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SYNTHESIS OF SPINOCHROME D, A METABOLITE OF VARIOUS SEA-URCHIN SPECIES

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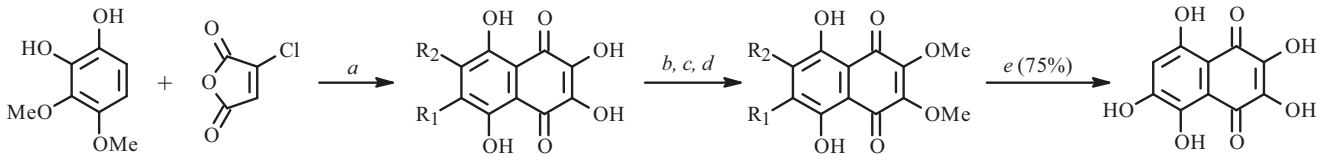
*The sea-urchin metabolite spinochrome D (**1**) was synthesized in 58% overall yield via oxidation of 2,3-dichloronaphthazarin (**13**) into 2-hydroxy-6,7-dichloronaphthazarin (**14**), O-methylation of **14**, nucleophilic substitution by MeO groups of the Cl atoms in the resulting 2-methoxy-6,7-dichloronaphthazarin (**19**), and hydrolysis of the obtained 2,3,6-trimethoxynaphthazarin (**10**).*

Keywords: sea-urchin metabolites, polyhydroxy-1,4-naphthoquinones, naphthazarins, spinochrome D, oxidation, *O*-alkylation, nucleophilic substitution, antioxidants.

2,3,5,6,8-Pentahydroxy-1,4-naphthoquinone (**1**) (spinochrome D) is one of six main naphthoquinoid pigments produced by various sea-urchin species [1]. The Histochrome® series of preparations that are used in cardiology and ophthalmology were based on 2,3,5,6,8-pentahydroxy-7-ethyl-1,4-naphthoquinone (echinochrome A) [2]. Like echinochrome A, spinochrome D exhibited high antioxidant [3–7], hepatoprotective [8], and anti-allergic [9] activity, could be used to design new drugs, and was a valuable synthetic precursor for preparing echinochrome A, 2-acetyl-3,5,6,7,8-pentahydroxy-1,4-naphthoquinone (spinochrome C) [10], and 2,2′-(ethan-1,1-diyl)*bis*(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone) [11]. The low content of spinochrome D in sea urchins (0.001–0.003% of dry wt.) limits severely the potential for its practical application. This problem can be solved by developing chemical syntheses of it.

The goal of the present work was to develop a relatively simple and efficient method for synthesizing spinochrome D (**1**) from available starting materials.

Two syntheses of spinochrome D were previously reported. The first began with 4-(2-hydroxy-3,4-dimethoxyphenyl)butyric acid [12], which was obtained in three steps by the known method from 1,2,3-trimethoxybenzene [13]. A key intermediate was 5,6,7,8-tetramethoxy-1-tetralone, oxidation of which by oxygen in the presence of *t*-BuOK formed the cyclic skeleton of the target compound. The overall yield of spinochrome D was <5% in 12 steps. In the second synthesis [14, 15], the spinochrome D naphthazarin skeleton was formed via cycloacylation of 1,2-dihydroxy-3,4-dimethoxybenzene (**2**) and monochloromaleic anhydride (**3**) (Scheme 1). The yield of target product **5** in the mixture of **4–6** was <25%. The researchers hypothesized that **4** and **6** were formed via disproportionation of two molecules of **5**. The mixture of **4–6** was worked up with CH_2N_2 in MeOH. The resulting mixture of diethers **7–9** (97%) was separated by TLC over SiO_2.



2 **3** **4 - 6** **7 - 10** **1**

4: $R_1 = R_2 = Cl$, 12.5%; **5:** $R_1 = Cl$, $R_2 = H$, 25%; **6:** $R_1 = R_2 = H$, 12.5%; **7:** $R_1 = R_2 = Cl$
8: $R_1 = Cl$, $R_2 = H$; **9:** $R_1 = R_2 = H$; **10**: $R_1 = OMe$, $R_2 = H$, 42%

a. $AlCl_3$, NaCl, 180–190°C, 6 min; *b*. CH_2N_2, MeOH, 22°C; *c*. TLC on SiO_2; *d*. MeONa, MeOH, bp, 48 h; *e*. 48% HBr, bp, 1 h

Scheme 1 (functionally substituted naphthazarins presented as dominant tautomer form).

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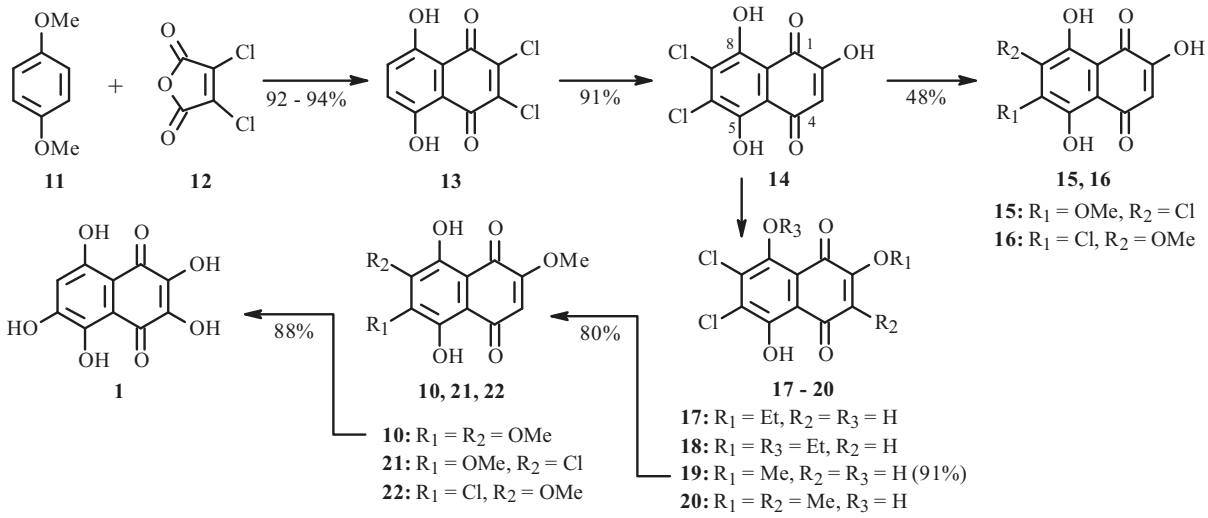
Treatment of **8** with saturated NaOMe in MeOH gave the trimethyl ether of spinochrome D (10%), cleavage of an O–Me bond of which by HBr (48%) gave target product **1**. The overall yield of spinochrome D in this formally four-step synthesis was <8%. Starting substrate **2** was not commercially available. It was synthesized from 1,2,3-trimethoxybenzene in three steps. The reported synthesis was unsuitable for preparative preparation of spinochrome D because it required chromatographic separation of a mixture of **7–9** and involved a step that seriously limited its potential.

The conversion **8**→**10** required an enormous excess of saturated NaOMe in MeOH. However, **8** could not be completely converted into triether **10**.

We proposed a simple synthesis of spinochrome D (Scheme 2) using essentially the same strategy as that shown in Scheme 1.



Scheme 2

The starting material was well-known 2,3-dichloronaphthazarin (**13**), which was prepared via cycloacylation of commercial 1,4-dimethoxybenzene (**11**) and dichloromaleic anhydride (**12**) [16]. In contrast with the published conditions [16], the cycloacylation was carried out at 175–180°C for 3 min and not at 170°C (1–2 min). The work up of the reaction mixture was also partially changed. All this allowed high yields (92–94%) of **13** to be obtained consistently. Compound **13** was oxidized by commercial MnO_2 in conc. H_2SO_4 to give hydroxydichloronaphthazarin **14** in 91% yield. An attempt to prepare **14** directly via cycloacylation of 1,2,4-trimethoxybenzene and anhydride **12** at 175–180°C for 4 min gave the desired product in only 2% yield. Nucleophilic substitution of the Cl atom in **14** by an MeO group using the MeOH–CsF–Al_2O_3 system developed by us earlier [17] formed a mixture of mono-substituted **15** (27%) and **16** (21%) with 90% substrate conversion. Both Cl atoms in **14** could not be substituted because the C(2)–OH group had to be protected. Ionization of it under the reaction conditions would inhibit the substitution due to the strong electron-donating effect of the alkoxide group.

The β-OH group in **14** was protected first using the orthoester method that was developed by us earlier for selective protection of such groups in 2-hydroxynaphthazarins with 3-alkyl substituents [18]. However, refluxing a solution of **14** in triethylorthoformate gave a complicated mixture of products, from which TLC on SiO_2 isolated ether **17** in 10% yield.

O-Alkylation of **14** by Et_2SO_4 in MeCN in the presence of Et_3N with heating also gave a complicated product mixture from which column chromatography over SiO_2 isolated monoether **17** (8%) and diether **18** (12%). Me_2SO_4 in MeCN in the presence of Et_3N under mild conditions (22°C, 24 h) produced ether **19** in 30% yield with 50% conversion of substrate.

The known method for *O*-methylation of β-OH groups of polyhydroxy-1,4-naphthoquinones by anhydrous MeOH saturated with dry HCl [19] also gave poor results. The yield of **19** was <33% with 40% substrate conversion. Treatment of **14** with CH_2N_2 in MeOH gave a good yield (85%) of **19**. However, this *O*-methylation method is unsuitable for preparative production of this ether. The best yield of **19** (91%) was obtained for *O*-methylation of substrate by MeI in DMF in the presence of dry K_2CO_3. The reaction products contained an insignificant amount of **20** (4%), which was formed by *C*-alkylation of **14**.

The reaction of **19** in the MeOH–CsF–Al_2O_3 system at 90–95°C gave the triether of spinochrome D (**10**) in 80% yield with full substrate conversion. Column chromatography of the product mixture over SiO_2 isolated small amounts of products

from incomplete substitution of Cl atoms **21** (8%) and **22** (2%). Refluxing a solution of triether **10** in HBr (48%) for 30 min gave target spinochrome D (**1**) in 88% yield.

Thus, the developed five-step synthetic scheme for spinochrome D enabled it to be produced from commercially available reagents in 54% overall yield. Considering that 2,3-dichloronaphthazarin (**13**) is now commercially available (Aldrich), the overall yield of spinochrome D in the four-step conversion increases to 58%.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were recorded from $CHCl_3$ solutions on a Bruker Equinox 55 spectrophotometer. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with Me_4Si internal standard on a Bruker Avance DPX-300 spectrometer (^1H, 300.13 MHz; ^{13}C, 75.47 MHz). Resonances of ^1H and ^{13}C atoms were assigned unambiguously using various 1D and 2D techniques (DEPT-135, COSY-45, HSQC, and HMBC). Mass spectra (EI) were obtained on an AMD 604 S instrument (8 kV) with direct sample introduction at ionization energy 70 eV. Elemental analyses for C, H, and N were performed on a Flash EA1112 analyzer. The course of reactions and purity of products were monitored by TLC on Silufol UV 254 plates using hexane–Me_2CO (2:1). Pure compounds were isolated from product mixtures on SiO_2 plates or over SiO_2 columns (Alfa Aesar, 70–230 μm) with elution by mixtures of hexane or benzene with Me_2CO. Commercial dichloromaleic anhydride (**12**) was mixed with an equal mass of P_2O_5 and distilled at atmospheric pressure at a temperature near the melting point of the anhydride before use. Anhydrous powdered $AlCl_3$ and dry NaCl were used in the work. All reagents and solvents were distilled at atmospheric or reduced pressure before use. Elemental analyses of all new compounds agreed with those calculated.

Cycloacylation of Diether 11 by Anhydride 12. A melt of anhydrous $AlCl_3$ (33.8 g, 0.253 mol) and dry NaCl (6.7 g, 0.114 mol) was stirred vigorously at 150°C and treated in portions with a mixture of dichloromaleic anhydride (9.5 g, 0.057 mol) and hydroquinone dimethyl ether (3.95 g, 0.028 mol) that was ground beforehand in a mortar. The reaction mixture was placed into a metal bath heated to 175–180°C, stirred for 3 min, cooled to room temperature, treated with conc. HCl (24 mL) in H_2O (360 mL), and left for 12 h. The precipitated product was separated, rinsed with hot (60°C) H_2O (15 × 100 mL) until the filtrate was no longer colored, and dried to constant mass in a vacuum desiccator over $CaCl_2$ to afford 6.89 g (93%) of **13**.

5,8-Dihydroxy-2,3-dichloro-1,4-naphthoquinone (13), red needles, mp 195–196°C (octane) (lit. [16] 198–199°C; [19] 195°C; [20] 192°C). IR spectrum (ν, cm^{-1}): 3400–2250 (α-OH), 1625 (C=O), 1571 (C=C), 1403. ^1H NMR spectrum ($CDCl_3$, δ, ppm): 7.33 (2H, s, H-6, 7), 12.34 (2H, s, 2α-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 110.41 (C-4a, 8a), 131.12 (C-6, 7), 142.91 (C-2, 3), 161.14 (C-5, 8), 177.25 (C-1, 4). Mass spectrum, *m/z* (I_{rel}, %): 259/261/263 ($[M + 1]^+$, 59), 258/260/262 ($[M]^+$, 100), 257/259/261 ($[M - 1]^+$, 45), 224/226 ($[M - Cl + 1]^+$, 19), 223/225 ($[M - Cl]^+$, 22), 222/224 ($[M - Cl - 1]^+$, 17).

Oxidation of Dichloronaphthazarin (13). A suspension of black commercial MnO_2 (0.9 g, 10.4 mmol) in conc. H_2SO_4 (50 mL) was stirred and treated over 45 min with a solution of **13** (3.0 g, 11.6 mmol) in conc. H_2SO_4 (70 mL) keeping the cooling-bath temperature at 10–15°C. When the addition was finished, the cooling bath was removed. When the temperature of the mixture reached ambient, more MnO_2 (0.9 g, 10.4 mmol) was added in portions. The mixture was stirred at room temperature for 1 h and poured into a mixture of ice (200 g) and H_2O (400 mL) saturated with NaCl. The product was extracted with EtOAc (5 × 80 mL). The combined extracts were dried over Na_2SO_4 and passed over a glass filter packed with a small amount of SiO_2. The filter was rinsed with hexane–Me_2CO (2:1, 3 × 25 mL). The solvent was evaporated at reduced pressure to afford **14** (2.90 g, 91%).

2,5,8-Trihydroxy-6,7-dichloro-1,4-naphthoquinone (14), red needles, 174–176°C (shape change with sublimation), mp 213–215°C. IR spectrum (ν, cm^{-1}): 3400–2300 (α-OH), 3242 (β-OH), 1610 (C=O), 1573 (C=C). ^1H NMR spectrum ($CDCl_3$, δ, ppm): 6.45 (1H, s, H-2), 7.80 (1H, br.s, 2-OH), 12.05 (1H, br.s, 8-OH), 13.38 (1H, s, 5-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 108.92 (C-4a), 109.13 (C-8a), 111.47 (C-3), 131.82 (C-7), 136.28 (C-6), 155.42 (C-5), 155.91 (C-8), 157.04 (C-2), 180.33 (C-1), 186.57 (C-4). Mass spectrum, *m/z* (I_{rel}, %): 274/276/278 ($[M]^+$, 100), 246/248/250 ($[M - CO]^+$, 13), 239/241 ($[M - Cl]^+$, 26), 218/220/222 ($[M - 2CO]^+$, 4), 211/213 ($[M - Cl - CO]^+$, 9), 204 ($[M - 2Cl]^+$, 20), 87 (11), 69 (19), 57 (12), 53 (12), 43 (11), 36 (26).

Nucleophilic Substitution of Cl atoms in 14. A mixture of **14** (275 mg, 1.0 mmol), anhydrous CsF (760 mg, 5.0 mmol), dry neutral Al_2O_3 (2.5 g), and anhydrous MeOH (40 mL) was placed into a hermetically sealed steel ampul and

stirred on a magnetic stirrer at 90–95°C for 12 h. The solvent was removed. The residue was treated with NaOH solution (10%, 40 mL) and acidified with HCl (15%) to pH 3. The products were extracted with EtOAc (5 × 20 mL). The combined extracts were rinsed with saturated NaCl solution (2 × 25 mL) and dried over Na_2SO_4. The solvent was removed at reduced pressure. The residue was chromatographed over a column of SiO_2 with elution by hexane–Me_2CO (5:1) to afford of **16** (51 mg, 21%).

2,5,8-Trihydroxy-7-methoxy-6-chloro-1,4-naphthoquinone (16), red plates, mp 216–219°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 6.44 (1H, s, H-3), 7.71 (1H, br.s, 2-OH), 4.26 (3H, s, OMe), 11.99 (1H, s, 8-OH), 13.23 (1H, s, 5-OH).

Elution by hexane–Me_2CO (4:1) gave **15** (66 mg, 27%).

2,5,8-Trihydroxy-6-methoxy-7-chloro-1,4-naphthoquinone (15), red plates, mp 220–223°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 6.45 (1H, s, H-3), 7.83 (1H, br.s, 2-OH), 4.15 (3H, s, OMe), 12.34 (1H, s, 8-OH), 13.37 (1H, s, 5-OH).

Elution by hexane–Me_2CO (3:1) gave starting **14** (28 mg, 10%).

***O*-Ethylation of 14 by Et_2SO_4.** A solution of **14** (275 mg, 1.0 mmol), Et_2SO_4 (1 mL), and Et_3N (1.2 mL) in MeCN (15 mL) was refluxed for 4 h, cooled to room temperature, treated with NaOH solution (10%, 15 mL) and HCl (20%, 20 mL), diluted with H_2O (20 mL), and extracted with EtOAc (4 × 20 mL). The usual work up of the extract gave a mixture of products that was chromatographed over a column of SiO_2 with elution by benzene–Me_2CO (10:1) to afford **17** (24 mg, 8%).

5,8-Dihydroxy-6,7-dichloro-2-ethoxy-1,4-naphthoquinone (17), reddish-orange plates, 188–190°C (crystallization with sublimation), mp 232–235°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.56 (3H, t, J = 6.8, Me), 4.16 (2H, q, J = 6.8, OCH_2), 6.24 (1H, s, H-3), 12.79 (1H, s, 5-OH), 13.28 (1H, s, 8-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.96 (Me), 66.27 (OCH_2), 108.51 (C-8a), 110.00 (C-3), 110.19 (C-4a), 132.99 (C-6), 135.53 (C-7), 156.49 (C-8), 157.81 (C-5), 159.94 (C-2), 178.58 (C-4), 184.65 (C-1).

Elution by benzene–Me_2CO (8:1) gave **18** (40 mg, 12%).

5-Hydroxy-6,7-dichloro-2,8-diethoxy-1,4-naphthoquinone (18), orange needles, mp 237–239°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.42 (3H, t, J = 6.8, $OCH_2\underline{CH_3}$-8), 1.54 (3H, t, J = 6.8, $OCH_2\underline{CH_3}$-2), 4.12 (2H, q, J = 6.8, $O\underline{CH_2}CH_3$-2), 4.33 (2H, q, J = 6.8, $O\underline{CH_2}CH_3$-8), 6.08 (1H, s, H-3), 13.63 (1H, s, 5-OH).

***O*-Methylation of 14 by MeI.** A solution of **14** (1.10 g, 4.0 mmol) and MeI (22 mL) in DMF (80 mL) was stirred vigorously and treated in small portions over 4 h with calcined K_2CO_3 (1.67 g), saturated aqueous NaCl (170 mL), and HCl (10%, 170 mL). The products were extracted with EtOAc (6 × 50 mL). The usual work up of the extract gave a product mixture that was chromatographed over a column of SiO_2 with elution by benzene–Me_2CO (9:1) to afford **19** (1.05 g, 91%).

5,8-Dihydroxy-2-methoxy-6,7-dichloro-1,4-naphthoquinone (19), reddish-orange plates, 179–180°C (recrystallization with sublimation), mp 227–230°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 3.97 (3H, s, OMe), 6.28 (1H, s, H-3), 12.76 (1H, s, 5-OH), 13.27 (1H, s, 8-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 56.99 (OMe), 108.39 (C-8a), 109.59 (C-3), 110.03 (C-4a), 133.02 (C-6), 134.95 (C-7), 156.61 (C-8), 157.91 (C-5), 160.53 (C-2), 178.02 (C-4), 184.17 (C-1).

Elution by benzene–Me_2CO (4:1) gave of **20** (46 mg, 4%).

2,5,8-Trihydroxy-3-methyl-6,7-dichloro-1,4-naphthoquinone (20), red needles, mp 192–193°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 2.16 (3H, s, Me), 9.61 (1H, br.s, 2-OH), 12.07 (1H, br.s, 8-OH), 13.55 (1H, s, 5-OH). Mass spectrum, *m/z* (I_{rel},%): 288/290/292 ($[M]^+$ (100)).

Nucleophilic Substitution of Cl Atoms in 19. Conditions analogous to those described above for conversion of **14** into the mixture of **15** and **16** (with the exception that the reaction time was 30 h) were used with **19** (1.45 g, 5.0 mmol) to give a product mixture that was chromatographed over a column of SiO_2 with elution by hexane–Me_2CO (12:1) to afford **22** (29 mg, 2%).

5,8-Dihydroxy-2,7-dimethoxy-6-chloro-1,4-naphthoquinone (22), red plates, mp 199–201°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 3.97 (3H, s, 2-OMe), 4.18 (3H, s, 7-OMe), 6.35 (1H, s, H-3), 12.68 (1H, s, 8-OH), 13.26 (1H, s, 5-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 57.09 (2-OMe), 61.84 (7-OMe), 105.73 (C-4a), 109.11 (C-3), 110.83 (C-8a), 128.06 (C-6), 154.47 (C-7), 158.92 (C-2), 164.07 (C-5), 171.52 (C-8), 172.74 (C-4), 177.71 (C-1).

Elution by hexane–Me_2CO (10:1) gave **21** (114 mg, 8%).

5,8-Dihydroxy-2,6-dimethoxy-7-chloro-1,4-naphthoquinone (21), red plates, mp 195–197°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 3.97 (3H, s, 2-OMe), 4.26 (3H, s, 6-OMe), 6.34 (1H, s, H-3), 13.02 (1H, s, 8-OH), 13.09 (1H, s, 5-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 57.09 (2-OMe), 62.11 (6-OMe), 107.78 (C-4a), 108.43 (C-3), 108.70 (C-8a), 124.97 (C-7), 156.41 (C-6), 160.33 (C-2), 163.60 (C-5), 167.25 (C-4), 168.71 (C-8), 177.54 (C-1).

Elution by hexane–Me_2CO (5:1) gave **10** (1.12 g, 80%).

5,8-Dihydroxy-2,3,6-trimethoxy-1,4-naphthoquinone (10), reddish-brown needles, mp 169–171°C (Me_2CO) (lit. [14, 15] mp 161–162°C, [21] 176–177°C; [22] 169–173°C). ^{1}H NMR spectrum (the dominant tautomer in $CDCl_3$ had 2,3,6-MeO groups) ($CDCl_3$, δ, ppm): 3.96 (3H, s, 6-OMe), 4.07 (3H, s, 3-OMe), 4.15 (3H, s, 2-OMe), 6.41 (1H, s, H-7), 12.93 (1H, s, 5-OH), 13.03 (1H, s, 8-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 56.71 (6-OMe), 61.56 (3-OMe), 61.68 (2-OMe), 105.01 (C-8a), 107.52 (C-7), 109.38 (C-4a), 146.87 (C-3), 149.53 (C-2), 159.20 (C-6), 161.41 (C-5), 170.21 (C-8), 172.28 (C-1), 174.67 (C-4).

Acid Hydrolysis of Triether 10. A solution of **10** (1.12 g, 4.0 mmol) in HBr (48%, 150 mL) was refluxed for 30 min, cooled to room temperature, diluted with H_2O (200 mL), and left overnight at 5°C. The precipitate was separated, rinsed with H_2O (4 × 10 mL), and dried to afford **1** (838 mg, 88%).

2,3,5,6,8-Pentahydroxy-1,4-naphthoquinone (1) (spinochrome D), reddish-brown needles, sublimed without melting at 282–288°C (lit. [12] sublimed at 285–290°C; [14, 15] sublimed at 280–290°C). ^{1}H NMR spectrum (the dominant tautomer in DMSO-d_6 had 2,6,7-β-OH groups) (DMSO-d_6, δ, ppm): 6.48 (1H, s, H-3), 10.10 (1H, br.s, 7-OH), 10.41 (1H, br.s, 6-OH), 11.46 (1H, br.s, 2-OH), 12.65 (1H, s, 5-OH), 12.70 (1H, br.s, 8-OH). ^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 102.02 (C-8a), 108.43 (C-4a), 109.32 (C-3), 140.14 (C-7), 142.25 (C-6), 151.06 (C-2), 157.13 (C-8), 161.02 (C-5), 179.12 (C-4), 181.48 (C-1). Mass spectrum, *m/z* (I_{rel},%): 238 ($[M]^+$, 100), 210 ($[M – CO]^+$, 65), 181 (14), 168 (15), 153 (8), 149 (9), 125 (11), 111 (17), 109 (10), 97 (21), 95 (16), 85 (18), 83 (21), 81 (15), 71 (29), 69 (24), 67 (10), 57 (37), 55 (30), 45 (32), 44 (29), 42 (18).

REFERENCES

1. R. H. Thomson, *Naturally Occurring Quinones*, 2nd Ed., Academic Press, London, New York, 1971; 3rd Ed., Chapman & Hall, London, New York, 1987; 4th Ed., Chapman & Hall, London, New York, 1997.
2. N. P. Mishchenko, S. A. Fedoreev, and V. L. Bagirova, *Pharm. Chem. J.*, **37**, 48 (2003).
3. H. Hatate, H. Murata, Y. Hama, R. Tanaka, and N. Suzuki, *Fish. Sci.*, **68**, 1641 (2002).
4. A. V. Lebedev, M. V. Ivanova, and D. O. Levitsky, *Life Sci.*, **76**, 863 (2005).
5. R. Kuwahara, H. Hatate, T. Yuki, H. Murata, R. Nanaka, and Y. Hama, *LWT – Food Sci. Technol.*, **42**, 1296 (2009).
6. D. Y. Zhou, B. W. Zhu, X. D. Wang, H. Tan, J. F. Yang, D. M. Li, X. P. Dong, H. T. Wu, L. M. Sun, X. L. Li, and Y. Murata, *Food Chem.*, **129**, 1521 (2011).
7. N. K. Utkina and N. D. Pokhilo, *Nat. Prod. Commun.*, **7**, 901 (2012).
8. A. A. Artyukov, A. M. Popov, A. V. Tsybulsky, O. N. Krivoshapko, and N. V. Polyakova, *Biochem. (Moscow), Ser. B, Biomed. Chem.*, **7**, 239 (2013).
9. O. N. Pozharitskaya, A. N. Shikov, M. N. Makarov, S. A. Ivanova, V. M. Kosman, V. G. Makarov, V. Bazgier, K. Berka, M. Otyepka, and J. Ulrichova, *Planta Med.*, **79**, 1698 (2013).
10. C. W. J. Chang, R. E. Moore, and P. J. Scheuer, *J. Am. Chem. Soc.*, **86**, 2959 (1964).
11. D. N. Pelageev, M. N. Panchenko, N. D. Pokhilo, and V. F. Anufriev, *Russ. Chem. Bull.,* **59**, 1472 (2010).
12. H. A. Anderson, J. Smith, and R. H. Thomson, *J. Chem. Soc.*, 2141 (1965).
13. P. C. Mitter and S. De, *J. Indian Chem. Soc.*, **16**, 35 (1939).
14. I. Singh, R. E. Moore, C. W. J. Chang, and P. J. Scheuer, *J. Am. Chem. Soc.*, **87**, 4024 (1965).
15. I. Singh, R. E. Moore, C. W. J. Chang, R. T. Ogata, and P. J. Scheuer, *Tetrahedron*, **24**, 2969 (1968).
16. R. Huot and P. Brassard, *Can. J. Chem.*, **52**, 838 (1974).
17. V. Ph. Anufriev and V. L. Novikov, *Tetrahedron Lett.*, **36**, 2515 (1995).
18. V. Ph. Anufriev, V. L. Novikov, G. V. Malinovskaya, and V. P. Glazunov, *Synth. Commun.*, **27**, 119 (1997).
19. H. Waldmann and E. Ulsperger, *Chem. Ber.*, **83**, 178 (1950).
20. D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1089 (1955).
21. K. Masuda, S. Funayama, K. Komiyama, and I. Umezawa, *J. Nat. Prod.*, **50**, 958 (1987).
22. D. N. Pelageev, M. N. Panchenko, N. D. Pokhilo, V. A. Denisenko, and V. F. Anufriev, *Chem. Nat. Compd.*, **44**, 719 (2008).