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Note

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Synthesis of Coumestrol and Aureol

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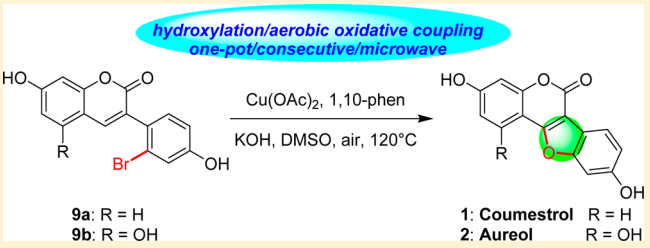
Supporting Information

ABSTRACT: A total synthesis of coumestrol (**1**) and aureol (**2**) is described. The Perkin condensation of 2-bromo-4-hydroxylphenylacetic acid (**6**) and *o*-hydroxybenzaldehydes (**7**) gave the corresponding 2′-bromo-3-arylcoumarins (**9**). A copper-catalyzed consecutive hydroxylation and aerobic oxidative coupling of **9** under microwave conditions facilitated the total synthesis of **1** and **2**, respectively, with spectroscopic data highly similar to those of natural products.



Coumestans are an important class of naturally occurring tetracyclic lactones that are characterized by the presence of a fused ring system comprising coumarin and benzofuran constituent units.[1] These compounds have been isolated from a variety of plant species belonging to botanical families such as the Leguminosae, Fabaceae, and Asteraceae[2] and have shown antioxidative,[1d,2b,3] anticarcinogenic,[4] phytoestrogenic,[5] antibacterial,[6] antifungal,[7] immunomodulatory,[8] neuroprotective,[9] anti-snake-venom,[10] antiosteoporsis,[11] and antihepatotoxic effects.[12]

Coumestrol (**1**) and aureol (**2**) are representative members in the coumestan family and were first isolated respectively from ladino clover, strawberry clover, and alfalfa by Bickoff in 1957[5a] and from *Phaseolus aureus* Roxb. by O'Neill in 1983.[13] Coumestrol has proved to be a phytoalexin, phytoestrogen (ERβ selective),[14] antioxidant,[3] HIF-1α inhibitor,[4c] α-glucosidase inhibitor,[2c] and mitochondrial biogenesis inducer.[8b] The coumestan aureol (**2**) was found to be an immunosuppressant and neuroprotectant.[9b,15] Owing to the wide variety of pharmacological activities, many synthetic approaches have been developed to construct the tetracyclic scaffold of coumestans.[11b,12,16−31] General strategies included arylcoumarin-based cyclization,[16] palladium-catalyzed carbonylative annulation (CO insertion),[11b,12,17] α- or β-keto ester-based annulation,[18] [3,3]-sigmatropic rearrangement-based cyclization and elimination,[19] iodonium ylide-based intramolecular Heck reaction,[20] flavylium salts-based oxidation and lactonization,[21] DreM-carbamoyl migration−transition-metal-catalyzed cross-coupling,[22] arylboronic acid-involved Pd-catalyzed C−S activation for [3 + 3] annulation,[23] aerobic iron-based cross-dehydrogenative coupling (CDC),[24] and tandem demethylation/annulation/oxidation of 2,3-bis(2-methoxyphenyl)-3-oxopropanals.[25] Certain coumestans could also be synthesized through oxidative radical coupling,[26] electrochemical or enzymatic oxidation and addition[27] (affording coumestans with catechol moieties), oxidative cycloaddition between 4-hydroxycoumarins and vinyl sulfides,[28] vinyl lithiation,[29] and $PtCl_2$-catalyzed cycloisomerization reactions.[30] Among these, the $FeCl_3$-mediated direct intramolecular oxidative annulation of 4-hydroxy-3-arylcoumarins, the di-*tert*-butyl peroxide (DTBP) or oxygen-involved CDC reaction between β-ketoesters and phenols, and the palladium-catalyzed ring-closure reaction of 3-arylcoumarins were relatively more efficient and straightforward. However, many of the reported methods still suffer from disadvantages such as harsh reaction conditions, the use of transition-metal catalysts, the necessity of complicated substrates, multistep processes, and atom-economic problems. Thus, a practical and effective route to obtain coumestan natural products is still in high demand. We recently disclosed a consecutive Cu-catalyzed hydroxylation/aerobic oxidative cycloetherification approach for the assembly of 2-arylbenzofurans.[32] Ongoing interest in the synthesis of natural products with $C_6-C_2-C_6$ and $C_6-C_3-C_6$ frameworks[33] prompted the development of a facile and practical route to the total synthesis of **1** and **2** via the combination of a Perkin condensation and a Cu(II)-catalyzed hydroxylation/aerobic oxidative coupling process.

RESULTS AND DISCUSSION

On the basis of previous findings, the synthesis of coumestrol (**1**) and aureol (**2**) could be realized through the consecutive hydroxylation and aerobic oxidative coupling of 3-(2-bromo-4-

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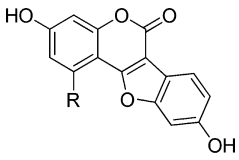
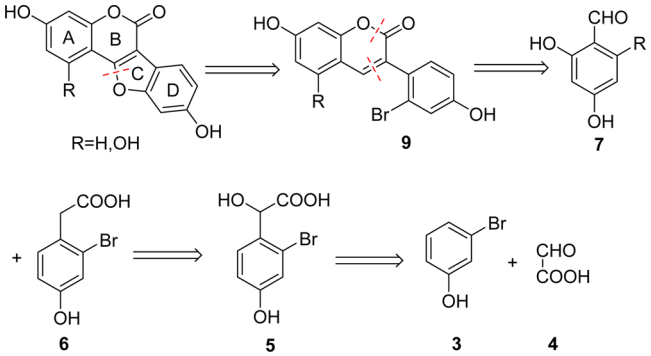


Figure 1. Structures of coumestrol (**1**) and aureol (**2**).

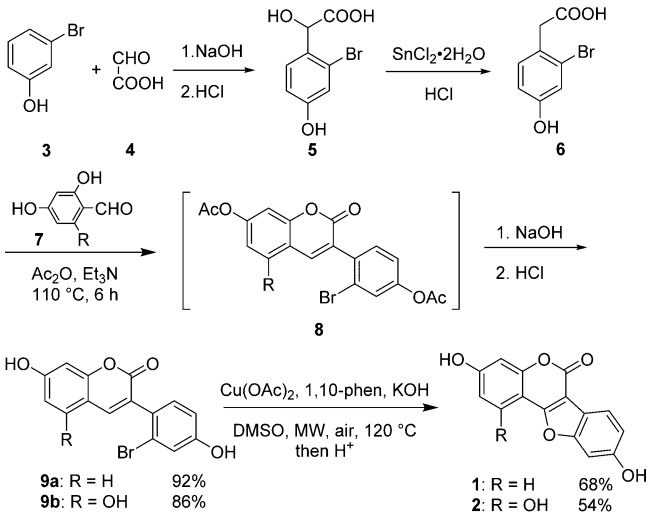
hydroxyphenyl)-7-hydroxycoumarins (**9**), which could be obtained through Perkin reaction between an *ortho*-hydroxybenzaldehyde (**7**) and 2-bromo-4-hydroxyphenylacetic acid (**6**). Intermediate **6** could be readily obtained via reduction of 2-bromo-4-hydroxymandelic acid (**5**), which could further be traced back to the commercially available starting materials *m*-bromophenol (**3**) and glyoxylic acid (**4**) (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Coumestrol (1) and Aureol (2)



Initially, 2-bromo-4-hydroxymandelic acid (**5**) was successfully obtained through nucleophilic addition of *m*-bromophenol (**3**) to glyoxylic acid (**4**) in aqueous NaOH (Scheme 2). Subsequent reduction of **5** in the presence of $SnCl_2$/HCl afforded 2-bromo-4-hydroxyphenylacetic acid (**6**). Perkin condensation between **6** and the commercially available *o*-hydroxybenzaldehydes (**7**) in the presence of Ac_2O/Et_3N smoothly gave acetylated 2′-bromo-3-arylcoumarins (**8**).

Scheme 2. Synthesis of Coumestrol (1) and Aureol (2)



Deacetylation in hot NaOH solution followed by acidification with diluted HCl afforded 2′-bromo-3-arylcoumarins **9a** and **9b** in 92% and 86% yields, respectively.

With the 2′-bromo-3-arylcoumarins **9** in hand, all that remained was to facilitate a consecutive Cu-catalyzed hydroxylation and aerobic oxidative cyclization to assemble the framework of coumestans. Although the established protocol that employed $Cu(OAc)_2$/1,10-phen in DMSO/H_2O (1:1) under microwave conditions could facilitate the hydroxylation and aerobic oxidative coupling processes,[32] the 3-arylcoumarin **9a** did not undergo analogous transformation to give coumestrol (**1**) in acceptable yield. However, when the reaction was performed at elevated temperature (120 °C) in anhydrous DMSO under microwave conditions for 3 h, coumestrol (**1**) was obtained in 68% yield. Likewise, using **9b** as the reactant, aureol (**2**) was obtained in 54% yield under the same reaction conditions. The physical data of coumestrol (**1**) and aureol (**2**) were in good agreement with reported data[2a,c] (Table 1). This is the first total synthesis of aureol (**2**).

In conclusion, we have developed a facile and efficient method to synthesize coumestrol (**1**) and aureol (**2**) based on Perkin condensation, copper-catalyzed consecutive hydroxylation, and aerobic oxidative coupling. This result paved the way for the straightforward synthesis of coumestan derivatives. Further investigations to optimize the reaction sequence and extend the substrate scope of this methodology are ongoing.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were recorded on a Thiele apparatus and are uncorrected. IR spectra were recorded on an Analect RFX-65A IR spectrometer as KBr disks. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) at 295 K using DMSO-d_6 as the solvent. Tetramethylsilane was used as the internal standard, and chemical shift (δ) values were given in parts per million (ppm). HRMS data were recorded on an LC-Q-TOF (ESI) apparatus. Column chromatography was performed on silica gel (300−400 mesh) using EtOAc/petroleum ether (60−90 °C) as the eluent. Microwave reactions were carried out with a scientific WBFY microwave reactor in a long-neck flask connected with a condenser. The temperatures of the microwave reactions were recorded using an infrared thermometer, and the ramp time (approximately 0.5 min) was included as part of the reaction time. Reagents were obtained commercially and used throughout without further purification unless otherwise stated.

Synthesis. *2-(2-Bromo-4-hydroxyphenyl)-2-hydroxyacetic Acid (5).* 3-Bromophenol (8.65 g, 0.05 mol) was added to a three-necked, round-bottom flask equipped with a condenser and a mechanical stirrer. When the reaction temperature was raised to 40 °C, a 50% aqueous solution of glyoxylic acid (0.05 mol) and an 8% aqueous NaOH (0.075 mol) solution were added simultaneously through two constant-pressure funnels over 1 h. The mixture was stirred for 8 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature and acidified to pH 1−2 with 2 M HCl. The aqueous solution was washed with toluene (2 × 50 mL), and the product was extracted with EtOAc (2 × 50 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a yellow oil (9.25 g, 75.2% yield): ^1H NMR (DMSO-d_6, 400 MHz, ppm) δ 12.50 (s, 1H), 9.90 (s, 1H), 7.25 (d, J = 8.4 Hz 1H), 6.96 (d, J = 2.4 Hz 1H), 6.77 (dd, J = 2.4, 2.4 Hz 1H), 5.19 (s, 1H), 7.25 (d, J = 8.4 Hz 1H), 1.97 (s, 1H).

2-(2-Bromo-4-hydroxyphenyl)acetic Acid (6). 2-(2-Bromo-4-hydroxyphenyl)-2-hydroxyacetic acid (**5**) (9.9 g, 0.04 mol), $SnCl_2·2H_2O$ (10.2 g, 0.045 mol), and concentrated HCl (20 mL) were added into a round-bottom flask equipped with a condenser, and the mixture was stirred at 80 °C for 3 h. After completion of the reaction as indicated by TLC, H_2O (40 mL) was added and the mixture was heated to

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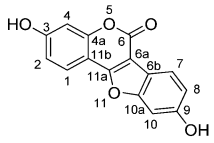
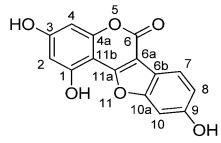
Table 1. NMR Data for Synthetic and Natural Coumestrol and Aureol in DMSO-d_6





atom	coumestrol(synthetic)		coumestrol(natural)[2c]		aureol(synthetic)		aureol (natural)[2a]	
	^{1}H (400 MHz)	^{13}C (100 MHz)	^{1}H (500 MHz)	^{13}C (125 MHz)	^{1}H (400 MHz)	^{13}C (100 MHz)	^{1}H (500 MHz)	^{13}C (125 MHz)
1	7.85, d (8.4)	122.7	7.85, d (8.4)	123.2	-	155.2	-	155.2
2	6.93, dd (2.0, 8.4)	113.7	6.93, dd (2.1, 8.5)	114.2	6.38, d (2.0)	99.1	6.36, d (1.8)	99.1
3	-	161.2	-	161.7	-	161.4	-	161.4
4	6.90, d (2.0)	103.0	6.91, d (1.9)	103.5	6.41, d (2.0)	94.9	6.39, d (1.8)	94.9
4a	-	154.6	-	155.1	-	155.6	-	155.6
6	-	157.6	-	158.0	-	157.7	-	157.7
6a	-	102.0	-	102.5	-	100.7	-	100.7
6b	-	114.6	-	115.0	-	114.4	-	114.4
7	7.69, d (8.4)	120.6	7.69, d (8.4)	121.1	7.67, d (8.4)	120.2	7.65, d (8.4)	120.2
8	6.95, dd (2.0, 8.4)	114.0	6.95, dd (2.1, 8.3)	114.4	6.93, dd (2.0, 8.4)	113.8	6.91, dd (2.1, 8.4)	113.8
9	-	155.9	-	156.4	-	156.6	-	156.6
10	7.16, d (2.0)	98.7	7.17, d (1.9)	99.1	7.14, d (1.6)	98.6	7.12, d (2.1)	98.6
10a	-	157.0	-	157.5	-	155.8	-	155.8
11a	-	159.5	-	160.0	-	159.8	-	159.8
11b	-	104.2	-	104.6	-	95.2	-	95.2

reflux until a clear solution was obtained. The resulting mixture was cooled to room temperature, whereupon compound **6** recrystallized to afford a white solid (7.2 g, 77% yield): mp 176−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.35 (s, 1H), 9.80 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.72 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.57 (s, 2H).

*3-(2-Bromo-4-hydroxyphenyl)-7-hydroxycoumarin (**9a**).* A mixture of 2-bromo-4-hydroxyphenylacetic acid (**6**, 2.31 g, 10 mmol), 2,4-dihydroxylbenzaldehyde (**7a**, 1.38g, 10 mmol), Ac_2O (4.73 mL, 50 mmol), and Et_3N (4.16 mL, 30 mmol) was added to a 25 mL round-bottom flask equipped with a condenser. The mixture was stirred at 110 °C for 6 h. After completion of the reaction (monitored by TLC), the hot mixture was poured into ice water and washed thoroughly while stirring. A brown solid was obtained and collected by filtration. The solid was dissolved in 10% aqueous NaOH, and the resulting aqueous solution was washed with EtOAc (2 × 50 mL). The aqueous layer was acidified with concentrated HCl to pH 3−4. The precipitated crude product was collected by filtration and recrystallized from EtOH to afford **9a** (3.06 g, 92%) as a white solid: mp 337−340 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 10.38 (s, OH), 9.94 (s, OH), 7.89 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 2.0, 8.8 Hz, 1H), 6.83 (dd, J = 2.0, 8.4 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ 161.3, 159.6, 158.2, 155.2, 143.0, 132.5, 129.9, 126.9, 123.6, 123.4, 118.9, 114.8, 113.4, 111.4, 102.0; IR (neat) 3346, 3118, 2829, 1678, 1608, 1573, 1495, 1463, 1426, 1285, 1259, 1206, 1125, 1030, 863, 621 cm^{-1}; HRMS m/z 354.9583 [M + Na]$^+$ (calcd for $C_{15}H_9{}^{79}BrO_4Na$, 354.9582).

*3-(2-Bromo-4-hydroxyphenyl)-5,7-dihydroxycoumarin (**9b**).* The experimental procedure to synthesize **9b** is the same as that of **9a**: white solid (3.0 g, 86% yield); mp 278−281 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 10.75 (s, OH), 10.46 (s, OH), 10.05 (s, OH), 7.78 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 2.4, 8.4 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ 162.1, 159.8, 158.1, 156.1, 156.1, 137.9, 132.5, 127.2, 123.6, 120.7, 118.9, 114.8, 101.6, 98.4, 93.9; IR (neat) 3336, 3175, 1690, 1601, 1579, 1505, 1436, 1373, 1272, 1222, 1160, 1080,801, 585 cm^{-1}; HRMS m/z 370.9528 [M + Na]$^+$ (calcd for $C_{15}H_9{}^{79}BrO_5Na$, 370.9526).

*Coumestrol (**1**).* 3-(2-Bromo-4-hydroxyphenyl)-7-hydroxycoumarin (**9a**, 0.3331 g, 1 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol, 20 mol %), 1,10-phen (36 mg, 0.2 mmol, 20 mol %), KOH (0.56 g, 10 mmol), and DMSO (10 mL) were added to a flask equipped with a condenser. The flask was placed in a microwave reactor and irradiated under air (240 W). The mixture was stirred at 120 °C for 3 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and the copper-containing solid was filtered off. The filtrate was poured into H_2O (50 mL) and acidified to pH 4−5 with 2 M HCl. The product was extrated with EtOAc (20 mL), washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash column chromatography (EtOAc/petroleum ether, 1:4) to afford coumestrol **1** as a white solid (0.18 g, 68%): mp 361−364 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 10.71 (s, OH), 10.04 (s, OH), 7.85 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.90−6.96 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ 161.2, 159.5, 157.6, 157.0, 155.9, 154.6, 122.7, 120.6, 114.6, 114.0, 113.7, 104.2, 103.0, 102.0, 98.7; IR (neat) 3417, 3269, 1719, 1633, 1607, 1512, 1437, 1379, 1297, 1264, 1237, 1091, 839, 807, 627 cm^{-1}; HRMS m/z 291.0259 [M + Na]$^+$ (calcd for $C_{15}H_8O_5Na$, 291.0264).

*Aureol (**2**).* The experimental procedure for the synthesis of **2** is the same as for **1**: white solid (0.53 g, 54% yield); mp 339−342 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 10.92 (s, OH), 10.50 (s, OH), 9.96 (s, OH), 7.67 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 1.6 Hz, 1H), 6.93 (dd, J = 2.0, 8.4 Hz, 1H), 6.41 (d, J = 2.0 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ 161.4, 159.8, 157.7, 156.6, 155.8, 155.6, 155.2, 120.2, 114.4, 113.8, 100.7, 99.1, 98.6, 95.2, 94.9; IR (neat) 3374, 3192, 2959, 1710, 1626, 1581, 1488, 1445, 1379, 1297, 1262, 1162, 1083, 807, 623 cm^{-1}; HRMS m/z 307.0215 [M + Na]$^+$ (calcd for $C_{15}H_8O_6Na$, 307.0213).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00510.

^{1}H and ^{13}C NMR spectra for the compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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