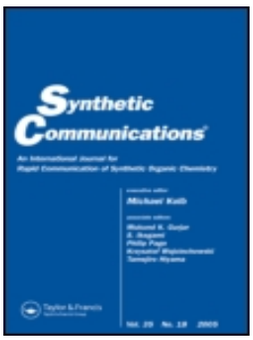

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SYNTHESIS OF 2,2-DIMETHYL-3, 4-EPOXY-2*H*-NAPHTHO[2,3-*b*]PYRAN-5, 10-DIONE

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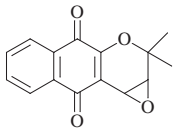
ABSTRACT

A short and convenient synthesis of benzopyranoquinone **6** and its application to the preparation of epoxynaphthopyanoquinone **1** is described.

Naphtho[2,3-*b*]pyranoquinones have long been known for their antimicrobial and antitumor activity (1–4). Considering that quinone epoxides seem to play an important role in metabolic processes (5), and that some natural epoxyquinones have shown antitumor activity (6), the synthesis of a naphtho [2,3-*b*]pyranoquinone epoxide arises as an important target in the search for novel anticancer activity. As part of our ongoing research on the synthesis of bioactive heterocyclic quinones (7–9), we describe a new synthesis of benzopyranoquinone **6** and the preparation of epoxynaphthopyranoquinone **1** using dimethyldioxirane.



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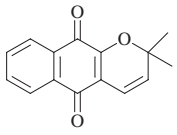

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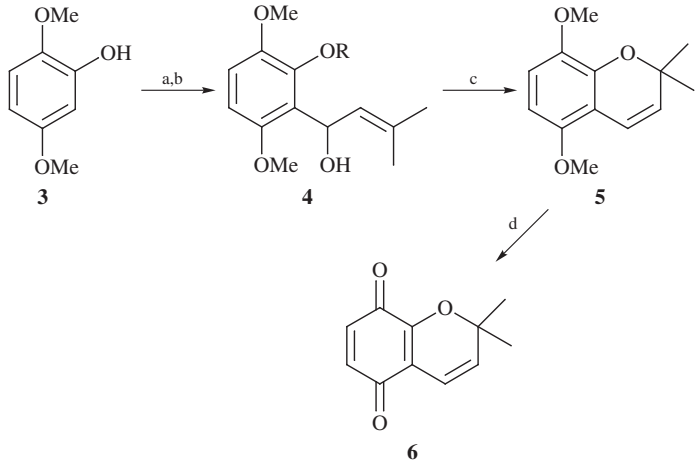
*Corresponding author.



Scheme 1. *Reagents*: a) DHP, TsOH; b) i, n-Buli, −78°C; ii, $(CH_3)_2C{=}CHCHO$, 88% over 2 steps; c) Acetone-H_2O, 55°C, 85%; d) AgO, HNO_3, THF, 25°C, 78%.

The preparation of naphthopyranoquinone **2** was achieved through a Diels-Alder reaction of benzopyranoquinone **6** and 1-trimethylsilyloxy-1,3-butadiene. The known routes to obtain benzopyranoquinone **6** (10,11) gave low yields, so we explored the approach shown in Scheme 1. This route starts from 2,5-dimethoxyphenole (12) and involves the addition of an aryllithium derivative to 3-methyl-2-butenal (13).

Protection of phenol **3** (14) as the tetrahydropyranyl ether, and treatment with *n*-butyllithium followed by reaction with 3-methyl-2-butenal, gave benzyl alcohol **4**. The attempt to hydrolyze the THP protection of compound **4** under acid conditions led to its decomposition. However, deprotection and cyclization to obtain benzopyrane **5** was carried out cleanly upon refluxing for 12 h an acetone-water solution of **4**.

Brown et al. (10) tried to obtain benzopyranoquinone **6** by oxidation of benzopyrane **5** with ceric ammonium nitrate without success. Nevertheless, the treatment of compound **5** with silver (II) oxide and nitric acid gave **6** in 78% yield. This sequence gave 58% yield of benzopyranoquinone **6** in four steps from 2,5-dimethoxyphenol. Reaction of benzopyranoquinone **6** with 1-trimethylsilyloxy-1,3-butadiene followed by aromatization *in situ* of the adduct gave naphthopyranoquinone **2** (65%).

The reaction of 2-hydroxy-1,4-naphtoquinone with 3-methyl-2-butenal, as an alternative approach to compound **3**, was also evaluated, although some examples of this reaction are known to give low yield (18–20%) (15). Heating of

2-hydroxy-1,4-naphtoquinone with 3-methyl-2-butenal in the presence of triethylamine gave a very low yield of naphthopyranoquinone **2** (5%). However, without adding base, the yield was improved to 35%.

Next, the epoxidation of **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) was investigated. The treatment of **2** with *m*-CPBA in the presence of a base produced decomposition of substrate and product. When this reaction was carried out in the absence of base, the epoxyquinone **1** was obtained, but the purification was tedious.

After the above result, the use of dimethyldioxirane was considered, based on recent reports concerning the successful epoxidation of enones with this reagent (16–18). Treatment of naphthopyranoquinone **2** with dimethyldioxirane in acetone gave epoxyquinone **1** in 84% yield.

I. EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and were not corrected. IR spectra were obtained on a Bruker Model Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-200 spectrometer, using tetramethylsilane as internal reference, and coupling constants are given in Hz. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). Elemental analyses were performed on a FISONS EA 1108 CHNS-O analyzer.

1-[2-(2-Tetrahydropyranyloxy)-3,6-dimethoxyphenyl]-3-methyl-2-buten-1-ol 4

To a solution of 2,5-dimethoxyphenol tetrahydropyranyl ether (14) (1.0 g, 4.20 mmol) in THF (25 mL) at −78°C under a nitrogen atmosphere, a 1.5-M solution of *n*-butyllithium in hexane (3.0 mL, 4.6 mmol) was added, the cooling bath was removed, and the mixture was stirred for 2 h at room temperature. The reaction mixture was cooled to −78°C and a solution of 3-methyl-2-butenal (0.42 g, 5.0 mmol) in THF (7.5 mL) was slowly added. The mixture was allowed to warm to room temperature and then it was stirred overnight. Water was added (25 mL) and the resulting mixture was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with water (2 × 15 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give benzyl alcohol **4** (1.25 g, 93%) as an oil; IR (neat, ν_{max}): 3440, 1620, 1190, 1040 cm^{-1}; ^{1}H-NMR δ: 1.6 (s, 3H, CH_3), 1.7 (s, 3H, CH_3), 1.4–2.0 (m, 6H, 3 × CH_2), 3.4–3.6 (m, 2H, CH_2), 3.70

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(s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.30 (br s, 1H, OH, exchangeable with D_2O), 5.70–5.80 (m, 1H, HC =), 5.90 (d, 1H, J = 7.1, CH), 6.0 (t, 1H, J = 9.2, CH), 6.50 (d, 1H, J = 9.0, ArH), 6.60 (d, 1H, J = 9.0, ArH); Anal. calcd. for $C_{18}H_{26}O_5$: C, 67.06, H, 8.13: Found: C, 66.85; H, 8.30.

2,2-Dimethyl-5,8-dimethoxy-2*H*-1-benzopyrane 5

A mixture of benzyl alcohol **4** (1.0 g, 3.1 mmol), acetone (10 mL), and water (1.0 mL) was heated to reflux for 12 h. Dichloromethane (25 mL) was then added and the mixture was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using dichloromethane as eluent to afford benzopyrane **5** (0.58 g, 85%); mp 64°–65°C. (Lit. (10) 65°C).

5,8-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-5,8-dione 6

To a mixture of benzopyrane **5** (150 mg, 0.68 mmol), silver (II) oxide (340 mg, 2.73 mmol) and THF (10 mL), 6N nitric acid (0.8 mL) was added. After 3 min, water (10 mL) was added and the mixture was extracted with dichloromethane (2 × 20 mL). The organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using dichloromethane as eluent to afford benzopyranoquinone **6** (100 mg, 78%); mp 79°–80°C. (Lit. (10) 79°–80°C).

2,2-Dimethyl-2*H*-naphtho [2,3-*b*] pyran-5,10-dione 2

A: To a solution of quinone **3** (100 mg, 0.52 mmol) in dichloromethane (10 mL) was added 1-trimethylsilyloxy-1,3-butadiene (100 mg, 0.52 mmol) and the mixture was stirred at room temperature for 4 h. Silica gel and pyridine were added and the reaction mixture was stirred at room temperature for 24 h. After filtration and evaporation, the residue was purified by column chromatography using dichloromethane as eluent to afford naphthopyranoquinone **2** (80 mg, 65%); mp 140°–141°C. (Lit. (19) 141°C).

B: A mixture of 2-hydroxy-1,4-naphthoquinone (174 mg, 1.0 mmol), 3-methyl-2-butenal (0.1 mL, 1.04 mmol) in benzene (15 mL) was heated to reflux for 4 h. Evaporation of the solvent and purification of the residue by chromatography on silica gel deactivated with 20% of water using dichloromethane as eluent, gave naphthopyranoquinone **2** (85 mg, 35%); mp 140°–141°C. (Lit. (19) 141°C).

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2,2-Dimethyl-3,4-epoxy-2*H*-naphtho[2,3-*b*]pyran-5,10-dione 1

A stirred mixture of quinone **2** (50 mg, 0.21 mmol) in dichloromethane (3 mL) was treated with dimethyldioxirane (20) (0.09 M in acetone, 3 mL) at 0°C for 3 h. Evaporation of the solvent and purification of the residue by chromatography on silica gel using dichloromethane as eluent afforded epoxyquinone 1 (45 mg, 84%); mp 138°–140°C; IR (KBr, ν_{max}): 1680, 1650, 1620 cm^{-1}. ^{1}H-NMR δ: 1.45 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 3.55 (d, 1H, J = 4.4, CH), 4.35 (d, 1H, J = 4.4, CH), 7.60–7.80 (m, 2H, ArH), 8.00–8.15 (m, 2H, ArH). ^{13}C-NMR δ: 23.3, 25.1, 43.8, 61.4, 78.0, 117.1, 126.2, 126.6, 131.1, 131.8, 133.4, 134.3, 153.8, 179.1, 183.0. Anal. calcd. for $C_{15}H_{12}O_4$: C, 70.31, H, 4.72: Found: C, 70.15; H, 4.93

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