Synthesis of Benzo[*b*]phenanthridines and Related Naturally Occurring 2-Aryl-1,4-naphthoquinones by Palladium- and Copper-Catalyzed Coupling of Organostannanes with Bromoquinones

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Syntheses of phenanthroviridone, gilvocarcin BE-12406X$_2$, antibiotic WS 5995B, and a key intermediate for the synthesis of jadomycin are described, based on palladium- and copper-catalyzed coupling reactions of sterically hindered arylstannanes with 2-bromonaphthoquinones.

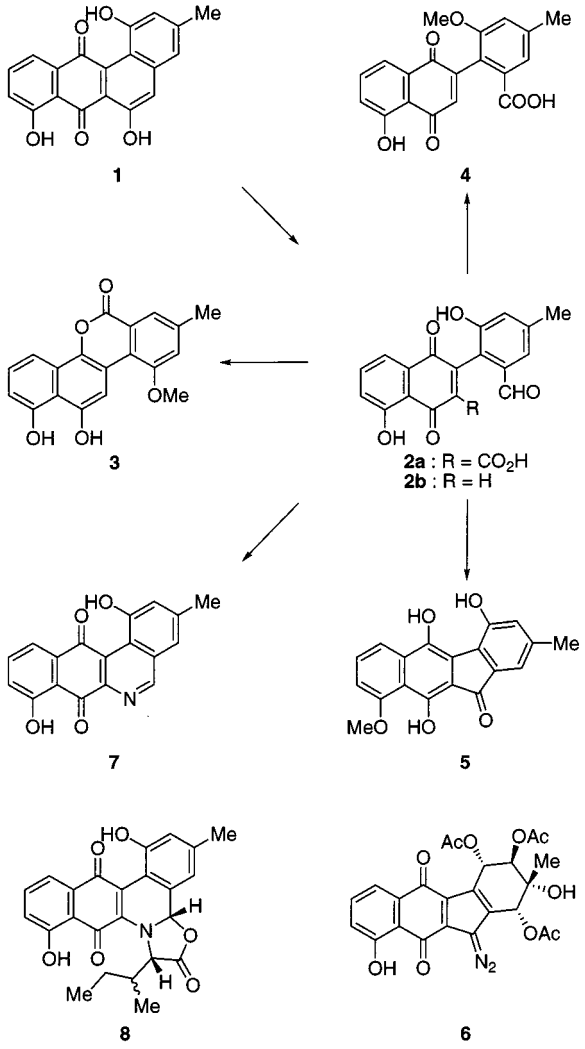
Introduction

It has recently been proposed by Gould that naturally occurring 2-arylnaphthoquinones and related metabolites derive from the oxidative cleavage of dehydrorabelomycin (**1**) to give 2-aryl-1,4-naphthoquinone **2a** (Scheme 1).[1,2] This key intermediate **2a**, or its decarboxylated derivative **2b**, would then be the precursor of gilvocarcins such as BE-12406X$_2$ (**3**)[3] and quinones such as antibiotic WS-5995 A (**4**).[4] Reduction of **2b** to the hydroquinone, followed by an intramolecular condensation with the aldehyde would provide closure of the C ring, giving rise to the carbocyclic skeleton of kinafluorenone (**5**)[5a] and the stealthins.[2a][5a,6] These benzo[*b*]fluorene natural products are biogenetically related to the important kinamycin antibiotics, represented in Scheme 1 by kinamycin C (**6**).[1] These quinones, originally isolated from *Streptomyces murayamaensis*, possess a rare diazobenzofluorenone structure.[7,8]

The benzo[*b*]phenanthridines are a small group of structurally related angucyclines[9] that have been isolated from different species of *Streptomyces*. Phenanthroviridone (**7**)[10] and its glycoside phenanthroviridine[11] have been isolated from *S. murayamaensis*. Structurally more complex jadomycin A (**8**) was isolated from *S. venezuelae*.[12] The configuration at the isoleucine side chain of **8** has not been determined.

We have developed a procedure for the selective alkylation, alkenylation, and arylation of naphthoquinones under mild conditions, using a variation of the palladium-catalyzed Stille coupling reaction between 2-bromonaphthoquinones and tetraorganostannanes.[13–17] In most cases, the best results were obtained by using CuBr as a co-catalyst.[18,19]

As part of a project aimed at the synthesis of jadomycin A (**8**) and determination of its configuration, we decided first to demonstrate the application of our approach in the synthesis of phenanthroviridone (**7**).[20,21] This metabolite might be formed from **2a** or **2b** by condensation with ammonia or the amino acid isoleucine, respectively. The



Scheme 1

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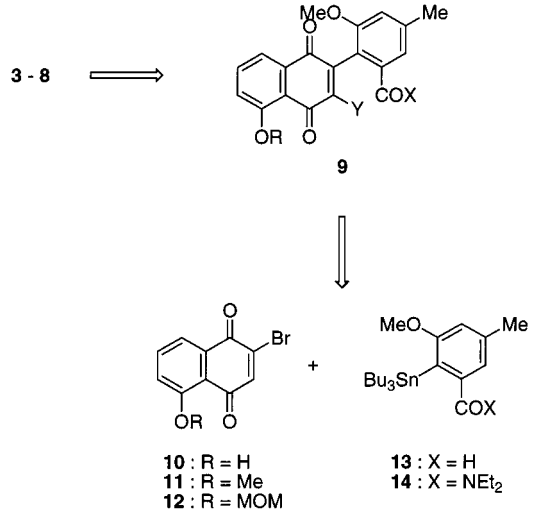
synthesis of natural products **3**−**8** could be carried out from intermediates **9**, which could be assembled by Stille coupling of quinones **10**−**12** with sterically hindered tributylarylstannanes **13** or **14** (Scheme 2).[13c] Particularly attractive intermediates were derivatives with a free aldehyde functionality (X = H) − or their protected derivatives − with a substituent Y at C-3 that could act as a good leaving group. Here, we report full details on the synthesis of **7** by palladium-catalyzed coupling of a sterically hindered arylstannane with a 2-bromonaphthoquinone.[22] Additionally, we have accomplished the syntheses of antibiotic WS 5995B (**4**),[23] gilvocarcin BE-12406X$_2$, and quinones related to **2b** that could be used as key intermediates for the total synthesis of jadomycin A (**8**).



Scheme 2

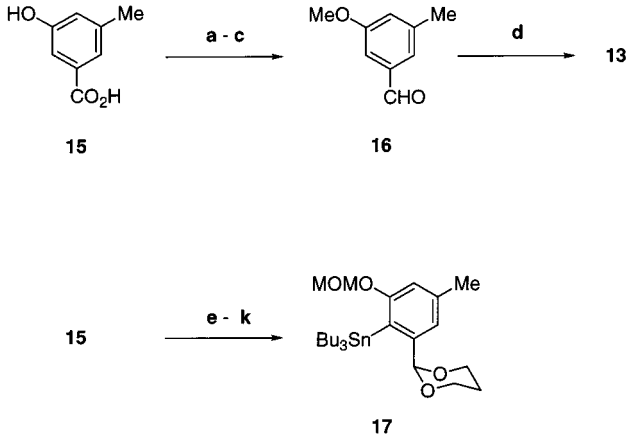
Results and Discussion

Synthesis of Sterically Hindered Arylstannanes

Arylstannane **13** was prepared from 3-hydroxy-5-methylbenzoic acid (**15**).[24] Hence, protection of the phenol as the methyl ether, and reduction of the carboxylic acid to the benzyl alcohol, followed by oxidation with PCC, gave benzaldehyde **16** (Scheme 3). This benzaldehyde was *ortho*-metallated, using methodology developed by Comins,[25] by treatment of **16** with the lithium amide of *N*,*N*,*N*′-trimethylethylenediamine, followed by addition of 3 equiv. of *n*BuLi to furnish the aryllithium compound, which was quenched with *n*Bu$_3$SnCl to give **13** in 85% yield. A protected version of this stannane (**17**) was similarly prepared by *ortho*-lithiation[26] of the corresponding acetal (Scheme 3).

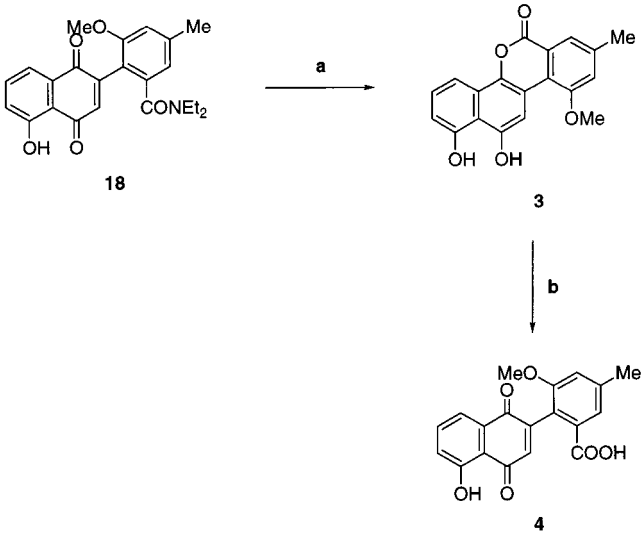
Synthesis of Gilvocarcin BE-12406X$_2$ and Antibiotic WS 5995B

A synthesis of gilvocarcin **3**, inspired by the proposed biosynthesis (Scheme 1), might be carried out from quinone **18**, a key intermediate in our previous synthesis of antibiotics WS 5995A and C.[13c] Thus, reduction of 2-aryl-1,4-naphthoquinone **18** with Zn in acetic acid, containing a small amount of TsOH·H$_2$O, proceeded readily at 23 °C to



Scheme 3. a: MeI (10 equiv.), K_2CO_3, acetone, 65 °C, 12 h (86%); b: $LiAlH_4$, THF, 23 °C, 12 h (90%); c: PCC (1.5 equiv.), CH_2Cl_2, 23 °C, 2.5 h (85%); d: i. *N*,*N*,*N*′-trimethylethylenediamine (1.1 equiv.), *n*BuLi (1.1 equiv.), THF, −20 °C, 15 min; ii. **16**, *n*BuLi (3 equiv.), THF, −20 °C, 10 h; iii. *n*Bu$_3$SnCl (2 equiv.), −78 to 5 °C, 12 h (85%); e: MeOH, H_2SO_4 (cat.), 23 °C, 14 h (94%); f: DHP (2.5 equiv.), PPTS (cat.), CH_2Cl_2, 23 °C, 48 h (93%); g: $LiAlH_4$, THF, 23 °C, 13 h (93%); h: PCC (1.5 equiv.), NaOAc, CH_2Cl_2, 23 °C, 3 h (81%); i: 1,3-propanediol, TsOH (cat.), toluene, reflux, 3 h (74%); j: chloromethyl methyl ether (2 equiv.), *i*Pr$_2$EtN, CH_2Cl_2, 40 °C, 24 h (80%); k: i. *n*BuLi (1.1 equiv.), hexanes, 0 °C; ii. *n*Bu$_3$SnCl (1.5 equiv.), 0 °C (97%)

give **3** in 75% yield (Scheme 4). This is the first synthesis of naturally occurring BE-12406X$_2$ (**3**),[3] the aglycon of gilvocarcin BE-12406A.[3a]



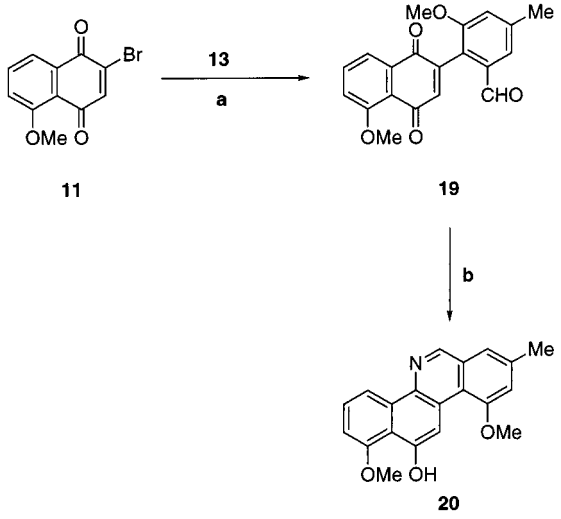
Scheme 4. a: Zn (4 equiv.), HOAc, TsOH (cat.), 23 °C, 13 h (75%); b: KOH (35 equiv.), THF−H_2O, 23 °C, 3 h (67%)

For the synthesis of intermediate of type **9** with a free aldehyde functionality on the D ring, we tried to reduce the lactone of **3** with *i*Bu$_2$AlH or lithium hydroaluminates. Unfortunately, neither the aldehyde or the lactol could be obtained directly from **3**. Although this approach to the preparation of quinones of type **9** (Y = H) failed, the ready availability of **3** allowed us to complete the synthesis of **4**, a cytotoxic pigment that proved impossible to prepare by the direct cleavage of the tertiary carboxamide of **18**.[13c] The synthesis of antibiotic WS 5995B (**4**) was achieved by saponification of lactone **3** with aqueous KOH in THF at

23 °C, which proceeded, in the presence of atmospheric oxygen, with concomitant oxidation to the naphthoquinone. Therefore, the synthesis of **4** completed the preparation of the three members of this family of antibiotics using the palladium- and copper-catalyzed reaction as the key step.[13c]

Synthesis of Phenanthroviridone

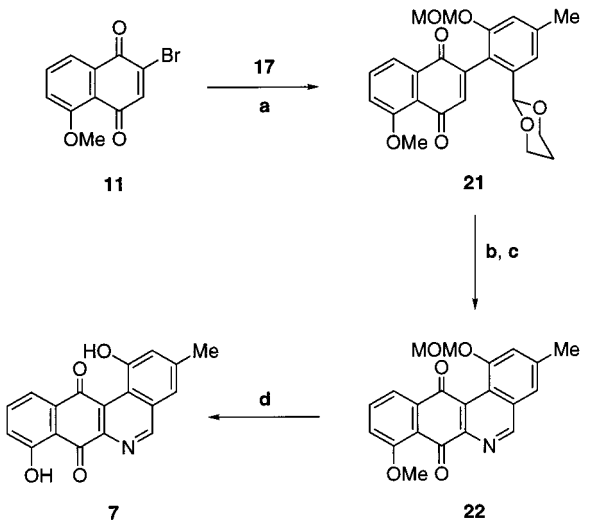
The coupling of 2-bromo-5-methoxy-1,4-naphthoquinone (**11**) with stannane **13** proceeded smoothly [in THF under reflux in the presence of $Pd(PPh_3)_4$ and CuBr or CuI as catalysts] to give **19** in 65% yield (Scheme 5).[27] Surprisingly, no reaction was observed in 1,4-dioxane at the same temperature.



Scheme 5. a: $Pd(PPh_3)_4$ (10 mol-%), CuI (20 mol-%), THF, 70 °C, 6 h (65%); b: NH_4OAc (4 equiv.), HOAc, 118 °C, 24 h (21%)

For the synthesis of phenanthroviridone (**7**), we tried to add ammonia to the 1,4-naphthoquinone in a Michael-type reaction. However, treatment of **19** with ammonia under a variety of conditions failed to furnish the phenanthroviridine chromophore, because of the higher reactivity of the aldehyde and subsequent reaction of the formed imine with the C-1 carbonyl of the quinone. Thus, benzo[*c*]phenanthridine (**20**) was obtained on treatment of **19** with NH_4Cl and $CeCl_3 \cdot 7\ H_2O$ as a Lewis acid,[28] or with NH_4OAc in HOAc under reflux.

To circumvent the addition of ammonia to the aldehyde, a protected version of **19** was prepared, using the Stille reaction between quinone **11** and stannane **17** (Scheme 6). This coupling reaction proceeded under relatively mild conditions, and furnished **21** in excellent yield despite the considerable steric hindrance of the 2,6-disubstituted arylstannane. The synthesis of phenanthroviridone (**7**) was achieved by treatment of **21** with ammonia to give the 2-aryl-3-aminoquinone, which was then treated immediately with aqueous acid to give **22** in 67% yield. The MOM group was not cleaved under these mild hydrolysis conditions. While deprotection of the methyl ether and MOM groups with BBr_3 in CH_2Cl_2 proceeded in variable yields, treatment of **22** with LiI in 2,6-lutidine at 140 °C led to phenanthroviridone (**7**) in 63% yield (Scheme 6). This synthesis of **7** proceeded in 11 steps from benzoic acid **15** (longest sequence) in 20% overall yield, which compared very favorably in terms of efficiency with alternative syntheses.[20,21]



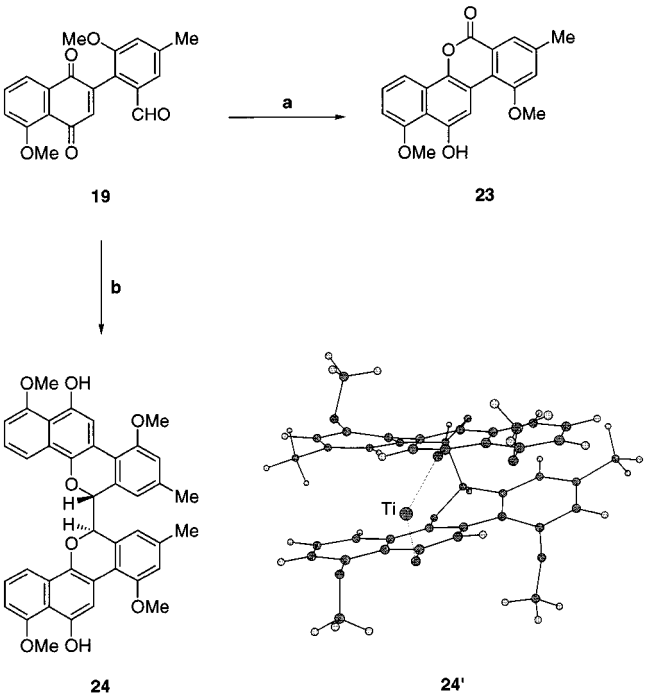
Scheme 6. a: $Pd(PPh_3)_4$ (10 mol-%), CuI (20 mol-%), THF, 70 °C, 12 h (85%); b: NH_4Cl (20 equiv.), NaOAc (20 equiv.), EtOH, 80 °C, 12 h; aq HCl, 1,4-dioxane, 23 °C, 3 h (67%); c: LiI (6 equiv.), 2,6-lutidine, 140 °C, 6 h (63%)

Attempted Reductive Coupling Route to Benzo[*b*]fluorenes

The intermolecular photochemical reaction of quinones with aldehydes is known to proceed by the abstraction of the aldehyde hydrogen by the quinone excited state, followed by radical coupling that leads to the formation of mixtures of *C*- and *O*-acylated hydroquinones.[29,30] Thus, we envisaged that simple irradiation of **19** might lead to the tetracyclic structure characteristic of the kinamycins. In the event, irradiation of a benzene solution of **19** gave exclusively the *O*-acylated product **23**: a monomethyl ether of gilvocarcin **3** (Scheme 7). The use of benzophenone as a sensitizer, which favors the formation of *C*-acyl hydroquinones,[31] failed to give any of the desired benzo[*b*]fluorene.

Gilvocarcin derivative **23** was cleanly obtained in a Tishchenko-type reaction,[32] upon treatment of **19** with catalytic 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide[33] and Et_3N (2 equiv.) in DMF, in 45% yield. Similarly, treatment of **19** with aqueous NaCN in 1,4-dioxane led to **5b**, albeit in lower yield.

As an alternative to the photochemical approach, we tried the reduction of **19** with low-valent Ti species,[34] with the expectation that the delocalized radical anion would attack the aldehyde to furnish the desired benzo[*b*]fluorene structure. Therefore, we decided to examine the reaction of **19** with $TiCl_4/Zn$[35] in THF at 0 °C. Surprisingly, this reaction led to the clean formation of dimer **24** in 75% yield (Scheme 7). A lower yield was obtained with $TiCl_3(DME)_{1.5}$/Zn-Cu in DME. Interestingly, this dimer was isolated as a single diastereomer. To demonstrate the configuration of **24** (racemic mixture or *meso* compound), we treated **24** with an excess of (−)-menthyl chloroformate in the presence of Et_3N and 4-dimethylaminopyridine



Scheme 7. a: 2-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.1 equiv.), Et_3N, DMF, 55 °C, 21 h (45%); b: $TiCl_4$ (5 equiv.), Zn (9 equiv.), THF, −10 to 0 °C, 1 h (75%)

(DMAP) in CH_2Cl_2 to form the bis(menthyl) carbonates. The ^1H NMR spectrum of the crude reaction mixture revealed the presence of a 1:1 mixture of carbonates, which is consistent with the chiral C_2 symmetry shown for **24**.

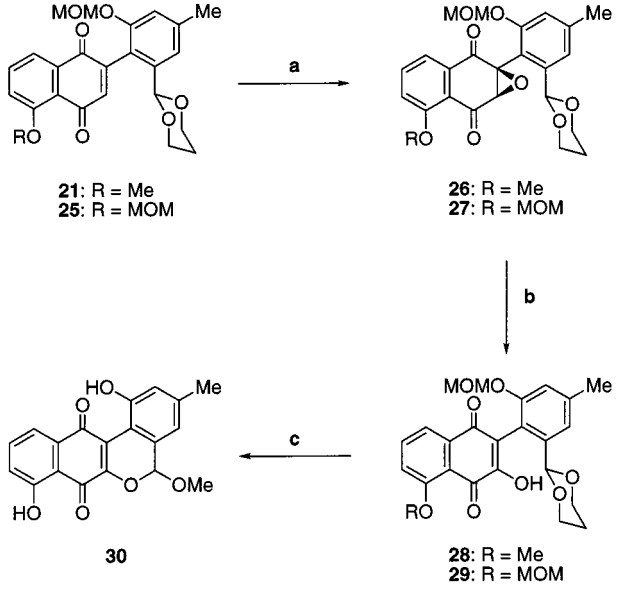
Dimer **24** is probably formed by coupling of two benzyl radicals resulting from deoxygenation of the lactol.[36] The high stereoselectivity observed in the final radical coupling could be accounted for if it took place intramolecularly, within a Ti^{II} coordination sphere. Thus, the antiparallel face-to-face dimerization would generate Ti^{II} diphenoxide species **24′** (Scheme 7).[37] Alternatively, a dimerization of the aldehyde **19** to a *trans*-stilbene, followed by the intramolecular radical addition, might also account for the formation of **24**.

Synthesis of 2-Aryl-3-hydroxynaphthoquinones

For the synthesis of derivatives of type **9** with a 2-hydroxy functionality that could be transformed into a leaving group − required in the synthesis of jadomycin A for the introduction of an amino acid − we decided to attempt the strategy that we had previously used for the synthesis of antibiotics WS5995 A and C.[13c] In this strategy, the 2-hydroxy group was introduced by a one-pot epoxidation of the C2−C3 double bond with *t*BuOOH, accompanied by mild basic opening of the epoxide under the reaction conditions used.

Epoxidation of **21** and its analog **25**, prepared by the Stille coupling of MOM-protected quinone **12** with stannane **17**, furnished epoxides **26** and **27** in 76 and 75% yields, respectively (Scheme 8). These epoxides were isolated as mixtures of atropoisomers and were remarkably stable under the basic conditions employed for the quinone epoxidation. Indeed, further mild basic treatment with aqueous NaOH or KOH failed to furnish the desired 2-hydroxy derivatives, as a result of the steric hindrance imposed by the substituted aryl ring. It was necessary, then, to heat **26** and **27** with an excess of aqueous NaOH to open the epoxides. Upon cooling of the reaction mixtures, the sodium salts of **28** and **29** could be isolated as dark red solids in 81% yield. The ^1H NMR spectra of these sodium salts in $CDCl_3$ were almost identical to those of the neutral compounds, with the exception of the chemical shift of the methyl on the aryl ring; that appeared at $\delta \approx 1.4$, almost 1 ppm upfield from that of the neutral compounds. On the other hand, although the ^1H NMR spectrum (in $[D_6]$DMSO) of a freshly prepared sample of this sodium salt showed the methyl signal at $\delta = 1.4$, after ca. 30 min this signal had shifted to $\delta = 2.4$. When the opening of epoxide **26** was carried out using KOH in MeOH and deionized H_2O, and the mixture was acidified with a 3.5% aqueous HCl solution, **28** was obtained as an orange solid (ca. 60% yield) displaying identical spectroscopic data, with the exception of the arylmethyl resonance, which appeared at: $\delta = 2.40$. The NOESY spectrum of the sodium salt of **28** in $CDCl_3$ showed NOEs between the methyl group on the aryl ring and the aryl hydrogen atoms of the naphthoquinone A ring. These NOEs and the anomalous shift of the methyl group are consistent with the existence of aggregate structures for the sodium salts of **28** and **29**, in which the C-2 aryl ring of one of the monomers is positioned under the naphthoquinone A ring of another monomer. Indeed, the FAB-MS of the sodium salt of **28** showed peaks corresponding to the aggregates **28**·Na_2, (**28**)$_2$·Na_3, (**28**)$_3$·Na_4, and (**28**)$_4$·Na_4.

Treatment of the sodium salt of **29** in refluxing methanol with TsOH as catalyst permitted the cleavage of the three protecting groups, leading to the clean formation of cyclic acetal **30** in 64% yield (Scheme 8).



Scheme 8. a: *t*BuOOH (2 equiv.), KF−Al_2O_3 (1.5 equiv.), MeCN, 23 °C, 16 h (76% for **26**, 75% for **27**); b: NaOH (25 equiv.), MeOH/H_2O (1:1), 80 °C, 16 h (81% for **28**·Na and **29**·Na); c: MeOH, TsOH (cat.), reflux, 6 h (64%)

Conclusion

This work highlights the synthetic utility of the palladium- and copper-catalyzed coupling reaction of sterically hindered arylstannanes with 2-bromonaphthoquinones. Thus, the syntheses of antibiotic WS 5995B (**3**), gilvocarcin BE-12406X$_2$ (**4**), and phenanthroviridone (**7**) were accomplished concisely by using this modified Stille coupling reaction as the key step. Unfortunately, the naphthohydroquinone dianion derived from **19** failed to condense with the aldehyde to yield the carbocyclic ring system characteristic of the kinamycin family of antibiotics. The synthesis of several advanced intermediates (**28**, **29** and **30**) for the synthesis of jadomycin was also accomplished, by the epoxidation of 2-aryl-1,4-naphthoquinones, followed by opening of the epoxides under forcing basic conditions. Preliminary experiments indicate that treatment of the sodium salts of **28** and **29** affords the corresponding triflates, which react with protected α-amino esters. Work based on this study and directed towards the synthesis of jadomycin A (**8**) is underway.

Experimental Section

General Remarks: NMR determinations were carried out at 23 °C. Only the most significant IR frequencies and MS fragmentations are given. − R_f values were determined on TLC aluminum sheets coated with 0.2 mm GF_{254} silica gel. − Elemental analyses were performed at the SIdI (UAM). The presence of water molecules in some of the samples was proven by ^{1}H NMR. − All reactions were carried out under Ar. Solvents were purified and dried by standard methods. Chromatographic purifications were carried out with flash grade silica gel. − "Usual workup" means: dilution with EtOAc, washing with a saturated NaCl aqueous solution, drying (Na_2SO_4), and concentration. CuI was purified as follows: CuI (13.5 g) was dissolved in a solution of KI (130 g) in H_2O (100 mL). Decolorizing carbon (1 g) was added. The mixture was stirred for 10 min, filtered, and the filtrate was diluted with H_2O to give a fine, white powder. The solid was filtered off and washed with H_2O, acetone, and Et_2O, and dried under reduced pressure. Pure CuI was stored under Ar. Quinones **10**,[38] **11**,[39] and **18**[13c] were prepared according to known procedures.

Stannane 13: This stannane was prepared in four steps.

(a) Methyl 3-Methoxy-5-methylbenzoate: To a solution of acid **15** (3.00 g, 19.72 mmol) in acetone (60 mL) was added K_2CO_3 (10.90 g, 78.88 mmol) and MeI (12.27 mL, 197.2 mmol), and the mixture was heated at 65 °C for 12 h. After the usual workup, the residue was chromatographed (hexane/EtOAc, 12:1) to give methyl 3-methoxy-5-methylbenzoate[40] (3.07 g, 86%) as a colorless oil. R_f = 0.39 (hexane/EtOAc, 12:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.83 (s, 3 H), 3.90 (s, 3 H), 6.91 (br. s, 1 H), 7.36 (br. s, 1 H), 7.46 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 52.0, 55.3, 110.9, 120.1, 122.8, 131.0, 139.5, 159.4, 167.0.

(b) 3-Methoxy-5-methylbenzyl Alcohol: To a suspension of $LiAlH_4$ (675 mg, 18.27 mmol) in THF (35 mL) was slowly added a solution of the above ester (2.992 g, 16.60 mmol) in THF (25 mL). The mixture was stirred at 23 °C for 12 h. After cooling to 0 °C, an aqueous solution of H_2SO_4 (30 mL, 1 M) was added. After the usual workup, the residue was chromatographed (hexane/EtOAc, 4:1) to give the title alcohol[41] (2.276 g, 90%) as a colorless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.71 (t, J = 5.4 Hz, 1 H), 2.33 (s, 3 H), 3.79 (s, 3 H), 4.63 (d, J = 5.4 Hz, 2 H), 6.66 (s, 1 H), 6.73 (s, 1 H), 6.77 (s, 1 H).

(c) Benzaldehyde 16: To a suspension of pyridinium chlorochromate (PCC) (4.691 g, 21.81 mmol) in CH_2Cl_2 (50 mL) was added a solution of the above benzyl alcohol (2.179 g, 14.51 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at 23 °C for 2.5 h. The mixture was diluted with Et_2O (25 mL) and decanted. The solid residue was triturated with additional Et_2O (3 × 25 mL), and decanted again. The combined extract was chromatographed (hexane/EtOAc, 10:1) to give benzaldehyde **16** (1.850 g, 85%) as a yellowish oil. − R_f = 0.35 (hexane/EtOAc, 10:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.85 (s, 3 H), 7.01 (br. s, 1 H), 7.21 (br. s, 1 H), 7.30 (br. s, 1 H), 9.93 (s, 1 H).

(d) Stannane 13: To a solution of *N*,*N*,*N*′-trimethylethylenediamine (1.56 mL, 1.23 g, 11.97 mmol) in THF (25 mL) at −20 °C was added *n*BuLi (4.57 mL, 2.5 M in hexane, 11.42 mmol). After 15 min at this temperature, **16** (1.633 g, 10.88 mmol) in THF (15 mL) was added at −20 °C. After 15 min, *n*BuLi (13.06 mL, 2.5 M in hexane, 32.64 mmol) was added, and the solution was stirred at −20 °C for 10 h. After cooling to −78 °C, Bu_3SnCl (7.437 g, 22.86 mmol) was added, and the mixture was stirred for 12 h, while the temperature was slowly allowed to rise to 5 °C. The mixture was diluted with *t*BuOMe, washed with a saturated aqueous solution of buffered NH_4Cl (pH = 8) and a saturated aqueous solution of KF, dried ($MgSO_4$), and concentrated. The residue was chromatographed (hexane/EtOAc, 70:1) to give the stannane **13** (4.049 g, 85%) as a colorless oil. − R_f = 0.20 (hexane/EtOAc, 70:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.0 Hz, 9 H), 1.10−1.02 (m, 6 H), 1.38−1.20 (m, 6 H), 1.57−1.40 (m, 6 H), 2.42 (s, 3 H), 3.79 (s, 3 H), 6.85 [s, J(Sn−H) = 13 Hz, 1 H], 7.35 [s, J(Sn−H) = 9 Hz, 1 H], 9.94 (s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.57 [^1J (^{13}C−^{119}Sn) = 181 Hz, ^1J (^{13}C−^{117}Sn) = 173 Hz], 13.66, 21.25, 27.32 [^2J (^{13}C−Sn) = 35 Hz], 29.17 [^3J (^{13}C−Sn) = 10 Hz], 55.30, 115.63 [^2J (^{13}C−Sn) = 10 Hz], 124.99 [^3J (^{13}C−Sn) = 14 Hz], 131.23, 140.26, 143.91 [^1J (^{13}C−Sn) = 6 Hz], 165.18, 194.19 [^3J (^{13}C−Sn) = 9 Hz]. − EIMS; *m*/*z*: 439 (4) $[M]^+$, 383 (100), 327 (6), 269 (68), 239 (12). − $C_{21}H_{36}O_2Sn$: calcd. C 57.43, H 8.26; found C 57.34, H 8.28.

Stannane 17: This stannane was prepared in seven steps.

(e) Methyl 3-Hydroxy-5-methylbenzoate: To a solution of **15** (5.00 g, 32.86 mmol) in MeOH (100 mL) was added H_2SO_4 (96%, 2 mL) and the mixture was stirred at 23 °C for 14 h. The mixture was diluted with H_2O (100 mL). After the usual workup (Et_2O instead of EtOAc), the residue was chromatographed (hexane/EtOAc, 5:1) to give the methyl ester (5.12 g, 94%) as a white solid. − R_f = 0.31 (hexane/EtOAc, 5:1). − M.p. 92−93 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.89 (s, 3 H), 5.41 (br. s, 1 H), 6.87 (br. s, 1 H), 7.36 (br. s, 1 H), 7.43 (br. s, 1 H).

(f) Methyl 3-Methyl-5-(2-tetrahydropyranyloxy)benzoate: A solution of the above methyl ester (980 mg, 5.90 mmol), 3,4-dihydro-2*H*-pyran (1.4 mL, 1.30 g, 14.8 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (ca. 5 mg) as catalyst, in CH_2Cl_2 (5 mL), was stirred for 48 h at 23 °C. After the usual workup, the residue was chromatographed (hexane/EtOAc, 15:1) to give the THP ether (1.373 g, 93%) as a colorless oil. − R_f = 0.37 (hexane/EtOAc, 15:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70−1.51 (m, 2 H), 1.99−1.79 (m, 2 H), 2.33 (s, 3 H), 3.64−3.53 (m, 1 H), 3.86 (s, 3 H), 3.92−3.80 (m, 1 H), 5.43 (dd, J = 3.2, 2.8 Hz, 1 H), 7.04 (br. s, 1 H), 7.47 (br. s, 1 H), 7.49 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 21.2, 25.0, 30.1, 51.8, 61.8, 96.1, 114.3, 121.8, 123.4, 131.0, 139.3, 156.8, 166.9.

(g) 3-Methyl-5-(2-tetrahydropyranyloxy)benzyl Alcohol: To a suspension of $LiAlH_4$ (217 mg, 5.88 mmol) in THF (15 mL) was slowly added a solution of the above THP derivative (1.475 g, 5.88 mmol) in THF (10 mL) at 23 °C, and the mixture was stirred at this temperature for 13 h. After cooling to 0 °C, an aqueous solution of NaOH (15 mL, 2 M) was slowly added. After the usual workup, the residue was chromatographed (hexane/EtOAc, 3:1) to give the benzyl alcohol (1.210 g, 93%) as a colorless oil: R_f = 0.34 (hexane/EtOAc, 5:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70−1.52 (m, 2 H), 2.07−1.78 (m, 2 H), 2.30 (s, 3 H), 3.16 (t, *J* = 5.3 Hz, 1 H), 3.54 (m, 1 H), 3.88 (m, 1 H), 4.53 (d, *J* = 5.3 Hz, 2 H), 5.39 (dd, *J* = 3.2, 3.0 Hz, 1 H), 6.77 (br. s, 2 H), 6.84 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 21.3, 25.0, 30.2, 61.8, 64.7, 96.0, 111.7, 116.1, 120.8, 139.3, 142.3, 156.9.

(h) 3-Methyl-5-(2-tetrahydropyranyloxy)benzaldehyde: To a suspension of pyridinium chlorochromate (PCC) (3.79 g, 17.59 mmol) and NaOAc (289 mg, 3.52 mmol) in CH_2Cl_2 (30 mL) was added a solution of the above alcohol (2.68 g, 11.73 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at 23 °C for 3 h. After diluting with Et_2O, the heterogeneous mixture was decanted. The solid residue was triturated with additional Et_2O and decanted again. The combined extracts were concentrated and the residue was chromatographed (hexane/EtOAc, 8:1) to give the benzaldehyde (2.06 g, 81%) as a pale yellow solid. − R_f = 0.33 (hexane/EtOAc, 8:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.73−1.54 (m, 2 H), 2.07−1.81 (m, 2 H), 9.90 (s, 1 H), 2.38 (s, 3 H), 3.66−3.55 (m, 1 H), 3.93−3.81 (m, 1 H), 5.46 (dd, *J* = 3.3, 2.8 Hz, 1 H), 7.11 (br. s, 1 H), 7.30 (br. s, 1 H), 7.35 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 21.2, 25.0, 30.1, 62.0, 96.3, 113.8, 123.6, 124.0, 137.6, 140.2, 157.4, 192.2.

(i) 2-(3-Hydroxy-5-methylphenyl)-1,3-dioxane: A solution of the above benzaldehyde (985 mg, 4.51 mmol), 1,3-propanediol (0.49 mL, 0.52 g, 6.77 mmol) and $TsOH·H_2O$ (17 mg, 0.09 mmol) in toluene (25 mL) was heated under refluxing conditions with azeotropic removal of H_2O for 3 h. After the usual workup, the residue was chromatographed (hexane/EtOAc, 4:1) to give the phenol acetal (648 mg, 74%) as a white solid. − R_f = 0.31 (hexane/EtOAc, 4:1). − M.p. 91−92 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34−1.42 (m, 1 H), 2.13−2.31 (m, 1 H), 2.21 (s, 3 H), 3.93 (td, *J* = 12.2, 2.2 Hz, 2 H), 4.22 (dd, *J* = 11.0, 4.9 Hz, 2 H), 5.39 (s, 2 H), 6.47 (br. s, 1 H), 6.70 (br. s, 1 H), 6.85 (br. s, 1 H), 6.98 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9, 25.3, 67.0 (2C), 101.4, 110.2, 116.5, 118.4, 139.2, 139.3, 155.5.

(j) 2-(3-Methoxymethoxy-5-methylphenyl)-1,3-dioxane: To a solution of the phenol described above (650 mg, 3.35 mmol) and diisopropylethylamine (0.93 mL, 0.69 g, 5.36 mmol) in CH_2Cl_2 (10 mL) was added chloromethyl methyl ether (0.51 mL, 0.54 g, 6.70 mmol) and the mixture was heated at 40 °C for 24 h. After the usual workup, the residue was chromatographed (hexane/EtOAc, 10:1) to give the MOM ether (591 mg, 80%) as a colorless oil. − R_f = 0.32 (hexane/EtOAc, 10:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33−1.59 (m, 1 H), 2.13−2.28 (m, 1 H), 2.33 (s, 3 H), 3.46 (s, 3 H), 3.97 (td, *J* = 12.3, 2.3 Hz, 2 H),), 4.26 (dd, *J* = 10.9, 5.1 Hz, 2 H), 5.16 (s, 2 H), 5.44 (s, 1 H), 6.82 (br. s, 1 H), 6.97 (br. s, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3, 25.6, 55.7, 67.1 (2C), 94.1, 101.3, 110.7, 117.2, 120.0, 139.3, 139.8, 157.1.

(k) Stannane 17: To a solution of the above derivative (648 mg, 2.72 mmol) in hexane (20 mL) at 0 °C was added *n*BuLi (1.3 mL, 2.5 M in hexane, 3.13 mmol). After 30 min, nBu_3SnCl (1330 mg, 4.08 mmol) in THF (15 mL) was added, and the mixture was stirred for 15 min at this temperature. An aqueous, buffered NH_4Cl solution (pH = 8, 0.2 mL) was then added, and the solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed (hexane/EtOAc, 70:1) to give **17** (1389 mg, 97%) as a colorless oil. − R_f = 0.45 (hexane/EtOAc, 50:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87−1.69 (m, 28 H), 2.13−2.31 (m, 1 H), 2.35 (s, 3 H), 3.46 (s, 3 H), 3.96 (td, *J* = 12.3, 2.2 Hz, 2 H), 4.25 (dd, *J* = 10.9, 5.0 Hz, 2 H), 5.12 (s, 2 H), 5.39 [s, *J*(Sn−H) = 2.6 Hz, 1 H], 6.91 [s, *J*(Sn−H) = 7.0 Hz, 1 H], 7.25 [s, *J*(Sn−H) = 5.7 Hz, 1 H]. − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.1 [$^1J(^{13}C-^{119}Sn)$ = 176 Hz, $^1J(^{13}C-^{117}Sn)$ = 169 Hz], 13.7, 21.5, 25.7, 27.4 [$^2J(^{13}C-Sn)$ = 31 Hz], 29.1 [$^3J(^{13}C-Sn)$ = 8.5 Hz], 55.7, 67.1 (2C), 94.4, 102.4 [$^3J(^{13}C-Sn)$ = 11 Hz], 113.6 [$^3J(^{13}C-Sn)$ = 10 Hz], 120.6 [$^3J(^{13}C-Sn)$ = 16 Hz], 125.7, 140.2, 146.5, 161.9. − $C_{25}H_{44}O_4Sn$: calcd. C 56.95, H 8.41; found C 57.12, H 8.79.

Gilvocarcin BE-12406X$_2$ (3): To a solution of **18** (274 mg, 0.70 mmol) in HOAc (20 mL) was added Zn (182 mg, 2.79 mmol) and $TsOH·H_2O$ (ca. 5 mg), and stirring at 23 °C was continued for 13 h. The solid was filtered off and washed with H_2O and Et_2O to give **3** (170 mg, 75%) as a reddish solid, which was recrystallized from MeOH. − M.p. > 300 °C (dec). − IR (KBr): $\tilde{\nu}$ = 3297, 3122, 2937, 1669, 1615, 1586, 1392, 1367, 1303 cm^{-1}. − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 12.12 (br. s, 2 H), 2.47 (s, 3 H), 4.06 (s, 3 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 7.46 (s, 1 H, overlaps with t), 7.46 (t, *J* = 8.1 Hz, 1 H), 7.76 (s, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 8.28 (s, 1 H). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.3, 56.2, 104.4, 109.8, 110.5, 114.1, 116.8, 118.7, 121.6, 121.7, 122.5, 128.4, 125.8, 137.7, 139.7, 155.0, 157.3, 159.9, 160.7. − EIMS; *m*/*z*: 322 (100) [M]$^+$, 307 (8), 279 (19), 251 (8), 165 (8).

Antibiotic WS-5995-B (4): A mixture of **3** (35 mg, 0.11 mmol) and KOH (196 mg, 3.49 mmol) in THF (3.5 mL) and H_2O (3.5 mL) was stirred at 23 °C for 3 h. The mixture was washed with CH_2Cl_2, and the aqueous phase was acidified with a 3.5% aqueous solution of HCl. After the usual workup, **4** (25 mg, 67%) was obtained as a red solid. − M.p. > 300 °C (dec). − IR (KBr): $\tilde{\nu}$ = 3369, 2924, 1689, 1640, 1604, 1417, 1307 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.76 (s, 3 H), 6.79 (s, 1 H), 7.01 (s, 1 H), 7.21−7.33 (m, 1 H), 7.53 (s, 1 H), 7.55−7.69 (m, 2 H), 11.17 (s, 1 H), 12.05 (s, 1 H). − EIMS; *m*/*z*: 338 (100) [M]$^+$, 309 (36), 293 (49), 148 (55), 120 (67), 92 (50).

2-Aryl-1,4-naphthoquinone 19: A solution of quinone **11** (300 mg, 1.12 mmol), stannane **13** (542 mg, 1.23 mmol), $Pd(PPh_3)_4$ (129 mg, 0.11 mmol), and CuI (43 mg, 0.22 mmol) in THF (40 mL) was heated at 70°C for 6 h. The mixture was cooled to room temperature, and washed with an aqueous solution of KF. After the usual workup, the residue was chromatographed (hexane/EtOAc, 1:1) to give quinone **19** (246 mg, 65%) as a red solid. − M.p. 194−195 °C. − IR (KBr) $\tilde{\nu}$ = 2922, 2851, 1652, 1467, 1310 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 3.78 (s, 3 H), 4.04 (s, 3 H), 6.80 (s, 1 H), 7.06 (br. s, 1 H), 7.30−7.37 (m, 2 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 7.78 (dd, *J* = 7.5, 1.6 Hz, 9.88 (s, 1 H), 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.38, 55.96, 56.35, 117.33, 117.62, 119.99, 119.48, 124.27, 130.76, 132.51, 133.13, 134.82, 139.39, 140.86, 143.00, 157.00, 159.36, 183.84 (2C), 191.18. − EIMS; *m*/*z*: 336 (100) [M]$^+$, 322 (23), 308 (48), 293 (35), 277 (25), 262 (83). − $C_{20}H_{16}O_5·0.33H_2O$: calcd. C 70.17, H 4.91; found C 70.19, H 4.74.

Benzo[*c*]phenanthridine 20: A solution of **19** (74 mg, 0.22 mmol) and NH_4OAc (70 mg, 0.91 mmol) in HOAc (4 mL) was heated at 118 °C for 24 h. The mixture was cooled to room temperature and, after the usual workup (CH_2Cl_2 instead of EtOAc), the residue was chromatographed (hexane/EtOAc, 3:2) to give **20** (15 mg, 21%) as a pale red solid. − R_f = 0.25 (hexane/EtOAc, 3:2). − M.p.

226−227 °C (dec). − IR (KBr): $\tilde{\nu}$ = 3394, 1725, 1619, 1365, 1261 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 4.13 (s, 6 H), 7.05 (m, 2 H), 7.46 (br. s, 1 H), 7.60 (t, *J* = 8.3 Hz, 1 H), 8.85 (s, 1 H), 9.10 (d, *J* = 8.3 Hz, 1 H), 9.13 (s, 1 H), 9.57 (s, 1 H). − EIMS; *m*/*z*: 319 (100) $[M]^+$, 304 (12), 276 (34), 246 (15).

2-Aryl-1,4-naphthoquinone 21: A mixture of **11** (400 mg, 1.50 mmol), **17** (950 mg, 1.80 mmol, $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), and CuI (57 mg, 0.30 mmol) in THF (50 mL) was heated at 70 °C for 12 h. After cooling to room temperature, the mixture was washed with an aqueous KF solution. After the usual workup, the residue was chromatographed (hexane/EtOAc, 1:1) to give quinone **21** (540 mg, 85%) as an orange solid. − R_f = 0.27 (hexane/EtOAc, 1:1). − M.p. 105−106 °C. − IR (KBr): $\tilde{\nu}$ = 2957, 2845, 1718, 1654, 1585, 1470, 1282, 1149 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24−1.30 (m, 1 H), 1.95−2.15 (m, 1 H), 2.36 (s, 3 H), 3.33 (s, 3 H), 3.63−3.80 (m, 2 H), 4.02 (s 3 H), 4.02−4.10 (m, 2 H), 5.00 (part B of AB system, *J* = 6.7 Hz, 1 H), 5.06 (part A of AB system, *J* = 6.7 Hz, 1 H), 5.29 (s, 1 H), 6.84 (s, 1 H), 6.98 (br. s, 1 H), 7.17 (br. s, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 6.9 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 25.4, 56.0, 56.4, 67.0, 67.1, 94.5, 100.0, 115.5, 117.4, 119.5, 120.0, 120.3, 134.7, 134.8, 137.4, 139.4, 140.4, 144.6, 154.3, 159.4, 183.6, 184.6, (a signal was not observed). − EIMS; *m*/*z*: 424 (64) $[M]^+$, 379 (92), 321 (90). − $C_{24}H_{24}O_7 \cdot 0.5\,H_2O$: calcd. C 66.49, H 5.82; found C 66.57, H 5.80.

Benzo[*b*]phenanthridine 22: A mixture of **21** (80 mg, 0.19 mmol), NH_4Cl (202 mg, 3.8 mmol), and NaOAc (308 mg, 3.8 mmol) in EtOH (10 mL) was heated at 80 °C for 12 h. After cooling to room temperature, and the usual workup, the residue was dissolved in 1,4-dioxane (4 mL), aqueous HCl (10%, 0.8 mL) was added, and the reaction mixture was stirred for 3 h at 23 °C. After the usual workup, the residue was chromatographed (EtOAc/MeOH, 95:5) to give **22** (46 mg, 67%) as a red solid. − R_f = 0.32 (EtOAc/MeOH, 95:5). − M.p. 166−167 °C. − IR (KBr): $\tilde{\nu}$ = 2953, 2827, 1672, 1561, 1485, 1373, 1268, 1051 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 3.62 (s, 3 H), 4.04 (s, 3 H), 5.32 (s, 2 H), 7.28 (dd, *J* = 7.0, 2.4 Hz, 1 H), 7.44 (br. s, 1 H), 7.51 (br. s, 1 H), 7.65−7.75 (m, 2 H), 9.37 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 56.6 (2C), 95.7, 117.0, 118.3, 118.9, 120.61, 120.9, 121.7, 129.2, 131.7, 135.1, 138.4, 142.2, 145.0, 154.1, 156.7, 159.9, 181.2, 185.8. − EIMS; *m*/*z*: 363 (100) $[M]^+$, 333 (25), 319 (30), 305 (40), 290 (27). − $C_{21}H_{17}NO_5 \cdot 0.5H_2O$: calcd. C 67.74, H 4.87; found C 67.79, H 4.37.

Phenanthroviridone 7: A mixture of **22** (10 mg, 0.028 mmol) and LiI (22 mg, 0.17 mmol) in 2,6-lutidine (2 mL) was heated at 140 °C for 6 h. After cooling to room temperature, EtOAc was added and the resulting solution was washed with an aqueous 3.5% HCl solution. After the usual workup, **7** (5 mg, 63%) was obtained as a red solid. − M.p. 228−229 °C (ref. [20b]: m.p. 227−229 °C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 7.35 (br. s, 1 H), 7.41 (d, *J* = 8.5 Hz, 1 H), 7.46 (br. s, 1 H), 7.74 (dd, *J* = 8.2, 7.8 Hz, 1 H), 7.91(d, *J* = 7.4 Hz, 1 H), 12.06 (s, 1 H), 12.31 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 114.5, 120.5, 121.2, 121.5, 123.6, 125.7, 128.3, 132.5, 133.5, 137.0, 144.0, 145.6, 155.0, 160.2, 162.1, 186.2, 189.6. − EIMS; *m*/*z*: 305 (100) $[M]^+$, 277 (45), 249 (17).

Benzo[*d*]naphtho[1,2-*b*]pyran-6-one 23: A mixture of **19** (62 mg, 0.18 mmol), 2-ethyl-5-(2-hydroxyethyl)-4-methylimidazolium bromide (5 mg, 0.02 mmol), and Et_3N (15 mg, 21 μL, 0.15 mmol) was heated in DMF (1 mL) at 55 °C for 21 h. After cooling to room temperature, the mixture was diluted with H_2O and the resulting solid was filtered to give **21** (28 mg, 45%) as a red solid. − M.p. 266−267 °C. − IR (KBr): $\tilde{\nu}$ = 3383, 2915, 1610, 1451, 1394, 1242, 1035 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H), 4.09 (s, 3 H), 4.10 (s, 3 H), 6.94 (d, *J* = 7.8 Hz, 1 H), 7.18 (br. s, 1 H), 7.48 (dd, *J* = 8.6, 7.8 Hz, 1 H), 7.96 (br. s, 1 H), 8.22 (d, *J* = 8.6 Hz, 1 H), 8.41 (s, 1 H), 9.16 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 55.9, 56.2, 105.7, 107.6, 114.7, 115.0, 116.0, 117.8, 121.6, 122.4, 123.1, 125.7, 126.4, 139.9, 149.8, 155.5, 157.4, 161.4, (one predicted signal was not observed). − EIMS; *m*/*z*: 336 (100) $[M]^+$, 321 (14), 293 (30), 250 (13).

Bis(benzo[*d*]naphtho[1,2-*b*]pyran) 24: To a solution of **19** (50 mg, 0.15 mmol) and $TiCl_4$ (128 mg, 74 μL, 0.68 mmol) in THF (2 mL) at −10 °C was added Zn (88 mg, 1.35 mmol), in small portions. The mixture was stirred at this temperature for 15 min and at 0 °C for 1 h. The resulting mixture was diluted with a 5% aqueous solution of $NaHCO_3$ and EtOAc and filtered through a short pad of Celite. After the usual workup, the residue was chromatographed (hexane/EtOAc, 3:1) to give **24** (36 mg, 75%) as a pale yellow solid. − R_f = 0.32 (hexane/EtOAc, 3:1). − M.p. 280 °C (dec). − IR (KBr): $\tilde{\nu}$ = 3447, 2954, 2868, 1756, 1456, 1390, 1255 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 2.12 (s, 6 H), 3.95 (s, 6 H), 4.11 (s, 6 H), 5.25 (s, 2 H), 5.73 (br. s, 2 H), 6.71 (br. s, 2 H), 6.88 (d, *J* = 7.6 Hz, 2 H), 7.42 (dd, *J* = 8.3, 7.6 Hz, 2 H), 8.06 (s, 2 H), 8.06 (d, *J* = 8.4 Hz, 2 H), 8.98 (s, 2 H). − Irradiation of the OH signal (δ = 8.98) gives a positive NOE for the signals at δ = 4.11 (s, 1%) and 8.08 (s, 6.5%). Irradiation of the signal at δ = 5.25 gives a positive NOE for the signals at δ = 5.73 (s, 20%), 8.06 (d, 2%), and 8.06 (s, 2%). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.14, 55.63, 56.16, 76.09, 104.78, 109.32, 112.45, 114.81, 115.70, 117.51, 117.99, 121.49, 124.77, 127.68, 132.72, 137.45, 139.97, 147.61, 155.75, 156.24. − EIMS; *m*/*z*: 642 (13) $[M]^+$, 321 (100). − The structure was also supported by COSY, HMQC, and HMBC experiments.

Bromo-1,4-naphthoquinone 12: A solution of **10** (500 mg, 1.98 mmol), diisopropylethylamine (1.14 g, 1.43 mL, 7.92 mmol), and chloromethyl methyl ether (0.32 g, 0.3 mL, 3.96 mmol) in CH_2Cl_2 (15 mL) was heated under reflux for 2.5 h. After the usual workup (CH_2Cl_2 instead of EtOAc), the residue was chromatographed (hexane/EtOAc, 3:1) to give **12** (424 mg, 72%) as an orange solid. − R_f = 0.29 (hexane/EtOAc, 3:1). − M.p. 125−126 °C. − IR (KBr): $\tilde{\nu}$ = 1676, 1636, 1454, 1306, 1239, 1090 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3 H), 5.31 (s, 2 H), 7.33 (s, 1 H), 7.52 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.62 (dd, *J* = 8.5, 7.6 Hz, 1 H), 7.80 (dd, *J* = 7.5, 1.3 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.53, 94.88, 120.00, 121.68, 122.51, 132.75, 134.66, 136.88, 142.04, 157.29, 177.87, 181.07. − EIMS; *m*/*z*: 298 (42) $[M]^+$, 267 (18), 254 (85), 236 (52), 173 (100). − $C_{12}H_9BrO_4$: calcd. C 48.51, H 3.05; found C 48.26, H 2.55.

2-Aryl-1,4-naphthoquinone 25: A mixture of quinone **12** (700 mg, 2.36 mmol), stannane **17** (1.374 g, 2.60 mmol), $Pd(PPh_3)_4$ (273 mg, 0.24 mmol), and CuI (90 mg, 0.47 mmol) in THF (90 mL) was heated at 70 °C for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with an aqueous solution of KF. After the usual workup, the residue was chromatographed (hexane/EtOAc, 1:1) to give quinone **25** (875 mg, 82%) as an orange solid. − R_f = 0.30 (hexane/EtOAc, 1:1). − M.p. 135−136 °C. − IR (KBr): $\tilde{\nu}$ = 2937, 2837, 1659, 1630, 1467, 1385, 1152, 1055 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (br. d, *J* = 11.0 Hz, 1 H), 1.99−2.12 (m, 1 H), 2.35 (s, 3 H), 3.32 (s, 3 H), 3.55 (s, 3 H), 3.66−3.78 (m, 2 H), 4.06 (dd, *J* = 12.5, 4.9 Hz, 2 H), 4.97 (part A of AB system, *J* = 6.8 Hz, 1 H), 3.75−4.08 (m, 3 H), 3.99 (s, 3 H), 5.07 (part B of AB system, *J* = 6.8 Hz, 1 H), 5.30 (s, 1 H), 5.32 (part A of AB system, *J* = 6.9 Hz, 1 H), 5.38 (part B of AB system, *J* = 6.9 Hz, 1 H), 6.84 (s, 1 H), 6.98 (br. s, 1 H), 7.17

(br. s, 1 H), 7.51 (dd, J = 8.4, 1.0 Hz, 1 H), 7.63 (dd, J = 8.4, 7.6 Hz, 1 H), 7.82 (dd, J = 7.6, 1.2 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.47, 25.21, 55.74, 56.36, 66.81, 66.93, 94.26, 94.99, 99.81, 115.20, 119.25, 120.17, 120.68, 120.78, 121.70, 134.25, 134.48, 137.24, 139.13, 140.14, 144.60, 154.14, 156.62, 183.17, 184.12. − EIMS; m/z: 454 (47) $[M]^+$, 409 (52), 291 (32). − $C_{25}H_{26}O_8 \cdot 0.33H_2O$: calcd. C 65.22, H 5.84; found C 65.29, H 5.79.

Naphthoquinone Epoxide 26: To a mixture of *t*BuOOH (462 mg, 0.51 mL, 4.06 mmol, 80% in *t*BuOO*t*Bu) and KF−Al_2O_3 (487 mg, 3.05 mmol) in MeCN (2 mL) was added **21** (860 mg, 2.03 mmol) in MeCN (5 mL) and stirring was continued at 23 °C for 16 h. The resulting mixture was filtered and, after the usual workup, the residue was chromatographed (hexane/EtOAc, 2:1) to give **26** (679 mg, 76%) as a yellow, vitreous solid (1.5:1 mixture of atropoisomers). − R_f = 0.31 (hexane/EtOAc, 2:1). − IR (KBr): $\tilde{\nu}$ = 2960, 2849, 1695, 1587, 1312, 1277, 1151 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (br. d, J = 9.1 Hz, 1 H, major isomer), 1.33 (br. d, J = 12.8 Hz, 1 H, minor isomer), 2.11−2.24 (m, 2 H), 2.35 (s, 3 H, major isomer), 2.36 (s, 3 H, minor isomer), 3.33 (s, 3 H, minor isomer), 3.43 (s, 3 H, major isomer), 3.91 (s, 1 H, minor isomer), 4.22 (dd, J = 11.2, 4.9 Hz, 1 H, minor isomer), 4.40 (s, 1 H, major isomer), 5.04 (part A of AB system, J = 6.8 Hz, 1 H, minor isomer), 5.11 (part A of AB system, J = 6.8 Hz, 1 H, minor isomer), 5.13 (part B of AB system, J = 6.8 Hz, 1 H, major isomer), 5.20 (part A of AB system, J = 6.8, 1 H, major isomer), 5.73 (s, 1 H, minor isomer), 5.48 (s, 1 H, major isomer), 6.95 (br. s, 1 H, major isomer), 6.93 (br. s, 1 H, minor isomer), 7.22 (br. s, 1 H, minor isomer), 7.00 (br. s, 1 H, major isomer), 7.24−7.28 (m, 1 H, major isomer), 7.53 (dd, J = 6.5, 1.2 Hz, 1 H, minor isomer), 7.61−7.66 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.17, 21.36, 24.43, 25.18, 55.55, 55.67, 55.89, 55.97, 61.80, 62.00, 62.11, 62.36, 62.47, 66.82, 67.07, 67.30, 76.58, 93.49, 93.70, 98.11, 101.85, 113.62, 114.84, 115.40, 115.90, 116.80, 116.91, 118.80, 119.31, 119.42, 119.86, 121.31, 133.92, 134.56, 134.67, 137.91, 138.91, 140.19, 154.72, 156.90, 158.18, 158.35, 189.86, 190.81, 190.89, 191.87, (two signals were not observed). − EIMS; m/z: 440 (16) $[M]^+$, 395 (100), 337 (20), 309 (32), 293 (93).

Naphthoquinone Epoxide 27: To a mixture of *t*BuOOH (91 mg, 0.10 mL, 0.92 mmol, 80% in *t*BuOO*t*Bu) and KF−Al_2O_3 (111 mg, 0.69 mmol) in MeCN (1.5 mL) was added **25** (210 mg, 0.46 mmol) in MeCN (4 mL), and the mixture was stirred at 23 °C for 16 h. The mixture was filtered and, after the usual workup, the residue was chromatographed (hexane/EtOAc, 1:1) to give **27** (162 mg, 75%) as a yellow, vitreous solid (3:1 mixture of atropoisomers). − R_f = 0.31 (hexane/EtOAc, 1:1). − M.p. 60−61 °C. − IR (KBr): $\tilde{\nu}$ = 2969, 2836, 1687, 1581, 1311, 1254, 1151 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20−1.36 (s, 1 H), 2.08−2.29 (m, 1 H), 2.35 (s, 3 H, major isomer), 2.36 (s, 3 H, minor isomer), 3.33 (s, 3 H, minor isomer), 3.43 (s, 3 H, major isomer), 3.52 (s, 3 H, major isomer), 3.54 (s, 3 H, minor isomer), 3.91 (s, 1 H, minor isomer), 3.73−3.99 (m, 2 H), 4.06 (dd, J = 11.5, 5.0 Hz, 2 H, major isomer), 4.22 (dd, J = 11.3, 5.0 Hz, 2 H, minor isomer), 4.40 (s, 1 H, major isomer), 5.01 (part A of AB system, J = 6.9 Hz, 1 H, minor isomer), 5.10 (part A of AB system, J = 6.9 Hz, 1 H, major isomer), 5.15 (part A of AB system, J = 6.9 Hz, 1 H, minor isomer), 5.22 (part B of AB system, J = 6.8 Hz, 1 H, major isomer), 5.23 (part B of AB system, J = 6.9 Hz, 1 H, major isomer), 5.27 (part A of AB system, J = 6.8 Hz, 1 H, minor isomer), 5.34 (part B of AB system, J = 6.8 Hz, 1 H, minor isomer), 5.39 (part B of AB system, J = 6.8 Hz, 1 H, major isomer), 5.47 (s, 1 H, major isomer), 5.72 (s, 1 H, minor isomer), 6.94 (br. s, 1 H, minor isomer), 6.96 (br. s, 1 H, major isomer), 7.00 (br. s, 1 H, major isomer), 7.21 (br. s, 1 H, minor isomer), 7.71−7.47 (m, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 21.4, 24.5, 25.3, 55.6, 55.7, 56.1, 61.9, 62.2, 62.3, 62.4, 66.9, 67.3, 93.5, 93.9, 94.8, 98.2, 101.9, 113.8, 114.9, 115.5, 116.0, 119.6, 120.2, 120.7, 120.9, 121.1, 121.3, 133.9, 134.3, 134.4, 134.6, 138.0, 139.0, 140.3, 154.8, 155.8, 155.9, 157.0, 189.7, 190.8, 191.8, (several signals were not observed). − EIMS; m/z: 470 (12) $[M]^+$, 441 (11), 425 (100), 381 (19), 307 (39), 279 (27).

2-Aryl-3-hydroxynaphthoquinone 28, Sodium Salt: A mixture of **26** (800 mg, 1.82 mmol) and NaOH (1817 mg, 45.5 mmol) in MeOH (22 mL) and H_2O (22 mL) was heated at 80 °C for 16 h. The mixture was cooled to room temperature and the solid was filtered off to give **28**·Na. The filtrate was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to give additional **28**·Na (overall: 682 mg, 81%) as a red solid. − M.p. 317−318 (dec.). − IR (KBr): $\tilde{\nu}$ = 3438 (br.), 2927, 2853, 1667, 1535, 1378, 1003 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21−1.28 (m, 1 H, acetal), 1.42 (s, aryl-Me), 2.16−2.39 (m, 1 H, acetal), 3.26 (s, CH_2O*Me*), 3.45 (br t, J = 11.1 Hz, 1 H, acetal), 3.86 (br. t, J = 11.4 Hz, 1 H, acetal), 4.07 (s, aryl-OMe), 4.22 (td, J = 7.1, 3.4 Hz, 1 H, acetal), 4.39 (br. s, 1 H, acetal), 5.20 (s, 1 H, acetal), 5.28 (part B of AB system, J = 6.8 Hz, 1 H, CH_2OMe), 5.98 (part A of AB system, J = 6.8 Hz, 1 H, CH_2OMe), 6.61 (br. s, 3′-H), 7.11 (br. s, 5′-H), 7.21 (d, J = 7.9 Hz, 6-H), 7.63 (dd, J = 8.2, 7.9 Hz, 7-H), 7.81 (d, J = 7.2 Hz, 8-H). − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.19−1.30 (m, 1 H), 1.77−1.98 (m, 1 H), 2.28 (s, 3 H), 3.26 (s, 3 H), 3.45−3.65 (m, 1 H), 3.87 (s, 3 H), 3.80−4.00 (m, 2 H), 4.89 (s, 2 H), 5.27 (s, 1 H), 6.78 (m, 1 H), 6.98 (s, 1 H), 7.15−7.23 (m, 1 H), 7.52−7.58 (m, 2 H). − NOESY (mixing time 500 ms; $CDCl_3$, 300 MHz) showed cross peaks between the aryl-Me group (δ = 1.42) and the A-ring aryl (δ = 7.21, 7.63, and 7.81) as well as the C-2 aryl hydrogen atoms (δ = 6.61 and 7.11). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.0, 26.4, 55.8 (2 C), 67.3, 67.6, 92.9, 100.5, 113.6, 114.6, 117.0, 119.1, 119.4, 119.7, 122.2, 135.1, 136.8, 137.4, 137.9, 152.1, 158.9, 170.9, 180.8, 186.5. − EIMS; m/z: 440 (17) $[M]^+$, 395 (30), 337 (44), 321 (100). − FAB-MS; m/z: 1850.6 (3), 1849.5 (3) [(**28**·Na)$_4$ + H], 1410.5 (24), 1409.4 (27) [(**28**·Na)$_3$ + Na], 948.3 (7), 947.3 (10) [**28**·Na]$_3$; 486.2 (28), 485.2 (100) [(**28**·Na) + Na]. − $C_{24}H_{23}O_8Na \cdot NaOH$: calcd. C 57.37, H 4.81; found C 57.20, H 4.54. − The structure was also supported by HMQC and HMBC experiments.

2-Aryl-3-hydroxy-1,4-naphthoquinone 29, Sodium Salt: A mixture of epoxide **27** (460 mg, 0.98 mmol) and NaOH (978 mg, 24.46 mmol) in MeOH (10 mL) and H_2O (10 mL) was heated at 80 °C for 16 h. The mixture was cooled to room temperature and the solid was filtered off. The filtrate was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated to give additional **29**·Na (overall: 391 mg, 81%) as a red solid. − M.p. 246−247 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 3448, 2958, 2854, 1666, 1540, 1480, 1152 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (br. d, J = 12.5 Hz, 1 H), 1.46 (s, 3 H), 2.28−2.45 (m, 1 H), 3.23 (s, 3 H), 3.49 (br. t, J = 10.6 Hz, 1 H), 3.60 (s, 3 H), 3.87 (br. t, J = 11.3 Hz, 1 H), 4.14 (br. d, J = 6.3 Hz, 1 H), 4.25 (br. d, J = 7.7 Hz, 1 H), 4.90 (part B of AB system, J = 6.6 Hz, 1 H), 5.21 (s, 1 H), 5.40 (part B of AB system, J = 7.3 Hz, 1 H), 5.50 (part A of AB system, J = 7.3 Hz, 1 H), 6.43 (part A of AB system, J = 6.6 Hz, 1 H), 6.76 (br. s, 1 H), 7.12 (br. s, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.61 (dd, J = 8.4, 7.5 Hz, 1 H), 7.87 (d, J = 7.0 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 25.66, 55.73, 56.75, 67.18, 67.46, 92.62, 95.24, 100.45, 113.81, 116.84, 118.4, 119.62, 119.69, 120.42, 122.10, 134.93, 136.74, 137.31, 137.52, 151.80, 156.79, 170.78, 180.60, 186.93. − EIMS; m/z: 470 (15) $[M]^+$, 395 (12), 351 (46), 307 (83), 278 (55). − $C_{25}H_{25}O_9Na \cdot 0.5H_2O$: calcd. C 59.88, H 5.23; found C 59.49, H 4.98.

5*H*-Benzo[*d*]naphtho[2,3-*b*]pyran-7,12-dione 30: A solution of **29** (200 mg, 0.42 mmol) and TsOH (ca. 5 mg) in MeOH (10 mL) was heated under reflux conditions for 6 h. After cooling to room temperature and the usual workup, the residue was chromatographed (hexane/EtOAc, 3:1) to give **30** as a dark red solid (93 mg, 64%). − R_f (hexane/EtOAc, 3:1) = 0.61. − M.p. 216−217 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 3.61 (s, 3 H), 6.70 (br. s, 1 H), 6.9 (br. s, 1 H), 7.29 (br. d, *J* = 7.6 Hz,1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.82 (br. d, *J* = 7.0 Hz, 1 H), 10.91 (s, 1 H), 11.76 (s, 1 H). − ^{13}C NMR (75.5 MHz,$CDCl_3$): δ = 32.7, 56.64, 100.81, 108.73, 113.50, 119.02, 121.20, 121.67, 124.07, 125.05, 130.40, 132.19, 136.95, 143.73, 151.96, 154.80, 161.50, 183.20, 186.68. − EIMS; *m*/*z*: 338 (99) $[M]^+$, 310 (34), 295 (10), 279 (199), 266 (18), 251 (11). − $C_{19}H_{14}O_6 \cdot H_2O$: calcd. C 64.04, H 4.17; found C 64.45, H 4.09.

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