Functionalization of naphthalene: a novel synthetic route to brominated naphthoquinones

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Dedicated to Professor Keith Smith on the occasion of his 65th anniversary

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Abstract

An efficient procedure is described for synthesis of 2,5,8-tribromonaphthoquinone (**12**) from naphthalene in four reaction steps. Silver-promoted solvolysis of hexabromide **3** produces the specific diastereostereoisomer **10**. Dehydrobromination of **10** using sodium methoxide gives tribromodihydronaphthalene-1,4-diol **11** in high yield. PCC oxidation of either **10** or **11** results in the formation of 2,5,8-tribromonaphthalene-1,4-dione (**12**).

Keywords: Bromonaphthalene, bromination, silver-induced substitution, 1,4-naphthoquinone, PCC oxidation

Introduction

The naphthoquinone structure exists in many natural products and biologically active compounds.[1] Among the naphthaquinones, 2-substituted-1,4-naphthoquinone derivatives are especially interesting molecules because of the their extremely important biological activities, such as antibacterial,[2] antitrypanosomal,[3] antileishmanial,[3] molluscicidal,[4] cytotoxic[5] and antitumor[6] properties.

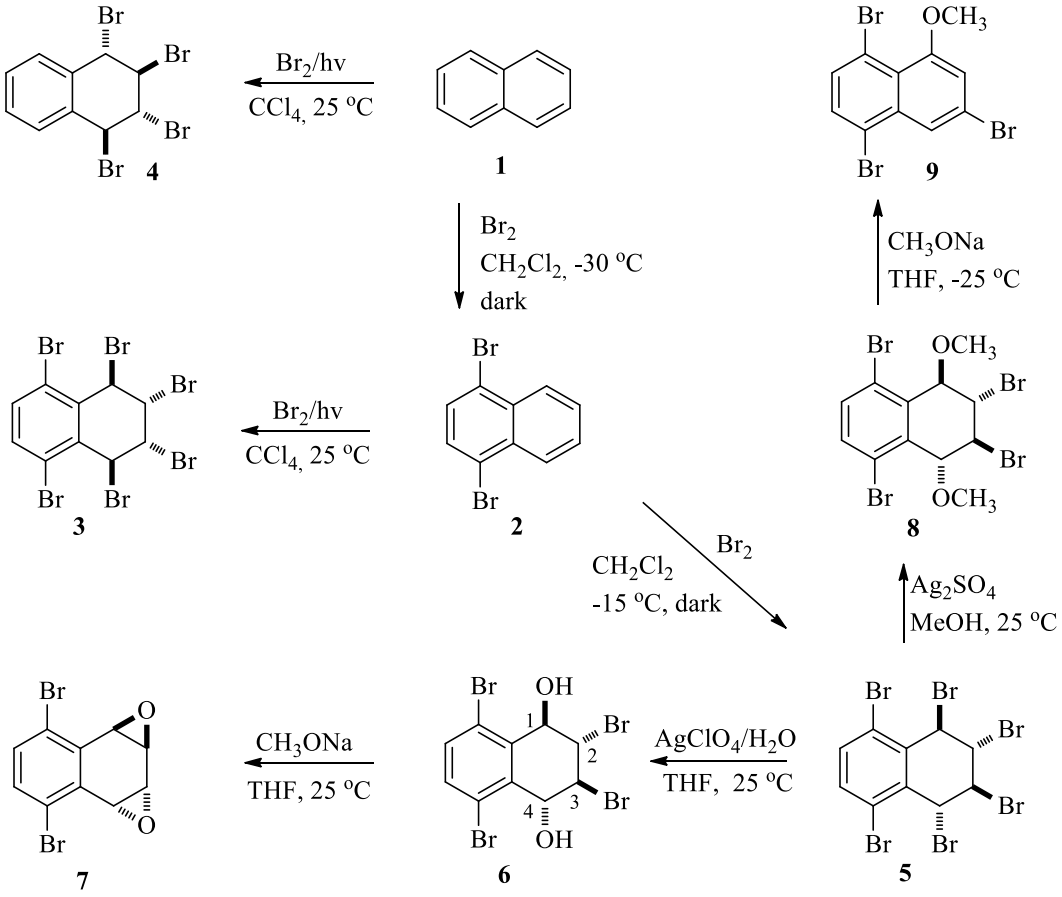
Naphthoquinones are industrially used as raw materials for pharmaceuticals, agrochemicals and other chemicals.[7] Therefore, development of novel synthetic methodologies for the synthesis of naphthoquinones is an important task for chemists.[8]

Our studies have shown that bromination conditions dramatically affect the regio- and stereo-selectivity of bromination reactions.[9] Different products are obtained depending on both the

structures of the starting materials and the reaction conditions. For example, while photobromination of naphthalene leads to *trans,trans,trans*-tetrabromide **4**,[9a] photobromination of 1,4-dibromonaphthalene **2** affords compound **3**.[10] On the other hand, bromination of naphthalene **1** at -30 ºC produces compound **2**.[9b]

We have developed a new strategy for the preparation of 1,4-dihydroxytetralins (and similarly their anthracene counterparts) by silver–induced hydrolysis of 1,2,3,4-tetra-bromotetralins, which are good precursors for the synthesis of naphthalene (or anthracene) epoxides.[9c-f] These studies showed that such 1,4-dihydroxy compounds are useful intermediates for polyfunctionalisation of aromatic compounds (Scheme 1). Thus, base-induced dehydro-bromination of **6** produces the epoxide **7**. By contrast, similar treatment of **8**, obtained from the hexabromide **5**, gives the aromatized product **9**. Recently, in the case of a 1,4-dihydoxy-3,4-dibromoanthracene, we showed that dehydrobromination led to a product that was neither aromatized nor contained an epoxide unit.[9g]

In this paper we describe the application of silver-induced hydrolysis to compound **3**, which led to a synthesis of 2,5,8-tribromonaphthoquinone **(12**) in four steps starting from naphthalene.



Scheme 1. Transformations of bromonaphthalenes.

Results and Discussion

Our previously reported simple synthetic method was used for the preparation of 1,4-dibromo-naphthalene **2**, and the stereoselective synthesis of hexabromide **3** was efficiently achieved by its photobromination, according to the literature method.[10]

Hexabromide **3** was subjected to silver ion-assisted hydrolysis in aqueous acetone. The substitution resulted in the stereoselective formation of product **10** in 87% yield (Scheme 2). On the basis of NMR data, the compound contains two hydroxy groups. The reaction can afford two stereoisomers, one of which is symmetrical. The ^{13}C NMR spectrum confirms the unsymmetrical structure, consisting of ten carbon signals: two CH and four quaternary aromatic carbons, two sp^3 carbons bearing hydroxyl groups and two sp^3 carbons bearing bromine atoms.

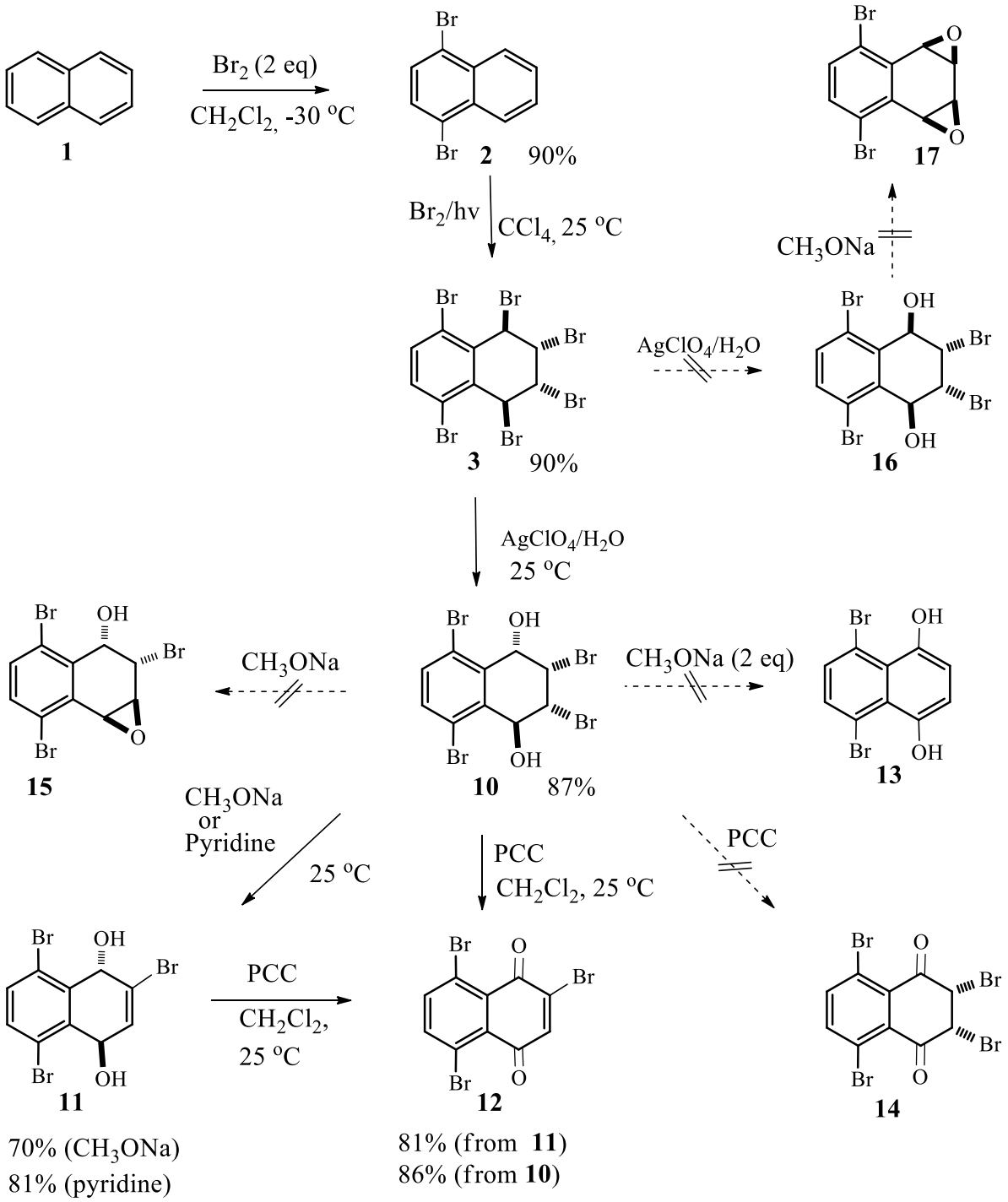
In the ^{1}H NMR spectrum, the aromatic H-6 and H-7 protons resonate at δ 7.58 and δ 7.53 as an AB system ($J_{6\text{-}7}$ 8.5 Hz,). Benzylic proton H-4 shows as a doublet of doublets at δ 5.07 ($J_{4\text{-}OH}$ 8 Hz; $J_{4\text{-}3}$ 5 Hz), while the resonance of the hydroxy proton (C-4–OH) is a doublet at δ 3.01 (C-4–OH, $J_{4\text{-}OH}$ 8 Hz). The H-1 proton resonance shows as a doublet of doublets at δ 5.51 ($J_{1\text{-}OH}$ 4 Hz, $J_{1\text{-}2}$ 2.8 Hz). The hydroxyl resonance (C-1–OH) appears as a doublet at δ 2.90 ($J_{1\text{-}OH}$ 4 Hz), and the H-2 and H-3 protons resonate at δ 4.72 (*bs*) and 5.12 (dd, $J_{3\text{-}4}$5 Hz, $J_{2\text{-}3}$ 2.8 Hz).

After efficient and selective synthesis of dihydroxy compound **10**, it was treated with one or two equivalents of sodium methoxide or pyridine. Surprisingly the reaction resulted in the formation of **11**, instead of aromatisation product **13** and/or formation of epoxide **15**. The favoured conformation of structure **10** will have one of the sp^3 bromines pseudo axial and the other three groups on the saturated ring will be pseudo-equatorial. Antiperiplanar elimination of H and Br will remove the axial Br and an axial H and it clearly favours the more acidic hydrogen next to the other Br, leading to **11**. Formation of the epoxide would require the alternative conformation with three of the groups pseudo axial and although one of the HBr eliminations is not so difficult in going to **13**, the other would also require the diaxial arrangement, which is unfavourable. Therefore the formation of the alkene **11** occurrs via an E1cB mechanism, as we discussed for transformation of its anthracene counterpart to alkene-1,4-diol.[9g]

The mass spectrum of compound **11** gave a molecular ion peak M$^+$ at *m/z* 396/398/400/402 corresponding to the formula $C_{10}H_7Br_3O_2$. The ^{1}H NMR spectrum of **11** showed an apparent singlet at δ 7.51 due to aryl protons H-6 and H-7, a doublet ($J_{3\text{-}4}$ 3.6 Hz) at δ 6.62 due to H-3 and a multiplet at δ 5.41-5.45 due to aliphatic protons H-1 and H-4. The hydroxyl protons appear as doublets at δ 3.17 (d, $J_{1\text{-}OH}$ 5.6 Hz) and δ 3.08 (d, $J_{4\text{-}OH}$ 6.0 Hz). The ^{13}C NMR spectrum confirmed the structure, having ten signals.

It is clear that 1,4-dihydroxy compounds are good precursors for 1,4-diketones. Therefore, diol **11** was treated with pyridinium chlorochromate (PCC) in dichloromethane. After the oxidation, 2,5,8-tribromo-1,4-naphthoquinone **12** was isolated as the sole product (yield: 81-78%, Scheme 2). The ^{1}H NMR spectrum of the compound consists of two signals, for H-6 and H-7 (δ 7.83, bs) and H-3 (δ 7.51, s). The ^{13}C NMR spectrum showed the absence of aliphatic

carbons. Two carbonyl signals at δ 179.8 and δ 176.0 were also consistent with the suggested structure. The IR spectrum showed two carbonyl bands at 1670 and 1608 cm^{-1}.



Scheme 2. Synthesis of 2,5,8-tribromo-1,4-naphthoquinone **12**.

Interestingly, when the diol **10** was subjected to PCC, diketone **12** was again obtained, in 86% yield, instead of the expected diketone **14**. Presumably, the pyridine moiety in the PCC acts as a base and the base removes either H-2 or H-3 in **10** to bring about elimination of one molecule of HBr. Subsequently, oxidation would have occurred to form **12** (Scheme 2). Pyridine-induced elimination also afforded compound **11**, which may support our assumption.

Conclusions

At the beginning of this study, we hoped to develop a convenient synthetic methodology for *syn*-diepoxide **17**, starting with hexabromide **3** and proceeding via diol **16** as shown in Scheme 2. However, the silver-induced hydrolysis afforded a stereoisomer, **10**, that was different from the one expected. Moreover base-promoted reaction of **10** resulted in the alkene **11** instead of expected epoxide **15**. These results directed our attention to a different possibility. Compound **11** was converted into 2,5,8-tribromo-1,4-naphthoquinone (**12**) by PCC oxidation. PCC oxidation of compound **10** also resulted in the formation of compound **12**, not the anticipated compound **14**. Thus, we have developed an effective and simple method for the synthesis of 2,5,8-tribromo-1,4-naphthoquinone (**12**) starting from naphthalene and using just four/five sequential, precisely selective and simple reactions that all proceed in high yields. We believe that **12** can provide a practical lead to many natural and bioactive products due to the presence of its three bromine substituents.

Experimental Section

General. Thin layer chromatography was carried out on Merck 0.255 mm silica gel F_{254} analytical aluminium plates and spots were visualized with UV fluorescence at 254 nm. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained from KBr pellet on a Jasco FT/IR 430 instrument. Elemental analyses were carried out on a LECO CHNS-93 analyser. Mass spectra were recorded on an Agilent 6890 GC System 5973 MSD spectrometer. NMR spectra were recorded on a Bruker Avance II spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR.

Hydrolysis of hexabromide 3; synthesis of diol 10. To a stirred solution of hexabromide **3** (4.0 g, 1.8 mmol) in acetone (40 mL) was added a solution of $AgClO_4.H_2O$ (1.22 g, 5.4 mmol) in aqueous acetone (40%) in a dropwise manner in the dark. The resulting mixture was stirred at room temperature for 7 days in the dark, during which the reaction was monitored by TLC. The precipitated AgBr was filtered off and the filtrate was diluted with dichloromethane (20 mL). The organic layer was washed with H_2O (3 × 20 mL) and dried over Na_2SO_4, and the solvent

was removed under reduced pressure. The crude product (2.92 g) was recrystallized from dichloromethane to give pure **10** (2.77 g, 87%).

***cis,cis,trans*-2,3,5,8-Tetrabromo-1,2,3,4-tetrahydronaphthalene-1,4-diol** (**10**). Mp 175-177 °C. R_f: 0.42 (hexane/ethyl acetate; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $J_{6\text{-}7}$ 8.5 Hz, 1H, ArH), 7.53 (d, $J_{6\text{-}7}$ 8.5 Hz, 1H, ArH), 5.51 (dd, $J_{1\text{-}OH}$ 4 Hz, $J_{1\text{-}2}$ 2.8 Hz, 1H, H-1), 5.12 (dd, $J_{3\text{-}4}$ 5 Hz, $J_{2\text{-}3}$ 2.8 Hz, 1H, H-3), 5.07 (dd, $J_{3\text{-}4}$ 5 Hz, $J_{4\text{-}OH}$ 8 Hz, 1H, H-4), 4.72 (bs, 1H, H-2), 3.01 (d, $J_{4\text{-}OH}$ 8 Hz, 1H, OH), 2.90 (d, $J_{1\text{-}OH}$ 4 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.3, 134.7, 134.4, 126.1, 124.8, 73.4, 68.9, 53.0, 48.5; MS (GC-MS/EI) *m/z* 378/380/382/384 [2, M-H_2O- Br]$^+$, 362/364/366/368 [3, M-2H_2O-Br-2H] $^+$, 317/319/321 [9, M- 2Br-3H]$^+$, 301 [1, M-H_2O-2Br]$^+$, 281 [15, M-2H_2O-2Br-3H]$^+$, 250, 252 (100), 235 [51, M-3Br-4H]$^+$, 219 (62), 207 (71), 193 (29), 147 [15, M-OH-4Br]$^+$, 131 (43), 102 (32), 86 (22), 75 (46), 69 (73), 50 (22), 44 (100); IR (KBr, cm^{-1}) 3303, 2873, 2358, 1671, 1432, 1340, 1311, 1282, 1182, 1145, 1064, 1012, 910, 863, 806, 765, 736, 676, 657, 615, 568, 511, 491, 430. Anal. calcd for $C_{10}H_8Br_4O_2$: C, 25.03; H, 1.68 Found C, 24.95; H, 1.65.

Synthesis of 2,5,8-tribromo-1,4-dihydronaphthalene-1,4-diol (**11**). To a solution of **10** (1.0 g, 2.08 mmol) in dry THF (20 mL) was added a solution of sodium methoxide (0.28 g, 5.0 mmol) in dry THF (15 mL). The mixture was stirred at room temperature for two days during which the progress was checked by TLC. The reaction was diluted with diethyl ether (20 mL) and washed with H_2O (3×20 mL). The organic layer was dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was purified by column chromatography (dichloromethane-hexane) followed by crystallization from dichloromethane to give **11** (0.58 g, 70%). The reaction was repeated using 2 mol equivalents of base ($NaOCH_3$) and a similar yield was obtained.

The reaction was repeated using pyridine instead of the both base and solvent. After stirring at room temperature for one day and then extraction, 2,5,8-tribromonaphthalene-1,4-diol **11** was obtained in a yield of 81%.

2,5,8-Tribromo-1,4-dihydronaphthalene-1,4-diol (**11**): Mp 129-131 °C; R_f: 0.55 (hexane/ethyl acetate; 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 2H, H-6 and H-7), 6.62 (d, J 3.6 Hz, 1H, H-3), 5.41-5.45 (m, 2H, H-1 and H-4), 3.17 (d, $J_{1\text{-}OH}$ 5.6 Hz, 1H, OH), 3.08 (1H, d, $J_{4\text{-}OH}$ 6.0 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 137.0, 134.3,134.2, 131.2, 125.4, 123.5, 123.3, 69.1, 66.7; MS (GC-MS/EI) *m/z* 396/398/400/402 [1, M]$^+$, 378/380/382/384 [9, M-H_2O-H]$^+$, 362/364/366/368 [11, M-2H_2O]$^+$, 317/319/321 [53, M-Br] $^+$, 300/302/304 [18, M-H_2O-Br]$^+$, 283/285/287 [5, M-2H_2O-Br]$^+$, 271/273/275 [24], 261/263/265 (7), 238/240 [54, M-2Br] $^+$, 220/222 [6, M-H_2O-2Br], 204/206 [30, M-2H_2O-2Br], 191/193/195 (32), 159 [15, M-3Br] $^+$, 140/142 [9, M-H_2O-3Br], 131(50), 125 [33, M-2H_2O-3Br], 113 [100, M-3Br-OH]$^+$, 102 (63), 86 (50), 74 (91), 62 (65), 56 (46), 51 (47), 38 (16); IR (KBr, cm^{-1}) 3313, 2923, 2649, 1671, 1581, 1440, 1390, 1315, 1282, 1257, 1214, 1184, 1165, 1062. Anal. calcd for $C_{10}H_7Br_3O_2$: C, 30.11; H, 1.77 Found C, 30.02; H, 1.79.

Synthesis of 2,5,8-tribromonaphthalene-1,4-dione (**12**). A solution of the diol **11** (0.46 g, 1.10 mmol) in dichloromethane (30 mL) was added to pyridinium chlorochromate (PCC, 200 mg, 0.72 mmol) in dichloromethane (20 mL). The mixture was stirred at room temperature for 3

days. The solid was filtered off and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel; dichloromethane) followed by crystallization from dichloromethane-hexane (2:1 in volume) to give pure **12** (132 mg, 78%).

2,5,8-Tribromonaphthalene-1,4-dione (**12**): Mp 188-190 ºC. R_f: 0.6 (hexane/ethyl acetate; 9:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (bs, 2H, H-6 and H-7), 7.56 (s, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 176.1, 141.0, 140.7, 139.9, 138.6, 131.4, 131.0, 123.2, 122.2; (GC-MS/EI), *m/z* 344/346/348 (7), 329/331/333 (6), 314/316/318/320 [2, M-Br]$^+$, 281 (1), 260 (12), 245/247/249 (13), 235 [7, M$^+$-2Br], 209 (9), 181 (4), 155 [27, M-3Br]$^+$, 153 [21, M-3Br-2H]$^+$, 119 (3), 99 (9), 87 (41), 74 (100), 69 (83), 53 (24), 44 (7), 41 (12); IR (KBr, cm^{-1}) 3411, 3068, 2921, 2360, 1679, 1608, 1538, 1427, 1365, 1307, 1253, 1209, 1064. Anal. Calcd for $C_{10}H_3Br_3O_2$: C, 30.42; H, 0.77 Found C, 30.50; H, 0.81.

The direct oxidation of 2,3,5,8-tetrabromonaphthalene-1,4-diol (**10**) **with PCC**. To a solution of pyridinium chlorochromate (PCC, 370 mg, 1.71 mmol) in methylene chloride (10 mL) was added a solution of 2,3,5,8-tetrabromo-1,4-dihydronaphthalene-1,4-diol (**10**) (0.37 g, 0.7 mmol) in methylene chloride (12 mL). The mixture was stirred at ambient temperature for 3 days. Reaction progress was monitored for consumption of the starting material by TLC. The residue was filtered through a short silica gel (10 g) column, eluting with dichloromethane (120 mL). After removal of the solvent under vacuum, 2,5,8-tribromoanaphthalene-1,4-dione (**12**) (280 mg, 86%) was obtained.

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