

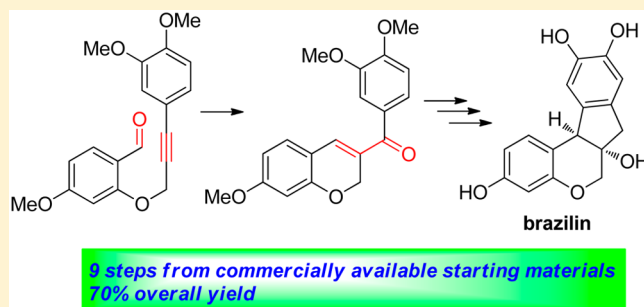
## Total Synthesis of Brazilin

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**S** Supporting Information

**ABSTRACT:** Described herein is a highly efficient total synthesis of brazilin from commercially available starting materials in 9 steps with 70% overall yield. Mitsunobu coupling followed by In(III)-catalyzed alkyne–aldehyde metathesis allowed for rapid construction of brazilin core skeleton in quantitative yield. Subsequent modulation of oxidation levels and acid-catalyzed cyclization led to the trimethyl ether of brazilin. Asymmetric dihydroxylation of the key intermediate was also demonstrated, which would permit asymmetric access to (+)-brazilin.



Brazilin, isolated from the alcoholic extracts of the heartwood of *Caesalpinia sappan* L. (Leguminosae),<sup>1</sup> is a tetracyclic homoisoflavanoid natural product wherein a chroman skeleton is structurally *cis*-fused with a 2,3-dihydro-1*H*-indene moiety. It has long been evaluated under various biological settings and is known to have a number of pharmacological functions including anticancer and anti-inflammatory activities.<sup>2</sup> These interesting biological activities prompted many synthetic efforts toward this molecule, which culminated in several racemic and asymmetric total syntheses.<sup>3,4</sup> Recently, Zhang and co-workers also reported the design and synthesis of brazilin-like compounds.<sup>5</sup> As part of our programs on the total synthesis of bioactive natural products,<sup>6</sup> we decided to pursue the total synthesis of this compound. Here we wish to describe a concise and scalable synthesis<sup>7</sup> of brazilin.

As outlined in Scheme 1, our recognition of structural similarity<sup>8</sup> between **1** and **2** guided us to choose **2** as a viable key intermediate. We envisioned that synthetic operations involving dihydroxylation, deoxygenation, and cyclization events with **2** in an appropriate manner would produce the trimethyl ether **1** of brazilin. As a means to reach the ketone **2**, we planned to employ alkyne-carbonyl metathesis.<sup>9</sup> For this purpose, *O*-propargyloxy salicylaldehyde **3** emerged as a direct precursor, which would be readily available from Mitsunobu type reaction<sup>10</sup> as indicated in Scheme 1.

Our synthesis began with Mitsunobu coupling of commercially available **4**<sup>11</sup> and **5**,<sup>12</sup> which afforded **3** in quantitative yield (Scheme 2). At this point, we screened several different reaction conditions for alkyne-aldehyde metathesis (Table 1). Reactions in the presence of several Lewis acids (0.2 equiv) revealed that In(OTf)<sub>3</sub> exhibited the best efficiency (entries 1–5). 1,2-Dichloroethane (DCE) was superior to dichloromethane as a solvent (entries 6 and 9). Interestingly, reducing the catalyst loading to 0.05 equiv in the case of FeCl<sub>3</sub> and In(OTf)<sub>3</sub>, respectively, affected the isolated yield of **2** in a

positive way (entries 7, 8, 10, and 11). Similarly, the desired product was obtained in 90% yield under the influence of 0.05 equiv of Bi(OTf)<sub>3</sub> (entry 13). The highest yield of the product was observed even in the presence of 0.01 equiv of In(OTf)<sub>3</sub>, although prolonged reaction time and room temperature were required (entry 12). It should be worthwhile to mention that the entire requisite carbon skeleton of brazilin was rapidly secured by this two-step procedure.

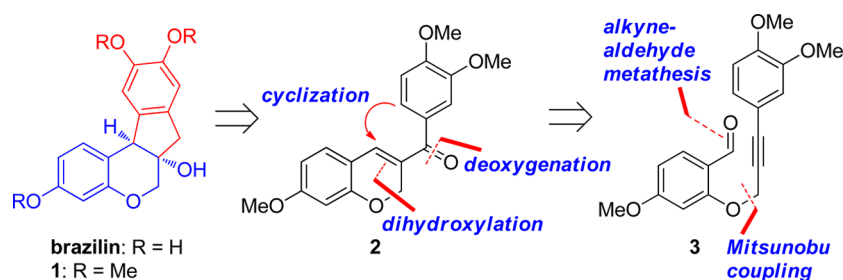
With gram quantities of **2** in hand, our initial plan was successive oxidation of the olefinic bond, cyclization, and excision of the carbonyl group in **2**. To this end, dihydroxylation of **2** was conducted by following the Upjohn process, providing **6** in good yield (Scheme 3).<sup>13</sup> Attempts to cyclize **6** under acid catalysis, however, failed to give **8** (in the box); rather  $\beta$ -diketone **7** was isolated in high yield, which presumably arose from acid-catalyzed regioselective dehydration at the tertiary alcohol site followed by 1,2-hydride shift.<sup>14</sup>

Thus, we decided to remove the carbonyl group first, as this seemed to hamper cyclization. Barton-McCombie protocol<sup>15</sup> was elected for this purpose. Along this line, a 1,2-diol unit in **6** was protected as acetonide to furnish **9** in 97% yield. The resulting ketone **9** was reduced to an alcohol as a diastereomeric 1:1 mixture, which was subsequently converted to a xanthate in quantitative yield. Deoxygenation occurred smoothly under radical conditions to afford **10** in quantitative yield. To our delight, cyclization proceeded rapidly upon exposure of **10** to acidic media, resulting in **1** in 95% yield. Racemic brazilin was obtained by global demethylation with BBr<sub>3</sub>.<sup>16</sup> Spectral data of the synthetic sample are in good agreement with those reported in the literature in all respects. Notably, only three chromatographic purifications were required from **4** to **1** (i.e., after Mitsunobu coupling,

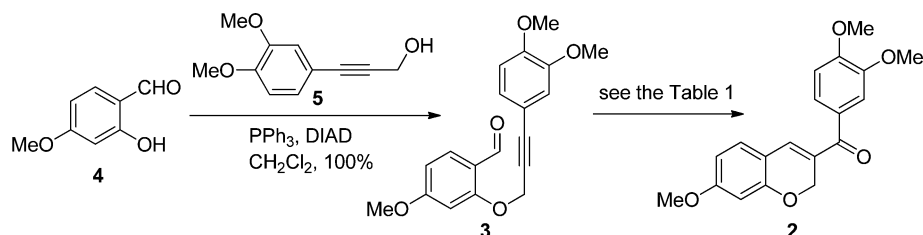
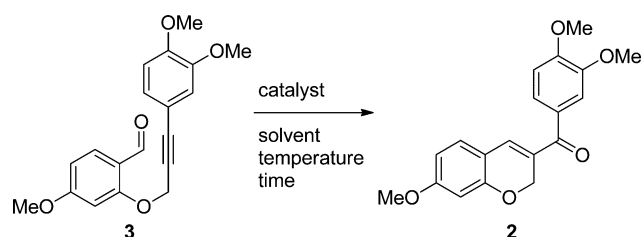
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## Scheme 1. Retrosynthetic Analysis for the Synthesis of Brazilin



## Scheme 2. Synthesis of Ketone 2

Table 1. Reaction Optimization for Alkyne-Aldehyde Metathesis<sup>a</sup>

entry	catalyst (equiv)	temperature	time (h)	solvent	yield <sup>b</sup> (%)
1	BF <sub>3</sub> ·Et <sub>2</sub> O (0.2)	0 °C	1	DCE	79
2	BiCl <sub>3</sub> (0.2)	rt	1	DCE	28
3	FeCl <sub>3</sub> (0.2)	0 °C	3	DCE	79
4	InCl <sub>3</sub> (0.2)	0 °C to rt	4	DCE	63
5	In(OTf) <sub>3</sub> (0.2)	0 °C	3	DCE	83
6	FeCl <sub>3</sub> (0.2)	0 °C	1	CH <sub>2</sub> Cl <sub>2</sub>	68
7	FeCl <sub>3</sub> (0.1)	0 °C	3	DCE	81
8	FeCl <sub>3</sub> (0.05)	0 °C	4	DCE	88 <sup>c</sup>
9	In(OTf) <sub>3</sub> (0.2)	0 °C	1	CH <sub>2</sub> Cl <sub>2</sub>	80
10	In(OTf) <sub>3</sub> (0.1)	0 °C	3	DCE	87
11	In(OTf) <sub>3</sub> (0.05)	0 °C	5	DCE	97
12	In(OTf) <sub>3</sub> (0.01)	0 °C to rt	18	DCE	100 <sup>c</sup>
13	Bi(OTf) <sub>3</sub> (0.05)	0 °C	6	DCE	90

<sup>a</sup>A mixture of **3** (0.09 mmol) and catalyst in solvent (1 mL) was stirred at the indicated temperature and time unless otherwise noted.

<sup>b</sup>Isolated yield (%). <sup>c</sup>0.3 mmol of **3** was used.

dihydroxylation, and radical deoxygenation steps).<sup>17</sup> The overall yield from **4** to brazilin is 70%, the highest overall yield to date for the synthesis of brazilin.

As optically active **9** would allow for asymmetric synthesis of brazilin, asymmetric dihydroxylation of **2** was attempted as well.<sup>18</sup> Sharpless asymmetric dihydroxylation of **2** in the presence of chiral ligand, (DHQD)<sub>2</sub>AQN, followed by acetonide protection of the resulting diol afforded **9** with 68:32 er.<sup>19</sup> The filtrate after trituration under isopropanol, however, provided 98.2% ee of the isomer indicated below (Scheme 4).<sup>20</sup>

In summary, a highly efficient synthetic route to brazilin was developed in 9 steps from commercially available starting

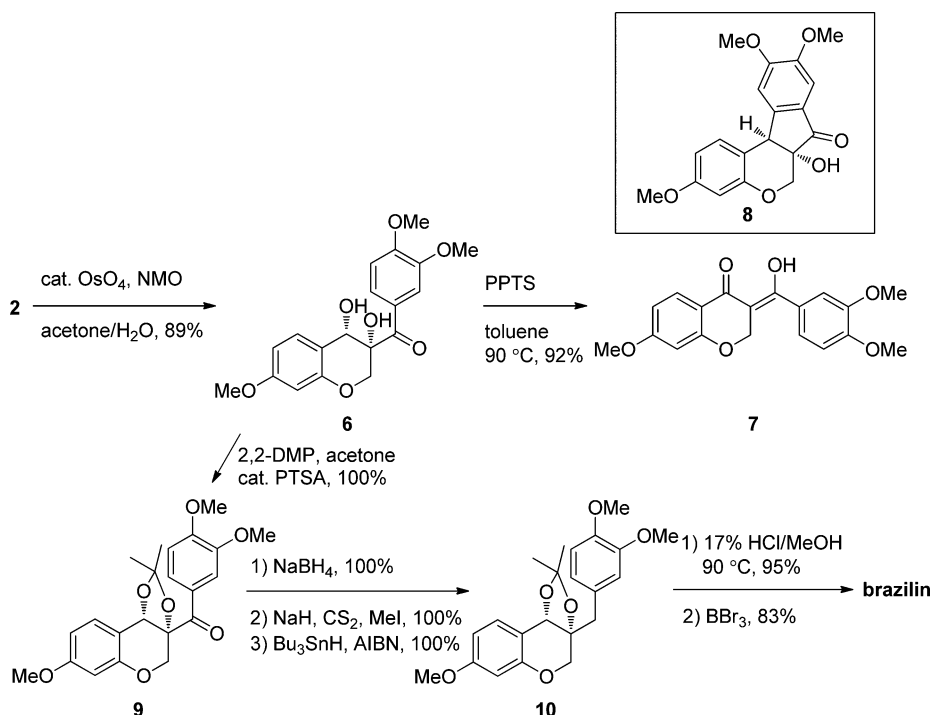
materials with 70% overall yield wherein Mitsunobu coupling and In(III)-catalyzed intramolecular alkyne-aldehyde metathesis allowed facile access to the whole carbon framework of brazilin. From there, total synthesis of brazilin was accomplished via a short series of high-yielding and simple reactions including oxidation, deoxygenation, and cyclization. Furthermore, asymmetric dihydroxylation of **2** enabled asymmetric synthesis of (+)-brazilin, although more optimization is needed. Ease of synthetic operations and high overall yields of this sequence should be useful for the large-scale synthesis of brazilin and its analogues.

## EXPERIMENTAL SECTION

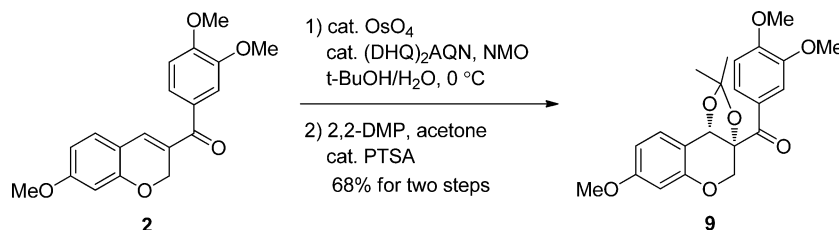
**General Methods.** Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. IR spectra were recorded on FT-IR using diamond ATR technique and were described as wavenumbers (cm<sup>-1</sup>). HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

**2-((3-(3,4-Dimethoxyphenyl)prop-2-yn-1-yl)oxy)-4-methoxybenzaldehyde (3).** To a stirred solution of **4** (1.2 g, 7.89 mmol, 1.5 equiv), **5** (1.01 g, 5.26 mmol), and PPh<sub>3</sub> (1.79 g, 6.84 mmol, 1.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was dropwise added DIAD (1.35 mL, 6.84 mmol, 1.3 equiv) at 0 °C. After being stirred at room temperature for 18 h, the reaction mixture was quenched with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The water layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 2) two more times. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give **3** (1.72 g, 100%). Pale yellow solid, mp: 114.6–116.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.35 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.01 (s, 2H), 3.89 (s, 6H), 3.87 (s,

Scheme 3. Completion of Total Synthesis of Brazilin



Scheme 4. Asymmetric Dihydroxylation of 2



3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.4, 166.0, 162.0, 150.1, 148.8, 130.7, 125.4, 119.7, 114.5, 114.1, 111.1, 106.8, 99.8, 88.5, 81.5, 57.6, 56.1, 55.8; IR (ATR) 3003, 2851, 2768, 2233, 1752, 1606, 1598, 1244, 1021  $\text{cm}^{-1}$ ; HRMS (ESI-QTOF)  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_5$  327.1227, found 327.1222.

(3*R*,4*S*\*)-3,4-Dihydroxy-7-methoxychroman-3-yl)methanone (2). To a stirred solution of 3 (100 mg, 0.3 mmol) in DCE (3 mL) was added  $\text{In}(\text{OTf})_3$  (1.7 mg, 0.003 mmol, 0.01 equiv) at 0 °C. After being stirred at rt for 18 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 10:1:2 to 5:1:2) to give 2 (100 mg, 100%). Yellow solid, mp: 101.7–104.6 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J$  = 8.4 Hz, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 7.03 (d,  $J$  = 8.4 Hz, 1H), 6.92 (d,  $J$  = 8.0 Hz, 1H), 6.50 (d,  $J$  = 8.4 Hz, 1H), 6.47 (s, 1H), 5.13 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  192.8, 163.5, 157.3, 152.6, 149.2, 136.5, 130.6, 130.4, 127.1, 123.5, 114.5, 111.7, 110.0, 108.7, 101.7, 65.9, 56.21, 56.19, 55.7; IR (ATR) 3008, 2962, 2835, 1749, 1595, 762  $\text{cm}^{-1}$ ; HRMS (ESI-QTOF)  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_5$  327.1227, found 327.1228.

((3*R*\*,4*S*\*)-3,4-Dihydroxy-7-methoxychroman-3-yl)(3,4-dimethoxyphenyl)methanone (6). To a stirred solution of 2 (200 mg, 0.61 mmol) in acetone/ $\text{H}_2\text{O}$  (3:1, 8 mL) were added NMO (215.4 mg, 1.84 mmol, 3 equiv) and  $\text{OsO}_4$  (2.5 wt % in *t*-BuOH, 0.3 mL, 0.025 mmol, 0.04 equiv) at 0 °C. After being stirred at 0 °C for 18 h, the reaction mixture was concentrated under reduced pressure and extracted with  $\text{CH}_2\text{Cl}_2$  (6 mL). The water layer was extracted with  $\text{CH}_2\text{Cl}_2$  (6 mL  $\times$  2) two more times. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was

purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give 6 (196.2 mg, 89%). White solid, mp: 155.9–157.8 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (dd,  $J$  = 1.6, 8.8 Hz, 1H), 7.72 (d,  $J$  = 1.6 Hz, 1H), 7.42 (d,  $J$  = 8.8 Hz, 1H), 6.90 (d,  $J$  = 8.4 Hz, 1H), 6.61 (dd,  $J$  = 2.0, 8.8 Hz, 1H), 6.45 (d,  $J$  = 2.4 Hz, 1H), 5.45 (d,  $J$  = 7.6 Hz, 1H), 4.37 (s, 2H), 4.02 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.78 (s, 3H), 2.64 (d,  $J$  = 8.0 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  198.0, 160.7, 154.2, 154.1, 149.1, 129.6, 127.4, 125.5, 115.5, 112.6, 110.1, 109.0, 101.0, 77.7, 69.9, 67.8, 56.3, 56.2, 55.5; IR (ATR) 3397, 2837, 1643, 1619, 1586, 1508, 1413, 1259, 1022  $\text{cm}^{-1}$ ; HRMS (ESI-QTOF)  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{19}\text{H}_{20}\text{NaO}_7$  383.1101, found 383.1100.

3-(3,4-Dimethoxybenzoyl)-7-methoxychroman-4-one (7). To a stirred solution of 6 (20 mg, 0.056 mmol) in toluene (1 mL) was added PPTS (18.1 mg, 0.07 mmol, 1.3 equiv) at rt. After being heated at 90 °C for 14 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 10:1:2) to give 7 (17.5 mg, 92%). Yellow gum;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (dd,  $J$  = 2.0, 8.4 Hz, 1H), 7.10 (d,  $J$  = 1.6 Hz, 1H), 6.83 (d,  $J$  = 8.4 Hz, 1H), 6.67 (d,  $J$  = 8.8 Hz, 1H), 6.57 (d,  $J$  = 2.4 Hz, 1H), 6.33 (dd,  $J$  = 2.4, 8.8 Hz, 1H), 4.56 (s, 2H), 3.93 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  191.7, 180.2, 158.8, 153.6, 152.2, 148.6, 128.2, 127.7, 123.2, 114.6, 111.9, 110.6, 108.7, 105.2, 102.9, 70.1, 56.1, 56.0, 55.5; IR (ATR) 3345, 3079, 2838, 1727, 1593, 1504, 1259, 1134  $\text{cm}^{-1}$ ; HRMS (ESI-QTOF)  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_6$  343.1176, found 343.1177.

(3*R*\*,4*S*\*)-3,4-Dihydroxy-7-methoxy-2,2-dimethyl-4,9*b*-dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]chromen-3*a*-yl)methanone

(9). To a stirred solution of **6** (287.3 mg, 0.8 mmol) and 2,2-dimethoxypropane (DMP) (3 mL) in acetone (12 mL) was added PTSA (15.2 mg, 0.08 mmol, 0.1 equiv) at rt. After being stirred at rt for 3 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give **9** (319 mg, 100%). White solid, mp: 158.3–160.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.64 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.59 (s, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.78 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 196.4, 160.9, 155.6, 153.9, 149.0, 131.4, 127.2, 126.0, 114.1, 112.3, 110.8, 110.1, 109.6, 101.6, 84.8, 73.0, 69.6, 56.2, 56.1, 55.5, 28.2, 26.7; IR (ATR) 3081, 2981, 2841, 1654, 1587, 1256, 1015 cm<sup>-1</sup>; HRMS (ESI-QTOF) *m/z* [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>25</sub>O<sub>7</sub> 401.1595, found 401.1595.

(3*aR*\*,9*bS*\*)-3*a*-(3,4-Dimethoxybenzyl)-7-methoxy-2,2-dimethyl-4,9*b*-dihydro-3*aH*-[1,3]dioxolo[4,5-*c*]chromene (**10**). To a stirred solution of **9** (316 mg, 0.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/EtOH (1:1, 12 mL) was added NaBH<sub>4</sub> (131.4 mg, 3.48 mmol, 4.4 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> (3 mL), concentrated under reduced pressure, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The water layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 2) two more times. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue (317.6 mg, 100%) was used for the next step without further purification.

To a solution of alcohol (470.8 mg, 1.17 mmol) in THF (10 mL) was added 60% NaH (234 mg, 5.85 mmol, 5 equiv) at 0 °C. After the reaction mixture was heated at 100 °C for 5 min, CS<sub>2</sub> (0.71 mL, 11.7 mmol, 10 equiv) was added to the reaction mixture upon heating. After the mixture was heated for 1 h, MeI (0.73 mL, 11.7 mmol, 10 equiv) was added and the reaction mixture was cooled to 0 °C after 30 min. After being quenched with sat. aq. NH<sub>4</sub>Cl (3 mL), the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL), and the layers were separated. The water layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 2) two more times. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo to give the residue (575.7 mg, 100%), which was used for the next step without further purification.

To a solution of xanthate (575.7 mg, 1.17 mmol) in benzene (6 mL) were added AIBN (38.4 mg, 0.234 mmol, 0.2 equiv) and *n*-Bu<sub>3</sub>SnH (0.465 mL, 1.755 mmol, 1.5 equiv) at rt. After being heated at 110 °C for 12 h, the mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 10:1:2 to 5:1:2) to give **10** (452 mg, 100%). Colorless gum; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 1.2 Hz, 1H), 6.70 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.60 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 4.58 (s, 1H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.75 (d, *J* = 10.4 Hz, 1H), 2.93 (d, *J* = 14.4 Hz, 1H), 2.82 (d, *J* = 14.4 Hz, 1H), 1.42 (s, 3H), 1.25 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.3, 156.0, 148.5, 148.0, 132.4, 128.5, 123.0, 114.3, 111.6, 110.9, 109.1, 108.8, 101.6, 77.4, 73.7, 68.4, 56.0, 55.5, 38.5, 29.0, 27.1; IR (ATR) 3239, 2984, 2834, 1619, 1507, 1458, 1236, 1028 cm<sup>-1</sup>; HRMS (ESI-QTOF) *m/z* [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>27</sub>O<sub>6</sub> 387.1802, found 387.1801.

(6*aS*\*,11*bR*\*)-3,9,10-Trimethoxy-6,6*a*,7,11*b*-tetrahydroindeno[2,1-*c*]chromen-6*a*-ol (**1**). A solution of **10** (440 mg, 1.14 mmol) in 17% HCl/MeOH (1:1, 12 mL) was heated at 90 °C for 3 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure to give the crude residue, diluted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL) and H<sub>2</sub>O (6 mL), and the layers were separated. The water layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL × 2) two more times. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give the residue which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give trimethylated brazilin **1** (355.2 mg, 95%). White solid, mp: 131.8–133.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 6.66 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.49 (d,

*J* = 2.4 Hz, 1H), 4.12 (s, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.26 (d, *J* = 15.6 Hz, 1H), 2.88 (d, *J* = 15.6 Hz, 1H), 2.48 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.6, 154.5, 148.8, 148.6, 136.2, 131.2, 130.7, 114.5, 109.0, 108.6, 107.8, 102.1, 77.6, 70.4, 56.23, 56.21, 55.5, 50.7, 41.5; IR (ATR) 3449, 2998, 2920, 2833, 1617, 1500, 1280, 1157 cm<sup>-1</sup>; HRMS (ESI-TOF) *m/z* [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>21</sub>O<sub>5</sub> 329.1384, found 329.1382.

(6*aS*\*,11*bR*\*)-6,6*a*,7,11*b*-Tetrahydroindeno[2,1-*c*]chromene-3,6*a*,9,10-tetraol (Brazilin). To a stirred solution of trimethylated brazilin **1** (21 mg, 0.064 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was dropwise added BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.32 mL, 0.32 mmol, 5 equiv) at -78 °C. After being stirred at -78 °C for 2 h, the reaction mixture was stirred at rt for 18 h. After being quenched with H<sub>2</sub>O, the mixture was extracted with ethyl acetate (4 mL). The water layer was extracted with ethyl acetate (4 mL × 2) two more times. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 1:1:1) to give brazilin (15.2 mg, 83%). Red solid; <sup>1</sup>H NMR (400 MHz, MeOH-*d*<sub>4</sub>) δ 7.18 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.60 (s, 1H), 6.46 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.29 (d, *J* = 1.6 Hz, 1H), 3.96 (s, 1H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.68 (d, *J* = 11.2 Hz, 1H), 3.31 (s, 1H), 3.01 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, MeOH-*d*<sub>4</sub>) δ 157.8, 155.7, 145.6, 145.3, 137.4, 132.2, 131.3, 115.5, 112.8, 112.4, 109.9, 104.2, 78.1, 70.8, 51.0, 42.9; IR (ATR) 3212, 2921, 2110, 1878, 1596, 1503, 1460, 842 cm<sup>-1</sup>; HRMS (ESI-TOF) *m/z* [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>O<sub>5</sub> 287.0914, found 287.0907.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

<sup>1</sup>H and <sup>13</sup>C NMR spectra of **1–3**, **6**, **7**, **9**, **10**, and synthetic brazilin and the chiral chromatographic data of **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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(19) The ee of **9** was determined by chiral HPLC analysis (CHIRALPAK IA column; flow, 0.5 mL/min; hexanes:*i*-PrOH = 80:20;  $\lambda$  = 254 nm). See Supporting Information for details.

(20) A suspension of **9** (20 mg) in *i*-PrOH (10 mL) was filtered. The ee of the filtrate (8 mg) was 98.2%.