# Synthesis of a Regioisomer of β-Lapachone and Analogs as Potent Antitumor Agents

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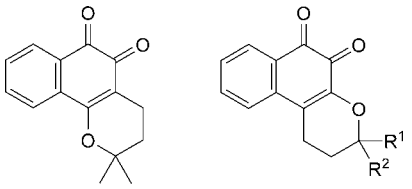
A regioisomer of β-lapachone and two analogs were synthesized and evaluated for their antitumor activities. All three compounds tested were found to exhibit promising activities against PC-3, HepG2, and Raji cancer cell lines in μM range.

**Introduction.** – β-Lapachone (**1**; *Fig.*) is a natural 1,2-naphthoquinone derivative, isolated from *Tabebuia* genus, with good antitumor activities [1–4]. Accordingly, a number of analogs and derivatives of β-lapachone have been synthesized and tested for their biological activities. However, structural modifications reported so far mainly focused on functionalization of the dihydropyran ring, as well as derivatization of the quinone moiety [5–10]. As part of our research program for the design of 3-oxygenated 1,2-naphthoquinones as antitumor agents [11], we herein report the synthesis and biological-activity study of **2a**, a regioisomer of β-lapachone (**1**), as well as its analogs **2b** and **2c**, which turned out to be active against several tumor cell lines in μM range.



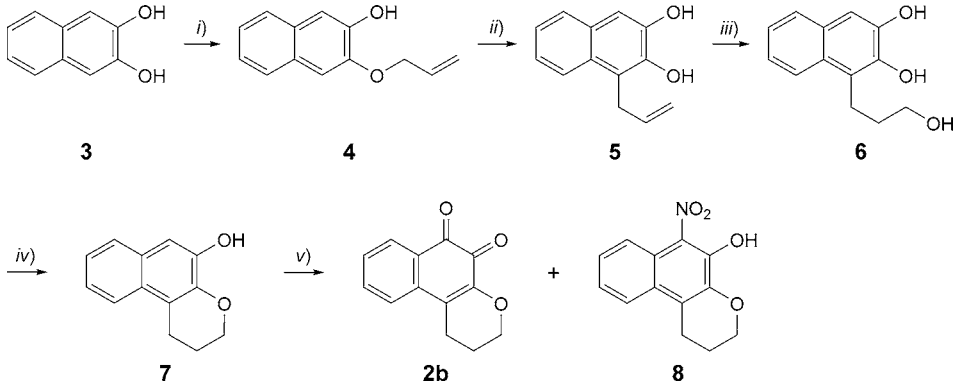

**1**

**2a** $R^1 = R^2 = Me$
**2b** $R^1 = R^2 = H$
**2c** $R^1 = MeO$, $R^2 = H$

Figure. *β-Lapachone* (**1**)*, Its Regioisomer* **2a***, and Analogs* **2b** *and* **2c**

**Results and Discussion.** – As outlined in *Scheme 1*, the synthesis of **2b** commenced with the monoallylation of commercially available naphthalene-2,3-diol (**3**). *Claisen* rearrangement of the allyloxy derivative **4** [12] gave **5** in 85% yield. Hydroboration/oxidation of the C=C bond in **5**, followed by ring closure of the resulting triol **6** *via Mitsunobu* reaction, led to the formation of dihydronaphtho[2,1-*b*]pyranol **7** in good

Scheme 1. *Synthesis of Naphthoquinone* **2b**

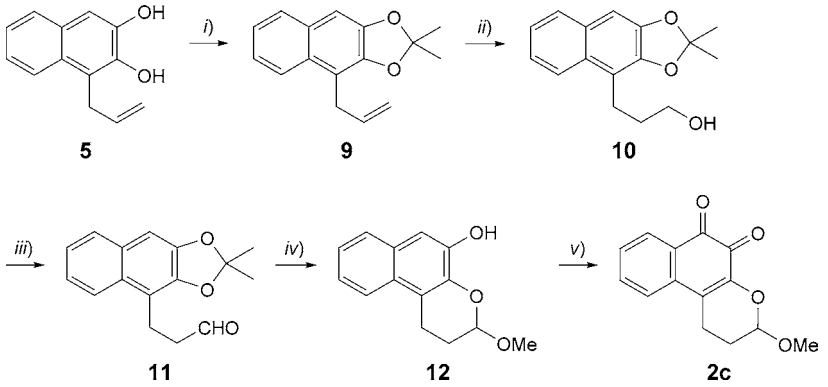



*i*) Allyl bromide, $K_2CO_3$, acetone, reflux, 4 h; 89%. *ii*) DMF, reflux, 1 h; 85%. *iii*) *a*) $BH_3 \cdot Me_2S$, THF, 0° – r.t., 2.5 h; *b*) $H_2O_2$, NaOH, THF/$H_2O$, reflux, 3 h; 75%. *iv*) Diisopropyl azodicarboxylate (DIAD), $Ph_3P$, THF, 0° – r.t., 1 h; 71%. *v*) *Dess–Martin* periodinane (DMP), $CH_2Cl_2$, r.t., 0.5 h; 50%.

yield. Treatment of **7** with $HNO_3$ in AcOH resulted in the formation of a mixture of the desired 1,2-naphthoquinone **2b** and the nitration product **8**, which could be isolated in 34 and 31% yield, respectively. A similar result was obtained when $(NH_4)_2Ce(NO_3)_6$ [13] was used as oxidant. Compound **8** could be converted to **2b** *via* reduction of the $NO_2$ group, followed by oxidation of the resulting aminonaphthalenol with concentrated $HNO_3$, but only in disappointing 21% yield. Fortunately, when *Dess–Martin* periodinane (DMP) was used as oxidant, **7** could be converted smoothly to **2b** in 50% yield.

To access to **2c**, the two vicinal OH groups in **5** were first protected to give **9** (*Scheme 2*). Hydroboration/oxidation of the C=C bond, followed by pyridinium

Scheme 2. *Synthesis of Naphthoquinone* **2c**



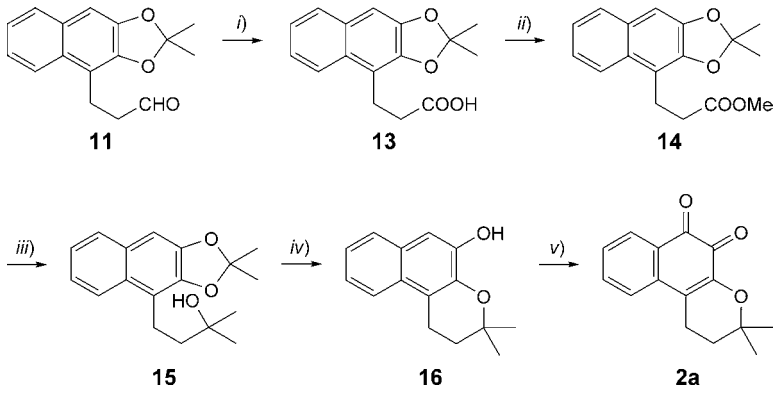

*i*) 2,2-Dimethoxypropane, TsOH, $CH_2Cl_2$, reflux, 21 h; 84%. *ii*) *a*) $BH_3 \cdot Me_2S$, THF, 0° – r.t., 2.5 h; *b*) $H_2O_2$, NaOH, THF/$H_2O$, reflux, 3 h; 71%. *iii*) Pyridinium chlorochromate (PCC), *Celite*, $CH_2Cl_2$, r.t., 3.5 h; 86%. *iv*) 10% HCl, MeOH, reflux, 3 h; 69%. *v*) DMP, $CH_2Cl_2$, r.t., 0.5 h; 50%.

chlorochromate (PCC) oxidation of the resulting alcohol **10**, provided aldehyde **11**, which was treated with HCl/MeOH to give **12** *via* sequential deprotection and acetal formation. Oxidation of **12** with DMP as described for the synthesis of **2b** gave **2c** in 50% yield.

The synthesis of **2a** is outlined in *Scheme 3*. Oxidation of aldehyde **11** with $^t$BuOOH in the presence of CuCl gave acid **13**, esterification of which, followed by treatment of the resulting ester **14** with MeLi, provided the tertiary alcohol **15** in good yield. It should be indicated that the $^i$Pr protecting group was not affected by the catalytic amount of $H_2SO_4$ used during the esterification step. Treatment of **15** with HCl furnished **16** in excellent yield. Finally, oxidation of **16** with DMP under identical conditions as for the synthesis of **2b** and **2c** gave 1*H*-naphtho[2,1-*b*]pyran-5,6-dione **2a** in 65% yield.

The *in vitro* antitumor activities of the synthesized compounds **2a**–**2c** against PC-3, HepG2, and *Raji* cell lines was evaluated by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay. The results are collected in the *Table*. All three compounds exhibited cytotoxic activities against the tested tumor cell lines in μM range. Compared with **2b**, **2a** and **2c** showed higher activities against all three tumor cell lines, indicating that the substituents at C(2) of the dihydropyran ring should

Scheme 3. *Synthesis of Naphthoquinone* **2a**




*i*) $^t$BuOOH, CuCl, MeCN, r.t., 15 h; 59%. *ii*) $H_2SO_4$, MeOH, reflux, 3 h; 89%. *iii*) MeLi, THF, −78° – r.t., 2 h; then $H^+$, 84%. *iv*) 10% HCl, MeOH, reflux, 8 h; 96%. *v*) DMP, $CH_2Cl_2$, r.t., 0.5, 65%.

Table. In Vitro *Antitumor Activities of* **2a**–**2c**

| Compound | $IC_{50}$ [μM] | | |
|---|---|---|---|
| | PC-3 | HepG2 | *Raji* |
| **2a** | 12.5 | 6.7 | 4.7 |
| **2b** | 25.6 | 34.3 | 10.0 |
| **2c** | 13.3 | 9.4 | 6.4 |
| *β*-Lapachone | 8.9 | 3.6 | 11.9 |

have a significant effect on the cytotoxicity. It is noteworthy that **2a** and **2c** exhibited higher activities against *Raji* cell lines, although they were not as potent as $\beta$-lapachone against PC-3 and HepG2 tumor cell lines.

**Conclusions.** – In summary, we synthesized a regioisomer of $\beta$-lapachone, together with two analogs, which showed promising activities against PC-3, HepG2, and *Raji* cell lines. Further structure–activity relationship studies are currently underway.

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## Experimental Part

*General*. Solvents were dried according to standard procedures [14] where needed. M.p.: *XT4A* Hot-stage apparatus; uncorrected. Flash column chromatography (FC): silica gel ($SiO_2$; 200–300 mesh). IR Spectra: *Bruker IFS25 FT-IR* spectrometer; $\tilde{\nu}$ in $cm^{-1}$. $^1$H- and $^{13}$C-NMR spectra: *Bruker AV400* instrument (400 and 100 MHz, resp.); $\delta$ in ppm rel. to $Me_4Si$ as internal standard, $J$ in Hz. MS: *Micromass Q-TOF* mass spectrometer; in $m/z$ (rel. %).

*1-(Prop-2-en-1-yl)naphthalene-2,3-diol* (**5**). A mixture of *2-(prop-2-enyloxy)naphthalen-1-ol* (**4**; 354 mg, 1.77 mmol) and DMF (2 ml) was heated under reflux for 1 h and then cooled. $H_2O$ (15 ml) was added. The resulting mixture was extracted with AcOEt (3 × 10 ml). The combined org. extracts were washed with brine (3 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 20% AcOEt in petroleum ether (PE)) to give **5** (302 mg, 85%). Colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.85 (*d*, *J* = 8.0, 1 H); 7.65 (*dd*, *J* = 7.6, 1.2, 1 H); 7.41–7.32 (*m*, 2 H); 7.14 (*s*, 1 H); 6.10 (*ddt*, *J* = 16.8, 10.4, 6.0, 1 H); 5.91 (br. *s*, 2 H); 5.15–5.09 (*m*, 2 H); 3.86 (*dt*, *J* = 5.6, 1.6). $^{13}$C-NMR (100 MHz, $CDCl_3$): 143.8; 142.5; 135.9; 129.7; 128.5; 127.1; 124.3; 124.1; 123.2; 118.2; 116.1; 108.9; 29.6. ESI-MS: 223 (50, $[M+Na]^+$), 201 (100, $[M+H]^+$).

*1-(3-Hydroxypropyl)naphthalene-2,3-diol* (**6**). $BH_3 \cdot Me_2S$ (2M soln. in THF, 1 ml, 2.0 mmol) was added dropwise to a soln. of **5** (205 mg, 1.03 mmol) in dry THF (10 ml) at 0° under $N_2$. After addition, the mixture was stirred at 0° for 0.5 h, before it was allowed to warm to r.t. and stirred for further 2 h. NaOH (3N, 0.4 ml) and 30% $H_2O_2$ (0.4 ml) were added. The resulting mixture was heated under reflux for 3 h. The bulk of solvent was evaporated *in vacuo*. The residue was partitioned between AcOEt (20 ml) and $H_2O$ (15 ml). The separated aq. layer was extracted with AcOEt (2 × 20 ml). The combined org. extracts were washed with brine (2 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 50% AcOEt in PE) to afford **6** (168 mg, 75%). Colorless oil. $^1$H-NMR (400 MHz, $CD_3OD$): 7.80 (*d*, *J* = 8.3, 1 H); 7.52 (*dd*, *J* = 7.9, 1.4, 1 H); 7.24–7.15 (*m*, 2 H); 6.99 (*s*, 1 H); 3.61 (*t*, *J* = 6.5, 2 H); 3.11 (*m*, 2 H); 1.86 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CD_3OD$): 146.9; 145.0; 131.1; 129.4; 127.7; 124.2; 124.0; 123.7; 121.3; 108.5; 62.8; 33.4; 22.3. ESI-MS: 217 (100, $[M-H]^+$).

*2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran-5-ol* (**7**). To a soln. of $Ph_3P$ (403 mg, 1.54 mmol) in dry THF (5 ml) at 0°, diisopropyl azodicarboxylate (DIAD; 311 mg, 1.54 mmol) was added within 0.5 h. A soln. of **6** (168 mg, 0.77 mmol) in dry THF (5 ml) was then added. Then, the mixture was allowed to warm to r.t. and stirred for 0.5 h. The bulk of solvent was evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 20% AcOEt in PE) to give **7** (109 mg, 71%). Reddish oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.75–7.67 (*m*, 2 H); 7.40–7.33 (*m*, 2 H); 7.18 (*s*, 1 H); 5.93 (*s*, 1 H); 4.35 (*t*, *J* = 5.2, 2 H); 3.08 (*t*, *J* = 6.4, 2 H); 2.21 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 145.2; 142.5; 129.4; 127.9; 127.2; 124.1; 123.8; 121.8; 114.8; 107.6; 66.8; 22.2; 21.0. ESI-MS: 223 (100, $[M+Na]^+$), 201 (24, $[M+H]^+$).

*2,2-Dimethyl-4-(prop-2-en-1-yl)naphtho[2,3-*d*][1,3]dioxole* (**9**). A mixture of **5** (240 mg, 1.2 mmol), 2,2-dimethoxypropane (250 mg, 2.4 mmol), and TsOH (20 mg, 0.12 mmol) in dry $CH_2Cl_2$ (5 ml) was heated under reflux for 21 h and then cooled. The bulk of solvent was evaporated *in vacuo*. The residue was partitioned between AcOEt (10 ml) and $H_2O$ (15 ml). The separated aq. layer was extracted with AcOEt (2 × 10 ml). The combined org. extracts were washed successively with sat. aq. $NaHCO_3$ soln. (2 × 10 ml) and brine (2 × 10 ml), and then dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The

residue was purified by FC ($SiO_2$; PE) to give **9** (242 mg, 84%). Orange oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.81 (*dd*, *J* = 8.0, 1.2, 1 H); 7.67 (*dd*, *J* = 7.6, 1.6, 1 H); 7.37 – 7.29 (*m*, 2 H); 6.98 (*s*, 1 H); 6.05 (*ddt*, *J* = 17.6, 9.6, 6.0, 1 H); 5.10 – 5.05 (*m*, 2 H); 3.73 (*dt*, *J* = 6.0, 1.6, 1 H); 1.75 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 147.2; 146.1; 135.7; 130.9; 129.4; 127.6; 123.9; 123.8; 123.2; 117.6; 115.7; 112.9; 102.5; 29.7; 26.2. ESI-MS: 263 (31, $[M + Na]^+$), 241 (100, $[M + H]^+$).

*3-(2,2-Dimethylnaphtho[2,3-*d*][1,3]dioxol-4-yl)propan-1-ol* (**10**). $BH_3 \cdot Me_2S$ (2M soln. in THF, 0.59 ml, 1.18 mmol) was added dropwise to a soln. of **9** (187 mg, 0.78 mmol) in dry THF (5 ml) at 0° under $N_2$. After addition, the mixture was stirred at 0° for 0.5 h before being allowed to warm to r.t. and stirred for further 2 h. NaOH (3N, 0.23 ml) and 30% $H_2O_2$ (0.23 ml) were added. The resulting mixture was heated under reflux for 3 h. The bulk of solvent was evaporated *in vacuo*. The residue was partitioned between AcOEt (20 ml) and $H_2O$ (15 ml). The separated aq. layer was extracted with AcOEt (2 × 20 ml). The combined org. extracts were washed with brine (2 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 20% AcOEt in PE) to give **10** (143 mg, 71%). Colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.83 (*d*, *J* = 8.0, 1 H); 7.65 (*dd*, *J* = 7.6, 1.6, 1 H); 7.37 – 7.28 (*m*, 2 H); 6.95 (*s*, 1 H); 3.63 (*t*, *J* = 6.4, 2 H); 3.08 (*t*, *J* = 7.2, 2 H); 1.99 – 1.92 (*m*, 3 H); 1.73 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 146.6; 145.7; 131.0; 129.0; 127.6; 123.9; 123.8; 122.7;117.5; 114.5; 102.3; 61.7; 31.8; 26.0; 21.0. ESI-MS: 281 (100, $[M + Na]^+$), 259 (47, $[M + H]^+$).

*3-(2,2-Dimethylnaphtho[2,3-*d*][1,3]dioxol-4-yl)propanal* (**11**). A mixture of **10** (143 mg, 0.55 mmol), PCC (237 mg, 1.1 mmol), and *Celite* (474 mg) in $CH_2Cl_2$ (10 ml) was stirred at r.t. for 3.5 h and then filtered. The filtrate was evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 11% AcOEt in PE) to give **11** (121 mg, 86%). Colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): 9.88 (*t*, *J* = 1.6, 1 H); 7.76 (*d*, *J* = 8.4, 1 H); 7.66 (*dd*, *J* = 8.0, 1.6, 1 H); 7.38 – 7.30 (*m*, 2 H); 6.96 (*s*, 1 H); 3.30 (*t*, *J* = 7.6, 2 H); 2.82 (*td*, *J* = 7.6, 1.6, 2 H); 1.73 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 202.0; 147.1; 145.9; 131.0; 128.8; 127.9; 124.2; 124.0; 122.3; 117.9; 113.3; 102.7; 43.4; 26.2; 18.3. ESI-MS: 279 (86, $[M + Na]^+$), 257 (100, $[M + H]^+$).

*2,3-Dihydro-3-methoxy-1*H*-naphtho[2,1-*b*]pyran-5-ol* (**12**). A mixture of aldehyde **11** (98 mg, 0.38 mmol) in MeOH (5 ml) and 10% aq. HCl (3 ml) was heated under reflux for 3 h and then cooled. MeOH was evaporated *in vacuo*. The residue was extracted with AcOEt (10 ml). The separated org. layer was washed with brine (3 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 15% AcOEt in PE) to give **12** (61 mg, 69%). Orange oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.77 – 7.65 (*m*, 2 H); 7.36 – 7.33 (*m*, 2 H); 7.19 (*s*, 1 H); 5.87 (br. *s*, 1 H); 5.34 (*t*, *J* = 2.8, 1 H); 3.52 (*s*, 3 H); 3.12 – 3.08 (*m*, 2 H); 2.31 – 2.25 (*m*, 1 H); 2.16 – 2.08 (*m*, 1 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 145.2; 139.1; 129.7; 127.5; 127.2; 124.3; 123.9; 122.0; 115.5; 108.0; 98.8; 56.1; 26.3; 17.2. ESI-MS: 253 (100, $[M + Na]^+$).

*3-(2,2-Dimethylnaphtho[2,3-*d*][1,3]dioxol-4-yl)propanoic Acid* (**13**). To a soln. of **11** (128 mg, 0.5 mmol) in dry MeCN (10 ml) were added CuCl (5 mg, 0.05 mmol) and *t*BuOOH (70% soln., 0.09 ml). The resulting mixture was stirred at r.t. for 15 h. The bulk of solvent was evaporated *in vacuo*. The residue was partitioned between AcOEt (10 ml) and $H_2O$ (10 ml). The separated org. layer was washed with brine (2 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 25% AcOEt in PE) to give **13** (80 mg, 59%). Colorless solid. $^1$H-NMR (400 MHz, $CDCl_3$): 7.82 (*d*, *J* = 8.0, 1 H); 7.67 (*dd*, *J* = 8.0, 1.2, 1 H); 7.40 – 7.30 (*m*, 2 H); 6.97 (*s*, 1 H); 3.32 (*t*, *J* = 8.0, 2 H); 2.76 (*t*, *J* = 8.0, 2 H); 1.73 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 179.3; 147.1; 146.1; 131.0; 128.8; 127.8; 124.3; 124.0; 122.4; 117.9; 113.1; 102.7; 33.6; 26.2; 20.9. ESI-MS: 295 (100, $[M + Na]^+$), 273 (18, $[M + H]^+$).

*Methyl 3-(2,2-Dimethylnaphtho[2,3-*d*][1,3]dioxol-4-yl)propanoate* (**14**). A mixture of **13** (70 mg, 0.25 mmol) and conc. $H_2SO_4$ (0.03 ml) in MeOH (5 ml) was heated under reflux for 3 h and then cooled. The bulk of solvent was evaporated *in vacuo*. The residue was partitioned between AcOEt (10 ml) and $H_2O$ (10 ml). The separated aq. layer was extracted with AcOEt (2 × 10 ml). The combined org. extracts were washed with brine (2 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 11% AcOEt in PE) to give **14** (66 mg, 89%). Colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.83 (*d*, *J* = 8.4, 1 H); 7.66 (*dd*, *J* = 8.0, 1.2, 1 H); 7.39 – 7.29 (*m*, 2 H); 6.96 (*s*, 1 H); 3.72 (*s*, 3 H); 3.33 – 3.29 (*m*, 2 H); 2.72 – 2.68 (*m*, 2 H); 1.74 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 173.4; 146.9; 145.8; 130.8; 128.8; 127.6; 124.0; 123.8; 122.3; 117.6; 113.4; 102.5; 51.7; 33.6; 26.0; 21.0. ESI-MS: 309 (20, $[M + Na]^+$), 287 (100, $[M + H]^+$).

*4-(2,2-Dimethylnaphtho[2,3-*d*][1,3]dioxol-4-yl)-2-methylbutan-2-ol* (**15**). To a soln. of **14** (66 mg, 0.23 mmol) in dry THF (5 ml) at $-78°$ under $N_2$ was added MeLi (1.6M soln. in $Et_2O$, 0.42 ml). Then, the mixture was allowed to warm to r.t. and stirred for 2 h, before the reaction was quenched with $H_2O$. 2M HCl was added until a pH of 7 was reached. The bulk of THF was evaporated *in vacuo*. The residue was extracted with AcOEt (2 × 10 ml). The combined org. extracts were washed with brine (2 × 10 ml), dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 15% AcOEt in PE) to give **15** (55 mg, 84%). Colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): 7.83 (*d*, *J* = 8.0, 1 H); 7.65 (*dd*, *J* = 7.6, 1.2, 1 H); 7.37–7.28 (*m*, 2 H); 6.93 (*s*, 1 H); 3.07–3.03 (*m*, 2 H); 1.85–1.81 (*m*, 2 H); 1.73 (*s*, 6 H); 1.36 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 147.1; 145.6; 131.0; 129.1; 127.7; 124.0; 123.8; 122.7; 117.6; 115.7; 102.1; 71.2; 43.1; 29.4; 26.2; 20.4. ESI-MS: 309 (100, $[M+Na]^+$), 287 (24, $[M+H]^+$).

*2,3-Dihydro-3,3-dimethyl-1*H-*naphtho[2,1-*b*]pyran-5-ol* (**16**). A mixture of **15** (40 mg, 0.14 mmol), 10% aq. HCl (1 ml), and MeOH (3 ml) was heated under reflux for 8 h and then cooled. MeOH was evaporated *in vacuo*. $H_2O$ (5 ml) was added, and the resulting mixture was extracted with AcOEt (3 × 10 ml). The combined org. extracts were dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$; 20% AcOEt in PE) to give **16** (31 mg, 96%). Colorless solid. M.p. 52–54°. $^1$H-NMR (400 MHz, $CDCl_3$): 7.75 (*m*, 1 H); 7.66 (*m*, 1 H); 7.38–7.30 (*m*, 2 H); 7.16 (*s*, 1 H); 5.98 (*s*, 1 H); 3.05 (*t*, *J* = 6.8, 2 H); 2.00 (*t*, *J* = 6.8, 2 H); 1.43 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 145.5; 141.1; 129.1; 127.6; 127.0; 123.8; 123.6; 121.7; 113.2; 107.3; 75.7; 32.7; 26.5; 19.1. ESI-MS: 251 (100, $[M+Na]^+$), 229 (40, $[M+H]^+$).

*General Procedure for the Synthesis of Naphthoquinones* **2a**, **2b**, *and* **2c**. To a soln. of phenol **16**, **7**, or **12** (1.0 mmol) in $CH_2Cl_2$ (4 ml) was added DMP (1.0 mmol). The resulting mixture was stirred in the dark for 0.5 h, before being washed successively with sat. aq. solns. of $NaHCO_3$ (3 × 5 ml) and $Na_2S_2O_3$ (3 × 5 ml). The separated org. layer was dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified by FC ($SiO_2$) to give **2a**, **2b**, or **2c**, resp.

*2,3-Dihydro-3,3-dimethyl-1*H-*naphtho[2,1-*b*]pyran-5,6-dione* (**2a**). The crude product was purified by FC ($SiO_2$; 25% AcOEt in PE) to give **2a** (65%). Red solid. M.p. 75–77°. $^1$H-NMR (400 MHz, $CDCl_3$): 8.01 (*dd*, *J* = 7.8, 1.5, 1 H); 7.59 (*td*, *J* = 7.8, 1.5, 1 H); 7.36–7.28 (*m*, 2 H); 2.65 (*t*, *J* = 6.6, 2 H); 1.92 (*t*, *J* = 6.6, 2 H); 1.41 (*s*, 6 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 179.1; 175.8; 146.6; 136.5; 136.1; 130.0; 128.6; 128.0; 124.3; 123.9; 75.7; 32.0; 26.3; 20.3. ESI-MS: 265 (100, $[M+Na]^+$), 243 (47, $[M+H]^+$).

*2,3-Dihydro-1*H-*naphtho[2,1-*b*]pyran-5,6-dione* (**2b**). The crude product was purified by FC ($SiO_2$; 40% AcOEt in PE) to give **2b** (50%). Red solid. M.p. 79–81°. $^1$H-NMR (400 MHz, $CDCl_3$): 8.01 (*dd*, *J* = 8.0, 1.5, 1 H); 7.59 (*td*, *J* = 7.5, 1.5, 1 H); 7.35–7.27 (*m*, 2 H); 4.24 (*t*, *J* = 5.0, 2 H); 2.67 (*t*, *J* = 6.5, 2 H); 2.13 (*m*, 2 H). $^{13}$C-NMR (100 MHz, ($D_6$)DMSO): 178.1; 174.3; 147.4; 136.1; 135.7; 128.6; 128.5; 127.7; 124.8; 124.2; 65.5; 21.1; 20.9. ESI-MS: 237 (100, $[M+Na]^+$), 215 (23, $[M+H]^+$).

*2,3-Dihydro-3-methoxy-1*H-*naphtho[2,1-*b*]pyran-5,6-dione* (**2c**). The crude product was purified by FC ($SiO_2$; 25% AcOEt in PE) to give **2c** (50%). Red solid. M.p. 80–82°. $^1$H-NMR (400 MHz, $CDCl_3$): 8.05 (*d*, *J* = 7.5, 1 H); 7.61 (*t*, *J* = 7.5, 1 H); 7.40–7.34 (*m*, 2 H); 5.30 (*m*, 1 H); 3.51 (*s*, 3 H); 2.81–2.59 (*m*, 2 H); 2.22 (*m*, 1 H); 2.00 (*m*, 1 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 178.9; 175.2; 144.3; 136.1; 135.9; 130.1; 128.8; 128.5; 127.7; 124.2; 97.7; 56.3; 25.4; 17.7. ESI-MS: 267 (100, $[M+Na]^+$).

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