

Total synthesis of demethylwedelolactone and wedelolactone by Cu-mediated/Pd(0)-catalysis and oxidative-cyclization

Chia-Fu Chang, Ling-Yi Yang, Shiao-Wei Chang, Yu-Ting Fang, Yean-Jang Lee*

Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan

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Abstract

Hedysarimcoumestan **B**, which can be isolated from Chinese herbal medicine, is achieved, in which the longest linear sequence is only eight steps, in 50% overall yield from commercially available phloroglucinol. The key transformations in the synthesis are Cu-mediated/Pd(0)-catalysis and I_2 /pyridine oxidative-cyclization reactions. This synthetic strategy can be applied to give access to the demethylwedelolactone (**4**) and wedelolactone (**5**), which were afforded from commercially available phloroglucinol in high 38 and 33% yields, respectively.
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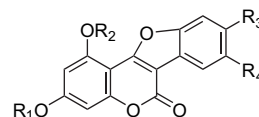
Keywords: Hedysarimcoumestans; Demethylwedelolactone; Wedelolactone; Pd-catalysis

1. Introduction

As part of a recent research to prepare new biologically active substances, we were attracted to the coumarin¹ and benzofuran² family whose members are widely distributed in biologically important natural products and pharmaceutical agents.³ Recently, Liang et al.⁴ have reported that 10 coumestans were isolated from the roots of *Hedysarum multijugum*, which is a plant in *Hedysarum* Linn. of the family *Leguminosae* used as a folk herbal drug in northwest China. Coumestans comprise a class of naturally occurring products with a variety of biological activities including phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects.⁵ For instance, hedysarimcoumestans, demethylwedelolactone, and wedelolactone are natural products and characteristic members of the coumestan family. These compounds are also important sources of phytoestrogens.⁶ In our previous studies,^{1,2} we became aware of the facile conversion of coumarins to α -bromocoumarins and the proceeding of Stille coupling of bromocoumarins and stannanes to arylcoumarin skeleton. Therefore, coumestans are ideal targets for the application of these reactions. Although coumestans and

wedelolactone (**5**) have been synthesized by several groups,⁷ they were achieved with very time-consuming and complicated synthetic approaches. To date, no demethylwedelolactone (**4**) and hedysarimcoumestan **B** (Fig. 1) have been synthesized and deficiently examined the biological activity of the molecules. In addition, to overcome these technical difficulties, we report our studies on the synthesis of hedysarimcoumestan **B** from the commercially available phloroglucinol by Pd-catalyzed coupling and I_2 /pyridine oxidative-cyclization reactions.

Perhaps the easiest route to **2** would have been to couple the known 3-bromo-5,7-dimethoxy-2-chromenone⁸ and the readily prepared 2-benzyloxy-4-methoxyphenyltributylstannane (**10**),⁹ and followed by an oxidative-cyclization reaction.



- 1 $R_1=Me, R_2=R_4=H, R_3=OMe$ Hedysarimcoumestan **A**
 2 $R_1=R_2=R_4=H, R_3=OMe$ Hedysarimcoumestan **B**
 3 $R_1=R_2=Me, R_3=OMe, R_4=H$
 4 $R_1=R_2=H, R_3=R_4=OH$ Demethylwedelolactone
 5 $R_1=Me, R_2=H, R_3=R_4=OH$ Wedelolactone

Figure 1. Coumestan natural products of *Hedysarum* Linn.

* Corresponding author. Tel.: +886 4 7232105x3511; fax: +886 4 7211190.

E-mail address: leeyj@cc.ncue.edu.tw (Y.-J. Lee).

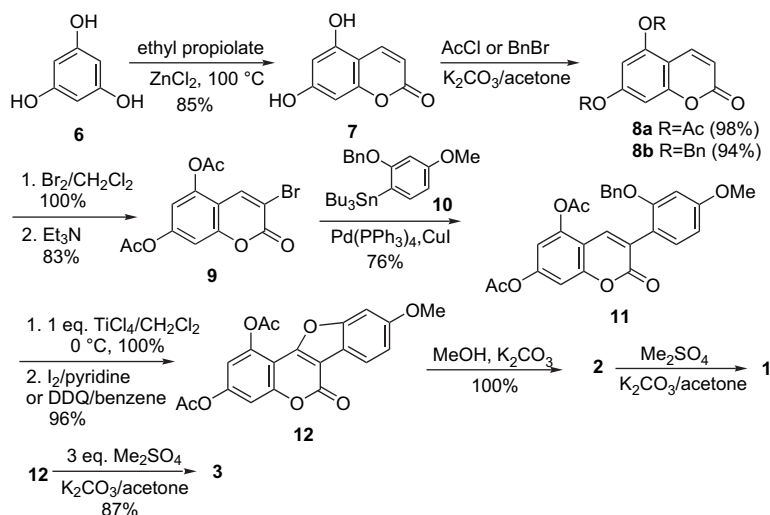
Accordingly, the synthesis of 3-substituted coumarins by the Stille coupling reaction between a bromopyrone and organostannane was reported.¹⁰ In addition, Bauerle et al.¹¹ have employed Suzuki–Miyaura for the synthesis of 3-substituted coumarins as well. In previous projects² we have also achieved such couplings by treating a mixture of benzofuran bromides and aryl stannanes with Pd(PPh₃)₄. The reaction is well known as a Pd-catalyzed cross-coupling reaction in a wide variety of transmetalation reagents including Sn, Mg, Zn, B, Al, Zr, and Cu.¹² Herein, we present the first synthesis of the naturally occurring hedysarimcoumestan **B** and demethylwedelolactone (**4**), and this approach allows access to readily provide the wedelolactone (**5**).

2. Results and discussion

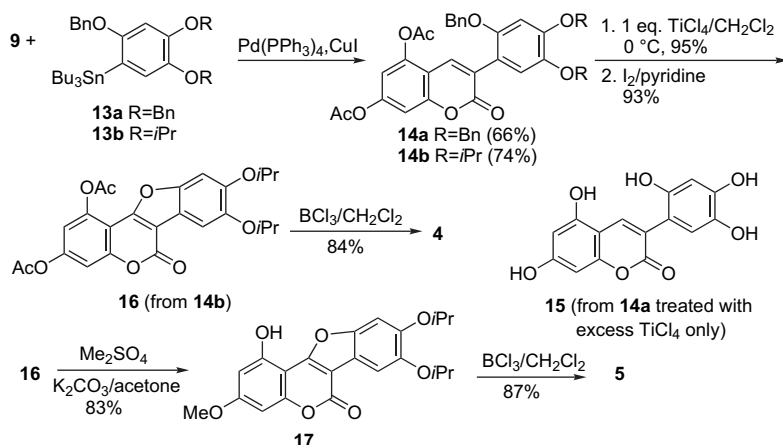
In the beginning of our synthesis, the known coumarin **7** prompted us to prepare the corresponding bromocoumarin **9** from this compound. It was anticipated that **9** was smoothly prepared by our previous method¹ as shown in Scheme 1. Starting with the commercially available phloroglucinol (**6**) and ethyl propiolate, the ZnCl₂-catalyzed esterification–cyclization reaction was undergone to provide the coumarin **7** in high 85% yield. 5,7-Dihydroxycoumarin **7** was readily treated with AcCl and BnBr to provide the corresponding acyl- and benzyl-coumarins **8** in excellent 98 and 94% yields, respectively. The following reaction was employed by sequence bromination and dehydrobromination conditions to afford the key intermediate **9** in high yield (two steps 83%). Although we did not know yet if the structure was 3- or 4-bromo coumarin, we did run the methylation reaction of **9** with dimethyl sulfate. ¹H and ¹³C NMR spectra of the synthetic product are in agreement with those reported for the known 3-bromo-5,7-dimethoxy-2-chromenone.⁸ Therefore, this indirectly confirmed that the structure for compound **9** should be 3-bromocoumarin. In case of **9** and **10**, however, the palladium-catalyzed cross-coupling reaction to give **11** was unsuccessful. The major products were the reductive benzyloxyanisole and starting

material **9**. This problem would be due its high steric demand, which often slows down the subsequent Sn/Pd transmetalation in the catalytic cycle. Liebeskind et al.¹³ have reported that the addition of CuI can increase the reaction rate. Fortunately, the cross-coupling of bromocoumarin **9** with stannane **10** proceeded readily in dioxane by Cu-mediated and Pd(0)-catalysis to give **11** in delighted 76% yield. The resultant arylcoumarin **11** was then transformed into coumestan **12** in two steps. Briefly, it involved removal of the benzyl protecting group with 1 equiv TiCl₄, followed by I₂/pyridine or DDQ¹⁴ oxidative-cyclization of the phenol to afford the desired coumestan **12** in excellent 96% yield. It is worth noting that the acyl groups of arylcoumarin **11** were liable to lose under the Lewis acid (TiCl₄ and BCl₃) or methanol conditions but survived in limited amount of TiCl₄ and short reaction time at low temperature (0 °C). In addition, we failed to obtain the cyclization product **12** under Ag₂O conditions. With precursor **12** in hand, completion of the final steps in the hedysarimcoumestans synthesis was straightforward requiring deacetylation and methylation. Methanolysis of the diacetyl groups in compound **12** provided a quantitative yield of hedysarimcoumestan **B** (**2**). Also, direct methylation of **12** with 3 equiv Me₂SO₄ obtained the expected product **3** in high 87% yield, and conversion of **2** with 1 equiv Me₂SO₄ gave the desired hedysarimcoumestan A (**1**) in high 81% yield as well. Melting points and ¹H and ¹³C NMR spectra of the synthetic products are in agreement with those reported for the naturally derived materials.⁴

It is worth noting that our synthetic strategy can be applied in the syntheses of **4** and **5**. The syntheses of **4** and **5** were achieved by using the same strategy that utilized the Liebeskind coupling conditions and I₂/pyridine oxidative-cyclization reactions described above. The reaction of bromocoumarin **9** with stannane **13** was readily converted to obtain the corresponding arylcoumarin **14** in satisfied yield between 66 and 74%. At this point, the final step of the demethylwedelolactone (**4**) synthesis was focused on the sequence deprotection and oxidative-cyclization reaction of **14a**. Like



Scheme 1.



Scheme 2.

previous debenzoylation of **11**, similarly **14a** can readily be converted with 5 equiv TiCl₄ at 0 °C to give the desired intermediate pentahydroxyl arylcoumarin **15**, but the catechol **15** was unstable under vacuum and acid conditions during isolation. With the aim of developing a successful route to **4**, we then sought to selectively deprotect only the required 2'-benzyl group of **14**. Therefore, **14b** smoothly proceeded the removal of the benzyl protecting group with 1 equiv TiCl₄ at 0 °C in excellent 95% yield, followed by I₂/pyridine oxidative-cyclization of the hydroxylaryl coumarin to afford the anticipated coumestan **16** in excellent 93% yield (Scheme 2). The structure of 3-aryl coumarin **14b** was assigned by X-ray crystallographic methods.¹⁵ Also, it is worth noting that the structure of 3-bromocoumarin **9** can be proved indirectly. Furthermore, the key precursor **16** readily carried out the deprotection with BCl₃ at 0 °C to generate the demethylwedelolactone (**4**) in high 84% yield. Finally, 5,7-acetoxycoumestan **16** was transformed by the selective methylation with 1 equiv Me₂SO₄ and followed by the deprotection with 2 equiv BCl₃ to provide the desired product **5** in high 72% yield (over two steps).

3. Conclusion

In summary, a concise route to hedysarimcoumestan **B** (**2**) has been achieved, in which the longest linear sequence is only eight steps, in 50% overall yield from commercially available phloroglucinol. This synthesis is high yielding and easily applied to give access to a variety of different hedysarimcoumestan **A** (**1**) and coumestan analogues, especially, demethylwedelolactone (**4**) and wedelolactone (**5**), which were afforded from commercially available phloroglucinol in high 38 and 33% yields, respectively. In addition, it demonstrated the usefulness of the Pd-catalyzed coupling reaction with CuI-mediated for 3-aryl-2-coumarin synthesis. Finally, the versatile I₂/pyridine is demonstrated by the oxidative-cyclization to optionally afford the desired furan products for acid sensitive substrates. Further biological assays are currently underway to evaluate the efficacy of these compounds as pharmaceutical agents.

4. Experimental¹

4.1. 5,7-Dihydroxychromen-2-one (**7**)

This compound was prepared as a white solid from phloroglucinol and ethyl propiolate according to the procedure of Kaufman and Kelly;¹⁶ mp 274–275 °C (lit.¹⁶ mp 280 °C). ¹H NMR (DMSO-*d*₆) δ 6.02 and 7.95 (d, *J*=9.6 Hz, 2H), 6.18 and 6.26 (d, *J*=1.8 Hz, 2H), 10.38 and 10.66 (br s, 2H); ¹³C NMR (DMSO-*d*₆) δ 94.4, 98.6, 102.1, 109.0, 140.0, 156.3, 156.8, 161.2, 162.5.

4.2. 5,7-Diacetoxychromen-2-one (**8a**)

A mixture of **7** (5.00 g, 28.0 mmol) and K₂CO₃ (19.40 g, 140.4 mmol) in dry acetone was heated to reflux (oil bath 90 °C) for 1 h, and added acetyl chloride (8.0 mL, 112.3 mmol) dropwise with syringe. The reaction suspension was stirred for 1.5 h at 90 °C, and the resulting solution was cooled down and filtrated out of the excess K₂CO₃. The solvent was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with CH₂Cl₂ to give compound **8a** (7.20 g, 98%) as a white solid; mp 134–135 °C (lit.¹⁷ mp 124–125 °C).

4.3. 5,7-Dibenzyloxychromen-2-one (**8b**)

The **8b** was prepared, using above procedure, from **7** (0.50 g, 0.3 mmol) and K₂CO₃ (0.85 g, 6.2 mmol) with benzyl bromide (0.7 mL, 5.9 mmol). The solvent was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with hexane/CH₂Cl₂ (2:1) to give compound **8b** (0.95 g, 94%) as a white solid; mp 132–133 °C (lit.¹⁸ mp 137–138 °C).

4.4. 3-Bromo-5,7-diacetoxychromen-2-one (**9**)

To a solution of **8a** (2.00 g, 7.6 mmol) in CH₂Cl₂ (50.0 mL) was added Br₂ (0.7 mL, 13.6 mmol) dropwise into the solution at 0 °C for 8 h. The brown solution was extracted with CH₂Cl₂

(2×100.0 mL). The organic layer concentrated in vacuo afforded dibromochromanone (3.20 g, 100%). To the dibromide in CH₂Cl₂ was added Et₃N at room temperature, and then stirred for 2 h. The resulting solution was removed from the solvent in vacuo and the residue was purified by flash chromatography on silica gel with hexane/CH₂Cl₂ (2:1) to give **9** (2.15 g, 83%) as a white solid; mp 146–147 °C. ¹H NMR (CDCl₃) δ 2.33 and 2.43 (s, 6H), 7.03 and 7.05 (d, *J*=2.1 Hz, 2H), 8.09 (s, 1H); ¹³C NMR (CDCl₃) δ 20.9, 21.1, 107.8, 110.8, 111.6, 112.6, 138.1, 146.3, 152.9, 153.9, 156.2, 167.9, 168.1; HRMS (EI) calcd for C₁₃H₉BrO₆ (M⁺) 339.9583, found 339.9584. Anal. Calcd for C₁₃H₉BrO₆: C, 45.77; H, 2.66; O, 28.14. Found: C, 45.62; H, 2.43; O, 28.30.

4.5. 3-Bromo-5,7-dimethoxychromen-2-one

To a mixture of **9** (0.24 g, 0.7 mmol) and K₂CO₃ (0.30 g, 2.1 mmol) in acetone (5.0 mL) was added Me₂SO₄ (0.20 mL, 2.1 mmol) at room temperature, and then refluxed at 70 °C for 1 h by TLC monitoring. After cooling, the solution was evaporated in vacuo, and the brown solid was subjected to flash chromatography (SiO₂, CH₂Cl₂/EtOAc 1:1) to give 3-bromo-5,7-dimethoxychromen-2-one (0.20 g, 0.7 mmol) in 100% yield.

4.6. 2-Benzyloxy-4-methoxyphenyltributylstannane (**10**)

The stannane **10** was prepared, using the previous procedure,⁹ from the known¹⁹ 2-benzyloxy-4-methoxyphenyl bromide (1.00 g, 3.4 mmol). The product **10** was isolated in 99% yield (1.70 g, 3.4 mmol) as a colorless oil. ¹H NMR [(CD₃)₂CO] δ 0.81 (t, *J*=6.6 Hz, 9H), 0.94 (t, *J*=6.6 Hz, 6H), 1.21–1.31 (m, 6H), 1.40–1.50 (m, 6H), 3.75 (s, 3H), 5.06 (s, 2H), 6.53 (dd, *J*=7.8, 2.1 Hz, 1H), 6.57 (d, *J*=2.1 Hz, 1H), 7.22 (d, *J*=7.8 Hz, 1H), 7.33–7.48 (m, 5H); ¹³C NMR [(CD₃)₂CO] δ 9.3, 13.0, 27.1, 28.9, 54.5, 69.7, 98.2, 105.7, 119.5, 127.8, 127.9, 128.3, 137.1, 137.3, 162.0, 164.2.

4.7. 5,7-Diacetoxy-3-(2-benzyloxy-4-methoxyphenyl)-chromen-2-one (**11**)

A mixture of bromocoumarin **9** (0.20 g, 0.6 mmol), CuI (0.02 g, 20 mol %), tetrakis(triphenylphosphine)palladium(0) (0.07 g, 10 mol %), and stannane **10** (0.38 g, 0.8 mmol) were introduced into a sealable tube containing anhydrous dioxane (5.0 mL), and the reaction mixture degassed. The tube was sealed and heated for 12 h at 160 °C, after cooling, and the solution was filtered and evaporated in vacuo. The filtrate residue was subjected to flash chromatography (SiO₂, CH₂Cl₂/hexane 3:2) to provide the desired **11** (0.21 g, 76%) as a yellow solid; mp 141–145 °C. ¹H NMR [(CD₃)₂CO] δ 2.29 and 2.32 (s, 6H), 3.81 (s, 3H), 5.14 (s, 2H), 6.60 (dd, *J*=8.4, 2.4 Hz, 1H), 6.72 and 7.00 (d, *J*=2.1 Hz, 2H), 7.08 (d, *J*=2.4 Hz, 1H), 7.33 (d, *J*=8.4 Hz, 1H), 7.27–7.45 (m, 5H), 7.95 (s, 1H); ¹³C NMR [(CD₃)₂CO] δ 20.2, 20.4, 55.2, 70.4, 100.2, 105.3, 107.6, 111.6, 112.8, 117.2, 126.0, 127.6, 127.9, 128.7, 132.0, 134.9, 137.5, 147.9, 152.8, 154.6, 157.8, 159.2, 161.9,

168.5, 168.7; HRMS (EI) calcd for C₂₇H₂₂O₈ (M⁺) 474.1315, found 474.1318.

4.8. 1,3-Diacetoxy-9-methoxy-benzo[4,5]furo[3,2-*c*]-chromen-6-one (**12**)

To a solution of **11** (0.20 g, 0.4 mmol) in CH₂Cl₂ (10.0 mL) was added TiCl₄ (0.04 mL, 0.4 mmol) dropwise at 0 °C for 10 min. The reaction was monitored by TLC and quenched by treatment with ice water. The solvent was removed and the residue was subjected to flash chromatography (SiO₂, CH₂Cl₂/EtOAc 20:1) to give the desired hydroxyaryl coumarin (0.16 g, 100%) as a yellow solid; mp 191–192 °C. ¹H NMR (CDCl₃) δ 2.34 and 2.41 (s, 6H), 3.83 (s, 3H), 6.60 and 7.06 (d, *J*=2.1 Hz, 2H), 6.61 and 7.16 (d, *J*=5.1 Hz, 2H), 7.20 (s, 1H), 7.68 (br s, 1H), 7.81 (s, 1H); ¹³C NMR (CDCl₃) δ 20.9, 21.1, 55.5, 104.1, 107.6, 108.3, 111.3, 112.8, 115.3, 126.6, 131.6, 135.7, 147.3, 152.6, 153.5, 156.4, 162.4, 162.8, 168.1, 168.2; HRMS (EI) calcd for C₂₀H₁₆O₈ (M⁺) 384.0845, found 384.0848. I₂ (1 equiv 0.4 mmol) or DDQ (0.12 g, 0.6 mmol) was added to a solution of the synthetic hydroxyaryl coumarin (0.15 g, 0.4 mmol) in anhydrous pyridine (15.0 mL) or benzene (15.0 mL) at ambient temperature. The mixture was heated for refluxing at 110 °C (oil bath) for 15 h. After cooling, the solution was evaporated in vacuo and the brown solid was subjected to flash chromatography (SiO₂, CH₂Cl₂/EtOAc 20:1). The coumestan **12** (0.14 g, 96%) was isolated as a white solid; mp 246–247 °C. ¹H NMR (CDCl₃) δ 2.36 and 2.55 (s, 6H), 3.92 (s, 3H), 6.99 and 7.23 (d, *J*=2.1 Hz, 2H), 7.08 and 7.98 (d, *J*=9.3 Hz, 2H), 7.09 (s, 1H); ¹³C NMR (CDCl₃) δ 21.0, 21.2, 55.9, 96.5, 105.7, 106.4, 108.8, 113.3, 114.0, 115.6, 122.1, 145.5, 152.2, 153.9, 156.6, 156.8, 157.3, 159.9, 168.3, 169.0; HRMS (EI) calcd for C₂₀H₁₄O₈ (M⁺) 382.0689, found 382.0687.

4.9. Hedysarimcoumestan **B** (**2**)

A mixture of **12** (0.050 g, 0.1 mmol) and K₂CO₃ (0.083 g, 0.6 mmol) in MeOH (3.0 mL) was refluxed at 70 °C (oil bath) for 30 min. The resulting reaction mixture was cooled down and neutralized with 1 M HCl and extracted with EtOAc (3×5.0 mL). The combined extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (SiO₂, MeOH/EtOAc 1:5) to obtain **2** (0.039 g, 100%) as a white solid; mp>300 °C (lit.⁴ mp>300 °C). ¹H NMR (DMSO-*d*₆) δ 3.89 (s, 3H), 6.42 and 6.46 (d, *J*=2.1 Hz, 2H), 7.10 (dd, *J*=8.4, 2.1 Hz, 1H), 7.53 (d, *J*=2.1 Hz, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 10.58 and 11.02 (br s, 2H); ¹³C NMR (DMSO-*d*₆) δ 56.9, 96.0, 96.2, 98.2, 100.2, 101.6, 114.3, 116.7, 121.2, 156.4, 156.7, 156.8, 158.8, 159.5, 161.4, 162.7; HRMS (ESI) calcd for C₁₆H₁₀O₆ (neg) 298.0477, found 298.0462.

4.10. Hedysarimcoumestan **A** (**1**)

Coumestan **2** (0.030 g, 0.1 mmol) was dissolved in acetone (4.0 mL). Me₂SO₄ (16.1 μL, 0.1 mmol) and K₂CO₃ (0.020 g,

0.2 mmol) were added and the suspension was heated at 70 °C for 1 h. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column (CH₂Cl₂/EtOAc 1:1) to give **1** (0.025 g, 81%) as a white solid; mp >300 °C (lit.⁴ mp >300 °C). ¹H NMR (CDCl₃+DMSO-*d*₆) δ 3.85 and 3.89 (s, 6H), 6.54 (br s, 2H), 7.03 (dd, *J*=8.4, 2.1 Hz, 1H), 7.24 (d, *J*=2.1 Hz, 1H), 7.91 (d, *J*=8.4 Hz, 1H); ¹³C NMR (CDCl₃+DMSO-*d*₆) δ 54.6, 54.7, 92.2, 95.8, 95.9, 97.5, 100.8, 112.0, 115.0, 119.6, 154.2, 154.7, 155.2, 157.3, 157.6, 159.3, 161.8; HRMS (ESI) calcd for C₁₇H₁₂O₆ (neg) 312.0634, found 312.0623.

4.11. 1,3,9-Trimethoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (**3**)

From **12** (0.03 g, 0.07 mmol) and Me₂SO₄ (32.0 μL, 0.2 mmol) with K₂CO₃ (0.020 g, 0.2 mmol), using above procedure, the coumestan **3** (0.02 g, 87%) was isolated as a white solid; mp 220–222 °C (lit.⁴ mp 220–225 °C). ¹H NMR (CDCl₃+DMSO-*d*₆) δ 3.90 and 4.05 (s, 9H), 6.46 and 6.60 (d, *J*=2.1 Hz, 2H), 7.03 (dd, *J*=8.7, 2.1 Hz, 1H), 7.22 (d, *J*=2.1 Hz, 1H), 7.87 (d, *J*=8.7 Hz, 1H); ¹³C NMR (CDCl₃+DMSO-*d*₆) δ 55.2, 55.3, 55.7, 93.1, 94.9, 96.1, 97.1, 102.0, 112.7, 115.3, 120.3, 155.2, 155.7, 156.0, 157.7, 158.3, 159.2, 162.4; HRMS (EI) calcd for C₁₈H₁₄O₆ (M⁺) 326.0790, found 326.0789.

4.12. 2-Benzylloxy-4,5-dibenzylloxyphenyltributylstannane (**13a**)

The stannane **13a** was prepared, using the previous procedure,⁹ from the 2,4,5-tribenzylloxyphenyl bromide (1.00 g, 2.1 mmol) in 96% yield (1.39 g, 2.0 mmol) as a colorless oil. ¹H NMR [(CD₃)₂CO] δ 0.82 (t, *J*=7.5 Hz, 9H), 0.95 (t, *J*=7.8 Hz, 6H), 1.21–1.29 (m, 6H), 1.41–1.50 (m, 6H), 5.02, 5.07, and 5.17 (s, 6H), 6.88 and 6.97 (s, 2H), 7.30–7.51 (m, 15H); ¹³C NMR [(CD₃)₂CO] δ 9.4, 13.2, 27.1, 29.0, 70.4, 70.7, 72.4, 99.7, 119.5, 125.1, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 137.5, 137.7, 138.3, 143.2, 150.9, 158.5.

4.13. 2-Benzylloxy-4,5-diisopropylloxyphenyltributylstannane (**13b**)

The product **13b** was isolated from the 2-benzylloxy-4,5-diisopropylloxyphenyl bromide (1.00 g, 2.6 mmol) in 94% yield (1.46 g, 2.5 mmol) as a colorless oil. ¹H NMR [(CD₃)₂CO] δ 0.97 (t, *J*=8.1 Hz, 9H), 1.06 (t, *J*=7.8 Hz, 6H), 1.21 and 1.25 (d, *J*=6.3 Hz, 12H), 1.21–1.32 (m, 6H), 1.39–1.55 (m, 6H), 4.30 and 4.56 (hept, *J*=6.3 Hz, 2H), 5.03 (s, 2H), 6.67 and 6.70 (s, 2H), 7.31–7.47 (m, 5H); ¹³C NMR [(CD₃)₂CO] δ 9.3, 13.0, 21.6, 21.7, 27.0, 28.9, 70.2, 70.8, 72.6, 101.5, 119.4, 127.6, 127.7, 128.2, 128.3, 137.5, 142.8, 150.8, 158.6.

4.14. 5,7-Diacetoxy-3-(2,4,5-tribenzylloxyphenyl)chromen-2-one (**14a**)

From bromocoumarin **9** (0.20 g, 0.6 mmol) and **13a** (0.60 g, 0.9 mmol), **14a** was obtained in 66% (0.25 g, 0.4 mmol) yield as a yellow solid; mp 141–142 °C. ¹H NMR (CDCl₃) δ 2.24 and 2.32 (s, 6H), 4.95, 5.12, and 5.14 (s, 6H), 6.68 and 7.10 (s, 2H), 6.95 and 7.02 (d, *J*=1.8 Hz, 2H), 7.25–7.46 (m, 15H), 7.74 (s, 1H); ¹³C NMR (CDCl₃) δ 20.7, 21.1, 71.5, 71.7, 72.6, 102.6, 107.5, 111.0, 112.0, 116.4, 118.8, 125.0, 127.2, 127.3, 127.6, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 135.0, 136.7, 136.8, 137.2, 142.9, 147.0, 150.5, 151.5, 152.1, 154.2, 159.7, 168.1, 168.4; HRMS (EI) calcd for C₄₀H₃₂O₉ (M⁺) 656.2046, found 656.2048.

4.15. 5,7-Diacetoxy-3-(2-benzylloxy-4,5-diisopropylloxyphenyl)chromen-2-one (**14b**)

Compound **14b** was prepared from **9** (0.20 g, 0.6 mmol) and **13b** (0.52 g, 0.9 mmol) in 74% (0.24 g, 0.4 mmol) yield as a yellow-green crystal; mp 158–159 °C. ¹H NMR (CDCl₃) δ 1.32 and 1.33 (d, *J*=6.3 Hz, 12H), 2.24 and 2.31 (s, 6H), 4.36 and 4.51 (hept, *J*=6.3 Hz, 2H), 5.04 (s, 2H), 6.64 and 7.01 (s, 2H), 6.96 and 7.03 (d, *J*=2.1 Hz, 2H), 7.27–7.40 (m, 5H), 7.81 (s, 1H); ¹³C NMR (CDCl₃) δ 20.7, 21.1, 22.1, 22.3, 71.5, 72.1, 73.6, 104.3, 107.5, 111.1, 112.0, 116.5, 122.2, 125.2, 127.2, 127.8, 128.5, 134.9, 136.8, 142.6, 147.0, 150.9, 151.8, 152.0, 154.2, 159.7, 168.2, 168.4. Anal. Calcd for C₃₂H₃₂O₉: C, 68.56; H, 5.75; O, 25.69. Found: C, 68.34; H, 5.69; O, 25.77.

4.16. 5,7-Dihydroxy-3-(2,4,5-trihydroxyphenyl)chromen-2-one (**15**)

Compound **15** was prepared, using above procedure, from **14a** (0.15 g, 0.2 mmol) and TiCl₄ (0.11 mL, 1.1 mmol) in 56% yield (0.04 g, 0.1 mmol) as a yellow solid. ¹H NMR [(CD₃)₂CO] δ 6.32 and 6.38 (d, *J*=2.1 Hz, 2H), 6.46 and 6.85 (s, 2H), 8.07 (s, 1H), 7.51, 7.77, 7.96, 9.36, and 9.65 (br s, 5H).

4.17. 1,3-Diacetoxy-8,9-diisopropylloxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (**16**)

The **14b** (0.30 g, 0.5 mmol) was transformed, using the general procedure, to generate the corresponding hydroxyaryl coumarin (0.24 g, 0.5 mmol) in 95% yield as a yellow solid; mp 165–166 °C. ¹H NMR (CDCl₃) δ 1.30 and 1.44 (d, *J*=6.3 Hz, 12H), 2.34 and 2.41 (s, 6H), 4.31 and 4.56 (hept, *J*=6.3 Hz, 2H), 6.61 and 6.86 (s, 2H), 7.05 and 7.13 (d, *J*=2.1 Hz, 2H), 7.47 (br s, 1H), 7.79 (s, 1H); ¹³C NMR (CDCl₃) δ 20.9, 21.1, 22.0, 22.2, 71.1, 74.4, 106.4, 107.5, 111.2, 112.8, 114.0, 123.2, 126.4, 135.8, 142.2, 147.2, 151.1, 152.5, 152.7, 153.4, 162.7, 168.2, 168.3; HRMS (EI) calcd for C₂₅H₂₆O₉ (M⁺) 470.1577, found 470.1585. Following oxidative-cyclization with I₂ (1 equiv 0.5 mmol), coumestan **16** was isolated in 93% yield (0.22 g, 0.5 mmol) as

a white solid; mp 223–224 °C. ^1H NMR (CDCl_3) δ 1.40 and 1.41 (d, $J=6.3$ Hz, 12H), 2.35 and 2.54 (s, 6H), 4.57 and 4.58 (hept, $J=6.3$ Hz, 2H), 6.98 and 7.22 (d, $J=2.1$ Hz, 2H), 7.13 and 7.59 (s, 2H); ^{13}C NMR (CDCl_3) δ 21.0, 21.1, 22.0, 22.1, 72.8, 73.1, 101.2, 105.8, 106.5, 108.5, 108.8, 113.2, 115.8, 145.4, 148.4, 149.7, 150.8, 152.0, 153.7, 156.5, 157.5, 168.3, 169.0; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{24}\text{O}_9$ (M^+) 468.1420, found 468.1423.

4.18. Demethylwedelolactone (**4**)

To a solution of **16** (0.10 g, 0.2 mmol) in CH_2Cl_2 (5.0 mL) was added BCl_3 (0.4 mL, 1.0 M) dropwise at 0 °C. The reaction was monitored by TLC and quenched by treatment with MeOH. The solvent was removed and the residue was subjected to flash chromatography (SiO_2 , EtOAc/MeOH 10:1) to give **4** (0.05 g, 84%) as a yellow solid; mp 305 °C (dec) (lit.^{7a} mp>330 °C). ^1H NMR [$(\text{CD}_3)_2\text{CO}$] δ 6.44 and 6.45 (d, $J=2.1$ Hz, 2H), 7.17 and 7.38 (s, 2H), 8.35, 8.36, 9.35, and 9.60 (br s, 4H); ^{13}C NMR [$(\text{CD}_3)_2\text{CO}+\text{DMSO}-d_6$] δ 95.1, 95.8, 98.5, 99.3, 101.4, 104.8, 114.7, 144.2, 145.2, 149.3, 155.4, 155.9, 158.0, 159.9, 161.5; HRMS (EI) calcd for $\text{C}_{15}\text{H}_8\text{O}_7$ (M^+) 300.0270, found 300.0272.

4.19. 1-Hydroxy-3-methoxy-8,9-diisopropoxybenzo[4,5]-furo[3,2-c]chromen-6-one (**17**)

The methylation reaction was employed, using above procedure, from **16** (0.10 g, 0.2 mmol) and Me_2SO_4 (32.0 μL , 0.2 mmol) with K_2CO_3 (0.04 g, 0.3 mmol). Compound **17** was isolated in 83% yield (0.07 g, 0.2 mmol) as a white solid; mp 194–195 °C. ^1H NMR (CDCl_3) δ 1.39 and 1.40 (d, $J=6.0$ Hz, 12H), 3.87 (s, 3H), 4.52 and 4.58 (hept, $J=6.0$ Hz, 2H), 6.49 and 6.61 (d, $J=1.5$ Hz, 2H), 7.23 and 7.57 (s, 2H); ^1H NMR [$(\text{CD}_3)_2\text{CO}+\text{DMSO}-d_6$] δ 1.33 and 1.35 (d, $J=6.3$ Hz, 12H), 3.86 (s, 3H), 4.55 and 4.67 (hept, $J=6.3$ Hz, 2H), 6.51 and 6.52 (d, $J=2.1$ Hz, 2H), 7.35 and 7.43 (s, 2H); ^{13}C NMR [$(\text{CD}_3)_2\text{CO}+\text{DMSO}-d_6$] δ 21.4, 21.6, 55.3, 71.8, 72.5, 93.1, 96.9, 98.3, 100.8, 102.0, 108.5, 116.0, 147.4, 148.8, 150.5, 155.5, 156.0, 157.7, 160.2, 163.0; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{22}\text{O}_7$ (M^+) 398.1366, found 398.1360.

4.20. Wedelolactone (**5**)

From **17** (0.12 g, 0.3 mmol) and BCl_3 (0.7 mL, 1.0 M), **5** was achieved in 87% (0.08 g, 0.3 mmol) yield as a yellow solid; mp 300 °C (dec) (lit.⁵ mp 300 °C (dec)). ^1H NMR [$(\text{CD}_3)_2\text{CO}+\text{DMSO}-d_6$] δ 3.90 (s, 3H), 6.51 and 6.53 (s, 2H), 7.17 and 7.37 (s, 2H), 8.81, 8.85, and 10.56 (br s, 3H); ^{13}C NMR [$(\text{CD}_3)_2\text{CO}+\text{DMSO}-d_6$] δ 55.3, 93.0, 97.0, 98.3, 98.5, 102.2, 104.8, 114.5, 144.3, 145.5, 149.5, 155.2, 155.8,

157.8, 159.4, 162.7; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{10}\text{O}_7$ (M^+) 314.0427, found 314.0425.

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