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The Acid-Catalyzed 2-*O*-Alkylation of Substituted 2-Hydroxy-1,4-naphthoquinones by Alcohols: Versatile Preparative Synthesis of Spinochrome D and Its 6-Alkoxy Derivatives

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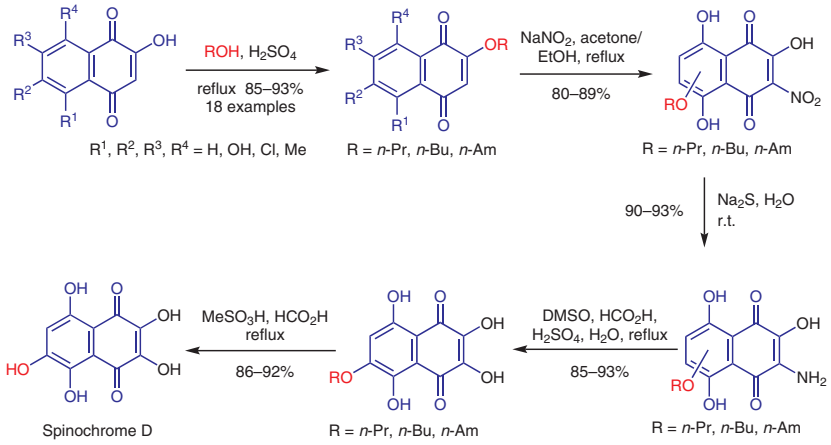

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Abstract A series of substituted 2-alkoxy-1,4-naphthoquinone derivatives were obtained by acid-catalyzed condensation of substituted 2-hydroxy-1,4-naphthoquinones with propan-1-ol, butan-1-ol, or pentan-1-ol in good yields. Based on this reaction a versatile preparative synthesis of spinochrome D was developed.

Key words 2-hydroxy-1,4-naphthoquinones, acid catalysis, 2-*O*-alkylation, *n*-alkanol, spinochrome D

1,4-Naphthoquinones represent a large class of natural compounds that are widely distributed in plants, marine invertebrates, fungi, and bacteria.[1] They revealed a diverse spectrum of activity: anticancer,[2] antibacterial,[3] antiprotozoal,[4] antimalarial,[5] and others. Some natural 2-hydroxy-1,4-naphthoquinones **1**–**10**, their analogues, and intermediates **11**–**15** are presented in Figure 1. The group of natural hydroxylated naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) derivatives **7**–**10** shows antioxidant activity.[6] Echinochrome A (**10**) is used, according to the Russian Pharmacopoeia, for the treatment of ischemia, myocardial infarction,[7a] traumas and burns of the eyes, also intraocular hemorrhages, various degenerative processes, dystrophic lesions of the cornea and inflammation of the eye.[7b,c] Recently, the ability of echinochrome to enhance mitochondrial biogenesis in cardiac[8] and skeletal muscles[9] was revealed. Echinochrome demonstrated a potential for improvement of the musculoskeletal system and lipid and protein metabolism in both types of diabetes mellitus.[10] It is assumed that echinochrome activity is due to the ability of β-hydroxyl groups to inhibit radical reactions and chelate transition metals cations that are responsible for the initiation of free-radical oxidation in biological systems.[11] There are numerous reports of the synthetic modification of echinochrome by conversion into *O*- or *S*-glycosides and *S*-glutathione conjugates with improved solubility and biological activity.[12] Spinochrome D (**9**) and echinochrome A (**10**) have an identical set of hydroxyl groups and differ only the presence of an ethyl group at C-7. The free position at C-7 next to the 6-OH group in the spinochrome D core allows various substituents to be attached to give new echinochrome-related analogues. The low content of spinochrome D in sea urchins (0.001–0.003% of dry wt) strongly limits the use of the natural quinone for its modifications.

During the development of our research project directed towards the design of a preparative synthesis of spinochrome D (**9**), we need to protect the 2-hydroxy group of starting quinone **13**. The free hydroxyl group of quinone **13** is easily ionized and forms a salt that reduces the reactivity of the quinone chlorine atoms to nucleophilic substitution in the next stage. The choice of protective group to use for the synthesis of spinochrome D should take into account the following aspects: (a) hydroxynaphthazarin **13** exists in various tautomeric forms that may react with formation of different reaction products, (b) spinochrome D is unstable in basic media and readily oxidized, (c) the use of halogen-containing reagents to remove the protective group should be excluded to avoid the formation of toxic impurities.

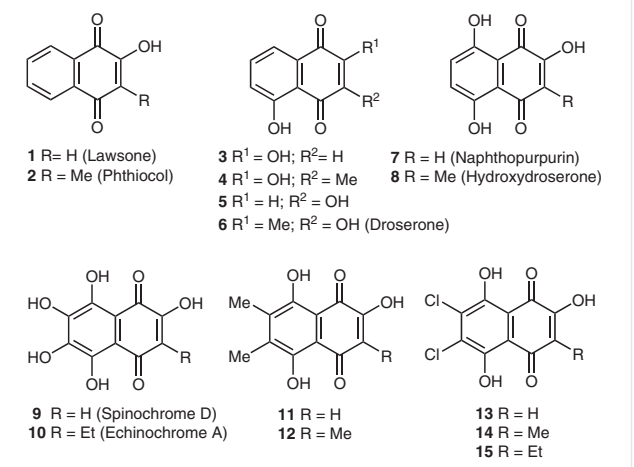


Figure 1 Structures of natural and synthetic 2-hydroxy-1,4-naphthoquinones

In our opinion, 2-alkoxy derivatives of naphthoquinone **13** with a long alkyl chain have suitable solubility and can be easily cleaved under acidic conditions. 2-Alkoxy derivatives of 2-hydroxynaphthoquinones showed significant antiplatelet, antiallergic, and anti-inflammatory activities.[13a] Some of these derivatives exhibited a potent inhibitory effect on neutrophil superoxide anion formation. The 1,4-naphthoquinones, bearing a 2-*O*-alkyl- and 3-*C*-alkyl group, were synthesized and their anticancer activity was evaluated against five human cell lines in vitro.[13b]

Two main approaches for preparation of 2-*O*-alkyl derivatives of hydroxynaphthoquinones are known. These are: (a) the base-catalytic direct S_N2 alkylation of the C-2 hydroxy group by alkyl halides and alkyl sulfates,[14] (b) the reaction of hydroxyquinones with diazomethane or alkyl orthoesters, where the acidic quinoid 2-hydroxy group self-catalyzes alkylation.[15] Both approaches have drawbacks and limitations. 2-Hydroxy-1,4-naphthoquinone readily undergoes tautomerization in the basic media and forms a mixture of isomeric 2-*O*-alkyl-1,4-naphthoquinone and 4-*O*-alkyl-1,2-naphthoquinone and also C-3 quinone *C*-alkylation products.[13] The orthoester *O*-alkylation procedure is limited by the nature of the orthoester and gives good yields only of 2-methoxy and 2-ethoxy derivatives, with the formation of C-3 carbon-substituted byproducts.[15b] The methylation of hydroxyquinones with diazomethane led to the required 2-methoxy derivatives in good yields, but other hydroxyl groups of the naphthoquinone core may also be involved in the formation of methyl ethers.[15c] Both approaches are not suitable for the preparative 2-*O*-alkylation of hydroxynaphthazarin **13**.

Fieser reported the appropriate 2-*O*-alkylation of lawsone (**1**) using a mixture of butan-1-ol/concd sulfuric acid, with the quinone/sulfuric acid molar ratio (1:12.8), and obtained 2-butoxynaphthoquinone **16** in 68% yield.[14a] We developed an acid-catalyzed procedure for the *O*-alkylation of various 2-hydroxynaphthoquinones by C_3–C_5 alcohols and synthesized a group of substituted 2-*O*-alkoxy-1,4-naphthoquinones **16**–**33** (Table 1). In our modification 2-hydroxyquinones **1**, **3**, **5**, **7**, **11**, and **13** reacted with propan-1-ol, butan-1-ol, and pentan-1-ol under sulfuric acid catalysis with azeotropic removal of water from the reaction medium at reflux within 5–11.5 h. Under these conditions the reaction was carried out at reduced molar ratio quinone/sulfuric acid (1:2.7) and it gave the respective 2-*O*-alkoxy derivatives **16**–**33** in good 81–93% yields.

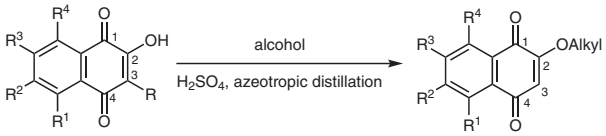
In control experiments without azeotrope removal of water, quinone **13** was converted into butoxy derivative **32** in 83% yield only after prolonged heating at reflux for 15 h. We examined also the utility of other acids to catalyze the alkoxylation of quinone **13** with butan-1-ol. Phosphoric acid was significantly less useful and its reaction gave **32** in 63% yield after 54 h. $MeSO_3H$ catalysis with quinone/catalyst molar ratio (1:7.5) for 35 h gave 2-butoxyquinone **32** in 73% yield.

In this experiment the minor 6,8-dibutoxy derivative **34** was also isolated from mother liquor in 7.7% yield (Scheme 1). A plausible reaction mechanism for 2-*O*-alkylation and 6,8-dialkoxyquinone **34** formation is shown in Scheme 1. The conversion of 2-hydroxyquinone **13** into 2-alkoxyquinone **32** involves several stages. In the first step tautomeric 1,2-naphthoquinone **A** is formed. The protonation of the carbonyl bond led to formation of the hemiacetal **C**, which undergoes dehydration to give the target 2-alkoxyquinone **32**. Protonation of the carbonyl group of quinone **32** again activates it to the addition of the alcohol and the hemiacetal **E** is formed, and this sequence ends as before with the loss of water. Finally, the rearrangement of the C=C bonds leads to a 6,8-dibutoxyquinone **34**. Under these conditions hydroxynaphthoquinones **2**, **4**, **6**, **8**, **12**, **14**, and **15**, bearing a C-3 alkyl substituent in the quinone ring did not reacted with butan-1-ol (Table 1, entries 4, 8, 12, 16, 20, 24, and 25). Possibly the low reactivity of 3-alkyl-2-hydroxynaphthoquinones is due to electron-donor and steric effects of the alkyl group in these reactions.[16]

With the designed method in hand we prepared the target naphthazarin derivatives **31**–**33** and developed the effective preparative synthesis of spinochrome D (**9**) and its 6-*O*-alkoxy derivatives.

The spinochrome D was first prepared by Thomson in 12-steps synthesis in low yield ~5%.[17] Today the most effective synthesis of spinochrome D (**9**) is based on the direct displacement of chlorine atoms in dichloroquinone **13**[18] or their 2-methoxy derivative by reaction of MeOH activated by fluoride anion $CsF/MeOH/Al_2O_3$ (Scheme 2). Despite the high yields at all stages of this synthesis, this approach has certain limitations due to using excess toxic MeI with the quinone/iodomethane molar ratio (1:88) and expensive dry CsF, and the low solubility of the intermediates, which pre-

Table 1 Acid-Catalyzed Reaction of Substituted 2-Hydroxy-1,4-naphthoquinones with Alcohols[a]

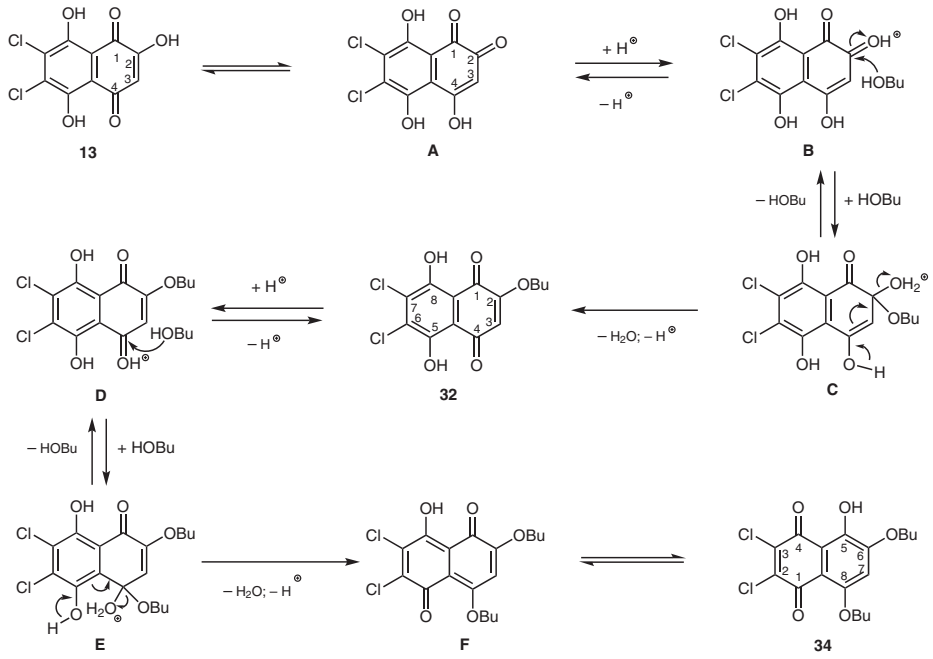


Entry	2-Hydroxy-1,4-naphthoquinones **1–15**						Alcohol	Time (h)	2-Alkoxy-1,4-naphthoquinones **16–33**	
		R	R^1	R^2	R^3	R^4				Yield (%)
1	**1**	H	H	H	H	H	BuOH	10.5	**16**	93
2	**1**	H	H	H	H	H	PrOH	11.5	**17**	85
3	**1**	H	H	H	H	H	pentan-1-ol	10	**18**	81
4	**2**	Me	H	H	H	H	BuOH	8	–	–[b]
5	**3**	H	OH	H	H	H	PrOH	6.5	**19**	85
6	**3**	H	OH	H	H	H	BuOH	9,5	**20**	85
7	**3**	H	OH	H	H	H	pentan-1-ol	5	**21**	87
8	**4**	Me	OH	H	H	H	BuOH	9	–	–[b]
9	**5**	H	H	H	H	OH	PrOH	6.5	**22**	91
10	**5**	H	H	H	H	OH	BuOH	8.5	**23**	89
11	**5**	H	H	H	H	OH	pentan-1-ol	4	**24**	89
12	**6**	Me	H	H	H	OH	BuOH	8	–	–[b]
13	**7**	H	OH	H	H	OH	PrOH	8	**25**	85
14	**7**	H	OH	H	H	OH	BuOH	12	**26**	83
15	**7**	H	OH	H	H	OH	pentan-1-ol	4	**27**	92
16	**8**	Me	OH	H	H	OH	BuOH	8	–	–[b]
17	**11**	H	OH	Me	Me	OH	PrOH	12	**28**	84
18	**11**	H	OH	Me	Me	OH	BuOH	8.5	**29**	92
19	**11**	H	OH	Me	Me	OH	pentan-1-ol	6	**30**	78
20	**12**	Me	OH	Me	Me	OH	BuOH	8	–	–[b]
21	**13**	H	OH	Cl	Cl	OH	PrOH	20	**31**	91
22	**13**	H	OH	Cl	Cl	OH	BuOH	8.5	**32**	88
23	**13**	H	OH	Cl	Cl	OH	pentan-1-ol	6	**33**	92
24	**14**	Me	OH	Cl	Cl	OH	BuOH	8	–	–[b]
25	**15**	Et	OH	Cl	Cl	OH	BuOH	8	–	–[b]

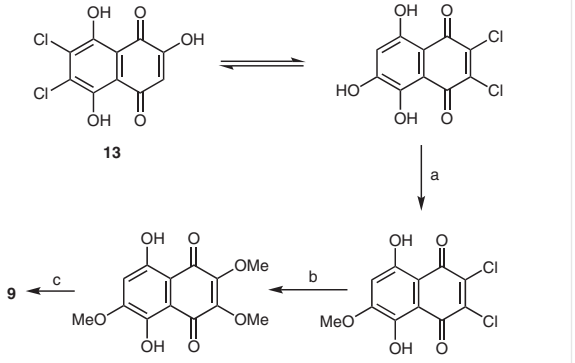
[a] Reactions were performed on 1.0-mmol scale.
[b] No reaction.

vents chromatographic purification from toxic impurities[19] of partial substituted chloronaphthazarins in the final product.

In our previous works,[20] we have developed an alternative effective approach for the synthesis of 2,3-dihydroxynapthazarins (spinazarins) by conversion of 6,7-substituted 2,3-dichloronaphthazarins with sodium nitrite, reduction of the thus formed 2-hydroxy-3-nitroquinones to aminoquinones with sodium sulfide or sodium dithionite, and acid-catalyzed transformation of 3-amino-2-hydroxynaphthazarins to spinazarins (Scheme 3). We have found that 2,3-dichloronaphthazarins, bearing hydrogen, alkyl, alkoxy, and chlorine groups at the 6,7-positions of the naphthoquinone core readily reacted with sodium nitrite at reflux in acetone/methanol solution and they are converted into 2-hydroxy-3-nitronaphthazarins in good yields after 2.5 h. Dichloronaphthazarins, bearing quinoid hydroxyl groups at C-2, did not react with sodium nitrite under these conditions. The 3-alkyl-6,7-dichloro-2-hydroxynaphthazarins **14** and **15** (Figure 1) reacted with sodium nitrite only in DMF at room temperature and after 2 h gave the corre-

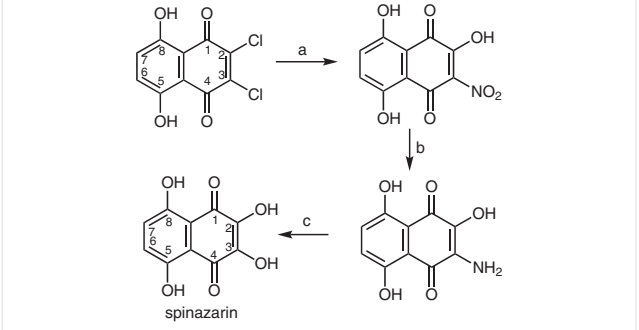


Scheme 1 Possible mechanism for the 2-*O*-alkylation of substituted 2-hydroxy-1,4-naphthoquinones and the formation of 6,8-dibutoxy-2,3-dichloro-5-hydroxy-1,4-naphthoquinone (**34**)

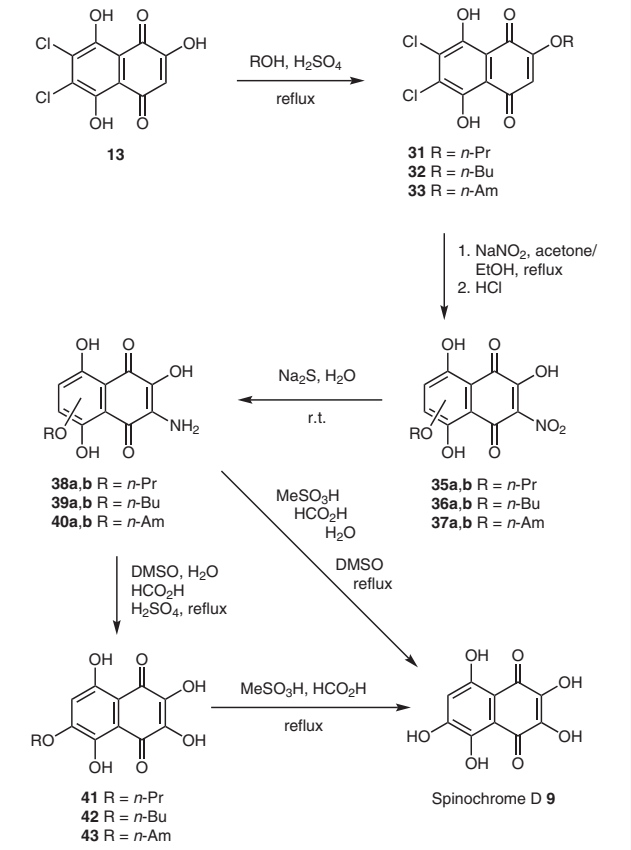


Scheme 2 A known route for the synthesis of spinochrome D. *Reagents and conditions*: (a) MeI, K_2CO_3, DMF, r.t., stirring 4 h, 80–93%; (b) CsF/MeOH/Al_2O_3, 90–95 °C, autoclave/stirring 12 h, 80%; (c) water HBr 48%, reflux, 0.5 h, 88%.

sponding nitroquinones in moderate yields 39–40%.[20b] Under these conditions hydroxychloroquinone **13** reacted with sodium nitrite and it was converted into an insoluble tar. Our procedure for the *O*-alkylation of 2-hydroxynaphthoquinones designed in this work allowed the formation of 2-alkoxy derivatives **31**–**33**. These were reacted with sodium nitrite in acetone/ethanol mixture at reflux to give after acidification mixtures of regioisomers **35a**/**35b**, **36a**/**36b**, and **37a**/**37b** in the ratio ~5:1 in good 85–92% yields (Scheme 4); **35a**,**b**–**37a**,**b** were highly soluble in organic solvents. It is well-known that the nitrite ion is an ambident nucleophile and it could react with dichloroquinone as an *O*-nucleophile forming appropriate chlorohydroxyquinones impurities.[20c] As expected, chlorohydroxyquinones also were obtained as byproducts in 3–5% yields and readily separated from the target nitroquinones by preparative TLC. Since nitroquinones are good soluble in water at basic pH values, the reduction of the nitro group was carried out in water solution.



Scheme 3 A known route for the synthesis of spinazarin. *Reagents and conditions*: (a) $NaNO_2$, K_2CO_3, acetone/MeOH, reflux, 2.5 h, 65–85%; (b) Na_2S, $Na_2S_2O_4$, water, 90–95 °C, 3–6 h, 86%; (c) HCO_2H, DMSO, H_2SO_4, H_2O (65–85%), reflux, 30 min, 88%.



Scheme 4 The designed route of spinochrome D synthesis

The reduction of nitroquinones **35a**,**b**–**37a**,**b** using excess sodium sulfide (10.0 mmol per 1 mmol of quinone) gave the expected aminoquinones **38a**,**b**–**40a**,**b** in good 90–93% yields. The reactions proceeded to completion after 7 h, and when the reaction was complete the acidification of the reaction mixture resulted in full precipitation of the aminoquinones. The aminoquinone precipitate was isolated by simply filtration and used without supplemental purification. Aminonaphthazarins **38a**,**b**–**40a**,**b** were readily converted into 6-alkoxy-2,3-dihydroxynaphthazarins **41**–**43** in $DMSO/H_2SO_4/HCO_2H/H_2O$ solution at reflux according to our published procedure.[20d] This step proceeds as a concerted process with participation of DMSO as oxidant and formic acid as a reducing agent under sulfuric acid catalysis and led to high purity 2,3-dihydroxynaphthazarins in good 85–93% yields. The reaction mechanism for this conversion was presented in our previous work.[20d]

The final deprotection of alkoxynaphthoquinones **41**–**43** was performed in $MeSO_3H/HCO_2H/H_2O$ solution at reflux for 3–4 h and gave spinochrome D (**9**) in 86–92% yields. Both of the final stages proceeded without the use of halogen-containing reagents and led to the target products with high purity and without toxic chlorine-containing impurities. We tried to convert alkoxyaminoquinones **38a**,**b**–**40a**,**b** into spinochrome D (**9**) in one-pot by using $MeSO_3H/H_2O/HCO_2H$ mixture at reflux for 6 h, but under these conditions the only dealkylation occurred; prolonged treatment of aminoquinones **38a**,**b**–**40a**,**b** for longer than 10 h led to ash formation. The reaction was initiated by addition of DMSO to the reaction media. The addition of DMSO and refluxing in 99% HCO_2H within 6 h led to 100% conversion of aminobutoxyquinone **38a**,**b** into spinochrome D (**9**) in only 29% yield. The treatment of aminobutoxyquinone **38a**,**b** by DMSO in 85% formic acid for 6 h led to spinochrome D (**9**) in 51% yield with formation intermediate butoxyspinazarin **42** in 5.5% yield.

The structures of the new compounds were confirmed by NMR, IR, and HRMS. Attachment of alcohols selectively to 2-OH group in naphthoquinone core of compounds **16**–**33** was evidenced by disappearance of the 2-OH signal together with the retention of other phenolic α-hydroxyl groups signals in a weak field at δ = 8–12 for derivatives **19**–**33**. The structure of 6,8-dibutoxy-2,3-dichloro-5-hydroxynaphthalene-1,4-dione (**34**) was based upon HMBC and HSQC correlations in its NMR spectra. Spectral characteristics of the other new nitro, amino, and alkoxy derivatives **35a**,**b**–**43** also were in a good agreement with their proposed structures.

In conclusion, we have developed a facile acid-catalyzed procedure for 2-*O*-alkylation of substituted 2-hydroxy-1,4-naphthoquinones with propan-1-ol, butan-1-ol, and pentan-1-ol. The C-3 alkyl group in the quinone ring blocked 2-*O*-alkylation. A series of substituted 2-alkoxy-1,4-naphthoquinone derivatives including 6-alkoxy-2,3-dichloronapthazarins were obtained in good yields. Based upon 6-alkoxy-2,3-dichloronapthazarins, we have designed a new four-step a operationally simple, versatile, and effective synthesis of natural pigment spinochrome D and its 6-alkoxy derivatives. Spinochrome D could be easily obtained by condensation of 6-alkoxy-2,3-dichloronapthazarins with sodium nitrite, reduction of regioisomeric nitroquinones, and acid-catalyzed conversion into alkoxyaminohydroxyquinones by treatment with $H_2SO_4/DMSO/H_2O$/formic acid to give 6-alkoxyspinazarins and deprotection of the alkoxy group by $MeSO_3H$/formic acid at reflux.

All reagents were obtained from commercial suppliers and used without further purification. All solvents were distilled before use. Lawsone (**1**) was purchased from Alfa Aesar. Hydroxyjuglones **3** and **5** were obtained from juglone as described in the literature.[21] Hydroxynaphthazarins **13**–**24** were prepared according to the literature.[22] Radical methylation of appropriate quinones **1**, **3**, and **5** by diacetyl peroxide[23a,b] in acetonitrile[23c] led to 2-hydroxy-3-methyl-1,4-naphthoquinone derivatives **2**, **4**, and **6**, respectively. Melting points were determined using a Boetius apparatus and are uncorrected. IR spectra in KBr and $CHCl_3$ were obtained using a Bruker Vector-22 FT-IR spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance III-500 HD (500 MHz) and Bruker Avance III-700 (700 MHz) spectrometers using $CDCl_3$, or DMSO-d_6 as the solvent with TMS as an

internal standard. ^{13}C NMR spectra were recorded on Bruker Avance III HD-500 spectrometer at 125 MHz and Bruker Avance III-700 spectrometer at 176 MHz. EIMS and HRMS-EI were recorded on AMD-604S at 70 eV. EIMS ESI were recorded on Agilent 6510 Q-TOF LC/MS. Silufol UV-VIS TLC plates treated vapor of HCl were used for analytical TLC. Preparative TLC was performed on silica gel 60 Merck (40–60 μm). TLC was developed in system A: hexane/benzene/acetone (4:1:1), system B: hexane/benzene/acetone (2:1:1), system C: hexane/benzene/acetone (2:1:2). Ratios of both isomeric products in mixtures quinones **35a**,**b**–**40a**,**b** were measured directly from the integration of ^1H NMR absorptions of the α-hydroxyl group protons, which are common to both of the regioisomers.

Alkylation of 2-Hydroxy-1,4-naphthoquinones 1–15; General Procedure

A mixture of quinone (1.0 mmol), alcohol (30 mL), and 90% H_2SO_4 (0.15 mL) was gently boiled with distillation dropwise of alcohol (5–7 mL) over 8–12 h in order to remove water and complete conversion of the starting quinone into the 2-alkoxy derivative. The mixture was transferred to a separatory funnel and diluted with toluene (20 mL) and washed with water (2 × 10 mL), and the organic layer was evaporated without drying. In the experiments with PrOH, the mixture was evaporated to a volume of ~5 mL and then mixed with toluene. After evaporation the residue was subjected to preparative TLC (system A) to give 2-*O*-alkoxy-1,4-naphthoquinones **16**–**33**.

2-Butoxynaphthalene-1,4-dione (16)

Light yellow crystals; yield: 214 mg (93%); mp 105–107 °C (Lit.[14a] 105.5 °C); R_f = 0.53 (system A).

IR ($CHCl_3$): 2964, 2935, 2876, 1686, 1652, 1608, 1579, 1466, 1332, 1306, 1262, 1244, 1063, 1042 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.88 (m, 2 H, OCH_2CH_2), 4.02 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.15 (s, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.74 (m, 1 H, ArH), 8.08 (dd, *J* = 1.5, 7.4 Hz, 1 H, ArH), 8.12 (dd, *J* = 1.5, 7.4 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 19.1, 30.2, 69.4, 110.2, 126.1, 126.7, 131.2, 132.1, 133.2, 134.2, 159.9, 180.1, 185.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0951.

2-Propoxynaphthalene-1,4-dione (17)

Light yellow crystals; yield: 184 mg (85%); mp 90–92 °C (Lit.[13a] 106–107 °C); R_f = 0.5 (system A).

IR ($CHCl_3$): 2960, 2931, 2875, 1686, 1651, 1608, 1579, 1467, 1356, 1332, 1306, 1263, 1245, 1042, 1017 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.93 (m, 2 H, CH_2CH_3), 3.97 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.15 (s, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.74 (m, 1 H, ArH), 8.08 (dd, *J* = 1.5, 7.4 Hz, 1 H, ArH), 8.12 (dd, *J* = 1.5, 7.4 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3, 21.7, 71.0, 110.2, 126.1, 126.7, 131.2, 132.1, 133.2, 134.2, 159.9, 180.1, 185.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}O_3$: 216.0786; found: 216.0795.

2-(Pentyloxy)naphthalene-1,4-dione (18)

Light yellow crystals; yield: 198 mg (81%); mp 69–70 °C (Lit.[13a] 80–81 °C); R_f = 0.56 (system A).

IR ($CHCl_3$): 2972, 2941, 2882, 1686, 1651, 1609, 1580, 1465, 1357, 1332, 1307, 1243, 1160, 1018, 1005 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.40 (m, 2 H, CH_2CH_3), 1.46 (m, 2 H, $OCH_2CH_2CH_2$), 1.90 (m, 2 H, OCH_2CH_2), 4.01 (t, *J* = 6.7 Hz, 2 H, OCH_2CH_2), 6.15 (s, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.74 (m, 1 H, ArH), 8.08 (dd, *J* = 1.5, 7.5 Hz, 1 H, ArH), 8.12 (dd, *J* = 1.5, 7.5 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 27.7 (2 C), 69.7, 110.2, 126.1, 126.7, 131.2, 132.1, 133.2, 134.2, 159.9, 180.2, 185.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_3$: 244.1099; found: 244.1107.

5-Hydroxy-2-propoxynaphthalene-1,4-dione (19)

Yellow crystals; yield: 198 mg (85%); mp 141–143 °C; R_f = 0.54 (system A).

IR ($CHCl_3$): 2973, 2941, 2883, 1686, 1635, 1601, 1458, 1376, 1337, 1263, 1245, 1163, 1114, 1074 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.93 (m, 2 H, CH_2CH_3), 3.98 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.07 (s, 1 H, ArH), 7.26 (dd, *J* = 1.1, 8.5 Hz, 1 H, ArH), 7.56 (t, *J* = 7.9 Hz, 1 H, ArH), 7.66 (dd, *J* = 1.1, 7.5 Hz, 1 H, ArH), 12.25 (s, 1 H, 5-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3, 21.7, 71.3, 109.7, 114.2, 119.4, 125.0, 131.2, 135.3, 160.6, 161.0, 179.4, 191.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}O_4$: 232.0735; found: 232.0745.

2-Butoxy-5-hydroxynaphthalene-1,4-dione (20)

Yellow crystals; yield: 210 mg (85%); mp 135–136 °C; R_f = 0.59 (system A).

IR ($CHCl_3$): 2964, 2931, 2877, 1686, 1635, 1601, 1458, 1376, 1337, 1262, 1246, 1163, 1114, 1052 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.88 (m, 2 H, OCH_2CH_2), 4.03 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.08 (s, 1 H, ArH), 7.26 (m, *J* = 1.1, 8.5 Hz, 1 H, ArH), 7.56 (t, *J* = 7.9 Hz, 1 H, ArH), 7.66 (dd, *J* = 1.1, 7.5 Hz, 1 H, ArH), 12.25 (s, 1 H, 5-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 13.6, 19.1, 30.2, 69.7, 109.7, 114.2, 119.4, 125.0, 131.2, 135.4, 160.6, 161.0, 179.4, 191.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0818.

5-Hydroxy-2-(pentyloxy)naphthalene-1,4-dione (21)

Yellow crystals; yield: 227 mg (87%); mp 85–88 °C; R_f = 0.62 (system A).

IR ($CHCl_3$): 2960, 2929, 2875, 1686, 1636, 1634, 1600, 1458, 1376, 1337, 1264, 1247, 1163, 1114, 1072 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.40 (m, 2 H, CH_2CH_3), 1.46 (m, 2 H, $OCH_2CH_2CH_2$), 1.90 (m, 2 H, OCH_2CH_2), 4.02 (t, *J* = 6.7 Hz, 2 H, OCH_2CH_2), 6.07 (s, 1 H, ArH), 7.26 (dd, *J* = 1.1, 8.5 Hz, 1 H, ArH), 7.56 (t, *J* = 7.9 Hz, 1 H, ArH), 7.66 (dd, *J* = 1.1, 7.4 Hz, 1 H, ArH), 12.25 (s, 1 H, 5-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 27.9 (2 C), 70.0, 109.7, 114.2, 119.4, 125.0, 131.2, 135.3, 160.6, 161.0, 179.4, 191.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_4$: 260.1048; found: 260.1035.

8-Hydroxy-2-propoxynaphthalene-1,4-dione (22)

Yellow crystals; yield: 211 mg (91%); mp 150–153 °C; R_f = 0.54 (system A).

IR ($CHCl_3$): 2972, 2942, 2883, 1646, 1606, 1579, 1458, 1361, 1306, 1292, 1243, 1170, 1067, 1021 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.93 (m, 2 H, CH_2CH_3), 3.97 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.12 (s, 1 H, ArH), 7.23 (dd, *J* = 2.5, 7.1 Hz, 1 H, ArH), 7.62 (m, 2 H, 2 ArH), 11.79 (s, 1 H, 5-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 10.3, 21.7, 71.2, 110.7, 114.4, 118.8, 123.7, 132.1, 137.0, 159.5, 161.9, 184.1, 185.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}O_4$: 232.0735; found: 232.0746

2-Butoxy-8-hydroxynaphthalene-1,4-dione (23)

Yellow crystals; yield: 220 mg (89%); mp 127–129 °C; R_f = 0.59 (system A).

IR ($CHCl_3$): 2963, 2930, 2877, 1645, 1606, 1579, 1485, 1458, 1376, 1361, 1306, 1291, 1243, 1170, 1067, 1028 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.88 (m, 2 H, OCH_2CH_2), 4.01 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.12 (s, 1 H, ArH), 7.22 (dd, *J* = 2.5, 7.1 Hz, 1 H, ArH), 7.62 (m, 2 H, 2 ArH), 11.79 (s, 1 H, 5-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 13.7, 19.1, 30.2, 69.6, 110.7, 114.4, 118.8, 123.7, 132.1, 137.0, 159.5, 162.0, 184.1, 185.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0883.

8-Hydroxy-2-(pentyloxy)naphthalene-1,4-dione (24)

Yellow crystals; yield: 231 mg (89%); mp 94–97 °C; R_f = 0.62 (system A).

IR ($CHCl_3$): 2960, 2932, 2875, 1646, 1606, 1579, 1458, 1375, 1361, 1307, 1291, 1243, 1170, 1065, 1029 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.41 (m, 2 H, CH_2CH_3), 1.46 (m, 2 H, $OCH_2CH_2CH_2$), 1.90 (m, 2 H, OCH_2CH_2), 4.01 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.12 (s, 1 H, ArH), 7.23 (dd, *J* = 3.2, 6.4 Hz, 1 H, ArH), 7.62 (m, 2 H, 2 ArH), 11.79 (s, 1 H, 5-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 28.0 (2 C), 69.9, 110.7, 114.4, 118.8, 123.7, 132.1, 137.0, 159.5, 161.9, 184.1, 185.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_4$: 260.1048; found: 260.1036.

5,8-Dihydroxy-2-propoxynaphthalene-1,4-dione (25)

Red solid; yield: 211 mg (85%); mp 167–170 °C; R_f = 0.58 (system A)

IR ($CHCl_3$): 2972, 2941, 2883, 1614, 1572, 1456, 1409, 1348, 1312, 1295, 1270, 1242, 1183, 1072 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.94 (m, 2 H, CH_2CH_3), 4.00 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.14 (s, 1 H, ArH), 7.20 (d, *J* = 9.4 Hz, 1 H, ArH), 7.27 (d, *J* = 9.4 Hz, 1 H, ArH), 12.21 (s, 1 H, α-OH), 12.65 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 10.3, 21.7, 71.5, 110.6, 110.7, 111.6, 128.2, 130.6, 156.8, 158.4, 160.4, 182.7, 188.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}O_5$: 248.0684; found: 248.0697.

2-Butoxy-5,8-dihydroxynaphthalene-1,4-dione (26)

Red solid; yield: 218 mg (83%); mp 123–125 °C (Lit.[24] 116–120 °C); R_f = 0.63 (system A).

IR (KBr): 2964, 2963, 2876, 1613, 1573, 1456, 1348, 1311, 1294, 1270, 1241, 1185, 1073 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.89 (m, 2 H, OCH_2CH_2), 4.04 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.12 (s, 1 H, ArH), 7.20 (d, *J* = 9.2 Hz, 1 H, ArH), 7.27 (d, *J* = 9.2 Hz, 1 H, ArH), 12.21 (s, 1 H, α-OH), 12.65 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 13.6, 19.1, 30.2, 69.8, 110.6, 110.7, 111.7, 128.1, 130.6, 156.9, 158.4, 160.5, 182.7, 188.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_5$: 262.0841; found: 262.0851.

5,8-Dihydroxy-2-(pentyloxy)naphthalene-1,4-dione (27)

Red solid; yield: 254 mg (92%); mp 122–125 °C; R_f = 0.67 (system A).

IR ($CHCl_3$): 2960, 2933, 2875, 1614, 1572, 1457, 1410, 1378, 1312, 1295, 1270, 1243, 1183, 1071 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.40 (m, 2 H, CH_2CH_3), 1.47 (m, 2 H, $OCH_2CH_2CH_2$), 1.91 (m, 2 H, OCH_2CH_2), 4.03 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.14 (s, 1 H, ArH), 7.20 (d, *J* = 9.4 Hz, 1 H, ArH), 7.27 (d, *J* = 9.4 Hz, 1 H, ArH), 12.21 (s, 1 H, α-OH), 12.65 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 13.9, 22.3, 27.9 (2 C), 70.1, 110.5, 110.7, 111.6, 128.1, 130.6, 156.9, 158.4, 160.5, 182.7, 188.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_5$: 276.0998; found: 276.0984.

5,8-Dihydroxy-6,7-dimethyl-2-propoxynaphthalene-1,4-dione (28)

Red solid; yield: 232 mg (84%); mp 157–159 °C; R_f = 0.67 (system A).

IR ($CHCl_3$): 2972, 2941, 2882, 1599, 1576, 1457, 1394, 1314, 1267, 1164, 1085 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.94 (m, 2 H, OCH_2CH_2), 2.26 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $ArCH_3$), 4.00 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.16 (s, 1 H, ArH), 13.02 (s, 1 H, α-OH), 13.34 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 10.3, 12.2, 12.6, 21.8, 71.2, 107.4, 109.5, 109.7, 137.7, 140.7, 160.0, 160.8, 162.6, 177.4, 184.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_5$: 276.0997; found: 276.0986.

2-Butoxy-5,8-dihydroxy-6,7-dimethylnaphthalene-1,4-dione (29)

Red solid; yield: 268 mg (92%); mp 133–134 °C; R_f = 0.72 (system A).

IR ($CHCl_3$): 2963, 2933, 2877, 1599, 1578, 1458, 1396, 1312, 1266, 1192, 1164, 1098, 1085 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.89 (m, 2 H, OCH_2CH_2), 2.25 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $ArCH_3$), 4.03 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.16 (s, 1 H, ArH), 13.01 (s, 1 H, α-OH), 13.34 (s, 1 H, α-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.2, 12.6, 13.7, 19.1, 30.3, 69.6, 107.4, 109.4, 109.7, 137.7, 140.7, 160.0, 160.7, 162.6, 177.5, 184.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{18}O_5$: 290.1154; found: 290.1143.

5,8-Dihydroxy-6,7-dimethyl-2-(pentyloxy)naphthalene-1,4-dione (30)

Red solid; yield: 265 mg (87%); mp 145–147 °C; R_f = 0.74 (system A).

IR ($CHCl_3$): 2960, 2930, 2874, 1599, 1577, 1459, 1396, 1312, 1267, 1163, 1085 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.41 (m, 2 H, CH_2CH_3), 1.47 (m, 2 H, $CH_2CH_2CH_3$), 1.91 (m, 2 H, OCH_2CH_2), 2.26 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $ArCH_3$), 4.02 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.16 (s, 1 H, ArH), 13.01 (s, 1 H, α-OH), 13.34 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 12.2, 12.6, 13.9, 22.3, 28.0, 28.1, 69.9, 107.4, 109.4, 109.7, 137.7, 140.7, 160.0, 160.7, 162.6, 177.5, 184.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{20}O_5$: 304.1310; found: 304.1319.

6,7-Dichloro-5,8-dihydroxy-2-propoxynaphthalene-1,4-dione (31)

Red solid; yield: 287 mg (91%); mp 202–204 °C; R_f = 0.56 (system A).

IR ($CHCl_3$): 2972, 2942, 2883, 1615, 1600, 1558, 1455, 1404, 1352, 1303, 1271, 1248, 1191 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.95 (m, 2 H, CH_2CH_3), 4.03 (t, J = 6.6 Hz, 2 H, OCH_2CH_2), 6.24 (s, 1 H, ArH), 12.78 (s, 1 H, α-OH), 13.29 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 10.2, 21.6, 70.8, 102.3, 106.7, 109.0, 140.6, 151.2, 157.1, 160.8 (2 C), 179.6, 181.5.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{13}H_9Cl_2O_5$: 314.9833; found: 314.9830.

2-Butoxy-6,7-dichloro-5,8-dihydroxynaphthalene-1,4-dione (32)

Red solid; yield: 291 mg (88%); mp 178–180 °C (Lit.[24] 165–170 °C); R_f = 0.58 (system A).

IR ($CHCl_3$): 2963, 2940, 2877, 1615, 1599, 1558, 1459, 1405, 1351, 1303, 1271, 1250, 1182, 1118 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.90 (m, 2 H, OCH_2CH_2), 4.07 (t, J = 6.6 Hz, 2 H, OCH_2CH_2), 6.24 (s, 1 H, ArH), 12.78 (s, 1 H, α-OH), 13.29 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 13.6, 19.1, 30.2, 70.2, 108.5, 109.9, 110.2, 132.8, 135.4, 156.3, 157.6, 160.2, 178.7, 184.7.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{14}H_{11}Cl_2O_5$: 328.9989; found: 328.9979.

6,7-Dichloro-5,8-dihydroxy-2-(pentyloxy)naphthalene-1,4-dione (33)

Red solid; yield: 317 mg (92%); mp 166–168 °C; R_f = 0.62 (system A).

IR ($CHCl_3$): 3054, 2960, 2875, 2361, 2342, 1615, 1600, 1558, 1458, 1404, 1304, 1272, 1250, 1204, 1192, 1118 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.41 (m, 2 H, CH_2CH_3), 1.48 (m, 2 H, $OCH_2CH_2CH_2$), 1.92 (m, 2 H, OCH_2CH_2), 4.06 (t, J = 6.7 Hz, 2 H, OCH_2CH_2), 6.23 (s, 1 H, ArH), 12.79 (s, 1 H, α OH), 13.29 (s, 1 H, α-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 27.91, 28.0, 70.5, 108.5, 109.9, 110.2, 132.8, 135.4, 156.3, 157.6, 160.2, 179.7, 184.8.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_{13}Cl_2O_5$: 343.0146; found: 343.0133.

Reaction of 6,7-Dichloro-2,5,8-trihydroxynaphthalene-1,4-dione (13) with Butanol under Methanesulfonic Acid Catalysis

Quinone **13** (275 mg, 1.0 mmol), BuOH (30 mL), and methanesulfonic acid (0.50 mL, 7.71 mmol) were placed in mini-Soxhlet apparatus, equipped with $CaCl_2$ drying tube and charged with activated molecular sieves 4 Å (4.5 g). The mixture was boiled at reflux for 34.5 h until quinone **13** was converted into two new red colored products with R_f = 0.58 and R_f = 0.50. The mixture was worked up according to the general procedure. After solvent evaporation the crude material dissolved in hot $CHCl_3$ (10 mL) then EtOH (15 mL) was added and solution to stand at –18 °C for 20 h. The crystalline red precipitate was filtered off, dried in vacuum and identified as 2-butoxy-6,7-dichloro-5,8-dihydroxynaphthalene-1,4-dione (**32**) (239 mg). The mother liquor was evaporated, subjected PTLC (system A) and gave additional quinone **32** (12 mg) and new 6,8-dibutoxynaphthoquinone **34**.

2-Butoxy-6,7-dichloro-5,8-dihydroxynaphthalene-1,4-dione (32)

Total yield: 251 mg (76%). R_f = 0.58 (system A).

6,8-Dibutoxy-2,3-dichloro-5-hydroxynaphthalene-1,4-dione (34)

Dark purple solid; yield: 30 mg (7.7%); mp 125–127 °C; R_f = 0.50 (system A).

IR ($CHCl_3$): 2963, 2936, 2876, 1655, 1635, 1583, 1457, 1428, 1414, 1373, 1337, 1310, 1279, 1233, 1181, 1108, 1067, 1033 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.02 (t, J = 7.4 Hz, 3 H, CH_2CH_3'), 1.56 (m, 2 H, CH_2CH_3), 1.61 (m, 2 H, CH_2CH_3'), 1.90 (m, 4 H, 2 OCH_2CH_2), 4.12 (t, J = 6.4 Hz, 2 H, OCH_2CH_2), 4.13 (t, J = 6.4 Hz, 2 H, OCH_2CH_2'), 6.74 (s, 1 H, ArH), 12.87 (s, 1 H, 5-OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 13.9, 19.15, 19.17, 30.8, 31.2, 69.5, 70.0, 105.6, 108.4, 113.2, 139.8, 147.2, 150.0, 156.0, 157.4, 171.5, 181.76.

HRMS (EI): m/z [M]$^+$ calcd for $C_{18}H_{20}Cl_2O_5$: 386.0687; found: 386.0673.

Reaction of 2-Alkoxy-6,7-dichloro-5,8-dihydroxynaphthalene-1,4-diones 31–33 with Sodium Nitrite

A mixture of quinone **31–33** (2.0 mmol), finely ground $NaNO_2$ (828 mg, 12.00 mmol), acetone (15 mL) and EtOH (15 mL) was gently refluxed for 1 h to full conversion of the starting quinone. The mixture was evaporated under reduced pressure and then dissolved in mixture of concd HCl (3 mL) and acetone (15 mL). The white precipitate of NaCl was filtered off, and the colored solution of reaction products was evaporated and subjected to preparative TLC (silica gel, system B, 2 developments) to give mixtures of nitro compounds **35a**,**b**–**37a**,**b**.

3,5,8-Trihydroxy-2-nitro-6-propoxynaphthalene-1,4-dione (35a) and 2,5,8-Trihydroxy-3-nitro-6-propoxynaphthalene-1,4-dione (35b) (Mixture)

Red solid; yield: 536 mg (87%); ratio **35a**/**35b** ~5:1; R_f = 0.52 (system B).

IR ($CHCl_3$): 2973, 2941, 2883, 1754, 1632, 1595, 1480, 1462, 1418, 1368, 1335, 1290, 1160 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 1.10 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.96 (m, 2 H, OCH_2CH_2), 4.11 (t, J = 6.5 Hz, 2 H, OCH_2CH_2), 6.51 (s, 1 H, ArH), 12.37 (s, 1 H, α-OH), 13.17 (s, 1 H, α-OH).

^1H NMR (500 MHz, $CDCl_3$): δ (minor isomer) = 1.09 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.96 (m, 2 H, OCH_2CH_2), 4.07 (t, J = 6.7 Hz, 2 H, OCH_2CH_2), 6.54 (s, 1 H, ArH), 12.17 (s, 1 H, α-OH), 13.23 (s, 1 H, α-OH).

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{13}H_{10}NO_8$: 308.0412; found: 308.0410.

6-Butoxy-3,5,8-trihydroxy-2-nitronaphthalene-1,4-dione (36a) and 6-Butoxy-2,5,8-trihydroxy-3-nitronaphthalene-1,4-dione (36b) (Mixture)

Red solid; yield: 575 mg (89%); ratio **36a**/**36b** ~5:1; R_f = 0.56 (system B).

IR ($CHCl_3$): 3492, 3347, 3100, 2964, 2877, 1755, 1661, 1630, 1610, 1595, 1545, 1480, 1460, 1418, 1368, 1332, 1294, 1137, 1069 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ (major isomer) = 1.00 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.90 (m, 2 H, OCH_2CH_2), 4.14 (t, J = 6.4 Hz, 2 H, OCH_2CH_2), 6.50 (s, 1 H, ArH), 12.38 (s, 1 H, α-OH), 13.11 (s, 1 H, α-OH).

^1H NMR (700 MHz, $CDCl_3$): δ (minor isomer) = 1.00 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.90 (m, 2 H, OCH_2CH_2), 4.10 (t, J = 6.4 Hz, 2 H, OCH_2CH_2), 6.53 (s, 1 H, ArH), 12.18 (s, 1 H, α-OH), 13.14 (s, 1 H, α-OH).

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{14}H_{12}NO_8$: 322.0568; found: 322.0565.

3,5,8-Trihydroxy-2-nitro-6-(pentyloxy)naphthalene-1,4-dione (37a) and 2,5,8-Trihydroxy-3-nitro-6-(pentyloxy)naphthalene-1,4-dione (37b) (Mixture)

Red solid; yield: 540 mg (80%); ratio **37a**/**37b** ~5:1; R_f = 0.58 (system B).

IR ($CHCl_3$): 3502, 3348, 3056, 2960, 2936, 2875, 1672, 1611, 1545, 1482, 1544, 1481, 1460, 1420, 1295, 1192, 1138, 1067 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 0.95 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.42 (m, 2 H, CH_2CH_3), 1.48 (m, 2 H, $CH_2CH_2CH_3$), 1.93 (m, 2 H, OCH_2CH_2), 4.14 (t, *J* = 6.4 Hz, 2 H, OCH_2CH_2), 6.51 (s, 1 H, ArH), 12.37 (s, 1 H, α-OH), 13.17 (s, 1 H, α-OH).

^1H NMR (500 MHz, $CDCl_3$): δ (minor isomer) = 0.95 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.42 (m, 2 H, CH_2CH_3), 1.48 (m, 2 H, $CH_2CH_2CH_3$), 1.93 (m, 2 H, OCH_2CH_2), 4.10 (t, *J* = 6.4 Hz, 2 H, OCH_2CH_2), 6.54 (s, 1 H, ArH), 12.17 (s, 1 H, α-OH), 13.23 (s, 1 H, α-OH).

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{15}H_{14}NO_8$: 336.0725; found: 336.0721.

Reduction of Nitroquinones 35a,b–37a,b with Sodium Sulfide

To a stirred mixture of nitroquinone **35a**,**b**–**37a**,**b** (2.0 mmol) and water (80 mL) was added a solution of $Na_2S{\cdot}H_2O$ (60%), (2601 mg, 20.00 mmol) in water (20 mL). The mixture was stirred for 7 h until TLC (system B) indicated the reaction to be complete. The mixture was acidified carefully with 5% HCl to pH ~6.0. The black-brown precipitate was filtered, washed with water (50 mL), and dried. The dried precipitate was dissolved in hot acetone (50 mL), cooled to r.t., and filtered through a dense glass filter to remove the sulfur impurities. The filtrate was evaporated under reduced pressure and the residue used in next step without purification.

2-Amino-3,5,8-trihydroxy-6-propoxynaphthalene-1,4-dione (38a) and 3-Amino-2,5,8-trihydroxy-6-propoxynaphthalene-1,4-dione (38b) (Mixture)

Black solid; yield: 503 mg (90%); ratio **38a**/**38b** ~5:1; R_f = 0.52 (system B).

IR ($CHCl_3$): 3511, 3450, 3399, 2971, 2938, 2881, 1712, 1664, 1632, 1599, 1563, 1480, 1461, 1407, 1337, 1311, 1279 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ (major isomer) = 0.98 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.76 (m, 2 H, OCH_2CH_2), 4.04 (t, *J* = 6.5 Hz, 2 H, OCH_2CH_2), 6.00 (br s, 2 H, NH_2), 6.67 (s, 1 H, ArH), 9.80 (br s, 1 H, β-OH), 12.66 (s, 1 H, α-OH), 13.00 (s, 1 H, α-OH).

^1H NMR (500 MHz, DMSO-d_6): δ (minor isomer) = 0.98 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.76 (m, 2 H, OCH_2CH_2), 4.05 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 6.43 (br s, 2 H, NH_2), 6.60 (s, 1 H, ArH), 9.52 (br s, 1 H, β-OH), 12.64 (s, 1 H, α-OH), 13.40 (s, 1 H, α-OH).

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{13}H_{12}NO_6$: 278.0670; found: 278.0668.

2-Amino-6-butoxy-3,5,8-trihydroxynaphthalene-1,4-dione (39a) and 3-Amino-6-butoxy-2,5,8-trihydroxynaphthalene-1,4-dione (39b) (Mixture)

Black solid; yield: 528 mg (90%); ratio **39a**/**39b** ~5:1; R_f = 0.56 (system B).

IR ($CHCl_3$): 3509, 3443, 3399, 3156, 2964, 2937, 2876, 1719, 1664, 1633, 1598, 1480, 1461, 1409, 1337, 1302, 1280, 1188, 1145, 1064 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ (major isomer) = 0.97 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 1.88 (m, 2 H, OCH_2CH_2), 4.07 (t, *J* = 6.5 Hz, 2 H, OCH_2CH_2), 4.60 (br s, 2 H, NH_2), 6.46 (s, 1 H, ArH), 6.54 (br s, 1 H, β-OH), 12.23 (s, 1 H, α-OH), 12.71 (s, 1 H, α-OH).

^1H NMR (700 MHz, $CDCl_3$): δ (minor isomer) = 0.97 (t, 3 H, CH_2CH_3, *J* = 7.4 Hz), 1.53 (m, 2 H, CH_2CH_3), 1.88 (m, 2 H, OCH_2CH_2), 4.07 (t, *J* = 6.5 Hz, 2 H, OCH_2CH_2), 4.88 (br s, 2 H, NH_2), 6.27 (br s, 1 H, β-OH), 6.41 (s, 1 H, ArH), 12.52 (s, 1 H, α-OH), 12.61 (s, 1 H, α-OH).

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{14}H_{14}NO_6$: 292.0827; found: 292.0832.

2-Amino-3,5,8-trihydroxy-6-(pentyloxy)naphthalene-1,4-dione (40a) and 3-Amino-2,5,8-trihydroxy-6-(pentyloxy)naphthalene-1,4-dione (40b) (Mixture)

Black solid; yield: 572 mg (93%); ratio **39a**/**39b** ~5:1; R_f = 0.58 (system B).

IR ($CHCl_3$): 3510, 3446, 3399, 2960, 2936, 2875, 2361, 2342, 1665, 1633, 1599, 1564, 1479, 1460, 1408, 1337, 1305, 12679, 1189, 1145 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 0.94 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.43 (m, 4 H, $CH_2CH_2CH_3$), 1.90 (m, 2 H, OCH_2CH_2), 4.06 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 4.69 (br s, 2 H, NH_2), 6.46 (s, 1 H, ArH), 6.54 (br s, 1 H, β-OH), 12.23 (s, 1 H, α-OH), 12.71 (s, 1 H, α-OH).

^1H NMR (500 MHz, $CDCl_3$): δ = (minor isomer) = 0.95 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.43 (m, 4 H, $CH_2CH_2CH_3$), 1.90 (m, 2 H, OCH_2CH_2), 4.07 (t, *J* = 6.6 Hz, 2 H, OCH_2CH_2), 4.89 (br s, 2 H, NH_2), 6.41 (s, 1 H, ArH), 6.50 (s, 1 H, β-OH), 12.53 (s, 1 H, α-OH), 12.62 (s, 1 H, α-OH).

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{15}H_{16}NO_6$: 306.0983; found: 306.0990.

Conversion of 6-*O*-Alkoxyaminoquinones 38a,b–40a,b into 6-*O*-Alkylspinazarins 41–43

To the stirred soln of aminoquinone **38a**,**b**–**40a**,**b** (2.00 mmol) in formic acid (85%, 32 mL) and H_2SO_4 (25%, 2.5 mL) was added DMSO (1.2 mL). The mixture was refluxed for 35 min until TLC (system B) indicated the reaction to be complete. The solution was cooled to r.t., diluted with water (50 mL), and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water and brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue subjected to preparative TLC (system B) to give 6-alkoxyspinazarins **41**–**43** in good yields.

2,3,5,8-Tetrahydroxy-6-propoxynaphthalene-1,4-dione (41)

Red solid; yield: 486 mg (87%); mp 211–213 °C; R_f = 0.46 (system B).

IR ($CHCl_3$): 3430, 2971, 2941, 2883, 1691, 1636, 1592, 1483, 1461, 1411, 1349, 1303, 1278, 1240, 1193, 1115, 1061, 1014 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.98 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.77 (m, 2 H, CH_2CH_3), 4.07 (t, *J* = 6.5 Hz, 2 H, OCH_2CH_2), 6.71 (s, 1 H, ArH), 10.37 (br s, 2 H, 2 β-OH), 12.73 (s, 2 H, 2 α-OH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 10.2, 21.6, 70.8, 102.3, 106.7, 109.0, 140.6, 142.3, 151.2, 157.1, 160.8, 179.6, 181.5.

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{13}H_{11}O_7$: 279.0510; found: 279.0511.

6-Butoxy-2,3,5,8-tetrahydroxynaphthalene-1,4-dione (42)

Red solid; yield: 547 mg (93%); mp 190–193 °C; R_f = 0.48 (system B).

IR ($CHCl_3$): 3431, 2964, 2940, 2877, 1710, 1691, 1637, 1592, 1483, 1460, 1412, 1356, 1302, 1279, 1240, 1192, 1115, 1067 cm^{-1}.

^1H NMR (700 MHz, DMSO-d_6): δ = 0.94 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.44 (m, 2 H, CH_2CH_3), 1.74 (m, 2 H, OCH_2CH_2), 4.11 (t, J = 6.5 Hz, 2 H, OCH_2CH_2), 6.72 (s, 1 H, ArH), 10.20 (br s, 1 H, β-OH), 10.48 (br s, 1 H, β-OH), 12.72 (s, 1 H, α-OH), 12.76 (s, 1 H, α-OH).

^{13}C NMR (176 MHz, DMSO-d_6): δ = 13.6, 18.6, 30.2, 69.1, 102.3, 106.8, 109.0, 140.6, 142.2, 151.2, 157.1, 160.8, 179.5, 181.5.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{14}H_{13}O_7$: 293.0667; found: 293.0662.

2,3,5,8-Tetrahydroxy-6-(pentyloxy)naphthalene-1,4-dione (43)

Red solid; yield: 522 mg (85%); mp 165–168 °C; R_f = 0.50 (system B).

IR ($CHCl_3$): 3429, 2960, 2936, 2875, 2865, 1691, 1636, 1592, 1483, 1460, 1411, 1379, 1348, 1303, 1277 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.90 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.37 (m, 4 H, $CH_2CH_2CH_3$), 1.76 (m, 2 H, OCH_2CH_2), 4.10 (t, J = 6.5 Hz, 2 H, OCH_2CH_2), 6.72 (s, 1 H, ArH), 10.37 (s, 2 H, 2 β-OH), 12.75 (s, 2 H, 2 α-OH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.9, 21.8, 27.6, 27.9, 69.4, 102.3, 106.8, 109.0, 140.6, 142.3, 151.2, 157.1, 160.8, 179.6, 181.5.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_{15}O_7$: 307.0823; found: 307.0828.

Conversion of 6-Alkoxyspinazarins 41–43 into Spinochrome D (2,3,5,6,8-Pentahydroxynaphthalene-1,4-dione, 9)

To the stirred soln of 6-alkoxyspinazarins **41**–**43** (1.0 mmol) in formic acid (99%, 13 mL) was added methanesulfonic acid (1.8 mL). The mixture was refluxed for 3.5 h until TLC (system B) indicated the reaction to be complete. The mixture was diluted with water (50 mL) and cooled to +5 °C for 2 h. The precipitate was filtered off, washed with water, and dried to give pure crystalline **9** as a red solid; yield 205 mg (86% from **41**); 219 mg (92% from **42**); 209 mg (88% from **43**); mp >285 °C; R_f = 0.27 (system B).

^1H NMR (700 MHz, acetone-d_6): δ = 6.55 (s, 1 H, ArH), 8.77 (br s, 1 H, β-OH), 8.98 (br s, 1 H, β-OH), 9.90 (br s, 1 H, β-OH), 12.34 (s, 1 H, α-OH), 12.49 (br s, 1 H, α-OH).

^{13}C NMR (176 MHz, acetone-d_6): δ = 103.2, 109.7, 110.2, 139.9, 141.9, 151.0, 157.3, 162.2, 180.4, 182.8.

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Supporting Information

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