JOC Article

Synthesis of Benzo[*f*]isoindole-4,9-diones

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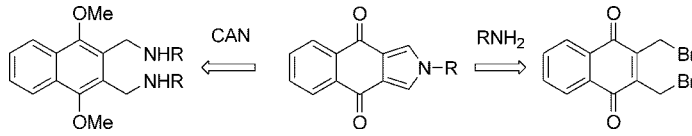

A synthesis of benzo[*f*]isoindole-4,9-diones **1** is presented starting from the reaction of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** with primary amines affording 2,3-bis(aminomethyl)-1,4-dimethoxynaphthalenes **14**, which could be converted by CAN-mediated oxidation in one step to benzo[*f*]isoindole-4,9-diones **1**. An alternative synthesis of benzo[*f*]isoindole-4,9-diones **1** starts from 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** via 2,3-dihydrobenzo[*f*]isoindoles **10** which spontaneously oxidize.

Introduction

During the past years, research was conducted at our departments toward the synthesis of quinones bearing annelated *N*-heterocyclic rings.[1] In this way, we managed to synthesize 6-deoxybostrycoidin[2] and several naturally occurring 2-azaanthraquinone analogues.[3] Only recently, a pathway was developed for the synthesis of 3-alkyl-2-aza-1-cyano-4-hydroxyanthraquinones.[4] Having experience in quinones with annelated pyridine moieties, it was felt necessary to synthesize the related quinones with annelated five-membered rings, i.e., benzo[*f*]isoindole-4,9-diones **1**, because of the link with natural product chemistry. The heterocyclic core of benzo[*f*]isoindole-4,9-diones **1** is found in natural products such as *Reniera* indole **2**, which has been isolated from the blue sponge *Reniera* sp.[5] Azamonosporascone **3** has been isolated from *Monosporascus cannonballus*, a fungus responsible for crop losses of musk melon and watermelon.[6] Bhimamycin C **4** and Bhimamycin D **5** were isolated from a terrestrial streptomycete[7] and display bioactivities against human ovarian cancer cell lines,[8] are EP_4 receptor agonists in the treatment of pain,[9] and are inhibitors of HIV-1 integrase.[10]

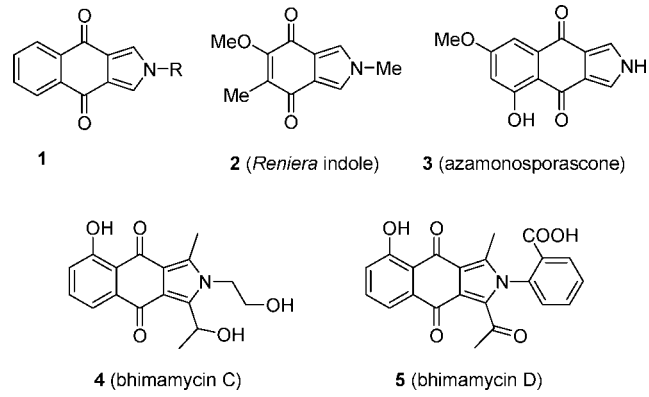

FIGURE 1. Isoindoles of interest.

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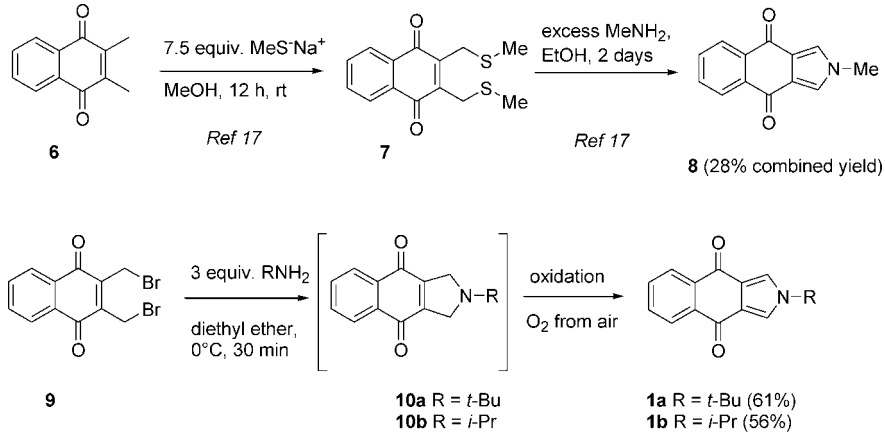
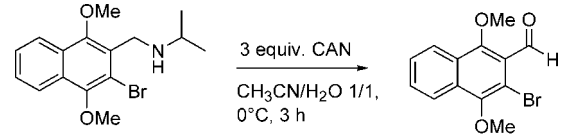
SCHEME 1



Although these benzo[*f*]isoindole-4,9-diones **1** have attracted considerable attention in the literature, only a limited number of synthetic pathways were developed toward compounds having a benzo[*f*]isoindole-4,9-dione core. These pathways are mainly based upon 1,3-dipolar cycloaddition of pyridinium or isoquinolinium ylids across 1,4-naphthoquinones,[11] 1,3-dipolar cycloadditions of azomethine ylids generated from amino acids[12] or nitrile oxides,[13] via an unusual rearrangement of 2,3-diacetylenyl-1,4-naphthoquinone with hydrazide,[14] starting from the annelated thiophenes[15] and a photochemical addition of 2,3-diphenyl-2*H*-azirine to 1,4-naphthoquinone.[16] The synthesis of 2-methyl-2*H*-benzo[*f*]isoindole-4,9-dione is based on the nucleophilic displacement of both methylthio groups in 2,3-bis(methylthiomethyl)-1,4-naphthoquinone with methylamine, followed by oxidation by oxygen to afford the benzo[*f*]isoindole.[17] The rearrangement of 2-azaanthraquinones employing 2,3-dichloro-5,6-dicyanopyrazine as the cyclization partner also resulted in the formation of benzo[*f*]isoindole-4,9-diones.[18] Drawbacks of these methods are the use of non-straightforward methods, unavailability of precursors and low yields. Therefore, a short and straightforward synthesis of this interesting class of compounds is of primordial importance.

SCHEME 2



11 **12** (79%)

Results and Discussion

We were interested in synthesizing 2-alkyl-2*H*-benzo[*f*]isoindole-4,9-diones **1** with only substituents on the nitrogen for which only one existing synthesis pathway is described by Thomson et al.[17] According to this procedure, only the 2-methyl substituted benzo[*f*]isoindole **8** was prepared making use of an alkylthiolation reaction of 2,3-dimethyl-1,4-naphthoquinone **6**. Subsequent reaction of 2,3-bis(methylthiomethyl)-1,4-naphthoquinone **7** with methylamine resulted in 2-methyl-2*H*-benzo[*f*]isoindole-4,9-dione **8** in a combined yield of 28%.

In order to avoid the use of expensive 2,3-dimethyl-1,4-naphthoquinone **6**, an alternative entry was sought. At first, it was thought that the reaction of primary amines with 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** would have some good chance to succeed, giving a short and straightforward synthesis of benzo[*f*]isoindoles-4,9-diones **1**. 2,3-Bis(bromomethyl)-1,4-naphthoquinone **9** was prepared according to literature by a double bromomethylation procedure starting from 1,4-naphthoquinone.[19] An alternative procedure reported in literature consists of the radical bromination of 2,3-dimethyl-1,4-naphthoquinone **6**.[20] The latter procedure is not preferred because it is also starting from 2,3-dimethyl-1,4-naphthoquinone **6**. Compound **9** proved to have limited stability and should be used within one week. Benzo[*f*]isoindole-4,9-diones **1a** and **1b** were obtained in reasonable yield after reaction of 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** with isopropylamine or *tert*-butylamine in diethyl ether at 0 °C for 30 minutes (Scheme 1). After the first substitution reaction, a second intramolecular nucleophilic substitution takes place to form 2,3-dihydrobenzo[*f*]isoindoles **10a** and **10b**. These intermediates **10a**,**b** are

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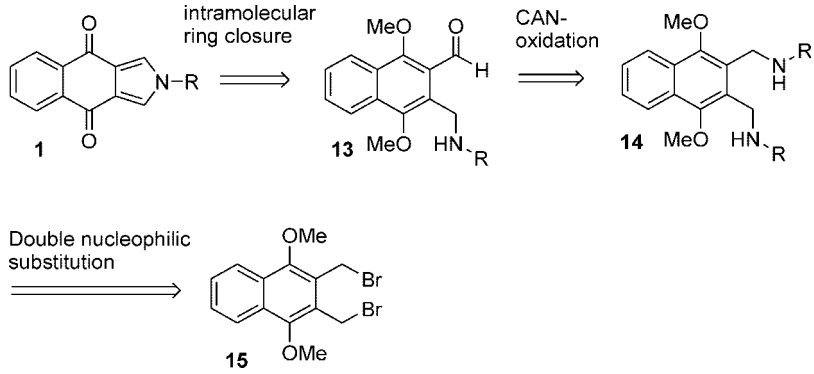
SCHEME 3



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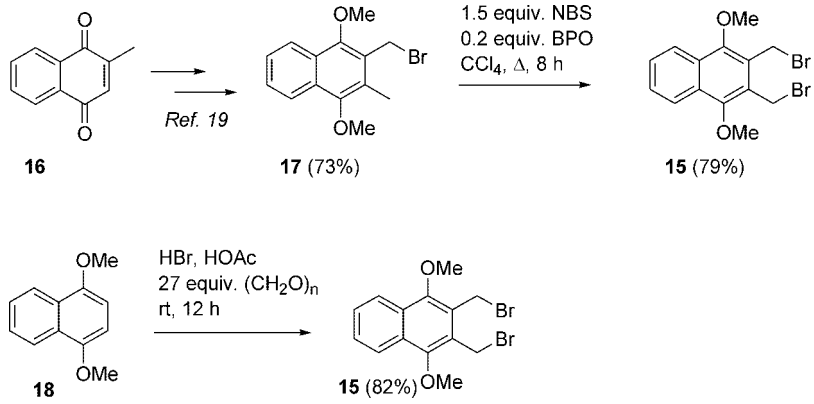


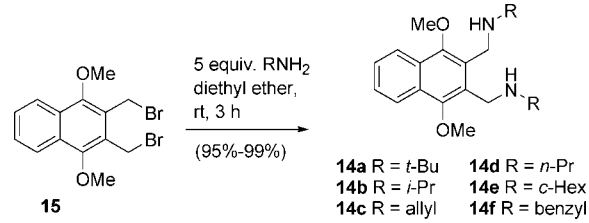
not stable and are oxidized spontaneously by oxygen in the air to the benzo[*f*]isoindole-4,9-diones **1a** and **1b** in 61% and 56%, respectively.

The obtained yields are rather moderate and it was felt that there was room for more improvement. During the course of our research towards 2-azaanthraquinones it was found that the reaction of amine **11** with cerium(IV) ammonium nitrate (CAN) did not give the expected oxidation towards a quinone but resulted in 3-bromo-1,4-dimethoxy-2-naphthaldehyde **12** in a yield of 79% instead (Scheme 2).

The aminomethyl moiety is not stable against CAN and becomes oxidized to the aldimine, which is hydrolyzed in situ to give the corresponding aldehyde. Here it was realized that this unexpected side-reaction can be directed to our favor. Therefore, the following retrosynthetic scheme was devised (Scheme 3). Based on the observation that CAN oxidizes aminomethyl moieties towards aldehydes, it is possible to obtain compounds **13** which will ring close to form the targeted compounds **1**.

At first, a reliable synthesis of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** was required. The known 2,3-bromomethyl-3-methyl-1,4-dimethoxynaphthalene **17**[21] was brominated in a radicalar way using 1.5 equivalents of *N*-bromo succinimide (NBS) and a catalytic amount of dibenzoyl peroxide (BPO) upon heating under reflux in tetrachloromethane. In this way, the target compound **15** was prepared in 58% overall yield starting from menadione **16** on a multigram scale (Scheme 4). A more straightforward synthesis of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** was found in the double bromomethylation reaction of 1,4-dimethoxynaphthalene **18** using hydrobromic acid (33 wt% in acetic acid) with a large excess of paraformaldehyde at room temperature for 12 hours. This resulted in the synthesis of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** in 82% yield (Scheme 4).

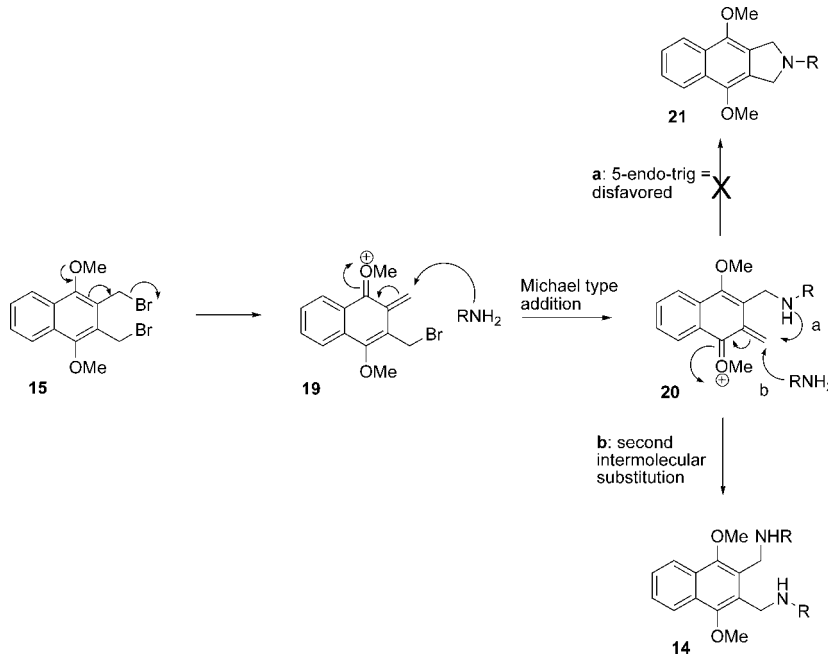
SCHEME 5



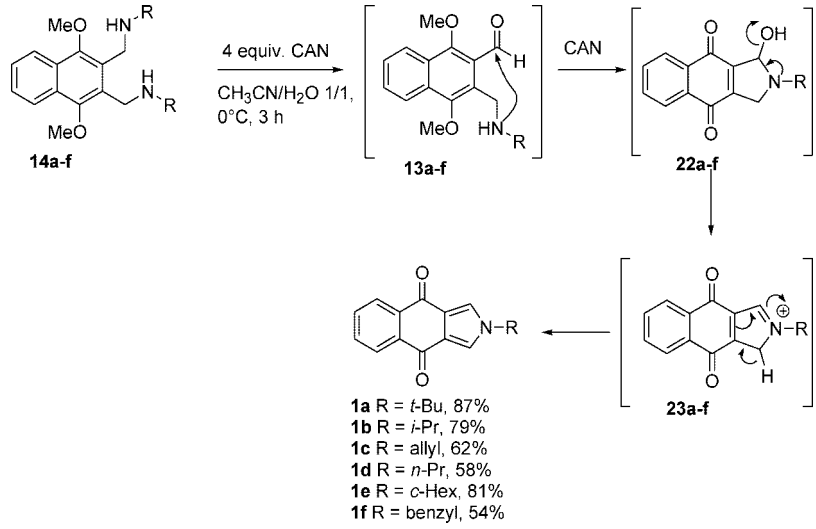
Next, it was realized that the reaction of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** with primary amines will result in double substitution products **14a–f** and not in the formation of 4,9-dimethoxy-2,3-dihydro-1*H*-benzo[*f*]isoindoles **21**. The fact that this reaction prefers to undergo twice an intermolecular substitution instead of chosing an intramolecular ring closure can be explained by the rules of Baldwin (Scheme 6). Presuming the ring closure is based on two successive S_N2-type substitutions, an intramolecular ring closure can occur because 5-exo-tet reactions are favored. This should result in 4,9-dimethoxy-2,3-dihydro-1*H*-benzo[*f*]isoindoles **21**. However, the bromide is benzylic and there is an electron-donating *ortho*-substituent present. As a consequence, this compound will very easily form *ortho*-quinodimethane **20** *via* an electron push mechanism, and the amine will add in a Michael-type way. An intramolecular ring closure of compound **20** is disfavored because it would be a 5-endo-trig ring closure.

Therefore, a second intermolecular substitution reaction is occurring, which gives rise to a double substitution product **14**. Although it can be stated that Baldwin's rules are not obliged

SCHEME 6



SCHEME 7



to be followed, they provide a good mechanistic explanation for this reaction.

Subsequently, it was thought that the formation of benzo[*f*]isoindole-4,9-diones **1** should be possible starting from the previously obtained double substitution products **14**, using a CAN-mediated oxidation (Scheme 7). It was reasoned that a first equivalent of CAN will oxidize one aminomethyl moiety to the corresponding monoaldehyde, after which a ring closure of the second aminomethyl moiety across the formed aldehyde will occur. Subsequently, further oxidation will result in the targeted benzo[*f*]isoindole-4,9-diones **1**. To confirm this statement, several 2,3-bis(aminomethyl)-1,4-dimethoxynaphthalenes **14a**−**f** were synthesized and subjected to reaction with CAN in aqueous acetonitrile. Using the theoretically required amount of CAN and conducting the reaction at 0 °C for 3 h gave nicely and in one step the predicted benzo[*f*]isoindole-4,9-diones **1a**−**f**. Mechanistically, the reaction probably proceeds via the monoaldehyde **13a**−**f**. The second unreacted amino moiety intramolecularly attacks the aldehyde in a favored 5-exo-trig ring closure reaction resulting in hemiaminals **22a**−**f**. Subsequently, hydroxide expulsion to generate an iminium ion and subsequent aromatization by loss of a proton gave rise to the targeted benzo[*f*]isoindole-4,9-diones **1a**−**f** in 54−87% yield.

Conclusions

It has been found that reaction of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** with primary amines results in the formation of double substitution products **14**. However, based on the observation that aminomethyl moieties are oxidized by cerium(IV) ammonium nitrate toward the corresponding aldehydes **13**, 2,3-bis(aminomethyl)-1,4-dimethoxynaphthalenes **14** were converted into the targeted benzo[*f*]isoindole-4,9-diones **1a**−**f**. The latter compounds were also prepared starting from 2,3-bis(bromomethyl)-1,4-naphthoquinone **9**.

Experimental Section

1. 2,3-Bis(bromomethyl)-1,4-dimethoxynaphthalene 15. Method A: Starting from 2-Bromomethyl-3-methyl-1,4-dimethoxynaphthalene 17. 2-Bromomethyl-3-methyl-1,4-dimethoxynaphthalene **7**[21] (11.6 g, 39.5 mmol) was dissolved in tetrachloromethane (100 mL) and NBS (10.32 g, 1.5 equiv) and BPO (2.5 g, 0.2 equiv) were added. The reaction mixture was stirred and heated under reflux for 8 h in daylight, after which it was cooled down in an ice bath to 0 °C. The reaction mixture was filtered, and the solvent was evaporated (tetrachloromethane was recovered and washed with sulfuric acid for reuse). The crude residue was purified by recrystallization (ether/petroleum ether) to yield 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene as orange crystals **15** (79%, 11.6 g).

Method B: Starting from 1,4-Dimethoxynaphthalene 18. 1,4-Dimethoxynaphthalene **18** (8.0 g, 118 mmol) was dissolved in a 30% solution of hydrobromic acid in acetic acid (85 mL). To this mixture was added paraformaldehyde (34 g, 1.15 mol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was then quenched with water and extracted with diethyl ether. The combined organic phases were subsequently washed with a saturated sodium bicarbonate solution, a saturated sodium bisulfite solution, and brine and dried over $MgSO_4$. After concentration in vacuo, purification by column chromatography on silica gel (EtOAc/cHexane 1:12) yielded 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene as white crystals **15** (82%, 13.2 g), mp 117−118 °C.[22] ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.09 (2H, dd, J = 3.3, 6.4 Hz), 7.54−7.58 (2H, m), 5.01 (4H, s), 4.07 (6H, s). ^{13}C NMR (63 MHz, $CDCl_3$): δ 152.2 (C_{quat}), 129.0 (C_{quat}), 127.4 (CH_{ar}), 125.8 (C_{quat}), 123.2 (CH_{ar}), 62.6 (CH_3), 24.7 (CH_2). IR (ATR): ν_{max} 1352, 1213, 1036, 778, 711 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 376/374/372 (M^+, 18/35/18), 296 (23), 295 (97), 294 (21), 293 (96), 214 (50), 200 (94), 199 (100), 171 (52), 141 (78), 139 (62), 128 (79), 115 (83). Anal. Calcd for $C_{14}H_{14}Br_2O_2$: C 44.95, H 3.77. Found: C 45.21, H 3.89.

2. 2,3-Bis(bromomethyl)-1,4-naphthoquinone 9. Method A: Starting from 2,3-Bis(bromomethyl)-1,4-dimethoxynaphthalene 15. To a flask containing a solution of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** (0.374 g, 1 mmol) in acetonitrile/dichloromethane 4:1 (5 mL) was added dropwise an aqueous solution of CAN (1.64 g, 3 equiv in 1 mL H_2O). After 30 min of stirring at room temperature, the reaction mixture was diluted with ethyl acetate (5 mL), poured in water (10 mL), extracted with ethyl acetate (3 × 5 mL), and dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel (petroleum ether/ethyl acetate 92:8) yielded 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** as yellow crystals (0.3 g, 87%).

Method B: Starting from 1,4-Naphthoquinone. This method has been developed by Ferreira[19] and yielded 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** in 43%. Only ^{1}H NMR spectra were reported.[19] Other spectral data are completed here. Mp: 153−154 °C (lit. 154 °C,[19] 153−154 °C[20]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.56 (4H, s, 2 × CH_2), 7.73−7.79 (2H, m, 2 × CH_{ar}), 8.10−8.16 (2H, m, 2 × CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (2 × CH_2), 127.0 (2 × CH_{ar}), 131.7 (2 × C_{quat}), 134.5 (2 × CH_2), 143.6 (C_{quat}), 182.4 (2 × C═O). IR (ATR): ν_{max} 1668 cm^{-1}. MS (ES^+) *m/z* (%): 342/344/346 (M^+, 100).

3. General Procedure for the Preparation of (1,4-Dimethoxynaphthalene-2,3-diyl)dimethylamine 14. To a stirred solution of 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **15** (0.15 g, 0.4 mmol) in diethyl ether (5 mL) was added the appropriate amine (5 equiv) at room temperature. The reaction mixture was stirred for 3 h after which it was filtered, and the solvent was evaporated in vacuo to yield the (1,4-dimethoxynaphthalene-2,3-diyl)dimethylamine **14**, which was used in the next step without purification (yield 95−99%). (1,4-Dimethoxynaphthalene-2,3-diyl)bis(*N-tert*-butyl)dimethylamine **14a**: red-pink crystals, mp 72.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (18H, s, 2 × $C(CH_3)_3$), 3.96 (4H, s, 2 × CH_2), 3.98 (6H, s, 2 × MeO), 7.44−7.50 (2H, m, 2 × CH_{ar}), 8.02−8.07 (2H, m, 2 × CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.1 (6 × CH_3), 38.7 (2 × CH_2), 51.1 (2 × C_{quat}), 63.0 (2 × MeO), 122.6 (2 × CH_{ar}), 125.9 (2 × CH_{ar}), 128.4 (2 × C_{quat}), 130.2 (2 × C_{quat}), 151.1 (2 × C_{quat}). IR (ATR): ν_{max} 3314, 1356 cm^{-1}. MS (ES^+) *m/z* (%): 359 ($M + H^+$, 100). Anal. Calcd for $C_{22}H_{34}N_2O_2$: C 73.70, H 9.56, N 7.81. Found: C 73.48, H 9.71, N 7.75.

4. General Procedure for the Synthesis of Benzo[*f*]isoindole-4,9-diones 1a,b Starting from 2,3-Bis(bromomethyl)-1,4-naphthoquinone 9. To a stirred solution of 2,3-bis(bromomethyl)-1,4-naphthoquinone **9** (0.25 g, 0.72 mmol) in diethyl ether (5 mL) was added the appropriate amine at 0 °C. The reaction mixture was stirred for 30 min and subsequently filtered over a silica patch. The filter cake was washed and the solvent evaporated in vacuo to yield crude benzo[*f*]isoindole-4,9-dione **1a,b**. The crude reaction mixture was purified by flash chromatography. 2-*tert*-Butyl-2*H*-benzo[*f*]isoindole-4,9-dione **1a**: Purification by flash chromatography over aluminium oxide (EtOAc/petroleum ether 1:4) provided a yellow powder (0.052 g, 93%), mp 172−173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (9H, s, 3 × CH_3), 7.62 (2H, s, CH-1 and CH-3), 7.68–7.70 (2H, m, 2 × CH_{ar}), 8.25 (2H, dd, J = 3.4, 5.8 Hz, 2 × CH_{ar}). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.5 (3 × CH_3), 57.5 (C_{quat}), 121.8 (CH-1 and CH-3), 122.6 (2 × C_{quat}), 126.9 (2 × CH_{ar}), 133.0 (2 × CH_{ar}), 135.6 (2 × C_{quat}), 180.4 (2 × C═O). IR (ATR): ν_{max} 3125, 1648, 1531, 1221, 970, 710 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 254 ($M + H^+$, 100). Anal. Calcd for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53, found: C 75.69, H 6.10, N 5.46.

5. General Procedure for the Synthesis of Benzo[*f*]isoindole-4,9-diones 1 using CAN-Oxidation of (1,4-Dimethoxynaphthalene-2,3-diyl)dimethylamine 14. To a stirred solution of (1,4-dimethoxynaphthalene-2,3-diyl)dimethylamine **14** (1.3 mmol) in acetonitrile (5 mL) was added CAN (4.04 g, 4 equiv) in water (5 mL) at 0 °C. The reaction mixture was allowed to reach ambient temperature over a period of 30 min. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic solution was dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude reaction mixture was purified by flash chromatography over silica gel using dichloromethane as eluens. 2-*tert*-Butyl-2*H*-benzo[*f*]isoindole-4,9-dione **1a**: yield 81%; spectral data, vide supra.

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Supporting Information Available: General experimental methods, spectral data of compounds **14b−f** and **1b−f**, and ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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