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Synthetic studies on the CDEF ring system of lactonamycin

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Abstract—Both (1) furan–maleimide Diels–Alder cycloaddition reaction and (2) furan–benzyne cycloaddition, Suzuki cross-coupling, boron-mediated aldol, and electrophilic aromatic substitution reactions were examined for the construction of the CDEF ring system of lactonamycin (**1**).

1. Introduction

Lactonamycin (**1**) and lactonamycin-Z (**2**) have intriguing structural features, which include a naphtho[*e*]isoindole ring system (DEF-rings) and a densely oxygenated fused perhydrofuran-furanone ring system (AB-rings) (Fig. 1).[1] Lactonamycin (**1**) shows significant levels of antimicrobial activity against Gram-positive bacteria being especially active against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) with minimum inhibitory concentration levels of 0.39 and 0.20 μg/mL, respectively. In addition, it shows significant levels of cytotoxicity against various tumor cell lines with IC_{50} ranging from 0.06 to 3.30 μg/mL. Whilst there has been no total synthesis of **1** yet published, synthetic studies toward lactonamycin **1** have been reported by four groups. Cox and Danishefsky have described two routes to model systems of the densely oxygenated ABCD portion,[2] while Kelly's group more recently reported an asymmetric synthesis of the AB ring system.[3] Of particular relevance to the work presented here, two syntheses of model systems related to the aromatic CDEF core of lactonamycin have also been reported. Behar's approach was based on the construction of ring E by an elegant tandem conjugate cyanide addition–Dieckmann condensation.[4] Shortly thereafter, Kelly published a second approach toward the same lactonamycin segment by the assemblage of the D and E rings using Diels–Alder cycloaddition reactions.[5] Danishefsky and co-workers recently completed a diastereoselective synthesis of the entire lactonamycin aglycon, with the CDEF fragment assembled using successive Diels–Alder reactions.[6] Finally, we have reported the synthesis of the ABCD tetracyclic ring system of lactonamycin using an iterative sequence of Michael addition and oxidation reactions.[7] Herein, we report our own studies on the approaches to the CDEF ring system using notably benzyne–furan and maleimide–furan cycloaddition reactions, Suzuki coupling reaction, and electrophilic aromatic substitutions.

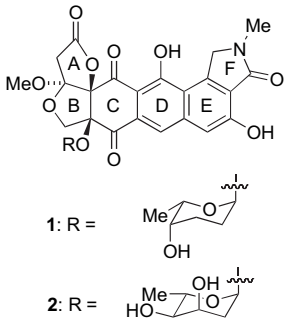

Figure 1. Structures of lactonamycin (**1**) and lactonamycin-Z (**2**).

2. Results and discussion

2.1. The benzyne cycloaddition strategy

Initially, we sought to synthesize the lactonamycin CDEF ring system **3** by formation of the hydroquinone ring C using a double Friedel–Crafts acylation of naphthol **5** using succinic anhydride **4** (Scheme 1). In turn, naphthalene **5** should be available using a [4+2] cycloaddition reaction of the aryne derived from iodo-triflate **7** and the diene **6**,[8] and subsequent aromatization.[9] Whilst the regioselectivity of the cycloaddition reaction could be problematical, the use of symmetrical dienes to replace **6** and ring D manipulation was considered as a fall back option. Finally, iodo-triflate

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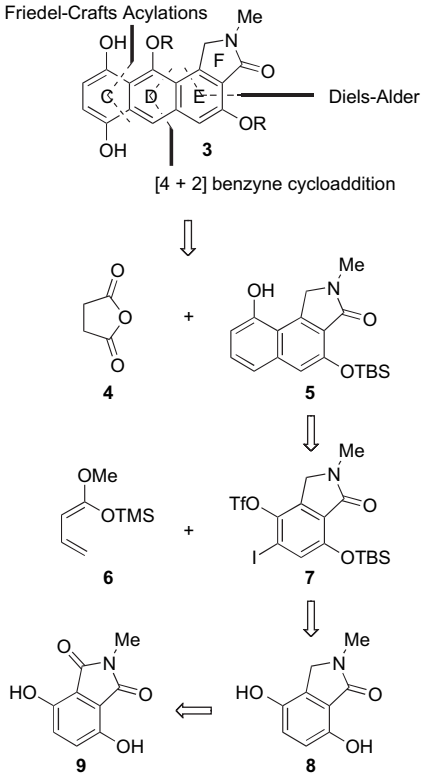
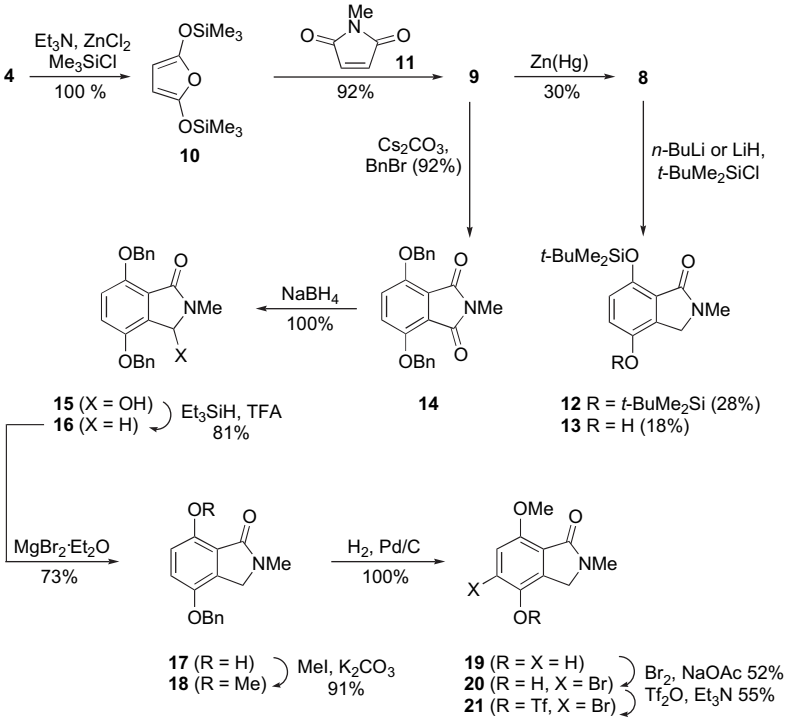
7 should be available from imide **9** via reduction, iodination, and triflation.



Scheme 1. Initial retrosynthetic analysis.

Diels–Alder reaction of diene **10**[10] with *N*-methylmaleimide **11** and in situ aromatization gave imide **9**[11] in excellent overall yield (92%) (Scheme 2).[12] In contrast, the synthesis of imide **9** from the hydrolysis of commercial 3,6-dihydroxyphthalonitrile[13] and subsequent coupling with $MeNH_2$ was less efficient (25%) due to the poor solubility of the intermediate phthalic acid and partial decarboxylation.[14] Subsequent conversion to the benzyne precursor **7** proved troublesome. Clemmensen reduction[15] of imide **9** to lactam **8** proceeded in poor yield and the product was difficult to purify. Attempted selective mono-*tert*-butyldimethylsilylation of hydroquinone **8** using excess lithium carbonate[16] gave an intractable mixture, whereas silylation using *n*-butyllithium or lithium hydride (1 equiv) gave the desired mono-protected hydroquinone **13** (18%), diether **12** (28%), and recovered hydroquinone **8** (30%). Finally, both iodination[17] and bromination of phenol **13** were unsuccessful giving mixtures of products. In the light of these difficulties the approach was modified with a two-step imide reduction[12b,18] and substrate benzylation to overcome the poor reactivity and low solubility of hydroquinone **9**. Sequential sodium borohydride and triethylsilane–TFA[18b,c] reduction of diether **14** gave lactam **16** (81%). We next sought to convert the diether **16** into the corresponding phenol **19** for regioselective ring halogenation. Selective mono-debenzylation using magnesium bromide[19] gave phenol **17** (73%) as the only isomer, the structure of which was established by NOE analysis and X-ray crystal structure determination. Methylation of phenol **17** and debenzylation by hydrogenolysis gave the methyl ether **19** (91% overall). Attempted iodination or bromination of phenol **19** largely proved unsatisfactory under diverse reaction conditions. However, reaction with bromine in the presence of sodium acetate in acetic acid[20] gave the bromide **20** (52%), the structure of which was established by X-ray crystal structure determination. Attempted conversion of the derived bromo-triflate **21** into the corresponding benzyne and trapping with 2-methoxyfuran[9b,21] via bromine–lithium exchange using



Scheme 2. Synthesis of imide **9** and derivatization to benzyne precursor **21**.

n- or *tert*-butyllithium in THF, diethyl ether, or hexane at −78 or −100 °C gave only intractable mixtures of products. Consequently, the benzyne strategy in Scheme 1 is abandoned.

2.2. The palladium coupling and Friedel–Crafts cyclization strategies

Our attention was next directed toward an approach whereby the carbon framework of the lactonamycin tetracyclic CDEF ring system would be assembled using either a sequential Michael addition or a palladium coupling reaction and subsequent Friedel–Crafts hydroxyalkylation (Fig. 2). The naphthalene partners **27** and **28** were prepared by the methods in Scheme 3 using a benzyne–furan cycloaddition reaction to provide naphthalene **25**[22] and regioselective *ortho*-bromination.[23,24] The substitution pattern of bromide **26** was defined by NMR experiments, and confirmed by X-ray crystal structure determination. Boronic acid **28** was readily prepared from bromide **27** by sequential bromine–lithium exchange at −78 °C to furnish the corresponding insoluble lithio-derivative, condensation with $B(O^iPr)_3$, and subsequent hydrolysis.

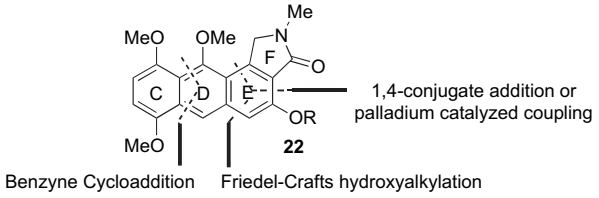
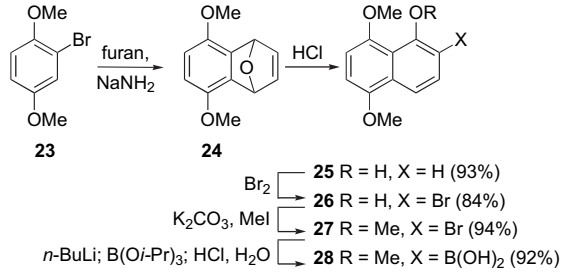
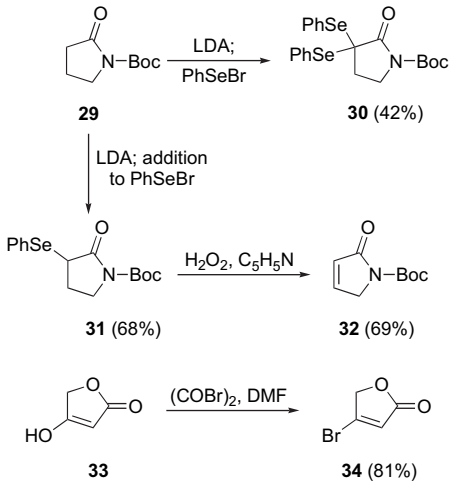


Figure 2. Summary of the conjugate addition and Friedel–Crafts reaction approach.



Scheme 3. Synthesis of naphthalene **28**.

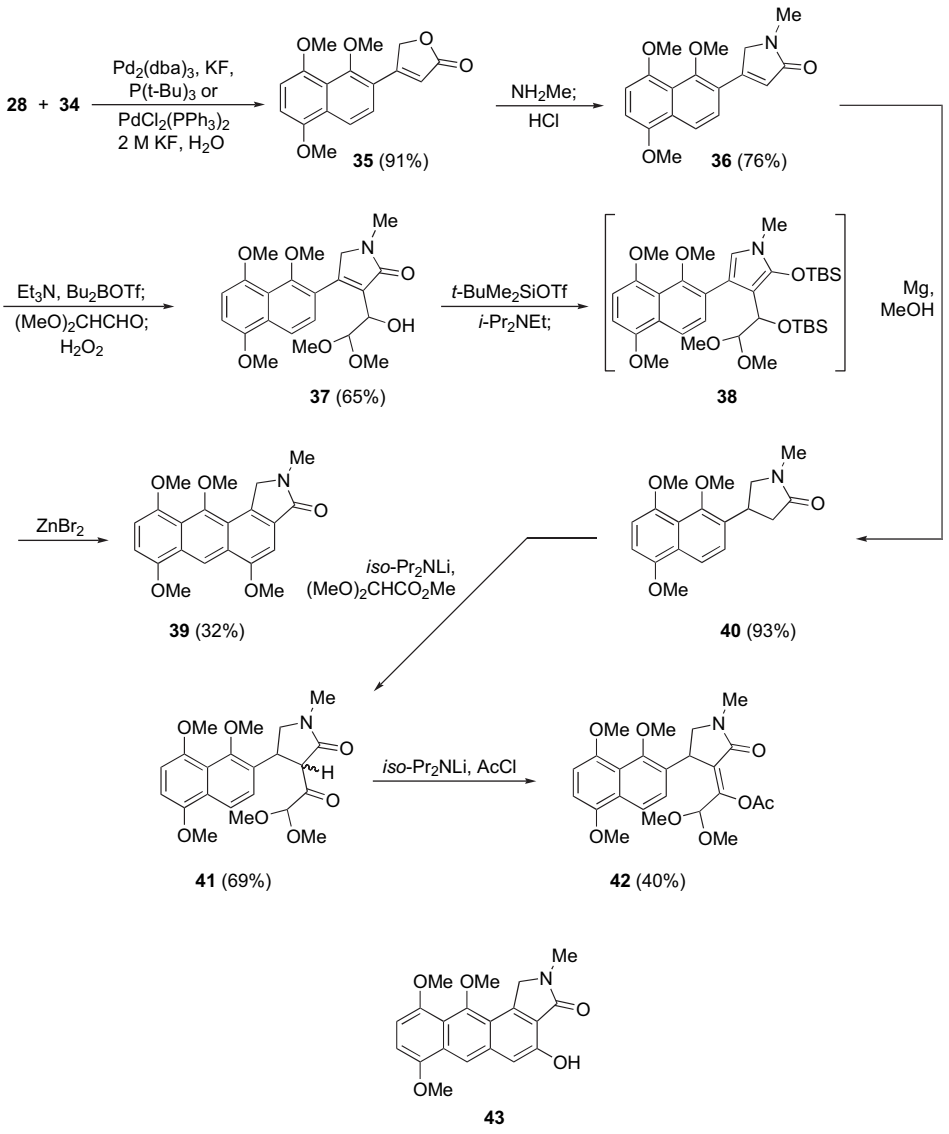
We planned to introduce the pyrrolinone unit 1) by Michael addition of organometallic reagents derived from bromide **27** to a 2-pyrrolinone derivative 2) or by palladium-catalyzed coupling of **28** with a related 4-bromo-2-pyrrolinone or a synthetic equivalent. Although such Michael addition reactions have indirect literature precedent, attempted additions to *N*-alkyl-2-pyrrolinones have been reported to be fruitless.[25] Not surprisingly, the presence of an electron-withdrawing group on the nitrogen appears to substantially increase the potency of the Michael acceptor.[25,26] Thus, carbamate **32** (Scheme 4) was selected as the Michael acceptor to be prepared by a selenoxide elimination reaction[27] and furanone **34** to explore the complimentary palladium coupling reaction. In contrast to the Zoretic and Soja results,[28] the conversion of lactam **29** into the selenide **31** was most conveniently carried out using only 1 equiv of lithium di-*iso*-propylamide and with inverse addition to suppress the formation of the diselenide **30**. Selenide oxidation with hydrogen peroxide in the presence of pyridine gave the unsaturated γ-lactam **32** in good overall yield. Bromobutenolide **34** was readily prepared from tetronic acid **33** using oxalyl bromide (81%).[29]



Scheme 4. Synthesis of the pyrrolinone and furanone coupling partners.

Unfortunately, attempted conversion of the bromide **27**, via the corresponding Grignard reagent or aryllithium, to a cuprate, and addition to the simple Michael acceptor 2-cyclohexenone or to lactam **32** proved to be unsuccessful, probably on account of proton transfer to the naphthyl carbanion.[30] In contrast, the Suzuki coupling reaction[31] of the boronic acid **28** and the bromide **34** smoothly provided the adduct **35** (Scheme 5). Reaction of the butenolide **35** with methylamine followed by reaction with hydrogen chloride in dioxane readily provided lactam **36**, which was presumably formed via reversible ring opening and an imine–enamine tautomerization.[32] In order to introduce the last carbon fragment α to the carbonyl of lactam **36**, an enol boration and aldol reaction sequence were examined. Thus, lactam **36** was converted into the aldol adduct **37** (65%) by sequential reaction with dibutylboron triflate, triethylamine, and dimethoxyacetaldehyde. Such a process, which presumably proceeds via the 2-(dibutylboryloxy)-pyrrole, has indirect precedent in aldol reactions of esters and enoates,[33] or with amides using dicyclohexylboron iodide,[34] although has not been applied to functionalize the unsaturated amides before.

Attempted cyclizations of the acetal **37** to produce the corresponding anthracene **43** or an equivalent system using diverse Brønsted and Lewis acid catalysts at −78 to 120 °C gave only intractable mixtures of products. We reasoned that these failures resulted from deactivation of the nucleophilicity of the naphthalene unit by the electron-withdrawing pyrrolinone carbonyl. The conversion of pyrrolinone **37** to a silyloxypyrrole was expected to not only alleviate this deactivation, but also incorporates an additional electron-donating substituent onto the naphthalene ring, *ortho* to the site of cyclization. Thus, the pyrrolinone **37** was converted into the pyrrole **38** by reaction with *tert*-butyldimethylsilyl triflate and Hünig's base.[35] Subsequent



Scheme 5. Synthesis and cyclization of lactam **36**.

reaction with zinc bromide gave an unstable adduct tentatively assigned as the anthracene **39**,[36] which presumably arose via the desired Friedel–Crafts methoxy alkylation and loss of water or silanol by an E_1 process via the pyrrole-stabilized carbenium ion. As an alternative possible route to the desired anthracene, pyrrolinone **36** was reduced using magnesium in methanol (93%)[37] and the resulting γ-lactam **40** was converted into the keto-lactam **41** (69%) by a crossed Claisen condensation reaction.[38] Acetal **41** was converted into the *Z*-enol acetate **42** (40%) by deprotonation with lithium di-*iso*-propylamide and O-acylation with acetyl chloride.[39] The geometry of the enol acetate **42** was confirmed as *Z* by an NOESY experiment. Frustratingly, attempted cyclization of either keto-ester **41** or the enol acetate **42** under acidic or Lewis acid condition gave complex mixtures of products.

3. Conclusion

The Suzuki coupling of boronic acid **28** with the bromobutenolide **34** and subsequent reaction with methylamine gave the naphthyl lactam **36**. Attempted conversion into the CDEF unit of the antibacterial natural product lactonamycin using an aldol reaction with dimethoxyacetaldehyde and Friedel–Crafts hydroxy alkylation gave the isomeric anthracene lactam **39** rather than the required tetracycle **43**.

4. Experimental[†]

4.1. 4,7-Dihydroxy-2-methyl-2,3-dihydro-1,3-isoindoledione (9)

(a) 3,6-Dihydroxyphthalonitrile (3.00 g, 18.7 mmol) and KOH (19.0 g, 339 mmol) in H_2O (19 mL) were heated at reflux for 3 h (Ar). After cooling to 0 °C, the mixture was acidified with 30% H_2SO_4 and extracted with EtOAc (15×75 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was

[†] General experimental conditions and additional experiments are available in Supplementary data.

dried over large quantities of P_4O_{10} under *vacuum* to yield 3,6-dihydroxyphthalic acid (3.59 g) as an off-white solid, which was used directly without further purification: ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.01 (s, 1H), 14.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 156.5, 124.7, 113.9; *m/z* (EI) 198 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_8H_6O_6$ ($M^{+\bullet}$): 198.0164; found: 198.0159. The crude dihydroxyphthalic acid (3.59 g) and $MeNH_2$ (2.0 M in THF; 18.7 mL, 37.5 mmol) in THF (45 mL) were stirred at room temperature for 1.5 h, heated at reflux for 1.5 h, after which time DCC (3.87 g, 18.7 mmol) was added at room temperature. The mixture was stirred overnight, heated at reflux for 10 h, and cooled. Dicyclohexylurea was filtered off and the filtrate was dried ($MgSO_4$), filtered, and rotary evaporated. The yellow solid was recrystallized from MeOH to give imide **9** as yellow needles (905 mg, 25%).

(b) Diene **10**[10] (85.0 g, 350 mmol) and *N*-methylmaleimide **11** (43.0 g, 385 mmol) were stirred at 40 °C for 72 h (Ar), with small aliquots of CH_2Cl_2 added to enable stirring. After cooling to 0 °C, TFA (10 mL) was added dropwise and the mixture was stirred for 45 min. The resultant solid was filtered off and washed with cold EtOAc and Et_2O to yield imide **9** (61.7 g, 92%) as a yellow solid. Recrystallization from MeOH gave imide **9** as yellow needles: R_f=0.36 (EtOAc/hexanes, 1:1); mp >230 °C (MeOH); IR (KBr disc) 3440, 3334, 1741, 1680, 1643, 1450, 1383, 1302, 1002, 928 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 2.91 (s, 3H), 7.04 (s, 2H), 10.15 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 148.3, 126.1, 114.7, 23.6; *m/z* (CI, NH_3) 211 $(M+NH_4)^+$, 194 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_9H_8NO_4$ $(M+H)^+$: 194.0453; found: 194.0450. Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.10; H, 3.48; N, 7.26%.

4.2. 4,7-Dihydroxy-2-methyl-2,3-dihydro-1-isoindolone (8)

Concd HCl (4.8 mL) was added to Zn powder (33.8 g, 518 mmol) and $HgCl_2$ (2.81 g, 10.4 mmol) at 0 °C. The mixture was stirred for 5 min at room temperature before being allowed to stand for 15 min. Concd HCl (52 mL), glacial AcOH (35 mL), and phthalimide **9** (5.00 g, 25.9 mmol) were successively added to the amalgam at 0 °C. The mixture was heated at reflux overnight, cooled to room temperature, and filtered. After the addition of H_2O (60 mL), the mixture was extracted with EtOAc (6×100 mL) and the combined organic extracts were rotary evaporated. The residue was dissolved in saturated aqueous sodium EDTA (50 mL) and the mixture was extracted with EtOAc (8×80 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 5:1) to give lactam **8** (1.4 g, 30%) as a white solid: R_f=0.35 (EtOAc/hexanes, 7:3); mp 220 °C (dec) (MeOH); IR (KBr disc) 3458, 3409, 3141, 1658, 1614, 1477, 1456, 1296 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.00 (s, 3H), 4.26 (s, 2H), 6.63 (d, 1H, J=8.5 Hz), 6.79 (d, 1H, J=8.5 Hz), 8.68 (br s, 1H), 9.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.4, 147.9, 145.1, 127.9, 119.9, 118.5, 115.9, 49.9, 29.1; *m/z* (CI, NH_3) 197 $(M+NH_4)^+$, 180 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_9H_{10}NO_3$ $(M+H)^+$: 180.0661; found: 180.0651. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.19; H, 4.83; N, 7.68%.

4.3. 7-*tert*-(Butyldimethylsilyloxy)-4-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (13)

(a) A suspension of hydroquinone **8** (303 mg, 1.69 mmol) in THF (12 mL) was heated at reflux for 10 min. After cooling to −78 °C, *n*-BuLi (2.5 M in hexanes; 744 μL, 1.86 mmol) was added dropwise and the solution was allowed to warm to room temperature over 1 h. *t*-BuMe_2SiCl (280 mg, 1.86 mmol) was added at −78 °C and the solution was allowed to warm to room temperature overnight. After rotary evaporation, the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (4×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated. Chromatography (EtOAc/hexanes, 3:7) gave the disilylated hydroquinone **12** (193 mg, 28%) and the desired monosilylated hydroquinone **13** (89 mg, 18%) as white solids.

(b) LiH (18 mg, 2.23 mmol) was added portionwise to a suspension of hydroquinone **8** (400 mg, 2.23 mmol) in DMF (8 mL) at −78 °C and the solution was allowed to warm to room temperature over 1 h. *t*-BuMe_2SiCl (336 mg, 2.23 mmol) was added at −78 °C and the solution was allowed to warm to room temperature overnight. After rotary evaporation, the residue was partitioned between H_2O (15 mL) and EtOAc (20 mL), the layers were separated and the aqueous phase was further extracted with EtOAc (4×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 3:7) to give the disilylated hydroquinone **12** (245 mg, 27%) and the desired mono-silylated hydroquinone **13** (98 mg, 15%) as white solids. Ether **13**: R_f=0.21 (EtOAc/hexanes, 4:1); mp >230 °C (MeOH/hexanes); IR (KBr disc) 3139, 1660, 1600, 1500, 1459, 1271 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.14 (s, 6H), 0.97 (s, 9H), 2.98 (s, 3H), 4.21 (s, 2H), 6.67 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 9.51 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 146.7, 145.1, 129.2, 123.3, 121.0, 119.1, 49.0, 29.3, 26.2, 18.6, −4.2; *m/z* (CI, NH_3) 294 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{15}H_{24}NO_3Si$ $(M+H)^+$: 294.1525; found: 294.1518. Anal. Calcd for $C_{15}H_{23}NO_3Si$: C, 61.40; H, 7.90; N, 4.77. Found: C, 61.40; H, 7.88; N, 4.68%. Diether **12**: R_f=0.29 (EtOAc/hexanes, 1:9); mp 106–108 °C (Et_2O/hexanes); IR (film) 1700, 1493, 1274, 1251, 1004, 836 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.21 (s, 6H), 0.99 (s, 9H), 1.03 (s, 9H), 3.11 (s, 3H), 4.16 (s, 2H), 6.67 (d, 1H, J=9.0 Hz), 6.76 (d, 1H, J=9.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 167.4, 147.4, 144.3, 132.9, 123.6, 122.1, 120.9, 49.4, 29.3, 25.9, 25.7, 18.5, 18.1, −4.2, −4.5; *m/z* (CI, NH_3) 408 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{21}H_{38}NO_3Si_2$ $(M+H)^+$: 408.2390; found: 408.2383. Anal. Calcd for $C_{21}H_{37}NO_3Si_2$: C, 61.88; H, 9.16; N, 3.44. Found: C, 62.08; H, 9.26; N, 3.51%.

4.4. 4,7-Di-(benzyloxy)-2-methyl-2,3-dihydro-1,3-isoindoledione (14)

Cs_2CO_3 (20.2 g, 62.1 mmol) was added to hydroquinone **9** (3.00 g, 15.5 mmol), $PhCH_2Br$ (9.3 mL, 77.7 mmol), and KI (258 mg, 1.55 mmol) in DMF (25 mL). The mixture was stirred at room temperature for 8 h, quenched with

iced H_2O (50 mL), and extracted with EtOAc (5×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/hexanes, 3:1 to CH_2Cl_2) to give isoindolinedione **14** (5.35 g, 92%) as a pale yellow solid. Recrystallization from MeOH yielded imide **14** as pale yellow needles: R_f=0.15 (CH_2Cl_2); mp 155 °C (MeOH); IR (film) 1689, 1500, 1453, 1265, 1058 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.09 (s, 3H), 5.20 (s, 4H), 7.03 (s, 2H), 7.24–7.46 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.5, 149.8, 136.3, 128.8, 128.1, 126.9, 122.3, 119.6, 71.4, 23.8; *m/z* (EI) 373 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_{23}H_{19}NO_4$ ($M^{+\bullet}$): 373.1314; found: 373.1313. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 74.01; H, 4.99; N, 3.63%.

4.5. 4,7-Di-(benzyloxy)-3-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (15)

$NaBH_4$ (172 mg, 4.54 mmol) was added portionwise to imide **14** (113 mg, 0.30 mmol) in MeOH (2 mL) and $CHCl_3$ (3 mL) at 0 °C. After 1 h and rotary evaporation, the residue was partitioned between H_2O (15 mL) and CH_2Cl_2 (15 mL). The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2×10 mL) and EtOAc (10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/CH_2Cl_2, 1:9 to 1:4) to give hydroxylactam **15** (114 mg, 100%) as a white solid. Recrystallization from EtOAc gave lactam **15** as colorless prisms: R_f=0.26 (EtOAc/CH_2Cl_2, 1:4); mp 136–137 °C (EtOAc); IR (film) 3344, 1687, 1501, 1453, 1274, 1027 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.41 (d, 1H, *J*=9.0 Hz), 5.03 (s, 2H), 5.10 (s, 2H), 5.71 (d, 1H, *J*=9.0 Hz), 6.74 (d, 1H, *J*=9.0 Hz), 6.87 (d, 1H, *J*=9.0 Hz), 7.21–7.48 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 165.8, 149.8, 148.5, 136.9, 136.6, 133.3, 128.7, 128.6, 128.1, 127.8, 127.3, 127.0, 120.1, 117.6, 116.8, 81.3, 71.5, 70.9, 26.2; *m/z* (CI, NH_3) 393 $(M+NH_4)^+$, 376 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{23}H_{22}NO_4$ $(M+H)^+$: 376.1549; found: 376.1552. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.67; H, 5.70; N, 3.70%.

4.6. 4,7-Di-(benzyloxy)-2-methyl-2,3-dihydro-1-isoindolone (16)

TFA (70 mL) and Et_3SiH (17.2 mL, 108 mmol) were added with stirring sequentially to hydroxylactam **15** (27.0 g, 71.9 mmol) in CH_2Cl_2 (70 mL) at 0 °C. After stirring for 15 min, the resulting colorless solution was rotary evaporated and the residue was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (200 mL), and the aqueous layer was further extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 to Et_2O/CH_2Cl_2, 7:3) to give lactam **16** (20.9 g, 81%) as a white solid. Recrystallization from MeOH and Et_2O gave lactam **16** as colorless crystals: R_f=0.32 (Et_2O/CH_2Cl_2, 1:9); mp 116 °C (MeOH/Et_2O); IR (film) 1690, 1500, 1453, 1265, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 4.31 (s, 2H), 5.09 (s, 2H), 5.23 (s, 2H), 6.83 (d, 1H, *J*=9.0 Hz), 6.92 (d, 1H, *J*=9.0 Hz), 7.28–7.41 (m, 8H), 7.54 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 150.3, 147.7, 137.4, 136.7, 131.9, 128.7, 128.5, 128.2, 127.6, 127.4, 127.0, 122.7, 115.2, 114.8, 71.7, 70.5, 49.5, 29.4; *m/z* (CI, NH_3) 736 $(2M+NH_4)^+$, 719 $(2M+H)^+$, 360 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{23}H_{22}NO_3$ $(M+H)^+$: 360.1600; found: 360.1596. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.96; H, 5.97; N, 3.80%.

4.7. 4-Benzyloxy-7-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (17)

$MgBr_2 \cdot OEt_2$ (10.4 g, 40.1 mmol) was added portionwise to diether **16** (13.1 g, 36.4 mmol) in PhMe (650 mL) and Et_2O (100 mL) at 75 °C (Ar). The mixture was heated to reflux overnight, cooled to 0 °C, quenched with ice-cold HCl (2 M, 250 mL), and diluted with EtOAc (400 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3×350 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated to yield a white solid, which was washed with hot hexanes and recrystallized from MeOH to give phenol **17** (7.16 g, 73%) as white needles: R_f=0.29 (Et_2O/hexanes, 1:1); mp 127–129 °C (MeOH); IR (film) 3400, 1678, 1503, 1453, 1283, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 4.32 (s, 2H), 5.09 (s, 2H), 6.80 (d, 1H, *J*=8.5 Hz), 6.97 (d, 1H, *J*=8.5 Hz), 7.35–7.41 (m, 5H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 149.5, 146.6, 136.8, 128.8, 128.6, 128.2, 127.5, 118.1, 117.5, 115.0, 71.0, 50.6, 28.9; *m/z* (CI, NH_3) 270 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{16}H_{16}NO_3$ $(M+H)^+$: 270.1130; found: 270.1130. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.46; H, 5.66; N, 5.13%. Crystal data for phenol **19**: $C_{16}H_{15}NO_3$, M=269.3, monoclinic, $P2_1$ (no. 14), a=13.727(11), b=6.873(4), c=15.329(8) Å, β=108.97(5)°, V=1367.8(15) $Å^3$, Z=4, D_c=1.308 g cm^{-3}, μ(Cu Kα)=0.74 mm^{-1}, T=293 K, colorless platy needles; 2121 independent measured reflections, F^2 refinement, R_1=0.051, wR_2=0.141, 1530 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 120°$], 175 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.8. 4-Benzyloxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (18)

Phenol **17** (11.3 g, 42.0 mmol), MeI (3.9 mL, 62.9 mmol), and K_2CO_3 (8.70 g, 62.9 mmol) in Me_2CO (210 mL) were heated at reflux for 8 h. The mixture was rotary evaporated and the residue was partitioned between H_2O (250 mL) and CH_2Cl_2 (250 mL). The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (3×250 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 4:1) to give methyl ether **18** (10.8 g, 91%) as a white solid: R_f=0.24 (EtOAc/hexanes, 4:1); mp 142–145 °C (CH_2Cl_2); IR (film) 1688, 1502, 1263, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.93 (s, 3H), 4.29 (s, 2H), 5.11 (s, 2H), 6.82 (d, 1H, *J*=9.0 Hz), 6.99 (d, 1H, *J*=9.0 Hz), 7.33–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 151.4, 147.2, 136.8, 132.0, 128.6, 128.1, 127.3, 121.5, 115.3, 111.2, 70.6, 56.3, 49.4, 29.4; *m/z* (CI, NH_3) 284 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{17}H_{18}NO_3$ $(M+H)^+$: 284.1287; found: 284.1288.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.97; H, 5.91; N, 4.82%.

4.9. 4-Hydroxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (19)

Benzyl ether **18** (9.70 g, 34.2 mmol) and 10% Pd/C (0.97 g, 10% w/w) in MeOH (50 mL) and EtOAc (50 mL) were stirred overnight under H_2 (atmospheric pressure), filtered through a pad of Celite®, and rotary evaporated. The residue was chromatographed (CH_2Cl_2 to MeOH/CH_2Cl_2, 1:19) to give phenol **19** (6.59 g, 100%) as a white solid. Recrystallization from MeOH yielded phenol **19** as white crystals: R_f=0.14 (EtOAc); mp >230 °C (MeOH); IR (KBr disc) 3172, 1662, 1612, 1502, 1427, 1267, 1061 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.98 (s, 3H), 3.75 (s, 3H), 4.23 (s, 2H), 6.83 (d, 1H, J=8.5 Hz), 6.89 (d, 1H, J=8.5 Hz), 9.47 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 150.1, 146.2, 130.0, 121.1, 118.9, 113.0, 56.6, 49.1, 29.3; *m/z* (CI, NH_3) 194 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{10}H_{12}NO_3$ $(M+H)^+$: 194.0817; found: 194.0817. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.28; H, 5.64; N, 7.14%.

4.10. 5-Bromo-4-hydroxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (20)

Br_2 (117 μL, 2.28 mmol) in glacial AcOH (0.5 mL) was added dropwise to phenol **19** (400 mg, 2.07 mmol) and NaOAc·$3H_2O$ (620 mg, 4.55 mmol) in glacial AcOH (2.4 mL). After stirring at room temperature for 30 min, saturated aqueous $Na_2S_2O_5$ (15 mL) was added and the mixture was extracted successively with CH_2Cl_2 (15 mL) and EtOAc (4×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (MeOH/CH_2Cl_2, 3:97) to give bromide **20** (295 mg, 52%) as a white solid. Recrystallization from MeOH yielded bromide **20** as white needles: R_f=0.18 (EtOAc); mp >230 °C (MeOH); IR (KBr disc) 3467, 1662, 1591, 1500, 1456, 1404, 1365, 1298, 1219, 1101, 1068 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.98 (s, 3H), 3.78 (s, 3H), 4.30 (s, 2H), 7.15 (s, 1H), 9.63 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 150.4, 142.9, 131.9, 120.7, 116.3, 114.6, 56.8, 49.7, 29.3; *m/z* (CI, NH_3) 274, 272 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{10}H_{11}{}^{81}BrNO_3$ $(M+H)^+$: 273.9902; found: 273.9903; calcd for $C_{10}H_{11}{}^{79}BrNO_3$ $(M+H)^+$: 271.9922; found: 271.9921. Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.26; H, 3.78; N, 5.06%. Crystal data for bromide **27**: $C_{10}H_{10}BrNO_3$, M=272.1, monoclinic, $P2_1$ (no. 15), a=12.273(16), b=10.084(17), c=17.528(4) Å, β=102.95(13)°, V=2114.1(7) $Å^3$, Z=8, D_c=1.710 g cm^{-3}, μ(Cu Kα)=5.22 mm^{-1}, T=293 K, colorless platy needles; 1514 independent measured reflections, F^2 refinement, R_1=0.064, wR_2=0.167, 1034 independent observed absorption corrected reflections $[|F_o| > 4\sigma(|F_o|),\ 2\theta \leq 120°]$, 147 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.11. 5-Bromo-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-4-isoindolyl trifluoromethanesulfonate (21)

$(CF_3SO_2)_2O$ (96 μL, 0.57 mmol) was added dropwise to phenol **20** (103 mg, 0.38 mmol) and freshly distilled Et_3N (105 μL, 0.76 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The mixture was allowed to warm to room temperature overnight and rotary evaporated. The residue was partitioned between saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (8 mL), the layers were separated and the aqueous phase was further extracted with EtOAc (2×8 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 4:1) to give triflate **21** (84 mg, 55%) as a white solid: R_f=0.41 (EtOAc); mp 156–159 °C (MeOH); IR (film) 1700, 1476, 1424, 1214, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.99 (s, 3H), 4.45 (s, 2H), 7.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 156.4, 137.4, 134.2, 121.8, 120.6, 118.5 (q, J_{C-F}=321 Hz), 116.8, 56.8, 49.4, 29.4; *m/z* (CI, NH_3) 406, 404 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{11}H_{10}{}^{81}BrF_3NO_5S$ $(M+H)^+$: 405.9395; found: 405.9392; calcd for $C_{11}H_{10}{}^{79}BrF_3NO_5S$ $(M+H)^+$: 403.9415; found: 403.9419.

4.12. 2-Bromo-5,8-dimethoxy-1-naphthol (26)[24]

(a) A freshly prepared solution of Br_2 in CH_2Cl_2 (1.0 M, 18.4 mL, 18.4 mmol) was added dropwise to naphthol **25**[22,41] (3.60 g, 17.5 mmol) in CH_2Cl_2 (170 mL) at −78 °C. After stirring for 30 min, the mixture was allowed to warm to room temperature, stirred for a further 30 min, and poured into ice-cold saturated aqueous $NaHCO_3$ (250 mL). The phases were separated, the aqueous portion was further extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9 to 3:7) to give bromonaphthol **26** (4.21 g, 84%) as a white solid.

(b) NBS (6.72 g, 37.7 mmol) in MeCN (75 mL) was added dropwise to naphthol **25**[22,40] (7.00 g, 34.3 mmol) in MeCN (100 mL) at −20 °C. After stirring at −20 °C for 1 h, the mixture was rotary evaporated and the residual solid was dissolved in CH_2Cl_2. The solution was washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9 to 3:7) to give bromonaphthol **26** (6.33 g, 65%) as a white solid. Recrystallization from Et_2O and hexanes yielded bromide **26** as transparent plates: R_f=0.28 (EtOAc/hexanes, 1:4); mp 135 °C (Et_2O/hexanes); IR (film) 3332, 1610, 1390, 1253, 1126, 1088, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.02 (s, 3H), 6.66 (d, 1H, J=8.5 Hz), 6.72 (d, 1H, J=8.5 Hz), 7.55 (d, 1H, J=9.0 Hz), 7.60 (d, 1H, J=9.0 Hz), 10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 150.3, 149.1, 130.8, 127.2, 116.1, 114.2, 105.5, 104.7, 103.4, 56.6, 55.7; *m/z* (CI, NH_3) 302, 300 $(M+NH_4)^+$, 285, 283 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{12}H_{12}{}^{81}BrO_3$ $(M+H)^+$: 284.9949; found: 284.9939; calcd for $C_{12}H_{12}{}^{79}BrO_3$ $(M+H)^+$: 282.9970; found: 282.9963. Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92. Found: C, 51.19; H, 4.03%. Crystal data for bromide **26**: $C_{12}H_{11}BrO_3$, M=283.1, orthorhombic, $P2_12_12_1$ (no. 61), a=6.032(13), b=15.959(4), c=23.569(3) Å, V=2268.8(8) $Å^3$, Z=8, D_c=1.658 g cm^{-3}, μ(Cu Kα)=4.86 mm^{-1}, T=293 K, colorless plates; 1673 independent measured reflections, F^2 refinement, R_1=0.075, wR_2=0.200, 1214 independent observed absorption corrected reflections $[|F_o| > 4\sigma(|F_o|),\ 2\theta \leq 126°]$, 150 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.13. 2-Bromo-1,5,8-trimethoxynaphthalene (27)

Naphthol **26** (5.50 g, 19.4 mmol), Cs_2CO_3 (12.7 g, 38.9 mmol), and MeI (3.6 mL, 58.3 mmol) in Me_2CO (25 mL) were heated at reflux overnight. The mixture was rotary evaporated, the residual solid was partitioned between EtOAc (100 mL) and H_2O (100 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (2×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/hexanes, 3:7) to give trimethoxynaphthalene **27** (5.43 g, 94%) as a white solid: R_f=0.44 (EtOAc/hexanes, 1:4); mp 67–69 °C (CH_2Cl_2/hexanes); IR (film) 1617, 1578, 1456, 1406, 1343, 1259, 1094, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 6H), 6.75 (d, 1H, J=8.5 Hz), 6.84 (d, 1H, J=8.5 Hz), 7.62 (d, 1H, J=9.0 Hz), 7.93 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 149.8, 149.3, 130.0, 128.0, 122.3, 119.6, 116.3, 107.6, 104.3, 61.8, 57.2, 55.8; m/z (CI, NH_3) 316, 314 $(M+NH_4)^+$, 299, 297 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{13}H_{17}{}^{81}BrNO_3$ $(M+NH_4)^+$: 316.0371; found: 316.0372; calcd for $C_{13}H_{17}{}^{79}BrNO_3$ $(M+NH_4)^+$: 314.0392; found: 314.0397. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.62; H, 4.35%.

4.14. 1,5,8-Trimethoxy-2-naphthaleneboronic acid (28)

n-BuLi (2.5 M in hexanes; 1.75 mL, 4.38 mmol) was added dropwise to bromonaphthalene **27** (1.00 g, 3.37 mmol) in THF (25 mL) at −78 °C. After 5 min, triisopropyl borate (1.01 mL, 4.38 mmol) was added dropwise with stirring. After 30 min at −78 °C, the solution was allowed to warm to room temperature and after 1 h, 10% aqueous HCl (20 mL) was added and the mixture was vigorously stirred for 45 min. The layers were separated and the aqueous phase was further extracted with EtOAc (4×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 1:4 to 2:3) to give boronic acid **28** (811 mg, 92%) as a white solid: R_f=0.41 (EtOAc/hexanes, 1:1); mp 128–132 °C (EtOAc/hexanes); IR (film) 3430, 1620, 1575, 1503, 1462, 1380, 1358, 1259, 1100, 1060, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.68 (br s, 2H), 6.82 (s, 2H), 7.91 (d, 1H, J=8.5 Hz), 8.10 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.8, 149.6, 131.5, 131.1, 119.7, 118.4, 106.0, 105.3, 64.0, 56.6, 55.9; m/z (CI, NH_3) 280 $(M+NH_4)^+$, 263 $(M+H)^+$. Anal. Calcd for $C_{13}H_{15}BO_5$: C, 59.58; H, 5.77. Found: C, 59.60; H, 5.79%. It was found to be essential to add the triisopropyl borate only 5 min after the addition of *n*-BuLi. Failure to do so gave the reduced 1,4,8-trimethoxynaphthalene[30a,41] as by-product, the amount of which increased on extending the metalation period.

4.15. *tert*-Butyl 2-oxo-3-phenylselenenyl-1-pyrrolidinecarboxylate (31)

n-BuLi (2.5 M in hexanes; 648 μL, 1.62 mmol) was added dropwise to freshly distilled *i*-Pr_2NH (250 μL, 1.78 mmol) in THF (5 mL) at 0 °C (Ar). After stirring for 45 min at 0 °C, the solution was cooled to −78 °C and transferred dropwise to pyrrolidinone **29**[42] (300 mg, 1.62 mmol) in THF (5 mL) at −78 °C (Ar). The resulting solution was stirred at −78 °C for 1.5 h before being transferred dropwise to PhSeBr (402 mg, 1.70 mmol) in THF (4 mL) at −78 °C (Ar). After stirring at −78 °C for 15 min, saturated aqueous NH_4Cl (10 mL) was added, the layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9) to give the selenide **31** (375 mg, 68%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.98–2.08 (m, 1H), 2.37–2.50 (m, 1H), 3.32–3.41 (m, 1H), 3.55–3.62 (m, 1H), 3.89–3.93 (m, 1H), 7.24–7.33 (m, 3H), 7.64 (d, 2H, J=7.0 Hz); m/z (CI, NH_3) 700 $(2M[^{80}Se^{78}Se]+NH_4)^+$, 359, 357 $(M+NH_4)^+$, 342, 340 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{15}H_{23}N_2O_3{}^{80}Se$ $(M+NH_4)^+$: 359.0874; found: 359.0877; calcd for $C_{15}H_{23}N_2O_3{}^{78}Se$ $(M+NH_4)^+$: 357.0882; found: 357.0890. Direct addition of PhSeBr to the lactam enolate gave an adduct that was tentatively assigned as the corresponding diselenide **30**. *n*-BuLi (2.5 M in hexanes; 7.3 mL, 18.3 mmol) was added dropwise with stirring to freshly distilled *i*-Pr_2NH (2.6 mL, 18.3 mmol) in THF (40 mL) at 0 °C (Ar). After 30 min, the solution was cooled to −78 °C and transferred dropwise with stirring via cannula to pyrrolidinone **29** (3.22 g, 17.4 mmol) in THF (40 mL) at −78 °C (Ar). After 1.5 h, PhSeBr (4.31 g, 18.3 mmol) in THF (40 mL) was added dropwise with stirring via cannula at −78 °C. After 3 h, saturated aqueous NH_4Cl (120 mL) was added, the layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (hexanes) to give an adduct that was tentatively assigned as the pyrrolidinone **30** (3.6 g, 42%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.24 (t, 2H, J=7.0 Hz), 3.29 (t, 2H, J=7.0 Hz), 7.31–7.43 (m, 6H), 7.73 (d, 4H, J=7.5 Hz).

4.16. *tert*-Butyl 2-oxo-2,5-dihydro-1*H*-1-pyrrolecarboxylate (32)

Pyridine (108 μL, 1.33 mmol) and aqueous H_2O_2 (35% w/w, 329 μL, 3.99 mmol) were successively added to selenide **31** (227 mg, 0.67 mmol) in CH_2Cl_2 (7.4 mL) at −78 °C and the mixture was allowed to warm to room temperature over 2 h. Saturated aqueous NH_4Cl (5 mL) was added, the layers were separated, and the organic phase was washed with aqueous HCl (1 M, 5 mL) and brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:3) to give lactam **32** (84 mg, 69%) as a white solid: R_f=0.29 (EtOAc/hexanes, 1:1); IR (film) 1774, 1739, 1718, 1359, 1321, 1296, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.37 (d, 2H, J=2.0 Hz), 6.17–6.20 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 149.6, 145.1, 128.0, 83.0, 51.6, 28.1; m/z (CI, NH_3) 201 $(M+NH_4)^+$, 184 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_9H_{14}NO_3$ $(M+H)^+$: 184.0974; found: 184.0974.

4.17. 4-Bromo-5*H*-2-furanone (34)[29]

Oxalyl bromide (10.0 mL, 108 mmol) was added dropwise over 1 h to a suspension of tetronic acid (**33**) (9.00 g, 89.9 mmol) in CH_2Cl_2 (200 mL) and DMF (9 mL), while carefully maintaining the reaction temperature at 0 °C. The yellow solution turned green and was stirred successively at 0 °C for 1 h and at room temperature for 2 h. H_2O

(250 mL) was added, the layers were separated, and the aqueous phase was further extracted with Et_2O (4×100 mL). The combined organic extracts were washed successively with H_2O, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and rotary evaporated. Recrystallization of the residual solid from Et_2O gave bromofuranone **34** (11.9 g, 81%) as white needles: R_f=0.41 (EtOAc/hexanes, 7:3); mp 76–77 °C (Et_2O); IR (film) 1776, 1748, 1600, 1264, 1154, 1014, 867 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, 2H, J=1.5 Hz), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 146.3, 121.7, 74.9; m/z (CI, NH_3) 182, 180 $(M+NH_4)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_4H_7{}^{81}BrNO_2$ $(M+NH_4)^+$: 181.9640; found: 181.9635; calcd for $C_4H_7{}^{79}BrNO_2$ $(M+NH_4)^+$: 179.9660; found: 179.9665.

4.18. 4-(1,5,8-Trimethoxy-2-naphthyl)-5*H*-2-furanone (35)

(a) P(*t*-Bu)$_3$ (3.6 mg, 0.018 mmol) was added to boronic acid **28** (135 mg, 0.52 mmol), bromofuranone **34** (80 mg, 0.49 mmol), $Pd_2(dba)_3$ (6.7 mg, 0.0074 mmol), and KF (86 mg, 1.47 mmol) in Ar sparged THF (2 mL) (Ar). The mixture was heated at 60 °C for 6 h, after which time a further amount of bromolactone **34** (80 mg, 0.49 mmol) was added (80 mg, 0.49 mmol). The mixture was heated at 60 °C for an additional 12 h, cooled to room temperature, diluted with EtOAc (5 mL), and filtered through a pad of Celite®. The filtered residue was washed repeatedly with EtOAc and the filtrate was rotary evaporated and chromatographed (Et_2O/hexanes, 1:1) to give furanone **35** (99 mg, 64%) as a yellow solid. Recrystallized from EtOAc and hexanes yielded furanone **35** as bright yellow needles.

(b) Boronic acid **28** (1.45 g, 5.53 mmol), bromofuranone **34** (1.17 g, 7.19 mmol), and $PdCl_2(PPh_3)_2$ (78 mg, 0.11 mmol) in aqueous KF (2 M, 15 mL) and THF (15 mL) were heated at reflux for 5 h. After cooling to room temperature, the layers were separated and the aqueous phase was further extracted with EtOAc (4×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:1) to give furanone **35** (1.52 g, 91%) as a yellow solid. Recrystallization from EtOAc and hexanes yielded furanone **35** as bright yellow needles: R_f=0.18 (Et_2O/hexanes, 1:1); mp 139–141 °C (EtOAc/hexanes); IR (film) 1746, 1603, 1572, 1455, 1417, 1369, 1347, 1260, 1159, 1077, 1050, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 5.42 (d, 2H, J=1.5 Hz), 6.60 (s, 1H), 6.87 (s, 2H), 7.46 (d, 1H, J=9.0 Hz), 8.07 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 162.1, 156.6, 150.2, 149.5, 130.0, 124.4, 120.7, 120.6, 119.3, 115.6, 107.0, 106.4, 73.4, 62.9, 56.6, 56.0; m/z (CI, NH_3) 318 $(M+NH_4)^+$, 301 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{17}H_{20}NO_5$ $(M+NH_4)^+$: 318.1341; found: 318.1352. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.98; H, 5.22%.

4.19. 1-Methyl-4-(1,5,8-trimethoxy-2-naphthyl)-1,5-dihydro-2-pyrrolone (36)

Furanone **35** (3.1 g, 10.3 mmol) and $MeNH_2$ (2.0 M in MeOH; 31 mL, 61.9 mmol) were heated at 65 °C for 3 h, and the mixture was rotary evaporated and the residue was dissolved in anhydrous dioxane (100 mL). HCl (4.0 M in dioxane; 7.7 mL, 31.0 mmol) was added and the mixture was heated at reflux for 6 h. After cooling to room temperature, the mixture was diluted with EtOAc (100 mL), carefully washed with saturated aqueous $NaHCO_3$ (2×150 mL) and brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc to MeOH/EtOAc, 1:19) to give pyrrolinone **36** (2.47 g, 76%) as a yellow solid. Recrystallization from EtOAc yielded pyrrolinone **36** as yellow crystals: R_f=0.16 (EtOAc); mp 165–167 °C (EtOAc); IR (film) 1678, 1452, 1414, 1367, 1350, 1260, 1111, 1074, 1035, 820, 800, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 3.79 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.54 (s, 2H), 6.71 (s, 1H), 6.79 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 7.46 (d, 1H, J=9.0 Hz), 8.04 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.4, 151.8, 150.2, 149.6, 129.3, 124.9, 124.2, 122.9, 120.9, 118.9, 106.7, 105.4, 62.3, 56.6 (2C), 55.9, 29.0; m/z (CI, NH_3) 627 $(2M+H)^+$, 331 $(M+NH_4)^+$, 314 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{18}H_{20}NO_4$ $(M+H)^+$: 314.1392; found: 314.1396. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.06; H, 6.13; N, 4.45%.

4.20. 3-(1-Hydroxy-2,2-dimethoxyethyl)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-1,5-dihydro-2-pyrrolone (37)

$Bu_2BOSO_2CF_3$ (1.0 M in CH_2Cl_2; 1.76 mL, 1.76 mmol) was added dropwise to pyrrolinone **36** (500 mg, 1.60 mmol) in anhydrous CH_2Cl_2 (8.5 mL) at −78 °C. The mixture was stirred for 5 min and freshly distilled Et_3N (267 μL, 1.91 mmol) was added dropwise. After stirring for 1.5 h at −78 °C, the solution was treated with freshly distilled anhydrous dimethoxyacetaldehyde[43,44] (664 mg, 6.38 mmol) in one portion. The mixture was stirred for 2 h at −78 °C, diluted with EtOAc (25 mL), and washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was further extracted with EtOAc (4×20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 then EtOAc) to give acetal **37** as an oil. Et_2O was added to the oil and evaporated in vacuo at 40 °C. The procedure was repeated three times to give acetal **37** (434 mg, 65%) as an off-white foam: R_f=0.11 (EtOAc); mp 105–108 °C (EtOAc); IR (film) 3404, 2935, 1671, 1452, 1414, 1261, 1072, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.34 (s, 3H), 3.42 (s, 3H), 3.77 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 4.34 (d, 1H, J=20.0 Hz), 4.47–4.54 (m, 2H), 4.91 (d, 1H, J=7.0 Hz), 6.79 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 7.53 (d, 1H, J=8.5 Hz), 8.09 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 154.2, 150.4, 150.0, 149.6, 132.0, 129.2, 127.6, 124.3, 120.9, 118.7, 106.2, 105.1, 104.8, 67.9, 62.6, 56.6, 55.9, 55.7 (2C), 54.1, 28.9; m/z (CI, NH_3) 418 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{22}H_{28}NO_7$ $(M+H)^+$: 418.1866; found: 418.1847. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.12; H, 6.32; N, 3.23%.

4.21. 5,7,10,11-Tetramethoxy-2-methyl-1,2-dihydronaphtho[2,3-*e*]isoindol-3-one (39)

i-Pr_2NEt (55 μL, 0.32 mmol) and TMSOTf (82 μL, 0.36 mmol) were successively added dropwise to acetal **37** (60 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (6 mL) at −78 °C (Ar). The mixture was allowed to warm to room temperature over 1 h, after which *i*-Pr_2NEt (28 μL,

0.22 mmol) and *t*-$BuMe_2OSO_2CF_3$ (49 μL, 0.22 mmol) were successively added dropwise at 0 °C. After stirring for further 2 h at room temperature, anhydrous $ZnBr_2$ (32 mg, 0.14 mmol) was added in one portion. The mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (6 mL) and H_2O (8 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (3×8 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and rotary evaporated. Preparative thin layer chromatography (EtOAc) gave an unstable yellow solid, tentatively assigned as the tetramethoxyanthracene **39** (17 mg, 32%), which decomposed within 36 h: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.99 (s, 3H), 4.07 (s, 6H), 4.15 (s, 3H), 4.95 (s, 2H), 6.72 (d, 1H, *J*=8.0 Hz), 6.79 (d, 1H, *J*=8.0 Hz), 7.28 (s, 1H), 9.13 (s, 1H); *m/z* (ES^+) 368 $(M+H)^+$; *m/z* (ES^-) 366 (M−H).

4.22. 1-Methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (40)

Mg turnings (419 mg, 17.2 mmol) were added to pyrrolinone **36** (270 mg, 0.86 mmol) in MeOH (24 mL) at 0 °C. After stirring for 30 min at 0 °C, a vigorous exothermic reaction occurred. The mixture was successively stirred at room temperature for 20 min and diluted with CH_2Cl_2 (25 mL) and saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/EtOAc gradient) to give pyrrolidinone **40** (253 mg, 93%) as a yellow oil, which crystallized upon standing: R_f=0.17 (EtOAc); mp 87–89 °C (EtOAc); IR (film) 1691, 1601, 1581, 1504, 1452, 1414, 1349, 1261, 1105, 1065, 1003, 802, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (dd, 1H, *J*=8.0, 17.0 Hz), 2.85 (dd, 1H, *J*=9.5, 17.0 Hz), 2.92 (s, 3H), 3.42 (dd, 1H, *J*=7.0, 10.0 Hz), 3.79 (dd, 1H, *J*=8.5, 10.0 Hz), 3.80 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.24–4.33 (m, 1H), 6.72 (d, 1H, *J*=8.5 Hz), 6.80 (d, 1H, *J*=8.5 Hz), 7.36 (d, 1H, *J*=9.0 Hz), 8.05 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 153.4, 149.6, 149.5, 132.7, 127.8, 123.9, 120.6, 119.1, 106.3, 103.8, 63.0, 56.7, 56.6, 55.8, 38.7, 29.6, 29.4; *m/z* (CI, NH_3) 631 $(2M+H)^+$, 333 $(M+NH_4)^+$, 316 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{18}H_{22}NO_4$ $(M+H)^+$: 316.1549; found: 316.1550. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.73; H, 6.84; N, 4.52%.

4.23. 3-(2,2-Dimethoxyacetyl)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (41)

n-BuLi (2.5 M in hexanes; 232 μL, 0.58 mmol) was added dropwise to freshly distilled *i*-Pr_2NH (76 μL, 0.58 mmol) in anhydrous THF (2 mL) at 0 °C. After stirring for 45 min at 0 °C and cooling to −78 °C, pyrrolidinone **40** (166 mg, 0.53 mmol) in anhydrous THF (3 mL) was added dropwise and the solution was stirred for further 1.5 h. The mixture was added dropwise to methyl dimethoxyacetate (258 μL, 2.11 mmol) in anhydrous THF (1.5 mL) at −78 °C. Stirring was continued for 5 min at −78 °C and 5 min at room temperature, after which saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) were successively added. The layers were separated and the aqueous phase was further extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 then EtOAc/hexanes, 1:1 to 7:3) to give ketoacetal **41** (151 mg, 69%) as an orange solid containing both diastereoisomers (1:9): R_f=0.30 (EtOAc/hexanes, 4:1); mp 125–127 °C (EtOAc/hexanes); IR (film) 2935, 1737, 1691, 1601, 1581, 1450, 1413, 1350, 1259, 1105, 1066, 1001, 800, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) selected peaks for major isomer δ 2.88 (s, 3H), 3.26–3.30 (m, 1H), 3.27 (s, 3H), 3.34 (s, 3H), 3.79–3.84 (m, 1H), 3.81 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.45 (d, 1H, *J*=8.5 Hz), 4.69–4.75 (m, 1H), 5.11 (s, 1H), 6.70 (d, 1H, *J*=8.5 Hz), 6.77 (d, 1H, *J*=8.5 Hz), 7.30 (d, 1H, *J*=9.0 Hz), 8.03 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) selected peaks for major isomer δ 200.7, 169.0, 153.8, 149.4, 149.3, 130.5, 127.9, 123.9, 120.5, 119.0, 106.2, 103.9, 102.3, 63.0, 57.1, 56.4, 55.6, 55.0, 54.25, 54.20, 32.3, 29.7; *m/z* (CI, NH_3) 418 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{22}H_{28}NO_7$ $(M+H)^+$: 418.1866; found: 418.1855. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.38; H, 6.67; N, 3.35%.

4.24. (3-(*Z*)-1-Acetoxy-2,2-dimethoxyethylidene)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (42)

LDA (1.8 M in heptane, THF, and PhEt; 114 μL, 0.21 mmol) was added dropwise to ketone **41** (78 mg, 0.19 mmol) in anhydrous THF (2 mL) at −78 °C. After stirring at this temperature for 1.5 h, freshly distilled AcCl (53 μL, 0.75 mmol) was added dropwise and the mixture was allowed to warm to room temperature overnight. EtOAc (8 mL) and H_2O (8 mL) were added, the layers were separated, and the aqueous phase was further extracted with EtOAc (3×8 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc) to give enol acetate **42** (34 mg, 40%) as a light amber oil: R_f=0.18 (EtOAc/hexanes, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.89 (s, 3H), 2.94 (s, 3H), 3.20–3.23 (m, 1H), 3.21 (s, 3H), 3.90 (s, 3H), 3.94–3.99 (m, 1H), 3.95 (s, 3H), 3.99 (s, 3H), 4.62 (d, 1H, *J*=0.5 Hz), 4.98 (dd, 1H, *J*=2.5, 8.5 Hz), 6.70 (d, 1H, *J*=8.5 Hz), 6.77 (d, 1H, *J*=8.5 Hz), 7.30 (d, 1H, *J*=9.0 Hz), 8.03 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.7, 152.7, 149.7, 149.3, 146.5, 134.2, 128.1, 125.3, 125.1, 120.6, 119.1, 106.1, 103.6, 100.2, 62.6, 56.6, 55.79, 55.76, 54.6, 54.2, 33.2, 29.9, 20.9; *m/z* (EI) 459 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_{24}H_{29}NO_8$ ($M^{+\bullet}$): 459.1893; found: 459.1888.

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Supplementary data

Additional experimental procedures and structural data for all new compounds and crystallographic data (including ORTEPs and CIFs) for compounds **17**, **20**, and **26** (CCDC 613463, 613464 and 613465, respectively). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.004.

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