Supporting Information
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Combretastatin A-4 Analogs. New Method of Synthesis and Biological Evaluation

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Supporting Information

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General Information

$^1$H and $^{13}$C NMR spectra were recorded on 300 MHz spectrometer Varian NMR-System INOVA 300. Chemical shifts are given as ppm relative to the residual solvent peak (chloroform-d$_1$: 7.26 ppm/77.0 ppm). Column chromatography purification was performed on Merck silica gel 60 (0.040 – 0.063 mm, 230 – 400 mesh ASTM). Melting points are uncorrected and were measured on a Büchi B.540 apparatus. Mass spectra were recorded on a Finnigan MAT 90 and Finnigan MAT 95Q instrument. Commercial reagents were used without prior purification.

Synthesis of Arylhalogenides (5a-m)

3-(tert-Butyldimethylsilyloxy)-4-methyloxyphenyl iodide (5a)$^{1,2}$

A stirring solution of guaiacol (20 g, 161 mmol) and pyridine (30 mL, 372 mmol) in 400 mL of CH$_2$Cl$_2$ was cooled in an ice bath and treated with acetyl chloride (12.8 mL, 180 mmol). After 30 min the reaction mixture was poured into ice cold 1 M H$_3$PO$_4$. The organic phase was extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with brine, dried with Na$_2$SO$_4$, and then concentrated to a light yellow oil. A solution of ICl (31 g, 191 mmol) in 200 mL of CH$_2$Cl$_2$ was added dropwise to a solution of yellow oil in 200 mL of CH$_2$Cl$_2$ cooled in an ice bath over a period of 2 h. The reaction was monitored by GC-MS. The reaction mixture was stirred at room temperature for 30 h and then poured into an ice cold saturated NaHSO$_3$ solution. The aqueous layer was extracted with CH$_2$Cl$_2$ and the organic phase was washed with brine, dried over Na$_2$SO$_4$, and then concentrated to a light yellow solid. To a solution of this solid in 120 mL of CH$_3$OH, 120 mL of THF and 40 mL of H$_2$O LiOH·H$_2$O (23.6 g, 562 mmol) was added in one portion. The reaction mixture was vigorous stirred at room temperature for 3.5 h, monitored by GC-MS. The reaction solution was poured into ice cold 1 M HCl, and this mixture was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and then concentrated to a yellow oil. Crystallization from 100 mL of methylcyclohexane and 10 mL of Et$_2$O yielded 19.5 g (48%) of 3-hydroxy-4-methyloxyphenyl iodide as colorless crystals.

3-Hydroxy-4-methyloxyphenyl iodide (7.5 g, 30 mmol) was added to a mixture of tert-butyldimethylsilyl chloride (5.4 g, 36 mmol) and imidazole (2.65 g, 39 mmol) in 10 mL of DMF cooled in an ice bath and the reaction mixture was stirred at room temperature for 15 h. 50 ml of pentane was added to the reaction solution, and the mixture was washed with 1 M H$_3$PO$_4$ solution, saturated NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$, and then concentrated in vacuo to 5a (9.7 g, 26.6 mmol, 89%) as a colorless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.15 (d, $J = 2.1$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 3.77 (s, 3H), 0.99 (s, 9H), 0.16 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 151.4, 146.2, 130.8, 129.9, 114.1, 82.3, 55.6, 25.8, 18.6, -4.5. MS (EI), m/z (%): 307 (100) [M]$^+$, 292 (95), 165 (7). HRMS (EI), m/z: caled for C$_{13}$H$_{21}$IO$_2$Si 364.0355, found 364.0342 [M]$^+$. 

2
3-Fluoro-4-methoxyphenyl iodide (5b)

\[
\begin{align*}
\text{I} & \quad \text{F} \\
\text{OMe} & \ 
\end{align*}
\]

Into a 200 ml beaker was placed 3-fluoro-4-methoxyaniline (761 mg, 5.4 mmol) in 10 ml of 6M HCl. The resulting suspension was heated for 5 min (heat gun). A solution of NaNO₂ (393 mg, 5.7 mmol) in 3 ml of water was added dropwise into the reaction mixture at -5 °C. The resulting clear solution was poured carefully to a solution of NaI (2.43 g, 16.2 mmol) in 20 ml of water. The reaction mixture was stirred at room temperature for 10 h and then extracted with CH₂Cl₂. The combined organic layers were washed with 10% NaHSO₃ solution, 2M NaOH solution, brine, dried over Na₂SO₄, and then concentrated to 5b (1.02 g, 4 mmol, 75%) as a brown oil.

\(^{1}\)H NMR (300 MHz, CDCl₃) δ 7.40 – 7.38 (m, 1H), 7.36 (s, 1H), 6.76 – 6.67 (m, 1H), 3.86 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl₃) δ 152.5 (d, \(J = 251.5 \text{ Hz}\)), 148.1 (d, \(J = 10.4 \text{ Hz}\)), 133.5 (d, \(J = 4.1 \text{ Hz}\)), 125.3 (d, \(J = 20.5 \text{ Hz}\)), 115.4 (d, \(J = 2.1 \text{ Hz}\)), 81.1 (d, \(J = 7.0 \text{ Hz}\)), 56.5 (s). MS (EI), m/z (%): 252 (93) [M]⁺, 250 (11), 237 (37), 234 (16), 209 (10). HRMS (EI), m/z: calcd for C₇H₆FIO 251.9447, found 251.9447 [M]⁺.

3-Chloro-4-methoxyphenyl iodide (5c)

\[
\begin{align*}
\text{I} & \quad \text{Cl} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

Following the synthetic procedure for 5b, 3-chloro-4-methoxyaniline (9.48 g, 60 mmol) in 100 ml of 6M HCl, NaNO₂ (4.35 g, 63 mmol) in 20 ml of water, NaI (27 g, 180 mmol) in 180 ml of water were used. The crude product was purified by filtration through silica gel to give 5c (10.41 g, 40 mmol, 64%) as a yellow solid, m.p. 89.1-93.7.

\(^{1}\)H NMR (300 MHz, CDCl₃) δ 7.65 (d, \(J = 2.2 \text{ Hz}\), 1H), 7.50 (dd, \(J = 8.6, 2.2 \text{ Hz}\), 1H), 6.68 (d, \(J = 8.7 \text{ Hz}\), 1H), 3.87 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl₃) δ 155.3, 138.4, 136.7, 124.0, 114.1, 82.0, 56.3. MS (EI), m/z (%): 268 (49) [M]⁺, 246 (55), 141 (80), 69 (71), 57 (100). HRMS (EI), m/z: calcd for C₇H₆ClIO 267.9152, found 267.9143 [M]⁺.

4-(N-tert-Butyloxycarbonyl-N-methylamino)phenyl bromide (5d)

\[
\begin{align*}
\text{Br} & \quad \text{NMeBoc} \\
\end{align*}
\]

Di-tert-butyl dicarbonate (2.3 g, 10.5 mmol) was added to a solution of 4-bromo-N-methylaniline (1.3 g, 7 mmol) in 20 ml of EtOH.\(^{3}\) The reaction mixture was stirred at room temperature for 70 h. The reaction solution was concentrated \textit{in vacuo} and the residue was purified by flash chromatography on silica gel (pentane/Et₂O, 3:1) to give 5d (1.9 g, 6.6 mmol, 95%) as a colorless oil.

\(^{1}\)H NMR (300 MHz, CDCl₃) δ 7.50 – 7.35 (m, 2H), 7.17 – 7.05 (m, 2H), 3.23 (s, 3H), 1.44 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl₃) δ 154.5, 143.0, 131.7, 127.2, 118.6, 80.8, 37.3, 28.4. MS (EI), m/z (%): 229 (15) [M]⁺, 97 (13), 85 (22), 71 (31), 69 (15), 57 (100), 43 (33). HRMS (EI), m/z: calcd for C₁₂H₁₆BrNO₂ 285.0364, found 285.0353 [M]⁺.
4-(N-tert-Butyloxycarbonyl-N-methylamino)-3-chlorophenyl iodide (5e)

A dry nitrogen-flushed Schlenk flask, equipped with a magnetic stirrer and a septum was charged with a solution of 2-chloro-N-methylaniline (1 g, 7 mmol) and NaHCO₃ (1.18 g, 14 mmol) in 5 ml of CH₂Cl₂ and 5 ml of MeOH. Then a solution of benzyltriethylammonium dichloroiodate (2.44 g, 7 mmol) in 5 ml of CH₂Cl₂ cooled in an ice bath was added dropwise over a period of 15 min and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 15 ml of water. The organic phase was extracted with CH₂Cl₂, and the combined organic layers were washed 15% NaHSO₃ solution and brine, dried over Na₂SO₄, and then concentrated to a brown oil. The product was purified by filtration through silica gel (pentane/CH₂Cl₂, 3:1) and crystallization from the mixture Et₂O/pentane to give 4-(N-methylamino)-3-chlorophenyl iodide (1.15 g, 4.3 mmol, 67%) as white crystals.

Di-tert-butyl dicarbonate (1.46 g, 6.76 mmol) was added to a solution of 4-(N-methylamino)-3-chlorophenyl iodide (0.91 g, 3.38 mmol) and DMAP (0.83 g, 6.76 mmol) in 20 ml of CH₃CN. The reaction mixture was stirred at 65 °C for 7 h. The reaction solution was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (pentane/Et₂O, 8:1) to give 5e (0.57 g, 1.5 mmol, 44%) as a white solid, m.p. 66.3-69.1.

1H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 1.8 Hz, 1H), 7.57 (dd, J = 8.3, 1.9 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.12 (s, 3H), 1.34 (s, 9H). 13C NMR (75 MHz, CDCl₃) δ 154.4, 141.2, 138.5, 136.9, 134.1, 130.9, 91.8, 80.7, 36.5, 28.3. MS (EI), m/z (%): 367 (3) [M]+, 267 (37), 57 (100), 40 (21). HRMS (EI), m/z: calcd for C₁₂H₁₅ClINO₂ 366.9836, found 366.9869 [M]+.

4-(Methyloxy)-3-(tert-butyldimethylsilyloxy)methylphenyl bromide (5f)

A suspension of 5-bromo-2-methyloxybenzaldehyde (4.95 g, 23 mmol) in 40 ml of i-PrOH was cooled in an ice bath, then NaBH₄ (0.44 g, 11.5 mmol) was added. The reaction mixture was stirred at room temperature for 20 h. The reaction solution was concentrated in vacuo and 50 ml of water was added. The mixture was extracted with Et₂O and the organic layers were washed with brine, dried over Na₂SO₄ and then concentrated to 3-hydroxymethyl-4-methyloxyphenyl bromide (4.7 g, 21.7 mmol, 94%) as white crystals.

The hydroxy-group was protected as described in the synthetic procedure for 5a. 3-Hydroxymethyl-4-methyloxyphenyl bromide (4.56 g, 21 mmol), tert-butyldimethylsilyl chloride (3.81 g, 25 mmol) and imidazole (1.86 g, 27 mmol) in 10 mL of DMF were used. The product 5f (6.94 g, 20.9 mmol, 99%) was obtained as white crystals, m.p. 31.3-33.0.

1H NMR (300 MHz, CDCl₃) δ 7.60 – 7.52 (m, 1H), 7.31 (dd, J = 8.6, 2.6 Hz, 1H), 6.68 (d, J = 8.6 Hz, 1H), 4.71 (s, 2H), 3.79 (s, 3H), 0.97 (s, 9H), 0.12 (s, 6H). 13C NMR (75 MHz, CDCl₃) δ 155.1, 132.4, 130.2, 129.7, 113.2, 111.3, 59.8, 55.5, 26.1, 18.6, -5.2. MS (EI), m/z (%): 275 (96) [M]+, 273 (100), 260 (44), 258 (43), 199 (30). HRMS (EI), m/z: calcd for C₁₄H₂₃BrO₂Si 330.0651, found 330.0700 [M]+.
3,5-Dichlorophenyl iodide (5g)

Following the synthetic procedure for 5b, 3,5-dichloroaniline (9.72 g, 60 mmol) in 100 ml of 6M HCl, NaNO₂ (4.35 g, 63 mmol) in 20 ml of water, NaI (27 g, 180 mmol) in 180 ml of water were used. The crude product was purified by filtration through silica gel to give 5g (11.78 g, 43 mmol, 72%) as an orange solid, m.p. 46.0-51.1.

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \delta 7.60 (d, J = 1.8 Hz, 2H), 7.33 (t, J = 1.9 Hz, 1H). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)} \delta 135.7, 135.6, 128.5, 93.8. \]

\[ \text{MS (EI), m/z (\%): 272 (100) [M] }^+ , 147 (34), 145 (51), 109 (20), 74 (21). \]

\[ \text{HRMS (EI), m/z: calcd for C}_6\text{H}_3\text{Cl}_2\text{I 271.8656, found 271.8662 [M] }^+ . \]

3-(N-tert-Butyloxycarbonyl-N-methylamino)-4-methyloxyphenyl iodide (5h)

Iodinating solution was prepared by addition of I₂ (24 g, 94.5 mmol) and then NaIO₄ (6.8 g, 31.8 mmol) slowly portionwise to stirred 96% H₂SO₄ (30 mL). Stirring was continued for 30 min to give a dark brown solution. Iodinating solution was added dropwise to a suspension of 2-nitroanizole (30 g, 196 mmol) in 150 ml of 96% H₂SO₄ over a period of 1 h, followed by stirring at room temperature for 30 min. The reaction mixture then quenched by slowly pouring into ice. The mixture was extracted with CH₂Cl₂, The organic layers were washed with 20% NaHSO₃ and concentrated to a yellow solid. The solid was washed on filter with EtOH to give 3-nitro-4-methyloxyphenyl iodide (27 g, 97 mmol, 49%).

A dry nitrogen-flushed round bottom flask, equipped with a magnetic stirrer was charged with a mixture of 3-nitro-4-methyloxyphenyl iodide (16.2 g, 58 mmol) and SnCl₂·2H₂O (65.5 g, 290 mmol) in 75 ml of EtOH and 30 ml of EtOAc. The reaction was heated at 70 °C for 30 min. Half of the solvents was evaporated and 100 ml of Et₂O was added. The mixture was left in the fridge over the night. The obtained precipitate was filtered and washed with Et₂O. The solid was dissolved in 150 ml of 15% NaOH cooled in an ice bath. The mixture was extracted with CH₂Cl₂, The organic layers were washed with 20% NaHSO₃ and concentrated to a yellow solid. The solid was washed on filter with EtOH to give 3-nitro-4-methyloxyphenyl iodide (9.5 g, 38 mmol, 66%) as a white solid.

To a mixture of 3-amino-4-methyloxyphenyl iodide (2.99 g, 12 mmol) and trimethyl orthoformate (1.97 ml, 18 mmol), sulfuric acid (1 drop) was added and slowly heated to 115-120 °C in a distillation setup suitable for collecting the methanol liberated. The initially thick reaction mixture went into solution at 110 °C and was maintained in the oil bath at around 120 °C for 3 h. The cooled reaction mixture was slowly neutralized with NaHCO₃ solution. The mixture was extracted with EtOAc, the organic layers were washed with brine, dried over Na₂SO₄ and concentrated to 3-amino-4-methyloxyphenyl iodide (9.5 g, 38 mmol, 66%) as a white solid.

Di-tert-butyl dicarbonate (883 mg, 4.1 mmol) was added to a solution of 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil. Di-tert-butyl dicarbonate (883 mg, 4.1 mmol) was added to a solution of 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil. The residue was purified by flash chromatography on silica gel (pentane/CH₂Cl₂, 3:2) to give 3-(N-methylamino)-4-methyloxyphenyl iodide (2.99 g, 12 mmol) and trimethyl orthoformate (1.97 ml, 18 mmol), sulfuric acid (1 drop) was added and slowly heated to 115-120 °C in a distillation setup suitable for collecting the methanol liberated. The initially thick reaction mixture went into solution at 110 °C and was maintained in the oil bath at around 120 °C for 3 h. The cooled reaction mixture was slowly neutralized with NaHCO₃ solution. The mixture was extracted with EtOAc, the organic layers were washed with brine, dried over Na₂SO₄ and concentrated to a brown oil. The residue was purified by flash chromatography on silica gel (pentane/CH₂Cl₂, 3:2) to give 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil.

To a mixture of 3-amino-4-methyloxyphenyl iodide (2.99 g, 12 mmol) and trimethyl orthoformate (1.97 ml, 18 mmol), sulfuric acid (1 drop) was added and slowly heated to 115-120 °C in a distillation setup suitable for collecting the methanol liberated. The initially thick reaction mixture went into solution at 110 °C and was maintained in the oil bath at around 120 °C for 3 h. The cooled reaction mixture was slowly neutralized with NaHCO₃ solution. The mixture was extracted with EtOAc, the organic layers were washed with brine, dried over Na₂SO₄ and concentrated to a brown oil. The residue was purified by flash chromatography on silica gel (pentane/CH₂Cl₂, 3:2) to give 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil.

Di-tert-butyl dicarbonate (883 mg, 4.1 mmol) was added to a solution of 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil. The residue was purified by flash chromatography on silica gel (pentane/CH₂Cl₂, 3:2) to give 3-(N-methylamino)-4-methyloxyphenyl iodide (0.97 g, 3.7 mmol, 31%) as a brown oil.

The reaction mixture was examined by TLC, and the amount of unreacted iodide was determined by UV/vis spectroscopy. The mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (pentane/CH₂Cl₂, 2:1) to give 5h (916 mg, 2.5 mmol, 93%) as a pale white solid, m.p. 147.7-150.3.
1H NMR (300 MHz, CDCl3) δ 7.49 (dd, J = 8.6, 2.2 Hz, 1H), 7.44 (s, 1H), 6.65 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.09 (s, 3H), 1.37 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 155.3, 155.2, 137.5, 136.8, 134.4, 113.8, 81.7, 80.1, 55.7, 37.0, 28.4. MS (EI), m/z (%): 363 (22) [M]+, 307 (49), 263 (100), 248 (67), 57 (74). HRMS (EI), m/z: calcd for C13H18INO3 363.0331, found 363.0324 [M]+.

2-(N-tetradecanoylaminomethyl)-4-methoxyphenyl iodide (5i)

C13H27(O)CHNH2CIO Me

10 ml of 96% H2SO4 in 50 ml of water was added to a solution of m-anisaldehyde (36.3 g, 267 mmol), I2 (30.5 g, 120 mmol), periodic acid (9.1 g, 40 mmol) in 250 ml of CH3COOH.10 The reaction solution was stirred at 70 °C for 24 h. The mixture then poured into 20% NaHSO3 solution. The precipitate was filtered, washed with cool water and dried under vacuum to give 2-iodo-5-methoxybenzaldehyde (29.5 g, 113 mmol, 42%).

A solution of SiCl4 (0.92 ml, 8 mmol) in 5 ml of 1,2-dichloroethane was added to a mixture of 2-iodo-5-methoxybenzaldehyde (1.05 g, 4 mmol) and NaI (1.2 g, 8 mmol) in 5 ml of CH3CN.11 The reaction mixture was stirred at room temperature for 48 h and then poured into 10 ml of water. The mixture was extracted with CH2Cl2, the organic layers were washed with brine, dried over Na2SO4 and concentrated to a brown solid. The residue was purified by filtration through silica gel (pentane/CH2Cl2 = 1:1; then pentane/EtOAc = 4:1) to give 2-aminomethyl-4-methoxyphenyl iodide (540 mg, 1.8 mmol, 45%).

A solution of tetradecanoic acid (520 mg, 2.28 mmol) and EDC·HCl (438 mg, 2.28 mmol) in 3 ml of CH2Cl2 was added to a solution of 2-aminomethyl-4-methoxyphenyl iodide (300 mg, 1.14 mmol) and DMAP (70 mg, 0.57 mmol) in 3 ml of CH2Cl2 at room temperature under nitrogen atmosphere.12 The obtained solution was stirred at this temperature for 2 h. The solvent was removed and the residue was purified by flash chromatography on silica gel (pentane/EtOAc, 6:1) to give 5i (501 mg, 1.06 mmol, 93%) as a white solid, m.p. 59.0-60.2.

1H NMR (300 MHz, CDCl3) δ 7.70 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 2.9 Hz, 1H), 6.62 (dd, J = 8.7, 3.0 Hz, 1H), 5.08 (s, 2H), 3.79 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.82 – 1.02 (m, 22H), 0.88 (t, J = 6.6 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 173.5, 160.2, 140.1, 139.6, 115.7, 115.6, 86.5, 69.9, 55.5, 34.4, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.2, 22.8, 14.3. MS (EI), m/z (%): 473 (5) [M]+, 347 (24), 247 (30), 137 (100), 57 (13), 43 (14). HRMS (EI), m/z: calcd for C22H36INO2 473.1791, found 473.1609 [M]+.

2-(N-acetylaminomethyl)-4-methoxyphenyl iodide (5j)

H3C(O)CHNH2C

Pyridine (1.21 ml, 15 mmol) was added to a solution of 2-aminomethyl-4-methoxyphenyl iodide (458 mg, 1.5 mmol) in 10 ml of Ac2O at room temperature. The obtained solution was stirred at this temperature for 3 h then was poured into 25 ml of water, extracted with CH2Cl2. The organic layers were washed with brine, dried over Na2SO4 and concentrated to a brown solid. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 6:1) to give 5j (337 mg, 0.97 mmol, 65%) as a white solid, m.p. 60.1-61.4.

1H NMR (300 MHz, CDCl3) δ 7.71 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.62 (dd, J = 8.6, 3.0 Hz, 1H), 5.08 (s, 2H), 3.80 (s, 3H), 2.15 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 170.7, 160.2,
Aqueous methyamine (40%) (8 ml, 88 mmol) was added to a solution of 6-bromo-2-naphtol (4 g, 18 mmol), Na2S2O5 (6.4 g, 34 mmol) and H2O (16 mL) in a pressure reactor. The reaction mixture was stirred at 140 °C for 4 days. After cooling the reaction mixture was dissolved in 200 ml of CH2Cl2, washed with 5% NaHCO3 solution and dried over Na2SO4. The solvent was removed and the residue was purified by flash chromatography on silica gel (CH2Cl2/pentane (1:1)) to give 6-(N-methyl)-2-bromo-naphthalene (2.1 g, 9 mmol, 50%) as a white solid.

2-Bromo-6-(N,N-dimethylamino)naphtalene (5m)

NaH (60%) (1.21 g, 50 mmol) was added to a solution of compound 5l (1 g, 4.2 mmol) and CH3I (2.6 ml, 42 mmol) in THF (50 ml). The reaction mixture was stirred at 60 °C for 18 h. The precipitate was removed by filtration. After evaporation of solvent, the residue was dissolved in 200 ml of CH2Cl2, washed with 5% NaHCO3 solution and dried over Na2SO4. The solvent was removed and the residue was purified by flash chromatography on silica gel (CH2Cl2/pentane, 1:1) to give 5m (0.75 g, 3 mmol, 72%) as a white solid, m.p. 131.7-132.9.
Synthesis of (Z)-3,4,5-trimethoxy-β-iodostyrene (2)

Into a flame-dried 2L round-bottom flask equipped with a magnetic stirrer and a septum was placed iodomethylenetriphenylphosphonium iodide (62 g, 117 mmol). The flask was then put under vacuum for 5 min and purged with nitrogen. Dry THF (350 mL) was added, and the yellow suspension was cooled to -20 °C. Then, NaHMDS in THF (62 mL of 1.9 M solution, 117 mmol) was added dropwise along the flask wall within 30 min. The mixture was stirred at -20 °C for 15 min, then cooled to -78 °C and 3,4,5-trimethoxybenzaldehyde (17.6 g, 90 mmol) in THF (200 mL) was added at this temperature within 1 h with good stirring. The reaction was stirred in the cooling bath for 2 h more, and then quenched while still cold with saturated aq. NH₄Cl. Diethyl ether was added to the mixture, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were filtered to remove Ph₃PO, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 4:1) to give 2 (20.5 g, 64 mmol, 71%, Z/E = 15:1) as a yellow oil.

1H NMR (300 MHz, CDCl₃) δ 7.20 (d, J = 8.6 Hz, 1H), 6.91 (s, 2H), 6.48 (d, J = 8.6 Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H). 13C NMR (75 MHz, CDCl₃) δ 152.8, 138.2, 138.1, 131.8, 105.8, 78.0, 60.8, 56.2. MS (EI), m/z (%): 320 (100) [M]+, 306 (5), 303 (45), 276 (5), 150 (5). HRMS (EI), m/z: calcd for C₁₁H₁₃IO₃ 319.9909, found 319.9910 [M]+.

Synthesis of Combretastatin A-4 Analogs (4a-m)

Typical procedure

A dry nitrogen-flushed Schlenk flask, equipped with a magnetic stirrer and a septum was charged with a solution of alkenyl iodide (320 mg, 1 mmol) in 3 ml of dry THF. The solution of i-PrMgCl-LiCl (0.92 ml of 1.19 M in THF, 1.1 mmol) was added slowly at -40 °C, and the reaction mixture was stirred at this temperature for 15 min to complete I/Mg exchange. A mixture of ZnCl₂ (0.5 ml of 1 M solution in THF, 0.5 mmol) and NMP (0.1 ml) was added dropwise for 1 min and the reaction was warmed to room temperature. 4-Methoxy-3-(tert-butyldimethylsilyloxy)iodobenzene (400 mg, 1.1 mmol) and (A-¹³Phos)₂PdCl₂ (14 mg, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for 30 min, poured into saturated aq. NH₄Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to get brown oil. It was purified by flash chromatography on silica gel (pentane/EtOAc, 5:1) to give 4a-OTBS (267 mg, 0.62 mmol, 62%) as a yellow oil.

3-tert-Butyldimethylsilyloxy-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4a-OTBS)

1H NMR (300 MHz, CDCl₃) δ 6.85 (dd, J = 8.3, 2.1 Hz, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.50 (s, 2H), 6.47 (d, J = 12.1 Hz, 1H), 6.41 (d, J = 12.1 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.70 (s, 6H), 0.93 (s, 9H), 0.06 (s, 6H). 13C NMR (75 MHz, CDCl₃) δ 153.1, 150.4, 144.7, 137.2, 133.2, 130.2, 129.8, 128.9, 123.0, 121.4, 111.8, 106.0, 61.1, 56.0, 55.6, 25.8, 18.5, -4.7. MS
(EI), m/z (%): 430 (40) [M]+, 373 (22), 359 (23), 358 (100), 343 (25). HRMS (EI), m/z: calcld for C$_{24}$H$_{34}$O$_5$Si 430.2176, found 430.2180 [M]+.

3-Fluoro-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4b)

![Chemical structure of 4b](image1)

After purification by flash chromatography on silica gel (pentane/EtOAc, 4:1) the title compound was isolated as a white solid (51%), m.p. 73.9-74.9 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.05 (dd, $J_1$ = 12.5, 2.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.89 – 6.79 (m, 1H), 6.51 – 6.45 (m, 3H), 6.43 (d, $J_2$ = 12.4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.1, 152.1 (d, $J_3$ = 245.3 Hz), 146.8 (d, $J_4$ = 10.9 Hz), 137.5, 132.4, 130.4 (d, $J_5$ = 6.7 Hz), 129.9, 128.5 (d, $J_6$ = 2.0 Hz), 125.3 (d, $J_7$ = 3.4 Hz), 116.6 (d, $J_8$ = 18.7 Hz), 113.1 (d, $J_9$ = 2.2 Hz), 106.1, 61.1, 56.3, 56.1. MS (EI), m/z (%): 318 (100) [M]+, 304 (12), 303 (67), 243 (6), 228 (5), 189 (6). HRMS (EI), m/z: calcld for C$_{18}$H$_{19}$FO$_4$ 318.1267, found 318.1244 [M]+.

3-Chloro-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4c)

![Chemical structure of 4c](image2)

After purification by flash chromatography on silica gel (pentane/EtOAc, 4:1) the title compound was isolated as a yellow solid (55%), m.p. 107.5-109.4 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J_1$ = 2.1 Hz, 1H), 7.14 (dd, $J_2$ = 8.5, 2.1 Hz, 1H), 6.80 (d, $J_3$ = 8.5 Hz, 1H), 6.50 (s, 2H), 6.47 (d, $J_4$ = 12.2 Hz, 1H), 6.41 (d, $J_5$ = 12.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.1, 153.1, 137.6, 132.4, 130.8, 130.7, 130.0, 128.7, 128.2, 122.1, 111.8, 106.1, 61.1, 56.3, 56.1. MS (EI), m/z (%): 334 (100) [M]+, 321 (23), 320 (13), 319 (6), 303 (67), 243 (6), 228 (5), 189 (6). HRMS (EI), m/z: calcld for C$_{18}$H$_{19}$ClO$_4$ 334.0972, found 334.0963 [M]+.

4-(N-tert-Butyloxycarbonyl-N-methylamino)-3',4,5'-trimethyloxy-(Z)-stilbene (4d-NBoc)

![Chemical structure of 4d-NBoc](image3)

After purification by flash chromatography on silica gel (pentane/EtOAc, 5:1) the title compound was isolated as a yellow oil (47%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24 (d, $J_1$ = 8.5 Hz, 2H), 7.12 (d, $J_2$ = 8.6 Hz, 2H), 6.66 – 6.38 (m, 4H), 3.83 (s, 3H), 3.67 (s, 6H), 3.22 (s, 3H), 1.44 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.7, 153.0, 142.9, 137.4, 134.4, 132.6, 130.2, 129.5, 129.3, 125.2, 106.2, 61.0, 56.0, 37.4, 28.5. MS (ESI), m/z (%): 399 (13) [M+H]+, 343 (75), 328 (22), 299 (63), 284 (85). HRMS (ESI), m/z: calcld for C$_{23}$H$_{29}$NO$_5$ 399.2046, found 399.2049 [M+H]+.
4-(N-tert-Butyloxycarbonyl-N-methylamino)-3-chloro-3',4',5'-trimethyloxy-(Z)-stilbene (4e-NBoc)

![Chemical structure](image)

After purification by flash chromatography on silica gel (pentane/EtOAc, 4:1) the title compound was isolated as a colorless oil (49%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.59 (s, 1H), 7.18 (d, $J = 8.3$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 6.58-6.41 (m 4H), 3.87 (s, 3H), 3.76 (s, 6H), 3.13 (s, 3H), 1.37 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.5, 153.0, 139.8, 137.5, 137.4, 131.7, 131.6, 130.1, 129.0, 128.7, 128.1, 127.7, 106.0, 80.1, 60.9, 55.9, 36.2, 28.1. MS (EI), m/z (%): 433 (41) [M$^+$], 379 (25), 377 (84), 333 (47), 318 (56), 57 (100). HRMS (EI), m/z: calcd for C$_{23}$H$_{28}$ClNO$_5$ 433.1656, found 433.1651 [M$^+$].

3-tert-Butyldimethylsilyloxymethyl-3',4',4',5'-tetramethyloxy-(Z)-stilbene (4f-OTBS)

![Chemical structure](image)

After purification by flash chromatography on silica gel (pentane/EtOAc, 5:1) the title compound was isolated as a white solid (53%), m.p. 54.2-56.1 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J = 2.1$ Hz, 1H), 7.17 (dd, $J = 8.4$, 2.1 Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 6.63 – 6.45 (m, 3H), 6.40 (d, $J = 12.2$ Hz, 1H), 4.69 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.68 (s, 6H), 0.89 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 155.4, 153.0, 137.2, 133.1, 130.1, 129.7, 129.5, 128.6, 128.4, 127.9, 109.4, 106.2, 61.0, 60.2, 56.0, 55.4, 26.1, 18.5, -5.3. MS (ESI), m/z (%): 444 (82) [M+H$^+$], 339 (5), 313 (100), 298 (4). HRMS (ESI), m/z: calcd for C$_{25}$H$_{36}$O$_5$Si 444.2332, found 444.2326 [M+H$^+$].

3,5-Dichloro-3',4',5'-trimethyloxy-(Z)-stilbene (4g)

![Chemical structure](image)

After purification by flash chromatography on silica gel (pentane/EtOAc, 6:1) the title compound was isolated as a yellow solid (36%), m.p. 56.1-61.1 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J = 1.8$ Hz, 2H), 7.22 (t, $J = 1.8$ Hz, 1H), 6.72 (s, 2H), 6.63 (s, 1H), 6.46 (s, 1H), 3.91 (s, 6H), 3.88 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.6, 140.5, 136.9, 135.4, 131.6, 127.4, 127.3, 125.4, 124.8, 104.1, 61.1, 56.3. MS (EI), m/z (%): 338 (100) [M$^+$], 325 (40), 323 (63), 209 (10), 202 (13), 139 (16). HRMS (EI), m/z: calcd for C$_{17}$H$_{16}$Cl$_2$O$_3$ 338.0476, found 338.0458 [M$^+$].
After purification by flash chromatography on silica gel (CH₂Cl₂/EtOAc, 50:1) the title compound was isolated as a white solid (39%), m.p. 110.7-116.6 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.29 (m, 2H), 7.02 – 6.84 (m, 3H), 6.71 (s, 2H), 3.91 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.16 (s, 3H), 1.36 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 153.5, 137.9, 133.4, 133.2, 132.7, 130.2, 128.8, 127.5, 127.1, 126.3, 103.6, 103.5, 61.1, 56.3, 55.7, 28.4, 1.2. MS (ESI), m/z (%): 429 (99) [M+H]⁺, 374 (96), 330 (36), 315 (4). HRMS (ESI), m/z: calcd for C₂₄H₃₁NO₆ 429.2151, found 429.2180 [M+H]⁺.

After purification by flash chromatography on silica gel (pentane/EtOAc, 6:1) the title compound was isolated as a yellow oil (42%). ¹H NMR (300 MHz, CDCl₃) δ 7.16 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 2.7 Hz, 1H), 6.79 (dd, J = 8.5, 2.7 Hz, 1H), 6.61 (d, J = 12.0 Hz, 1H), 6.51 (d, J = 12.0 Hz, 1H), 6.32 (s, 2H), 5.06 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59 (s, 6H), 2.28 (t, J = 7.5 Hz, 2H), 1.68 – 1.51 (m, 2H), 1.41 – 1.12 (m, 20H), 0.88 (t, J = 6.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 159.1, 152.3, 137.4, 135.6, 132.3, 131.5, 130.9, 129.8, 127.3, 114.5, 113.8, 106.4, 64.4, 61.0, 55.9, 55.5, 34.4, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.3. MS (ESI), m/z (%): 376 (6) [M-H]⁻, 358 (18), 357 (100). HRMS (ESI), m/z: calcd for C₃₃H₄₉NO₅ 539.3611, found 539.3528 [M+H]⁺.

After purification by flash chromatography on silica gel (pentane/EtOAc, 3:1) the title compound was isolated as a colorless oil (64%). ¹H NMR (300 MHz, CDCl₃) δ 7.16 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 2.7 Hz, 1H), 6.80 (dd, J = 8.5, 2.7 Hz, 1H), 6.61 (d, J = 12.0 Hz, 1H), 6.52 (d, J = 12.0 Hz, 1H), 6.32 (s, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.59 (s, 6H), 2.02 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 159.1, 152.8, 137.4, 135.3, 132.2, 131.5, 130.9, 129.8, 127.2, 114.6, 113.9, 106.3, 64.6, 61.0, 55.9, 55.5, 21.0. MS (EI), m/z (%): 371 (100) [M]⁺, 358 (11), 357 (30), 238 (11), 181 (12), 43 (12). HRMS (EI), m/z: calcd for C₂₁H₂₅NO₅ 371.1735, found 371.1735 [M]⁺.
3,4,5-Trimethyloxy-3',4'-(4''-methyloxybenzo)-(Z)-stilbene (4k)

After purification by flash chromatography on silica gel (pentane/EtOAc, 5:1) the title compound was isolated as a yellow solid (56%), m.p. 56.7-58.9 °C. \(^1\) H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.71 (s, 1H), 7.64 (d, \(J = 8.8\) Hz, 1H), 7.58 (d, \(J = 8.6\) Hz, 1H), 7.39 (dd, \(J = 8.5, 1.7\) Hz, 1H), 7.15 – 7.05 (m, 2H), 6.70 (d, \(J = 12.3\) Hz, 1H), 6.59 – 6.48 (m, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.61 (s, 6H). \(^1\)^13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 158.0, 153.0, 137.4, 133.9, 132.9, 132.7, 130.1, 129.8, 129.5, 129.0, 128.1, 127.7, 126.4, 119.0, 106.3, 105.9, 61.0, 56.0, 55.4. MS (EI), m/z (%): 350 (100) [M]+, 335 (4). HRMS (EI), m/z: calcd for C\(_{22}\)H\(_{22}\)O\(_4\) 350.1518, found 350.1524 [M]+.

3,4,5-Trimethyloxy-3',4'-(4''-N-tert-butyloxycarbonyl-N-methylaminobenzo)-(Z)-stilbene (4l-NBoc)

After purification by flash chromatography on silica gel (pentane/EtOAc, 4:1) the title compound was isolated as a yellow solid (63%), m.p. 88.8-91.3 °C. \(^1\) H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.74 (s, 1H), 7.67 (d, \(J = 8.9\) Hz, 1H), 7.62 (d, \(J = 8.6\) Hz, 1H), 7.56 (d, \(J = 2.0\) Hz, 1H), 7.39 (td, \(J = 8.5, 1.9\) Hz, 2H), 6.71 (d, \(J = 12.2\) Hz, 1H), 6.58 (d, \(J = 12.2\) Hz, 1H), 6.53 (s, 2H), 3.84 (s, 3H), 3.60 (s, 6H), 3.35 (s, 3H), 1.46 (s, 9H). \(^1\)^13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 154.9, 153.1, 141.7, 137.5, 134.7, 132.7, 132.7, 131.3, 130.5, 129.9, 128.2, 127.9, 127.5, 127.2, 125.4, 122.4, 106.3, 80.6, 61.0, 56.0, 37.6, 28.5. MS (ESI), m/z (%): 449 (74) [M+H]+, 394 (98), 348 (8). HRMS (ESI), m/z: calcd for C\(_{27}\)H\(_{31}\)NO\(_5\) 449.2202, found 449.2209 [M+H]+.

3,4,5-Trimethyloxy-3',4'-(4''-N,N-dimethylaminobenzo)-(Z)-stilbene (4m)

After purification by flash chromatography on silica gel (pentane/EtOAc, 5:1) the title compound was isolated as a yellow oil (56%). \(^1\) H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.79 – 7.58 (m, 3H), 7.52 (d, \(J = 8.4\) Hz, 1H), 7.35 (d, \(J = 9.9\) Hz, 1H), 6.77 (s, 1H), 6.67 (d, \(J = 12.2\) Hz, 1H), 6.57 (s, 2H), 6.51 (d, \(J = 12.1\) Hz, 1H), 3.85 (s, 3H), 3.62 (s, 6H), 3.07 (s, 6H). \(^1\)^13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 153.6, 153.0, 137.4, 133.6, 133.0, 130.3, 129.2, 128.0, 127.7, 126.5, 126.0, 116.8, 116.6, 106.2, 103.6, 61.1, 56.3, 56.0. MS (ESI), m/z (%): 363 (100) [M+H]+, 348 (12), 262 (5), 189 (4). HRMS (ESI), m/z: calcd for C\(_{23}\)H\(_{25}\)NO\(_3\) 363.1834, found 363.1836 [M+H]+.
TBS-group cleavage

3-Hydroxy-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4a)

KF (887 mg, 15.3 mmol) was added to a solution of 4a-OTBS (1.47 g, 3.4 mmol) in 20 ml of MeOH under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h and then poured into 5 ml of water. The mixture was extracted with CH₂Cl₂. The organic layers were washed with brine, dried with Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 5:1, then pentane/EtOAc, 2:1) to give 4a (946 mg, 3 mmol, 88%) as a white solid, m.p. 82.6-85.6 °C.

1H NMR (300 MHz, CDCl₃) δ 6.92 (d, J = 2.0 Hz, 1H), 6.80 (dd, J = 8.3, 2.0 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.53 (s, 2H), 6.57 (d, J = 12.2 Hz, 1H), 6.41 (d, J = 12.2 Hz, 1H), 5.53 (br.s, 1 H), 3.86 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H). 13C NMR (75 MHz, CDCl₃) δ 153.0, 145.9, 145.4, 137.3, 132.8, 130.8, 129.6, 129.2, 121.2, 115.2, 110.5, 106.2, 61.0, 56.1, 56.1. MS (ESI), m/z (%): 316 (96) [M-H]+, 286 (100), 271 (39), 228 (28), 171 (4). HRMS (ESI), m/z: calcd for C₁₈H₂₀O₅ 316.1311, found 316.1314 [M-H]+.

3-Hydroxymethyl-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4f)

Tetra-n-butylammonium fluoride (126 mg, 0.4 mmol) was added to a solution of 4f-OTBS (160 mg, 0.36 mmol) in 2 ml of THF under nitrogen atmosphere, followed by the addition of 0.2 ml of CH₃COOH. The reaction mixture was stirred at room temperature for 18 h and then poured into 5 ml of water. The mixture was extracted with CH₂Cl₂. The organic layers were washed with NaHCO₃ solution, brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 1:1, then pentane/EtOAc, 1:2) to give 4f (83 mg, 0.25 mmol, 70%) as a colorless oil.

1H NMR (300 MHz, CDCl₃) δ 7.24 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.4, 2.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.54 – 6.46 (m, 3H), 6.42 (d, J = 12.2 Hz, 1H), 4.60 (s, 2H), 3.83 (s, 6H), 3.68 (s, 6H), 2.21 (s, 1H). 13C NMR (75 MHz, CDCl₃) δ 156.7, 153.0, 137.3, 132.9, 129.7, 129.7, 129.4, 129.0, 128.9, 110.1, 106.1, 62.0, 61.0, 56.1, 55.5. MS (ESI), m/z (%): 330 (100) [M+H]+, 313 (61), 251 (4). HRMS (ESI), m/z: calcd for C₁₉H₂₂O₅ 330.1467, found 330.1464 [M+H]+.
Boc-group cleavage

4-(N-Methylamino)-3',4',5'-trimethyloxy-(Z)-stilbene (4d)

1 ml of CF₃COOH in 3 ml of CH₂Cl₂ was added dropwise to a solution of 4d-NBoc (180 mg, 0.45 mmol) in 6 ml of CH₂Cl₂ under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then at room temperature for 2.5 h. Toluene was then added, the mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (pentane/EtOAc, 2:1) to give 4d (120 mg, 0.40 mmol, 89%) as a yellow solid, m.p. 129.1-144.4.

1H NMR (300 MHz, CDCl₃) δ 7.17 (d, J = 8.6 Hz, 2H), 6.56 (s, 2H), 6.53 (d, J = 8.5 Hz, 2H), 6.46 (d, J = 12.1 Hz, 1H), 6.34 (d, J = 12.1 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 6H), 2.83 (s, 3H). 13C NMR (75 MHz, CDCl₃) δ 153.0, 148.0, 137.0, 133.6, 128.5, 127.8, 124.8, 112.5, 103.3, 61.0, 56.1, 31.2. MS (EI), m/z (%): 299 (100) [M]+, 284 (85), 170 (7), 150 (8), 57 (11), 55 (8). HRMS (EI), m/z: calcd for C₁₈H₂₁NO₃ 299.1521, found 299.1509 [M]+.

4-(N-Methylamino)-3-chloro-3',4',5'-trimethyloxy-(Z)-stilbene (4e)

Following the synthetic procedure for 4d, 4e-NBoc (90 mg, 0.21 mmol) in 3 ml of CH₂Cl₂, 0.5 ml of CF₃COOH in 2 ml of CH₂Cl₂ were used. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 3:1) to give 4e (55 mg, 0.16 mmol, 80%) as a white solid, m.p. 60.7-65.2.

1H NMR (300 MHz, CDCl₃) δ 7.28 (d, J = 1.9 Hz, 1H), 7.16 (dd, J = 8.7, 1.9 Hz, 1H), 6.59-6.55 (m, 3H), 6.39 (d, J = 12.0 Hz, 1H), 6.37 (d, J = 12.0 Hz, 1H), 4.41 (s, 1H), 3.82 (s, 3H), 3.71 (s, 6H), 2.89 (s, 3H). 13C NMR (75 MHz, CDCl₃) δ 153.0, 143.8, 137.2, 132.8, 129.8, 128.7, 128.0, 118.5, 110.2, 105.9, 103.2, 60.9, 56.0, 30.4. MS (EI), m/z (%): 333 (100) [M]+, 320 (25), 318 (76), 197 (7), 167 (6). HRMS (EI), m/z: calcd for C₁₈H₂₀ClNO₃ 333.1132, found 333.1118 [M]+.

3-(N-Methylamino)-3',4,4',5'-tetramethyloxy-(Z)-stilbene (4h)

Following the synthetic procedure for 4d, 4h-NBoc (150 mg, 0.35 mmol) in 3 ml of CH₂Cl₂, 1 ml of CF₃COOH in 3 ml of CH₂Cl₂ were used. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 2:1) to give 4h (112 mg, 0.34 mmol, 97%) as a yellow solid, m.p. 118.2-127.0 °C (decomp.).

1H NMR (300 MHz, CDCl₃) δ 7.02 – 6.85 (m, 3H), 6.84 – 6.60 (m, 4H), 3.92 (s, 6H), 3.88 (s, 3H), 3.87 (s, 3H), 2.95 (s, 3H). 13C NMR (75 MHz, CDCl₃) δ 153.5, 147.9, 137.7, 133.7, 130.8, 128.6,
3,4,5-Trimethoxy-3',4''-(4''-N-methylaminobenzo)-(Z)-stilbene (4l)

Following the synthetic procedure for 4d, 4l-NBoc (278 mg, 0.62 mmol) in 5 ml of CH₂Cl₂, 1 ml of CF₃COOH in 5 ml of CH₂Cl₂ were used.¹⁶ The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 3:1, then pentane/EtOAc, 1:1) to give 4l (205 mg, 0.58 mmol, 95%) as a yellow solid, m.p. 111.8-116.6 °C.

¹H NMR (300 MHz, CDCl₃) δ 7.63 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.34 (dd, J = 8.5, 1.6 Hz, 1H), 6.87 (dd, J = 8.8, 2.3 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.67 (d, J = 12.1 Hz, 1H), 6.57 (s, 2H), 6.50 (d, J = 12.1 Hz, 1H), 3.85 (s, 3H), 3.62 (s, 6H), 2.94 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 153.0, 146.6, 137.3, 134.5, 133.1, 131.1, 130.4, 129.1, 129., 128.2, 127.7, 127.7, 125.8, 118.2, 106.2, 104.7, 61.1, 31.2. MS (EI), m/z (%): 349 (100) [M⁺], 335 (12), 334 (44), 175 (10), 43 (12). HRMS (EI), m/z: calcd for C₂₂H₂₃NO₃ 349.1678, found 349.1671 [M⁺].

References