New Synthetic Procedure for 2-Aryl-1,4-naphthoquinone-1-oxime Methyl Ethers with Potent Antitumor Activity

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Received: 09.05.2014; Accepted after revision: 26.05.2014

Abstract: 1,4-Naphthoquinone 1-oxime methyl ethers carrying an ester-substituted aryl pendant at 2-position were concisely prepared as seed compounds with structural flexibility for structure–activity relationship studies on antitumor activity. The key synthetic intermediate was a phthalide–tetralone spiro compound, which was provided by palladium-coupling reaction between 2-bromobenzoate and 1-tetralone followed by OsO_4–NMO oxidation.

Key words: coupling reaction, oxidation, oxime, quinone, spiro compound

2-Aryl-6,7-methylenedioxy-1,4-naphthoquinone-1-oxime methyl ether derivatives **1**, the synthetic intermediates for 12-methoxybenzo[*c*]phenanthridine alkaloids,[1] showed potent antitumor activity, and preliminary structure–activity relationship (SAR) suggested that the 6,7-methylenedioxy-1,4-naphthoquinone 1-oxime methyl ether skeleton was responsible, while the 2-aryl pendant was tolerant, for the strong cytotoxicity.[2] Thus, at this stage, although 2-methoxy-4,5-methylenedioxyphenyl- (**1a**),[1a] 7-methoxy-2-methylbenzofuran-4-yl- (**1b**),[1b,3] and 3,4-dimethoxy-2-methoxycarbonylphenyl-substituted naphthoquinone oximes (**1c**)[1b,3] were nominated as seed compounds for optimization, the last ester-substituted **1c** could be the most likely candidate as one of easily functionalizable naphthoquinone derivatives for further in vivo assay experiments. The 2-arylnaphthoquinone oximes **1** (Figure 1) could be prepared by either basic nitrosation (*i*-AmONO, K_2CO_3 in DMF)[4] of the corresponding 3-aryl-1-naphthols **2** followed by methylation or DDQ oxidation[5] of 2-aryl-1-tetralone oxime ethers **3** in hot AcOH–benzene. However, these synthetic precursors **2** and **3** had been prepared from aryl benzyl ketones and chalcones, respectively, through a linear step-by-step procedure. In addition, the latter DDQ oxidation was limited to the preparation of naphthoquinone oximes carrying an electron-rich aryl pendant such as the trialkoxyphenyl function.[5] These synthetic limitation forced us to develop an alternative concise method for the synthesis of the ester-substituted naphthoquinone oxime **1c** and its analogues with structural flexibility. We previously reported the convergent asymmetric synthesis of (–)-arnottin II [6,7-methylenedioxy-1-tetralone-2-spiro-3′-(6,7-dimethoxyphthalide), (**4**)],[6] a unique neutral natural product with phthalide–tetralone spiro structure, via dihydroarnottin I {7,8-dimethoxy-2,3-methylenedioxy-6*H*-benzo[*d*]-3,4-dihydronaphtho[1,2-*b*]pyran-6-one, (**7a**)}[7] directly prepared by palladium-catalyzed coupling reaction between 2-bromobenzoate and 1-tetralone.[8] In this paper we present the alternative concise preparation of ester-substituted naphthoquinone oximes like **1c** through spiro compounds like **4** as key synthetic intermediates.

At first we examined the synthesis of the known ester-substituted naphthoquinone oxime **1c**[1b,3] and their congeners **1d–f** using dihydroarnottin II (**8a**)[6,7] as a key intermediate (Scheme 1).[9] According to the reported procedure,[6] the spiro tetralone **8a** was prepared by palladium-catalyzed coupling reaction between 6-bromo-2,3-dimethoxybenzoate (**5a**) and 6,7-methylenedioxy-1-tetralone (**6**) followed by dihydroxylation of dihydroarnottin I (**7a**) formed with osmium tetroxide–*N*-methylmorpholine (OsO_4–NMO) system. Direct construction of the 1,4-naphthoquinone 1-oxime unit by oxidation with hypervalent iodine reagents such as IBX and PIFA, after conversion of the tetralone **8a** into oxime compound **9a**, resulted in ineffective production of the carboxyl-substituted naphthoquinone oxime skeleton **1d** (ca. 10%). Although trials for the introduction of hydroxyl function to the spiro oxime **9a** by successive treatment of NBS and aqueous THF failed, when the same treatment was applied to the spiro tetralone **8a** the oxidation reaction was successfully proceeded to give the hydroxyl-inserted spiro tetralone **10a**,[10] which was composed of a ca 1:1 diastereoisomeric mixture of *cis* (31%) and *trans* isomers (28%). The stereochemistry of the isomers was determined by NOE experiments.[11] Independent treatment of each isomer *cis*- and *trans*-**10a** with NH_2OMe smoothly afforded the intended hydroxyl-inserted oxime derivative *cis*- and *trans*-**11a**, respectively, with a major *Z* configuration of the oxime function (*E*/*Z* = 1:3). In practical preparation, a diastereoisomeric mixture of hydroxyl-inserted spiro tetralones **10a** was subjected to oximation without separation. The hydroxyl oxime mixture **11a** obtained was oxidized with IBX followed by treatment with Et_3N to provide the carboxyl-substituted naphthoquinone oxime skeleton **1d**[12] in high yield. Conventional esterification of **1d** smoothly afforded the target ester-substituted naphthoquinone oxime **1c**,[1b,3,13] and the corresponding phenolic derivatives **1e** and **1f**[14] were also prepared by selective demethylation of

SYNLETT 2014, 25, 2059–2063
Advanced online publication: 01.07.2014
DOI: 10.1055/s-0034-1378342; Art ID: st-2014-d0406-l

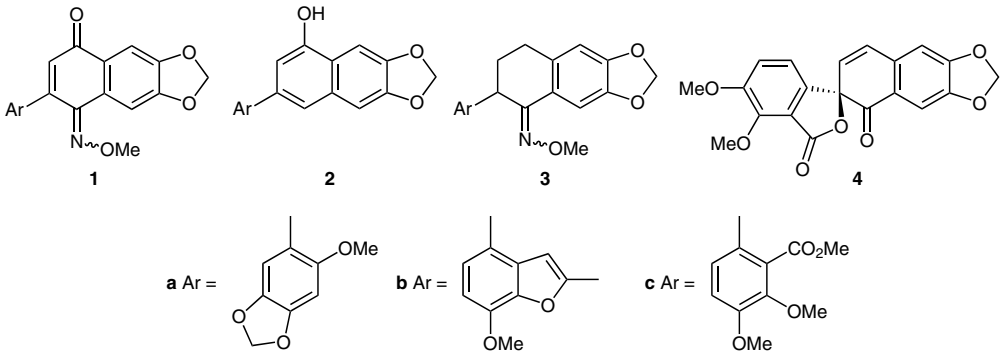
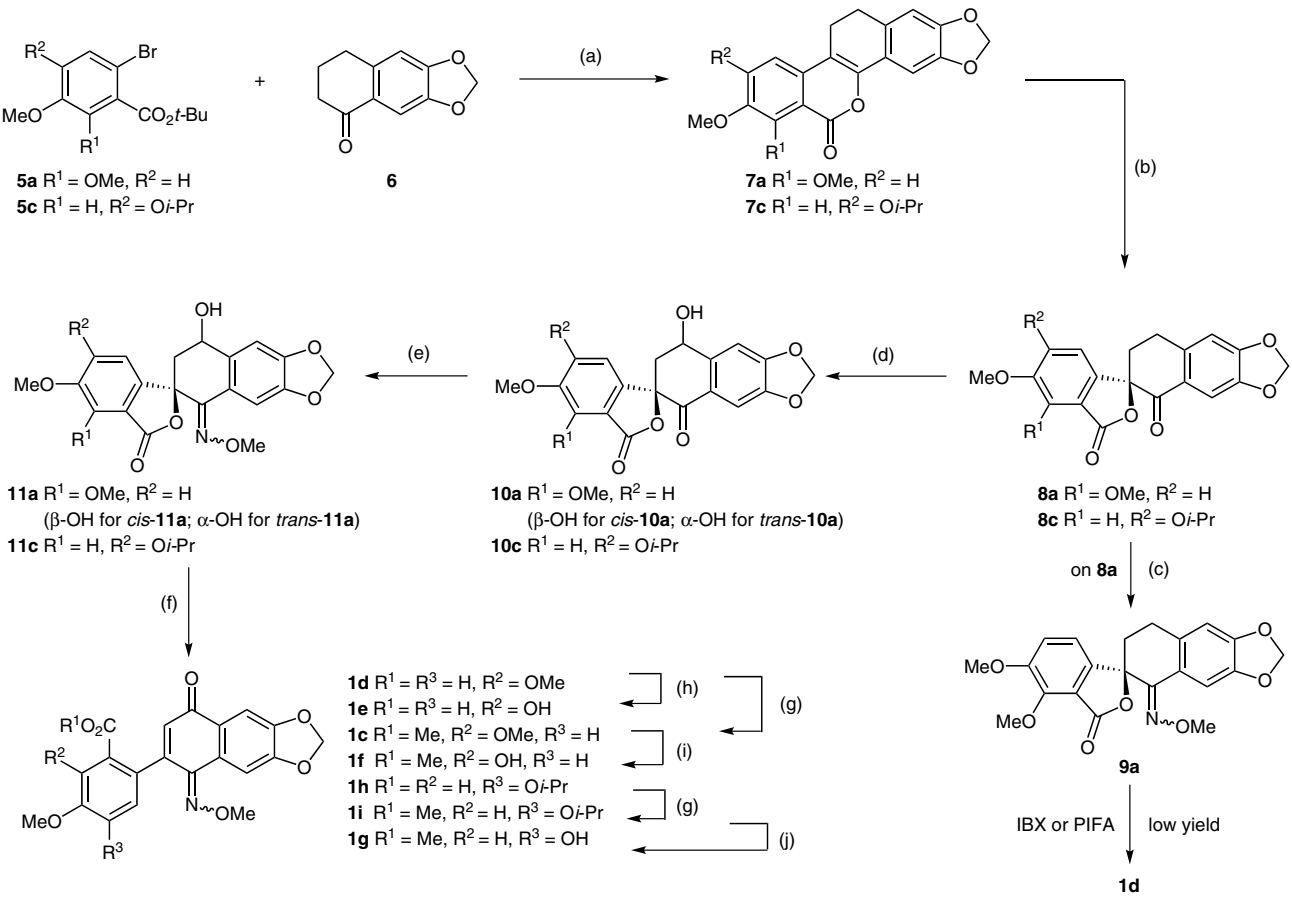


Figure 1 Structures of 2-aryl-1,4-naphthoquinone 1-oxime methyl ethers **1**, 3-aryl-1-naphthols **2**, 2-aryl-1-tetralone oxime ethers **3**, and (–)-arnottin II (**4**)

a methoxy function next to the carboxyl group of **1d** and **1c**, respectively.

Next, the synthesis of a structurally isomeric ester-substituted naphthoquinone oxime **1g** with 5-hydroxy-4-methoxy-2-methoxycarbonylphenyl pendant at the 2-position was carried out using the benzyl group as phenol protection (Scheme 2).[9] The spiro tetralone **8b** was prepared from 4-benzyloxy-2-bromo-5-methoxybenzoate (**5b**), which was derived from the corresponding benzaldehyde by Pinnick oxidation and esterification, by palladium-coupling reaction followed by OsO_4–NMO



Scheme 1 Preparation of carboxylate-substituted naphthoquinone oximes **1c**–**i**. *Reagents and conditions*: (a) $Pd(dba)_3$, Cs_2CO_3, Xantphos, $Na_2S_2O_5$, toluene, 100 °C, 48 h, argon (**7a**: 72%; **7c**: 73%); (b) OsO_4, NMO, CH_2Cl_2–acetone–H_2O, 40 °C, 10 d on **7a** (30 °C, 5 d on **7c**; **8a**: 96%; **8c**: 79%); (c) NH_2OMe·HCl, pyridine, 80 °C, 41 h (95%); (d) (1) NBS, AIBN, benzene, 85 °C, 1.5 h on **8a** (2 h on **8c**), argon; (2) THF, H_2O, r.t., 16 h on **8a** [17 h on **8c**; **10a**: 59% (*trans*-**10a**: 28%; *cis*-**10a**: 31%); **10c**: 66%]; (e) NH_2OMe·HCl, pyridine, 65 °C, 2 d on *trans*-**10a** (1 d on *cis*-**10a** and **10c**; *trans*-**11a**: 92%; *cis*-**11a**: 94%; **11c**: 86%); (f) (1) IBX, DMSO, 60 °C, 2 h; (2) Et_3N, CH_2Cl_2, r.t., 17 h (**1d**: 90%; **1h**: 69%); (g) MeI, K_2CO_3, DMF, r.t., 2 h (**1e**: 92%; **1i**: 68%); (h) BCl_3, CH_2Cl_2, –40 °C, 16 h (63%); (i) BCl_3, CH_2Cl_2, –78 °C, 2 h (92%); (j) (1) MeI, K_2CO_3, DMF, r.t., 1 h (68%); (2) BBr_3, CH_2Cl_2, –78 °C, 40 min (73%).

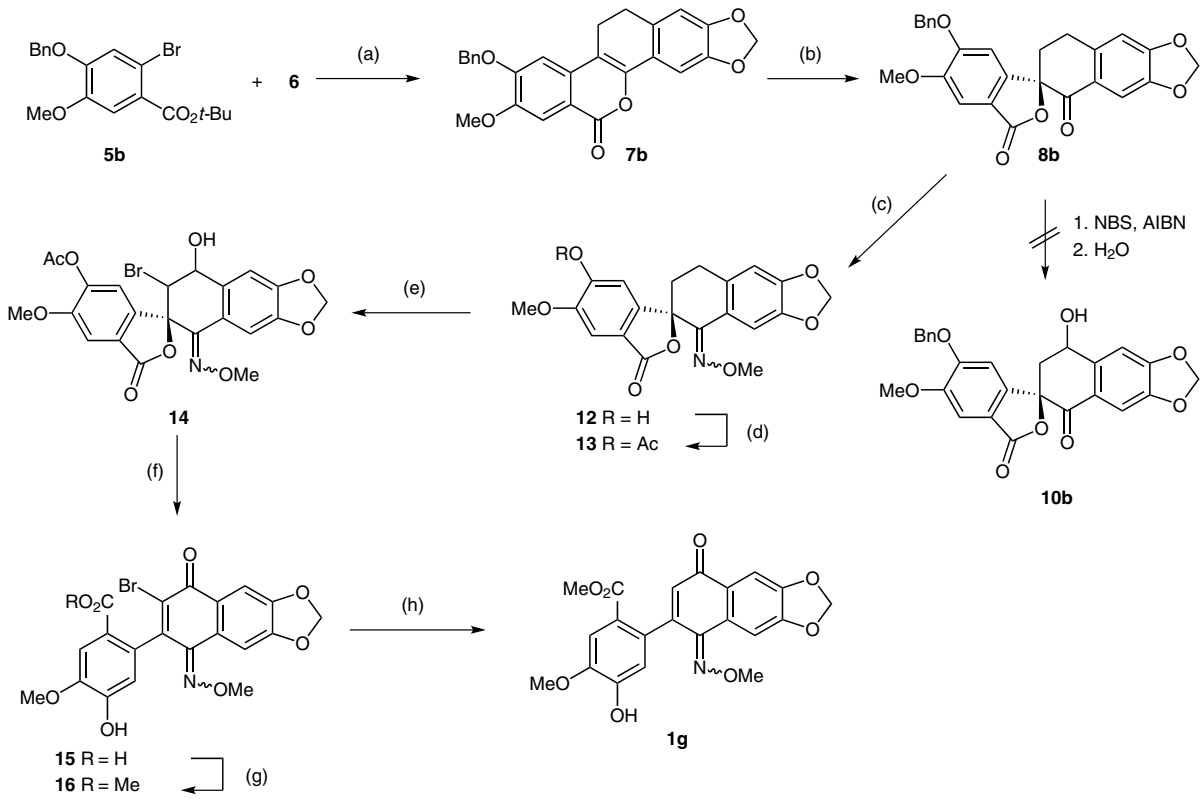
oxidation as described in Scheme 1. Unfortunately, the NBS-mediated hydroxyl-insertion giving hydroxyl-inserted spiro tetralone **10b** was unsuccessful. Although the failure may be caused by the presence of benzyloxy group, no products were formed even after removal of the benzyl protection. Therefore, our attention was turned to spiro oxime **13** with easily deprotectable acetyl function albeit in much lower yield in comparison with tetralone oxime **9a**. The spiro oxime **13** was smoothly prepared by three-step reactions of debenzylation, oximation, and acetylation. However, an additionally bromine-incorporating hydroxyl oxime **14**, not a hydroxyl oxime like **11**, was unexpectedly formed in 29% yield when **13** was subjected to NBS-mediated hydroxylation. Extra insertion of the bromine atom during the reaction could be deduced by three successive reactions of benzylic bromination, dehydrobromination, and bromohydrin formation. Conversion of the spiro bromohydrin **14** into the naphthoquinone oxime structure **15** was similarly achieved by combination of IBX oxidation and base treatment as shown in Scheme 1 (**11a** → **1d**). Finally, palladium-catalyzed reductive debromination[15] of **15** smoothly afforded the target naphthoquinone oxime **1g**[16] after methylation. Thus, **1g** was provided in overall 11% yield in 13 steps from the 2-bromobenzoate **5b**; however, there was a drawback of additional exchange of the protecting group in this synthetic procedure. The problem was caused by the selection of the benzyl group as a phenol protection.

Therefore, we further examined the alternative synthesis of **1g** by use of isopropyl group as a protecting group (Scheme 1).[9] In the improved method the ester-substituted naphthoquinone oxime **1g** was provided in shorter eight steps from the 2-bromobenzoate **5c**, albeit in the almost same overall yield (12%).

In conclusion we established the concise preparation method for potentially antitumor active naphthoquinone oximes with structural flexibility for structure–activity relationship study. Strong cytotoxic activity has been observed in 2-(3-hydroxy-4-methoxy-2-methoxycarbonylphenyl)-1,4-naphthoquinone 1-oxime methyl ether (**1f**) among the ester-substituted naphthoquinone oximes and their analogues synthesized here.[17] Further chemical modifications based on the ester-substituted naphthoquinone oxime **1f** applicable to in vivo assay experiments are in progress in our laboratory.

Acknowledgment

The project was financially supported by JSPS Grants-in-Aid for Scientific Research (C) (Grant No. 23590041).



Scheme 2 Preparation of 5-hydroxy-4-methoxy-2-methoxycarbonylphenyl-naphthoquinone oxime **1g**. *Reagents and conditions*: (a) $Pd(dba)_3$, Cs_2CO_3, Xantphos, $Na_2S_2O_5$, toluene, 100 °C, 36 h (81%); (b) OsO_4, NMO, CH_2Cl_2–acetone, r.t., 5 d (86%); (c) (1) TfOH, IPy_2BF_4, CH_2Cl_2, 0 °C, 20 min; (2) $NH_2OMe{\cdot}HCl$, pyridine, 90 °C, 12 h (98%); (d) Ac_2O, Et_3N, I_2, THF, 40 °C, 7 h (90%); (e) (1) NBS, AIBN, benzene, 70 °C, 3 h; (2) acetone, H_2O, 40 °C, 20 h (29%); (f) (1) IBX, DMSO, 50 °C, 2 h; (2) Et_3N, CH_2Cl_2, r.t., 2 h (99%); (g) MeI, K_2CO_3, DMF, r.t., 2 h (65%); (h) $Pd(OAc)_2$, K_2CO_3, Ph_3P, BuOH, 100 °C, 2 h (93%).

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(9) Synthetic procedures for compounds shown in Schemes 1 and 2, except those described in Note, are given in Supporting Information.

(10) **4-Hydroxy-6,7-methylenedioxy-1-tetralone-2-spiro-3′-(6,7-dimethoxyphthalide) (10a)**
A mixture of **8a** (82 mg, 0.223 mmol), NBS (43 mg, 0.243 mmol), and AIBN (5 mg, 0.029 mmol) in dry benzene (8 mL) was stirred at 85 °C for 1.5 h under argon. After addition of EtOAc (30 mL) the solution was washed with H_2O (20 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated. The residual oil was dissolved in THF (10 mL) and H_2O (8 mL). The mixture was stirred at r.t. for 16 h and extracted with $CHCl_3$ (3 × 20 mL). The combined organic solutions were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Column chromatography of the residue (SiO_2, toluene–EtOAc = 10:1 → 1:1) afforded *trans*-**10a** (24 mg, 28%) as colorless solid, mp 212–213 °C, and *cis*-**10a** (27 mg, 31%) as colorless solid, mp 209–211 °C.
trans-**10a**: IR (ATR): 1767, 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (d, *J* = 7.1 Hz, 1 H, exchangeable), 2.63 (dd, *J* = 13.7, 9.4 Hz, 1 H), 2.71 (dd, *J* = 13.7, 4.9 Hz, 1 H), 3.93 (s, 3 H), 4.14 (s, 3 H), 5.36 (ddd, *J* = 9.4, 7.1, 4.9 Hz, 1 H), 6.09 (s, 2 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 7.21 (s, 1 H), 7.24 (d, *J* = 8.3 Hz, 1 H), 7.41 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.6, 56.8, 62.4, 64.4, 85.3, 102.2, 106.2, 106.6, 117.1, 117.9, 119.7, 124.2, 141.8, 144.5, 147.9, 148.3, 153.2, 153.7, 167.3, 187.9. MS–FAB: *m/z* = 407 $[M + Na]^+$, 385 $[M + H]^+$. Anal. calcd for $C_{20}H_{18}O_8$: C, 62.50; H, 4.20. Found: C, 62.21; H, 3.96.
cis-**10a**: IR (ATR): 1769, 1684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.59 (d, *J* = 9.7 Hz, 1 H, exchangeable), 2.71 (dd, *J* = 13.6, 7.1 Hz, 1 H), 2.83 (dd, *J* = 13.6, 5.1 Hz, 1 H), 3.90 (s, 3 H), 4.14 (s, 3 H), 5.16 (ddd, *J* = 9.7, 7.1, 5.1 Hz, 1 H), 6.11 (s, 2 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 7.14 (d, *J* = 8.2 Hz, 1 H), 7.18 (s, 1 H), 7.43 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2, 56.8, 62.4, 65.5, 84.7, 102.4, 106.7, 107.5, 116.5, 117.9, 119.1, 124.2, 140.2, 142.3, 148.8, 148.9, 153.4, 153.9, 166.5, 188.1. MS–FAB: *m/z* = 407 $[M + Na]^+$, 385 $[M + H]^+$. Anal. calcd for $C_{20}H_{18}O_8 \cdot 1/3H_2O$: C, 61.54; H, 4.30. Found: C, 61.79; H, 4.11.

(11) The same orientation of oxygen functions at the 2- and 4-positions of the tetralone unit is assigned to be *cis* configuration.

(12) **2,3-Dimethoxy-6-[2-(1-methoxyimino-6,7-methylenedioxy-4-oxo-1,4-dihydronaphthyl)]benzoic Acid (1d)**
A mixture of **11a** (230 mg, 0.556 mmol) and IBX (260 mg, 0.929 mmol) in DMSO (4 mL) was stirred at 60 °C for 2 h. After addition of H_2O (10 mL) insoluble precipitate was removed by filtration, and the filtrate was extracted with EtOAc (3 × 20 mL). The combined organic solutions were washed with H_2O (3 × 1 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), stirred with Et_3N (0.2 mL, 1.42 mmol) at r.t. for 1 h, and extracted with H_2O (3 × 20 mL). The combined aqueous solutions were acidified with 10% HCl aqueous solution (pH ca. 3) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic solutions were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Column chromatography of the residue (SiO_2, acetone–toluene = 1:20) afforded **1d** (211 mg, 92%) as pale yellow solid, mp 207–209 °C. IR (ATR): 1725, 1624 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.98 (s, 3 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 6.10 (s, 2 H), 6.54 (s, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 7.68 (s, 1 H), 8.33 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (*Z*-isomer) = 55.9, 61.0, 64.4, 102.8, 105.0, 109.2, 113.1, 123.7, 125.8, 127.5, 127.8 (2 C), 130.2, 144.8, 145.2, 149.4, 151.3, 151.4, 153.0, 167.8, 182.1. MS–FAB: *m/z* = 434 $[M + Na]^+$, 412 $[M + H]^+$. Anal. calcd for $C_{21}H_{17}NO_8$: C, 61.31; H, 4.17; N, 3.40. Found: C, 61.14; H, 3.98; N, 3.28.

(13) **Methyl 2,3-Dimethoxy-6-[2-(1-methoxyimino-6,7-methylenedioxy-4-oxo-1,4-dihydronaphthyl)]benzoate (1c)**
A mixture of **1d** (211 mg, 0.512 mmol), MeI (0.07 mL, 1.10 mmol), and K_2CO_3 (140 mg, 1.01 mmol) in DMF (5 mL) was stirred at r.t. for 2 h, diluted with H_2O (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic solutions were washed with H_2O (2 × 10 mL), sat. $NaHCO_3$ aqueous solution (5 mL), and brine (10 mL), dried over Na_2SO_4, and evaporated. Column chromatography of the residue (SiO_2, EtOAc–hexane = 1:6 → 1:3) afforded **1c** (201 mg, 92%) as pale yellow solid, mp 172–173 °C (lit.[1b] mp 171–173 °C). IR (ATR): 1715, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.66 (s, 3 H), 3.93 (s, 2 × 3 H), 4.08 (s, 3 H), 6.12 (s, 2 H), 6.57 (s, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 7.11 (d, *J* = 8.3 Hz, 1 H), 7.69 (s, 1 H), 8.33 (s, 1 H). ESI–HRMS: *m/z* calcd for $C_{22}H_{19}NNaO_8$: 448.10084; found: 448.10020.

(14) **Methyl 2-Hydroxy-3-methoxy-6-[2-(1-methoxyimino-6,7-methylenedioxy-4-oxo-1,4-dihydronaphthyl)]benzoate (1f)**
To a stirred solution of **1c** (29 mg, $6.8 \cdot 10^{-2}$ mmol) in CH_2Cl_2 (7 mL) was added a 1 mol solution of BCl_3 in CH_2Cl_2 (0.14 mL, $7.0 \cdot 10^{-2}$ mmol) at –78 °C under argon, and the mixture was stirred at the same temperature for 2 h. After addition of H_2O (5 mL) the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic solutions were washed with brine (5 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by PTLC ($CHCl_3$) afforded **1f** (26 mg, 92%) as yellow solid, mp 154–156 °C. IR (ATR): 2919, 1667, 1634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.60 (s, 3 H), 3.96 (s, 3 H), 3.97 (s, 3 H), 6.13 (s, 2 H), 6.54 (s, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 7.72 (s, 1 H), 8.34 (s, 1 H), 10.8 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 52.4, 56.1, 64.5, 102.2, 106.2,

109.8, 113.6, 114.2, 120.7, 124.1, 126.8, 128.7, 130.3, 146.3, 148.9, 149.4, 150.0, 151.4, 153.7, 170.7, 183.6. ESI-HRMS: *m/z* calcd for $C_{21}H_{17}NNaO_8$: 434.08519; found: 434.08440.

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(16) **Methyl 4-Hydroxy-5-methoxy-2-[2-(1-methoxyimino-6,7-methylenedioxy-4-oxo-1,4-dihydronaphthyl)]benzoate (1g)**
A mixture of **16** (7 mg, $1.3 \cdot 10^{-3}$ mmol), $Pd(OAc)_2$ (0.15 mg, $7 \cdot 10^{-5}$ mmol), and Ph_3P (0.7 mg, $2.6 \cdot 10^{-4}$ mmol) in *n*-BuOH (3 mL) was stirred at 100 °C for 2 h under nitrogen, diluted with EtOAc (6 mL), and filtered through Celite pad. The filtrate was washed with H_2O (2 × 3 mL) and brine (3 mL), dried over Na_2SO_4, and evaporated. Column chromatography of the residue (SiO_2, EtOAc–hexane = 1:1) afforded **1g** (5 mg, 93%) as pale yellow solid, mp 89–91 °C. IR (ATR): 3437, 1771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.64 (s, 3 H), 3.97 (s, 3 H), 4.00 (s, 3 H), 6.12 (s, 2 H), 6.49 (s, 1 H), 6.91 (s, 1 H), 7.49 (s, 1 H), 7.70 (s, 1 H), 8.35 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 52.2, 56.4, 64.5, 102.3, 106.4, 110.2, 112.4, 116.6, 123.1, 124.6, 127.3, 129.0, 133.2, 146.1, 146.5, 148.7, 149.5, 151.5, 153.4, 167.1, 183.6. ESI-HRMS: *m/z* calcd for $C_{21}H_{17}NNaO_8$: 434.08519; found: 434.08329.

(17) Results on the cytotoxic activity of these naphthoquinone oximes will be reported elsewhere.

