°C (colorless prism); ^{1}H NMR (CCl_4) δ 0.72 (d, J = 7.5 Hz, 3), 0.93 (t, J = 7 Hz, 3), 1.3–1.8 (m, 2), 2.05 (d, J = 7.5 Hz, 3), 2.38 (qdd, J = 7.5, 5, and 10 Hz, 1 H at C-5), 2.5–2.9 (m, 1), 2.99 (dd, J = 1.5 and 10 Hz, 1 H at C-6), 3.1–3.7 (m, 1), 4.16 (qd, J = 7.5 and 1.5 Hz, 1), 4.51 (d, J = 5 Hz, 1 H at C-4), 7.2–7.5 (m, 5); $^3J_{H^4-H^5}$ = 5 Hz and $^3J_{H^5-H^6}$ = 10 Hz indicate the cis,trans form (cf. Table IV); MS, m/e (M$^+$) 387. The stereochemistry of **11f** was not able to be determined by the iodolactonization.

6-(α-Iodoethyl)-3-isopropyl-5-methyl-4-propylperhydro-1,3-oxazin-2-one was produced in 70% yield; ^{1}H (400 MHz, $CDCl_3$) δ 0.964 (t, J = 7.019 Hz, 3), 0.984 (d, J = 6.714 Hz, 3), 1.264 (d, J = 6.714 Hz, 3), 1.309 (d, J = 6.713 Hz, 3), 1.2–1.7 (m, 4), 2.073 (d, J = 7.019 Hz, 3), 3.07–3.13 (m, 3), 4.013 (sp, J = 6.714 Hz, 1), 4.264 (q, J = 7.019 Hz, 1); MS, m/e (M$^+$) 353.

The dehydroiodination produced **6-ethylidene-3-isopropyl-5-methyl-4-propylperhydro-1,3-oxazin-2-one** in 75% yield: ^{1}H NMR (CCl_4) δ 0.92 (br, 3), 1.09 (d, J = 7 Hz, 3), 1,26 (d, J = 7.5 Hz, 3), 1.29 (d, J = 7.5 Hz, 3), 1.1–1.5 (m, 4), 1.66 (dd, J = 2.0 and 7.5 Hz, 3), 2.4–2.7 (m, 1), 3.0–3.2 (m, 1), 3.82 (sp, J = 7.5 Hz, 1), 4.46 (qd, J = 7.5 and 2.0 Hz, 1 H at the sp^2 carbon); the long-range coupling constant (J = 2 Hz) indicates the cis geometry (cf. Table V); MS, m/e (M$^+$) 225. The stereochemistry of **11g** was determined by the iodolactonization.

6-(α-Iodoethyl)-4-isopropyl-5-methyl-3-propylperhydro-1,3-oxazin-2-one was produced in 65% yield: mp 68.5–6.95 °C (colorless plate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.932 (t, J = 7.325 Hz, 3), 0.960 (d, J = 7.019 Hz, 3), 1.000 (d, J = 7.019 Hz, 3), 1.104 (d, J = 7.104 Hz, 3), 1.6–1.7 (m, 2), 1.9–2.1 (m, 1), 2.069 (d, J = 7.019 Hz, 3), 2.17–2.25 (, 1), 2.688 (m, 1), 3.053 (t, J = 4.273 Hz, 1), 3.022 (dd, J = 6.304 and 7.524 Hz, 1 H at C-4), 3.0921 (dd, J = 1.526 and 10.681 Hz, 1 H at C-6), 4.253 (qd, J = 7.019 and 1.526 Hz, 1); $^3J_{H^5-H^6}$ = 10.681 and $^3J_{H^4-H^5}$ = 6.304 or 7.524 indicate the cis,trans isomer; MS, m/e (M$^+$) 353. Consequently, the structure of the minor isomer **12g** was determined to be threo.

Supplementary Material Available: Spectroscopic data for **13**, **14**, **15**, **16**, **17**, **18**, and **19** (8 pages). Ordering information is given on any current masthead page.

A Regioselective Route to Gossypol Analogues: The Synthesis of Gossypol and 5,5′-Didesisopropyl-5,5′-diethylgossypol

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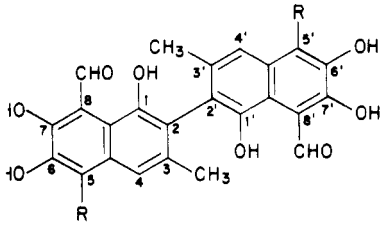
The synthesis of 5,5′-diethyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-[2,2′-binaphthalene]-8,8′-dicarboxaldehyde is described. The synthetic route developed utilizes the regioselective bisformylation of a precursor obtained from gossypol. The route provides access to 5,5′-disubstituted gossypol analogues as well as completing a total synthesis of gossypol itself.

The search for a male antifertility agent has been hampered by the absence of a lead compound. Consequently, the 1978 Chinese report[1] that the cotton seed pigment gossypol (1) was an effective male antifertility agent



1, R = CH(CH$_3$)$_2$
2, R = CH$_2$CH$_3$

spawned enormous interest. We initiated a program designed to explore the molecular determinants of biological activity of gossypol. In the course of these studies we learned that minor molecular manipulation of the phenolic and aldehydic groups led to substantial loss of in vivo activity. However, the role of the isopropyl moieties in biological activity was unexplored. Herein we describe a synthesis of the diethyl analogue of gossypol, 5,5′-didesisopropyl-5,5′-diethylgossypol (2).

The structure of gossypol had been formulated by Adams et al.[6] as early as 1938. The first conclusive proof by total synthesis was presented 20 years later by Edwards.[2] Venuti,[3] in 1981, published a synthesis of a precursor to gossypol and relied on the earlier work for formal completion of his synthesis. In none of the above reports, however, were details of the introduction of the 8,8′-formyl groups presented. We now also describe a means of obtaining gossypol from apogossypol (3).

The synthetic route reported here is expected to be of general applicability in regard to the introduction of functionality in the 5,5′-positions.

We chose to approach the synthesis of 5,5′-didesisopropyl-5,5′-diethylgossypol (2) by manipulation of a biphenyl precursor available from gossypol itself (Scheme I). Thus gossypol[4] (1) was treated with base to provide apogossypol (3), which was readily methylated to furnish the hexamethyl ether 4.[5-8] Didesisopropylapogossypol hexamethyl ether 5 was subsequently obtained on acid treatment of 4.[9] The known compounds 4 and 5 served as starting materials for our synthesis.

It was necessary to introduce the ethyl group in the

(1) National Coordinating Group on Male Antifertility Agents, *Chin. Med. J. (Beijing, Engl. Ed.)* **1978**, *4*, 417. For a recent review, see: Qian, S.-Z.; Wang, Z.-G. *Ann. Rev. Pharmacol. Toxicol.* **1984**, *24*, 329.
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(11) Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* **1962**, *95*, 308.
(12) O'Connor, R. T.; Von der Haar, P.; DuPre, E. F.; Brown, L. E.; Pominski, C. H. *J. Am. Chem. Soc.* **1953**, *76*, 2368.

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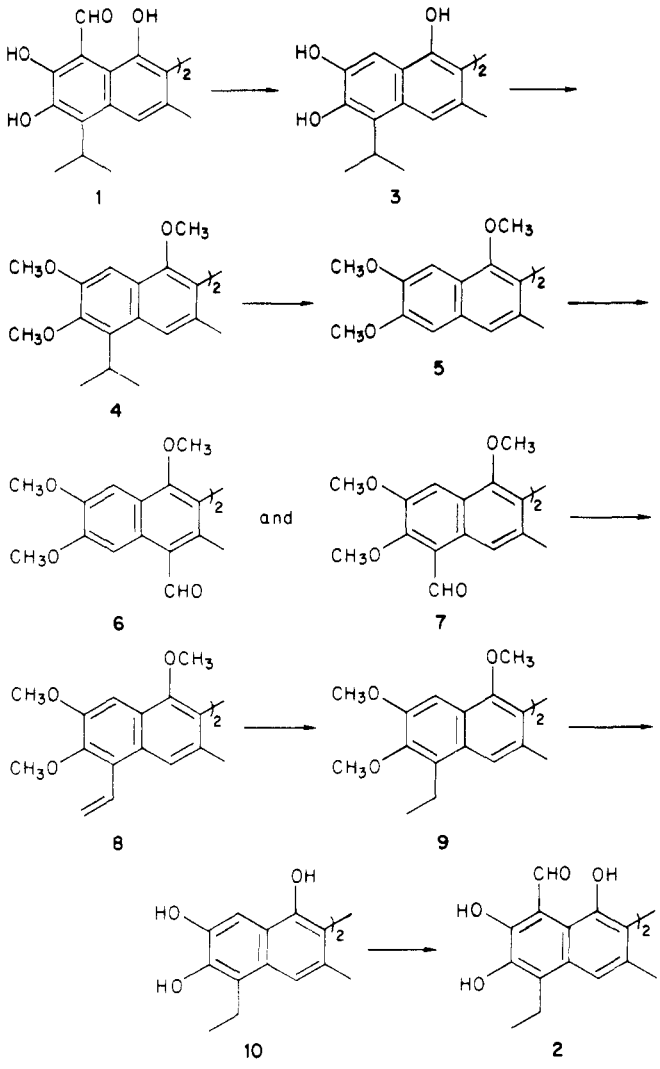
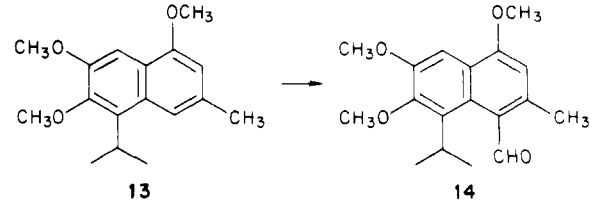
Scheme I



5,5′-positions, and we elected to do this via a regiospecific formylation. This formylation was complicated by the presence of a binaphthyl system and the requirement that the reaction take place symmetrically. A variety of conditions were examined, and it was discovered that a careful control was required to avoid erratic functionalization.

Formylation of **5** with titanium tetrachloride and dichloromethyl methyl ether provided a mixture of two dialdehydes **6** and **7** with the latter as major product. On the other hand, treatment of **5** under Vilsmeier–Haack conditions provided only a single dialdehyde, **6** (74%). In the presence of an isopropyl group a surprising selectivity was discovered. Bisformylation and concomitant loss of both isopropyl groups occurred on reaction of **4** with titanium tetrachloride and dichloromethyl methyl ether to yield **7** (70%). The reasons for this reaction are, as yet, unclear. This result is particularly surprising in view of the fact that identical treatment of the monomeric compound **13** gave **14** in quantitative yield.[13] Thus, the aldehydes **6** and **7** could both be obtained in good yield with complete regiospecificity.

The regiospecificity obtained was established unequivocally by an examination of the nuclear magnetic resonance spectra of these two compounds. The possibility of an 8,8′-bisformylated product was immediately excluded. The aromatic resonances for the dialdehydes obtained appear at δ 7.4–7.8 (1 H) and 8.8 (1 H), while the starting material **5** displays no resonances downfield of δ 7.42. A downfield shift of 1.4 ppm to δ 8.8 is significantly greater than that expected on electronic grounds (ca. 0.3 ppm)[10] and consequently such a shift can only result from the deshielding effect of a peri-carbonyl function such as in **6** or **7**.



Both **6** and **7** were expected to display a relatively upfield resonance for H-8 and a strongly deshielded resonance for the remaining peri proton at H-5 or H-4 in their respective NMR spectra. The spectrum measured for compound **6** showed sharp aromatic resonances at δ 7.48 and 8.79 and a sharp aromatic methyl resonance at δ 2.52. In contrast, the spectrum measured for **7** showed a sharp resonance at δ 7.77 and a slightly broader resonance at δ 8.87. The aromatic methyl resonance at δ 2.20 was also broader than that displayed for compound **6**. Furthermore, the aromatic resonances for **7** were consistently downfield of those for **6**. We ascribed the broad resonances seen in **7** for both the methyl and one aromatic proton to a coupling between them. Furthermore, the relatively downfield position of the H-8 resonance (δ 7.77) is consistent with a proton in the para aldehyde position as in **7**. In order to confirm these assignments, nuclear Overhauser difference spectra were measured. A clear NOE of H-4 was seen upon irradiation of the 3-CH_3 in **7** while similar irradiation of the 3-CH_3 group in **6** displayed a marked NOE enhancement of the aldehyde resonance at δ 10.93. The identity of each of these compounds was thus unequivocally established. The further elaboration of compound **6** will be presented elsewhere.

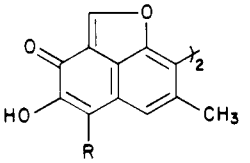
Wittig reaction of the dialdehyde **7** with methylenetriphenylphosphorane provided the divinyl compound **8** in 87% yield, which was then catalytically hydrogenated to yield the diethyl compound **9** in 96% yield. Deprotection and subsequent formylation of **9** was not straightforward. Initial attempts at formylation of **9** under a variety of conditions (Vilsmeier–Haack; *N,N*-diphenylformamidine) failed, as did formylation attempts on **10**, obtained upon removal of the methyl protecting groups from **9** with boron tribromide in chloroform. We reasoned that the coordinating ability of an ortho-hydroxyl group, such as in **3** or **10**, might facilitate delivery of a judiciously chosen formylating agent to the desired 8,8′-positions. Indeed, Gross et al.[11] had studied formylation of aromatic phenols, and they reported a preponderance of the ortho-formylated product when 2-naphthol was treated with dichloromethyl methyl ether and titanium tetrachloride.

Consequently, when **9** was first deprotected with boron tribromide and then subjected to these formylating conditions, the target compound 5,5′-didesisopropyl-5,5′-diethylgossypol (**2**) was obtained. Evidence suggests that the gossypol analogue **2** is moderately unstable, and consequently, although a reasonable crude yield was obtained for the two steps, purification resulted in an isolated analytically pure final product **2** in only 5% yield from **9**. Similar treatment of apogossypol (**3**) with titanium tetrachloride and dichloromethyl methyl ether provided gossypol (**1**). In contrast, although the Edwards procedure,[2] which utilizes *N,N*-diphenylformamidine, was successful in our hands when applied to apogossypol, it failed

(13) Manmade, A.; Herlihy, P.; Quick, J.; Duffley, R. P.; Burgos, M.; Hoffer, A. P. *Experientia* **1983**, *39*, 1276.

completely to effect formylation of the ethyl analogue **10**.

The regiospecificity of the formylation of both **3** and **10** was once more confirmed by an examination of the MS, IR, and NMR spectra. Thus, the product obtained from **3** was identical with authentic gossypol in all respects including thin-layer chromatographic and mixed melting point behavior. The mass spectra of both gossypol and the analogue **2** are particularly interesting. The base peak evident upon electron impact for both compounds **1** and **2** results from the anhydro form of each, **11** (*m/e* 482, 100%) and **12** (*m/e* 454, 100%), respectively.



11, R = $CH(CH_3)_2$
12, R = CH_2CH_3

Accurate mass determinations were carried out on these anhydro compounds since neither **1** nor **2** was evident in the mass spectra at all. It should be noted that the presence of the anhydro form of **2** is, in itself, clear evidence of regiospecific bisformylation in the 8,8′-positions.

The structure of the ethyl analogue **2** is further confirmed by the infrared spectrum. Thus, the carbonyl stretching frequency reflects intramolecular hydrogen bonding and appears at 1610 cm^{-1}. The comparable band for gossypol[12] appears at 1615 cm^{-1}, while, in the absence of the hydrogen bond, this aldehyde absorption appears at 1680 cm^{-1} (see, for example, **7**). A hydrogen-bonded hydroxyl stretching frequency is visible at 3470 cm^{-1}. In the NMR spectrum of **2**, the aromatic proton resonance appears at δ 7.55 and is broad, thus reflecting coupling to the 3,3′-methyl groups. The analogous broad resonance (H-4) in gossypol appears at δ 7.70; this downfield shift is a consequence of the increased steric compression which results from the more bulky isopropyl group in **1**. These data lead to an unequivocal assignment of regiochemistry for compound **2**.

In vivo antifertility activity of **2** is currently under investigation. The in vitro spermicidal activity of **2** appears equivalent to that of gossypol.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary or Fisher-Johns melting point apparatus and are uncorrected. Routine NMR spectra were recorded on a Varian T-60 spectrometer. An FT-80A Varian spectrometer was used for NOE experiments. Spectra are expressed in parts per million from Me_4Si as internal standard. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. Satisfactory microanalyses (within experimental error) were performed by Atlantic Microlab, Inc. High-pressure liquid chromatographic separations were performed on a Waters Associates Prep LC/System 500 (Prep Pak-500/silica column). Precoated TLC plates (silica gel 60F EM Reagent) were used for thin-layer chromatographic analyses and were visualized under ultraviolet light or exposure to I_2. Mass spectra were measured at Cornell University. Organic extracts were dried over anhydrous sodium sulfate. Flash chromatography was carried out over silica gel 60 (230–400 mesh).

5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-2,2′-binaphthalene (4). Gossypol acetic acid[4] (**1**) (36.0 g, 0.06 mol) was heated in 40% aqueous sodium hydroxide (225 mL) at 85 °C under a nitrogen atmosphere for 1.75 h. The reaction mixture was poured onto ice containing concentrated sulfuric acid. The resultant precipitate was extracted with ether, and the combined extracts were washed with water, dried, and concentrated in vacuo to yield crude apogossypol (**3**), which was immediately dissolved in acetone (1.5 L). Potassium carbonate (powdered and dried; 106 g, 0.76 mol) was added to the acetone solution, and dimethyl sulfate (96 g, 0.76 mol) was then added dropwise. The reaction mixture, protected by a nitrogen atmosphere, was stirred under reflux for 12 h and then cooled to 22 °C. Solids were removed by filtration, and the cake was washed with chloroform. The combined organic extracts were evaporated in vacuo to provide the crude product to which ether was added. The resultant yellow solid was collected by filtration, washed with ether, and dried to yield **4** (27.6 g, 81%): mp 273–274 °C; NMR ($CDCl_3$) δ 2.17 (s, 6 H, Ar CH_3), 3.57 (s, 6 H, 1,1′-OCH_3), 4.00 (s, 12 H, OCH_3), 7.10 (s, 2 H, Ar H), 7.42 (s, 4 H, Ar H). Anal. ($C_{34}H_{42}O_6$) C, H.

1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-[2,2′-binaphthalene]-5,5′-dicarboxaldehyde (7). Titanium tetrachloride (73.68 g, 0.388 mol) was added dropwise over 20 min to a cooled (ice/water bath) solution of **4** (8.32 g, 0.015 mol) in dry methylene chloride (molecular sieves, 200 mL). After addition was completed, the deep purple reaction mixture was stirred an additional 15 min at 0 °C.

Dichloromethyl methyl ether (14.9 g, 0.13 mol) was added dropwise over 20 min, and the reaction mixture was stirred at ambient temperature under nitrogen for 12 h. The reaction mixture was poured onto ice, and the layers were separated. The aqueous phase was extracted twice with methylene chloride, and the combined organic fractions were washed consecutively with water and brine, dried, and concentrated to provide a brown foam. Purification by HPLC (silica gel; 3% acetonitrile in dichloroethane) followed by trituration of the crude products with ether yielded **7** as a yellow solid (5.6 g, 70%): mp 225–226.5 °C; NMR ($CDCl_3$) δ 2.20 (s, 6 H, Ar CH_3), 3.50 (s, 6 H, 1,1′-OCH_3), 4.00 and 4.05 (s, 12 H, OCH_3), 7.77 (s, 2 H, H-8), 8.87 (br s, 2 H, H-4), 10.77 (s, 2 H, CHO); IR (Nujol) 1680 (C=O) cm^{-1}. Anal. ($C_{30}H_{30}O_8 \cdot 0.5H_2O$) C, H.

1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-5,5′-divinyl-2,2′-binaphthalene (8). Tetrahydrofuran (HPLC grade; 800 mL) was added to a mixture of methyltriphenylphosphonium bromide (93.7 g, 0.26 mol) and potassium *tert*-butoxide (29.4 g, 0.26 mol), and the resultant yellow mixture was stirred at ambient temperature under a nitrogen atmosphere for 45 min. The mixture was cooled in an ice bath, and a solution of **7** (13.6 g, 0.26 mol) in tetrahydrofuran (300 mL) was added, over 75 min, dropwise. The reaction mixture was stirred overnight at ambient temperature, cooled in an ice bath, and quenched by the addition of 20% ammonium chloride (200 mL) followed by water. Chloroform was added, the layers were separated, and the aqueous phase was extracted twice with chloroform. The combined organic fractions were washed with brine and water, dried, and concentrated to provide a solid. Purification by HPLC (silica gel; 3% acetonitrile in dichloroethane) followed by trituration of the product with ether yielded **8** as a white solid (11.8 g, 87%): mp 175–176 °C; NMR ($CDCl_3$) δ 2.18 (s, 6 H, Ar CH_3), 3.60 (s, 6 H, 1,1′-OCH_3), 3.90 and 4.00 (s, 12 H, OCH_3), 5.67–6.03 (m, 4 H, CH=CH_2), 6.93–7.40 (m, 2 H, CH=CH_2), 7.53 (s, 2 H, H-8), 7.87 (br s, 2 H, H-4); IR (Nujol) 1580 cm^{-1}. Anal. ($C_{32}H_{34}O_6$) C, H.

5,5′-Diethyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-2,2′-binaphthalene (9). The divinyl compound **8** (10.6 g, 0.02 mol) was dissolved in ethyl acetate (115 mL) with heating and diluted with glacial acetic acid (115 mL). Palladium on charcoal catalyst (10%, 1.06 g) was added and Parr hydrogenation commenced at an initial pressure of 49 psi. After 15 min the catalyst was removed by filtration through a Celite pad and washed with chloroform. Removal of the solvent, followed by recrystallization of the residue from ether/hexane gave **9** (10.3 g, 96%): mp 186–187 °C; NMR ($CDCl_3$) δ 1.33 (t, 6 H, CH_2CH_3, J = 7 Hz), 2.17 (s, 6 H, Ar CH_3), 3.13 (q, 4 H, CH_2CH_3, J = 7 Hz), 3.53 (s, 6 H, 1,1′-OCH_3), 3.90 and 3.93 (s, 12 H, OCH_3), 7.35 (s, 2 H, H-8), 7.58 (s, 2 H, H-4); IR (Nujol) 1440 cm^{-1}. Anal. ($C_{32}H_{38}O_6$) C, H.

5,5′-Diethyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-2,2′-binaphthalene (10). A solution of the ethyl derivative **9** (10.2 g, 0.02 mol) in chloroform (100 mL) was added to a solution of boron tribromide (59.1 g, 0.236 mol) in chloroform (300 mL) at 0 °C. The reaction mixture was then stirred under a nitrogen atmosphere, at ambient temperature, for 1 h, and poured onto ice containing sufficient 50% sodium hydroxide to attain pH 10.

Addition of concentrated sulfuric acid provided a precipitate, which was extracted into ether. The combined organic extracts

were washed with water and brine, dried, and concentrated in vacuo to obtain **10** as a brown solid (10.3 g). This product was not further purified but used directly in the next reaction.

5,5′-Diethyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-[2,2′-binaphthalene]-8,8′-dicarboxaldehyde (2). The ethyl compound **10** (ca. 10 g), obtained from the previous reaction, was dissolved in dry ether (200 mL) and diluted with dry methylene chloride (molecular sieves, 700 mL). Titanium tetrachloride (76 g, 0.4 mol) was added dropwise to the cooled (ice/water bath) stirred solution. After 15 min at 0 °C, dichloromethyl methyl ether (25.3 g, 0.22 mol) was added dropwise. The reaction mixture was stirred at ambient temperature under nitrogen for 12 h and then poured onto a mixture of ice and ether. The solids were removed by filtration through Celite, and the filtrate was separated into organic and aqueous phases. The aqueous phase was extracted with ether, and the combined organic extracts were washed consecutively with water and brine, dried, and concentrated in vacuo to provide crude **2** (5.6 g; TLC shows the presence of other components).

Purification was effected by two consecutive flash chromatographic separations (silica gel; 5% methanol in chloroform) and final filtration of a chloroform solution through a silica gel pad. Solid product was obtained by repeated dissolution of the residue in benzene and then precipitation of material by addition of hexane. The process was repeated with ether as solvent and petroleum ether as precipitant. The filtered material was dried in vacuo to give **2** as a yellow, analytically pure, solid (515 mg, 5% from **9**): mp 208–210 °C; NMR (acetone-d_6) δ 1.30 (t, 6 H, CH_2CH_3, J = 7 Hz), 2.10 (s, 6 H, Ar CH_3), 3.17 (q, 4 H, CH_2CH_3, J = 7 Hz), 7.55 (br s, 2 H, H-4), 11.25 (s, 2 H, CHO); IR (Nujol) 3470, 1610 cm^{-1}; MS, m/z (relative intensity) 454 (100); accurate mass determination, calcd for $C_{28}H_{22}O_6$ (anhydro form) 454.1416, found 454.1418. Anal. ($C_{28}H_{26}O_8$) C, H.

5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-2,2′-binaphthalene (3). By application of the procedure used for **10**, compound **4** (2.0 g, 3.6 mmol) gave **3** as a dark brown foam. This was used crude for the formylation step.

5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-[2,2′-binaphthalene]-8,8′-dicarboxaldehyde (1) (Gossypol). Method A. The crude foam **3** (3.6 mmol, assumed 100% yield from previous step) was heated together with dry *N*,*N*-diphenylformamidine (6.17 g, 0.032 mol) in the presence of a few milligrams of hydroquinone at 180 °C under vacuum (9–15 torr) for 2.5 h and then left at ambient temperature overnight. The crude product was taken up in chloroform and passed over a silica gel pad. Chloroform was removed, and the residue (1.47 g) was heated at 100 °C in concentrated sulfuric acid (10 mL) for 2 min. The resultant cherry red solution was then stirred at ambient temperature for 0.5 h. Ice, water, and ether were added, and the mixture was filtered to remove solids. The layers were separated, and the aqueous phase was extracted three times more with ether. The combined ethereal fractions were washed with water and brine, dried, and concentrated to provide crude **1** (1.37 g, 72%). The product was dissolved in ether and passed through a short filtration column of silica gel, eluted with ether, and concentrated to a red solid. The crude material was then dissolved in ether (7 mL) and glacial acetic acid (5 mL) and allowed to stand overnight to yield **1** as the yellow acetic acid complex (712 mg, 37%); mp 173–174 °C, mmp 172.5–174 °C; MS, m/z (relative intensity) 482 (100).

Method B. Crude **3** (1.0 g, 1.73 mmol, assumed 100% yield from **4**) was dissolved in dry ether (8 mL) and diluted with dry (sieves) methylene chloride (50 mL). Titanium tetrachloride (3.3 g, 17 mmol) was added to the cooled (ice/water bath) solution. After stirring for 15 min, dichloromethyl methyl ether (2.2 g, 19 mmol) was added dropwise over 20 min. The mixture was stirred at ambient temperature and under a nitrogen atmosphere overnight. The reaction mixture was cooled in an ice bath and quenched by addition of 5% hydrochloric acid. The solids formed were removed by filtration and washed with ether. The combined organic fractions were washed with water and brine, dried, and concentrated to provide **1** as a dark gum (1.1 g). A portion (700 mg) of crude **1** was dissolved in benzene (10 mL), and to this was added dimethylethylene diamine (0.56 g, 6.3 mmol) and a few milligrams of potassium carbonate. After being stirred for 10 min, the crude product was passed through a silica pad, washed with petroleum ether, concentrated, and purified by flash column chromatography (silica gel, 20% methanol in chloroform). The purified residue was stirred overnight in an ether/chloroform/4 N hydrochloric acid (0.5:0.5:1) solution. The layers were separated, and the aqueous phase was extracted with chloroform. The combined organic fractions were washed with water and brine, dried, passed through a short silica gel pad to remove polar materials, and concentrated in vacuo to yield a yellow film. This was dissolved in ether (4 mL) and glacial acetic acid (3 mL) and kept at ambient temperature overnight. The yellow solid which precipitated was identical by mp, MS, NMR, IR, and TLC with the product obtained by method A and to the authentic gossypol acetic acid complex.[4]

1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-2,2′-binaphthalene (5). Solid **4** (1.8 g, 3.29 mmol) was added in small portions and with vigorous stirring to concentrated sulfuric acid (36 mL). After the addition was complete, the deep red mixture was stirred an additional 0.5 h at room temperature. The reaction mixture was poured onto a mixture of ice and water. Chloroform and methanol were added to dissolve the resultant precipitate, and the organic phase was washed consecutively with water, dilute ammonium hydroxide, and brine, dried, and concentrated to 0.7 g. Purification by flash chromatography (silica gel; 10% acetonitrile in dichloroethane) followed by recrystallization from benzene/methanol yielded **5** (1.06 g, 68%) as a white solid: mp >250 °C; NMR ($CDCl_3$) δ 2.17 (s, 6 H, Ar CH_3), 3.57 (s, 6 H, OCH_3), 4.00 (s, 12 H, OCH_3), 7.10 (s, 2 H, H-5), 7.42 (s, 4 H, H-4 and H-8). Anal. ($C_{28}H_{30}O_6$) C, H.

1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-[2,2′-binaphthalene]-4,4′-dicarboxaldehyde (6). A mixture of phosphorous oxychloride (10.63 g, 0.07 mol) and *N*-methylformanilide (9.38 g, 0.07 mol) was stirred at room temperature for 0.75 h during which time the solution changed from clear to yellow and finally to a yellow solid. Solid **5** (4.01 g, 8.5 mmol) was added, and the reaction mixture was heated to 95–105 °C for 1 h. The reaction mixture was poured onto an iced sodium acetate solution and then extracted with chloroform. The organic fractions were washed consecutively with 4 N hydrochloric acid, water, and brine, dried, and concentrated to 9.1 g. This was combined with material from another batch to make a total of 27.6 g crude product. Purification of the combined batch was effected by first passing the crude product through a silica gel pad followed by HPLC (silica gel, 10% acetonitrile in dichloroethane) and finally recrystallization from chloroform/methanol to obtain **6** as a tan solid (10.3 g, 74%): mp 251–253 °C; NMR ($CDCl_3$) δ 2.52 (s, 6 H, Ar CH_3), 3.58 (s, 6 H, OCH_3), 4.02 (s, 6 H, OCH_3), 4.10 (s, 6 H, OCH_3), 7.48 (s, 2 H, H-8), 8.79 (s, 2 H, H-5), 10.93 (s, 2 H, CHO); IR (Nujol) 1660 cm^{-1}; MS, m/z (relative intensity) 518 (100); accurate mass determination, calcd 518.1914, found 518.1932. Anal. ($C_{30}H_{30}O_8 \cdot 0.5CHCl_3$) C, H.

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