43. Synthesis of Gossypol Analogues

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Dedicated to the memory of Professor Dr. *Pierre Crabbé*

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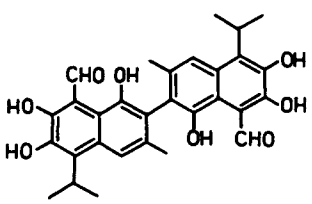
Two gossypol analogues **2a** and **2b** were synthesized for biological evaluation as male contraceptive agents. The naphthol **8c** was prepared by analogy with a known procedure starting from 3-isopropylcatechol (**3**). $(t\text{-Bu})_2O_2$-Mediated phenolic coupling of **8c** furnished the binaphthol **9c** which, after pyrane ring closure, deprotection, and selective bisformylation with $SnCl_4/Cl_2CHOCH_3$, gave the target compound **2a**. The corresponding tetrahydroxy analogue **2b** was prepared in a similar way.

The cotton-seed pigment gossypol (**1**) has been the subject of extensive studies [1]. Recently, considerable interest in this compound has been arisen since Chinese scientists found that gossypol is active as a male antifertility agent [2]. In 1982, the *Special Programme of Research in Human Reproduction* of the *World Health Organization (WHO)* initiated an international programme for the synthesis and biological evaluation of gossypol analogues. Herein, we describe the synthesis of analogues of the type **2** as a part of the *WHO* programme.



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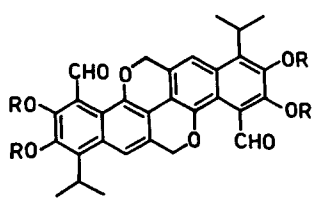


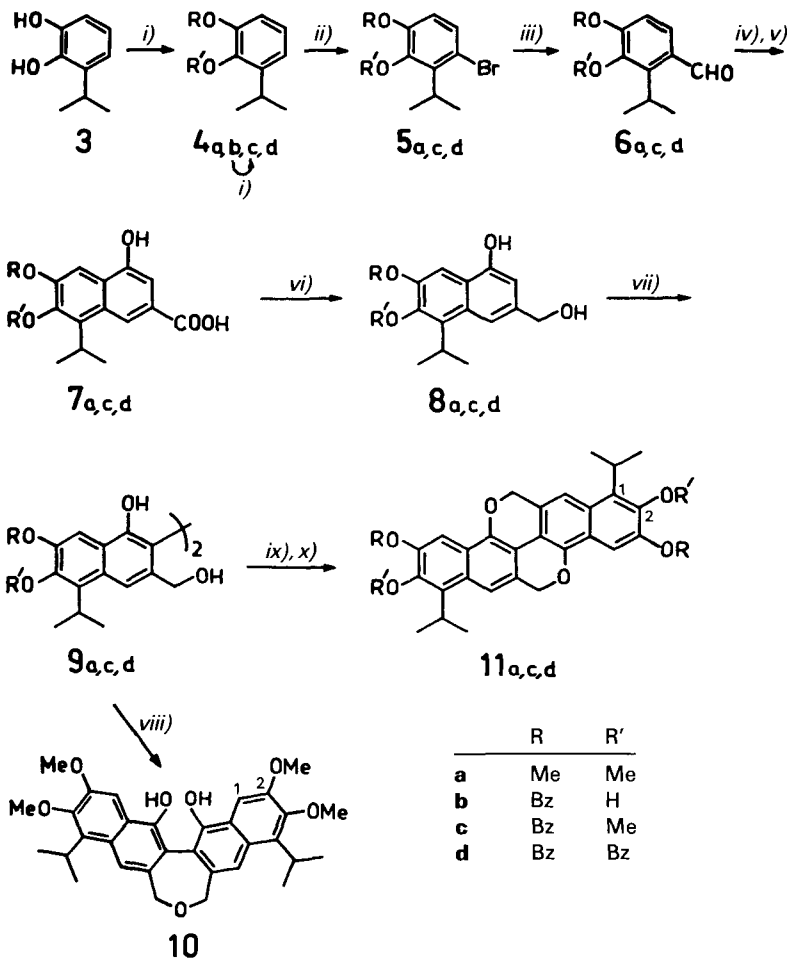
2 R=H, Me

The transformation of **1** into **2** by intramolecular cyclization seemed rather difficult due to the lack of methods for selective functionalization of the two Me groups involved. Therefore, in planning the preparation of **2**, we decided to follow the previously developed basic strategy for the total synthesis of gossypol (**1**) [3–5]. Carring out an early-stage phenolic coupling, we expected to obtain a binaphthol derivative with the desired functionalization of the Me groups. Further pyrane ring closure followed by selective bisformylation could lead to the target structure **2**.

Commercially available 3-isopropylcatechol (**3**) was exhaustively methylated with Me_2SO_4/K_2CO_3/acetone to give the dimethoxybenzene **4a** in 84% yield. The bromoben-

zene **5a** [6] and the benzaldehyde **6a** [5] were prepared from **4a** according to published procedures in 94 and 91% yield, respectively. *Stobbe* condensation of **6a** with $(CH_2CO_2Et)_2$/*t*-BuOK [7] provided a half-ester which, after cyclodehydratation with Ac_2O followed by saponification [3], was converted into the hydroxynaphthalenecarboxylic acid **7a** in 60% overall yield. Reduction of **7a** with $LiAlH_4$/THF [3] gave the (hydroxymethyl)naphthol **8a** in 91% yield. Attempts for thermal dimerization of **8a** under the conditions described for a similar synthetic gossypol precursor [3] gave a tarry material. The phenolic coupling of **8a** into the binaphthalenediol **9a** was achieved with $(t\text{-Bu})_2O_2/C_6H_5Cl$ [8] in 92% yield. The next step was the preparation of the two pyrane

Scheme 1



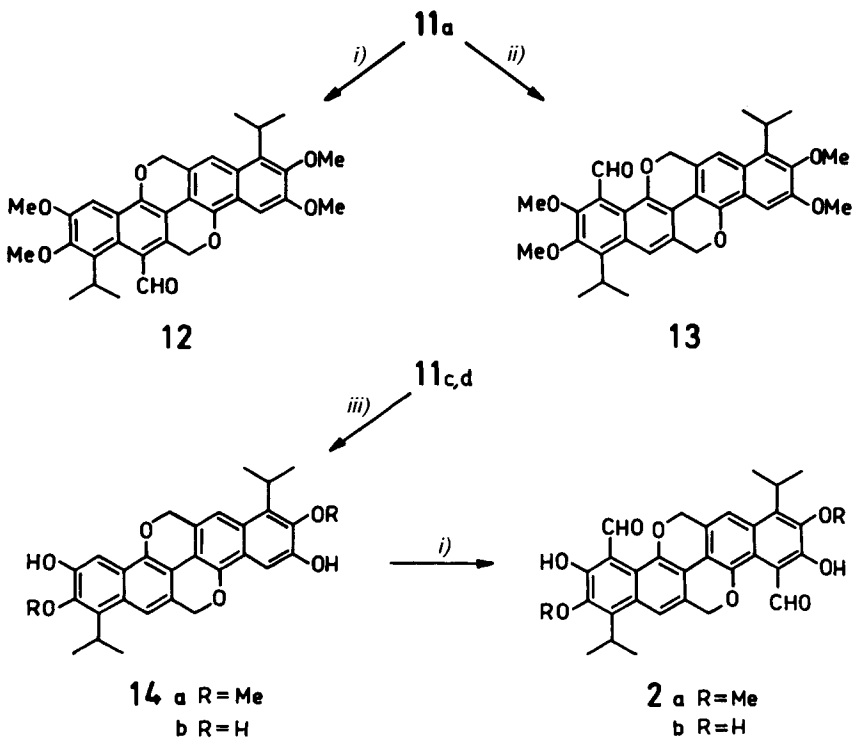
	R	R'
a	Me	Me
b	Bz	H
c	Bz	Me
d	Bz	Bz

i) For **4a,c**: Me_2SO_4/K_2CO_3/acetone, reflux; for **4b,d**: $PhCH_2Cl/K_2CO_3$/acetone, reflux. *ii)* For **5a**: Br_2/CCl_4, 0°; for **5c,d**: Br_2/AcONa/AcOH, r.t. *iii)* 1. EtBr/Mg/THF, reflux; 2. DMF, 0°. *iv)* $(CH_2CO_2Et)_2$/*t*-BuOK/*t*-BuOH, reflux. *v)* 1. AcONa/Ac_2O/AcOH, reflux; 2. 10% NaOH/MeOH, reflux. *vi)* $LiAlH_4$/THF, r.t. *vii)* *t*-Bu_2O_2/PhCl, reflux. *viii)* TsOH/C_6H_6, reflux. *ix)* PBr_3/THF, r.t. *x)* K_2CO_3/acetone, reflux.

rings of **2** by intramolecular cyclization. Unexpectedly, the cyclodehydratation of **9a** with a catalytic amount of TsOH in boiling C_6H_6 proceeded selectively with the formation of the oxepine compound **10** in 94% yield. Experiments for thermal cyclization [9] of **9a** gave complex mixtures containing traces of the desired bipyran **11a**. The yield of **11a** was improved by conversion of **9a** with PBr_3 into the corresponding bis(bromomethyl) compound which, without isolation, was cyclized with K_2CO_3/acetone into the bipyran **11a** in 50% yield *(Scheme 1)*.

To complete the synthesis of **2**, it was necessary to achieve regioselective bisformylation of **11a**. Attempts for *Vilsmeier-Haack* formylation of **11a** were unsuccessful. Treatment of **11a** with $SnCl_4/Cl_2CHOCH_3$ [10] afforded the monoaldehyde **12** in 60% yield. On the other hand, preliminary experiments for formylation of **11a** by metalation with *t*-BuLi/C_6H_6 followed by treatment with DMF [11] gave a complex mixture containing traces of the monoaldehyde **13** *(Scheme 2)*. The structure of the two isomeric aldehydes **12** and **13** was established by comparison of their ^{1}H-NMR spectra *(cf. Exper. Part)*.

Scheme 2



i) $Cl_2CHOCH_3/SnCl_4/CH_2Cl_2$, 0°→r.t. *ii)* 1. *t*-BuLi/C_6H_6, r.t.; 2. DMF, r.t. *iii)* H_2/Pd/C/EtOH/THF/EtOAc, r.t.

The resonance of one of the CH_2 groups in **12** is shifted downfield by 0.3 ppm in comparison to the resonance of the second one due to the deshielding effect of the neighbouring formyl group. The isomer **13** displays an unsignificant difference in the CH_2 resonances, while its formyl proton appears downfield due to the influence of the neighbouring O-atoms.

The observed regiospecificity of the formylation of **11a** is well consistent with a relevant precedent [11]. On the other hand, we failed to detect any loss of the isopropyl groups of **11a** under the conditions employed for the preparation of **12**, as previously described for apogossypol hexamethyl ether [12].

The difficulties in the selective formylation of **11a** could be overcome by using analogues of **11a** possessing free phenolic groups. In a similar case [12], the desired regioselectivity was achieved by means of the coordinating ability of an *ortho*-OH group. Thus, we decided to repeat the foregoing transformations starting from **3** and utilizing benzylic protective groups[1]). Treatment of **3** with 1,2 equiv. of $C_6H_5CH_2Cl/K_2CO_3$/acetone gave the mono- and the dibenzylated compounds **4b** and **4d** in 61 and 31% yield, respectively. Methylation of **4b** with Me_2SO_4/K_2CO_3/acetone afforded the protected phenol **4c** in 98% yield. The dibenzylated compound **11c** was prepared by the sequence **4c**→**5c**→**6c**→**7c**→**8c**→**9c**→**11c** as already described for **11a** *(Scheme 1)*. Further deprotection of **11c** with H_2/Pd/C produced the dihydroxy compound **14a** in 90% yield. Finally, the formylation of **14a** with $SnCl_4/Cl_2CHOCH_3$ proceeded regioselectively with the formation of the desired gossypol analogue **2a** in 62% yield *(Scheme 2)*. The structure of **2a** was confirmed by examination of its spectral data *(cf. Exper. Part)*.

The ^{1}H-NMR spectrum of **2a** displays only 1 *s* in the aromatic region due to the high symmetry of the molecule. In the IR spectrum, the strong carbonyl absorption at 1610 cm^{-1}, reflecting the presence of an intramolecular H-bonding, indicates *ortho*-situated OH and CHO functions. Thereby, the position of the two formyl groups in **2a** was unequivocally established.

Next we decided to prepare the tetrahydroxy analogue **2b** following the foregoing synthetic scheme for **2a**. Thus, the tetrabenzylated compound **11d** was synthesized by the sequence **4d**→**5d**→**6d**→**7d**→**8d**→**9d**→**11d** *(Scheme 1)*. Deprotection of **11d** with H_2/Pd/C gave the unstable tetrahydroxy compound **14b** in 90% yield, and formylation of the latter with $SnCl_4/Cl_2CHOCH_3$ afforded the tetrahydroxy gossypol analogue **2b** in 27% yield *(Scheme 2)*.

The described synthetic procedures offer a convenient route for the preparation of gossypol analogues of type **2**.

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Experimental Part

General. Column chromatography: *Merck* silica gel *60* (70–230 μm). M.p. (uncorrected): *Kofler* apparatus. IR spectra (cm^{-1}): *UR-20* (*Zeiss*, Jena). ^{1}H-NMR spectra: *Bruker-WM-250* spectrometer at 250 MHz and *Tesla* spectrometer at 60 and 80 MHz; δ values in ppm relative to internal TMS; coupling constants (*J*) in Hz. MS: *JEOL JMS D300* apparatus.

1. *1-Isopropyl-2,3-dimethoxybenzene* (**4a**). To a soln. of **3a** (*Aldrich;* 100 g, 0.66 mol) in acetone (1 l) and Me_2SO_4 (192.5 ml, 2.03 mol), K_2CO_3 (280 g, 2.03 mol) was added, and the mixture was refluxed with stirring under N_2 for 45 h. After addition of H_2O (1 l), heating was continued for 20 min, the org. solvent evaporated, and the residue extracted with Et_2O (5 × 300 ml). The combined org. extracts were washed with 5% NaOH soln. and H_2O,

[1]) Attempted deprotection of **11a** with Br_3B [13] failed.

dried, and evaporated. The resulting oil was purified by fractional distillation (20-cm *Vigreux* column): **4a** (99.8 g, 84%) as an oil. B.p. 119–121°/24 Torr. Spectral data: in accord with those reported [13].

2. *2-(Benzyloxy)-6-isopropylphenol* (**4b**) *and 1,2-Bis(benzyloxy)-3-isopropylbenzene* (**4d**). To a soln. of **3a** (106.4 g, 0.7 mol) and $C_6H_5CH_2Cl$ (132.9 ml, 1.05 mol) in acetone (700 ml), K_2CO_3 (289 g, 2.1 mol) was added and the mixture refluxed with stirring under N_2 for 32 h. The solvent was evaporated, H_2O (1 l) added, and the mixture extracted with Et_2O (4 × 400 ml). The combined org. layer was evaporated, the residue dissolved in pentane (1 l), and the soln. washed with 0.5% NaOH (3 × 300 ml) and evaporated: oil which, after bulb-to-bulb distillation, furnished **4b** (103 g, 61%), b.p. 160°/0.03 Torr, and **4d** (72 g, 31%), b.p. 210°/0.03 Torr.

Data of **4b**: Oil. IR: 3515, 1600, 1575. ^{1}H-NMR (60 MHz, CCl_4): 7.25 (*s*, 5 H); 6.58 (*m*, 3 H); 5.50 (*s*, OH, exchangeable with D_2O); 4.90 (*s*, 2 H); 3.25 (*sept.*, J = 7, 1 H); 1.17 (*d*, J = 7, 6 H). MS: 242 (9, $M^{+\cdot}$, $C_{16}H_{18}O_2$), 150 (3), 91 (100).

Data of **4d**: Oil. IR: 1602, 1587. ^{1}H-NMR (60 MHz, CCl_4): 7.50–7.15 (*m*, 10 H); 7.00–6.65 (*m*, 3 H); 5.06 (*s*, 2 H); 5.01 (*s*, 2 H); 3.37 (*sept.*, J = 7, 1 H); 1.15 (*d*, J = 7, 6 H). MS: 332 (5, $M^{+\cdot}$, $C_{23}H_{24}O_2$), 241 (3), 181 (7), 91 (100).

3. *1-(Benzyloxy)-3-isopropyl-2-methoxybenzene* (**4c**). Under reflux, **4b** (101 g, 0.42 mol) was methylated with Me_2SO_4 (79 ml, 0.82 mol) and K_2CO_3 (173 g, 1.25 mol) in acetone (500 ml) for 60 h. Workup as described for **4a** and bulb-to-bulb distillation gave **4c** (105 g, 98%) as an oil. B.p. 135°/0.03 Torr. IR: 1570, 1450. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.49–6.76 (*m*, 8 H); 5.08 (*s*, 2 H); 3.87 (*s*, 3 H); 3.38 (*sept.*, J = 7, 1 H); 1.23 (*d*, J = 7, 6 H). MS: 256 (4, $M^{+\cdot}$, $C_{17}H_{20}O_2$), 165 (4), 91 (100).

4. *1-Bromo-2-isopropyl-3,4-dimethoxybenzene* (**5a**). Bromination (Br_2/CCl_4) of **4a** according to [6] gave **5a** in 94% yield. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.19 (*d*, J = 8.5, 1 H); 6.55 (*d*, J = 8.5, 1 H); 3.80 (*s*, 3 H); 3.78 (*s*, 3 H); 3.54 (*sept.*, J = 7, 1 H); 1.35 (*d*, J = 7, 6 H). MS: 260, 258 (100, $M^{+\cdot}$, $C_{11}H_{15}BrO_2$); 245, 243 (56).

5. *1-(Benzyloxy)-4-bromo-3-isopropyl-2-methoxybenzene* (**5c**) *and 1,2-Bis(benzyloxy)-4-bromo-3-isopropylbenzene* (**5d**). To a stirred soln. of **4c** or **4d** (0.35 mol) and AcONa (0.42 mol) in AcOH (600 ml) was added, at 0°, a soln. of Br_2 (0.38 mol) in AcOH (40 ml). Stirring was continued for 1 h at 20°, H_2O (800 ml) added, and the mixture treated with sat. $Na_2S_2O_5$ soln. until total discoloration and extracted with Et_2O/hexane 2:1 (3 × 300 ml). The combined org. extracts were washed with H_2O, 10% NaOH soln., and H_2O, dried and evaporated and the residue purified by bulb-to-bulb distillation: **5c** (110.1 g, 94%) or **5d** (120.9 g, 84%), resp.

Data of **5c**: Oil. IR: 1550, 1435. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.50–7.26 (*m*, 5 H); 7.21 (*d*, J = 9, 1 H); 6.65 (*d*, J = 9, 1 H); 5.07 (*s*, 2 H); 3.89 (*s*, 3 H); 3.58 (*sept.*, J = 7, 1 H); 1.35 (*d*, J = 7, 6 H). CI-MS: 337/335 (20, $[M + 1]^+$, $C_{17}H_{19}BrO_2$), 91 (100).

Data of **5d**: Oil. IR: 1556, 1550, 1450. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.60–6.95 (*m*, 11 H); 6.58 (*d*, J = 9, 1 H); 5.02 (*s*, 2 H); 4.88 (*s*, 2 H); 3.70 (*sept.*, J = 7, 1 H); 1.35 (*d*, J = 7, 6 H). MS: 412, 410 (3, $M^{+\cdot}$, $C_{23}H_{23}BrO_2$); 321 (4), 319 (4); 91 (100).

6. *2-Isopropyl-3,4-dimethoxybenzaldehyde* (**6a**), *4-(Benzyloxy)-2-isopropyl-3-methoxybenzaldehyde* (**6c**), *and 3,4-Bis(benzyloxy)-2-isopropylbenzaldehyde* (**6d**). Compounds **6a**, **6c**, and **6d** were prepared by reaction of **5a**, **5c**, or **5d** with EtMgBr and subsequent treatment of the resulting *Grignard* reagents with DMF according to [14]. Yields: 80, 62, and 65%, resp.

Data of **6a**: Oil. IR and ^{1}H-NMR: see [5]. MS: 208 (100, $M^{+\cdot}$, $C_{12}H_{16}O_3$), 194 (55), 179 (31), 177 (26).

Data of **6c**: Oil. IR: 1680, 1580. ^{1}H-NMR (250 MHz, $CDCl_3$): 10.28 (*s*, 1 H); 7.63 (*d*, J = 9, 1 H); 7.50–7.30 (*m*, 5 H); 6.95 (*d*, J = 9, 1 H); 5.02 (*s*, 2 H); 4.05 (*sept.*, J = 7, 1 H); 3.87 (*s*, 3 H); 1.43 (*d*, J = 7, 6 H). MS: 284 (17, $M^{+\cdot}$, $C_{16}H_{20}O_3$), 91 (100).

Data of **6d**: Oil. IR: 1665, 1570. ^{1}H-NMR (60 MHz, $CDCl_3$): 10.18 (*s*, 1 H); 7.58 (*d*, J = 9, 1 H); 7.46–7.00 (*m*, 10 H); 6.90 (*d*, J = 9, 1 H); 5.08 (*s*, 2 H); 4.94 (*s*, 2 H); 3.98 (*sept.*, J = 7, 1 H); 1.34 (*d*, J = 7, 6 H). MS: 360 (12, $M^{+\cdot}$, $C_{24}H_{24}O_3$), 269 (31), 181 (14), 163 (8), 91 (100).

7. *4-Hydroxy-8-isopropyl-6,7-dimethoxynaphthalene-2-carboxylic Acid* (**7a**), *6-(Benzyloxy)-4-hydroxy-8-isopropyl-7-methoxynaphthalene-2-carboxylic Acid* (**7c**), *and 6,7-Bis(benzyloxy)-4-hydroxy-8-isopropylnaphthalene-2-carboxylic Acid* (**7d**). A soln. of **6a**, **6c**, or **6d** (0.163 mol) and $(CH_2CO_2Et)_2$ (42.7 g, 0.245 mol) in dry *t*-BuOH (25 ml) was added dropwise within 1 h to a boiling soln. of *t*-BuOK in *t*-BuOH (prepared from K (6.98 g, 0.179 mol) and *t*-BuOH (180 ml)) with stirring under N_2. The mixture was then refluxed for 45 min, the solvent evaporated, and the residue dissolved in cold H_2O (300 ml). The soln. was acidified with 20% HCl soln. and extracted with Et_2O (3 × 200 ml). The combined org. layers were extracted with 10% Na_2CO_3 soln. (3 × 200 ml) and the alkaline extracts acidified with 20% HCl soln. and reextracted with Et_2O (3 × 200 ml). Evaporation of the solvent gave an oily residue which was further subjected, without purification, to cyclodehydratation with Ac_2O/AcONa and

saponification with 10% NaOH in MeOH according to [3]. Crystallization from C_6H_6 or C_6H_6/hexane gave **7a** (28.4 g, 60%), **7c** (28.0 g, 47%), or **7d** (29.6 g, 41%), resp.

Data of **7a**: M.p. 224–226° (C_6H_6/hexane; [3]: 226–227° (C_6H_6)). IR (KBr): 3420, 1680, 1600. ^{1}H-NMR (60 MHz, (D$_6$)DMSO): 10.5 (br. *s*, OH, exchangeable with D_2O); 8.58 (*s*, 1 H); 7.78 (*s*, 1 H); 7.63 (*s*, 1 H); 4.50–3.90 (*m*, 7 H; therein at 4.23 (*s*, 3 H) and at 4.07 (*s*, 3 H)); 1.70 (*d*, J = 7, 6 H). MS: 290 (100, $M^{+\cdot}$, $C_{16}H_{18}O_5$), 275 (68), 260 (10).

Data of **7c**: M.p. 218–220° (C_6H_6/hexane). IR (KBr): 3480, 3190, 1670, 1600. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 8.38 (br. *s*, OH, exchangeable with D_2O); 7.80–7.25 (*m*, 8 H); 5.30 (*s*, 2 H); 4.14–3.75 (*m*, 4 H; therein at 3.88 (*s*, 3 H)); 1.48 (*d*, J = 7, 6 H). MS: 366 (12, $M^{+\cdot}$, $C_{22}H_{22}O_5$), 91 (100).

Data of **7d**: M.p. 215–218° (C_6H_6). IR (KBr): 3335, 1675, 1600. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 10.42 (br. *s*, OH, exchangeable with D_2O); 8.36 (*s*, 1 H); 7.88–7.26 (*m*, 12 H); 5.35 (*s*, 2 H); 5.09 (*s*, 2 H); 4.00 (*m*, 1 H); 1.42 (*d*, J = 7, 6 H). MS: 442 (8, $M^{+\cdot}$, $C_{28}H_{26}O_5$), 351 (5), 215 (3), 181 (12), 91 (100).

8. *3-(Hydroxymethyl)-5-isopropyl-6,7-dimethoxy-1-naphthol* (**8a**), *7-(Benzyloxy)-3-(hydroxymethyl)-5-isopropyl-6-methoxy-1-naphthol* (**8c**), *and 6,7-Bis(benzyloxy)-3-(hydroxymethyl)-5-isopropyl-1-naphthol* (**8d**). Reduction of **7a**, **7b**, or **7d** (0.087 mol) with $LiAlH_4$ (0.493 mol) in dry THF (700 ml) according to [3] gave **8a** (21.9 g, 91%), **8c** (25.0 g, 82%), and **8d** (34.3 g, 92%), resp.

Data of **8a**: M.p. 205–207° (C_6H_6; [3]: 207–209° (C_6H_6)). IR (KBr): 3420, 3210, 1600, 1460. ^{1}H-NMR (60 MHz, (D$_6$)DMSO): 10.15 (*s*, OH, exchangeable with D_2O); 7.79 (*s*, 1 H); 7.70 (*s*, 1 H); 7.10 (*s*, 1 H); 5.45 (*t*, J = 5, OH, exchangeable with D_2O); 4.87 (*d*, J = 5, 2 H; after D_2O exchange, *s*); 4.40–3.90 (*m*, 7 H; therein at 4.20 (*s*, 3 H) and at 4.09 (*s*, 3 H)); 1.70 (*d*, J = 6.5, 6 H). MS: 276 (100, $M^{+\cdot}$, $C_{16}H_{20}O_4$), 261 (41), 231 (26).

Data of **8c**: M.p. 190–192° (C_6H_6). IR (KBr): 3360, 3250, 1600, 1450. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 9.95 (br. *s*, OH, exchangeable with D_2O); 7.80–7.30 (*m*, 7 H); 6.83 (*s*, 1 H); 5.25 (*s*, 2 H); 4.60 (*s*, 2 H); 4.00 (*m*, 1 H); 3.88 (*s*, 3 H); 3.45 (br. *s*, OH, exchangeable with D_2O); 1.46 (*d*, J = 7, 6 H). MS: 352 (44, $M^{+\cdot}$, $C_{22}H_{24}O_4$), 261 (27), 91 (100).

Data of **8d**: M.p. 214–216° (C_6H_6). IR (KBr): 3440, 3210, 1596. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 10.00 (br. *s*, OH, exchangeable with D_2O); 7.74–7.26 (*m*, 12 H); 6.86 (*s*, 1 H); 5.29 (*s*, 2 H); 5.09 (*s*, 2 H); 4.62 (*d*, J = 5, 2 H; after D_2O exchange, *s*); 4.04 (*sept.*, J = 7, 1 H); 3.50 (br. *s*, OH; exchangeable with D_2O); 1.42 (*d*, J = 7, 6 H). MS: 428 (34, $M^{+\cdot}$, $C_{28}H_{28}O_4$), 91 (100).

9. *3,3'-Bis(hydroxymethyl)-5,5'-diisopropyl-6,6',7,7'-tetramethoxy[2,2'-binaphthalene]-1,1'-diol* (**9a**), *7,7'-Bis(benzyloxy)-3,3'-bis(hydroxymethyl)-5,5'-diisopropyl-6,6'-dimethoxy[2,2'-binaphthalene]-1,1'-diol* (**9c**), *and 6,6',7,7'-Tetrakis(benzyloxy)-3,3'-bis(hydroxymethyl)-5,5'-diisopropyl[2,2'-binaphthalene]-1,1'-diol* (**9d**). A soln. of **8a**, **8c**, or **8d** (0.05 mol) and $(t\text{-Bu})_2O_2$ (7.3 g, 0.05 mol) in C_6H_5Cl (600 ml) was heated under reflux for 9 h. Evaporation of the solvent and crystallization from C_6H_6 gave **9a** (12.7 g, 92%), **9c** (29.2 g, 83%), and **9d** (32.5 g, 76%), resp.

Data of **9a**: M.p. 161–163° (C_6H_6). IR (KBr): 3500, 3300, 1590, 1450. ^{1}H-NMR (250 MHz, (D$_6$)DMSO): 8.34 (br. *s*, OH, exchangeable with D_2O); 7.86 (*s*, 2 H); 7.55 (*s*, 2 H); 5.08 (br. *s*, OH, exchangeable with D_2O); 4.30–3.80 (*m*, 18 H; therein at 4.22, 4.05 (*AB*, J = 14.5, 4 H), at 3.94 (*s*, 6 H), and at 3.85 (*s*, 6 H)); 1.51 (*d*, J = 6.5, 12 H). MS: 550 (5, $M^{+\cdot}$, $C_{32}H_{38}O_8$), 532 (27), 514 (100).

Data of **9c**: M.p. 172–174° (C_6H_6). IR (KBr): 3360, 1590, 1440. ^{1}H-NMR (250 MHz, (D$_6$)DMSO): 7.87 (*s*, 2 H); 7.70 (*s*, 2 H); 7.66–7.34 (*m*, 10 H); 5.27 (*s*, 4 H); 4.25, 4.09 (*AB*, J = 14, 4 H); 4.00 (*m*, 2 H); 3.91 (*s*, 6 H); 1.54 (*d*, J = 6.5, 12 H). MS: 684 (7), 668 (8), 666 (10), 91 (100).

Data of **9d**: M.p. 213–215° (dec., C_6H_6). IR (KBr): 3510, 3400, 1594. ^{1}H-NMR (250 MHz, (D$_6$)DMSO): 8.38 (*s*, OH, exchangeable with D_2O); 7.88 (*s*, 2 H); 7.72 (*s*, 2 H); 7.66–7.21 (*m*, 20 H); 5.27 (*s*, 4 H); 5.06 (*s*, 4 H); 4.32–3.89 (*m*, 6 H; therein at 4.25, 4.05 (*AB*, J = 14, 4 H)); 3.34 (br. *s*, OH, exchangeable with D_2O); 1.46 (*d*, J = 7, 12 H). MS: 442 (0.5), 181 (0.9), 91 (100).

10. *6,8-Dihydro-4,10-diisopropyl-2,3,11,12-tetramethoxydinaphtho[2,3-c:2',3'-e]oxepine-14,15-diol* (**10**). A soln. of **9a** (2.2 g, 4 mmol) and TsOH (0.068 g, 0.4 mmol) in C_6H_6 (150 ml) was heated under reflux for 10 min. The mixture was cooled, washed with 10% $NaHCO_3$ soln., dried, and evaporated: **10** (2.0 g, 94%). M.p. 179–181° (C_6H_6). IR (KBr): 3300, 1600, 1460. ^{1}H-NMR (250 MHz, (D$_6$)DMSO): 9.37 (br. *s*, OH, exchangeable with D_2O); 7.86 (*s*, 2 H); 7.72 (*s*, 2 H); 4.66, 4.19 (*AB*, J = 11, 4 H); 4.05 (*m*, 2 H); 4.00 (*s*, 6 H); 3.87 (*s*, 6 H); 1.51 (*d*, J = 6.5, 12 H). MS: 532 (100, $M^{+\cdot}$, $C_{32}H_{36}O_7$), 514 (76).

11. *1,8-Diisopropyl-2,3,9,10-tetramethoxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene* (**11a**), *3,10-Bis(benzyloxy)-1,8-diisopropyl-2,9-dimethoxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene* (**11c**), *and 2,3,9,10-Tetrakis(benzyloxy)-1,8-diisopropyl-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene* (**11d**). To a soln. of **9a**, **9c**, or **9d** (10 mmol) in dry THF (200

ml), a soln. of PBr_3 (2.07 ml, 22 mmol) in THF (10 ml) was added dropwise with stirring under N_2 at 0°. Stirring was continued at 20° for 1 h, dry MeOH (5 ml) was added and the solvent evaporated. The residue was dissolved in dry acetone (100 ml), anh. K_2CO_3 (4 g) was added and the mixture refluxed with stirring under N_2 for 2 h. The solvent was evaporated, H_2O (100 ml) added, and the mixture extracted with Et_2O (4 × 30 ml). The combined org. extracts were washed with 10% NaOH soln., H_2O, dried, and evaporated. The residue was chromatographed (50 g of silica gel, C_6H_6) and crystallized from C_6H_6: **11a** (2.57 g, 50%), **11c** (3.00 g, 45%), or **11d** (3.28 g, 42%), resp.

Data of **11a**: M.p. 223–225° (C_6H_6). IR (KBr): 1580, 1440, 1400. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.55 (*s*, 2 H); 7.48 (*s*, 2 H); 5.52 (*s*, 4 H); 4.05–3.75 (*m*, 14 H; therein at 4.01 (*s*, 6 H) and at 3.92 (*s*, 6 H)); 1.53 (*d*, J = 6.5, 12 H). MS: 514 (100, M^+, $C_{32}H_{34}O_6$).

Data of **11c**: M.p. 242–244° (C_6H_6). IR (KBr): 1595, 1450, 1420. ^{1}H-NMR (250 MHz, (D_6)DMSO): 7.79 (*s*, 2 H); 7.73–7.39 (*m*, 12 H); 5.63 (*s*, 4 H); 5.34 (*s*, 4 H); 4.00 (*m*, 2 H); 3.92 (*s*, 6 H); 1.53 (*d*, J = 7, 12 H). MS: 666 (31, M^+, $C_{44}H_{42}O_6$), 186 (13), 139 (17), 91 (34), 78 (72), 51 (100).

Data of **11d**: M.p. 211–213° (dec.; C_6H_6). IR (KBr): 1590, 1490, 1440. ^{1}H-NMR (250 MHz, (D_6)DMSO): 7.73 (*s*, 2 H); 7.67–7.23 (*m*, 22 H); 5.58 (*s*, 4 H); 5.31 (*s*, 4 H); 5.03 (*s*, 4 H); 3.98 (*m*, 2 H); 1.42 (*d*, J = 7, 12 H). MS: 121 (20), 107 (26), 91 (100).

12. *1,8-Diisopropyl-2,3,9,10-tetramethoxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-7-carbaldehyde* (**12**). To a stirred soln. of **11a** (0.159 g, 0.31 mmol) in dry CH_2Cl_2 (5 ml), $SnCl_4$ (0.11 ml, 0.9 mmol) was added at 0° under N_2. After addition of Cl_2CHOCH_3 (0.075 ml, 0.9 mmol), stirring was continued for 30 min at 20°, the mixture poured into cold H_2O and extracted with CH_2Cl_2, the combined org. layer washed with 10% Na_2CO_3 soln., H_2O, and dried, the solvent evaporated, and the residue chromatographed (20 g of silica gel, Et_2O/hexane 1:3): **12** (0.17 g, 60%). M.p. 213–215° (dec.; C_6H_6). IR (KBr): 1665, 1590. ^{1}H-NMR (80 MHz, $CDCl_3$): 10.25 (*s*, 1 H); 7.50 (*s*, 1 H); 7.48 (*s*, 1 H); 7.43 (*s*, 1 H); 5.78 (*s*, 2 H); 5.46 (*s*, 2 H); 4.10–3.50 (*m*, 14 H; therein at 4.00 (*s*, 6 H), at 3.97 (*s*, 3 H), and at 3.90 (*s*, 3 H)); 1.52 (*d*, J = 6.5, 6 H); 1.46 (*d*, J = 6, 6 H). MS: 542 (63, M^+, $C_{33}H_{34}O_7$), 499 (100).

13. *1,8-Diisopropyl-2,3,9,10-tetramethoxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-4-carbaldehyde* (**13**). To a soln. of **11a** (0.165 g, 0.32 mmol) in dry C_6H_6 (40 ml), *t*-BuLi (1.4M in pentane; 0.92 ml, 1.28 mmol) was added dropwise at 20° with stirring under N_2. After stirring at 20° for 4 h, DMF (0.12 ml, 1.5 mmol) was added and stirring continued at 20° for 30 min. The mixture was poured into 5% HCl soln. and extracted with C_6H_6. The org. phases were washed with 5% $NaHCO_3$ soln. and H_2O, dried, and evaporated. The residue was purified by column chromatography (20 g of silica gel, C_6H_6): **13** (0.017 g, 10%). ^{1}H-NMR (250 MHz, $CDCl_3$): 10.80 (*s*, 1 H); 7.62 (*s*, 1 H); 7.52 (*s*, 1 H); 7.46 (*s*, 1 H); 5.52 (*s*, 2 H); 5.45 (*s*, 2 H); 4.10–3.80 (*m*, 14 H; therein at 4.02 (*s*, 3 H), at 3.93 (*s*, 6 H), and at 3.91 (*s*, 3 H)); 1.54 (*d*, J = 7, 6 H); 1.52 (*d*, J = 7, 6 H). MS: 542 (100, M^+, $C_{33}H_{34}O_7$).

14. *1,8-Diisopropyl-2,9-dimethoxy-6*H-*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-3,10-diol* (**14a**) *and 1,8-Diisopropyl-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-2,3,9,10-tetrol* (**14b**). To a soln. of **11c** or **11d** (2 mmol) in EtOH/THF/AcOEt 4:1:1 (90 ml), 10% Pd/C (0.664 g) was added, and the mixture was shaken under 760 Torr of H_2 for 1 h. The catalyst was filtered off and washed with hot THF, the solvent evaporated, and the residue crystallized from C_6H_6/hexane: **14a** (0.88 g, 91%) and **14b** (0.82 g, 90%), resp.

Data of **14a**: M.p. > 300° (dec.; C_6H_6/hexane). IR (KBr): 3290, 1600, 1450, 1420. ^{1}H-NMR (250 MHz, (D_6)DMSO): 10.2 (br. *s*, OH, exchangeable with D_2O); 7.67 (*s*, 2 H); 7.42 (*s*, 2 H); 5.53 (*s*, 4 H); 3.90 (*m*, 2 H); 3.87 (*s*, 6 H); 1.48 (*d*, J = 7, 12 H). MS: 486 (100, M^+, $C_{30}H_{30}O_6$), 471 (6), 428 (12), 243 (14), 228 (15).

Data of **14b**: M.p. > 280° (dec.; C_6H_6/hexane). IR (KBr): 3380, 1610, 1510, 1418. ^{1}H-NMR (250 MHz, (D_6)DMSO): 10.18 (br. *s*, OH, exchangeable with D_2O); 8.50 (br. *s*, OH, exchangeable with D_2O); 7.48 (*s*, 2 H); 7.27 (*s*, 2 H); 5.41 (*s*, 4 H); 3.77 (br. *s*, 2 H); 1.39 (*d*, J = 7, 12 H). MS: 458 (0.7, M^+, $C_{28}H_{26}O_6$), 249 (0.6), 78 (69), 40 (100).

15. *3,10-Dihydroxy-1,8-diisopropyl-2,9-dimethoxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-4,11-dicarbaldehyde* (**2a**). To a suspension of **14a** (0.243 g, 0.5 mmol) in dry CH_2Cl_2 (20 ml), $SnCl_4$ (0.354 ml, 3 mmol) was added dropwise with stirring at 20° under N_2. After stirring for 15 min, Cl_2CHOCH_3 (0.267 ml, 3 mmol) was added and stirring continued for 4 h at 20°. The mixture was poured into cold 5% HCl soln. and extracted with $CHCl_3$. The combined org. phases were washed with 5% $NaHCO_3$ soln. and H_2O, dried, and evaporated. Purification of the residue by column chromatography (10 g of silica gel, C_6H_6/hexane/Et_2O 1:1:1) and crystallization from CH_2Cl_2/hexane gave **2a** (0.168 g, 62%). M.p. 312–313° (dec.). IR (KBr): 1610, 1440, 1420. ^{1}H-NMR (250 MHz, $CDCl_3$): 14.53 (*s*, OH, exchangeable with D_2O); 11.28 (*s*, 2 H); 7.70 (*s*, 2 H); 5.49 (*s*, 4 H); 4.00 (*s*, 6 H); 3.98 (*m*, 2 H); 1.53 (*d*, J = 7, 12 H). MS: 542 (100, M^+, $C_{32}H_{30}O_8$). Anal. calc. for $C_{32}H_{30}O_8$ (542.56): C 70.83, H 5.57; found: C 70.73, H 5.75.

16. *2,3,9,10-Tetrahydroxy-6*H,*13*H-*5,12-dioxadibenzo[*b,i*]pyrene-4,11-dicarbaldehyde* (**2b**). A soln. of **14b** (0.05 g, 0.11 mmol) in dry CH_2Cl_2/THF 4:1 (2.5 ml) was added dropwise to a soln. of $SnCl_4$ (0.5 ml, 4.2 mmol) and Cl_2CHOCH_3 (1 ml, 11.2 mmol) in dry CH_2Cl_2 (5 ml) with stirring at 0° under N_2. The mixture was stirred at 0° for 2 h and at 20° for 1 h. Workup as described for **2a** and crystallization from CH_2Cl_2/C_6H_6 gave **2b** (0.015 g, 27%). M.p. > 250° (dec.). IR (KBr): 3510, 3300, 1610. ^{1}H-NMR (250 MHz, $CDCl_3$/(D_6)DMSO): 14.70 (br. *s*, OH, exchangeable with D_2O); 11.25 (*s*, 2 H); 8.80 (br. *s*, OH, exchangeable with D_2O); 7.88 (*s*, 2 H); 5.53 (*s*, 4 H); 3.91 (*m*, 2 H); 1.50 (*d*, J = 7, 12 H). MS: 514 (100, $M^{+\cdot}$, $C_{30}H_{26}O_8$).

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