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Total synthesis of four naturally occurring 2-azaanthraquinone antibiotics, 6-deoxy-8-methylbostrycoidin, 6-deoxybostrycoidin, 7-*O*-demethyl-6-deoxybostrycoidin and scorpinone

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Abstract—A total synthesis of four natural 2-azaanthraquinones, 6-deoxy-8-methylbostrycoidin, 6-deoxybostrycoidin, 7-*O*-demethyl-6-deoxybostrycoidin and scorpinone was accomplished using an optimized procedure for 2-azaanthraquinone synthesis, involving a [4+2]-cycloaddition protocol, of a polyoxygenated diene with a suitably functionalized benzoquinone, acetonylation with pyridinium ylids, cyclisation with ammonia and *O*-demethylation with boron(III) bromide. 2-Azaanthraquinones are rarely found in nature and reveal interesting physiological properties.

1. Introduction

Naturally occurring 2-azaanthraquinones are of special interest due to their important physiological properties.[1] Benz[*g*]isoquinoline-5,10-dione **1**, the unsubstituted azaanthraquinone, has been isolated from *Psychotricha camponutans* and *Mitracarpus scaber*, and exhibits growth inhibition against multi-drug resistant pathogens, for example, *Staphylococcus aureus* and *Plasmodium falciparum*.[1,2] This 2-azaanthraquinone **1** also revealed antimalarial activity, and recently, in vivo and in vitro trypanocidal activity against *Trypanosoma congolense* was discovered (Fig. 1).[2,3]

Besides the unsubstituted 2-azaanthraquinone **1**, also some oxygenated derivatives, for example, bostrycoidin **2** and analogues **3**–**8** as representative members, were found in nature and showed interesting activities. Bostrycoidin **2** and 9-*O*-methylbostrycoidin **3**, two metabolites of numerous *Fusarium* species, showed antibiotic activity against the tubercle bacil and G^+ bacteria, respectively.[4,5] Tolypocladin **4**, from the mycelium of *Tolypocladium inflatum*, displayed metal-chelating properties.[6] In addition, 2-azaanthraquinone derivatives interfere with the activity of DNA topoisomerases and attract considerable attention in cancer chemotherapy as intercalating DNA binding agents.[7] Recently, two new 2-azaanthraquinones, scorpinone **8** and 6-deoxy-8-methylbostrycoidin **5**, were identified in the mycelium of a Bispora-like tropical fungus and in the cultures of the mycobionts of the lichen *Haematomma* sp., respectively.[8,9] From a yellow strain mutant of *Nectria haematococca*, grown in a medium enriched with asparagin 6-deoxybostrycoidin **6**[10] and 7-*O*-demethyl-6-deoxybostrycoidin **7**[11] were isolated as intermediates in the bostrycoidin biosynthesis.

Because of the physiological importance of 2-azaanthraquinones, several methods have been developed for their synthesis. Most pathways deal with a Diels–Alder cyclization of appropriate building blocks, in which the nitrogen is already incorporated.[12–14] However, these methods suffer from the disadvantage of low yield and poor regioselectivity of the incorporation of the methoxy groups. The synthetic pathway used by Watanabe et al. was based on a condensation of C(4)-lithiated nicotinamide with a 2,3,5-trimethoxybenzamide as the key reaction for the construction of the azaanthraquinones.[14] The drawback of this regiospecific method is the low yield due to its multistep pathway, that is, condensation of aromatic rings, selective methylation at the pyridine ring, reduction, ring closure, oxidation and partial demethylation. Recently, we published a straightforward synthesis of 2-azaanthraquinones via an ammonia-induced cyclization of 2-acetonyl-3-bromomethyl-1,4-naphthoquinones.[15] An optimized procedure without the interference of side products, for example, naphtho[2,3-*c*]pyran-5,10-diones, was now developed to synthesize the natural product 6-deoxy-8-methylbostrycoidin **5** for the first time and to result in an improved

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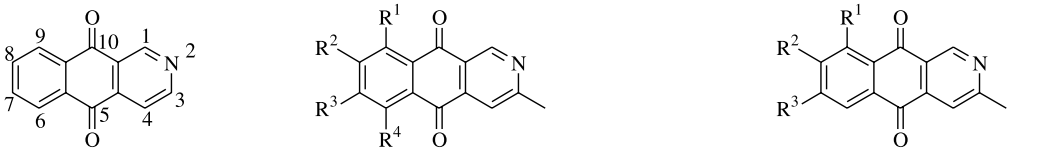


1

2 R^1=R^4=OH, R^2=H, R^3=OMe (bostrycoidin)
3 R^1=R^3=OMe, R^4=OH (9-*O*-methylbostrycoidin)
4 R^1=R^3=R^4=OH, R^2=H (tolypocladin)

5 R^1=OH, R^2=Me, R^3=OMe (6-deoxy-8-methylbostrycoidin)
6 R^1=OH, R^2=H, R^3=OMe (6-deoxybostrycoidin)
7 R^1=R^3=OH, R^2=H (7-*O*-demethyl-6-deoxybostrycoidin)
8 R^1=R^3= OMe, R^2=H (scorpinone)

Figure 1.

synthesis of three natural 2-azaanthraquinone antibiotics, 6-deoxybostrycoidin **6**, 7-*O*-demethyl-6-deoxybostrycoidin **7** and scorpinone **8**.

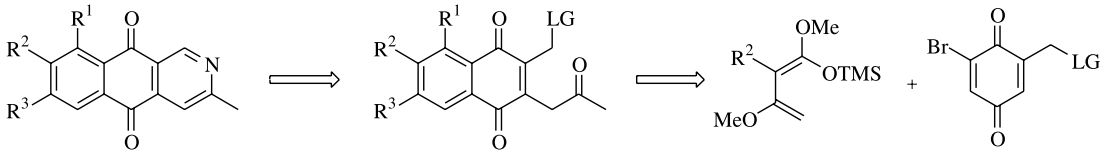
2. Results and discussion

The strategy for the synthetic pathway of the azaanthraquinones **5**–**8** consists of the synthesis of naphthoquinone **9** (LG, leaving group) which leads directly to the desired 2-azaanthraquinone system after treatment with ammonia via an intramolecular substitution (Scheme 1). The idea behind this approach was based on the hypothesis that naturally occurring 2-azaanthraquinones originate in vivo from the incorporation of ammonia into their *O*-analogues.[16] The naphthoquinone skeleton can be synthesized by a cycloaddition of an appropriate electron-rich and oxygenated diene **10** with the brominated benzoquinone **11**. In this strategy the choice of the leaving group in naphthoquinone **9** is determining the outcome of the cyclization reaction towards **5**–**8**. Earlier experiments showed that the use of a bromo atom as leaving group resulted in a mixture of pyranonaphthoquinones and 2-azaanthraquinones when treating naphthoquinones, analogous to **9**, with ammonia. However, when phenoxide was used as a leaving group, the reaction gave predominantly rise to 2-azaanthraquinones with almost no side products.[15,17]

For that reason 4,6-dibromo-2-(phenoxymethyl)phenol **14** was used as a starting material to synthesize 2-azaanthraquinones. The synthesis of **14** was accomplished by treating bromomethylphenol **13** with an excess of phenol under alkaline conditions. The latter brominated phenol **13** was synthesized by reacting *o*-cresol **12** with 3 equiv of bromine, first at 30 °C with 2 equiv of bromine to give the aromatic bromination, and afterwards at 120 °C with 1 equiv of bromine to introduce the bromine at the benzylic position.[18] The substitution reaction of **13** with phenoxide was carried out in good yield without the need for protection of the hydroxyl function of the brominated cresol **13**. Formation of byproducts was successfully suppressed by adding the brominated cresol to a refluxing solution of phenol in acetone in the presence of potassium carbonate (Scheme 2).

2,4-Dibromo-6-(phenoxymethyl)phenol **14** was oxidized by reaction with CrO_3 at room temperature to the benzoquinone **15**, which served as a dienophile in the subsequent regioselective cycloaddition. (1,3-Dimethoxy-1,3-butadien-1-yloxy)trimethylsilane **10a** was synthesized from methyl acetoacetate, while the analoguous 1,3-dimethoxy-2-methyl-1,3-butadien-1-yloxy)trimethylsilane **10b** was prepared from methyl 2-methylacetoacetate.[19] These dienes **10a** and **10b** were subsequently reacted with benzoquinone **15** to yield the substituted naphthoquinones **16a**–**b** in 62 and 55% yield, respectively. Dehydrobromination of the intermediate occurred spontaneously when treated with SiO_2 (during column chromatography). The naphthoquinones **16a**–**b**, bearing a free hydroxyl function, were protected as methyl ethers **17a** and **17b** by reaction with iodomethane and silver(I) oxide, prior to the introduction of an acetonyl group.

In this way, 6,8-dimethoxy-2-(phenoxymethyl)-1,4-naphthoquinones **17a**–**b** were reacted with *N*-(acetylmethyl)pyridinium ylide, formed in situ by reaction of *N*-acetonylpyridinium chloride and triethylamine



5 R^1=OH, R^2=Me, R^3=OMe
6 R^1=OH, R^2=H, R^3=OMe
7 R^1=R^3=OH, R^2=H
8 R^1=R^3=OMe, R^2=H

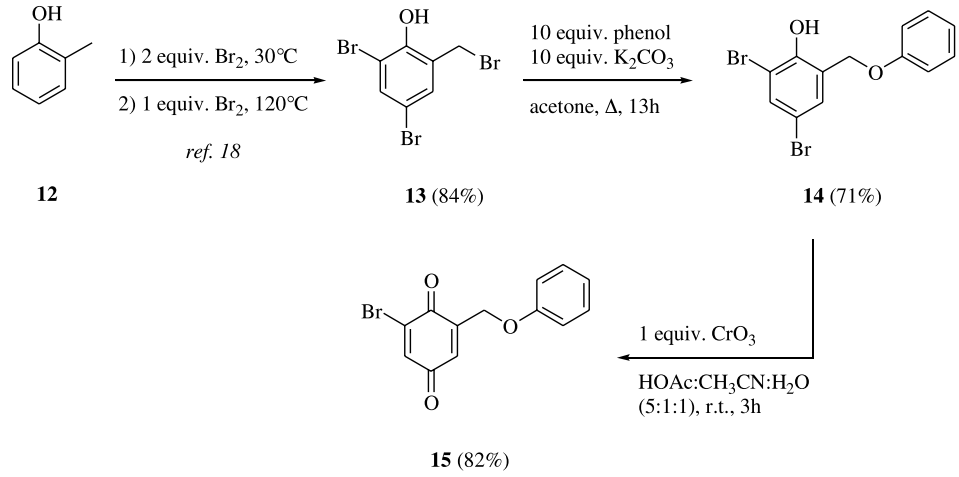
9

LG = Leaving group

10a R^2 = H
10b R^2 = Me

11

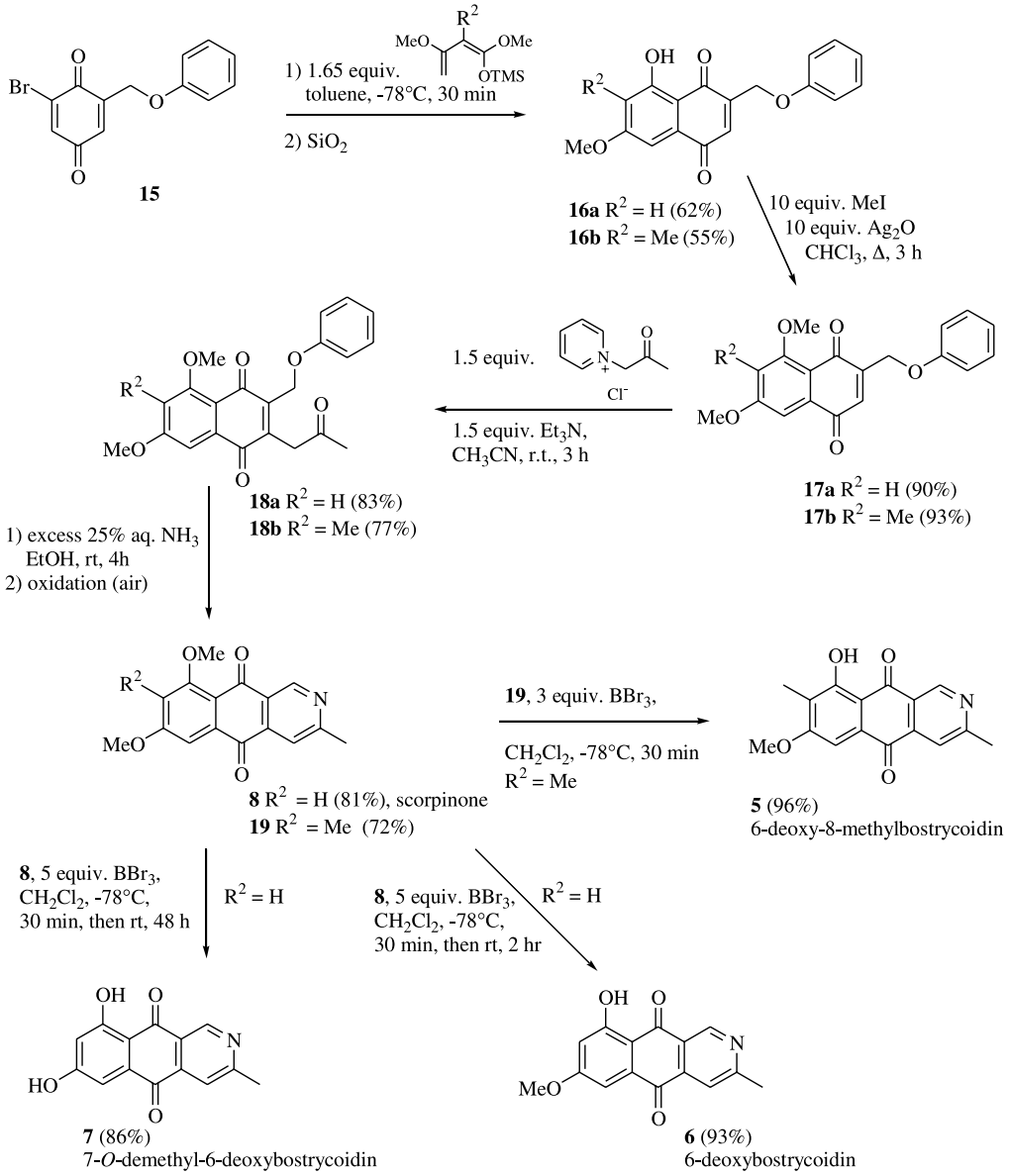
Scheme 1.



12 **13** (84%) **14** (71%)

15 (82%)

Scheme 2.



Scheme 3.

(Scheme 3).[20] The acetonylated products **18a–b** were treated with 10 equiv of ammonia resulting in a nucleophilic addition across the carbonyl of the acetonyl moiety and intramolecular substitution of the phenoxy group. The cyclized product oxidized spontaneously and afforded 2-azaanthraquinone **19** in 72% yield (from **18a**) and the natural product scorpinone **8** in 81% (from **18b**). No naphtho[2,3-*c*]pyran-5,10-dione was formed as side product, contrary to reactions of similar substrates with a bromine instead of a phenoxy group as leaving group. To obtain the recently discovered natural product 6-deoxy-8-methylbostrycoidin **5**, compound **19** was 9-*O*-demethylated using boron(III) bromide in dichloromethane in 96% yield in the final step (Scheme 3). In order to obtain the natural product 6-deoxybostrycoidin **6**, the natural product scorpinone **8** was selectively 9-*O*-demethylated by using 5 equiv of boron(III) bromide and stirring for 2 h at room temperature. A complete *O*-demethylation was obtained by reacting **8** with boron(III) tribromide in dichloromethane at room temperature for 48 h affording the natural product 7-*O*-demethyl-6-deoxybostrycoidin **7** in 86% yield.

In conclusion, using an optimized synthetic approach via dioxygenated 2-phenoxymethyl naphthoquinones, 2-aza-anthraquinones were synthesized by cyclization of 2-phenoxymethyl-3-acetonylnaphthoquinones with ammonia. This reaction pathway resulted in the first straightforward synthesis of the natural product 6-deoxy-8-methylbostrycoidin **5** and an optimized procedure for the natural products scorpinone **8**, 6-deoxybostrycoidin **6** and 7-*O*-demethyl-6-deoxybostrycoidin **7**.

3. Experimental

3.1. General methods

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR assignments were obtained from a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were measured with an Agilent 1100 Series mass spectrometer (detector VL, 70 eV, ES 4000 V). Melting points were measured with a Buchi B-540 apparatus. The elemental analysis was performed on a Perkin Elmer 2400 Elemental Analyzer. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). All solvents and reagents were obtained from commercial suppliers and were used without further purification.

3.1.1. 2,4-Dibromo-6-(phenoxymethyl)phenol (14). A solution of 2,4-dibromo-6-(bromomethyl)phenol **13**[15] (5 g, 14.5 mmol) in 50 ml of acetone was added dropwise to a refluxing mixture of phenol (13.6 g, 0.145 mol) and potassium carbonate (20 g, 0.145 mol) in 100 ml of acetone. After reflux overnight, the solvent was evaporated and the residue was redissolved in dichloromethane. After washing with water, the organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Residual phenol was distilled off at high vacuum (0.5 mmHg, at 70 °C). To remove some minor impurities, **14** was purified by column chromatography with 5% ethyl acetate in hexane as eluent, yielding 3.7 g of white crystals (71%), mp 68–69 °C. ^{1}H NMR ($CDCl_3$): δ 5.12 (2H, s, CH_2), 6.10 (1H, s, OH), 6.98–7.03 (3H, m, 3×=CH), 7.26–7.35 (2H, m, 2×=CH), 7.50 (1H, d, J=2.3 Hz, =CH), 7.58 (1H, d, J=2.3 Hz, =CH). ^{13}C NMR ($CDCl_3$): δ 65.3 (CH_2O), 110.9 (C_{quat}), 112.7 (C_{quat}), 114.7 (2×=CH), 121.6 (=CH), 126.2 (C_{quat}), 129.6 (2×=CH), 130.6 (=CH), 133.5 (=CH), 149.2 (=C–O), 157.9 (=C–O). IR (KBr) ν 3408 (OH), 1598 (C=C), 1587 (C=C), 1497 (C=C), 1451 (C=C), 1245, 1222 cm^{-1}. MS *m/z* (%) 355/7/9 ($M-H^+$, 100). Anal. Calcd $C_{13}H_{10}Br_2O_2$: C 43.61%, H 2.82%; found: C 43.24%, H 2.93%.

3.1.2. 2-Bromo-6-(phenoxymethyl)benzo-1,4-quinone (15). To a solution of 2,4-dibromo-6-(phenoxymethyl)-phenol **14** (895 mg, 2.5 mmol) in 20 ml of HOAc:CH_3CN/4:1 was added CrO_3 (250 mg, 2.5 mmol) in 2 ml of aqueous HOAc (50%). The solution was stirred for 3 h at room temperature and, after completion of the oxidation, the mixture was poured in water and extracted with dichloromethane. Evaporation of the solvent in vacuo yielded 700 mg of crude benzoquinone **15**, which was recrystallised from hexane:EtOAc/70:30 (600 mg, 82%), mp 145–146 °C. ^{1}H NMR ($CDCl_3$): δ 4.92 (1H, d, J=2.0 Hz, CH_aH$_b$O), 4.96 (1H, d, J=2.0 Hz, CH$_a$$H_b$O), 6.94–7.05 (4H, m, 4×=CH), 7.26–7.35 (3H, m, 3×=CH). ^{13}C NMR ($CDCl_3$): δ 63.5 (CH_2), 114.6 (2×=CH), 121.9 (=CH), 129.7 (2×=CH), 132.0 (=CH), 137.1, 138.2 and 144.0 (2×C_{quat}, 1×=CH), 157.4 (C_{quat}), 178.9 and 184.4 (2×C=O). IR (KBr) ν 1674 (C=O), 1660 (C=O), 1634 (C=C), 1599 (C=C), 1498 (C=C), 1293, 1250 cm^{-1}. MS *m/z* (%) 293/5 ($M-H^+$, 100). Anal. Calcd $C_{13}H_7BrO_3$: C 53.27%, H 3.09%; found: C 53.41%, H 3.21%.

3.1.3. 8-Hydroxy-6-methoxy-2-(phenoxymethyl)-naphthoquinone (16a). To a solution of 2-bromo-6-(phenoxymethyl)benzo-1,4-quinone **15** (450 mg, 1.54 mmol) in 20 ml of dry toluene at −78 °C was added dropwise a solution of vinyl ketene acetal **10a**[17] (513 mg, 2.54 mmol) in 5 ml of toluene. The reaction was kept at this temperature for 30 min. Then, the resulting mixture was allowed to warm to room temperature and was stirred for 3 h. After the reaction mixture was filtered through silica gel, the filtrate was concentrated in vacuo and the resulting Diels–Alder adduct was recrystallized from ethanol to give 300 mg of the pure product **16a** (62%), mp 151–152 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (3H, s, CH_3O), 5.05 (2H, d, J=2.3 Hz, CH_2), 6.64 (1H, d, J=2.3 Hz, H-5), 7.00 (1H, s, H-3), 7.03–7.07 (2H, m, 2×=CH), 7.08 (1H, t, J=2.3 Hz, C_3–H), 7.17 (1H, d, J=2.3 Hz, H-7), 7.21–7.36 (2H, m, 2×=CH), 12.10 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 53.1 (CH_3O), 63.2 (CH_2), 106.7 (C-7), 108.0 (C-5), 114.7 (2×=CH), 116.5 (C-9$_{quat}$), 121.7 (=CH), 129.7 (2×=CH), 132.6 (C-10$_{quat}$), 134.1 (C-3), 146.8 (C-2), 157.7 (=C–O),, 164.5 (=C–O), 166.4 (=C–O), 183.8 and 187.6 (2×C=O). IR (KBr) ν 1640 (C=O), 1620 (C=O), 1609 (C=C), 1588, 1388, 1311, 1241 cm^{-1}. MS *m/z* 497 (100), 311 ($M+H^+$, 50). Anal Calcd $C_{18}H_{14}O_5$: C 69.67%, H 5.55%; found: C 69.55%, H 5.42%.

3.1.4. 8-Hydroxy-6-methoxy-7-methyl-2-(phenoxy-methyl)naphthoquinone (16b). Mp 188–189 °C (55%).

^{1}H NMR ($CDCl_3$): δ 2.18 (3H, s, CH_3), 3.99 (3H, s, CH_3O), 5.07 (2H, d, J=2.0 Hz, CH_2O), 6.99–7.06 (3H, m, 3×=CH), 7.07 (1H, t, J=2 Hz, =CH), 7.21–7.36 (3H, m, 3×=CH), 12.21 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 8.1 (CH_3), 53.4 (CH_3O), 63.2 (CH_2), 102.5 (C-5), 109.7 (C_{quat}), 114.6 (2×=CH), 120.3 (C_{quat}), 121.7 (=CH), 129.0 (C_{quat}), 129.7 (2×=CH), 133.9 (C-3), 146.4 (C-2), 157.7 (=C–O), 161.3 (=C–O), 163.5 (=C–O), 184.2 and 188.2 (2×C=O). IR (KBr) ν 1661 (C=O), 1638 (C=O), 1609 (C=C), 1598 (C=C), 1497 (C=C), 1323, 1248, 1120 cm^{-1}. MS m/z (%) 323 (M−H$^+$, 35), 309 (M−CH_3, 100).

3.1.5. 6,8-Dimethoxy-2-(phenoxymethyl)naphthoquinone (17a). To a solution of naphthoquinone **16a** (256 mg, 0.83 mmol) in 10 ml of chloroform was added iodomethane (1.17 g, 8.3 mmol) and silver(I) oxide (2.02 g, 8.3 mmol). The mixture was refluxed for 3 h, under protection from light by covering the flask with aluminum foil. After cooling, the reaction mixture was filtered over celite and evaporated in vacuo to give 240 mg of the pure naphthoquinone **17a**. The resulting product was pure and was used without further purification (90%), mp 176–177 °C. ^{1}H NMR ($CDCl_3$): δ 3.91 (3H, s, CH_3O), 3.94 (3H, s, CH_3O), 5.01 (2H, d, J=2.0 Hz, CH_2), 6.68 (1H, d, J=2.3 Hz, H-5), 6.94 (1H, s, H-3), 6.97–6.98 (2H, m, 2×=CH), 6.99 (1H, t, J=2.0 Hz, C_3-H), 7.19 (1H, d, J=2.3 Hz, H-7), 7.26–7.32 (2H, m, 2×=CH). ^{13}C NMR ($CDCl_3$): δ 56.3 and 56.7 (2×CH_3O), 64.2 (CH_2), 103.5 (CH-7), 104.4 (CH-5), 115.0 (2×=CH), 121.8 (=CH), 130.0 (2×=CH), 131.5 (C-3), 132.8 (C_{quat}), 136.3 (C_{quat}), 148.5 (C-2), 158.2, 162.4 and 165.2 (3×=C–O), 182.9 and 185.0 (2×C=O). IR (KBr) ν 1651 (C=O), 1633 (C=O), 1597, 1458, 1331, 1251, 1159 cm^{-1}. MS m/z 325 (M+H$^+$, 100). Anal. Calcd $C_{19}H_{16}O_5$: C 70.36%, H 4.79%; found: C 70.22%, H 5.18%.

3.1.6. 6,8-Dimethoxy-7-methyl-2-(phenoxymethyl)-naphthoquinone (17b). Mp 151–153 °C (93%). ^{1}H NMR ($CDCl_3$): δ 2.23 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 3.99 (3H, s, CH_3O), 5.07 (2H, d, J=2.0 Hz, CH_2), 6.98–7.06 (3H, m, 3×=CH), 7.07 (1H, t, J=2.0 Hz, C_3-H), 7.26–7.41 (3H, m, 3×=CH). ^{13}C NMR ($CDCl_3$): δ 9.4 (CH_3), 56.5 and 61.4 (2×CH_3O), 64.2 (CH_2), 104.6 (CH-5), 115.0 (2×=CH), 118.6 (C_{quat}), 121.9 (=CH), 128.5 (C_{quat}), 130.0 (2×=CH), 132.0 (C-3), 133.2 (C_{quat}), 147.8 (C-2), 158.2, 160.4 and 163.1 (3×=C–O), 183.3 and 185.0 (2×C=O). IR (KBr) ν 1657 (C=O), 1634 (C=O), 1583, 1497, 1323, 1243, 1128 cm^{-1}. MS m/z (%) 339 (M+H$^+$, 100). Anal. Calcd $C_{20}H_{18}O_5$: C 70.99%, H 5.36%; found: C 70.63%, H 5.54%.

3.1.7. 2-Acetonyl-5,8-dimethoxy-3-(phenoxymethyl)-naphthoquinone (18a). To a solution of naphthoquinone **17a** (220 mg, 0.68 mmol) and acetonylpyridinium chloride (174 mg, 1.02 mmol) in 10 ml acetonitrile was added dropwise a solution of triethylamine (82 mg, 1.02 mmol) in 2 ml of acetonitrile. The resulting mixture was stirred for 3 h at room temperature under a nitrogen atmosphere and protected from light. After evaporation of the solvent, 5 ml of aq 2 M HCl was added and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography with 30% EtOAc in hexane as eluent yielded 200 mg of naphthoquinone **18a** (83%), mp 146–147 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 3.91 (3H, s, CH_3O), 3.92 (2H, s, CH_2C=O), 3.96 (3H, s, CH_3O), 5.08 (2H, s, CH_2O), 6.73 (1H, d, J=2.3 Hz, H-5), 6.90–6.98 (3H, m, 3×=CH), 7.22 (1H, d, J=2.3 Hz, H-7), 7.24–7.30 (2H, m, 2×=CH). ^{13}C NMR ($CDCl_3$): δ 30.1 (CH_3C=O), 41.2 (CH_2C=O), 55.8 (CH_3O), 56.4 (CH_3O), 61.3 (CH_2O), 103.2 (C-7), 104.3 (CH-5), 114.2 (C_{quat}), 114.5 (2×=CH), 121.3 (=CH), 129.5 (2×=CH), 132.3 (C_{quat}), 135.5 (C-3), 141.4 (C-2), 158.0, 161.9 and 164.6 (3×=C–O), 181.4 and 184.6 (2×C=O), 203.3 (CH_3C=O). IR (KBr) ν 1715 (C=O), 1663 (C=O), 1654 (C=O), 1597, 1556, 1354, 1334, 1273, 1164 cm^{-1}. MS m/z 381 (M+H$^+$, 100). Anal. Calcd $C_{22}H_{20}O_6$: C 69.46%, H 5.30%; found: C 69.52% H 5.42%.

3.1.8. 2-Acetonyl-5,7-dimethoxy-6-methyl-3-(phenoxymethyl)naphthoquinone (18b). Mp 162–163 °C (77%). ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.83 (3H, s, CH_3O), 3.92 (2H, s, CH_2C=O), 3.96 (3H, s, CH_3O), 5.08 (2H, s, CH_2O), 6.91–7.00 (3H, m, 3×=CH), 7.25–7.31 (2H, m, 2×=CH), 7.38 (1H, s, C_5–H). ^{13}C NMR ($CDCl_3$): δ 9.0 (CH_3), 30.2 (CH_3C=O), 41.2 (CH_2C=O), 56.1 (CH_3O), 61.0 and 61.2 (CH_2O and CH_3O), 104.3 (CH-5), 114.5 (2×=CH), 118.1 (C_{quat}), 121.4 (=CH), 128.5 (C_{quat}), 129.5 (2×=CH), 132.4 (C_{quat}), 142.0 (C_{quat}), 143.0 (C_{quat}), 158.0, 159.6 and 162.5 (3×=C–O), 181.8 and 184.6 (2×C=O), 203.5 (CH_3C=O). IR (KBr) ν 1696 (C=O), 1670 (C=O), 1626, 1580, 1334, 1222, 1143 cm^{-1}. MS m/z (%) (M+H$^+$,100), 301 (M−C_6H_5O, 75). Anal. Calcd $C_{23}H_{22}O_6$: C 70.04%, H 5.62%; found: C 70.20%, H 5.48%.

3.1.9. 7,9-Dimethoxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (8, scorpinone). To a solution of 3-acetonyl-5,7-dimethoxy-2-(phenoxymethyl)naphthoquinone **18a** (100 mg, 0.26 mmol) in 10 ml of ethanol was added dropwise a 25% aqueous solution of ammonia (0.43 ml, 5.2 mmol). The solution was protected from light and stirred at room temperature for 4 h in an open flask, allowing contact with air. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$) and evaporated. After recrystallization from ethanol 60 mg of 2-azaanthraquinone **8** was obtained (81%), mp 213–214 °C (lit. mp 195 °C).[1] Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, MS) were in accordance with those reported in literature.[1,8]

3.1.10. 7,9-Dimethoxy-3,8-dimethylbenzo[*g*]isoquinoline-5,10-dione (19). Mp 186–187 °C (72%). ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, s, CH_3), 2.77 (3H, s, CH_3C=N), 3.93 (3H, s, CH_3O), 4.05 (3H, s, CH_3O), 7.60 (1H, s, =CH), 7.84 (1H, s, CH–C=N), 9.43 (1H, s, HC=N). ^{13}C NMR ($CDCl_3$): δ 9.3 (CH_3), 25.1 (CH_3C=N), 56.2 and 61.3 (2×CH_3O), 104.7 (HC-5), 117.5 (H*C*–C=N), 119.5, 125.2, 130.0, 133.9 and 137.7 (5×C_{quat}), 149.6 (HC=N), 160.3, 162.9 and 164.4 (3×C_{quat}), 180.8 and 183.2 (2×C=O). IR (KBr) ν 1674 (C=O), 1661 (C=O), 1579, 1319, 1229, 1127 cm^{-1}. MS m/z (%) 298 (M+H$^+$, 100). Anal. Calcd $C_{17}H_{15}NO_4$: C 68.68%, H 5.09%, N 4.71%; found: C 68.88%, H 4.96%, N 5.01%.

3.1.11. 6-Deoxy-8-methylbostrycoidin (6). To a solution of 2-azaanthraquinone **19** (120 mg, 0.4 mmol) in 10 ml of dry

dichloromethane was added dropwise boron(III) bromide (301 mg, 1.2 mmol) under a nitrogen atmosphere at −78 °C. After 30 min, the reaction was quenched with water and poured into 5 ml of 2 M NaOH. 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated. 6-Deoxy-8-methylbostrycoidin **6** was obtained as a pure product in almost quantitative yield (108 mg, 96%), mp 150–151 °C (decomposed, lit. mp[9] 149–153 °C). Spectroscopic data (^1H NMR, ^{13}C, IR, MS) were in accordance with those reported in literature.[9]

3.1.12. 7-Methoxy-9-hydroxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (6-deoxybostrycoidin) (5). To a solution of 2-azaanthraquinone **8** (50 mg, 0.28 mmol) in 10 ml of dry dichloromethane was added dropwise boron(III) bromide (350 mg, 1.4 mmol) under a nitrogen atmosphere at −78 °C. After 30 min, the reaction was allowed to warm till room temperature. After stirring for 2 additional hours the reaction was quenched with water and poured into 5 ml 2 M NaOH. 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated. 6-Deoxybostrycoidin **7** was obtained as a pure product in good yield (45 mg, 93%), mp 193–194 °C (lit. mp 195–196 °C). Spectroscopic data (^1H NMR, IR, MS) were in accordance with those reported in literature.[10] ^{13}C NMR ($CDCl_3$): δ 25.3 (CH_3), 56.1 (CH_3O), 107.4 (C-8), 108.2 (C-6), 110.4 (C_{quat}), 118.5 (C-4), 124.1 (C_{quat}), 134.5 (C_{quat}), 138.6 (C_{quat}), 149.1 (C-1), 165.5 (C-3), 165.9 (=C–O), 166.4 (=C–O), 182.2 (C=O), 186.1 (C=O).

3.1.13. 7,9-Dihydroxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (7-*O*-demethyl-6-deoxy-bostrycoidin) (7). To a solution of 2-azaanthraquinone **8** (30 mg, 0.1 mmol) in 10 ml of dry dichloromethane was added dropwise boron(III) bromide (125 mg, 0.5 mmol) under a nitrogen atmosphere at −78 °C. The reaction mixture was kept at this temperature for 30 min, then the mixture was allowed to warm to room temperature and stirred for 48 h. After the reaction was quenched with water and poured into 5 ml 2 M NaOH, 1 M HCl was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give the crude compound **7**. This product was washed two times with dichloromethane and 7-*O*-demethyl-6-deoxybostrycoidin **7** was obtained as a pure product (22 mg, 86%), mp 291–292 °C (decomp.), lit.[1] mp 288–290 °C (decomp.) lit.[11] mp 300–305 °C (decomp.). Spectroscopic data (^1H NMR, ^{13}C NMR, IR, MS) were in accordance with those reported in literature.[11]

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