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Total Synthesis of Norbadione A†

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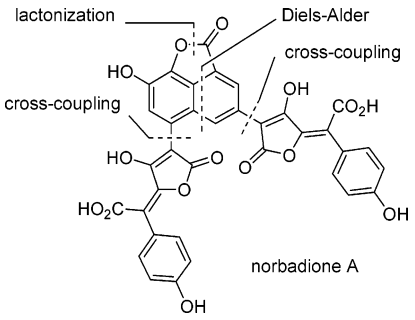

A short, convergent synthesis of the mushroom pigment norbadione A is described. The construction of an appropriately substituted naphtholactone intermediate involved a regioselective Diels−Alder reaction between a bis(triisopropylsilyloxy)diene and 2,6-dichlorobenzo-1,4-quinone. A double Suzuki−Miyaura cross-coupling between a diboronate and two identical enol triflates was another key feature of the synthesis.

Introduction

Norbadione A (**1**) is a pigment of the common edible mushroom bay boletus [*Xerocomus badius* (Fr.) Kühn. ex Gilb.], which was first isolated by Steglich.[1] It was also found in another mushroom, *Pisolithus tinctorius* (Pers.) Coker & Couch, by Gill.[2] Following the Chernobyl nuclear reactor accident, it was found that specimens of several mushrooms, including bay boletus, collected in Europe contained significant amounts of cesium 137.[3] Steglich et al. showed that in contaminated bay boletus, ^{137}Cs was associated with norbadione A and with badione A, a related pigment.[4] Complexation of cesium by norbadione A was then further characterized.[5−7] This compound was also shown to display important antioxidant properties.[8] Structurally, **1** is a naphtholactone related to a more common family of mushroom pigments, the pulvinic acids. Indeed, it has been proposed that the biosynthesis of norbadione A as well as badione A involves two molecules of a pulvinic acid, xerocomic acid.[1,2b,9] Here we report the first total synthesis of this natural product.

† Dedicated to the memory of Dr. Charles Mioskowski (deceased June 2, 2007).

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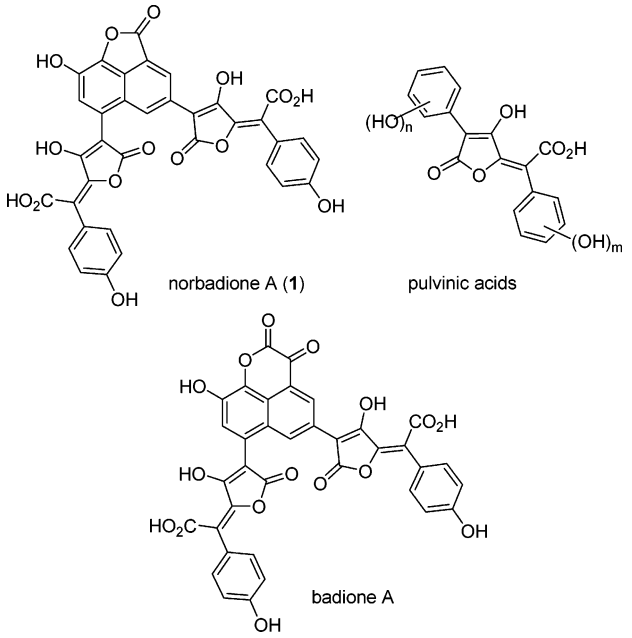


Results and Discussion

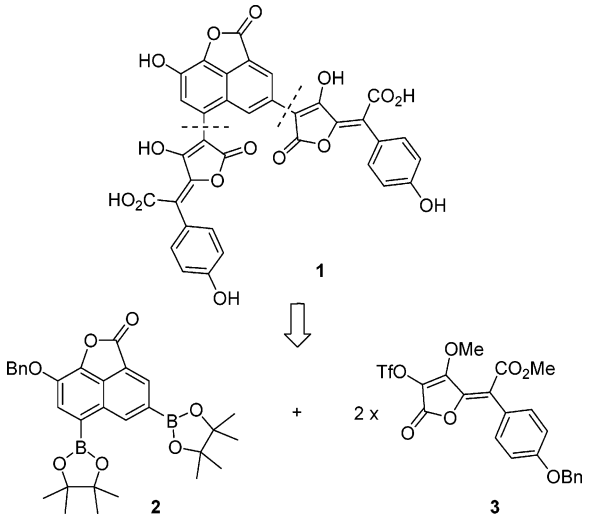
The strategy for this synthesis was based primarily on two bond disconnections (Scheme 1). Suzuki−Miyaura cross-couplings between naphtholactone **2** containing two boronate functions and 2 equiv of alkenyl triflate **3** would lead to a protected precursor of norbadione A.

Pulvinic compounds have been synthesized from triflates such as **3** and aryl boronates, including a 1,7-bis(boronated)naphthalene,[10] or aryl boronic acids.[11] Triflate **3** was previously prepared from the corresponding enol,[10] obtained via the cyclocondensation of oxalyl chloride and a 1,3-bis(trimethylsilyloxy)diene, according to the method developed by Langer.[12,13]

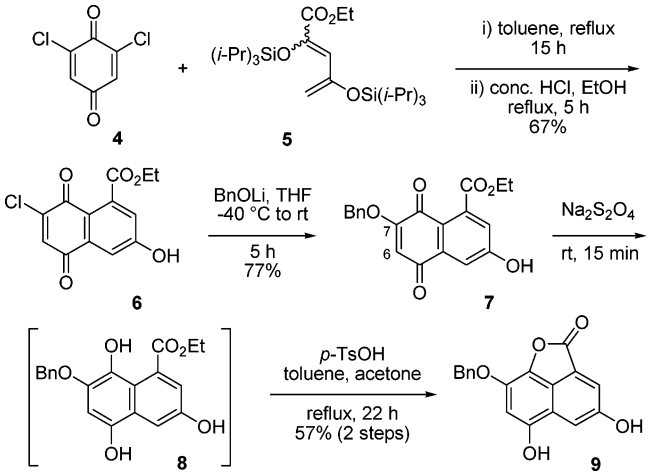
The boronate functions of the naphtholactone **2** were intended to be introduced from a ditriflate, derived from the corresponding diphenol **9**, via a palladium-mediated double borylation. The synthesis of **9** started by the Diels−Alder reaction of commercially available 2,6-dichloro-1,4-benzoquinone (**4**) with bis(triisopropylsilyloxy)diene **5**, prepared in one step from ethyl 2,4-dioxovalerate, in refluxing toluene (Scheme 2). Treatment of the crude product with HCl in ethanol at reflux allowed the aromatization to naphthoquinone **6**,[14] obtained in 67% yield.

It was then necessary to introduce an oxygenated function in place of the chlorine atom, via the conjugate addition of an oxygen-centered nucleophile, followed by chloride elimination. In preliminary studies, treatment of **6** with KOH in ethanol led to mixtures of regioisomers, hydroxylated on either carbon atom

SCHEME 1. Retrosynthetic Analysis of Norbadione A (1)



SCHEME 2. Preparation of Lactone 9



C-6 or C-7. Finally, by employing excess lithium benzylate as the nucleophile in THF at low temperature, a clean conversion to naphthoquinone **7**, obtained as a single adduct, was achieved. Moreover, an adequate protecting group for the hydroxyl function was thus introduced. The reduction of naphthoquinone **7** with sodium dithionite then led to hydroquinone **8**, a very unstable compound, prone to reoxidizing readily. Hence, it was not isolated but directly engaged in an acid-mediated lactonization, affording lactone **9** (57% yield over two steps). An X-ray crystallographic analysis of lactone **9** confirmed the regioselectivity of the Diels−Alder reaction and that of the introduction of the benzyloxy group (see ORTEP drawing in Figure 1).

Lactone **9** was readily converted to the ditriflate **10** (Scheme 3). When applied to this compound, the borylation method of Masuda et al.,[15] employing pinacolborane and $PdCl_2$(dppf) in dioxane, did not yield any diboronate **2** but instead naphtholactone **11**, which formed readily at room temperature. This indicated that pinacolborane had acted as a hydride source.

An extensive screening of conditions was performed, using bis(pinacolato)diboron (**12**) as the borylation agent,[16] in order

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(12) (a) Langer, P.; Stoll, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1803−1805. (b) Langer, P.; Eckardt, T. *Synlett* **2000**, 844−846. (c) Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.* **2000**, *6*, 3204−3214. (d) Langer, P. *Synlett* **2006**, 3369−3381.

(13) We recently described the synthesis of an iodide analogous to triflate **3**, according to a different reaction scheme, and its use in Suzuki−Miyaura cross-couplings. See: Willis, C.; Bodio, E.; Bourdreux, Y.; Billaud, C.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 6421−6424.

(14) For selected examples, see: (a) Boisvert, L.; Brassard, P. *J. Org. Chem.* **1988**, *53*, 4052−4059. (b) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843−5844. (c) Cameron, D. W.; Skene, C. E. *Aust. J. Chem.* **1996**, *49*, 617−624.

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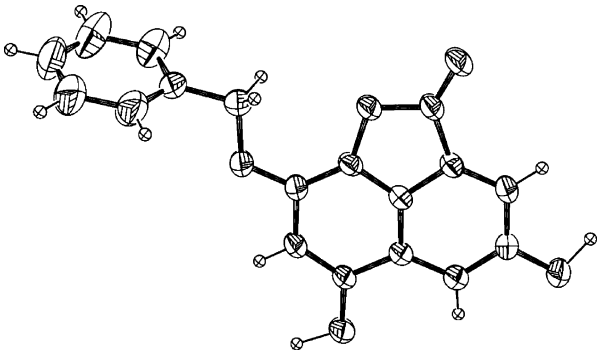
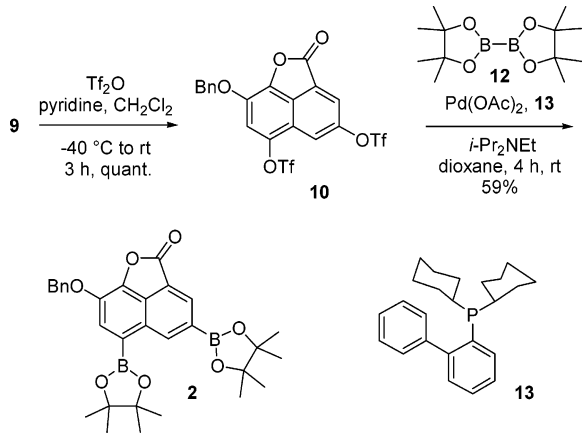
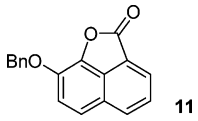


FIGURE 1. ORTEP drawing of the X-ray structure of lactone **9**.

SCHEME 3. Preparation of Diboronate 2



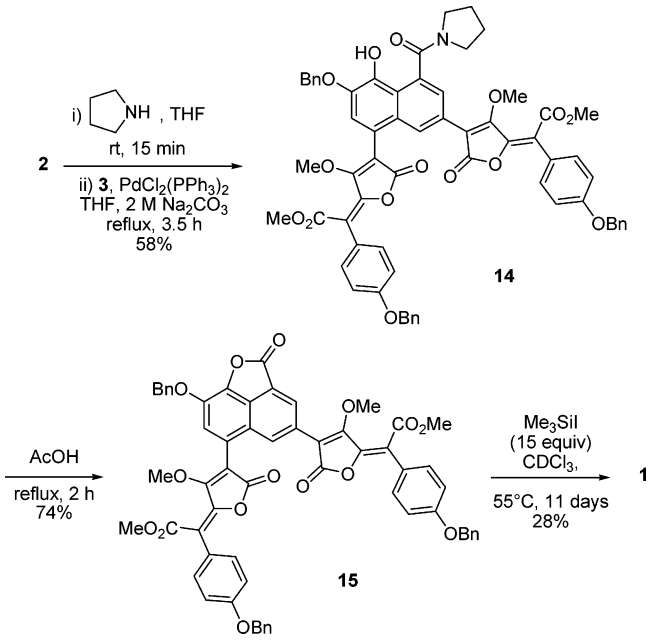
to avoid any reduction. Eventually, diboronate **2** was obtained in 59% yield by treatment of ditriflate **10** with **12**, in the presence of $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl (**13**),[17] and diisopropylethylamine in dioxane. The reaction actually proceeded at *room temperature*. To the best of our knowledge, all the reported palladium-mediated borylations of aryl halides or triflates using **12** require heating at 50−100 °C.



Both components necessary for the key cross-coupling were thus available. Conditions that we had used previously in similar couplings[10] involving triflate **3** [$PdCl_2(PPh_3)_2$, refluxing mixture of THF and 2 M Na_2CO_3] did not lead to the expected adduct when applied to diboronate **2**. Other conditions and catalysts tested did not give better results. The low reactivity of diboronate **2** was attributed to the presence of three electron-withdrawing groups on the naphthalene. The lactone might also have reacted with the base necessary for the activation of the boronates. Examination of a crude product obtained under the conditions described above showed that a yellow compound, much more polar than the expected adduct, had been formed. Its spectroscopic characteristics corresponded to a hydroxyacid resulting from the opening of the expected lactone. This was proved by heating this compound in acetic acid for 6 days at 110 °C, which led to lactone **15**, albeit in a low overall yield (6%).

(17) For a palladium-catalyzed borylation of aryl halides using this phosphine and pinacolborane, see: Baudouin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271.

SCHEME 4. Completion of the Total Synthesis of Norbadione A



The coupling procedure was then modified. Prior to the other components of the coupling, 1 equiv of pyrrolidine was added to a THF solution of **2**. In the hydroxyamide formed intermediately, one of the electron-withdrawing groups, the amide carbonyl function, should not be in the same plane as the naphthalene ring and this should make the reacting species more nucleophilic. To the THF solution of hydroxyamide were then added $PdCl_2(PPh_3)_2$, 2 M Na_2CO_3, and triflate **3**. After 3.5 h at reflux, compound **14** resulting from two cross-couplings was obtained in 58% yield (Scheme 4). Treatment of this compound at reflux in acetic acid for 2 h then afforded lactone **15** (74%).

The remaining, important task was the removal of the protecting groups. We had initially scheduled to cleave the benzyl ethers and the methyl ethers and esters in several consecutive steps. However, treatment of **15** with iodotrimethylsilane[18] (15 equiv) in deuterated chloroform at 55 °C for 11 days allowed cleavage of the seven protecting groups in a single step, leading to **1** in 28% yield. The spectroscopic data of synthetic norbadione A were in full agreement with those reported for the natural product (see Supporting information).

In conclusion, the first total synthesis of the unusual mushroom pigment norbadione A has been performed via a convergent strategy. The key steps were a Diels−Alder cycloaddition employed in the preparation of an appropriately substituted naphtholactone intermediate and a double Suzuki−Miyaura coupling allowing the completion of the carbon framework of the target molecule. Application of a similar strategy to the synthesis of badione A is under way.

Experimental Section

2,4-Bis(triisopropylsilanyloxy)penta-2,4-dienoic Acid Ethyl Ester (5). A solution of ethyl 2,4-dioxovalerate (6.92 g, 43.5 mmol) in dichloromethane (250 mL) was stirred at 0 °C, under argon. Triethylamine (25 mL, 180 mmol, 4.1 equiv) and triisopropylsilyl triflate (23.5 mL, 87 mmol, 2 equiv) were successively added via

(18) Gedge, D. R.; Pattenden, G.; Smith, A. G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2127−2131.

syringe at 0 °C, and then the reaction mixture was allowed to warm slowly to room temperature over 5.5 h. Ether (200 mL) was added to the red solution obtained. The organic phase was washed successively with 1 N aqueous NaOH solution (3 × 100 mL) and saturated aqueous $NaHCO_3$ solution (3 × 100 mL), dried over $MgSO_4$, then filtered, and concentrated under vacuum, leading to 23.6 g of crude product. Silica gel chromatography (pentane containing 1% Et_3N) afforded diene **5** as a pale yellow oil (14.2 g, 70%). A single isomer was obtained, but its configuration was not elucidated. IR (NaCl) ν_{max}: 680, 738, 770, 836, 883, 920, 951, 1032, 1139, 1229, 1271, 1367, 1388, 1465, 1630, 1723, 2868, 2893, 2946 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 7 Hz, 18 H), 1.10 (d, J = 7 Hz, 18 H), 1.15−1.25 (m, 3 H), 1.28−1.37 (m, 3 H), 1.32 (t, J = 7 Hz, 3 H), 4.23 (q, J = 7 Hz, 2 H), 4.73 (d, J = 1.5 Hz, 1 H), 5.21 (s, 1 H), 6.11 (d, J = 1.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 14.1, 14.2, 18.1, 18.2, 61.4, 99.1, 115.6, 141.6, 151.5, 165.3. MS (ESI-TOF) *m*/*z* 471 (100, $[M + H]^+$). HRMS (ESI-TOF) calcd for $C_{25}H_{50}NaO_4Si_2$ $[M + Na]^+$ 493.3145, found 493.3127.

7-Chloro-3-hydroxy-5,8-dioxo-5,8-dihydro-naphthalene-1-carboxylic Acid Ethyl Ester (6). A solution of diene **5** (11.47 g, 24 mmol, 1.2 equiv) in toluene (25 mL) was added via syringe to a solution of 2,6-dichloro-1,4-benzoquinone (3.6 g, 20 mmol) in toluene (13 mL), under argon. The mixture was refluxed overnight, then cooled to room temperature, and concentrated under vacuum. A solution of concentrated HCl (1.8 mL) in ethanol (45 mL) was added to the residue, and then the mixture was heated at 100 °C for 5 h. After cooling down to room temperature, ethyl acetate (100 mL) was added. The organic phase was washed twice with water (50 mL), dried over $MgSO_4$, then filtered, and concentrated under vacuum. Silica gel chromatography (8:2 pentane/AcOEt) afforded naphthoquinone **6** as a orange solid (3.76 g, 67%). Mp = 180 °C. TLC: R_f = 0.15 (8:2 pentane/AcOEt). IR (KBr pellet) ν_{max}: 574, 857, 881, 1012, 1063, 1102, 1178, 1212, 1239, 1271, 1318, 1346, 1378, 1469, 1560, 1588, 1670, 1727, 2985, 3073, 3402 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ 1.35 (t, J = 7.3 Hz, 3 H), 4.39 (q, J = 7.3 Hz, 2 H), 7.17 (d, J = 2.4 Hz, 1 H), 7.33 (s, 1 H), 7.52 (d, J = 2.4 Hz, 1 H). ^{13}C NMR (75 MHz, acetone-d_6): δ 14.2, 62.4, 114.2, 120.0, 121.3, 135.9, 136.2, 139.2, 147.0, 163.5, 168.5, 176.5, 182.7. Anal. Calcd for $C_{13}H_9O_5Cl$: C, 55.63; H, 3.23; Cl, 12.63. Found: C, 55.83; H, 3.44; Cl, 12.70.

7-Benzyloxy-3-hydroxy-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylic Acid Ethyl Ester (7). A solution of butyllithium (55 mL, 1.58 M in hexanes, 87 mmol, 6.5 equiv) was added dropwise via syringe to a solution of benzyl alcohol (12.5 mL, 120 mmol, 9 equiv) in THF (55 mL), cooled at −40 °C, under argon. After 1 h of stirring at −40 °C, a solution of naphthoquinone **6** (3.76 g, 13.4 mmol) in THF (30 mL) was added dropwise, and then the stirring was continued for 1 h at −40 °C. The reaction mixture turned to red. It was allowed to warm to room temperature over 5 h. Aqueous 3 N HCl (50 mL) was added, and then the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated under vacuum, leading to a solid that was washed with ether. Naphthoquinone **7** was thus obtained as a yellow solid (3.64 g, 77%). Mp = 245 °C. TLC: R_f = 0.18 (8:2 pentane/AcOEt). IR (KBr pellet) ν_{max}: 699, 743, 848, 1022, 1099, 1184, 1232, 1293, 1350, 1379, 1456, 1494, 1602, 1633, 1675, 1733, 2987, 3065, 3269 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ 1.33 (t, J = 7.2 Hz, 3 H,), 4.37 (q, J = 7.2 Hz, 2 H), 5.22 (s, 2 H), 6.37 (s, 1 H), 7.10 (s, 1 H), 7.35−7.55 (m, 6 H), 10.25 (br s, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 14.3, 62.2, 71.9, 111.0, 113.7, 119.2, 121.3, 129.0, 129.4, 129.5, 136.1, 136.13, 138.5, 160.8, 163.3, 168.8, 178.3, 184.4. HRMS (ESI-TOF) calcd for $C_{20}H_{16}NaO_6$ $[M + Na]^+$ 375.0845, found 375.0818. Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 67.86; H, 4.55.

8-Benzyloxy-4,6-dihydroxynaphtho[1,8-*bc*]furan-2-one (9). The solvents and aqueous solutions used in this synthesis were all degassed with a stream of argon for 30 min. A saturated aqueous solution of sodium dithionite (87 mL) was added to a solution of naphthoquinone **7** (1 g, 2.84 mmol) in acetone (150 mL) placed under argon, under vigorous stirring. The initial yellow solution turned red during the addition. After stirring for 15 min at room temperature, the reaction mixture, which had become orange, was poured into a separatory funnel placed in a nitrogen-filled glovebox. Water (50 mL) was added, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, then filtered, and concentrated under vacuum. All of these operations were carried out under an argon atmosphere. The reddish oil obtained was then dissolved in a mixture of toluene (32 mL) and acetone (10 mL). The solution was equipped with a Dean−Stark apparatus, the trap of which was filled with 4 Å molecular sieves, and *p*-toluenesulfonic acid (63.3 mg, 0.37 mmol, 0.13 equiv) was added. The reaction mixture was refluxed for 22 h. After cooling to room temperature, ethyl acetate (50 mL) was added. The organic phase was washed with brine (2 × 30 mL), dried over $MgSO_4$, then filtered, and concentrated under vacuum. Ether was added to the residue, leading to the formation of a precipitate that was removed by filtration. The solid obtained (160 mg) was essentially the naphthoquinone **7**. The filtrate was concentrated under vacuum. Silica gel chromatography (98:2 CH_2Cl_2/CH_3OH) afforded lactone **9** as an orange solid (500 mg, 57%). Mp = 228 °C. TLC: R_f = 0.30 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet) ν_{max}: 708, 997, 1077, 1149, 1172, 1202, 1248, 1292, 1374, 1409, 1462, 1527, 1615, 1653, 1727, 3291, 3520 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ 5.47 (s, 2 H), 6.62 (s, 1 H), 7.25−7.45 (m, 3 H), 7.53 (d, J = 1.7 Hz, 2 H), 7.68 (d, J = 1.7 Hz, 1 H), 7.73 (d, J = 1.7 Hz, 1 H), 9.26 (br s, 2 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 73.6, 105.4, 113.3, 117.3, 120.4, 121.0, 127.0, 127.4, 128.8, 129.0, 129.3, 137.6, 138.1, 151.0, 157.9, 167.4. HRMS (ESI-TOF) calcd for $C_{18}H_{12}NaO_5$ $[M + Na]^+$ 331.0582, found 331.0558.

Trifluoromethanesulfonic Acid 8-Benzyloxy-2-oxo-6-trifluoromethanesulfonyloxy-2*H*-naphtho[1,8-*bc*]furan-4-yl Ester (10). A solution of diphenol **9** (290 mg, 0.94 mmol) in dichloromethane (4.5 mL) and pyridine (1.5 mL) was cooled at 0 °C, under argon. Triflic anhydride (0.50 mL, 2.9 mmol, 3.2 equiv) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature over 3.3 h, and then ethyl acetate (20 mL) was added. The organic phase was washed thrice with 1 N aqueous HCl, dried over $MgSO_4$, then filtered, and concentrated under vacuum. The solid obtained was washed with pentane and dried. Compound **10** was thus obtained as a yellow solid (538 mg, quantitative). Mp = 85 °C. TLC: R_f = 0.70 (9:1 pentane/AcOEt). IR (KBr pellet) ν_{max}: 506, 609, 740, 752, 840, 896, 933, 965, 1001, 1030, 1070, 1116, 1139, 1223, 1250, 1270, 1358, 1428, 1455, 1481, 1500, 1616, 1653, 1803, 3091 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ 5.68 (s, 2 H), 7.36−7.47 (m, 3 H), 7.58−7.61 (d, J = 6.7 Hz, 2 H), 7.83 (s, 1 H), 8.43 (d, J = 1.7 Hz, 1 H), 8.53 (d, J = 1.7 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 74.5, 119.5, 119.7 (q, J_{C-F} = 318 Hz), 119.7 (q, J_{C-F} = 318 Hz), 119.9, 120.9, 123.0, 123.5, 128.8, 129.3, 129.4, 130.4, 134.0, 136.7, 139.9, 141.6, 150.4, 164.6. HRMS (ESI-TOF) calcd for $C_{21}H_{14}F_6NaO_{10}S_2$ $[M + Na + MeOH]^+$ 626.9830, found 626.9813.

8-Benzyloxy-4,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphtho[1,8-*bc*]furan-2-one (2). Degassed 1,4-dioxane (3.5 mL) and anhydrous diisopropylethylamine (174 μL, 1 mmol, 5.7 equiv) were added to a mixture of ditriflate **10** (100 mg, 0.175 mmol, 1 equiv), palladium(II) acetate (3.9 mg, 0.0175 mmol, 0.1 equiv), 2-dicyclohexylphosphinobiphenyl (24.5 mg, 0.07 mmol, 0.4 equiv), and bis(pinacolato)diboron (133 mg, 0.52 mmol, 3 equiv) placed in a flask under argon. The suspension obtained was stirred for 4 h. The initial orange mixture rapidly turned to brown. A saturated aqueous NH_4Cl solution (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated under vacuum. Methanol was added to the solid residue obtained. The solid that precipitated was recovered on a sintered

glass and dried. The filtrate was concentrated, and methanol was added. The solid that precipitated was recovered. The two portions were combined, leading to diboronate **2** as a beige solid (55 mg, 59%). Mp = 221−224 °C. TLC: R_f = 0.50 (9:1 pentane/AcOEt). IR (KBr pellet) ν_{max}: 700, 740, 847, 970, 1046, 1084, 1145, 1214, 1345, 1374, 1500, 1628, 1790, 2929, 2980 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 12 H), 1.43 (s, 12 H), 5.61 (s, 2 H), 7.25−7.45 (m, 3 H), 7.52 (d, J = 7.0 Hz, 2 H), 7.90 (s, 1 H), 8.57 (s, 1 H), 9.19 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 73.4, 84.3, 84.4, 118.4, 128.0, 128.4, 128.7, 128.8, 132.5, 133.4, 136.8, 138.6, 141.1, 167.2. HRMS (ESI-TOF) calcd for $C_{30}H_{34}{}^{11}B_2NaO_7$ [M + Na]$^+$ 551.2388, found 551.2408.

8-Benzyloxynaphtho[1,8-*bc*]furan-2-one (11). A reaction carried out as above but using pinacolborane instead of bis(pinacolato)diboron did not lead to diboronate **2** but afforded lactone **11**, isolated as the main product. This compound was identified on the basis of its ^{1}H NMR spectrum and its mass spectrum. TLC: R_f = 0.16 (95:5 pentane/ether). IR (NaCl) ν_{max}: 2924, 2854, 1774, 1457, 1253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (s, 2 H), 7.31 (d, J = 8 Hz, 1 H), 7.34−7.42 (m, 3 H), 7.51 (d, J = 7.4 Hz, 1 H), 7.61 (d, J = 9 Hz, 1 H), 7.69 (d, J = 7.5 Hz, 1 H), 8.09 (m, 1 H), 8.15 (d, J = 7.1 Hz, 1 H). MS (ESI-TOF) m/z: 277 [M + H]$^+$ (100%). HRMS (ESI-TOF) calcd for $C_{18}H_{12}NaO_3$ [M + Na]$^+$ 299.0684, found 299.0708.

{4-[3-Benzyloxy-7-{5-[(4-benzyloxyphenyl)methoxycarbonylmethylene]-4-methoxy-2-oxo-2,5-dihydrofuran-3-yl}-4-hydroxy-5-(pyrrolidine-1-carbonyl)naphthalen-1-yl]-3-methoxy-5-oxo-5*H*-furan-2-ylidene}(4-benzyloxyphenyl)acetic Acid Methyl Ester (14). Pyrrolidine (29 μL, 0.347 mmol, 1.2 equiv) was slowly added to a solution of diboronate **2** (150 mg, 0.284 mmol) in THF (25 mL), under argon. After stirring at room temperature for 15 min, $PdCl_2(PPh_3)_2$ (80 mg, 0.114 mmol, 0.4 equiv) and triflate **3** (438 mg, 0.852 mmol, 3 equiv) were successively added. Argon was bubbled in the suspension, and then an aqueous 2 M Na_2CO_3 solution (6.1 mL) was added. The reaction mixture was refluxed under argon for 3.5 h. Its color turned from red to black after about 15 min. After cooling to room temperature, brine (50 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (ether, then CH_2Cl_2, then 1:1 CH_2Cl_2/ether, then 1:1 CH_2Cl_2/AcOEt, then AcOEt) afforded amide **14** as an orange solid (178 mg, 58%). Mp = 106−108 °C. TLC: R_f = 0.45 (AcOEt). IR (NaCl) ν_{max}: 614, 679, 697, 737, 783, 834, 887, 920, 977, 1046, 1098, 1132, 1183, 1230, 1254, 1285, 1323, 1386, 1453, 1510, 1602, 1627, 1733, 1769, 2875, 2950, 3033 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6): δ 1.85 (m, 2 H), 1.92 (m, 2 H), 3.15 (m, 2 H), 3.55 (s, 3 H), 3.59 (m, 2 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 5.20 (s, 2 H), 5.21 (s, 2 H), 5.39 (s, 2 H), 7.12 (d, J = 9.0 Hz, 2 H), 7.13 (d, J = 9.0 Hz, 2 H), 7.32−7.43 (m, 9 H), 7.48−7.56 (m, 7 H), 7.63 (d, J = 9.0 Hz, 2 H), 7.67 (d, J = 9.0 Hz, 2 H), 7.77 (s, 1 H), 8.12 (d, J = 1.5 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 24.2, 25.5, 45.3, 48.0, 52.0, 52.1, 60.2, 61.2, 69.60, 69.62, 71.5, 103.7, 106.4, 115.1, 115.5, 115.7, 118.4, 120.4, 123.95, 123.98, 125.1, 125.5, 127.5, 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 130.5, 134.4, 136.91, 136.94, 140.1, 159.55, 159.57, 162.8, 163.8, 166.45, 166.47, 167.1, 167.5, 169.2. HRMS (ESI-TOF) calcd for $C_{64}H_{53}NNaO_{15}$ [M + Na]$^+$ 1098.3313, found 1098.3311.

[4-(8-Benzyloxy-4-{5-[(4-benzyloxyphenyl)methoxycarbonylmethylene]-4-methoxy-2-oxo-2,5-dihydrofuran-3-yl}-2-oxo-2*H*-naphtho[1,8-*bc*]furan-6-yl)-3-methoxy-5-oxo-5*H*-furan-2-ylidene](4-benzyloxyphenyl)acetic Acid Methyl Ester (15). A solution of hydroxyamide **14** (68 mg, 0.063 mmol) in acetic acid (8 mL) was heated at reflux under argon for 2 h. After cooling to room temperature, water (40 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (gradient from 1:9 to 1:1 AcOEt/pentane) afforded lactone **15** as an yellow solid (47 mg, 74%). Mp = 132−134 °C. TLC: R_f = 0.45 (6:4 pentane/AcOEt). IR (NaCl) ν_{max}: 515, 548, 614, 696, 736, 780, 834, 901, 1510, 920, 976, 1045, 1132, 1183, 1227, 1284, 1310, 1375, 1454, 1431, 1600, 1630, 1732, 1772, 2949, 3032 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 6 H), 5.13 (s, 4 H), 5.64 (s, 2 H), 7.02 (d, J = 8.9 Hz, 2 H), 7.03 (d, J = 8.8 Hz, 2 H), 7.34−7.53 (m, 16 H), 7.67 (d, J = 8.9 Hz, 2 H), 7.70 (d, J = 8.8 Hz, 2 H), 8.15 (s, 1 H), 8.37 (s, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 52.88, 52.90, 61.4, 62.1, 70.0, 73.6, 101.6, 105.9, 115.2, 117.7, 117.9, 119.7, 123.3, 123.4, 124.6, 127.4, 127.9, 128.1, 128.5, 128.62, 128.64, 128.9, 130.99, 131.03, 131.2, 132.4, 133.6, 135.9, 136.28, 136.30, 138.33, 138.4, 139.4, 159.8, 159.9, 163.8, 164.7, 165.7, 166.8, 166.9, 167.68, 167.74. HRMS (ESI-TOF) calcd for $C_{60}H_{44}NaO_{15}$ [M + Na]$^+$ 1027.2578, found 1027.2593.

[4-(4-{5-[Carboxy-(4-hydroxyphenyl)-methylene]-4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl}-8-hydroxy-2-oxo-2*H*-naphtho[1,8-*bc*]furan-6-yl)-3-hydroxy-5-oxo-5*H*-furan-2-ylidene](4-hydroxyphenyl)acetic Acid (Norbadione A) (1). A solution of lactone **15** (47 mg, 0.047 mmol) in deuterated chloroform (2.25 mL) was placed in a tube wrapped in an aluminum foil, under argon. Iodotrimethylsilane (100 μL, 0.705 mmol, 15 equiv) was added dropwise. The tube was closed by a screwed cap, and the solution was heated at 55 °C. Samples were taken every 2−3 days and analyzed by ^{1}H NMR. After 11 days, the reaction mixture was cooled at 0 °C, and methanol (5 mL) was added. After stirring for 30 min, the solvents were eliminated under vacuum. The residue was subjected to reverse phase chromatography (10 μm C18, 40:60:1 water/MeOH/acetic acid). The solid obtained was dissolved in acetone. Concentrated HCl was added until formation of a precipitate, and the solid was recovered by filtration. This operation was repeated twice, leading to norbadione A (**1**) as a red solid (8.9 mg, 28%). Mp > 300 °C (lit.[1] >300 °C). Reverse phase TLC: R_f = 0.45 (40:60:1 water/MeOH/acetic acid). IR (NaCl) ν_{max}: 595, 671, 704, 746, 794, 904, 959, 1046, 1180, 1046, 1180, 1259, 1328, 1391, 1466, 1514, 1571, 1645, 1749, 2853, 2922, 3376 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6): δ 6.92 (d, J = 8.6 Hz, 2 H), 6.94 (d, J = 8.6 Hz, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.57 (s, 1 H), 8.91 (d, J = 1 Hz, 1 H), 9.06 (d, J = 1 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 103.4, 103.6, 115.4, 115.5, 118.4, 118.5, 120.6, 124.0, 124.4, 125.0, 125.1, 126.5, 126.6, 129.7, 131.0, 131.9, 132.59, 132.62, 133.7, 137.8, 154.3, 154.6, 158.46, 158.54, 163.3, 163.4, 166.87, 166.92, 167.1, 173.7, 173.9.

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Supporting Information Available: Crystallographic data of lactone **9** in CIF format and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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