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Total Synthesis of Wedelolactone

Chuang Chuang Li,[†] Zhi Xiang Xie,[†] Yan Dong Zhang, Jia Hua Chen,*[,†] and Zhen Yang*[,†,‡]

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry, Peking University, Beijing, P. R. China, 100871, and VivoQuest, Inc., 711 Executive Blvd, Valley Cottage, New York, 10989

zyang@chem.pku.edu.cn

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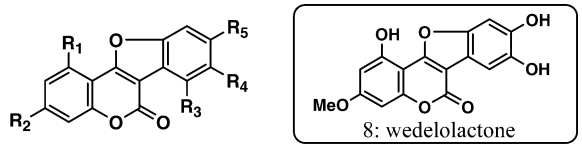
The total synthesis of wedelolactone, a naturally occurring direct inhibitor of IKK complex that can suppress LPS-induced caspase-11 expression, using a convergent synthetic approach, is described. The key steps involved in this synthesis include the palladium-catalyzed Sonogashira reaction and the palladium-catalyzed carbonylative annulation reaction. This approach allows access to diversified analogues of wedelolactone.

Introduction

Coumestan, otherwise known as 6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one, comprises a class of naturally occurring products with a variety of biological activities that include phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects.[1] Figure 1 illustrates some of the naturally occurring biologically active coumestans.

Wedelolactone (**8** in Figure 1) was first isolated from the extract of *Wedelia calandulaceae* in 1956,[2] and later from *Eclipta prostrate*.[3] Wedelolactone exhibits a broad range of biological activities. Its uses include an antidote for snake venom,[3a,b] beneficial effects in liver disease, stimulation of liver cell regeneration,[3c,d] and direct inhibition of IKK complex, resulting in suppression of LPS-induction of NFKB-mediated caspase-11 expression.[3e,f]

Structurally, wedelolactone contains a dense pattern of oxygenated polyphenols that readily decompose under basic conditions, making purification from natural resources difficult. Two early reports detailing the synthesis of wedelolactone were published in 1963[4] and 1989;[5]



1: R_1= R_2= R_3 = H ; R_4= R_5= OH	11,12-dihydroxy coumestan
2: R_1= R_2= R_4= R_5= OH ; R_3= H	demethylwedelolactone
3: R_1= R_3= R_4= H ; R_2= R_5= OH	coumestrol
4: R_1= R_2= R_5= OH ; R_3= R_4= H	aureol
5: R_1= R_3= H ; R_2= OH ; R_4, R_5= -CH_2OCH_2-	medicagol
6: R_1= R_4= H ; R_2= R_3= OH; R_5= OMe	trifiliol
7: R_1= R_3= R_4= H ; R_5= OH; R_2=isopentenyl	psoralidin

FIGURE 1. Naturally occurring coumestans.

however, the first paper provided IR data to support their results, and the second paper provided ^{1}H NMR data, which do not match the results that we obtained from our isolated natural wedelolactone.

One aspect of our drug development program is focused on identifying drugs for treatment or prevention of diseases that induce cell death or apoptosis and inflammation.[3e,f] To include wedelolactone as a new chemical entity (NCE) for this effort, we began to develop a strategy for the synthesis of wedelolactone early in 1999. Many alternative synthetic strategies were evaluated. We report here our recent successful efforts to develop an efficient approach for the synthesis of wedelolactone on a gram scale, which now enables further biological investigation of this compound.

As a privileged scaffold,[6] coumestan has recently attracted considerable attention and many synthetic methods[7] have been developed for the synthesis of the individual targets illustrated in Figure 1. However, a

[†] Peking University.

[‡] VivoQuest, Inc.

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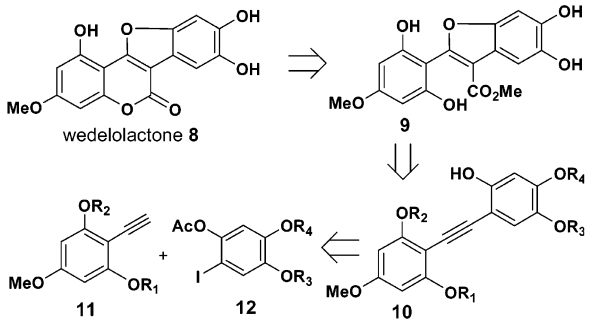
SCHEME 1. Retrosynthetic Analysis

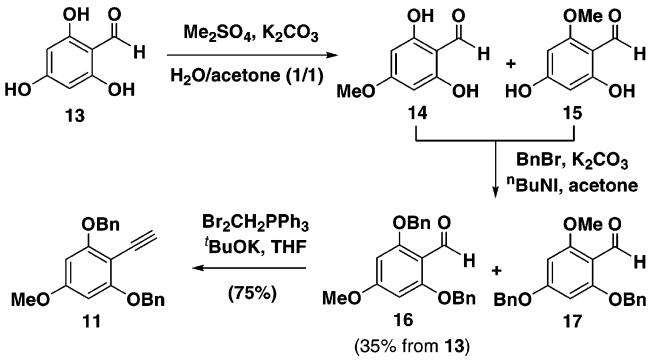


combinatorial synthesis for this type of molecule has not been reported. Inspired by the recent success with combinatorial syntheses to generate many interesting natural product libraries,[8] we decided to attempt to develop a less complicated and more efficient strategy for the combinatorial synthesis of coumestans. To achieve this goal we decided to focus on developing a convergent approach for the synthesis of wedelolactone, and other coumestan family members, as a priority (see Scheme 1).

Results and Discussion

Retrosynthetically, wedelolactone **8** can be logically disconnected by the ring opening of lactone to afford intermediate **9**, which is further disconnected through C−O bond cleavage to provide *o*-hydroxyarylacetylene **10**. Thus the intermediate **10** can naturally be traced back to terminal acetylene **11** and phenyl iodide **12**, respectively. A similar synthetic strategy has been used by larock (a tandem mercury/palladium procedure)[9] and by Sakamoto (a palladium-mediated reaction)[10] for the synthesis of other members of this same family of compounds. Synthetically, we expected that **10** could be obtained by the palladium-catalyzed Sonogashira coupling of **11** and **12**, and **9** could be generated by the palladium-thiourea-catalyzed carbonylative annulation reaction from **10**,[11] followed by deprotection.

SCHEME 2. Synthesis of Intermediate 11



Several features of this strategy were attractive. First, the convergent pathway minimizes the number of synthetic steps while maximizing product diversity. Second, the Sonogashira reaction utilized to couple intermediates **11** and **12** is a powerful reaction that has been extensively studied and is one of the few reactions that is well understood in solid-phase synthesis.[8a,12] Third, a variety of phenyl iodides and phenyl acetylenes are commercially available, providing abundant starting material that could be used for the synthesis of a variety of coumestan-based natural products. Our ultimate goal for this program was to achieve a high quality and large quantity wedelolactone library.

Unfortunately, our original synthesis was disappointing, because the overall yield was rather low. In retrospect it is clear that the low yield resulted from a lack of information regarding the instability of intermediate **9**, which decomposed easily under weakly basic conditions (such as Et_3N or TBAF). Therefore, the reaction conditions used selectively to generate intermediate **9** had to be neutral or acidic. In addition, the methods that we used to synthesize intermediates **11** and **12** were also complicated and less effective. To improve the synthesis and increase the yield, we undertook the challenge of designing a new synthetic scheme. In consideration of the instability and high polarity of intermediate **9**, a key goal for the new plan was to synthesize this intermediate under neutral conditions in high yield without purification.

To this end, in contrast to the original synthesis in which MEM, TBS, and benzoyl were used to differentiate the phenolic groups, in the new strategy we decided to use benzyl and acetyl to differentiate them on the substrates. The benzyl group is advantageous because of its high stability toward many reagents, and its easy removal by hydrogenation under neutral conditions.

Scheme 2 illustrates the synthesis of intermediate **11**. In this new design, it seemed reasonable to expect that benzaldehyde **13** could be converted to phenyl acetylene **11**.[13] To realize this approach, commercially available **13** was treated with Me_2SO_4 under basic conditions, and compounds **14** and **15** were obtained in 50% yield as a mixture (**14**/**15** = 4/1 according to ^1H NMR analysis), which underwent direct benzylation to provide com-

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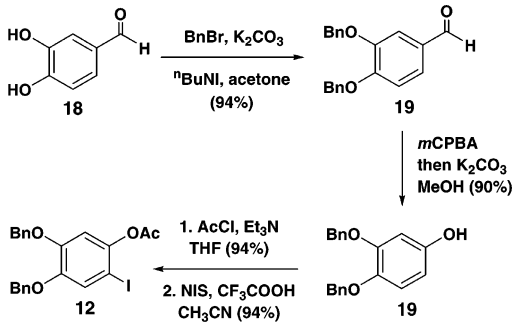
SCHEME 3. Synthesis of Intermediate 12



pounds **16** and **17**. After chromatography, compound **16** was obtained in an overall yield of 35% from **13**, and its regionisomer **17** (7% derived from **13**) will be a useful starting material for the late wedelolactone analog's synthesis. As expected, exposure of a solution of **16** in THF to 1.5 equiv of $Br_2CH_2PPh_3$ and 3 equiv of *t*-BuOK resulted in the formation of intermediate **11** in high yield (75%).

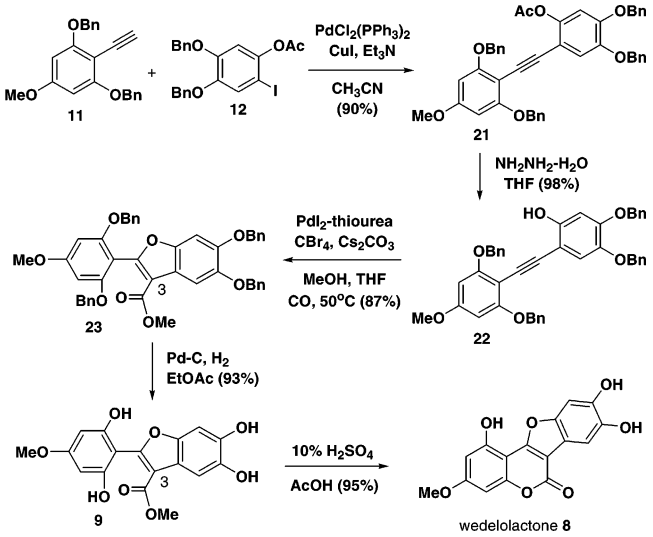
Next we focused on the generation of the intermediate **12**. Initially we were intrigued by the synthetic challenge posed by selective protection of the three phenolic groups. After reviewing a number of approaches, we selected commercially available 3,4-dihydroxybezaldehyde **18** as the starting material to make intermediate **12**. The key feature of this strategy (see Scheme 3) is that the projected *m*CPBA-mediated Baeyer−Villiger oxidation reaction can be used to convert an aldehyde into a phenol, which resolved the issue of the selective protection of polyphenol-based intermediate **12**. Synthetically, compound **18** was first converted to its dibenzyl ether **19** (94%), followed by *m*CPBA oxidation and hydroxlysis to generate phenol **20** (90%). Phenol **20** was first protected as its acetate, then iodinated with NIS in the presence of trifluoroacetic acid[14] to give the desired target **12** (94%).

With key intermediates **11** and **12** in hand, we were able to focus on combining them, setting the stage for the crucial carbonylative annulation. Thus, compounds **11** and **12** were first coupled under typical Sonogashira coupling conditions[15] to give **21** (90%) (Scheme 4), which was then treated with hydrazine in THF[9] to remove the acetyl group, generating compound **22** (98%).

We have considerable experience with the palladium-catalyzed carbonylative annulation of *o*-hydroxyarylacetylene to its corresponding methyl benzo[*b*]furan-3-carboxylate both in the solution phase and in the solid phase.[11] Unfortunately, when we applied this established chemistry to convert compound **22** into **23**, the results were not what we expected (see Scheme 4) since substrate **22** was neither decomposed nor cyclized. In an effort to improve the product yield we raised the reaction temperature; however, no improvement was observed.

To optimize the reaction conditions we initiated an experiment to systematically evaluate the effect of the various parameters (palladium catalyst, base, temperature, etc.) on the reaction outcome. We eventually determined that a combined solvent (30% THF in MeOH) was critical for promoting this cyclization of substrate **22**. Thus, after modifying our standard palladium-catalyzed carbonylative annulation conditions[11a] to include a combined solvent of THF in methanol, the desired cyclization product **23** was obtained in 87% yield (see Scheme 4).

SCHEME 4. Total Synthesis of Wedelolactone



With product **23** in hand, completion of the final steps in the wedelolactone synthesis was straightforward requiring deprotection and cyclization. Hydrogenolysis of the four benzyl ethers in compound **23** provided a high yield of the tetraphenolic compound **9**, a highly polar molecule that is very sensitive to bases, including triethylamine. The physical properties of intermediate **9** account for our early synthetic failures because of the protecting groups that we originally selected, giving a poor yield of tetraphenolic compound **9** after deprotection, which created a lot of difficulty with purification.

The total synthesis of wedelolactone **8** was achieved by treatment of compound **9** with 10% sulfuric acid in acetic acid[7h] in very high yield (93%), and the wedelolactone that we synthesized exhibited identical physical and spectroscopic properties to the natural wedelolactone that we isolated and purified.

Interestingly, wedelolactone was observed to have different ^{1}H NMR chemical shifts in different deuterium solvents (such as DMSO-d_6, acetone-d_6, and $CDCl_3$); we therefore derived the natural and synthetic wedelolactone into their acetates, respectively, and performed ^{1}H NMR studies on both derivatives. To this end, the natural and synthetic wedelolactone were acetylated under identical conditions (AcCl, Et_3N, THF, 25 °C, 2 h). The ^{1}H NMR spectra of the acetate derivatives were compared and are identical (see Figure 2).

In summary, we have developed an efficient synthetic approach to synthesize wedelolactone. The structure of the synthesized wedelolactone was determined synthetically and spectroscopically, and was identical with natural wedelolactone. Most importantly, the chemistry methods that we developed can be applied to synthesize both wedelolactone and other coumestan family members in high yield. These methods will allow us to generate rather diversified coumestan-based compounds considering many terminal acetylenes and phenyl iodides are

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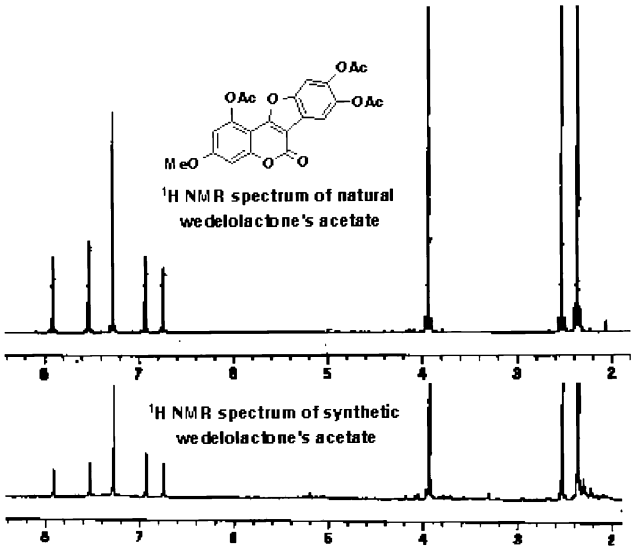

FIGURE 2. ^{1}H NMR spectra of wedelolacton's acetate.

commercially available and easily synthetically accessible. Furthermore, our extensive experience with the chemistries involved in both the palladium-catalyzed Sonogashira reaction and the carbonylative annulation on solid phase[11c,12] should enable us to complete a diversified combinatorial library of coumestan soon.

Experimental Section

Unless stated otherwise, the commercially available reagents were used as received. All solvents were dried by standard methods under nitrogen atmosphere: The reactions for the palladium-catalyzed carbonylation with CO and hydrogenation with H_2 were performed in a ventilated hood. THF and diethyl ether were distilled over Na−K; CH_2Cl_2, Et_3N, and pyridine were distilled from CaH_2. Silica gel (200−300 mesh) for purification and silica gel TLC (F_{254}) were purchased from Qing Dao Hai Yang Chemical Industry Co. of China [EA = ethyl acetate and PE = petroleum ether (60−90 °C)].

Synthesis of compound 14: 2,4,6-Trihydroxybenzaldehyde **13** (16.0 g, 104 mmol) was added to a solution of predissolved K_2CO_3 (72.0 g, 0.52 mol) in H_2O (500 mL) and acetone (500 mL). To this solution was added Me_2SO_4 (20.0 g, 0.158 mol) in acetone (50 mL) over 2 h, and the mixture was stirred for an additional 30 min. After removal of acetone, the reaction mixture was extracted with EtOAc (3 × 500 mL), and the combined organic extracts were washed with water (2 × 50 mL) and brine (2 × 50 mL) and finally dried over Na_2SO_4. The extracts were filtered and concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (elution with 1:2 EA/PE) to afford **14** and **15** (8.74 g, 50%) as a mixture (4:1 determined by ^{1}H NMR): R_f 0.55 (2:3:1 EA/ PE/ CH_3OH); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.10 (s, 1 H), 5.99 (s, 2 H), 3.82 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 191.2, 167.8, 163.6, 104.9, 92.2, 54.7; MS [$C_8H_8O_4$], m/z (M^+) calcd 168, found 168.

Synthesis of compound 16: Compounds **14** and **15** (7.2 g, 42.8 mmol), ^{n}Bu$_4$NI (1.0 g, 2.5 mmol), and K_2CO_3 (23.6 g, 172 mmol) were first dissolved in acetone (100 mL) then treated with benzyl bromide (29.3 g, 172 mmol), and the mixture was stirred under refluxing for 20 h. After removal of solvent, the residue was dissolved in ether (250 mL) and then washed with H_2O (2 × 15 mL) and brine (2 × 15 mL) and dried over Na_2SO_4. The organic phases were filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:6 EA/PE) to provide compound **16** (10.5 g, 35% overall yield from compound **13**) as a white solid. Mp 91−92 °C; R_f 0.4 (1:3 EA /PE); IR ν 2962 (CHO), 1674 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.51 (s, 1 H), 7.48−7.27 (m, 10 H), 6.12 (s, 2 H), 5.14 (s, 4 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 165.8, 162.9, 136.1, 128.6, 127.9, 126.9, 109.5, 91.9, 70.5, 55.4; MS ($C_{22}H_{20}O_4$), m/z (M^+) calcd 348, found 348.

Synthesis of compound 11: To a suspension of bromomethyl triphenyl phosphonium bromide (11.4 g, 26 mmol) in dry THF (60 mL) at −78 °C was added the first batch of potassium *tert*-butoxide (2.9 g, 26 mmol), and the mixture was stirred at 0 °C for 30 min to generate the corresponding Wittig reagent. To this mixture was added compound **16** (6.0 g, 17 mmol) in dry THF (13 mL) by a cannular at −78 °C, and the mixture was continuously stirred at 0 °C until compound **16** disappeared (monitored by TLC). After cooling back to −78 °C, the second batch of potassium *tert*-butoxide (2.9 g, 26 mmol) and the mixture were stirred at 25 °C for 5 h. The reaction was quenched with acetic acid (5 mL), and the mixture was first diluted with a saturated NH_4Cl solution (30 mL) and then extracted with ether (3 × 50 mL). The combined extracts were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL) and dried over Na_2SO_4. The extracts were filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:10 EA/PE) to afford compound **11** (4.38 g, 75%) as a white solid. Mp 106−107 °C; R_f 0.25 (1:6 EA/PE); IR ν 3285 (C≡CH), 2103 (C≡C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.28 (m, 10 H), 6.10 (s, 2 H), 5.14 (s, 4 H), 3.67 (s, 3 H), 3.49 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.4, 136.7, 128.5, 127.7, 126.8, 94.8, 92.6, 84.2, 70.5, 55.3; MS ($C_{23}H_{20}O_3$), m/z 344 (M^+) calcd 344, found 344.

Synthesis of compound 19: The aldehyde **18** (6.9 g, 50 mmol), K_2CO_3 (14.5 g) and ^{n}Bu$_4$NI (0.5 g, 1.4 mmol) were dissolved in acetone (150 mL), the solution was treated with benzyl bromide (15 mL (21.5 g), 126 mmol), and the reaction mixture was stirred under refluxing for 24 h. After removal of acetone, the aqueous phase was extracted with ether (2 × 150 mL), and the combined extracts were washed with H_2O (2 × 25 mL) and brine (2 × 25 mL) and dried over Na_2SO_4. The extracts were filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:10 EA/PE) to give compound **19** (15.0 g, 94%) as a white solid. Mp 88−89 °C; R_f 0.5 (1:3 EA/PE); IR ν 2819 (CHO), 1677 (C=O), 1282 (C−O), 1024 (C−O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1 H), 7.40−7.18 (m, 12 H), 6.85 (d, J = 8.4 Hz, 1 H), 5.01 (s, 2 H), 4.99 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 153.6, 148.6, 136.1, 135.8, 129.8, 128.1, 128.0, 127.6, 127.5, 126.8, 126.6, 126.1, 112.4, 111.6, 70.2, 70.1; MS [$C_{21}H_{18}O_3$], m/z (M^+) calcd 318, found 318.

Synthesis of compound 20: To a solution of compound **19** (12.0 g, 37.8 mmol) in dichloromethane (200 mL) was added *m*-chloroperbenzoic acid (10.2 g with 25−30% of H_2O, ca. 41.4 mmol), and the mixture was then stirred at room temperature for 15 h. The reaction was quenched with dimethyl sulfide (1 mL), and the mixture was first diluted with ether (500 mL) and then successively washed with saturated aqueous Na_2CO_3 solution (3 × 100 mL) and brine (2 × 50 mL), and finally dried over Na_2SO_4. After removal of organic solvent, the residue was first dissolved in MeOH (150 mL), then treated with K_2CO_3 (5.2 g, 38 mmol), and the mixture was stirred at 25 °C for 30 min. After removal of MeOH, the residue was dissolved in ether (200 mL), washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), and dried over Na_2SO_4. The organic phases were filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:10 EA/PE) to give compound **20** (10.4 g, 90%) as a white solid. Mp 109−110 °C; R_f 0.25 (1:3 EA/PE); IR ν 3452 (OH), 1312 (C−O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 10 H), 6.75 (d, J = 8.7 Hz, 1 H), 6.44(d, J = 3.0 Hz, 1 H), 6.24 (dd, J_1 = 8.7 Hz, J_2 = 3.0 Hz, 1 H), 5.19 (s, 1 H), 5.03 (s, 2 H), 5.10 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 150.2, 142.5, 137.4, 136.8, 128.5, 128.4, 127.8, 127.8, 127.6, 127.3, 117.7, 106.9,

103.2, 72.9 (CH_2), 70.9 (CH_2); MS [$C_{20}H_{18}O_3$], *m/z* (M^+) calcd 306, found 306.

Synthesis of compound 20a: To a solution of phenol **20** (9.0 g, 29 mmol) in dried THF (100 mL) were added Et_3N (5.6 g, 55 mmol) and AcCl (4.0 g, 51 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction was then quenched with a saturated solution of NaCl (30 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:3 EA/PE) to afford compound **20a (**10.0 g (28.7 g, 99%) as a white solid. Mp 96−97 °C; R_f 0.35 (1:4 EA/PE); IR *v* 1764 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.30 (m, 10 H), 6.91 (d, J = 8.7 Hz, 1 H), 6.72 (d, J = 2.7 Hz, 1 H), 6.61 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1 H), 5.13 (s, 4 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 149.5, 146.7, 144.8, 137.1, 136.7, 128.4, 128.4, 127.8, 127.8, 127.3, 115.4, 113.7, 108.7, 71.8 (CH_2), 71.2 (CH_2), 20.9 (CH_3); MS [$C_{22}H_{20}O_4$], *m/z* (M^+) calcd 348, found 348.

Synthesis of compound 12: To a solution of **20a** (8.8 g, 25.6 mmol) in CH_3CN (120 mL) was added dropwise a solution of NIS (6.24 g, 28 mmol) and CF_3COOH (0.91 g, 8 mmol) in CH_3CN (50 mL) at 40 °C for 2 h. After addition, the mixture was stirred at 40 °C for an additional 10 h. After removal of CH_3CN, the residue was dissolved in ether (200 mL), washed sequentially with aqueous $NaHSO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (10 mL), and dried over Na_2SO_4. The extracts were filtered and concentrated and the residue was purified by flash chromatography on silica gel (elution with 1:9 EA/PE) to give compound **12** (11.4 g, 94%) as a gray solid. Mp 90−91 °C dec, R_f 0.55 (1:4 EA/PE); IR *v* 1761 (C═O), 474 (C−I); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.30 (m, 10 H), 6.73 (s, 1 H), 5.09 (s, 2 H), 5.08 (s, 2 H), 2.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 149.8, 147.6, 145.5, 136.5, 136.3, 128.5, 128.0, 127.4, 127.3, 124.2, 109.4, 78.5, 71.9, 71.2, 21.2; MS [$C_{22}H_{19}IO_4$], *m/z* (M^+) calcd 474, found 474.

Synthesis of compound 21: To a N_2-degassed solution of CH_3CN (50 mL) and Et_3N (3.1 mL) were added compounds **11** (2.6 g, 7.5 mmol), **12** (3.5 g, 7.4 mmol), $PdCl_2(PPh_3)_2$ (61.6 mg, 0.088 mmol), and CuI (16.8 mg, 0.088 mmol), and the mixture was stirred at 25 °C for 12 h. After removal of the solvent, the residue was filtered, concentrated, and purified by flash chromatography on silica gel (elution with 1:10 EA/PE) to give compound **19** (4.58 g, 90%) as a white solid. Mp 131−132 °C dec; R_f 0.25 (1:3 EA/PE); IR *v* 2360 (C≡C), 1757 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.25 (m, 20 H), 7.03 (s, 1 H), 6.70 (s, 1 H), 6.16 (s, 2 H), 5.15 (s, 4 H), 5.11 (s, 2 H), 4.97 (s, 2 H), 3.74 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 161.2, 149.3, 146.5, 145.4, 136.9, 136.8, 136.5, 128.5, 128.4, 127.9, 127.8, 127.4, 127.3, 127.1, 118.0, 110.7, 108.9, 96.2, 92.8, 91.5, 85.9, 71.6, 71.1, 70.6, 55.3, 20.4; MS [$C_{45}H_{38}O_7$], *m/z* (M^+) calcd 690, found 690.

Synthesis of compound 22: To a solution of **19** (2.07 g, 3 mmol) in THF (50 mL) was added hydrazine monohydrate (1.25 g, 25 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was first diluted with PE (100 mL), then filtered through a silica gel pad and eluted with 1:3 EtOAc/PE. The elute was concentrated and the residue was purified by flash chromatography on silica gel (elution with 1:1 EA/PE) to give compound **22** (1.91 g, 98%) as a white solid. Mp 149−150 °C; R_f 0.35 (1:1 CH_2Cl_2/PE); IR *v* 2360 (C≡C), 1313 (C−O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.27 (m, 2 OH), 6.94 (s, 1 H), 6.56 (s, 1 H), 6.35 (s, 1 H), 6.13 (s, 2 H), 5.16 (s, 4 H), 5.0 9 (s, 2 H), 5.01 (s, 2 H), 3.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 152.8, 150.9, 141.9, 137.4, 136.7, 136.4, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 117.1, 101.9, 101.3, 95.6, 92.6, 91.2, 89.1, 72.6, 70.7, 70.7, 55.3; MS [$C_{43}H_{36}O_6$], *m/z* (M^+) calcd 648, found 648.

Synthesis of Compound 23: To a solution of MeOH (40 mL) and THF (20 mL) were added compound **22** (1.3 g, 2 mmol), PdI_2 (72 mg, 0.2 mmol), thiourea (15 mg, 0.2 mmol), CBr_4 (4.56 g, 14 mmol), and Cs_2CO_3 (4.65 g, 14 mmol), and the reaction mixture was first degassed with CO and then stirred at 50 °C for 2 h under a balloon pressure of CO. The reaction was quenched by addition of a saturated solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:6 EA/PE) to give compound **23** (1.23 g, 87%) as a white solid. Mp 141−142 °C; R_f 0.7 (2:3 EA/PE); IR *v* 1709 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.11 (m, 22 H), 6.20 (s, 2 H), 5.22 (s, 2 H), 5.18 (s, 2 H), 5.02 (s, 4 H), 3.73 (s, 3 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 162.7, 159.0, 155.7, 149.43, 147.8, 146.7, 137.4, 136.9, 136.7, 128.4, 128.3, 128.2, 127.7, 127.7, 127.5, 127.2, 127.1, 126.5, 119.5, 111.9, 107.3, 102.8, 98.2, 92.7, 72.1, 71.5, 70.4, 55.2, 50.9; MS [$C_{45}H_{38}O_8$], *m/z* (M^+) calcd 706, found 706.

Synthesis of Compound 9: To a solution of compound **23** (1.0 g, 1.4 mmol) in distilled ethyl acetate (25 mL) was added Pd−C (10% on charcoal, 100 mg), and the mixture was stirred under a balloon pressure of H_2 at 25 °C for 24 h. The mixture was filtered and concentrated to give compound **9** (450 mg, 93%) as a white solid (NMR study indicated the product is pure). Mp150 °C dec; R_f =0.3 (4:1 CH_2Cl_2/CH_3OH); IR *v* 1695 (C═O); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.44 (s, 1 H), 7.00 (s, 1 H), 6.11 (s, 2 H), 3.76, 3.74 (s, 6 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 163.0, 160.9, 156.5, 153.9, 147.3, 142.6, 141.3, 117.1, 110.2, 104.4, 98.4, 96.0, 91.6, 53.1, 49.1; MS [$C_{17}H_{14}O_8$], *m/z* ($M^+ - 1$) calcd 345, found 345.

Synthesis of wedelolactone: To a solution of compound **9** (300 mg, 0.867 mmol) was added AcOH (4.0 mL), followed by addition of 40% H_2SO_4 (2.0 mL), and the reaction mixture was stirred at 50 °C for 1 h. The reaction was quenched with NH_4OAc (2.0 g) at 25 °C, and the mixture was first diluted with ethyl acetate (25 mL), then filtered through a silica gel pad and eluted with 20:1 EA/MeOH. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (elution with 20:1 EA) to give wedelolactone **8** (253 mg, 93%) as a gray solid. Mp 300 °C dec; R_f 0.35 (4:1 CH_2Cl_2/CH_3OH); IR *v* 1700 (C═O); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.42 (s, 1 H), 7.22 (s, 1 H), 6.58 (d, J = 2.1 Hz, 1 H), 6.55 (d, J = 2.4 Hz, 1 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 162.3, 158.9, 157.6, 155.2, 154.3, 149.0, 144.6, 143.4, 113.9, 104.1, 101.6, 97.8, 97.6, 96.4, 92.7, 54.7; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23 (s, 1 H), 7.15 (s, 1 H), 6.55 (d, J = 1.8 Hz, 1 H), 6.40 (d, J = 2.1 Hz, 1 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 158.9, 157.8, 155.3, 154.8, 148.9, 145.4, 144.3, 113.8, 104.6, 101.7, 98.9, 98.1, 96.7, 93.2, 55.7; MS [$C_{16}H_{10}O_7$] *m/z* ($M^+ - 1$) calcd 313, found 313.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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