Synthesis of Two Naphthoquinone Antibiotics, Dehydroherbarin and 6-Deoxybostrycoidin

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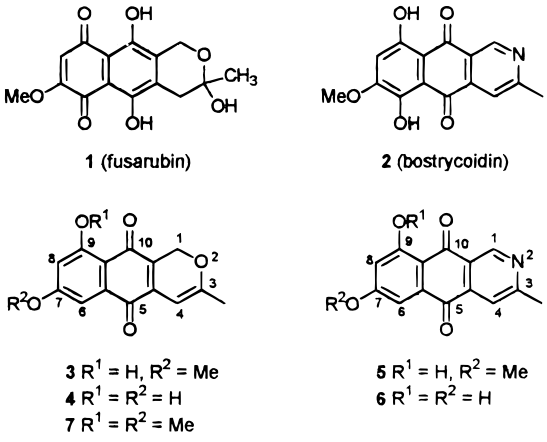
The synthesis of two naphthoquinone antibiotics, dehydroherbarin (**7**) and 6-deoxybostrycoidin (**5**), was accomplished by reaction of 3-acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (**23**) with either triethylamine or ammonia, respectively. This is the first report on their synthesis.

Introduction

Cultures of *Nectria haematococca*, the sexual stage of the phytopathogenous fungus *Fusarium solani*, produce a wide series of highly colored naphthoquinone pigments related to fusarubin (**1**) and bostrycoidin (**2**).[1] In a study directed toward the biosynthesis of these two naphthoquinone antibiotics, mutants of *N. haematococca*, blocked at different points in their pigment synthesis, were found to produce the fusarubin intermediate metabolites 6-deoxy-3,4-anhydrofusarubin (**3**)[2] and 7-*O*-demethyl-6-deoxy-3,4-anhydrofusarubin (**4**)[3] (according to the present numbering system). From a yellow strain mutant of *N. haematococca*, grown in a medium enriched in asparagin, 6-deoxybostrycoidin (**5**)[4] and 7-*O*-demethyl-6-deoxybostrycoidin (**6**)[5] were isolated as intermediates in the bostrycoidin biosynthesis. The pyranonaphthoquinone pigments **3** and **4** were found to exhibit moderate antimicrobial activity and recently they were also isolated from the Ascomycete *Trichopezizella nidulus* in the course of a screening for inhibitors of the dihydroxynaphthalene melanin biosynthesis in fungi.[6] Dehydroherbarin (**7**), a 9-*O*-methyl derivative of pigment **3**, was obtained earlier from *Torula herbarum*, a dermatoceous fungus regularly associated with dry leaves and twigs of *Felia microphylla*, and also this pyranonaphthoquinone derivative was found to possess weak antimicrobial activity and antiamoebic activity against *Entamoeba histolytica*.[7]

From the similarity in the substitution pattern between the pyranonaphthoquinone pigments **1**, **3**, and **4** and their 2-azaanthraquinone analogues **2**, **5**, and **6**, respectively, it was postulated that the occurrence of 2-azaanthraquinone pigments in *N. haematococca* originates in vivo from incorporation of ammonia into the pyranonaphthoquinone skeleton, probably by reaction of ammonia with one of the intermediates in the biosynthesis of the pyranonaphthoquinone pigments.[8] This reaction might serve as a detoxification process of ammonia. On the basis of this hypothesis and since none of the naphthoquinone antibiotics **3**−**7** were synthesized before, we were tempted to develop a new synthetic pathway that would allow both the synthesis of the pyranonaphthoquinone pigments as well as their 2-azaanthraquinone analogues in one and the same synthetic scheme. For this purpose, we used a 1,4-naphthoquinone **8**, bearing an acetonyl group at C(3) and a leaving group L at the C(2)-methylene group. This functionalized 1,4-naphthoquinone **8** can either be cyclized with a base to a 3,4-dehydropyranonaphthoquinone **9** or react with ammonia to give the corresponding 2-azaanthraquinone **10** (Scheme 1). Using this synthetic approach we succeeded in the first total synthesis of two naphthoquinone antibiotics, 6-deoxybostrycoidin (**5**) and dehydroherbarin (**7**).



Results and Discussion

8-Hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**13**), as a starting material, was obtained in 76% yield from the regioselective cycloaddition of benzoquinone **11** with vinyl ketene acetal **12**.[9] An acetonyl group at C(3) was introduced by reaction of 1,4-naphthoquinone **13** with acetonylpyridinium chloride (**14**)[10] and 1 equiv of trieth-

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(2) Parisot, D.; Devys, M.; Barbier, M. *J. Antibiot.* **1992**, *45*, 1799−1801.

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(9) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455−3464.

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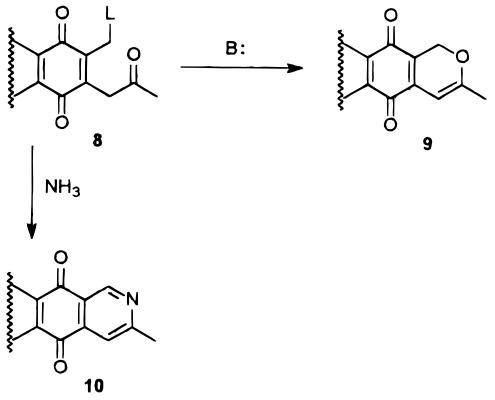
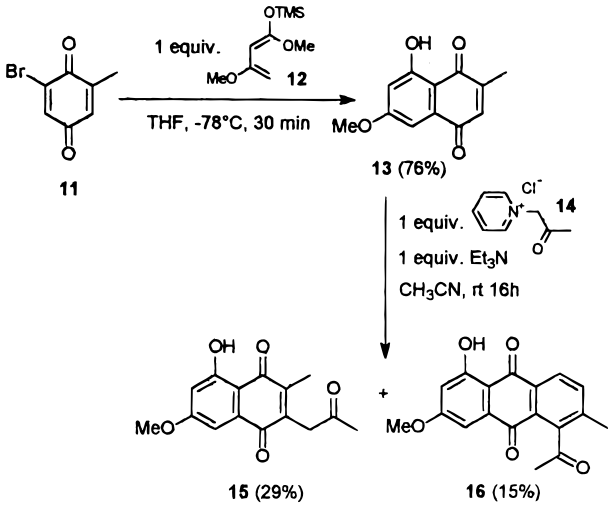
Scheme 1



Scheme 2

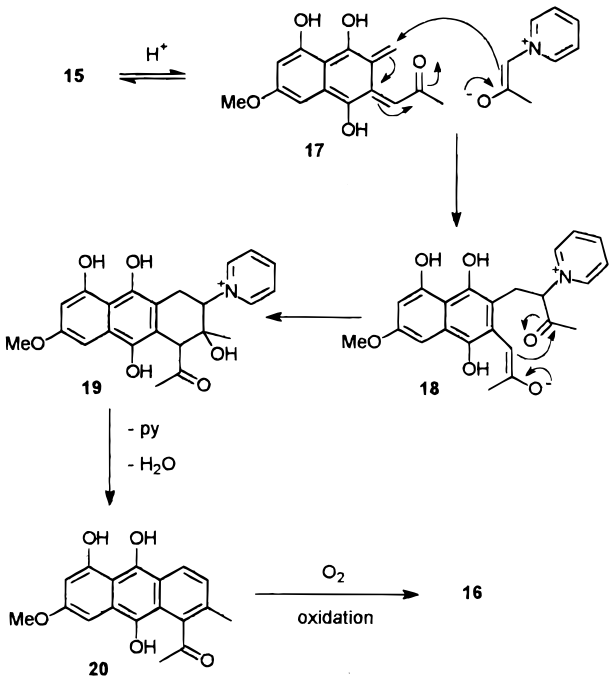


ylamine. The desired 3-acetonylnaphthoquinone **15** was obtained in a yield of 29% only, together with 15% of a side product **16**. Anthraquinone **16** resulted from the reaction of naphthoquinone **15** with a second equivalent of pyridinium ylide (Scheme 2).

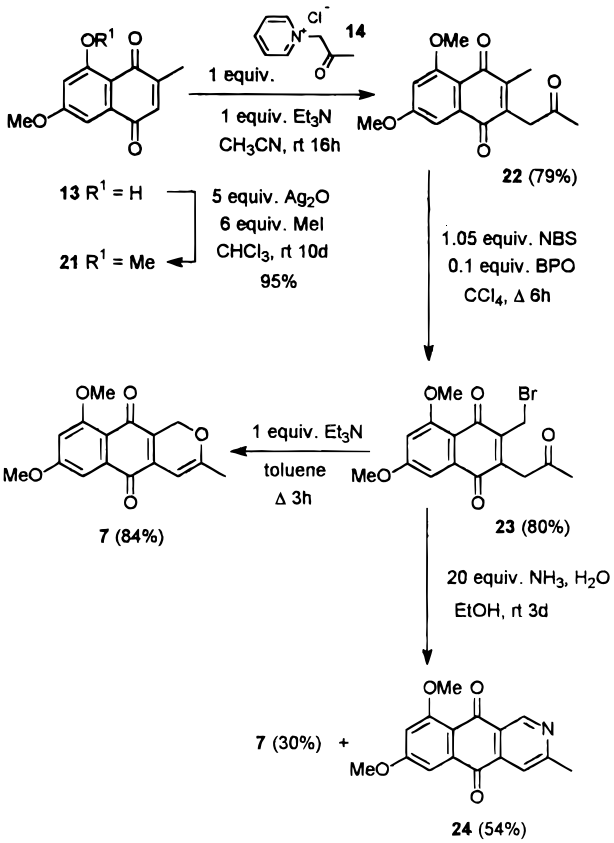
A possible reaction mechanism for the formation of this 1-acetylanthraquinone **16** is shown in Scheme 3. It is assumed that the phenolic protons in the medium and/or triethylammonium protons (Et_3NH^+) resulting from the deprotonation of the phenolic group catalyze the tautomerization of compound **15**. The reactive methide **17** in a Michael-type addition with a second equivalent of pyridinium ylide affords compound **18**. Intramolecular aldol condensation, elimination of pyridine and water, and oxidation in the presence of air finally gave 1-acetylanthraquinone **16**.

To avoid the formation of the anthraquinone side product, the 8-hydroxyl group of compound **13** was protected by *O*-methylation using iodomethane and silver(I) oxide (Scheme 4). Alternatively, this 6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**21**) could also be prepared in 63% yield by a regioselective 1:2-addition of benzoquinone **11** with ketene dimethyl acetal in dimethyl sulfoxide. Reaction of **21** with acetonylpyridinium chloride (**14**) and 1 equiv of triethylamine gave the 3-acetonylnaphthoquinone **22** as the sole product in a yield of 79%. Compound **22** was monobrominated selectively at

Scheme 3



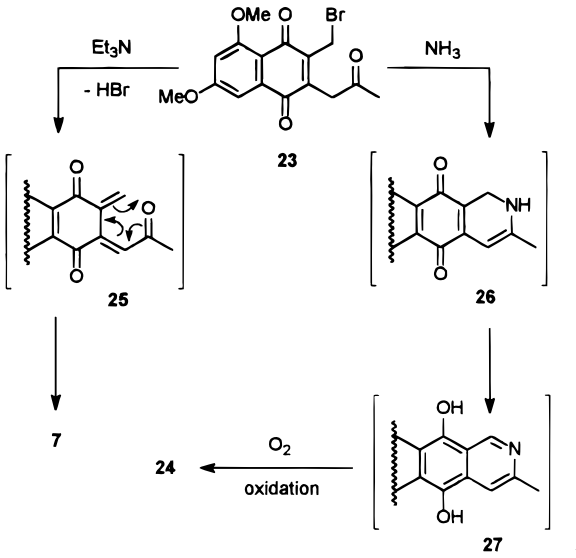
Scheme 4



the C(2)-methyl position using 1 equiv of *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide to give the 3-acetonyl-2-bromomethyl-1,4-naphthoquinone **23** in 80% yield. Compound **23** was used as a precursor for the synthesis of both the pyranonaphthoquinone pigments and their 2-azaanthraquinone analogues. Thus, upon treatment of this 3-acetonyl-2-bromomethyl-1,4-naphthoquinone **23** with triethylamine, it cyclized selectively to the pyranonaphthoquinone pigment dehydro-

(10) Aldersley, M. F.; Dean, F. M.; Nayyir-Mazhir, R *J. Chem. Soc., Perkin Trans. 1* **1983**, 1753−1757.

Scheme 5



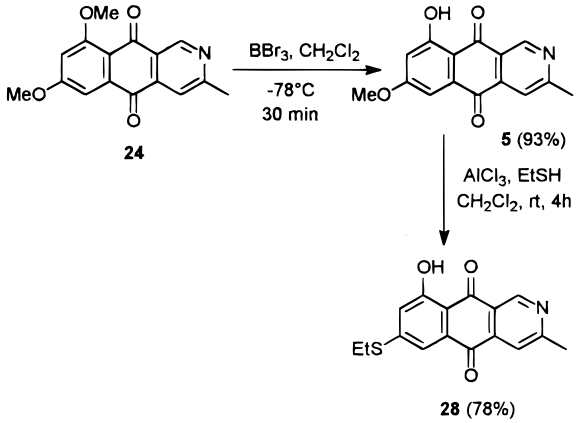
herbarin (**7**) in 84% yield. On the other hand, reaction of **23** with excess ammonia in aqueous ethanol gave a mixture of dehydroherbarin (**7**) and the corresponding 7,9-dimethoxy-3-methyl-2-azaanthraquinone (**24**) in a ratio of 1:2, respectively. Compounds **7** and **24** were isolated in yields of 30% and 54%, respectively, after separation by means of flash chromatography.

The reaction mechanism which explains the formation of both compounds **7** and **24** is shown in Scheme 5. In the presence of triethylamine, naphthoquinone **23** eliminates hydrogen bromide, leading to the intermediate methide **25** which rapidly cyclizes to dehydroherbarin (**7**). In reaction with ammonia, on the other hand, ammonia is incorporated in the naphthoquinone skeleton of compound **23** via nucleophilic substitution of the bromine and condensation with the acetonyl carbonyl group to afford the 2-azaanthraquinone derivative **26**. Tautomerization and spontaneous aromatization of compound **26** leads to hydroquinone **27**. Oxidation in the presence of air finally affords the 2-azaanthraquinone **24**. Direct oxidation of intermediate **26** may also produce **24**. The formation of dehydroherbarin (**7**) via the reaction of **23** with ammonia can be explained from the competitive action of ammonia as a base. In an attempt to increase the selectivity for the 2-azaanthraquinone formation, **23** was reacted with ammonium acetate as an example of a less basic form of ammonia, but surprisingly the ratio of pyranonaphthoquinone **7** to 2-azaanthraquinone **24** increased to 84:16. On the other hand, reaction of naphthoquinone **23** with a solution of 7 M ammonia in methanol afforded a 1:1 mixture of dehydroherbarin (**7**) and the 2-azaanthraquinone **24**. Compound **24** had been prepared previously by a 1:2-cycloaddition reaction of 3-methylisoquinoline-5,8-dione and ketene dimethyl acetal.[11] This reaction however suffers from the disadvantage of poor regioselectivity as 7,9-dimethoxy-3-methylbenz[*g*]isoquinoline-5,10-dione **24** was only obtained as the minor regioisomer in a ratio of 1:7 together with 6,8-dimethoxy-3-methylbenz[*g*]isoquinoline-5,10-dione.[11]

For the synthesis of the naturally occurring pigments **3**−**6**, which contain free hydroxyl groups at C(7) and C(9),

(11) Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I. *Tetrahedron Lett.* **1980**, *21*, 5089−5090. Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I. *Aust. J. Chem.* **1982**, *35*, 1439−1450.

Scheme 6



dehydroherbarin (**7**) and the 2-azaanthraquinone **24** needed to be further *O*-demethylated. Therefore, **24** was first treated with excess boron tribromide in dichloromethane at −78 °C to give selective O-demethylation at the peri-position, resulting in 6-deoxybostrycoidin (**5**) in 93% yield (Scheme 6). Surprisingly, the 9-*O*-demethylation of dehydroherbarin (**7**), using boron tribromide or aluminum trichloride, gave only tars. Furthermore, all efforts for the 7-*O*-demethylation of **5** using $AlCl_3$, BBr_3, BCl_3, HBr, or hydrochloric acid under several different reaction conditions were unsuccessful. Only the reaction of **5** with excess $AlCl_3$ and ethanethiol in dichloromethane for 4 h at room temperature gave a complete conversion of **5** into a new sulfur-containing 2-azaanthraquinone, characterized as 7-ethylthio-9-hydroxy-3-methylbenz[*g*]isoquinoline-5,10-dione **28**.

In conclusion, reaction of 3-acetonyl-2-bromomethyl-7,9-dimethoxy-1,4-naphthoquinone **23** with triethylamine or ammonia provided a facile entry to the synthesis of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones and benz[*g*]isoquinoline-5,10-diones, respectively. Using this synthetic approach, two naphthoquinone antibiotics, 6-deoxybostrycoidin (**5**) and dehydroherbarin (**7**), were synthesized.

Experimental Section

General Methods. ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra, and HETCOR spectra. All solvents and reagents were obtained from commercial suppliers and were used without purification. Dry tetrahydrofuran was distilled from sodium/benzophenone ketyl.

8-Hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (13). Under a nitrogen atmosphere, a solution of vinyl ketene acetal **12**[9] (6.67 g, 0.033 mol) in dry tetrahydrofuran (50 mL) was added over a period of 30 min at −78 °C to a solution of 2-bromo-6-methyl-1,4-benzoquinone (**11**) (6.60 g, 0.033 mol) in dry tetrahydrofuran (100 mL), and the solution was allowed to warm to ambient temperature over a period of 1 h. The solvent was evaporated in vacuo and evaporation was continued until the residue solidified to a yellow substance. Recrystallization from ethanol afforded 8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**13**) (5.47 g, 76%) as a yellow powder, mp 187.3−187.6 °C. ^{1}H NMR ($CDCl_3$): δ 2.17 (3H, d, J = 1.7 Hz, CH_3), 3.90 (3H, s, MeO), 6.64 (1H, d, J = 2.3 Hz, H-7), 6.75 (1H, q, J = 1.7 Hz, H-3), 7.15 (1H, d, J = 2.3 Hz, H-5), 12.29 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 15.98 (CH_3), 56.01 (MeO), 106.00 (C-7), 107.33 (C-5), 109.68 (=C_{quat}), 133.89 (=C_{quat}), 135.85 (C-3), 148.68 (=C_{quat}), 164.38 (=C−O), 166.05 (=C−O), 184.09 (C=O), 188.84 (C=O). IR (KBr): ν_{max} 3446 (OH), 1656 (C=O), 1630 (C=O), 1598 (C=C) cm^{-1}. MS *m*/*z* (%): 218 (M^+, 100), 190 (21), 150 (16). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.78; H, 4.54.

Synthesis of 3-Acetonyl-8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (15) and 1-Acetyl-6-hydroxy-8-methoxy-2-methyl-5,10-anthraquinone (16). Under a nitrogen atmosphere, a solution of triethylamine (0.25 g, 2.5 mmol) in acetonitrile (5 mL) was added dropwise to a stirred solution of 8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**13**) (0.55 g, 2.5 mmol) and acetonylpyridinium chloride (**14**)[10] (0.45 g, 2.6 mmol) in acetonitrile (30 mL). Stirring was continued for 16 h, and then most of the solvent was evaporated in vacuo. The residue was dissolved in 2 N hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo to give a mixture of 3-acetonyl-8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**15**) and 1-acetyl-6-hydroxy-8-methoxy-2-methyl-5,10-anthraquinone (**16**) in a ratio of 3:1 which could not be separated by flash chromatography using ethyl acetate−petroleum ether (1:1) as eluent. Selective recrystallization from ethyl acetate afforded 1-acetyl-6-hydroxy-8-methoxy-2-methyl-5,10-anthraquinone (**16**) (110 mg, 15%) as a yellow powder, mp 217.5−218 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 2.58 (3H, s, CH_3C=O), 3.92 (3H, s, MeO), 6.72 (1H, d, J = 2.3 Hz, H-7), 7.30 (1H, d, J = 2.3 Hz, H-9), 7.65 (1H, d, J = 7.9 Hz, H-3), 8.24 (1H, d, J = 7.9 Hz, H-4). ^{13}C NMR ($CDCl_3$): δ 19.12 (CH_3), 31.02 (CH_3C=O), 56.06 (MeO), 107.13 (C-9), 107.99 (C-7), 110.37 (=C_{quat}), 127.20 (C-4), 130.01 (=C_{quat}), 131.88 (=C_{quat}), 134.55 (=C_{quat}), 136.57 (C-3), 140.32 (=C_{quat}), 143.56 (=C_{quat}), 165.33 (=C−O), 166.45 (=C−O), 182.85 (C=O), 186.02 (C=O), 205.19 (C=O). IR (KBr): ν_{max} 3465 (OH), 1694 (C=O), 1669 (C=O), 1622 (C=O) cm^{-1}. MS *m*/*z* (%): 310 (M$^+$, 62), 296 (41), 294 (100). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 68.65; H, 4.85. Evaporation of the mother liquor and recrystallization from ethanol gave pure 3-acetonyl-8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**15**) (200 mg, 29%) as a yellow powder, mp 124.5−124.8 °C. ^{1}H NMR ($CDCl_3$): δ 2.10 (3H, s, CH_3), 2.31 (3H, s, CH_3C=O), 3.77 (2H, s, CH_2), 3.89 (3H, s, MeO), 6.62 (1H, d, J = 2.6 Hz, H-7), 7.14 (1H, d, J = 2.6 Hz, H-5), 12.33 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 12.72 (CH_3), 30.26 (CH_3C=O), 41.69 (CH_2), 55.97 (MeO), 106.05 (C-7), 107.74 (C-5), 109.65 (=C_{quat}), 133.30 (=C_{quat}), 140.91 (=C_{quat}), 146.263 (=C_{quat}), 164.24 (=C−O), 165.86 (=C−O), 183.36 (C=O), 188.03 (C=O), 203.20 (C=O). IR (KBr): ν_{max} 1709 (C=O), 1658 (C=O), 1633 (C=O), 1609 (C=C) cm^{-1}. MS *m*/*z* (%): 274 (M$^+$, 30), 232 (100), 204 (11), 43 (77). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.59; H, 4.96.

Synthesis of 6,8-Dimethoxy-2-methyl-1,4-naphthoquinone (21) from 8-Hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (13). A mixture of 8-hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**13**) (0.65 g, 3 mmol), silver(I) oxide (3.48 g, 15 mmol), and iodomethane (2.59 g, 18 mmol) in chloroform (30 mL) was protected from light with aluminum foil and stirred for 10 days under a nitrogen atmosphere. The reaction mixture was filtered over Celite and evaporated in vacuo. Recrystallization of the residue from methanol gave 6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**21**) (0.66 g, 95%) as a yellow powder, mp 153.8−155.6 °C. ^{1}H NMR ($CDCl_3$): δ 2.15 (3H, d, J = 1.3 Hz, CH_3), 3.94 (3H, s, MeO), 3.97 (3H, s, MeO), 6.72−6.74 (2H, m, H-3 and H-7), 7.22 (1H, d, J = 2.3 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 16.86 (CH_3), 55.87 (MeO), 56.30 (MeO), 102.69 (C-5), 103.89 (C-7), 114.48 (=C_{quat}), 132.94 (C-3), 136.21 (C_{quat}), 150.35 (=C_{quat}), 161.83 (=C−O), 164.45 (=C−O), 183.39 (C=O), 184.87 (C=O). IR (KBr): ν_{max} 1652 (C=O), 1625 (C=O), 1593 (C=C) cm^{-1}. MS *m*/*z* (%): 232 (M$^+$, 100), 217 (10), 203 (41). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.98; H, 5.42.

Synthesis of 6,8-Dimethoxy-2-methyl-1,4-naphthoquinone (21) from 2-Bromo-6-methyl-1,4-benzoquinone (11). To a solution of 2-bromo-6-methyl-1,4-benzoquinone (**11**) (6.03 g, 0.03 mol) in dimethyl sulfoxide (30 mL) was added at 0 °C dimethyl ketene acetal (13.2 g, 0.15 mol), and the solution was stirred for 4 days under a nitrogen atmosphere. The reaction mixture was poured into water and extracted three times with ether, and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization from ethanol afforded the 6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**21**) (4.38 g, 63%) as a yellow powder. For the spectral data of compound **21**, vide supra.

3-Acetonyl-6,8-dimethoxy-2-methyl-1,4-naphthoquinone (22). To a solution of 6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**21**) (0.35 g, 1.5 mmol) and acetonylpyridinium chloride (**14**)[10] (0.26 g, 1.5 mmol) in acetonitrile (20 mL) was added dropwise a solution of triethylamine (0.15 g, 1.5 mmol) in acetonitrile (5 mL), and the resulting solution was stirred for 16 h at room temperature under a nitrogen atmosphere and protected from light with aluminum foil. Most of the solvent was evaporated in vacuo, and the residue was mixed with 2 N hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization from ethyl acetate afforded 3-acetonyl-6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**22**) (0.34 g, 79%) as a yellow powder, mp 181.7−182.9 °C. ^{1}H NMR ($CDCl_3$): δ 2.09 (3H, s, CH_3), 2.30 (3H, s, CH_3C=O), 3.74 (2H, s, CH_2), 3.92 (3H, s, MeO), 3.96 (3H, s, MeO), 6.71 (1H, d, J = 2.3 Hz, H-7), 7.21 (1H, d, J = 2.3 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 13.53 (CH_3), 30.13 (CH_3C=O), 41.62 (CH_2), 55.88 (MeO), 56.42 (MeO), 103.09 (C-5), 104.10 (C-7), 114.68 (=C_{quat}), 135.69 (=C_{quat}), 137.72 (=C_{quat}), 147.94 (=C_{quat}), 161.74 (=C−O), 164.42 (=C−O), 182.76 (C=O), 184.35 (C=O), 203.66 (C=O). IR (KBr): ν_{max} 1707 (C=O), 1646 (C=O), 1596 (C=C) cm^{-1}. MS *m*/*z* (%): 288 (M$^+$, 18), 246 (30), 209 (41), 45 (100). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.24; H, 5.54.

3-Acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (23). A mixture of 3-acetonyl-6,8-dimethoxy-2-methyl-1,4-naphthoquinone (**22**) (0.86 g, 3 mmol), *N*-bromosuccinimide (0.56 g, 3.15 mmol), and benzoyl peroxide (0.07 g, 0.3 mmol) in carbon tetrachloride (80 mL) was heated under reflux for 6 h, cooled to room temperature, and evaporated in vacuo. Recrystallization from ethyl acetate gave 3-acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (**23**) (0.88 g, 80%) as a yellow powder, mp 140 °C (dec). ^{1}H NMR ($CDCl_3$): δ 2.36 (3H, s, CH_3), 3.83 (2H, s, CH_2C=O), 3.94 (3H, s, MeO), 3.98 (3H, s, MeO), 4.38 (2H, s, CH_2Br), 6.74 (1H, d, J = 2.3 Hz, H-7), 7.23 (1H, d, J = 2.3 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 22.46 (CH_2Br), 30.48 (CH_3), 41.44 (CH_2C=O), 55.99 (MeO), 56.51 (MeO), 103.47 (C-5), 104.47 (C-7), 114.21 (=C_{quat}), 135.61 (=C_{quat}), 139.85 (=C_{quat}), 145.42 (=C_{quat}), 162.21 (=C−O), 164.87 (=C−O), 179.67 (C=O), 184.56 (C=O), 202.78 (C=O). IR (KBr): ν_{max} 1706 (C=O), 1651 (C=O), 1595 (C=C) cm^{-1}. MS *m*/*z* (%): 366/8 (M$^+$, 1), 287 (3), 245 (14), 75 (100). Anal. Calcd for $C_{16}H_{15}BrO_5$: C, 52.34; H, 4.12. Found: C, 52.80; H, 3.98.

Dehydroherbarin (7). A solution of triethylamine (0.10 g, 1 mmol) in toluene (5 mL) was added dropwise to a stirred solution of 3-acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (**23**) (0.36 g, 1 mmol) in toluene (30 mL), and the mixture was heated under reflux for 3 h. The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel with ethyl acetate−petroleum ether (1:1) as eluent to give dehydroherbarin (**7**) (240 mg, 84%) as a red powder. Recrystallization from ethanol afforded dehydroherbarin as fine red needles, mp 187.2−187.5 °C (lit.[7] mp 186−188 °C). The spectral data (^{1}H NMR, IR, and MS) of the synthetic dehydroherbarin (**7**) were identical with those of the natural product reported in the literature.[7] Additionally, its ^{13}C NMR spectral data are given here. ^{1}H NMR ($CDCl_3$): δ 1.99 (3H, d, J = 1 Hz, CH_3), 3.93 (3H, s, MeO), 3.94 (3H, s, MeO), 5.11 (2H, s, CH_2), 5.82 (1H, m, H-4), 6.69 (1H, d, J = 2.3 Hz, H-8), 7.22 (1H, d, J = 2.3 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 20.09 (CH_3), 55.88 (MeO), 56.37 (MeO), 63.32 (CH_2), 93.78 (C-4), 103.48 (C-6), 104.26 (C-8), 114.57 (=C_{quat}), 124.76 (=C_{quat}), 135.33 (=C_{quat}), 135.58 (=C_{quat}), 161.49 (=C−O), 163.20 (=C−O), 164.11 (=C−O), 180.86 (C=O), 182.23 (C=O). IR (KBr): ν_{max} 1652 (C=O), 1622 (C=O), 1586 (C=C), 1552 (C=C) cm^{-1}. MS *m*/*z* (%): 286 (M$^+$, 96), 271 (100), 243 (18). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.08; H, 5.23.

Reaction of 3-Acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (23) with Ammonia. To a solution

of 3-acetonyl-2-bromomethyl-6,8-dimethoxy-1,4-naphthoquinone (**23**) (0.32 g, 0.9 mmol) in ethanol (30 mL) was added dropwise a 25% aqueous solution of ammonia (1.5 mL, 18 mmol). The solution was protected from light with aluminum foil and stirred for 3 days in an open vessel, allowing contact with the air. Most of the solvent was evaporated in vacuo, and the residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate−petroleum ether (1:1) gave dehydroherbarin (**7**) (80 mg, 30%) as a red powder. Elution with ethyl acetate as eluent afforded 7,9-dimethoxy-3-methylbenz[*g*]isoquinoline-5,10-dione (**24**) as yellow powder (138 mg, 54%). After recrystallization from ethanol, **24** was obtained as fine yellow needles, mp 213.0−213.4 °C (lit.[11] mp 214−215 °C). ^{1}H NMR ($CDCl_3$): δ 2.74 (3H, s, CH_3), 3.97 (3H, s, MeO), 4.01 (3H, s, MeO), 6.80 (1H, d, J = 2.3 Hz, H-8), 7.37 (1H, d, J = 2.3 Hz, H-6), 7.78 (1H, s, H-4), 9.37 (1H, s, H-1). ^{13}C NMR ($CDCl_3$): δ 25.03 (CH_3), 56.05 (MeO), 56.57 (MeO), 103.54 (C-6), 105.39 (C-8), 115.54 (=C_{quat}), 117.46 (C-4), 125.41 (=C_{quat}), 136.89 (=C_{quat}), 137.48 (=C_{quat}), 149.68 (C-1), 162.73 (C-3), 164.11 (=C−O), 164.96 (=C−O), 180.43 (C=O), 183.41 (C=O). IR (KBr): ν_{max} 1675 (C=O), 1655 (C=O), 1595 (C=C) cm^{-1}. MS *m*/*z* (%): 283 (M^+, 100), 266 (19), 254 (53). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.94; H, 4.53; N, 4.73.

6-Deoxybostrycoidin (5). To a solution of 7,9-dimethoxy-3-methylbenz[*g*]isoquinoline-5,10-dione (**24**) (80 mg, 0.28 mmol) in dry dichloromethane (10 mL) at −78 °C and under a nitrogen atmosphere was added boron tribromide (1 mL) dropwise. After 30 min, the reaction was quenched by the addition of water (0.5 mL), and the reaction mixture was poured into 2 N sodium hydroxide (50 mL). Then, 1 N hydrochloric acid was added in portions of 10 mL until the color of the reaction mixture turned yellow (pH <7), and the resulting solution was extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization from ethyl acetate afforded pure 6-deoxybostrycoidin (**5**) (70 mg, 93%) as a yellow powder, mp 193.8−194 °C (lit.[4] mp 195−196 °C). ^{1}H NMR ($CDCl_3$): δ 2.77 (3H, s, CH_3), 3.94 (3H, s, MeO), 6.72 (1H, d, J = 2.3 Hz, H-8), 7.31 (1H, d, J = 2.3 Hz, H-6), 7.84 (1H, s, H-4), 9.39 (1H, s, H-1). ^{13}C NMR ($CDCl_3$): δ 25.30 (CH_3), 56.14 (MeO), 107.37 (C-8), 108.16 (C-6), 110.40 (=C_{quat}), 118.49 (H-4), 124.11 (=C_{quat}), 134.45 (=C_{quat}), 138.58 (=C_{quat}), 149.05 (C-1), 165.53 (C-3), 165.89 (=C−O), 166.43 (=C−O), 182.21 (C=O), 186.14 (C=O). IR (KBr): ν_{max} 1681 (C=O), 1636 (C=O), 1588 (C=C) cm^{-1}. MS *m*/*z* (%): 269 (M^+, 2), 215 (31), 170 (24), 110 (35), 107 (34), 106 (49), 100 (51), 91 (100). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.66; H, 4.25; N, 4.95. The spectral data of the natural 6-deoxybostrycoidin (**5**)[4] and the synthetic product were identical.

7-Ethylthio-9-hydroxy-3-methylbenz[*g*]isoquinoline-5,10-dione (28). To a cooled (0 °C) solution of 6-deoxybostrycoidin (**5**) (30 mg, 0.11 mmol) in dichloromethane (10 mL) was added first ethanethiol (0.5 mL) and then aluminum trichloride (1 g), and the reaction was stirred for 4 h at room temperature. The reaction was quenched by careful addition of water (5 mL), and the reaction mixture was poured into 1 N hydrochloric acid (100 mL), extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization from ethyl acetate afforded **28** (25 mg, 78%) as yellow needles, mp 178.5−179.8 °C. ^{1}H NMR ($CDCl_3$): δ 1.44 (3H, t, J = 7.3 Hz, CH_3CH_2S), 2.78 (3H, s, Me), 3.10 (2H, q, J = 7.3 Hz, CH_3CH_2S), 7.10 (1H, d, J = 2.0 Hz, H-8), 7.63 (1H, d, J = 2.0 Hz, H-6), 7.88 (1H, s, H-4), 9.43 (1H, s, H-1), 12.66 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 13.55 (CH_3CH_2S), 25.35 (Me), 25.73 (CH_2S), 112.56 (=C_{quat}), 117.37 (=CH), 118.51 (=CH), 119.32 (=CH), 124.06 (=C_{quat}), 132.59 (=C_{quat}), 138.43 (=C_{quat}), 149.05 (=CH), 151.46 (=C_{quat}), 162.89 (=C_{quat}), 166.19 (=C_{quat}), 182.26 (C=O), 186.78 (C=O). IR: ν_{max} 3325 (OH), 1674, 1625, 1581, 1350, 1279, 755 cm^{-1}. MS *m*/*z* (%): 299 (M^+, 98), 284 (24), 271 (100), 266 (32), 243 (18).

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