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Studies on the Total Synthesis of Lactonamycin: Synthesis of the Fused Pentacyclic B–F Ring Unit

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This paper describes an approach towards the total synthesis of lactonamycin with the elaboration of a key pentacyclic unit. Key steps include the synthesis of benzyl bromide **8** in eight steps and 23 % overall yield starting from 4-methoxyphenol; a high-yielding Suzuki coupling between boronic ester **9** and benzyl bromide **8**; and a Lewis acid mediated, intramolecular Friedel–Crafts acylation to obtain the fused BCDEF ring core.

Introduction

Lactonamycin (**1**)[1] and the more recently isolated lactonamycin-Z (**2**)[2] possess unique structural architectures and intriguing biological activities. The novel, highly functionalized hexacyclic aglycon core, known as lactonamycinone (**3**), contains, in the western half, a highly oxygenated fused perhydrofuranfuranone ring functionalized by a labile tertiary methoxy group, and in the eastern half, a naphtha[*e*]isoindole ring system. Both natural products contain a 2-deoxysugar unit (**1**, α-L-rhodinopyranose; **2**, α-L-2,6-dideoxyribopyranose) attached through a tertiary α-keto glycosidic linkage (Figure 1). Biological evaluation of lactonamycin (**1**) against Gram-positive bacteria showed significant levels of antimicrobial activity.[3] Remarkably, it was especially active against clinically isolated methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). In addition, lactonamycin (**1**) showed significant levels of cytotoxicity against various tumor cell lines.[3]

The interesting biological properties combined with the challenging structure of lactonamycin (**1**) have generated considerable interest in the total synthesis of this complex and fascinating molecule. So far, six groups have reported synthetic studies directed towards the total synthesis of lactonamycin (**1**). Danishefsky and Cox were the first to report two routes towards the construction of the model ABCD ring system by using an oxidative dearomatization reaction[4] and a diastereoselective dihydroxylation reaction.[5] Danishefsky et al. also completed the diastereoselective synthesis of aglycon core **3** by using a Diels–Alder cycloaddition reaction.[6] Deville and Behar reported the synthesis of the model ABCD ring system by using a tandem conjugate cyanide addition/Dieckmann condensation.[7] Kelly et al. reported a short synthesis of the model CDEF ring system by using a Diels–Alder reaction and an asymmetric synthesis of the model AB ring system.[8a,8b] Parsons et al. reported the synthesis of the model CDEF ring system by using an elegant cascade cyclization reaction.[9] Recently, Saikawa and Nakata published the synthesis of the model BCDEF ring system by using a palladium-catalyzed cyclization/methoxy carbonylation.[10] In 2010, Tastuta et al. reported the first total synthesis of lactonamycin (**1**) by using a sequential intramolecular conjugate addition reaction, a stereoselective glycosidation, and a Michael–Dieckmann-type cyclization as key steps.[11] We reported the model studies on the synthesis of the ABCD rings by using several iterative Michael addition reactions and oxidations to construct the oxygenated lactone entity.[12a] Of particular relevance to the work presented here, two syntheses of the CDEF ring system have also been reported. The first approach to such units was based on a Lewis acid mediated

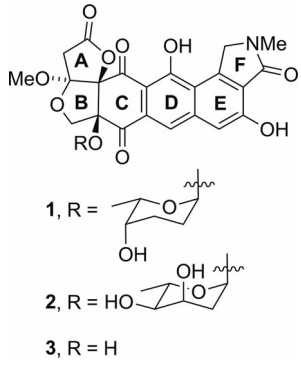

Figure 1. Structures of lactonamycin (**1**), lactonamycin-Z (**2**), and lactonamycinone (**3**).

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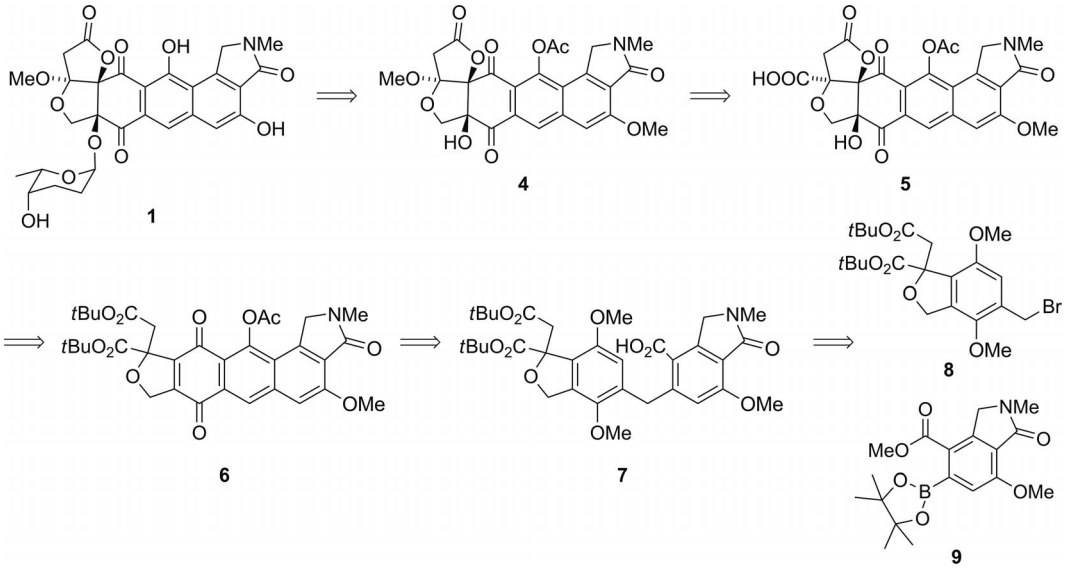


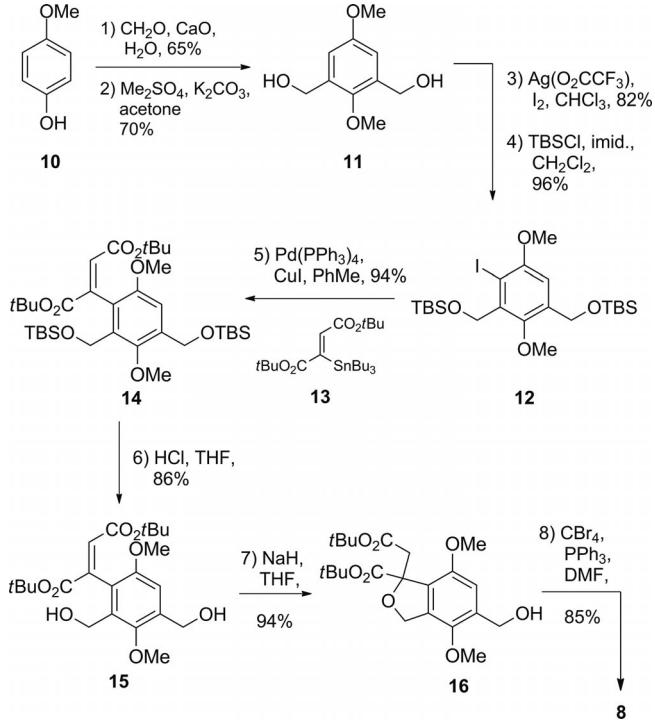
Scheme 1. Retrosynthetic approach to lactonamycin (**1**).

intramolecular Friedel–Crafts acylation and Negishi coupling reaction,[12b] whereas the second approach was based on benzyne–furan and maleimide–furan cycloaddition reactions, Suzuki coupling, and electrophilic aromatic substitutions.[12c] Herein, we wish to report more recent studies towards the synthesis of lactonamycin (**1**) by using a Suzuki coupling reaction and Friedel–Crafts acylation as key steps.

As we had previously been unsuccessful in our attempts to construct the B ring with the CDEF ring system already in place, we thought to synthesize lactonamycin (**1**) by using a precursor initially containing the BC ring system. Retrosynthetically, we considered that **1** could be obtained from aglycon core **4** after glycosidation and cleavage of the protecting groups (Scheme 1). On the basis of previous results, which showed that the tertiary methoxy group was difficult to introduce, we sought to install it through electrodecarboxylation of acid **5**, which could in turn be obtained from pentacycle **6** after dihydroxylation and lactonization. Pentacycle **6** could be obtained from carboxylic acid **7** by Friedel–Crafts acylation, protection of the resulting phenol, and subsequent selective oxidation of the C ring. Finally, acid **7** should be available from boronic ester **9** and benzyl bromide **8** through Suzuki coupling followed by selective saponification. We also considered that boronic ester **9** should be available from known triflate **17**, whereas benzyl bromide **8** should be available from 4-methoxyphenol.

Results and Discussion

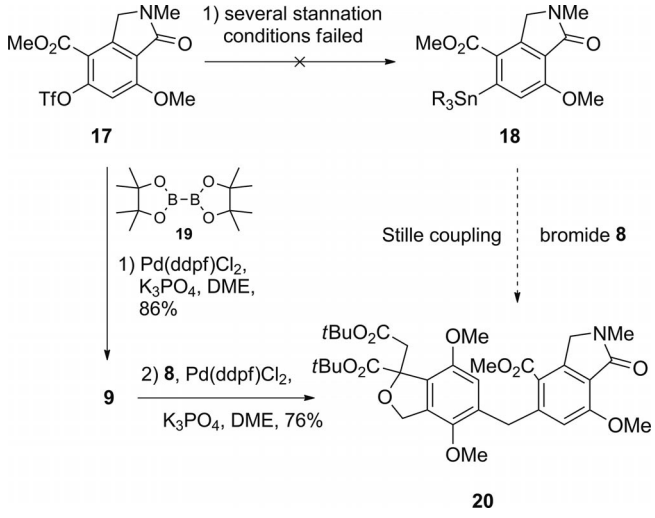
Bromide **8** was synthesized on a multigram scale from commercially available 4-methoxyphenol (**10**, Scheme 2). Double hydroxymethylation with formaldehyde in the presence of calcium oxide[13] followed by selective phenolic methylation gave diol **11** (70%). Ag^I-assisted monoiodination[14] and protection by *tert*-butyldimethylsilylation gave iodide **12** (82%), which was coupled with freshly prepared stannane **13**[15] in the presence of a Pd^0 catalyst and copper iodide to yield alkene **14** (94%).[16] We first focused our attention on a one-step approach to construct the B ring. Treatment of silyl ether **14** with tetrabutylammonium fluoride at 0 °C followed by additional heating at 60 °C resulted in cleavage of both silyl ethers, and the desired intramolecular Michael addition reaction occurred at the same time. Unfortunately, alcohol **16** was formed in a low 50% yield. Therefore, a two-step procedure was considered to close the B ring. Firstly, both silyl ethers were cleaved by using HCl



Scheme 2. Synthesis of bromide **8**.

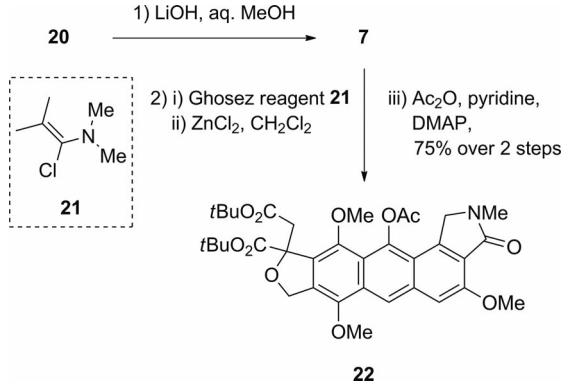
at 0 °C to produce diol **15**, which was converted into the corresponding benzofuran derivative **16** by reaction with NaH at high dilution. Finally, bromide **8** was obtained by using a classical Appel reaction.[17] Starting from commercially available 4-methoxyphenol, benzyl bromide **8** was successfully obtained on a multigram scale in eight steps with an overall yield of 23%.

With known triflate **17**[12b] in hand, we first thought to obtain coupled product **20** from the corresponding organozinc compounds derived from bromide **8**.[12c] Unfortunately, none of the conditions tested proved to be successful. Dissatisfied by these results, we decided to investigate alternative Stille coupling reactions. At this stage, it was planned to convert triflate **17** into the corresponding stannane **18**, which, with further Stille coupling with bromide **8**, should lead to ester **20** (Scheme 3). Triflate **17** was subjected to a variety of different stannylation reaction conditions; however, none of these successfully afforded desired stannane **18** and gave only an intractable mixture of alkylated and/or reduced products. Therefore, an alternative strategy was investigated. It was envisaged that bromide **8** could be coupled with a boronic ester derived from triflate **17**. Triflate **17** was smoothly converted into boronic ester **9** in one step by a Miyaura borylation reaction by using pinacoldiborane (**19**, 86%).[18] It is of interest to note that the success of this reaction was largely dependent on the concentration of the reaction mixture (0.5 M). In contrast, when the reaction was performed at lower concentration the formation of the corresponding reduction product was observed. With benzyl bromide **8** and boronic ester **9** in hand, the Suzuki coupling was investigated. Extensive experiments revealed that coupling product **20** could be isolated in 76% yield on a gram-scale following reaction with $PdCl_2$(dppf) and K_3PO_4 at 80 °C in DME.



Scheme 3. Synthesis of boronic ester **9** and Suzuki coupling with bromide **8**.

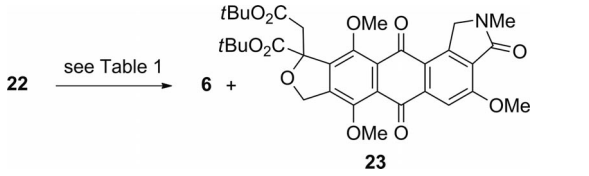
Unfortunately, selective monosaponification of the methyl ester moiety in **20** proved to be problematic. Thus, when methyl ester **20** was allowed to react with *n*PrSLi in HMPA or DMF,[19] acid **7** was isolated in a poor 37% yield. In a similar manner, when methyl ester **20** was allowed to react with an excess amount of Me_3SnOH in 1,2-DCE at 80 °C,[20] no conversion was observed even after prolonged reaction times. Reaction of methyl ester with $Ba(OH)_2$ in an aqueous THF and MeOH resulted in no conversion, whereas reaction in pure MeOH gave mostly highly polar side products. Finally, we found that saponification with the use of LiOH in aqueous MeOH gave required acid **7**, which was used without further purification in the next step. On the basis of previous results within the group,[12b] acid **7** was allowed to react with the Ghosez reagent (1-chloro-*N*,*N*,2-trimethyl-1-propyleneamine)[21] and zinc chloride to form pentacycle **13** in 75% yield after acetate protection. The structure of pentacycle **22** (Scheme 4) was further confirmed by X-ray crystallographic analysis.[22]



Scheme 4. Synthesis of pentacycle **22**.

The synthesis was continued with an oxidative demethylation to afford quinone derivative **6** (Scheme 5). Previous reported attempts for the oxidation on similar model systems showed that ceric ammonium nitrate (CAN) was an excellent oxidation reagent for this transformation.[12b] As a result, pentacycle **22** was allowed to react with an excess amount of CAN at 0 °C. Surprisingly and contrary to Begar's studies,[23] an inseparable mixture of quinones **6**/**23** was obtained in a 1:5 ratio (Table 1, Entry 1). The ratio could be reduced to 1:1.7 when the reaction was conducted only at 0 °C, but undesirable quinone **23** was still obtained as the major product (Table 1, Entry 2). Thus, this key oxidative reaction was examined by using a variety of oxidative agents (Table 1). Treatment of pentacycle **22** with iodobenzene bis-trifluoroacetate gave a complex mixture, and quinones **6**/**23** could be isolated in a 1:10 ratio (Table 1, Entry 3), whereas treatment with DDQ or silver(I) oxide (Ag_2O) resulted in little or no conversion after 12 h (Table 1, Entries 4 and 5). Much to our delight, oxidation of pentacycle **22** with an excess amount of silver(II) oxide and concentrated nitric acid at room temperature favored the formation of the desired quinone with quinones **6** and **23** being obtained in a 2.7:1 ratio (Table 1, Entry 6).[24] Upon treatment under the same conditions at –10 °C, the ratio was further increased to 5:1 in favor of quinone **6** (Table 1, Entry 7). Finally, the reaction was conducted at

–45 °C and only trace amounts of quinone **23** were detected; pure quinone **6** was obtained in 60% yield (Table 1, Entry 8).

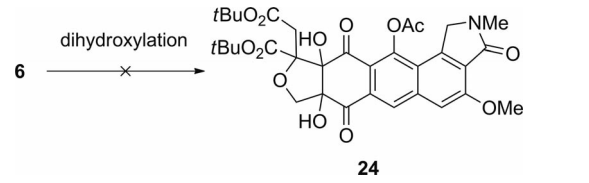


Scheme 5. Selective oxidation of pentacycle **22**.

Table 1. Selective oxidation of pentacycle **22**.

Entry	Oxidant (equiv.)	*T* [°C]	Ratio **6/23**
1	CAN (3.0)	0 to 23	1:5
2	CAN (3.0)	0	1:1.7
3	$PhI(OCOCF_3)_2$ (1.1)	0 to 23	1:10
4	DDQ (2.5)	23	no reaction
5	Ag_2O (3.0)	–20	no reaction
6	AgO (5.0), 4 N HNO_3	23	2.7:1
7	AgO (5.0), 4 N HNO_3	–20	5:1
8	AgO (5.0), 4 N HNO_3	–45	>99:1

Unfortunately, attempted dihydroxylation of quinone **6** under the conditions previously described by Danishefsky (*N*-methylmorpholine *N*-oxide in the presence of 3.25 mol-% OsO_4)[5,6b] or by using stoichiometric quantities of OsO_4 led to complete decomposition. Additionally, attempted dihydroxylation with ruthenium chloride and sodium periodate[25] was also unsuccessful, despite being applied earlier to other lactonamycin intermediates. Finally, attempted dihydroxylation under Sharpless conditions[26] also failed (Scheme 6). We suggest that the electron deficiency of the double bond due to the enedione system in addition to the possible steric hindrance of both *t*Bu esters constitute a challenge at the frontier of difficult dihydroxylations.



Scheme 6. Attempted dihydroxylation to form diol **24**.

Conclusions

A zinc chloride mediated, intramolecular Friedel–Crafts acylation of carboxylic acid **7** has been successfully used to synthesize the lactonamycin BCDEF pentacycle **22**. Whereas CAN oxidation afforded an inseparable mixture of quinones **6/23**, the use of silver(II) oxide and concentrated nitric acid successfully provided desired quinone **6**. Of particular importance is the multigram synthesis of benzyl bromide **8**, which was coupled with boronic ester **9** in a high-yielding Suzuki coupling to form precursor **20**. Given the difficulties with the late-stage dihydroxylation reaction, alternative ABC ring coupling intermediates are currently being investigated.

Experimental Section

General Methods: All reactions were carried out in flame-dried or oven-dried glassware under an atmosphere of dry N_2 or Ar unless otherwise stated. Prolonged periods of vessel cooling were attained by the use of a CryoCool apparatus. All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under an atmosphere of N_2: Et_2O and THF from Na/benzophenone ketyl, PhMe from Na, CH_2Cl_2 and Et_3N from CaH_2. MeOH was dried by heating at reflux over Mg turnings and I_2, followed by distillation from CaH_2 under an atmosphere of N_2. Flash column chromatography was performed by using silica unless otherwise stated. Melting points were measured with a Reichert-Thermovar melting point apparatus. IR spectra were recorded with a Mattson 5000 FTIR apparatus with automatic background subtraction. ^1H NMR spectra were recorded at 400 MHz with a Bruker DRX-300 or Bruker DRX-400 spectrometer or at 500 MHz with a Bruker AM 500 spectrometer. ^{13}C NMR spectra were recorded at 75 or 100 MHz with a Bruker DRX-300 or a Bruker DRX-400 spectrometer, respectively, or at 125 MHz with a Bruker AM 500 spectrometer.

Synthesis of Benzyl Bromide 8 and Boronic Ester 9

(2,5-Dimethoxy-1,3-benzene)dimethanol (11): Finely ground *p*-methoxyphenol (**10**; 31.0 g, 0.25 mol, 1.0 equiv.) was suspended in H_2O (200 mL), and the mixture was degassed by passing through a stream of N_2 for 30 min. Formalin (47 mL, 0.60 mol, 2.4 equiv.) and CaO (7.0 g, 0.125 mol, 0.5 equiv.) were added at room temperature, and the mixture was stirred for 5 d with the exclusion of light. Glacial AcOH (20 mL) was added, and the mixture was heated until most of the solid was dissolved. Charcoal (10 g) was added, and the solution was filtered hot. The filtrate was cooled to room temperature and placed in a freezer at –30 °C for 12 h. The resulting mixture was warmed to room temperature and filtered to give a white solid. The solid was subsequently washed with cold water and dried under reduced pressure to give the triol (29.9 g, 65%) as a white solid. R_f = 0.32 (hexanes/EtOAc, 1:2). M.p. 126–127 °C (EtOAc). IR (film): $\tilde{\nu}$ = 1731, 1611, 1483, 1314, 860, 789 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.65 (s, 2 H, Ar-*H*), 4.78 (s, 4 H, CH_2), 3.75 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 153.0, 145.6, 136.2 (2 C), 111.6 (2 C), 63.6 (2 C), 55.8 ppm. MS (ESI): *m*/*z* = 184 $[M]^+$. HRMS (ESI): calcd. for $C_9H_{12}O_4$ $[M]^+$ 184.0732; found 184.0736. $C_9H_{12}O_4$ (184.19): calcd. C 58.69, H 6.57; found C 58.63, H 6.52. The triol (88.2 g, 0.479 mol, 1.0 equiv.) was dissolved in Me_2CO (1.2 L) and K_2CO_3 (79.4 g, 0.574 mol, 1.2 equiv.) and dimethyl sulfate (49.8 mL, 0.527 mol, 1.1 equiv.) were added at room temperature, and the mixture was heated to reflux for 4.5 h. The mixture was allowed to cool to room temperature and was quenched by the addition of a mixture of MeOH (200 mL) and saturated aqueous NH_3 (100 mL). The insoluble solid was filtered off and washed with EtOAc (150 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L) and saturated aqueous $NaHCO_3$ (300 mL) and H_2O (100 mL) were added; the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow residue was purified by crystallization (EtOAc/Et_2O, 2:1) to

give diol **11** (66.8 g, 70%) as a white solid. R_f = 0.40 (EtOAc/hexanes, 4:1). M.p. 106–108 °C (EtOAc/hexane, 1:1). IR (film): $\tilde{\nu}$ = 3261, 3165, 1607, 1473, 1362, 1317, 1234, 1208, 1146, 1052, 997, 949, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.87 (s, 2 H, Ar-*H*), 4.70 (s, 4 H, CH_2), 3.79 (s, 3 H, OMe), 3.78 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.2, 149.4, 134.9 (2 C), 113.5 (2 C), 62.2, 60.9 (2 C), 55.6 ppm. MS (ESI): *m*/*z* = 198 $[M]^+$. HRMS (ESI): calcd. for $C_{10}H_{14}O_4$ $[M]^+$ 198.0892; found 198. 0894. $C_{10}H_{14}O_4$ (198.22): calcd. C 60.59, H 7.12; found C 60.57, H 7.00.

(1,3-Di-*tert*-butyldimethylsilyloxymethyl)-4-iodo-2,5-dimethoxybenzene (12): Diol **11** (9.9 g, 50 mmol, 1.0 equiv.) was dissolved in $CHCl_3$ (150 mL), and the resulting mixture was cooled to 0 °C. $Ag(O_2CCF_3)$ (19.9 g, 90 mmol, 1.8 equiv.) was added followed by the immediate dropwise addition of I_2 (13.9 g, 55 mmol, 1.1 equiv.) in $CHCl_3$ (300 mL). The mixture was stirred for 1 h at 0 °C. Because TLC showed incomplete conversion, additional $Ag(O_2CCF_3)$ (1.1 g, 49.7 mmol, 0.1 equiv.) and I_2 (1.3 g, 5.1 mmol, 0.1 equiv.) in $CHCl_3$ (100 mL) were added, and the reaction mixture was stirred at 0 °C for 1 h. The mixture was filtered through cotton and SiO_2 and washed with CH_2Cl_2 and MeOH (25:1). The crude product was purified by recrystallization (pentane/EtOAc, 1:1) to give 1,3-bis(hydroxymethyl)-4-iodo-2,5-dimethoxybenzene (13.4 g, 82%) as a white solid. R_f = 0.41 (CH_2Cl_2/MeOH, 10:1). M.p. 126–127 °C (pentane/EtOAc, 1:1). IR (film): $\tilde{\nu}$ = 3338, 1582, 1424, 1395, 1314, 1227, 1080, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.89 (s, 1 H, Ar-*H*), 4.87 (s, 2 H, CH_2), 4.74 (s, 2 H, CH_2), 3.88 (s, 3 H, OMe), 3.84 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 154.9, 150.4, 137.7, 135.1, 110.4, 91.7, 64.1, 63.3, 60.7, 56.9 ppm. MS (CI): *m*/*z* = 342 $[M + NH_4]^+$. HRMS (CI): calcd. for $C_{10}H_{17}NIO_4$ $[M + NH_4]^+$ 342.0202; found 342.0199. $C_{10}H_{13}IO_4$ (324.11): calcd. C 37.06, H 4.04; found C 36.94, H 4.07. 1,3-Bis(hydroxymethyl)-4-iodo-2,5-dimethoxybenzene (73.3 g, 226 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C. Imidazole (68.1 g, 678 mmol, 3.0 equiv.) and *t*$BuMe_2SiCl$ (85.2 g, 565 mmol, 2.5 equiv.) were added in CH_2Cl_2 (250 mL), and the resulting mixture was stirred at 0 °C for 2 h. Aqueous HCl (0.2 M, 300 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes/EtOAc, 200:1, 100:1, 50:1, 25:1) to give iodide **12** (120.3 g, 96%) as a white solid. R_f = 0.69 (CH_2Cl_2/MeOH, 10:1). M.p. 38–40 °C (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 1583, 1460, 1424, 1368, 1255, 1109, 1075, 1007, 837, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.02 (s, 1 H, Ar-*H*), 4.84 (s, 2 H, CH_2), 4.77 (s, 2 H, CH_2), 3.86 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 0.95 [s, 9 H, Si-C(CH_3)$_3$], 0.93 [s, 9 H, Si-C(CH_3)$_3$], 0.19 (s, 6 H, SiMe_2), 0.12 (s, 6 H, SiMe_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 154.9, 149.6, 137.0, 135.6, 109.4, 91.7, 64.1, 63.0, 59.8, 56.7, 26.0 (3 C), 25.8 (3 C), 18.5, 18.3, –5.1 (2 C), –5.3 (2 C) ppm. MS (CI): *m*/*z* = 570 $[M + NH_4]^+$. HRMS (CI): calcd. for $C_{22}H_{44}NIO_4Si_2$ $[M + NH_4]^+$ 570.1932; found 570.1942. $C_{22}H_{41}IO_4Si_2$ (552.64): calcd. C 47.81, H 7.48; found C 47.85, H 7.53.

Di-*tert*-butyl 2-(Tributylstannyl)fumarate (13):[15] Bu_3SnH (13.1 mL, 48.6 mmol, 1.1 equiv.) was added dropwise with stirring to a solution of di-*tert*-butyl acetylenedicarboxylate (10.0 g, 44.2 mmol, 1.0 equiv.) in benzene (170 mL). at room temperature. After 3 h, rotary evaporation and chromatography (hexanes/EtOAc, 200:1, 100:1, 50:1, 25:1) gave stannane **13** (22.8 g, 99%) as a colorless oil. R_f = 0.46 (hexanes/EtOAc, 10:1). IR (film): $\tilde{\nu}$ = 1704, 1458, 1368, 1322, 1247, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.66 (s, 1 H), 1.51–1.44 (m, 6 H), 1.49 (s, 9 H), 1.47 (s, 9 H), 1.34–1.25 (m, 6 H), 1.03–0.99 (m, 6 H), 0.87 (t, *J* = 7.4 Hz, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.1, 166.6, 161.5, 135.0, 81.3, 81.0, 28.9 (3 C), 28.2 (3 C), 27.9 (3 C), 27.3 (3 C), 13.7 (3 C), 12.0 (3 C) ppm. MS (CI): *m*/*z* = 519 $[M + H]^+$, 536 $[M + NH_4]^+$. HRMS (CI): calcd. for $C_{24}H_{50}NO_4Sn$ $[M + NH_4]^+$ 536.2762; found 536.2781. $C_{24}H_{46}O_4Sn$ (517.32): calcd. C 55.72, H 8.96; found C 55.63, H 8.86.

Di-*tert*-butyl 2-{2,4-Bis[(*tert*-butyldimethylsilyloxy)methyl]-3,6-dimethoxyphenyl}fumarate (14): Stannane **13** (85.5 g, 165 mmol, 1.2 equiv.), CuI (10.5 g, 55 mmol, 0.4 equiv.), and $Pd(PPh_3)_4$ (6.3 g, 5.4 mmol, 4 mol-%) were sequentially added to iodide **12** (76.0 g, 137.6 mmol, 1.0 equiv.) in PhMe (500 mL), and the mixture was heated at 120 °C for 12 h. Because the crude ^1H NMR spectrum showed incomplete conversion, additional CuI (2.6 g, 13.8 mmol, 0.1 equiv.) and $Pd(PPh_3)_4$ (3.1 g, 2.7 mmol, 2 mol-%) were added, and the reaction mixture was stirred for 12 h at 120 °C. Rotary evaporation and double chromatography (hexanes/EtOAc, 50:1, 25:1, 10:1, followed by hexanes/EtOAc, 100:1, 50:1, 25:1, 10:1) gave alkene **14** (84.1 g, 94%) as a yellow oil. R_f = 0.69 (hexanes/EtOAc, 10:1). IR (film): $\tilde{\nu}$ = 1711, 1462, 1368, 1252, 1155, 837, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.01 (s, 1 H, Ar-*H*), 6.90 (s, 1 H, C=C*H*), 4.83 (d, *J* = 13.6 Hz, 1 H, CH_2), 4.78 (d, *J* = 13.6 Hz, 1 H, CH_2), 4.57 (d, *J* = 10.8 Hz, 1 H, CH_2), 4.47 (d, *J* = 10.8 Hz, 1 H, CH_2), 3.75 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 1.44 [s, 9 H, C(CH_3)$_3$], 1.17 [s, 9 H, C(CH_3)$_3$], 0.95 [s, 9 H, Si-C(CH_3)$_3$], 0.88 [s, 9 H, Si-C(CH_3)$_3$], 0.11 (s, 6 H, SiMe_2), 0.05 (s, 6 H, Me_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.2, 164.8, 152.9, 149.0, 140.5, 134.6, 131.7, 131.1, 124.8, 109.2, 81.4, 80.7, 62.7, 60.0, 57.6, 55.8, 27.9 (3 C), 27.6 (3 C), 26.1 (3 C), 25.9 (3 C), 18.6, 18.4, –5.3 (2 C), –5.5 (2 C) ppm. MS (CI): *m*/*z* = 653 $[M + H]^+$. HRMS (CI): calcd. for $C_{34}H_{61}O_8Si_2$ $[M + H]^+$ 653.3905; found 653.3921. $C_{34}H_{60}O_8Si_2$ (653.02): calcd. C 62.54, H 9.26; found C 62.47, H 9.18.

Di-*tert*-butyl 2-[2,4-Bis(hydroxymethyl)-3,6-dimethoxyphenyl]fumarate (15): Concentrated HCl (40 mL, 476 mmol, 4.0 equiv.) was added with stirring to silyl ether **14** (77.9 g, 119 mmol, 1.0 equiv.) in THF (1 L) at 0 °C. After 3 h, saturated aqueous $NaHCO_3$ (500 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes/EtOAc, 1:1) to give diol **15** (36.6 g, 86%) as a colorless oil. R_f = 0.23 (hexanes/EtOAc, 1:1). IR (film): $\tilde{\nu}$ = 3442, 1708, 1641, 1602, 1461, 1369, 1251, 1153, 1070, 1010, 850, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.98 (s, 1 H, Ar-*H*), 6.92 (s, 1 H, C=C*H*), 4.77 (s, 2 H, CH_2), 4.53 (d, *J* = 11.6 Hz, 1 H, CH_2), 4.42 (d, *J* = 11.2 Hz, 1 H, CH_2), 3.89 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 1.46 [s, 9 H, C(CH_3)$_3$], 1.25 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.7, 165.2, 152.6, 150.2, 139.7, 134.8, 133.3, 131.8, 124.4, 110.3, 82.5, 82.0, 63.1, 61.1, 58.1, 55.9, 27.8 (3 C), 27.7 (3 C) ppm. MS (CI): *m*/*z* = 447 $[M + Na]^+$. HRMS (CI): calcd. for $C_{22}H_{32}O_8Na$ $[M + Na]^+$ 447.1995; found 447.2000. $C_{22}H_{32}O_8$ (424.49): calcd. C 62.25, H 7.60; found C 62.22, H 7.56.

***tert*-Butyl 1-[2-(*tert*-Butoxy)-2-oxoethyl]-5-(hydroxymethyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-1-carboxylate (16):** NaH (3.1 g, 77.7 mmol, 3.0 equiv.) was added with stirring to diol **15** (11.0 g, 25.9 mmol, 1.0 equiv.) in THF (1 L) at 0 °C. After 1 h, the reaction was quenched by addition of H_2O (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (hexanes/EtOAc, 1:1) to give benzofuran derivative **16** (10.3 g, 94%) as a yellow solid. R_f = 0.24 (hexanes/EtOAc, 1:1). M.p. 74–76 °C (Et_2O). IR (film): $\tilde{\nu}$ = 3442, 1735, 1637, 1486, 1465, 1367, 1249, 1160, 1049, 846 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$,

25 °C): δ = 6.78 (s, 1 H, Ar-*H*), 5.39 (d, *J* = 11.6 Hz, 1 H, CH_2O), 5.25 (d, *J* = 12.0 Hz, 1 H, CH_2O), 4.68 (s, 2 H, CH_2), 3.80 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.47 (d, *J* = 16 Hz, 1 H, CH_2CO_2tBu), 2.94 (d, *J* = 16 Hz, 1 H, CH_2CO_2tBu), 1.38 [s, 9 H, C(CH_3)$_3$], 1.33 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.1, 169.3, 150.2, 145.4, 134.0, 132.3, 128.1, 110.7, 88.6, 81.3, 80.2, 72.4, 61.1, 60.0, 55.6, 41.1, 27.9 (3 C), 27.7 (3 C) ppm. MS (CI): *m*/*z* = 447 [M + Na]$^+$. HRMS (CI): calcd. for $C_{22}H_{32}O_8Na$ [M + Na]$^+$ 447.1995; found 447.2003. $C_{22}H_{32}O_8$ (424.49): calcd. C 62.25, H 7.60; found C 62.26, H 7.75.

***tert*-Butyl 5-(Bromomethyl)-1-(2-*tert*-butyloxycarbonylmethyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-1-carboxylate (8):** PPh_3 (12.4 g, 47.4 mmol, 2.0 equiv.) and CBr_4 (15.7 g, 47.4 mmol, 2.0 equiv.) were added with stirring to alcohol **16** (10.1 g, 23.7 mmol, 1.0 equiv.) in DMF (100 mL) at room temperature. After 4 h, the reaction was quenched by addition of H_2O (200 mL) followed by hexanes/EtOAc (1:1, 200 mL). The aqueous layer was extracted with hexanes/EtOAc (1:1, 5 × 50 mL), and the combined organic layers were washed with H_2O (3 × 50 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes/EtOAc, 5:1) to give bromide **8** (9.8 g, 85%) as a white solid. R_f = 0.85 (CH_2Cl_2/MeOH, 10:1). M.p. 98–102 °C (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 1734, 1491, 1416, 1367, 1249, 1160, 1056, 847, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.74 (s, 1 H, Ar-*H*), 5.38 (d, *J* = 12 Hz, 1 H, CH_2O), 5.24 (d, *J* = 12 Hz, 1 H, CH_2O), 4.56 (d, *J* = 10 Hz, 1 H, CH_2Br), 4.51 (d, *J* = 9.6 Hz, 1 H, CH_2Br), 3.82 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.40 (d, *J* = 16 Hz, 1 H, CH_2CO_2tBu), 2.98 (d, *J* = 15.6 Hz, 1 H, CH_2CO_2tBu), 1.39 [s, 9 H, C(CH_3)$_3$], 1.31 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.8, 169.2, 150.2, 146.0, 133.0, 131.2, 129.7, 112.3, 88.8, 81.5, 80.3, 72.5, 60.1, 55.7, 41.1, 28.2, 27.9 (3 C), 27.8 (3 C) ppm. MS (EI): *m*/*z* = 509 [M{^{79}Br} + Na]$^+$, 511 [M{^{81}Br} + Na]$^+$. HRMS (EI): calcd. for $C_{22}H_{31}{}^{79}BrO_7Na$, $C_{22}H_{31}{}^{81}BrO_7Na$ [M + Na]$^+$ 509.1151, 511.1142; found 509.1151, 511.1142. $C_{22}H_{31}BrO_7$ (487.39): calcd. C 54.22, H 6.41; found C 54.29, H 6.46.

Methyl 7-Methoxy-2-methyl-1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-4-carboxylate (9): Triflate **17** (6.4 g, 16.7 mmol, 1.0 equiv.), bis(pinacolato)diboron **19** (6.4 g, 25.0 mmol, 1.5 equiv.), Pd(dppf)Cl_2 (341 mg, 418 μmol, 2.5 mol-%), and NaOAc (4.1 g, 50.1 mmol, 3.0 equiv.) were added to freshly degassed PhH (35 mL), and the reaction mixture was stirred for 13 h at 80 °C. After cooling to room temperature, the mixture was filtered through silica (CH_2Cl_2/MeOH, 10:1). The filtrate was concentrated, and the residue was chromatographed (CH_2Cl_2/MeOH, 20:1, 10:1) to give boronic ester **9** (4.9 g, 86%) as an off-white solid. R_f = 0.47 (CH_2Cl_2/MeOH, 10:1). M.p. 166–170 °C (pentane/Et_2O, 1:1). IR (film): $\tilde{\nu}$ = 1681, 1580, 1442, 1361, 1300, 1247, 1143, 1051, 845 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.93 (s, 1 H), 4.53 (s, 2 H), 4.02 (s, 3 H), 3.93 (s, 3 H), 3.15 (s, 3 H), 1.44 (s, 12 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.2, 166.5, 159.9, 145.3 (2 C), 121.3, 119.9, 113.6, 84.2 (2 C), 56.0, 52.9, 52.2, 29.1, 24.9 (4 C) ppm. MS (ESI): *m*/*z* = 362 [M + H]$^+$. HRMS (ESI): calcd. for $C_{18}H_{25}BNO_6$ [M + H]$^+$ 362.1758; found 362.1775.

Synthesis of Quinone 6

Methyl 5-[(1-*tert*-Butyloxycarbonylmethyl)-1-(*tert*-butoxycarbonyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-5-yl]methyl-7-methoxy-2-methyl-1-oxoisoindoline-4-carboxylate (20): Boronic ester **9** (1.0 g, 2.76 mmol, 1.0 equiv.) and bromide **8** (1.5 g, 3.31 mmol, 1.2 equiv.) were dissolved in DME (7 mL), and the solution was degassed with Ar. Pd(dppf)Cl_2 (56 mg, 69.0 μmol, 2.5 mol-%) and K_3PO_4 (1.8 g, 8.30 mmol, 3.0 equiv.) were added, and the mixture was heated with stirring at 80 °C for 38 h. After cooling to room temperature, the mixture was quenched with H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (EtOAc/MeOH, 100:1) to give methyl ester **20** (1.4 g, 76%) as a pale brown solid. R_f = 0.36 (EtOAc/MeOH, 10:1). M.p. 78–80 °C (Et_2O). IR (film): $\tilde{\nu}$ = 1686, 1596, 1487, 1366, 1249, 1154, 1054, 845 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.70 (s, 1 H), 6.41 (s, 1 H), 5.37 (d, *J* = 12.0 Hz, 1 H), 5.21 (d, *J* = 12.0 Hz, 1 H), 4.51 (s, 2 H), 4.39 (s, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.41 (d, *J* = 15.9 Hz, 1 H), 3.10 (s, 3 H), 2.91 (d, *J* = 15.9 Hz, 1 H), 1.34 (s, 9 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.0, 169.2 (2 C), 166.3, 158.7, 150.1, 148.6, 146.5, 145.6, 133.7, 132.5, 126.9, 119.0, 117.2, 113.4, 111.9, 88.5, 81.1, 80.0, 72.4, 59.7, 55.9, 55.5, 53.3, 51.5, 40.9, 34.4, 28.9, 27.7 (3 C), 27.6 (3 C) ppm. MS (ESI): *m*/*z* = 641 [M]$^+$, 642 [M + H]$^+$. HRMS (ESI): calcd. for $C_{34}H_{44}NO_{11}$ [M + H]$^+$ 642.2914; found 642.2913. $C_{34}H_{43}NO_{11}$ (641.71): calcd. C 63.64, H 6.75, N 2.18; found C 63.63, H 6.73, N 2.19.

***tert*-Butyl 12-Acetoxy-10-(*tert*-butyloxycarbonylmethyl)-4,7,11-trimethoxy-2-methyl-3-oxo-2,3,8,10-tetrahydro-1*H*-furo[3′,4′:6,7]naptho[2,3-*e*]isoindole-10-carboxylate (22):** LiOH (689 mg, 28.8 mmol, 10.0 equiv.) was added with stirring to methyl ester **20** (1.8 g, 2.88 mmol, 1.0 equiv.) in MeOH/H_2O (1:1, 100 mL) at room temperature. After 48 h, the reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the aqueous layer was acidified with conc. HCl to pH 3 and extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give crude acid **7**, which was used without any further purification. $Me_2C{=}C(Cl)NMe_2$ (**21**; 1.52 mL, 11.4 mmol, 5.0 equiv.) was added with stirring to crude acid **7** (1.4 g, 2.3 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) at room temperature. After 2 h, the mixture was cooled to 0 °C and $ZnCl_2$ (3.9 mL, 3.9 mmol, 1.7 equiv.) was added. After stirring for 2 h at 0 °C, DMAP (13.9 mg, 114 μmol, 0.05 equiv.) was added followed by pyridine (50 mL) and Ac_2O (35 mL), and the resulting mixture was stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes/EtOAc, 5:1 to EtOAc/MeOH, 100:1, 50:1, 20:1). Recrystallization (EtOAc) gave the lactonamycin BCDEF pentacycle **22** (1.4 g, 75% over two steps) as bright yellow crystals. R_f = 0.47 (CH_2Cl_2/MeOH, 10:1). M.p. 216–218 °C (EtOAc). IR (film): $\tilde{\nu}$ = 1773, 1729, 1687, 1620, 1453, 1362, 1154, 1038 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.58 (s, 1 H), 7.25 (s, 1 H), 5.61 (d, *J* = 12.4 Hz, 0.6 H, rotamer 2), 5.53 (d, *J* = 12.6 Hz, 0.4 H, rotamer 1), 5.48 (d, *J* = 12.6 Hz, 0.4 H, rotamer 1), 5.40 (d, *J* = 12.4 Hz, 0.6 H, rotamer 2), 5.03 (d, *J* = 18.4 Hz, 1 H), 4.61 (d, *J* = 18.7 Hz, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 3.88 (s, 1 H, rotamer 1), 3.79 (d, *J* = 16.2 Hz, 0.6 H, rotamer 2), 3.78 (s, 2 H, rotamer 2), 3.58 (d, *J* = 16.2 Hz, 0.4 H, rotamer 1), 3.26 (s, 3 H), 3.15 (d, *J* = 16.0 Hz, 0.4 H, rotamer 1), 3.05 (d, *J* = 16.0 Hz, 0.6 H, rotamer 2), 2.52 (br. s, 3 H), 1.45 (s, 6 H, rotamer 1), 1.37 (s, 3 H, rotamer 1), 1.34 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.9, 169.5, 169.1, 169.0, 168.3, 168.0, 166.8, 154.5, 144.8, 144.7, 144.4, 142.2, 141.8, 141.2, 134.7, 131.2, 130.6, 130.5, 125.8, 124.4, 118.7, 118.5 118.4, 117.5, 105.1, 87.9, 87.6, 82.2, 81.9, 80.9, 80.5, 71.6, 71.5, 63.3, 62.8, 60.1, 55.9, 53.6, 42.0, 41.2, 29.3, 27.9, 27.8, 27.6, 21.1 ppm (contains rotamers). MS (ESI): *m*/*z* = 652 [M + H]$^+$. HRMS (ESI): calcd. for $C_{35}H_{42}NO_{11}$ [M + H]$^+$ 652.2753; found 652.2748. $C_{35}H_{41}NO_{11}$ (651.71): calcd. C 64.50, H 6.34, N 2.15; found C 64.59, H 6.39, N 2.23.

***tert*-Butyl 12-Acetoxy-10-(*tert*-butyloxycarbonylmethyl)-4-methoxy-2-methyl-3,7,11-trioxo-2,3,7,8,10,11-hexahydro-1*H*-furo[3′,4′:6,7]-naphtho[2,3-*e*]isoindole-10-carboxylate (6):** Pentacycle **22** (150 mg, 0.23 mmol, 1.0 equiv.) was dissolved in PhMe (5 mL) and concentrated under reduced pressure. This process was repeated three times. DME (10 mL) was added, and the reaction mixture was cooled to –45 °C. AgO (85.5 mg, 0.69 mmol, 3.0 equiv.) was added, and the resulting mixture was sonicated for 30 s, when aqueous HNO_3 (4 M; 600 μL) was added. The mixture was stirred for 10 min at –45 °C. The mixture was poured into a separation funnel containing precooled CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed (EtOAc/MeOH, 100:1, 50:1, 20:1) to give quinone **6** (86.0 mg, 60%) as an orange solid. R_f = 0.47 (CH_2Cl_2/MeOH, 10:1). M.p. 108–110 °C (Et_2O). IR (film): $\tilde{\nu}$ = 1780, 1695, 1666, 1367, 1279, 1157, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.53 (s, 1 H), 7.39 (s, 1 H), 5.23 (d, J = 16.0 Hz, 1 H), 5.16 (d, J = 15.4 Hz, 1 H), 4.89 (br. s, 1 H), 4.58 (br. s, 1 H), 4.14 (s, 3 H), 3.28 (d, J = 15.4 Hz, 1 H), 3.25 (s, 3 H), 3.23 (d, J = 16.0 Hz, 1 H), 2.63 (s, 3 H), 1.45 (s, 9 H), 1.36 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.2, 178.7, 168.4, 165.6, 157.8, 148.2, 147.1, 144.8, 142.6, 139.4, 131.5, 126.1, 125.4, 120.5, 117.9, 108.9, 91.6, 83.2, 81.1, 73.2, 56.3, 52.8, 40.6, 29.4, 27.9 (3 C), 27.7 (3 C), 21.8 ppm (2 carbonyl signals missing). MS (ESI): m/z = 622 $[M + H]^+$. HRMS (ESI): calcd. for $C_{33}H_{36}NO_{11}$ $[M + H]^+$ 622.2288; found 622.2269. $C_{33}H_{35}NO_{11}$ (621.64): calcd. C 63.76, H 5.68, N 2.25; found C 63.70, H 5.53, N 2.17.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for the intermediates for the synthesis of bromide **8**, boronic ester **9**, and diesters **20** and **22** and quinone **6**; X-ray crystal structure of compound **22**.

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