIAN UNITY-INOVA 400 (400 MHz) spectrometers. Chemical shifts of $^1$H NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 7.24) in $CDCl_3$ or from $CD_3OD$ as an internal standard (δ = 3.35). Chemical shifts of $^{13}$C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 77.0) in $CDCl_3$ or from $CD_3OD$ as an internal standard (δ = 49.3). Analytical thin layer chromatography (TLC) was performed on a glass plates (Merck Kieselgel 60 $F_{254}$, layer thickness 0.2 mm or RP-18 $F_{254s}$, layer thickness 0.2 mm). Visualization was accompanied by UV light (254 nm), $I_2$ and $KMnO_4$. Column chromatography was performed on silica gel (Merck Kieselgel 70-230 mesh). All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Most chemicals and solvents were analytical grade and used without further purification.

**4'-Bromo-3,4,5-trimethoxybenzhydrol (6a).** To a mixture of 1-bromo-4-iodobenzene (**5a**) (8.5 g, 30 mmol) in THF (90 mL) was added *n*-butyllithium (1.6 M in hexane, 19 mL, 30 mmol) at -80 ºC under argon, and the mixture was stirred for 3 h. A solution 3,4,5-trimethoxybenzaldehyde (5.9 g, 30 mmol) in THF (60 mL) was then added to the reaction mixture dropwise, and the reaction mixture allowed to warm to room temperature for 1 h with stirring. The reaction was

quenched by saturated aqueous $NH_4Cl$ solution and the mixture was extracted with dichloromethane, dried over anhydrous $MgSO_4$, and concentrated. Purification by silica gel column chromatography with hexane/ethyl acetate (2:1) gave **6a** (8.7 g, 25 mmol, 82%) as a colorless oil: $^1$H NMR data were in agreement with those in the reported in the literature[17]: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.55 (s, 2H), 5.71 (d, *J* = 3.2 Hz, 1H), 3.81 (s, 6H), 3.81 (s, 3H), 2.19 (d, *J* = 3.2 Hz, 1H); $^{13}$C NMR (75 MHz; $CDCl_3$) : δ 153.1, 142.6, 139.1, 137.1, 131.3, 128.1, 121.2, 103.4, 75.4, 60.7, 55.9.

**3'-Iodo-3,4,5-trimethoxybenzhydrol (6b).** This compound was synthesized from 1,3-diiodobenzene (**5b**) (3.3 g, 10 mmol) and 3,4,5-trimethoxybenzaldehyde (2.1 g, 11 mmol) using the procedure described for **6a** to give **6b** (2.6 g, 6.5 mmol, 65%) as a colorless oil: $^1$H NMR (400 MHz; $CDCl_3$) δ 7.73 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.53 (s, 2H), 5.64 (d, *J* = 2.8 Hz, 1H), 3.80 (s, 6H), 3.80 (s, 3H), 2.49 (d, *J* = 2.8 Hz, 1H); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 153.3, 145.8, 138.8, 137.4, 136.6, 135.3, 130.1, 125.7, 103.5, 94.4, 75.5, 60.8, 56.1; HRMS (ESI, positive) *m/z* calcd. for $C_{17}H_{19}BrO_5$ $[M+Na]^+$: 405.0314, found: 405.0313

**4'-Bromo-3,4,5-trimethoxybenzophenone (7a).** To a mixture of pyridinium chlorochromate (PCC; 3.4 g, 16 mmol), sodium acetate (2.6 g) and $MgSO_4$ (2.6 g) in $CH_2Cl_2$ (50 mL) was added a solution of **6a** (3.7 g, 10 mmol) in $CH_2Cl_2$ (10 mL) and the mixture was stirred at rt for 1 d. After removal of solvents under reduced pressure, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (5:1) to yield the benzophenone **7a** (3.5 g, 9.9 mmol, 95%) as a white solid: $^1$H NMR data were in agreement with those in the reported in the literature 17: mp 101-103 ºC; $^1$H NMR (300 MHz; $CDCl_3$) δ 7.64 (s, 2H), 7.63 (s, 2H), 7.01 (s, 2H), 3.92 (s, 3H), 3.85 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 194.5, 152.9, 142.2, 136.5, 132.0, 131.5, 131.3, 127.2, 107.6, 60.9, 56.2.

**3'-Iodo-3,4,5-trimethoxybenzophenone (7b).** This compound was synthesized from **6b** (2.5 g, 6.5 mmol) and PCC (2.1 g, 9.7 mmol) using the procedure described for **7a** to give **7b** (2.3 g, 5.8 mmol, 92%) as a white solid: mp 113-115 ºC; $^1$H NMR (400 MHz; $CDCl_3$) δ 8.11 (t, *J* = 7.6 Hz, 1H), 7.89 (dq, *J* = 7.6, 1.6 Hz, 1H), 7.71 (dq, *J* = 7.6, 1.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 2H), 3.93 (s, 3H), 3.86 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 194.0, 153.0, 142.5, 141.0, 139.7, 138.6, 131.8, 129.9, 128.9, 107.8, 94.0, 61.0, 56.3; HRMS (ESI, positive) *m/z* calcd. for $C_{16}H_{17}IO_4$ $[M+Na]^+$: 423.0069, found: 423.0066

**4'-Bromo-3,4,5-trimethoxybenzophenone dimethyl acetal (8a).** To a mixture of **7a** (1.1 g, 3.1 mmol) and *p*-toluenesulfonic acid monohydrate (0.030 g, 0.16 mmol) in MeOH (15 mL) was added trimethoxymethane (0.40 mL, 3.7 mmol) and the mixture was stirred under reflux for 8 h. Sodium methoxide (28%w/w in methanol; 0.31 mL, 1.6 mmol) was added to the reaction mixture, which was stirred for further 5 min and then the solvents were evaporated. Saturated aq. $NaHCO_3$ solution was added and the mixture was extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid was washed with cold MeOH to afford **8a** (1.0 g, 2.6 mmol, 86%) as a white solid. This solid was pure enough to perform the next step: mp 125-127 ºC; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.67 (s,

2H), 3.80 (s, 9H), 3.09 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 152.8, 141.3, 137.4, 137.2, 131.0, 128.5, 121.6, 103.9, 102.3, 60.6, 56.0, 49.3; HRMS (ESI, positive) *m/z* calcd. for $C_{18}H_{21}BrO_5$ $[M+Na]^+$: 419.0470, found: 419.0472

**3'-Iodo-3,4,5-trimethoxybenzophenone dimethyl acetal (8b).** This compound was synthesized from **7b** (1.2 g, 3.0 mmol) and trimethoxymethane (0.39 mL, 3.6 mmol) using the procedure described for **8a** to give **8b** (1.1 g, 2.4 mmol, 81%) as a white solid: mp 113-115 °C; $^1$H NMR (400 MHz; $CDCl_3$): δ 7.88 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.68 (s, 2H), 3.80 (s, 9H), 3.10 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$) : δ 152.9, 144.6, 137.3, 137.3, 136.6, 135.6, 129.8, 126.2, 104.0, 101.9, 94.1, 60.7, 56.1, 49.4; HRMS (ESI, positive) *m/z* calcd. for $C_{18}H_{21}IO_5$ $[M+Na]^+$: 467.0331, found: 467.0331

**4'-(Dihydroxylboryl)-3,4,5-trimethoxybenzophenone (4a).** To a mixture of **8a** (1.0 g, 2.6 mmol) and triisopropyl borate (0.73 mL, 3.1 mmol) in THF (2 mL) and toluene (8 mL) was added *n*-butyllithium (1.6 M in hexane; 1.8 mL, 2.9 mmol) dropwise at – 78 °C. The mixture was stirred for 1.5 h at – 78 °C and allowed to warm to – 20 °C for 30 min with stirring. The reaction was quenched by aqueous HCl solution (1 N) and the mixture was extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography on silica gel with hexane/EtOAc (2/1) gave **8a**, which was dissolved in $CH_2Cl_2$ (4 mL) and conc. HCl (4 mL) was added. The mixture was stirred for 2 h and then diluted with water. The aqueous mixture was extracted with EtOAc and the organic layer was neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. The resulting white solid was washed with co-solvent of ether and hexane to afford **4a** (0.31 g, 0.97 mmol, 37 % in 2 steps) as a white solid: mp 134-136 °C; $^1$H NMR (400 MHz; $CD_3OD$) : δ 7.93 (s, 2H), 7.77 (s, 2H), 7.13 (s, 2H), 3.90 (s, 3H), 3.89 (s, 6H); $^{13}$C NMR (75 MHz; $CD_3OD$) : δ 197.5, 154.0, 143.3, 140.0, 134.5, 133.6, 129.5, 108.8, 61.2, 56.7, 49.9. Anal. calcd for $C_{16}H_{17}BO_6$: C, 60.79; H, 5.42. found: C, 60.53; H, 5.29.

**3'-(Dihydroxylboryl)-3,4,5-trimethoxybenzophenone (4b).** This compound was synthesized from **8b** (0.60 g, 1.4 mmol) and triisopropyl borate (0.38 mL, 1.6 mmol) using the procedure described for **4a** to give **4b** (0.31 g, 0.98 mmol, 72%) as a white solid: mp 91-93 °C; $^1$H NMR (400 MHz; $CD_3OD$) : δ 8.20 (bs, 1H), 8.05 (bd, *J* =8.0 Hz, 1H), 7.84 (d, *J* =8.0 Hz, 1H), 7.55 (t, *J* =8.0 Hz, 1H), 7.13 (s, 2H), 3.91 (s, 3H), 3.89 (s, 6H); $^{13}$C NMR (75 MHz; $CD_3OD$) : δ 197.9, 154.3, 143.5, 138.9, 138.2, 136.4, 133.9, 132.4, 128.7, 109.0, 61.2, 56.7. Anal. calcd for $C_{16}H_{17}BO_6$: C, 60.79; H, 5.42. found: C, 60.57; H, 5.31.

**3'-Bromo-3,4,4',5-tetramethoxybenzhydrol (9).** To a mixture of 5-bromo-1,2,3-trimethoxybenzene (1.3 g, 5.1 mmol) in THF (15 mL) was added *n*-butyllithium (1.6 M in hexane, 3.3 mL, 5.3 mmol) at -80 °C under argon dropwise, and the mixture was stirred for 1.5 h. A solution 3-bromo-4-methoxybenzaldehyde (1.2 g, 5.3 mmol) in THF (10 mL) was then added to the reaction mixture dropwise for 1 h, and the reaction mixture allowed to warm to 0 °C for 1 h with stirring. The reaction was quenched by saturated aqueous $NH_4Cl$ solution and the mixture was extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$, and concentrated. Purification by silica gel column chromatography with hexane/EtOAc (2:1) gave **9** (1.6 g, 4.2 mmol, 83%) as a

colorless oil: $^1$H NMR (400 MHz; $CDCl_3$): δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 2H), 5.68 (d, *J* = 3.2 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 6H), 3.81 (s, 3H), 2.23 (d, *J* = 3.2 Hz, 1H); $^{13}$C NMR (75 MHz; $CDCl_3$) : δ 155.0, 153.1, 139.2, 137.3, 137.0, 131.4, 126.6, 111.6, 111.4, 103.2, 75.0, 60.7, 56.1, 55.9; HRMS (ESI, positive) *m/z* calcd. for $C_{17}H_{19}BrO_5$ $[M+Na]^+$: 405.0314, found: 405.0313

**3'-Bromo-3,4,4',5-tetramethoxybenzophenone (10).** To a mixture of PCC (1.3g, 5.9 mmol), sodium acetate (1.0 g) and $MgSO_4$ (1.0 g) in dichloromethane (16 mL) was added a solution of **9** (1.5 g, 3.9 mmol) in dichloromethane (16 mL) and the mixture was stirred at room temperature for 2 days. After removal of solvents under reduced pressure, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (2:1) to yield the benzophenone **10** (1.4 g, 3.7 mmol, 94%) as a white solid: mp 105-107 ºC; $^1$H NMR (400 MHz; $CDCl_3$) : δ 8.05 (d, *J* = 2.4 Hz, 1H), 7.76 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.98 (s, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.86 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$) : δ 193.1, 159.0, 152.7, 141.7, 135.3, 132.5, 131.2, 131.1, 111.6, 110.8, 107.4, 61.0, 56.5, 56.3; HRMS (ESI, positive) *m/z* calcd. for $C_{17}H_{17}BrO_5$ $[M+Na]^+$: 403.157, found: 403.0161

**3'-(Dihydroxylboryl)-3,4,4',5-tetramethoxybenzophenone (4c).** To a mixture of **10** (0.99 g, 2.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.025 g, 0.13 mmol) in MeOH (13 mL) was added trimethoxymethane (0.40 mL, 3.7 mmol) and the mixture was stirred under reflux for 4 h. Sodium methoxide (28%w/w in MeOH; 0.31 mL, 13 mmol) was added to the reaction mixture, which was stirred for further 5 min and then the solvents were evaporated. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$, and concentrated. The resulting dimethyl ketal was dissolved in THF (2.6 mL) and toluene (10 mL), and triisopropyl borate (0.73 mL, 3.1 mmol) wad added. *n*-Butyllithium (1.6 M in hexane; 1.9 mL, 3.0 mmol) was added dropwise at – 78 ºC to this mixture, which was stirred for 1.5 h at – 78 ºC and allowed to warm to – 20 ºC for 30 min with stirring. The reaction was quenched by aqueous HCl solution (1 N) and the mixture was extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid was dissolved in $CH_2Cl_2$ (4 mL) and conc. HCl (4 mL) was added. The mixture was stirred for 2 h and then diluted with water. The aqueous mixture was extracted with EtOAc and the organic layer was neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography on silica gel with $CH_2Cl_2$/EtOH (100:1) gave **4c** (0.44 g, 1.3 mmol, 43% in 3 steps) as a white solid: mp 160-162 ºC; $^1$H NMR (400 MHz; $CDCl_3$) : δ 8.33 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (s, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 5.76 (s, 2H), 4.00 (s, 3H), 3.92 (s, 3H), 3.86 (s, 6H); $^{13}$C NMR (75 MHz; $CDCl_3$): δ 194.5, 167.5, 152.8, 141.8, 139.6, 135.3, 132.9, 130.8, 110.0, 107.6, 60.9, 56.3, 56.0. Anal. calcd for $C_{17}H_{19}BO_7$: C, 58.99; H, 5.53. found: C, 58.89; H, 5.45.

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