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Regioselective Oxidative Dehydrogenation under Nonenzymatic Conditions: A Synthetic Route to Gossypol

Ling Li,[a] Yuxiu Liu,[a] and Qingmin Wang*[a]

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A practical and scalable route was developed for the total synthesis of gossypol to allow for the construction of dozens of gossypol derivatives. tBuO$_2$Ac was found to be a highly efficient oxidant for the polymerization of hemigossypol through a biosynthetic process under nonenzymatic conditions to give gossypol. Hemigossypol was synthesized on a gram scale by starting from commercially available carvacrol and dimethyl succinate and using a Stobbe condensation, an electrophilic cyclization, and the Michael addition of *ortho*-quinone methide as key steps.

Introduction

Natural products are a treasure trove of medicinally relevant compounds. For example, between 1981 and 2010, 80% of cancer drugs and 47% of treatments for infection were either natural products, direct derivatives of them, or substances inspired by naturally occurring compounds.[1] The generation of natural product analogues is important, as it provides tools for chemical biology, enables the determination of structure–activity relationships (SAR), and provides insight into the way in which natural products interact with their target biomolecules. Moreover, the synthesis of natural product analogues is also necessary to improve bioavailability, fine-tune biological activity, and reduce the toxicity of medicinal compounds.[2]

Gossypol (**1**, see Figure 1), a complicated polyphenolic compound, was first discovered at the end of the 19th century by Longmore[3] and Marchlewski[4] from the foots of cottonseed-oil refining. It is proposed to be a part of a plant's defense system against pathogenic fungi and insects[5] and exhibits multiple biological properties, which include spermicidal,[6] antiparasitic,[7] antitumor,[8] and antiviral activities.[9] (–)-(*R*)-Gossypol is currently in phase II clinical trials as it displays single-agent antitumor activity in patients with advanced malignancies.[10] Those studies have stimulated great interest in the development of gossypol derivatives to explore SAR.[11]

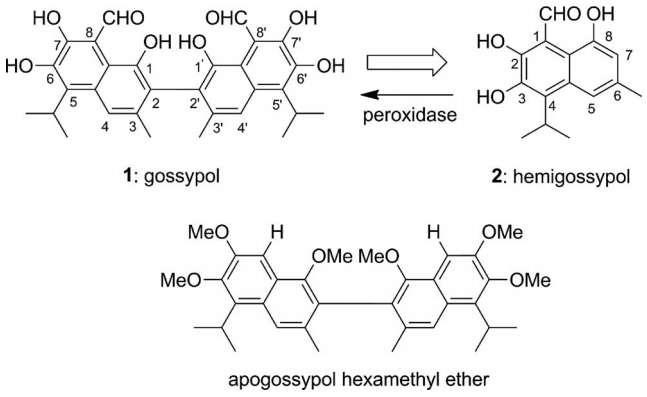

Figure 1. Structure of gossypol (**1**), hemigossypol (**2**), and apogossypol hexamethyl ether as well as the biosynthesis of gossypol.

Several groups have completed the synthesis of gossypol and its binaphthyl backbone.[12] For example, in 1957, Edwards reported the synthesis of apogossypol hexamethyl ether (see Figure 1) through the dimerization of molten 1-naphthol at high temperature.[12a] In the following year, he reported the first total synthesis of gossypol by introducing a formyl group *ortho* to a phenoxy group in the key step.[12b] In 1997, Meyers and Willemsen reported the synthesis of (+)-(*S*)-gossypol by using the asymmetric Ullmann reaction of chiral oxazoline-activated arenes.[12g,12h] Nevertheless, the syntheses of the varied gossypol derivatives are largely restricted to a semisynthesis process, that is, to the modification of gossypol,[13] which greatly limits the range of accessible structures that might be studied as new candidates.

An oxidative coupling of phenolic compounds contributes to the biosynthesis of biaryl natural products.[14] However, the regioselectivity that results from that biosynthetic process has rarely been achieved under nonenzymatic conditions.[15] Stipanovic and Liu suggested that the biosynthesis of gossypol proceeds through the peroxidative dimeriza-

[a] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University,
Tianjin 300071, P. R. China
E-mail: wang98h@263.net
wangqm@nankai.edu.cn
http://skleoc.nankai.edu.cn/professors/wangqm/index.html
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tion of hemigossypol. (see Figure 1)[16] An oxidative dehydrogenative coupling of hemigossypol is really the most effective method for the construction of gossypol. Therefore, we wish to carry out the highly regioselective synthesis of gossypol through the biomimetic oxidative coupling of hemigossypol. This will provide a new approach to obtain new gossypol analogues to explore SAR.

Herein, to obtain libraries of gossypol analogues to advance the development of SAR, we report a practical and scalable route that leads to the convergent total synthesis of gossypol through the oxidative dehydrogenative coupling of hemigossypol.

Results and Discussion

Retrosynthetic Analysis

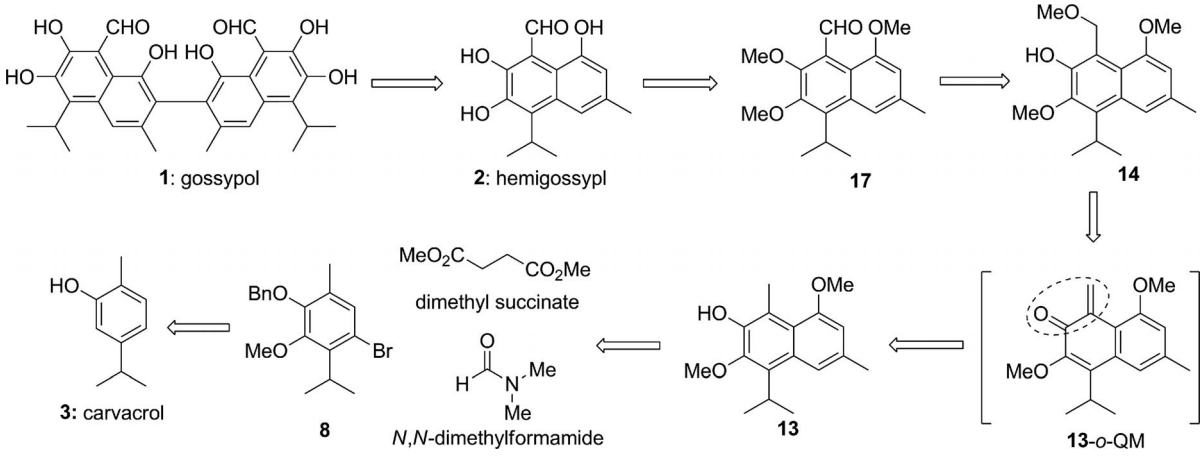
The effective introduction of the aldehyde group is one of the main bottlenecks to the efficient synthesis of gossypol.[12] An *ortho*-quinone methide (*o*-QM)[17] is an important and universal intermediate in organic synthesis and can undergo rapid rearomatization through either a Michael addition of nucleophilic reagents or a cycloaddition reaction. We, thus, envisioned to introduce the aldehyde group of gossypol through a Michael addition of *o*-QM, which is a key step in the synthesis.

Retrosynthetically, the preparation of gossypol relied on the dimerization of hemigossypol (**2**), which is available through the deprotection of **17** (see Scheme 1). An oxidative dearomatization/Michael addition followed by a selective deprotection and oxidation would provide hemigossypol trimethyl ether **17** from **13**. The key intermediate **13** would be assembled from substituted bromobenzene **8** through a formylation reaction, a Stobbe condensation with dimethyl succinate, an electrophilic cyclization, and a reduction reaction. Bromobenzene **8** was further traced back to commercially available carvacrol (**3**).

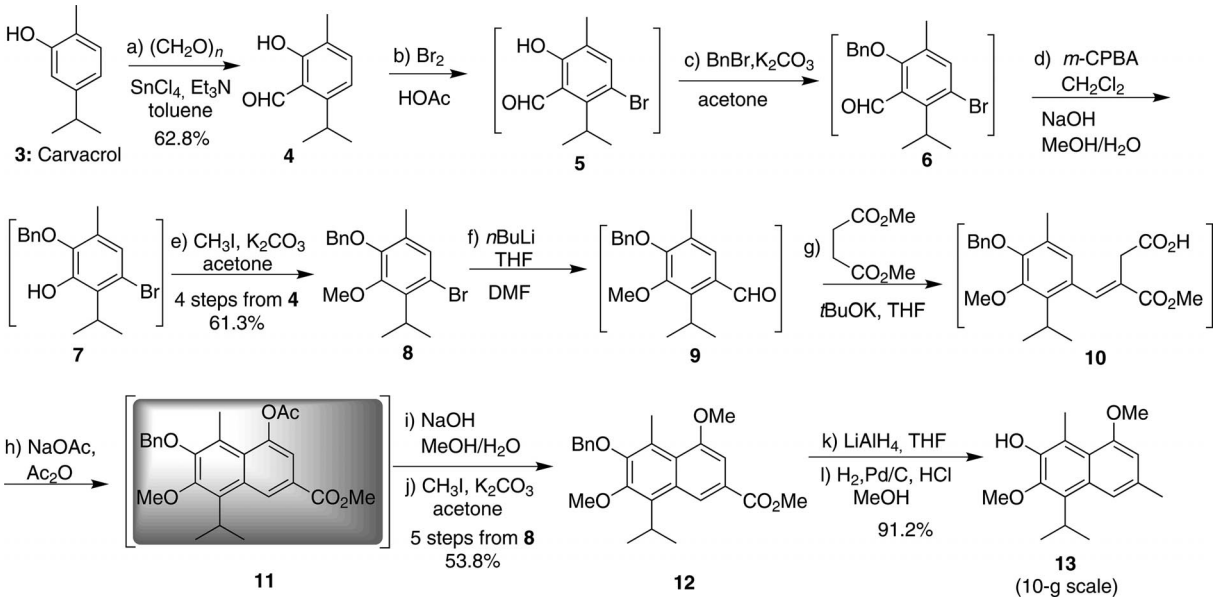
Synthesis of Hemigossypol

On the basis of the retrosynthetic analysis, we first focused our attention to the assembly of 1-methyl-2-naphthol **13** (see Scheme 2). The selective *ortho*-formylation of carvacrol (**3**) through Casiraghi's $SnCl_4$-catalyzed method gave salicylaldehyde **4** in 62.8% yield.[18] The bromination of **4** followed by the protection of the hydroxy group with benzyl bromide gave intermediate **6**. A Dakin oxidation of aromatic aldehyde **6** gave the corresponding phenol **7**, and subsequent protection with methyl iodide followed by flash column chromatography provided substituted bromobenzene **8** in 61.3% yield (four steps from **4**). The halogen–lithium exchange of **8** followed by a formylation reaction, a Stobbe condensation with dimethyl succinate, and then an electrophilic cyclization with sodium acetate afforded the highly substituted naphthalene **11**.[12d] The acetyl-protected naphthol was converted into methyl ether **12**, which was isolated in 53.8% yield over five steps from bromobenzene **8**. The methyl ester moiety of **12** was converted into a methyl group by reduction with $LiAlH_4$ and then H_2 (1 atm) in the presence of 10% Pd/C. In the latter step, a simultaneous reduction of the benzyl ether protecting group of the naphthol produced the desired 1-methyl-2-naphthol **13** in an overall yield of 91.2%. The scaleup of the above sequence reliably occurred, and **13** was readily prepared on a 10 gram scale. Furthermore, the existence of the different hydroxy protecting groups on the phenol moieties of compound **11** provides opportunities to investigate their respective influence on the biological activity of the molecule, which heretofore has been scarcely explored.

With the key intermediate **13** in hand, it then underwent an oxidation reaction through intermediate **13i** followed by a Michael addition to functionalize the C-1 methyl group (see Table 1). First, Br_2[19] was employed as an oxidant and nucleophilic reagent, but it failed to provide the desired product **14** (see Table 1, Entry 1). Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant and methanol as the nucleophilic reagent under reflux conditions afforded intermediate **13i** in excellent yields (see Table 1, Entry 2), whereas using Ag_2O as the oxidant provided the desired product **14** (35.7%) and byproduct **14**-D–A (22.9%, D–A = Diels–Alder), which was definitely formed through a Diels–Alder cycloaddition (see Table 1, Entry 3). Although the stabilization of *ortho*-quinone



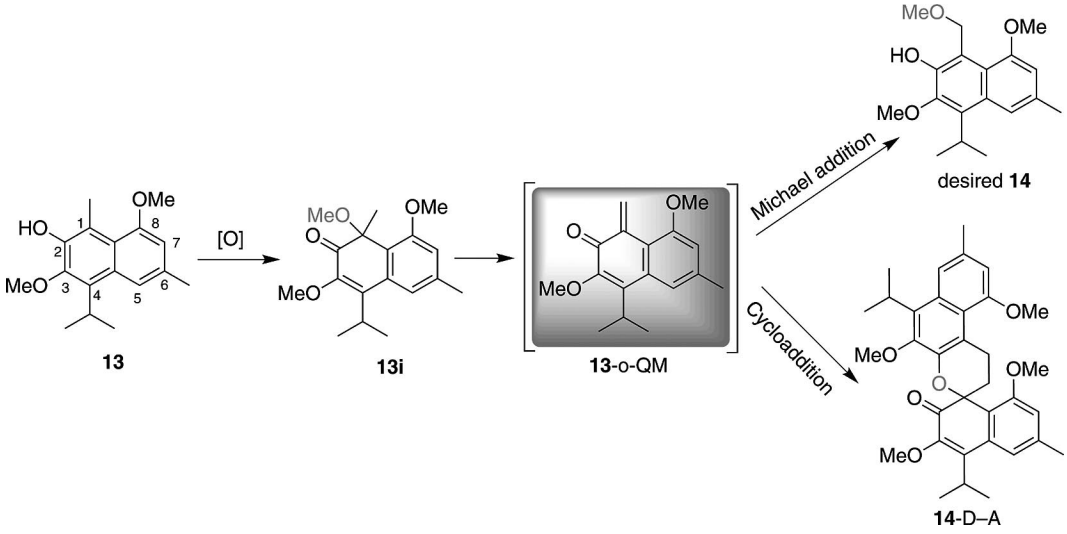
Scheme 1. Retrosynthesis of gossypol (**1**).



Scheme 2. Synthesis of substituted 1-methyl-2-naphthol **13**. Reagents and conditions: (a) $SnCl_4$, Et_3N, toluene, then $(CH_2O)_n$, 100 °C, 8 h, 62.8%; (b) Br_2, $HOAc/H_2O$, room temp.; (c) benzyl bromide (BnBr), K_2CO_3, acetone, room temp.; (d) *meta*-chloroperoxybenzoic acid (*m*-CPBA), CH_2Cl_2, room temp.; NaOH, $MeOH/H_2O$, reflux; (e) CH_3I, K_2CO_3, acetone, room temp. 61.3% (four steps from **4**); (f) *n*BuLi, tetrahydrofuran (THF), Ar, –78 °C; *N*,*N*-dimethylformamide (DMF), –78 to –30 °C; (g) dimethyl succinate, *t*BuOK, THF, room temp.; (h) NaOAc, Ac_2O, reflux; (i) NaOH, $MeOH/H_2O$, reflux; (j) CH_3I, K_2CO_3, acetone, room temp. 53.8% (five steps from **8**); (k) $LiAlH_4$, THF, room temp.; (l) H_2 (1 atm), 10% Pd/C, HCl (12 M), MeOH, 91.2%.

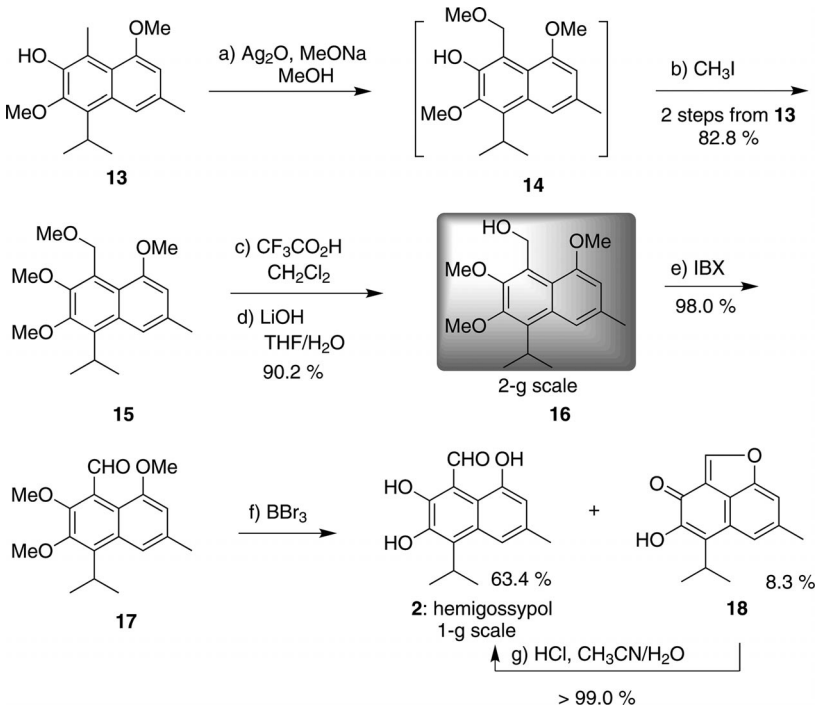
methides could decrease the formation of the Diels–Alder reaction products,[20] the same effect could be achieved by enhancing the nucleophilicity of nucleophilic reagent. The replacement of MeOH with MeONa as the nucleophilic reagent averted the dimerization and rendered Michael addition product **14** in good yield (see Table 1, Entry 4). Further improvement of the yield could be realized by the slow addition of 1-methyl-2-naphthol **13** at room temperature by using a constant pressure funnel (see Table 1, Entry 5).

Table 1. Optimization of conditions for synthesis of **14** through oxidation and Michael addition reactions.



Entry	Reaction conditions	Product [% yield]
1	Br_2(1.3 equiv.), CCl_4, 50 °C, 4 h	decomposition
2	DDQ (1.5 equiv.), MeOH, reflux, 6 h	**13i** (91.4)
3	Ag_2O(1.5 equiv.), MeOH, reflux, 2 h	**14** (35.7), **14**-D–A (22.9)
4	Ag_2O (1.5 equiv.), MeONa (3 equiv.), MeOH, room temp., 3 h	**14** (69.9)
5[a]	Ag_2O(1.5 equiv.), MeONa (3 equiv.), MeOH, room temp., 3 h	**14** (89.5)

[a] Slow addition of 1-methyl-2-naphthol **13** by using a constant pressure funnel.



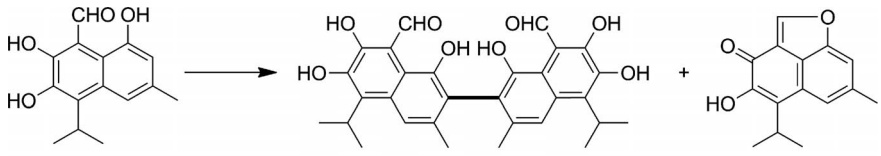
Scheme 3. Synthesis of hemigossypol (**2**). Reagents and conditions: (a) Ag_2O, MeONa, MeOH, then **13** in MeOH, room temp.; (b) CH_3I, acetone. 82.8% (two steps from **13**); (c) CF_3CO_2H, CH_2Cl_2, room temp.; (d) LiOH, THF/H_2O, room temp.; (e) IBX, DMSO, room temp.; (f) BBr_3, CH_2Cl_2, –78 to –10 °C; (g) HCl (12 M), CH_3CN/H_2O, room temp.

Under the optimized conditions, the in situ addition product **14** was methylated by treatment with CH_3I in acetone to give **15** in a two-step yield of 82.8% (see Scheme 3). To our delight, the methoxy group at the benzyl position of **15** could be selectively demethylated to give the 1-naphthalenemethanol **16** in a yield of 90.2% through formation of the corresponding trifluoroacetyl ester and subsequent hydrolysis. This provides access to a wide range of hemigossypol and gossypol analogues with a modified aldehyde group, which probably causes hepatotoxicity and glycemic index (GI) toxicity in vivo. Next, the oxidation of 1-naphthalenemethanol **16** by using *o*-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO) produced 1-naphthaldehyde **17** in 98.0% yield. The demethylation of the multiple methoxy groups in **17** by treatment with boron tribromide afforded hemigossypol (**2**) in 63.4% yield and anhydrohemigossypol (**18**) in 8.3% yield. Analogue **18** could be converted back into hemigossypol (**2**) in quantitive yield by using dilute hydrochloric acid in acetonitrile. The scaleup of the above sequence was reliable, and **2** was readily prepared on gram scales. The NMR spectroscopic data of our synthetic hemigossypol (**2**) are identical to those reported.[21]

Synthesis of Gossypol through Oxidative Dehydrogenation of Hemigossypol

Having accomplished the synthesis of hemigossypol (**2**), we then turned our attention to the synthesis of its dimer gossypol (**1**). As reported, hemigossypol is unstable in the presence of oxygen,[22] and gossypol readily dehydrates to form anhydrogossypol when heated.[23] These issues pose a great challenge for the completion of the synthesis of gossypol through the dimerization of hemigossypol. First, we attempted Edwards's method,[12a] but unfortunately the dimer gossypol could not be obtained. Second, a large number of oxidative aryl–aryl coupling reagents and catalysts such as $CuCl_2/R–NH_2$,[24] $FeCl_3$,[25] $NaNO_2$,[26] $SnCl_4$,[27] DDQ, and VOF_3 were screened for this reaction, but all failed. Finally, a variety of peroxides were examined (see Table 2). Using 30% H_2O_2[16] as an oxidant did not provide the dimer gossypol, and after the reaction mixture was stirred at room temperature for 12 h, hemigossypol was recovered in 85.0% yield (see Table 2, Entry 1). The complete decomposition of hemigossypol was observed when *m*-CPBA was employed as the oxidant (see Table 2, Entries 2 and 3). To our delight, using $(t\text{BuO})_2$[12d] with the reaction mixture at 130 °C afforded the desired gossypol (**1**) in 45.7% yield. Taking into consideration the instability of hemigossypol and gossypol, a decrease in the reaction temperature may improve the yield. However, the half life of $(t\text{BuO})_2$ is 0.15 h at 130 °C, 34 h at 115 °C, and 218 h at 100 °C. Therefore, we changed the oxidant to more active $t\text{BuO}_2\text{Ac}$, and gossypol was obtained in 52.5% yield when the reaction mixture was heated at reflux in toluene (Table 2, Entry 5). When the reaction was heated at reflux in 1,2-dichloroethane (DCE), the lower reaction temperature of 80 °C gave a higher yield (see Table 2, Entry 6). For this oxidative dehydrogenative coupling reaction, it was important that the hemigossypol was freshly prepared, otherwise anhydrohemigossypol (**18**) was partly or completely obtained (see Table 2, Entries 7 and 8). Therefore, the optimal method to obtain gossypol was to treat hemigossypol (**2**) with

Table 2. Optimizing conditions for synthesis of gossypol with peroxides as oxidants.



2: hemigossypol **1**: gossypol **18**

Entry	Oxidant [2.2 equiv.]	Solvent	Temperature [°C]	Time [h]	Isolated product [% yield]
1	30% H_2O_2	CH_3CN	room temp.	12	**2** (85.0)
2	*m*-CPBA	CH_2Cl_2	room temp.	7	decomposition
3	*m*-CPBA	CH_3CN	room temp.	7	decomposition
4	$(t\text{BuO})_2$	C_6H_5Cl	130	2	**1** (45.7)
5	$t\text{BuO}_2\text{Ac}$	toluene	110	3.5	**1** (52.5)
6	$t\text{BuO}_2\text{Ac}$	DCE	80	4	**1** (76.1)
7[a]	$t\text{BuO}_2\text{Ac}$	DCE	80	4	**1** (49.7), **18** (34.8)
8[b]	$t\text{BuO}_2\text{Ac}$	DCE	80	12	**18** (81.2)

[a] The freshly prepared hemigossypol was stored in the refrigerator for two days. [b] The freshly prepared hemigossypol was stored in refrigerator for two weeks.

$t\text{BuO}_2\text{Ac}$ in DCE at 80 °C (see Table 2, Entry 6). The analytical information that was obtained from our synthesized gossypol (**1**) agreed with the reported data.[12g,12h]

Conclusions

We developed a practical route for total synthesis of gossypol. First, hemigossypol, the biosynthetic precursor of gossypol, was synthesized on a gram scale by using a Stobbe condensation, an electrophilic cyclization, and the Michael addition of an *ortho*-quinone methide as key steps. Hemigossypol was further converted into gossypol through a biosynthetic process under nonenzymatic conditions. Of equal importance is that the route allows for the modification of the aldehyde groups to give other functional groups, with the exception of imines, as well as for an investigation of the influence of the various phenoxy groups on the biological activity of the molecule, which heretofore has been scarcely explored. The synthesis of these new gossypol analogues to explore SAR is currently under way in our laboratory.

Experimental Section

General Methods: All anhydrous solvents were dried and purified by standard techniques prior to use. All reagents were purchased from commercial suppliers without further purification. Reactions were monitored by thin layer chromatography with silica plates using UV light as a visualizing agent. Flash column chromatography was carried out with silica gel (200–300 mesh). Chemical shifts (δ) of ^{1}H and ^{13}C NMR spectroscopic data were given in parts per million (ppm) and were recorded downfield from internal tetramethylsilane. High resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T).

2-Hydroxy-6-isopropyl-3-methylbenzaldehyde (4): To a solution of carvacrol (**3**, 30.00 g, 0.20 mol) in anhydrous toluene (200 mL) were added $SnCl_4$ (5.2 g, 0.02 mol) and Et_3N (8.08 g, 0.08 mol) under argon. After the resulting mixture was stirred at room temperature for 20 min, paraformaldehyde (13.19 g, 0.44 mol) was added. The resulting yellowish solution was heated at 100 °C for 8 h. After cooling, the reaction mixture was acidified to pH ≈ 2 by the addition of hydrochloric acid (2 M), and the resulting mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with saturated brine, dried with $MgSO_4$, and concentrated to give the crude salicylaldehyde. The residue was purified by flash chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 200:1 v/v] to give **4** (22.4 g, 62.8%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.42 (s, 1 H), 10.40 (s, 1 H), 7.32 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 3.67–3.56 (m, 1 H), 2.21 (s, 3 H), 1.32 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 161.8, 150.4, 138.3, 124.5, 116.4, 115.6, 27.3, 24.3, 15.0 ppm.

2-(Benzyloxy)-5-bromo-4-isopropyl-3-methoxy-1-methylbenzene (8)

To an ice-cold solution of **4** (20.00 g, 112.2 mmol) in 90% acetic acid (200 mL) was added dropwise bromine (17.93 g, 112.2 mmol) over 15 min. After the resulting mixture was stirred at room temperature for 20 h, it was poured into cold water (300 mL). The mixture was then extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water (3 × 200 mL) and brine, dried with anhydrous $MgSO_4$, and then concentrated under reduced pressure to give crude **5**, which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.57 (s, 1 H), 10.53 (s, 1 H), 7.53 (s, 1 H), 3.95–3.80 (m, 1 H), 2.19 (s, 3 H), 1.47 (d, J = 7.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 162.3, 147.3, 141.8, 127.5, 118.9, 23.6, 19.5, 14.8 ppm.

To a solution of crude **5** in acetone (400 mL) were added K_2CO_3 (23.26 g, 168.3 mmol) and benzyl bromine (13.3 mL, 19.19 g, 112.2 mmol). After the reaction mixture was stirred at 30 °C for 15 h, the acetone was evaporated in vacuo. The residue was dissolved in water (200 mL) and dichloromethane (100 mL), and the resulting mixture was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude **6**, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.48 (s, 1 H), 7.55 (s, 1 H), 7.41–7.35 (m, 5 H), 4.84 (s, 2 H), 3.95–3.80 (m, 1 H), 2.26 (s, 3 H), 1.34 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 194.6, 157.2, 145.0, 139.2, 136.2, 133.1, 131.5, 128.7, 128.5, 128.2, 77.0, 21.2, 15.4 ppm.

To a solution of crude **6** in dichloromethane (500 mL) was added *m*-chloroperoxybenzoic acid (85%, 38.72 g, 190.7 mmol), and the mixture was stirred at room temperature for 6 h. After the mixture was cooled to room temperature, the white insoluble solid was removed by filtration, and a solution of Na_2CO_3 was added to the filtrate to give pH ≈ 8. The organic layer was then separated, washed with brine, and concentrated under reduced pressure. The residue was dissolved in MeOH (300 mL) and H_2O (100 mL), and a solution of NaOH (8.98 g, 224.4 mmol) in H_2O (20 mL) was added. The mixture was heated at reflux for 2 h. After the reaction mixture was cooled, the MeOH was evaporated in vacuo. To the residue was added hydrochloric acid (2 M solution) to give pH ≈ 2, and the mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude **7**, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.38 (s, 5 H), 6.94 (s, 1 H), 5.74 (s, 1 H), 4.85 (s, 1 H), 3.53–3.43 (m, 1 H), 2.27 (s, 3 H), 1.29 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 144.0, 136.5, 131.0, 129.2, 128.9, 128.8, 128.2, 125.5, 119.3, 75.5, 19.9, 15.7 ppm.

To a solution of crude **7** in acetone (400 mL) were added K_2CO_3 (46.52 g, 336.6 mmol) and CH_3I (11.4 mL, 31.85 g, 224.4 mmol). After the reaction mixture was stirred at room temperature for 12 h, the acetone was evaporated in vacuo. The residue was dissolved in water (100 mL) and dichloromethane (200 mL), and the resulting mixture was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 150:1 v/v) to give **8** (24.02 g, 68.8 mmol; 61.3% yield over four steps from **4**) as a white solid; m.p. 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 7.41–7.32 (m, 3 H), 7.11 (s, 1 H), 4.92 (s, 2 H), 3.88 (s, 3 H), 3.58–3.49 (m, 1 H), 2.13 (s, 3 H), 1.36 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.1, 138.5, 137.5, 131.7, 129.8, 128.6, 128.4, 128.2, 118.2, 74.1, 61.0, 21.2, 15.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}BrNaO_2$ $[M + Na]^+$ 371.0617; found 371.0622.

Methyl 6-(Benzyloxy)-8-isopropyl-4,7-dimethoxy-5-methyl-2-naphthoate (12): To a solution of **8** (22.40 g, 64.1 mmol) in anhydrous tetrahydrofuran (400 mL) was added *n*BuLi (2.4 M solution, 28.1 mL, 67.4 mmol) at –78 °C, and the resulting mixture was stirred at this temperature for 0.5 h under argon. To the mixture was added DMF (9.9 mL, 9.38 g, 128.3 mmol). The solution was warmed to –30 °C over the course of 2 h and then stirred at this temperature for 8 h. The reaction was quenched with aqueous ammonium chloride (150 mL). The aqueous phase was separated and then extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude **9**, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.36 (s, 1 H), 7.46–7.43 (m, 3 H), 7.41–7.34 (m, 3 H), 5.04 (s, 2 H), 4.01–3.93 (m, 1 H), 3.87 (s, 3 H), 2.20 (s, 3 H), 1.44 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 155.4, 152.3, 143.1, 137.1, 130.9, 130.6, 128.5, 128.4, 128.4, 128.3, 74.2, 60.8, 25.9, 23.1, 16.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_3$ $[M + H]^+$ 299.1642; found 299.1644.

To a solution of crude **9** and dimethyl succinate (12.29 g, 84.1 mmol) in anhydrous THF (250 mL) was added *t*BuOK (8.71 g, 77.6 mmol), and the resulting mixture was stirred at room temperature for 3 h. Water (200 mL) and diethyl ether (150 mL) were then added. To the organic phase was added hydrochloric acid (2 M solution) to give pH ≈ 2. The aqueous layer was separated and then extracted with ethyl acetate (2 × 150 mL). The combined organic phases were washed with water (200 mL) and brine (200 mL), dried with anhydrous $MgSO_4$, and concentrated in vacuo. To a solution of the crude product in Ac_2O (300 mL) was added NaOAc (7.96 g, 97.0 mmol), and the resulting mixture was heated at reflux for 2 h. After the mixture was cooled to room temperature, water (500 mL) was slowly added at 0 °C. The yellow slurry was filtered, and the filter cake was washed with water to afford crude **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 7.60 (d, J = 1.5 Hz, 1 H), 7.51–7.47 (m, 2 H), 7.44–7.33 (m, 3 H), 4.97 (s, 2 H), 4.07–4.00 (m, 1 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 2.63 (s, 3 H), 2.39 (s, 3 H), 1.54 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 166.7, 152.2, 147.9, 137.2, 136.1, 131.5, 128.6, 128.4, 128.2, 127.7, 126.0, 125.5, 124.1, 118.5, 75.1, 61.3, 52.4, 27.2, 22.5, 21.6, 14.1 ppm.

Crude **11** was dissolved in MeOH (300 mL) and H_2O (100 mL), and then a solution of NaOH (5.17 g, 129.3 mmol) in H_2O was added. The mixture was heated at reflux until the material had disappeared. After cooling the reaction mixture, the MeOH was evaporated in vacuo. To the residue was added hydrochloric acid (2 M solution) to give pH ≈ 2. The resulting mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. To a solution of the crude product in acetone (500 mL) were added K_2CO_3 (35.76 g, 258.7 mmol) and CH_3I (9.8 mL, 27.44 g, 193.3 mmol). After the reaction mixture was stirred at room temperature for 12 h, the acetone was evaporated in vacuo. The residue was dissolved in water (200 mL) and dichloromethane (200 mL), and the resulting mixture was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 50:1 v/v) to give **12** (14.10 g, 34.5 mmol, 53.8% yield over five steps) as a yellow solid; m.p. 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1 H), 7.53 (d, J = 7.2 Hz, 2 H), 7.41 (t, J = 7.2 Hz, 2 H), 7.36 (d, J = 7.2 Hz, 1 H), 7.31 (s, 1 H), 4.95 (s, 2 H), 3.99–3.95 (m, 4 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 2.79 (s, 3 H), 1.54 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 158.6, 151.1, 137.5, 135.1, 131.1, 128.6, 128.4, 128.1, 127.5, 126.9, 126.2, 125.7, 103.3, 74.9, 61.3, 55.5, 52.3, 23.8, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{29}O_5$ $[M + H]^+$ 409.2010; found 409.2010.

4-Isopropyl-3,8-dimethoxy-1,6-dimethylnaphthalen-2-ol (13): To a solution of **12** (20.00 g, 49.0 mmol) in THF (300 mL) was added $LiAlH_4$ (3.72 g, 98.0 mmol). After the reaction mixture was stirred at room temperature for 1 h, hydrochloric acid (2 M solution) was added at 0 °C until the floccule disappeared. The aqueous phase was separated and then extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give the crude product. A mixture of the crude product, hydrochloric acid (12 M solution, 3 mL), and 10% Pd/C (2.0 g) in CH_3OH (400 mL) was stirred under hydrogen (1 atm) at room temperature for 10 h. The solution was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 30:1 v/v] to give **13** (12.27 g, 44.7 mmol, 91.2% yield) as a white solid; m.p. 87–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50

(s, 1 H), 6.60 (s, 1 H), 5.94 (s, 1 H), 3.92–3.84 (m, 4 H), 3.81 (s, 3 H), 2.74 (s, 3 H), 2.45 (s, 3 H), 1.54 (d, J = 7.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 145.4, 144.7, 132.0, 131.0, 129.5, 122.6, 117.4, 116.3, 107.3, 62.0, 55.4, 26.7, 22.4, 22.3, 14.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{23}O_3$ $[M + H]^+$ 275.1642; found 275.1645.

1-Isopropyl-2,3,5-trimethoxy-4-(methoxymethyl)-7-methylnaphthalene (15): To a mixture of CH_3ONa (1.42 g, 26.24 mmol) and Ag_2O (3.04 g, 13.12 mmol) in CH_3OH (150 mL) was slowly added **13** (2.40 g, 8.75 mmol) in CH_3OH (50 mL) through a constant pressure funnel. After the reaction mixture was stirred at room temperature for 3 h, the solution was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in acetone (150 mL), and CH_3I (2.22 mL, 6.21 g, 43.74 mmol) was added. The solution was stirred at room temperature for 5 h, and then the acetone was evaporated in vacuo. The residue was dissolved in water (100 mL) and dichloromethane (100 mL), and the resulting mixture was extracted with dichloromethane (2× 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 30:1, v/v] to give **15** (2.31 g, 7.25 mmol, 82.8% yield) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 6.68 (s, 1 H), 5.08 (s, 2 H), 3.98–3.90 (m, 10 H), 3.50 (s, 3 H), 2.48 (s, 3 H), 1.49 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 151.8, 135.9, 133.9, 132.2, 124.3, 120.8, 107.9, 66.9, 61.6, 60.9, 58.3, 56.0, 22.3, 22.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}O_4Na$ $[M + Na]^+$ 341.1723; found 341.1724.

Byproduct 13i: Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (s, 1 H), 6.77 (s, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.41–3.32 (m, 1 H), 2.95 (s, 3 H), 2.39 (s, 3 H), 1.41–1.34 (m, 6 H) ppm.

Byproduct 14-D–A: Yellow solid; m.p. 159–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 7.08 (s, 1 H), 6.76 (s, 1 H), 6.57 (s, 1 H), 4.01–3.89 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 2 H), 3.77–3.73 (m, 1 H), 3.65 (s, 3 H), 3.36–3.25 (m, 1 H), 3.04–2.93 (m, 1 H), 2.57–2.47 (m, 2 H), 2.45 (s, 3 H), 2.38 (s, 3 H), 3.13–2.07 (m, 1 H), 1.50 (d, J = 7.1 Hz, 6 H), 1.44 (d, J = 6.9 Hz, 3 H), 1.38 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 158.5, 157.7, 147.4, 146.7, 144.0, 138.8, 131.9, 129.4, 125.1, 120.6, 119.0, 115.0, 113.4, 107.1, 81.6, 60.9, 58.9, 56.8, 55.4, 28.2, 27.5, 22.7, 22.3, 22.2, 21.8, 21.1, 21.0, 20.3 ppm. HRMS (ESI): calcd. for $C_{34}H_{40}O_6$ $[M + H]^+$ 545.2898; found 545.2898.

(4-Isopropyl-2,3,8-trimethoxy-6-methylnaphthalen-1-yl)methanol (16): To a solution of **15** (2.20 g, 6.91 mmol) in CH_2Cl_2 (250 mL) was added CF_3COOH (5.3 mL, 7.88 g, 69.09 mmol) with stirring. After the reaction mixture was stirred at room temperature for 0.5 h, aqueous sodium hydrogen carbonate (150 mL) was added, and the mixture was stirred at room temperature for 20 min. The aqueous layer was separated and then extracted with CH_2Cl_2 (2× 100 mL). The combined organic phases were washed with water (200 mL) and brine (200 mL) and then concentrated in vacuo. The residue was dissolved in THF (180 mL) and H_2O (60 mL), and a solution of $LiOH·H_2O$ (2.90 g, 69.09 mmol) in H_2O was added. The mixture was stirred at room temperature for 1 h, and then the THF was evaporated in vacuo. To the residue was added hydrochloric acid (2 M solution) to give pH ≈ 2, and the resulting mixture was extracted with CH_2Cl_2 (2× 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 10:1 then 5:1 v/v] to give **16** (1.90 g, 6.24 mmol, 90.3% yield) as a light yellow solid; m.p. 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1 H), 6.72 (s, 1 H), 5.12 (d, J = 7.6 Hz, 2 H), 4.02 (s, 3 H), 3.91 (s, 7 H), 3.24 (t, J = 7.6 Hz, 1 H), 2.49 (s, 3 H), 1.49 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 150.9, 135.4, 134.0, 132.3, 127.2, 120.5, 117.5, 107.6, 77.4, 77.1, 76.8, 61.9, 60.9, 57.7, 56.0, 29.7, 22.3, 22.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_4Na$ $[M + Na]^+$ 327.1567; found 327.1569.

4-Isopropyl-2,3,8-trimethoxy-6-methyl-1-naphthaldehyde (17): To a solution of **16** (1.90 g, 6.24 mmol) in DMSO (150 mL) was added *o*-iodoxybenzoic acid (5.24 g, 18.72 mmol). After the reaction mixture was stirred at room temperature for 12 h, water (400 mL) was added, and the resulting mixture was extracted with ethyl acetate (2× 150 mL). The combined organic layers were washed with water (3× 200 mL) and brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 30:1 v/v) to give **17** (1.85 g, 6.12 mmol, 98.0% yield) as a white solid; m.p. 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.65 (s, 1 H), 7.54 (s, 1 H), 6.64 (s, 1 H), 4.01–3.79 (m, 10 H), 2.49 (s, 3 H), 1.49 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 154.3, 148.0, 136.7, 134.2, 130.1, 126.7, 117.8, 115.5, 106.1, 61.2, 59.9, 54.8, 28.7, 21.5, 21.0 ppm.

Hemigossypol (2) and Anhydrohemigossypol (18): To a solution of **17** (1.80 g, 5.95 mmol) in CH_2Cl_2 (100 mL) was added BBr_3 (1.0 M solution, 50 mL, 50 mmol) at –78 °C. The resulting mixture was stirred under argon at this temperature for 1 h, at –40 °C for 1 h, and then at –10 °C for 4 h. The reaction mixture was added to a solution of NaOH (10 g) in H_2O (40 mL), and then it was acidified with hydrochloric acid (2 M solution, 120 mL). The resulting mixture was extracted with Et_2O (80 mL). The aqueous layer was further extracted with Et_2O (2× 80 mL), and the combined organic extracts were washed with H_2O (150 mL) and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl acetate, 15:1, 5:1 v/v) to give hemigossypol (**2**, 1.00 g, 3.85 mmol, 64.6% yield) as a bright yellow solid and **18** (0.12 g, 0.50 mmol, 8.3% yield) as a yellow solid. Data for **2**: M.p. 151–153 °C; ref.[21] m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.15 (s, 1 H), 11.21 (s, 1 H), 7.55 (s, 1 H), 6.70 (s, 1 H), 6.34 (s, 1 H), 5.45 (s, 1 H), 3.91–3.79 (m, 1 H), 2.45 (s, 3 H), 1.50 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.60, 155.68, 151.84, 142.81, 134.44, 134.02, 129.52, 116.86, 114.47, 113.31, 111.68, 27.95, 21.57, 20.20 ppm. Data for **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 7.52 (s, 1 H), 7.33 (s, 1 H), 7.30 (s, 1 H), 3.59–3.48 (m, 1 H), 2.58 (s, 3 H), 1.48 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 153.1, 149.6, 149.6, 137.3, 130.5, 126.1, 122.5, 118.8, 116.5, 111.3, 27.0, 22.5, 20.4 ppm.

The anhydrohemigossypol (**18**) was dissolved in CH_3CN (9 mL) and H_2O (3 mL), and hydrochloric acid (12 M solution, 0.10 mL) was added. The mixture was stirred at room temperature for 5 h, and then the CH_3CN was evaporated in vacuo. To the residue were added H_2O (10 mL) and Et_2O (20 mL), and the resulting mixture was extracted with Et_2O (2× 20 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give hemigossypol (**2**, >99.0% yield).

Gossypol (1): To a solution of **2** (0.100 g, 0.384 mmol) in anhydrous 1,2-dichloroethane (40 mL) was added $tBuO_2Ac$ (0.223 g, 0.85 mmol), and the resulting mixture was stirred at 80 °C under argon until the hemigessypol was consumed. Then, the DCE was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel [petroleum ether (60–90 °C)/ethyl

acetate, 10:1, 5:1 v/v] to give gossypol (**1**, 0.076 g, 0.146 mmol, 76.1% yield) as a yellow solid, m.p. 184–186 °C; ref.[12g,12h] m.p. 186.1–186.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.18 (s, 2 H), 11.14 (s, 2 H), 7.79 (s, 2 H), 6.42 (s, 2 H), 5.79 (s, 2 H), 4.01–3.84 (m, 2 H), 2.16 (s, 6 H), 1.56 (d, J = 5.7 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 156.1, 150.4, 143.5, 134.1, 133.7, 129.7, 118.2, 115.8, 114.6, 111.8, 77.3, 77.0, 76.7, 27.8, 20.3, 20.2 ppm.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**–**18** and byproduct **14**-D–A.

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