

### 43. Synthesis of Gossypol Analogues

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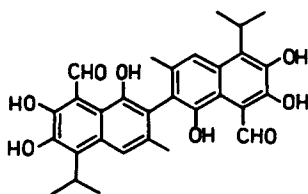
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Dedicated to the memory of Professor Dr. *Pierre Crabbé*

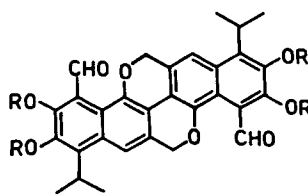
(24. XI. 88)

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**).  $(t\text{-Bu})_2\text{O}_2$ -Mediated phenolic coupling of **8c** furnished the binaphthol **9c** which, after pyrane ring closure, deprotection, and selective bisformylation with  $\text{SnCl}_4/\text{Cl}_2\text{CHOCH}_3$ , 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.



**1**



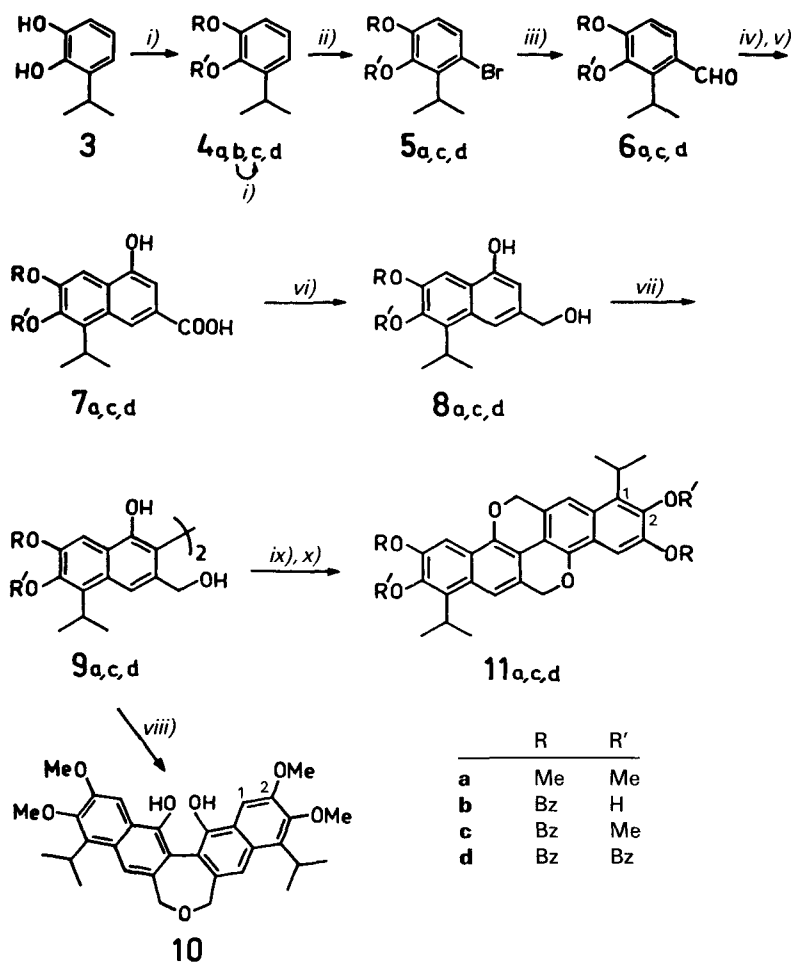
**2** R=H, Me

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]. Carrying 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  $\text{Me}_2\text{SO}_4/\text{K}_2\text{CO}_3/\text{acetone}$  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  $(\text{CH}_2\text{CO}_2\text{Et})_2/t\text{-BuOK}$  [7] provided a half-ester which, after cyclodehydration with  $\text{Ac}_2\text{O}$  followed by saponification [3], was converted into the hydroxynaphthalenecarboxylic acid **7a** in 60% overall yield. Reduction of **7a** with  $\text{LiAlH}_4/\text{THF}$  [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  $(t\text{-Bu})_2\text{O}_2/\text{C}_6\text{H}_5\text{Cl}$  [8] in 92% yield. The next step was the preparation of the two pyrane

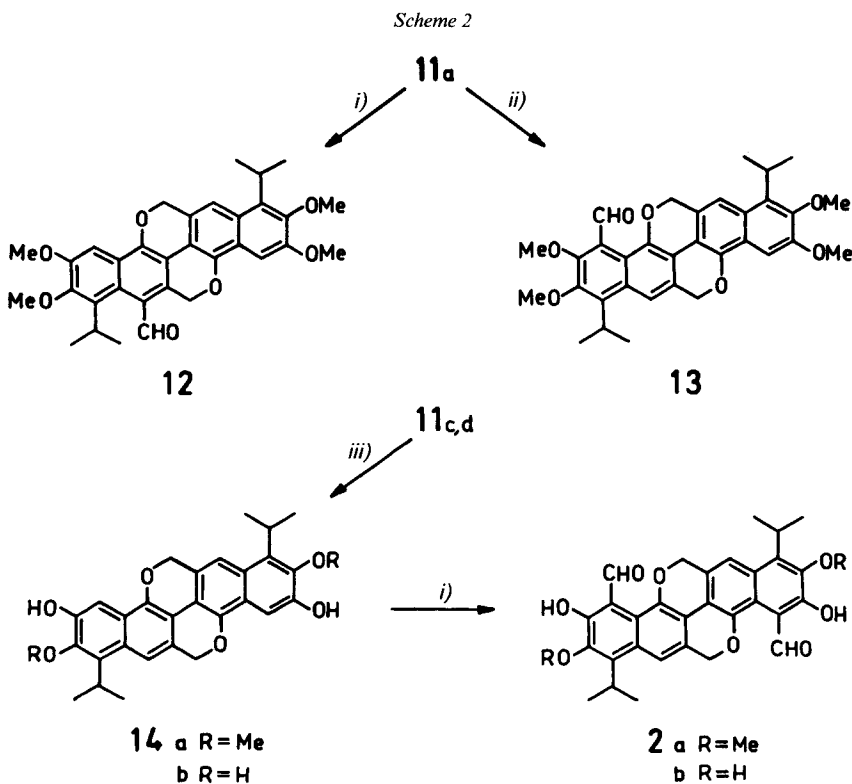
Scheme 1



i) For **4a,c**:  $\text{Me}_2\text{SO}_4/\text{K}_2\text{CO}_3/\text{acetone}$ , reflux; for **4b,d**:  $\text{PhCH}_2\text{Cl}/\text{K}_2\text{CO}_3/\text{acetone}$ , reflux. ii) For **5a**:  $\text{Br}_2/\text{CCl}_4$ ,  $0^\circ$ ; for **5c,d**:  $\text{Br}_2/\text{AcONa}/\text{AcOH}$ , r.t. iii) 1.  $\text{EtBr}/\text{Mg}/\text{THF}$ , reflux; 2.  $\text{DMF}$ ,  $0^\circ$ . iv)  $(\text{CH}_2\text{CO}_2\text{Et})_2/t\text{-BuOK}/t\text{-BuOH}$ , reflux. v) 1.  $\text{AcONa}/\text{Ac}_2\text{O}/\text{AcOH}$ , reflux; 2. 10%  $\text{NaOH}/\text{MeOH}$ , reflux. vi)  $\text{LiAlH}_4/\text{THF}$ , r.t. vii)  $t\text{-Bu}_2\text{O}_2/\text{PhCl}$ , reflux. viii)  $\text{TsOH}/\text{C}_6\text{H}_6$ , reflux. ix)  $\text{PBr}_3/\text{THF}$ , r.t. x)  $\text{K}_2\text{CO}_3/\text{acetone}$ , reflux.

rings of **2** by intramolecular cyclization. Unexpectedly, the cyclodehydration 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  $^1H$ -NMR spectra (*cf. Exper. Part*).



i)  $Cl_2CHOCH_3/SnCl_4/CH_2Cl_2$ ,  $0^\circ \rightarrow r.t.$  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 insignificant difference in the  $CH_2$  resonances, while its formyl proton appears downfield due to the influence of the neighbouring O-atoms.

The observed regioselectivity 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<sup>1)</sup>. 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  $^1H$ -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  $1610\text{ cm}^{-1}$ , 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  $\mu m$ ). M.p. (uncorrected): *Kofler* apparatus. IR spectra ( $cm^{-1}$ ): *UR-20* (*Zeiss*, Jena).  $^1H$ -NMR spectra: *Bruker-WM-250* spectrometer at 250 MHz and *Tesla* spectrometer at 60 and 80 MHz;  $\delta$  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  $\times$  300 ml). The combined org. extracts were washed with 5 % NaOH soln. and  $H_2O$ ,

<sup>1)</sup> 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  $Et_2O$  ( $4 \times 400$  ml). The combined org. layer was evaporated, the residue dissolved in pentane (1 l), and the soln. washed with 0.5% NaOH ( $3 \times 300$  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.  $^1H$ -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,  $M^+$ ,  $C_{16}H_{18}O_2$ ), 150 (3), 91 (100).

Data of **4d**: Oil. IR: 1602, 1587.  $^1H$ -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,  $M^+$ ,  $C_{23}H_{24}O_2$ ), 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.  $^1H$ -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,  $M^+$ ,  $C_{17}H_{20}O_2$ ), 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.  $^1H$ -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,  $M^+$ ,  $C_{11}H_{15}BrO_2$ ); 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 ( $3 \times 300$  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.  $^1H$ -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.  $^1H$ -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,  $M^+$ ,  $C_{23}H_{23}BrO_2$ ); 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  $^1H$ -NMR: see [5]. MS: 208 (100,  $M^+$ ,  $C_{12}H_{16}O_3$ ), 194 (55), 179 (31), 177 (26).

Data of **6c**: Oil. IR: 1680, 1580.  $^1H$ -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,  $M^+$ ,  $C_{16}H_{20}O_3$ ), 91 (100).

Data of **6d**: Oil. IR: 1665, 1570.  $^1H$ -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,  $M^+$ ,  $C_{24}H_{24}O_3$ ), 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-isopropyl-naphthalene-2-carboxylic Acid (**7d**). A soln. of **6a**, **6c**, or **6d** (0.163 mol) and  $(CH_3CO_2Et)_2$  (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  $Et_2O$  ( $3 \times 200$  ml). The combined org. layers were extracted with 10%  $Na_2CO_3$  soln. ( $3 \times 200$  ml) and the alkaline extracts acidified with 20% HCl soln. and reextracted with  $Et_2O$  ( $3 \times 200$  ml). Evaporation of the solvent gave an oily residue which was further subjected, without purification, to cyclodehydration 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.  $^1H$ -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,  $M^+$ ,  $C_{16}H_{18}O_5$ ), 275 (68), 260 (10).

*Data of 7c:* M.p. 218–220° ( $C_6H_6$ /hexane). IR (KBr): 3480, 3190, 1670, 1600.  $^1H$ -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,  $M^+$ ,  $C_{22}H_{22}O_5$ ), 91 (100).

*Data of 7d:* M.p. 215–218° ( $C_6H_6$ ). IR (KBr): 3335, 1675, 1600.  $^1H$ -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,  $M^+$ ,  $C_{28}H_{26}O_5$ ), 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.  $^1H$ -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,  $M^+$ ,  $C_{16}H_{20}O_4$ ), 261 (41), 231 (26).

*Data of 8c:* M.p. 190–192° ( $C_6H_6$ ). IR (KBr): 3360, 3250, 1600, 1450.  $^1H$ -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,  $M^+$ ,  $C_{22}H_{24}O_4$ ), 261 (27), 91 (100).

*Data of 8d:* M.p. 214–216° ( $C_6H_6$ ). IR (KBr): 3440, 3210, 1596.  $^1H$ -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,  $M^+$ ,  $C_{28}H_{28}O_4$ ), 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*-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.  $^1H$ -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,  $M^+$ ,  $C_{32}H_{38}O_8$ ), 532 (27), 514 (100).

*Data of 9c:* M.p. 172–174° ( $C_6H_6$ ). IR (KBr): 3360, 1590, 1440.  $^1H$ -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.  $^1H$ -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.  $^1H$ -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,  $M^+$ ,  $C_{32}H_{36}O_7$ ), 514 (76).

11. 1,8-Diisopropyl-2,3,9,10-tetramethoxy-6H,13H-5,12-dioxadibenzo[b,i]pyrene (**11a**), 3,10-Bis(benzyloxy)-1,8-diisopropyl-2,9-dimethoxy-6H,13H-5,12-dioxadibenzo[b,i]pyrene (**11c**), and 2,3,9,10-Tetrakis(benzyloxy)-1,8-diisopropyl-6H,13H-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  $\text{PBr}_3$  (2.07 ml, 22 mmol) in THF (10 ml) was added dropwise with stirring under  $\text{N}_2$  at  $0^\circ$ . Stirring was continued at  $20^\circ$  for 1 h, dry MeOH (5 ml) was added and the solvent evaporated. The residue was dissolved in dry acetone (100 ml), anh.  $\text{K}_2\text{CO}_3$  (4 g) was added and the mixture refluxed with stirring under  $\text{N}_2$  for 2 h. The solvent was evaporated,  $\text{H}_2\text{O}$  (100 ml) added, and the mixture extracted with  $\text{Et}_2\text{O}$  ( $4 \times 30$  ml). The combined org. extracts were washed with 10% NaOH soln.,  $\text{H}_2\text{O}$ , dried, and evaporated. The residue was chromatographed (50 g of silica gel,  $\text{C}_6\text{H}_6$ ) and crystallized from  $\text{C}_6\text{H}_6$ : **11a** (2.57 g, 50%), **11c** (3.00 g, 45%), or **11d** (3.28 g, 42%), resp.

**Data of 11a:** M.p.  $223\text{--}225^\circ$  ( $\text{C}_6\text{H}_6$ ). IR (KBr): 1580, 1440, 1400.  $^1\text{H-NMR}$  (80 MHz,  $\text{CDCl}_3$ ): 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,  $M^+$ ,  $\text{C}_{32}\text{H}_{34}\text{O}_6$ ).

**Data of 11c:** M.p.  $242\text{--}244^\circ$  ( $\text{C}_6\text{H}_6$ ). IR (KBr): 1595, 1450, 1420.  $^1\text{H-NMR}$  (250 MHz,  $(\text{D}_6)\text{DMSO}$ ): 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,  $M^+$ ,  $\text{C}_{44}\text{H}_{42}\text{O}_6$ ), 186 (13), 139 (17), 91 (34), 78 (72), 51 (100).

**Data of 11d:** M.p.  $211\text{--}213^\circ$  (dec.;  $\text{C}_6\text{H}_6$ ). IR (KBr): 1590, 1490, 1440.  $^1\text{H-NMR}$  (250 MHz,  $(\text{D}_6)\text{DMSO}$ ): 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-6H,13H-5,12-dioxadibenzo[b,i]pyrene-7-carbaldehyde (12)*. To a stirred soln. of **11a** (0.159 g, 0.31 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 ml),  $\text{SnCl}_4$  (0.11 ml, 0.9 mmol) was added at  $0^\circ$  under  $\text{N}_2$ . After addition of  $\text{Cl}_2\text{CHOCH}_3$  (0.075 ml, 0.9 mmol), stirring was continued for 30 min at  $20^\circ$ , the mixture poured into cold  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$ , the combined org. layer washed with 10%  $\text{Na}_2\text{CO}_3$  soln.,  $\text{H}_2\text{O}$ , and dried, the solvent evaporated, and the residue chromatographed (20 g of silica gel,  $\text{Et}_2\text{O}/\text{hexane}$  1:3): **12** (0.17 g, 60%). M.p.  $213\text{--}215^\circ$  (dec.;  $\text{C}_6\text{H}_6$ ). IR (KBr): 1665, 1590.  $^1\text{H-NMR}$  (80 MHz,  $\text{CDCl}_3$ ): 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,  $M^+$ ,  $\text{C}_{33}\text{H}_{34}\text{O}_7$ ), 499 (100).

13. *1,8-Diisopropyl-2,3,9,10-tetramethoxy-6H,13H-5,12-dioxadibenzo[b,i]pyrene-4-carbaldehyde (13)*. To a soln. of **11a** (0.165 g, 0.32 mmol) in dry  $\text{C}_6\text{H}_6$  (40 ml),  $t\text{-BuLi}$  (1.4M in pentane; 0.92 ml, 1.28 mmol) was added dropwise at  $20^\circ$  with stirring under  $\text{N}_2$ . After stirring at  $20^\circ$  for 4 h, DMF (0.12 ml, 1.5 mmol) was added and stirring continued at  $20^\circ$  for 30 min. The mixture was poured into 5% HCl soln. and extracted with  $\text{C}_6\text{H}_6$ . The org. phases were washed with 5%  $\text{NaHCO}_3$  soln. and  $\text{H}_2\text{O}$ , dried, and evaporated. The residue was purified by column chromatography (20 g of silica gel,  $\text{C}_6\text{H}_6$ ): **13** (0.017 g, 10%).  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ): 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,  $M^+$ ,  $\text{C}_{33}\text{H}_{34}\text{O}_7$ ).

14. *1,8-Diisopropyl-2,9-dimethoxy-6H-13H-5,12-dioxadibenzo[b,i]pyrene-3,10-diol (14a) and 1,8-Diisopropyl-6H,13H-5,12-dioxadibenzo[b,i]pyrene-2,3,9,10-tetrol (14b)*. To a soln. of **11c** or **11d** (2 mmol) in  $\text{EtOH}/\text{THF}/\text{AcOEt}$  4:1:1 (90 ml), 10% Pd/C (0.664 g) was added, and the mixture was shaken under 760 Torr of  $\text{H}_2$  for 1 h. The catalyst was filtered off and washed with hot THF, the solvent evaporated, and the residue crystallized from  $\text{C}_6\text{H}_6/\text{hexane}$ : **14a** (0.88 g, 91%) and **14b** (0.82 g, 90%), resp.

**Data of 14a:** M.p.  $> 300^\circ$  (dec.;  $\text{C}_6\text{H}_6/\text{hexane}$ ). IR (KBr): 3290, 1600, 1450, 1420.  $^1\text{H-NMR}$  (250 MHz,  $(\text{D}_6)\text{DMSO}$ ): 10.2 (br. s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 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,  $M^+$ ,  $\text{C}_{30}\text{H}_{30}\text{O}_6$ ), 471 (6), 428 (12), 243 (14), 228 (15).

**Data of 14b:** M.p.  $> 280^\circ$  (dec.;  $\text{C}_6\text{H}_6/\text{hexane}$ ). IR (KBr): 3380, 1610, 1510, 1418.  $^1\text{H-NMR}$  (250 MHz,  $(\text{D}_6)\text{DMSO}$ ): 10.18 (br. s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 8.50 (br. s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 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,  $M^+$ ,  $\text{C}_{28}\text{H}_{26}\text{O}_6$ ), 249 (0.6), 78 (69), 40 (100).

15. *3,10-Dihydroxy-1,8-diisopropyl-2,9-dimethoxy-6H,13H-5,12-dioxadibenzo[b,i]pyrene-4,11-dicarbaldehyde (2a)*. To a suspension of **14a** (0.243 g, 0.5 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 ml),  $\text{SnCl}_4$  (0.354 ml, 3 mmol) was added dropwise with stirring at  $20^\circ$  under  $\text{N}_2$ . After stirring for 15 min,  $\text{Cl}_2\text{CHOCH}_3$  (0.267 ml, 3 mmol) was added and stirring continued for 4 h at  $20^\circ$ . The mixture was poured into cold 5% HCl soln. and extracted with  $\text{CHCl}_3$ . The combined org. phases were washed with 5%  $\text{NaHCO}_3$  soln. and  $\text{H}_2\text{O}$ , dried, and evaporated. Purification of the residue by column chromatography (10 g of silica gel,  $\text{C}_6\text{H}_6/\text{hexane}/\text{Et}_2\text{O}$  1:1:1) and crystallization from  $\text{CH}_2\text{Cl}_2/\text{hexane}$  gave **2a** (0.168 g, 62%). M.p.  $312\text{--}313^\circ$  (dec.). IR (KBr): 1610, 1440, 1420.  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ): 14.53 (s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 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,  $M^+$ ,  $\text{C}_{32}\text{H}_{30}\text{O}_8$ ). Anal. calc. for  $\text{C}_{32}\text{H}_{30}\text{O}_8$  (542.56): C 70.83, H 5.57; found: C 70.73, H 5.75.

16. 2,3,9,10-Tetrahydroxy-6H,13H-5,12-dioxadibenzo[b,i]pyrene-4,11-dicarbaldehyde (**2b**). A soln. of **14b** (0.05 g, 0.11 mmol) in dry  $\text{CH}_2\text{Cl}_2/\text{THF}$  4:1 (2.5 ml) was added dropwise to a soln. of  $\text{SnCl}_4$  (0.5 ml, 4.2 mmol) and  $\text{Cl}_2\text{CHOCH}_3$  (1 ml, 11.2 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 ml) with stirring at  $0^\circ$  under  $\text{N}_2$ . The mixture was stirred at  $0^\circ$  for 2 h and at  $20^\circ$  for 1 h. Workup as described for **2a** and crystallization from  $\text{CH}_2\text{Cl}_2/\text{C}_6\text{H}_6$  gave **2b** (0.015 g, 27%). M.p.  $> 250^\circ$  (dec.). IR (KBr): 3510, 3300, 1610.  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3/(\text{D}_6)\text{DMSO}$ ): 14.70 (br. s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 11.25 (s, 2 H); 8.80 (br. s, OH, exchangeable with  $\text{D}_2\text{O}$ ); 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,  $M^+$ ,  $\text{C}_{30}\text{H}_{26}\text{O}_8$ ).

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