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Enantioselective syntheses of (+)- and (−)-brazilin

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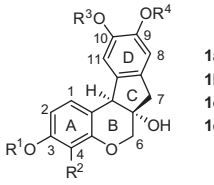
ABSTRACT

Two enantiomers of brazilin were prepared in 9 steps from 7-hydroxychroman-4-one using the AD-mix-α and AD-mix-β-directed enantioselective dihydroxylation of 3-(4-hydroxy-3-methoxyphenyl)-2*H*-chromen-7-ol as a key step.

1. Introduction

(+)-Brazilin **1a** was first isolated as a crystalline solid by Chevreul in 1808 from the brazilwood tree which belongs to the species *Caesalpinia*.[1] However, its molecular formula and structure remained controversial until Libermann and Burg determined a molecular formula of $C_{16}H_{14}O_5$ and a partial structure of three phenolic hydroxyl groups and an alcoholic hydroxyl group.[2] A series of elegant chemical degradations and syntheses by Perkin et al. revealed a 6,6a,7,11b-tetrahydrobenzindeno[2,1-*c*]pyran as the basic skeleton.[3–5] Subsequent spectroscopic[6] and synthetic studies[7,8] finally led to assignments of the four hydroxyl-groups and the *cis* geometry of the B/C ring junction, which were later confirmed by X-ray crystallography of *O*-trimethylbrazilin **1d**.[9] In addition, the absolute configuration of brazilin was later confirmed using Horeau's partial resolution method and from chemical correlations.[10,11]

The brazilin analogs, (+)-hematoxylin **1b** and (+)-3′-*O*-methylbrazilin **1c** were additionally isolated from *Haematoxylon campethianum*[11] and *Caesalpinia sappan*,[12] respectively, whereas *O*-trimethylbrazilin **1d** was prepared by reacting brazilin with methyl iodide in the presence of $NaOCH_3$.[13,14]



1a $R^1 = R^2 = R^3 = R^4 = H$ [(+)-Brazilin]
1b $R^1 = R^3 = R^4 = H$, $R^2 = OH$ [(+)-Haematoxylin]
1c $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$ (3′-*O*-Methylbrazilin)
1d $R^1 = R^3 = R^4 = CH^3$, $R^2 = H$ (*O*-Trimethylbrazilin)

The metal [especially Fe(III) or Al(III)] complexes of brazilin and hematoxylin are commonly used to stain sections of animal tissues for microscopic examination,[15] and hematoxylin is one of the most commonly used histologic stains. Brazilin also has a variety of biological properties, such as hepatoprotective,[16] immunomodulatory,[17] hypoglycemic,[18] anticonvulsant,[19] antiinflammatory,[20] and antioxidant (IC_{50} = 8.8 μM)[21] activities. In addition, it has been reported to inhibit aldose reductase (IC_{50} = 100 μM)[22] and lipopolysaccharide-induced NO production (IC_{50} = 24.3 μM).[23] Brazilin also showed strong antibacterial activity against antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA, MIC = 16 μg/mL) and vancomycin-resistant enterococci #222 (VRE #222, MIC = 16 μg/mL), and multidrug resistant *Burkholderia cepacia* (MIC = 64 μg/mL) as well as against other bacteria at MICs of 4–32 μg/mL.[24] Furthermore, it has been recently reported to have anti-cervical activity (IC_{50} = 0.28 μg/mL),[25] and DNA nicking activity.[26]

Such biological properties and its unique structure have led researchers to develop several synthetic procedures for brazilin including a couple of enantioselective routes.[7,8,12,27,28] However, most of the procedures suffer from low chemical yield and long reaction sequences, and required expensive chiral catalysts.

Herein we describe a new enantioselective synthesis of the (+) and (−)-brazilin from resorcinol by the AD-mix-α and AD-mix-β-directed enantioselective dihydroxylation of 3-(4-hydroxy-3-methoxyphenyl)-2*H*-chromen-7-ol as a key step.

2. Results and discussion

The enantioselective synthetic scheme for brazilin is quite straightforward as shown below. The classical acid-catalyzed Claisen–Schmidt reaction of 7-hydroxychroman-4-one **2**[29] with

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4-hydroxy-3-methoxybenzaldehyde **3** in absolute EtOH saturated with HCl (*g*) afforded the corresponding chalcone **4** in 95% yields, whereas a reaction under basic condition afforded the corresponding chalcone **4** in a somewhat lower yield (56–62%). Catalytic hydrogenation of **4** in EtOH in the presence of a catalytic amount of 5% Pd/C under a H_2 atmosphere (50 psi) afforded the corresponding ketone **5** in 98% yield. To address the inactivity of **5a** toward reduction by $NaBH_4$ and $LiAlH_4$, two phenolic hydroxyl groups were protected by benzylation to the corresponding dibenzyl ether **6**, which was then reduced with $NaBH_4$ to the corresponding alcohol **7** in 88% yield as a 1:1 diastereomeric mixture. Although these diastereomers were separable, vide infra, the diastereomeric mixture was dehydrated by *p*-TsOH-mediated dehydration to yield the 2*H*-chromene derivative **8** in 70% yield. The resulting **8** was then subjected to AD-mix-mediated enantioselective dihydroxylation.[30] More specifically, reaction of **8** with an equimolar amount of AD-mix-α afforded the (3*R*,4*S*)-3-(4-hydroxy-3-methoxybenzyl)chroman-3,4,7-triol **9**, and the enantiomeric excess, as determined by chiral HPLC, was 63% ee. Acid-catalyzed cyclization of **9** yielded protected brazilin **10** in 92% yield, and this was then subjected to hydrogenolysis to 3′-*O*-methylbrazilin in quantitative yield. Subsequent AlCl3-catalyzed demethylation yielded (+)-brazilin **1** in 69% yield. Note that the BBr_3-catalyzed demethylation of (+)-1,3,8-*O*-trimethylbrazilin afforded a complex product mixture[28a] and pyridine-HCl-catalyzed processes resulted in low yields (36%) even under harsh reaction condition (190–200 °C, 3 h),[27d] either stepwise or direct deprotection of (+)-**10** proceeded smoothly to yield (**+**)-**1a**.

The absolute configurations of diols **8** and 3′-*O*-methylbrazilins **9** were determined by comparing their specific rotations with that of brazilin finally obtained from the reaction sequence described above, which reflected the stereochemistries of **9** and **10** and literature values of (+)-brazilin.[31] Accordingly, the absolute stereochemistries at C-3 and C-4 of **9** prepared using an AD-mix-α are (3*S*,4*R*), that is, **9** is (3*R*,4*S*)-3-(4-hydroxy-3-methoxybenzyl) chroman-3,4,7-triol and 3′-*O*-methylbrazilin **10b** is (6a*S*,11b*R*), or more accurately, (6a*S*,11b*R*)-9-methoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromene-3,6a,10-triol, as shown in Scheme 1.

The same procedure described for (**+**)-**1a** was applied to **8** using an AD-mix-β to afford (−)-**1a** via (3*S*,4*R*)-3-(4-hydroxy-3-methoxybenzyl)chroman-3,4,7-triol (83%, 67% ee), followed by concd HCl-catalyzed cyclization, and deprotection by $AlCl_3$ in 47% yield.

3. Conclusion

Both the (+)- and (−)-brazilin were prepared in 9 steps from 7-hydroxychroman-4-one via the AD-mix-α- and AD-mix-β-directed enantioselective dihydroxylation of 3-(4-hydroxy-3-methoxyphenyl)-2*H*-chromen-7-ol as a key step. Structural modifications of brazilin using the synthetic procedure described and biological studies on the products obtained are in progress.

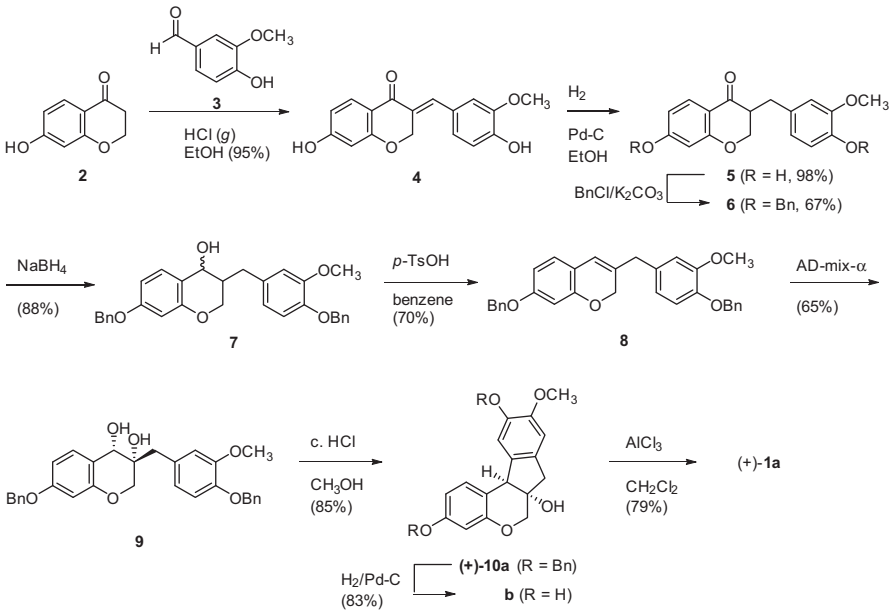
4. Experimental

4.1. General

Melting points were determined using a Fischer-Jones melting point apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz or 600 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). Chemicals and solvents were commercial reagent grade and used without further purification. TLC was performed on precoated Silica gel 60 F254 plates (0.25 mm thickness, Merck) and the spots were visualized by UV irradiation (254 nm). Electrospray ionization (ESI) mass spectrometry (MS) were performed on a LCQ advantage-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA). Specific rotations were measured with a JASCO DIP-181 digital polarimeter. The starting 7-hydroxychroman-4-one 2 was prepared from resorcinol by employing a previously reported method.[29]

4.2. (*E*)-3-(4-Hydroxy-3-methoxybenzylidene)-7-hydroxychroman-4-one 4

Method A: A mixture of 7-hydroxychroman-4-one (**2**, 1.64 g, 10 mmol) and the 4-hydroxy-3-methoxybenzaldehyde (**3**, vanillin, 1.67 g, 11 mmol) in dry EtOH (25 mL) was saturated with dry HCl gas under cooling and then stirred at room temperature. After



Scheme 1. Enantioselective synthesis of (+)-brazilin.

20 h, the mixture was poured into water (100 mL), and 1 N NaOH aq (20 mL) was added. The mixture was stirred at room temperature for 5 h, and the precipitate was filtered off, washed sufficiently with H_2O, and dried over P_2O_5 to give compound **4** (2.26 g, 76%). The filtrate was chromatographed on silica gel eluting with CH_2Cl_2/EtOAc (9:1) (R_f = 0.35) to give an additional product (0.57 g, 19%): mp 248–250 °C. ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 1H, OH), 9.68 (s, 1H, OH), 7.73 (d, 1H, J = 7.6 Hz, H-5), 7.61 (br s, 1H, vinylic H), 7.02 (s, 1H), 6.87 (s, 2H, H5′ and H6′), 6.54 (1H, dd, J = 7.6, 2.2 Hz, H-6), 6.31 (1H, d, J = 2.2 Hz, H-8), 5.39 (2H, d, J = 1.8 Hz, H-2), 3.82 (s, 3H). ^{13}C NMR (DMDO-d_6) δ 180.4, 165.4, 163.3, 149.3, 148.5, 136.9, 130.2, 128.9, 126.3, 125.0, 116.5, 115.5, 115.2, 111.9, 103.3, 68.5, 56.6. MS (ESI) m/z: 300 $[M+H]^+$. Anal. Calcd For $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.71; H, 4.72.

Method B: To a mixture of 7-hydroxychroman-4-one (**2**, 1.64 g, 10 mmol) and 4-hydroxy-3-methoxybenzaldehyde (**3**, vanillin, 1.67 g, 11 mmol) in a mixture of H_2O/EtOH (1:2, 25 mL) was added KOH (300 mg). The resulting mixture refluxed for 8 h and extracted with EtOAc (100 mL × 3). The organic layers were combined and washed with water and dried over $MgSO_4$. Evaporation of the solvent afforded a solid material which was chromatographed on silica gel eluting with CH_2Cl_2/EtOAc (10:1) (R_f = 0.35) to give the product and additional product (1.71 g, 57%): mp 240–242 °C. The spectroscopic data were identical to those obtained from Method A.

4.3. (*E*)-3-(4-Hydroxy-3-methoxybenzyl)-7-hydroxychroman-4-one 5

A mixture of **4** (2.98 g, 0.01 mol) and 5% Pd/C (100 mg) in EtOH (60 mL) was hydrogenated under a H_2 atmosphere (50 psi) for 6 h. Filtration of the reaction mixture through Celite® gave an oily material which was chromatographed on silica gel eluting with CH_2Cl_2/EtOAc (10:1). The early fractions (R_f = 0.35) afforded a white powder (CH_3OH) (2.94 g, 98%): mp 178–179 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 10.51 (br. s, 1H, OH), 8.72 (br. s, 1H, OH), 7.65 (1H, d, J = 8.7 Hz, H5), 6.79 (1H, d, J = 1.5 Hz, H5′), 6.68 (1H, d, J = 8.0 Hz, H2′), 6.59 (1H, dd, J = 8.0, 2.0 Hz, H6′), 6.50 (1H, dd, J = 8.7, 2.0 Hz, H6), 6.30 (1H, d, J = 2.0 Hz, H8), 4.29 (1H, dd, J = 11.5, 4.6 Hz, H2A), 4.10 (1H, dd, J = 11.0, 9.0 Hz, H2B), 3.75 (s, 3H), 3.02 (dd, J = 13.7, 4.8 Hz, H9A), 2.87 (1H, m, H3), 2.50 (1H, dd, J = 13.7, 4.8 Hz, H9B). ^{13}C NMR (acetone-d_6) δ 191.5, 164.4, 163.0, 147.5, 144.9, 129.2, 128.8, 121.1, 115.3, 113.1, 112.9, 110.6, 102.2, 69.4, 55.5, 46.3, 31.4. Anal. Calcd For $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 70.23; H, 5.35.

4.4. 3-(4-Benzyloxy-3-methoxybenzyl)-7-benzyloxychroman-4-one 6

To a stirring solution of **5** (3.00 g, 10.0 mmol) in THF (20 mL), K_2CO_3 (4.00 g, 28.9 mmol), and NaI (200 mg) was slowly added benzyl chloride (3.30 g, 27.0 mmol) and the resulting mixture was stirred at room temperature for 2 h. Evaporation of the solvent gave a solid material which was then re-dissolved in CH_2Cl_2 (80 mL) and washed with water (20 mL × 3), brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a solid material which was chromatographed on silica gel eluting with hexane/EtOAc (4:1, R_f = 0.36) to give 3.2 g (67%) of the desired product as light orange needles: mp 77–79 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.88 (d, 1H, J = 7.5 Hz, H5), 7.42–7.29 (m, 10H), 6.83 (1H, d, J = 7.5 Hz, H4′), 6.79 (1H, d, J = 2.5 Hz, H8), 6.70 (1H, dd, J = 7.5, 2.5 Hz, H5), 6.68 (1H, dd, J = 7.5, 2.5 Hz, H6), 6.49 (1H, d, J = 2.5 Hz, H2′), 5.12 (s, 2H), 5.07 (s, 2H), 4.34 (dd, 1H, J = 11.3, 5.0 Hz, H2A), 4.14 (dd, 1H, J = 11.3, 7.5 Hz, H2B), 3.87 (s, 3H), 3.19 (dd, 1H, J = 13.8, 1.8 Hz, H9A), 2.87–2.76 (m, 1H, H3), 2.50 (1H, dd, J = 13.8, 10.0 Hz, H9B), ^{13}C NMR ($CDCl_3$) δ 192.6, 165.2, 163.6, 150.0, 147.2, 137.4, 136.1, 131.75, 129.37, 128.8, 128.6, 127.651, 127.614, 127.612, 127.3, 121.3, 114.8, 114.6, 113.0, 110.7, 101.9, 71.4, 70.4, 69.9, 56.2, 47.6, 32.4. Anal. Calcd For $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 76.75; H, 5.86.

4.5. 3-(4-Benzyloxy-3-methoxybenzyl)-7-benzyloxy-3,4-dihydro-2*H*-chromen-4-ol 7

To a solution of **6** (1.78 g, 3.7 mmol) in THF (20 mL) was added a solution of $NaBH_4$ (15 mg, 3.7 mmol) in ethanol (10 mL). The resulting mixture was stirred at room temperature for 5 h. Evaporation of the solvent gave a solid material (off white in color) which was then re-dissolved in CH_2Cl_2 (20 mL). To the mixture was added water (5 mL) and the CH_2Cl_2 layer was separated and dried over $MgSO_4$. A thick viscous liquid (1.57 g, 88%) was obtained, and chromatographed on silica gel eluting with hexane/EtOAc (7:3). ***cis*-Isomer 7a**: Pale yellow oil (45%). R_f = 0.45 [hexane/EtOAc (7:3)]. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.33–7.26 (m, 10 H), 7.09 (1H, d, J = 8.5 Hz, H5), 6.84 (1H, d, J = 8.3 Hz, H5′), 6.80 (1H, d, J = 1.8 Hz, H2′), 6.72 (1H, dd, J = 8.0, 1.8 Hz, H6′), 6.55 (1H, dd, J = 8.5, 2.5 Hz, H6), 6.45 (1H, d, J = 2.5 Hz, H8), 5.13 (s, 2H), 5.01 (s, 2H), 4.45 (br. s, 1H, H4), 4.04 (d, 2H, J = 6.8 Hz, H2), 3.87 (s, 3H), 2.80 (1H, dd, J = 13.8, 7.5 Hz, H9A), 2.50 (1H, dd, J = 13.8, 7.5 Hz, H9B), 2.15 (1H, m, H3). ^{13}C NMR ($CDCl_3$) δ 180.3, 155.6, 150.0, 147.0, 137.6, 137.0, 132.6, 131.1, 128.8, 128.7, 128.1, 128.0, 127.6, 127.5, 121.3, 117.4, 114.6, 113.2, 108.6, 102.5, 71.5, 70.2, 65.2, 64.7, 56.2, 40.4, 32.7. Anal. Calcd For $C_{31}H_{30}O_5$: C, 77.16; H, 6.27. Found: C, 76.99; H, 6.29. ***trans*-Isomer 7b**: Pale yellow oil (43%). R_f = 0.31 [hexane/EtOAc (7:3)]. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.38–7.28 (m, 10H), 7.18 (1H, d, J = 8.5 Hz, H5), 6.81 (1H, d, J = 8.4 Hz, H5′), 6.70 (1H, d, J = 1.8 Hz, H2′), 6.63 (1H, dd, J = 7.3, 1.8 Hz, H6), 6.60 (1H, dd, J = 8.4, 1.8 Hz, H8), 6.49 (d, 1H, J = 2.5 Hz, H), 5.11 (s, 2H), 5.02 (s, 2H), 4.41 (d, 1H, J = 3.3 Hz, H4), 4.19 (d, 1H, J = 11.1, 2.5 Hz, H2A), 3.94 (d, 1H, J = 11.1, 2.5 Hz, H2B), 3.84 (s, 3H), 2.60 (1H, dd, J = 13.8, 6.7 Hz, H9A), 2.44 (1H, dd, J = 13.8, 6.7 Hz, H9B), 2.78 (1H, m, H3). ^{13}C NMR ($CDCl_3$) δ 180.3, 155.6, 150.0, 147.0, 137.6, 137.0, 132.6, 131.1, 128.8, 128.7, 128.1, 128.0, 127.6, 127.5, 121.3, 117.4, 114.6, 113.2, 108.6, 102.5, 71.5, 70.2, 65.2, 64.7, 56.2, 40.4, 32.7. Anal. Calcd For $C_{31}H_{30}O_5$: C, 77.16; H, 6.27. Found: C, 77.42; H, 6.29.

4.6. 3-(4-Benzyloxy-3-methoxybenzyl)-7-benzyloxy-2*H*-chromene 8

Method A: A mixture of **7** (1.78 g, 3.7 mmol) and *p*-TsOH (30 mg, 0.17 mmol) in benzene (40 mL) was refluxed for 40 min. The reaction mixture was cooled to room temperature and then washed with saturated $NaHCO_3$ (3 × 20 mL), then water (2 × 20 mL). The organic layers were dried over $MgSO_4$. The benzene was evaporated and thick viscous liquid was obtained, which was chromatographed on silica gel eluting with hexane/EtOAc (4:1) to give the desired product [R_f = 0.39, hexane/EtOAc (4:1)] (1.2 g, 70%) as off-white crystals: mp 129–131 °C. ^{1}H NMR (CD_3COCD_3, 250 MHz) δ 7.48–7.32 (m, 10H), 6.79 (d, 1H, J = 8.1 Hz, H5), 6.75 (d, 1H, J = 8.0 Hz, H5′), 6.72 (d, 1H, J = 2.1 Hz, H2′), 6.57 (dd, 1H, J = 8.0, 2.1 Hz, H6′), 6.33 (dd, 1H, J = 8.1, 2.6 Hz, H6), 6.22 (d, 1H, J = 2.6 Hz, H8), 6.14 (br. s, 1H, H4), 4.54 (s, 2H, H2), 3.79 (s, 3H), 3.27 (s, 2H). ^{13}C NMR (CD_3COCD_3, 62.5 MHz) δ 159.5, 154.3, 150.1, 147.2, 137.5, 137.2, 131.33, 131.11, 128.752, 128.713, 128.534, 128.116, 127.990, 127.617, 127.504, 126.9, 121.2, 120.0, 116.4, 114.6, 112.9, 108.0, 102.6, 71.4, 70.3, 68.4, 56.3, 39.6. Anal. Calcd For $C_{31}H_{28}O_4$: C, 80.15; H, 6.08. Found: C, 79.98; H, 6.07.

Method B: A solution of 7 (300 mg, 0.62 mmol) in dry pyridine (10 mL) was cooled in an ice bath, to which freshly distilled $POCl_3$ (1.39 mL, 14.86 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 24 h. To the resulting

red brown mixture, water was added carefully to hydrolyze the excess $POCl_3$. The reaction mixture was extracted with ether (3 × 30 mL). The ethereal layers were washed with 10% HCl, water, brine, and dried over $MgSO_4$. The solvent was evaporated to give an oily material which was purified as described above in Method A. All spectroscopic data were identical to those obtained above for Method A.

4.7. (3*R*,4*S*)-3-(4-Benzyloxy-3-methoxybenzyl)-7-benzyloxy-3,4-dihydro-2*H*-chromene-3,4-diol (+)-9

To a solution of CH_3CN (15 mL) and H_2O (15 mL) was added dropwise AD-mix-α (1.85 g, 0.17 mmol) with stirring at room temperature, then methanesulfonamide (80 mg) was added. The resulting mixture was cooled to 0 °C, to which **8** (0.34 g, 0.73 mmol) was added and then the heterogeneous slurry was stirred vigorously at 0 °C for 48 h. While the mixture was stirred at 0 °C, solid sodium sulfite (1.30 g) was added and the resulting mixture was allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was extracted with EtOAc (20 mL × 3). The organic layers were combined and washed with water (50 mL × 3), brine, and dried over $MgSO_4$. Evaporation of the solvent afforded a pale yellow solid, which was chromatographed on silica gel eluting with hexanes/EtOAc (7:3) to afford (**+**)-**9** as pale yellow needles (0.55 g, 65%, R_f = 0.14 (hexane/EtOAc = 7:3)], $[\alpha]_D^{25}$ = +75.7 (*c* 0.038, $CHCl_3$), ee 63%. ^{1}H NMR (CD_3CN, 250 MHz) δ 7.46–7.34 (m, 10H), 7.22 (d, 1H, *J* = 8.8 Hz, H2′), 6.90 (d, 1H, *J* = 8.0 Hz, H5′), 6.79 (d, 1H, *J* = 1.9 Hz, H6′), 6.68 (dd, 1H, *J* = 8.1, 2.0 Hz, H6), 6.62 (dd, 1H, *J* = 8.5, 2.5 Hz, H8), 6.45 (d, 1H, *J* = 2.4 Hz, H8), 5.07 (s, 2H), 5.06 (s, 2H), 4.25 (d, 1H, *J* = 3.9 Hz, H4), 3.86 (d, 1H, *J* = 10.8 Hz, H2A), 3.78 (s, 3H), 3.70 (d, 1H, *J* = 10.8 Hz, H2B), 2.69 (AB quartet, 2H, H9). ^{13}C NMR (62.5 MHz, CD_3OD) δ 161.3, 156.1, 150.6, 148.3, 139.1, 138.8, 133.0, 131.1, 129.94, 129.88, 129.3, 129.1, 124.2, 118.7, 116.4, 115.1, 109.9, 103.2, 97.0, 72.1, 71.1, 70.8, 69.7, 68.9, 56.9, 41.4. Anal. Calcd For $C_{31}H_{30}O_6$: C, 74.68; H, 6.07. Found: C, 74.39; H, 6.09.

4.8. (3*S*,4*R*)-3-(4-Benzyloxy-3-methoxybenzyl)-7-benzyloxy-3,4-dihydro-2*H*-chromene-3,4-diol (−)-9

The same procedure as described above for (**+**)-**9** was employed for **8** using AD-mix-β and afforded (−)-**9** (64%). White powder: mp 129–131 °C, $[\alpha]_D^{25}$ = −92.7 (*c* 0.038, $CHCl_3$), ee 67%. ^{1}H NMR (CD_3CN, 250 MHz) δ 7.45–7.34 (m, 10H), 7.22 (d, 1H, *J* = 8.8 Hz, H2′), 6.90 (d, 1H, *J* = 8.0 Hz, H5′), 6.79 (d, 1H, *J* = 1.9 Hz, H6′), 6.68 (dd, 1H, *J* = 8.1, 2.0 Hz, H6), 6.62 (dd, 1H, *J* = 8.5, 2.5 Hz, H8), 6.45 (d, 1H, *J* = 2.4 Hz, H8), 5.07 (s, 2H), 5.06 (s, 2H), 4.25 (d, 1H, *J* = 3.9 Hz, H4), 3.86 (d, 1H, *J* = 10.8 Hz, H2A), 3.78 (s, 3H), 3.70 (d, 1H, *J* = 10.8 Hz, H2B), 2.69 (AB quartet, 2H, H9). ^{13}C NMR (62.5 MHz, CD_3CN) δ 161.1, 155.9, 150.3, 148.2, 138.9, 138.6, 132.8, 130.8, 129.84, 129.79, 129.2, 129.0, 124.0, 117.8, 116.1, 114.7, 109.7, 103.0, 96.7, 71.8, 71.0, 70.6, 69.5, 68.7, 56.7, 41.2. Anal. Calcd For $C_{31}H_{30}O_6$: C, 74.68; H, 6.07. Found: C, 74.42; H, 6.09.

4.9. (6a*S*,11b*R*)-3,10-Bis(benzyloxy)-6,6a,7,11b-tetrahydro-9-methoxyindeno[2,1-*c*]chromen-6a-ol (+)-10a

To a solution of (**+**)-**9** (30 mg, 0.06 mmol) in methanol (10 mL) was added 5 drops of concd HCl. The reaction mixture was refluxed for 2 h. Evaporation of the solvent lead to a thick liquid which was chromatographed on silica gel eluting with CH_2Cl_2/EtOAc (9:1). The early fractions afforded (+)-**10** (25 mg, 85%), as a white crystalline solid: mp 130–132 °C. ^{1}H NMR (CD_3OD, 250 MHz) δ 7.36–7.23 M, 10H), 7.18 (d, 1H, *J* = 8.5 Hz, H1), 6.88 (s, 1H, H11), 6.80 (s, 1H, H8), 6.63 (dd, 1H, *J* = 8.5, 2.5 Hz, H2), 6.47 (d, 1H, *J* = 2.5 Hz, H5), 4.99 (s, 2H), 4.98 (s, 2H), 4.00 (br s, 1H, C6a-OH), 3.93 (dd, 1H, *J* = 11.6, 2.0 Hz, H6A), 3.77 (s, 3H), 3.70 (d, 1H, *J* = 11.6 Hz, H6B), 3.06 (d, 1H, *J* = 16.0 Hz, H7A), 2.88 (d, 1H, *J* = 16.0 Hz, H7B). ^{13}C NMR (CD_3OD, 62.5 MHz) δ 159.9, 155.9, 151.2, 148.9, 138.96, 138.92, 138.3, 133.8, 132.2, 129.6, 129.5, 129.0, 128.9, 128.6, 116.9, 113.1, 110.8, 110.2, 104.2, 78.4, 72.9, 71.2, 71.1, 56.9, 51.6, 43.3. Anal. Calcd For $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 77.43; H, 5.89.

4.10. (6a*R*,11b*S*)-3,10-Bis(benzyloxy)-6,6a,7,11b-tetrahydro-9-methoxyindeno[2,1-*c*]chromen-6a-ol (−)-10a

The same procedure described above for (+)-**10a** was applied to (−)-**9** (50 mg, 0.10 mmol) to afford (−)-**10a** (40 mg, 83%). White crystalline solid: mp 130–132 °C. ^{1}H NMR (CD_3OD, 250 MHz) δ 7.34–7.24 M, 10H), 7.18 (d, 1H, *J* = 8.5 Hz, H1), 6.88 (s, 1H, H11), 6.80 (s, 1H, H8), 6.64 (dd, 1H, *J* = 8.4, 2.5 Hz, H2), 6.47 (d, 1H, *J* = 2.5 Hz, H5), 5.00 (s, 2H), 4.98 (s, 2H), 3.97 (br s, 1H, C6a-OH), 3.94 (dd, 1H, *J* = 11.6, 2.0 Hz, H6A), 3.76 (s, 3H), 3.70 (d, 1H, *J* = 11.6 Hz, H6B), 3.07 (d, 1H, *J* = 16.0 Hz, H7A), 2.89 (d, 1H, *J* = 16.0 Hz, H7B). ^{13}C NMR (CD_3OD, 62.5 MHz) δ 159.9, 155.9, 151.2, 148.9, 138.96, 138.92, 138.3, 133.8, 132.2, 129.6, 129.5, 129.0, 128.9, 128.6, 116.9, 113.1, 110.8, 110.2, 104.2, 78.4, 72.9, 71.2, 71.1, 56.9, 51.6, 43.3. Anal. Calcd For $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 77.39; H, 5.89.

4.11. (+)-9-Methoxybrazilin [3′-*O*-methoxylbrazilin, (6a*S*,11b*R*)-9-methoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]-chromene-3,6a,10-triol, (+)-10b]

To a solution of (+)-**10a** (10 mg, 0.021 mmol) in EtOAc (1 mL) and EtOH (2 mL) was added Pd/C (1 mg) under nitrogen. The nitrogen line was replaced by a hydrogen balloon and the reaction mixture was stirred for 48 h. Filtration through Celite and evaporation of the solvent gave the debenzylated product (**+**)-**10b** (5 mg, 83%). Spectroscopic data were identical to those reported previously.[12,32]

4.12. (−)-9-Methoxybrazilin [3′-*O*-methoxylbrazilin, (6a*R*,11b*S*)-9-methoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]-chromene-3,6a,10-triol, (−)-10b)

To a solution of (−)-**10a** (30 mg, 0.06 mmol) in EtOAc (3 mL) and EtOH (6 mL) was added Pd/C (1 mg) under nitrogen. The nitrogen line was replaced by a hydrogen balloon and the reaction mixture was stirred for 48 h. Filtration through Celite and evaporation of the solvent gave the debenzylated product (−)-**10b** (16 mg, 85%). ^{1}H NMR (CD_3OD, 250 MHz) δ 7.23 (d, 1H, *J* = 8.4 Hz, H1), 6.87 (s, 1H, H11), 6.80 (s, 1H, H8), 6.64 (dd, 1H, *J* = 8.4, 2.5 Hz, H2), 6.48 (d, 1H, *J* = 2.5 Hz, H5), 5.00 (s, 2H), 4.98 (s, 2H), 3.98 (br s, 1H, C6a-OH), 3.94 (dd, 1H, *J* = 11.8, 2.0 Hz, H6A), 3.78 (s, 3H), 3.69 (d, 1H, *J* = 11.8 Hz, H6B), 3.06 (d, 1H, *J* = 16.0 Hz, H7A), 2.87 (d, 1H, *J* = 16.0 Hz, H7B). ^{13}C NMR (CD_3OD, 62.5 MHz) δ 158.7, 156.2, 148.7, 147.0, 139.0, 132.4, 132.1, 116.5, 112.7, 110.0, 109.9, 78.7, 71.6, 56.9, 52.0, 43.6. MS (ESI) for $C_{16}H_{15}O_5$ $[M+H]^+$ 301.

4.13. (+)-Brazilin [(6a*S*,11b*R*)-3,6a,9,10-tetrahydroxy-6a,11b-dihydro-7*H*-indeno[2,1-*c*]chromene, (+)-1a]

A solution of (+)-**10b** (300 mg, 1 mmol) and $AlCl_3$ (500 mg) in CH_2Cl_2 (30 mL) was stirred for 2 h and poured into ice-cold dilute HCl to form a solid material which was chromatographed on silica gel eluting with $CHCl_3$/CH_3OH (9:1). The early fractions (R_f = 0.3) afforded (+)-**1** as a yellow powder (225 mg, 79%): mp 248–250 °C (lit.[25]mp 249–250 °C) $[\alpha]_D^{25}$ = +125.6 (*c* 0.61, CH_3OH). ^{1}H NMR (acetone-d_6, 250 MHz) δ 7.35 (d, 1H, *J* = 8.3 Hz, H1), 6.92 (s, 1H, H8), 6.80 (s, 1H, H11), 6.66 (dd, 1H, *J* = 8.3, 2.5 Hz, H2), 6.45 (d, 1H,

J = 2.5 Hz, H4), 4.12 (s, 1H, H12), 4.10 (d, 1H, ^2J = 11.0 Hz, H6A), 3.87 (d, 1H, ^2J = 11.0 Hz, H6B), 3.18 (d, 1H, ^2J = 15.8 Hz, H7A), 2.98 (d, 1H, ^2J = 15.8 Hz, H7B). ^{13}C NMR (acetone-d_6, 62.5 MHz) δ 157.9, 155.8, 145.4, 145.1, 137.6, 132.3, 131.7, 115.8, 113.0, 112.6, 110.0, 104.3, 78.2, 70.9, 51.4, 43.2. MS (ESI) for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.

4.14. (−)-Brazilin [(6a*R*,11b*S*)-3,6a,9,10-tetrahydroxy-6a,11b-dihydro-7*H*-indeno[2,1-*c*]chromene, (−)-1a]

The same procedure described above for (+)-brazilin was applied to (−)-**10a** (240 mg, 0.5 mmol) with $AlCl_3$ (300 mg) to yield (−)-brazilin (134 mg, 89%). $[\alpha]_D^{25}$ = −94.0 (*c* 1.45, CH_3OH). ^{1}H NMR (acetone-d_6, 250 MHz) δ 7.36 (d, 1H, J = 8.3 Hz, H1), 6.93 (s, 1H, H8), 6.80 (s, 1H, H11), 6.67 (dd, 1H, J = 8.3, 2.5 Hz, H2), 6.46 (d, 1H, J = 2.5 Hz, H4), 4.13 (s, 1H, H12), 4.09 (d, 1H, ^2J = 11.0 Hz, H6A), 3.87 (d, 1H, ^2J = 11.0 Hz, H6B), 3.19 (d, 1H, ^2J = 15.8 Hz, H7A), 2.97 (d, 1H, ^2J = 15.8 Hz, H7B). ^{13}C NMR (acetone-d_6, 62.5 MHz) δ 157.8, 155.8, 145.6, 145.3, 137.3, 132.4, 131.5, 115.6, 113.1, 112.7, 109.9, 104.4, 78.5, 71.1, 51.6, 43.6. MS (ESI) for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.

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References

1. Chevreul, P. M. *Ann. Chim.* **1808**, *66*, 225.
2. Libermann, C.; Burg, O. *Ber.* **1883**, *1876*, 9.
3. Perkin, W. H., Jr.; Robinson, R. *J. Chem. Soc., Trans.* **1908**, *93*, 489.
4. Perkin, W. H., Jr.; Robinson, R. *J. Chem. Soc., Trans.* **1909**, *95*, 381.
5. The early studies on brazilin and haematoxylin are summarized in Robinson, R. *Bull. Soc. Chim. Fr.* **1958**, 125.
6. Craig, J. C.; Naik, A. R.; Pratt, R.; Johnson, E.; Bhacca, N. S. *J. Org. Chem.* **1965**, *30*, 1573.
7. Dann, O.; Hofmann, H. *Justus Liebig's Ann. Chem.* **1963**, *667*, 116.
8. Kirkiacharian, B. S. *C. R. Acad. Sic., Ser. C* **1972**, *274*, 2096.
9. Gupta, M. P.; Gupta, N. P. *Curr. Sci.* **1968**, *37*, 250 [*Chem. Abstr.* **1968**, *69*, 39531y].
10. Horeau, A. Stereochemistry In *Determination of Configurations by Chemical Methods*; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 3, pp 51–94.
11. Chevreul, M. *Ann. Chim. Phys., [ii]* **1810**, *82*, 53.
12. Namikashi, M.; Nakata, H.; Yamada, H.; Nagai, M.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, *35*, 2761.
13. Schall, C.; Dralle, G. *Ber.* **1888**, *21*, 3009.
14. Gilbody, A. W.; Perkin, W. H., Jr.; Yates, J. *J. Chem. Soc., Trans.* **1901**, *79*, 1396.
15. Hickson, S. J. *Q. J. Microscopy. Sci.* **1901**, 469.
16. Moon, C.-K.; Park, K. S.; Kim, S. G.; Won, H. S.; Chung, J. H. *Drug Chem. Toxicol.* **1992**, *15*, 81.
17. Choi, S. Y.; Yang, K. M.; Jeon, S. D.; Kim, J. H.; Khil, L. Y.; Chang, T. S.; Moon, C.-K. *Planta Med.* **1997**, *63*, 405.
18. Kim, Y. M.; Kim, S. G.; Khil, L. Y.; Moon, C. K. *Planta Med.* **1995**, *61*, 297.
19. Baek, N. I.; Jeon, S. G.; Ahn, E. M.; Hahn, J. T.; Bahn, J. H.; Cho, S. W. *Arch. Pharm. Res.* **2000**, *23*, 344.
20. Hikino, H.; Taguchi, T.; Fujimura, H.; Hiramatsu, Y. *Planta Med.* **1977**, *31*, 214.
21. Batubara, I.; Mitsunaga, T.; Ohashi, H. *J. Wood Sci.* **2010**, *56*, 77.
22. Moon, C. K.; Yun, Y. P.; Lee, J. H.; Wager, H.; Shin, Y. H. *Planta Med.* **1985**, *47*, 66.
23. Bae, I.-K.; Min, H.-Y.; Han, A.-R.; Seo, E.-K.; Lee, S. K. *Eur. J. Pharmacol.* **2005**, *513*, 237.
24. Xu, H.-X.; Lee, S. F. *Phytother. Res.* **2004**, *18*, 647.
25. Kitdamrongtham, W.; Manosroi, A.; Akazawa, H.; Gidado, A.; Stienrut, P.; Manosroi, W.; Lohcharoenkal, W.; Akihisa, T.; Manosroi, J. *J. Ethnopharmacol.* **2013**, *149*, 288.
26. Mar, W.; Lee, H.-T.; Je, K.-H.; Choi, H.-Y.; Seo, E.-K. *Arch. Pharm. Res.* **2003**, *26*, 147.
27. (a) Pfeiffer, P.; Oberlin, H.; Konermann, E. *Ber.* **1947**, *1925*, 58; (b) Gregory, R. A.; Tomlinson, M. L. *J. Chem. Soc.* **1956**, 795; (c) Morsingh, F.; Robinson, R. *Tetrahedron* **1970**, *26*, 281; (d) Huang, Y.; Zhang, J.; Pettus, R. R. *Org. Lett.* **2005**, *7*, 5841; (e) Yen, C.-T.; Nakagawa-Goto, K.; Hwang, T.-L.; Wu, P.-C.; Morris-Natscheke, S. L.; Lai, W.-C.; Bastow, K. F.; Chang, F.-R.; Wu, Y.-C.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1037; (f) Li, L.-Q.; Li, M.-M.; Wang, K.; Qin, H.-B. *Tetrahedron Lett.* **2013**, *54*, 6029.
28. (a) Davis, F. A.; Chen, B. C. *J. Org. Chem.* **1993**, *63*, 1751; (b) Wang, X.; Zhang, H.; Yang, X.; Zhao, J.; Pan, C. *Chem. Commun.* **2013**, 5405.
29. (a) Naylor, P.; Ramage, G. R.; Schofield, F. *J. Chem. Soc.* **1958**, 1190; (b) Breytenbach, J. C.; Rall, G. J. H. *J. Chem. Soc., Perkin Trans. 1* **1804**, 1980.
30. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768.
31. Fuke, C.; Yamahara, J.; Shimokawa, T.; Kinjo, J.; Tomomatsu, T.; Nohara, T. *Phytochemistry* **1985**, *24*, 2403.
32. Fu, L.-C.; Huang, X.-A.; Lai, Z.-Y.; Hu, Y.-J.; Hu, H.-J.; Cai, X.-L. *Molecules* **1923**, *2008*, 13.