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Studies on the Total Synthesis of Lactonamycin: Synthesis of the CDEF Ring System

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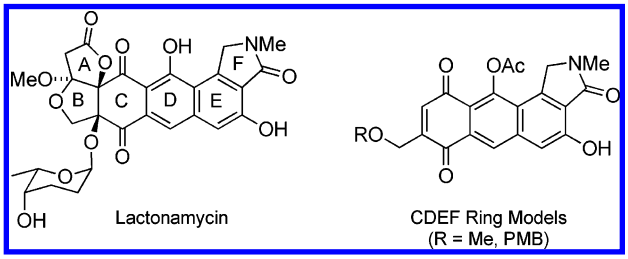
Received June 28, 2006



A concise and efficient synthesis of the tetracyclic CDEF ring system of lactonamycin (**1**) is described. The key step involved the Lewis acid mediated, intramolecular Friedel−Crafts acylation of carboxylic acid **6** to produce the tetracyclic CDEF core structure of target **1**. The synthesis of **6** was carried out using a high-yielding Negishi coupling of benzyl bromide **7** with triflate **8**, which was accessible in 11 steps and 31% overall yield on a multigram scale starting from trihydroxy acid **9**.

Introduction

Lactonamycin (**1**)[1] and lactonamycin-Z (**2**)[2] have intriguing structural features, which include a naphtho[*e*]isoindole ring system (EF-rings) and a densely oxygenated fused perhydrofuran−furanone ring system containing a labile tertiary methoxy group (AB-rings) (Figure 1). Both natural products contain a 2-deoxy sugar unit (**1**, α-L-rhodinopyranose; **2**, α-L-2,6-dideoxyribopyranose) attached through a tertiary α-keto-glycosidic linkage. Lactonamycin (**1**) shows significant levels of antimicrobial activity toward Gram-positive bacteria, being especially effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). In addition, lactonamycin (**1**) shows significant levels of cytotoxicity against various tumor cell lines.[3]

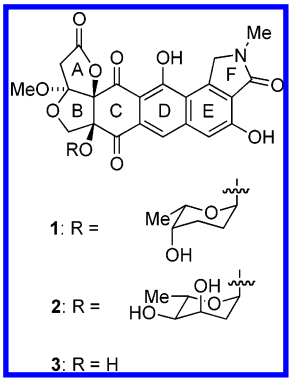


FIGURE 1. Structures of lactonamycin (**1**), lactonamycin-Z (**2**), and the aglycon lactonamycinone (**3**).

Four groups have reported synthetic studies directed toward the total synthesis of lactonamycin (**1**). Two different routes for the construction of model CDEF ring systems were reported by Danishefsky and Cox,[4] and the Danishefsky group followed up these initial studies with the total synthesis of (±)-lactonamycinone (**3**).[5] Both Deville and Behar[6] and Kelly and co-workers[7] have published routes for the synthesis of the CDEF

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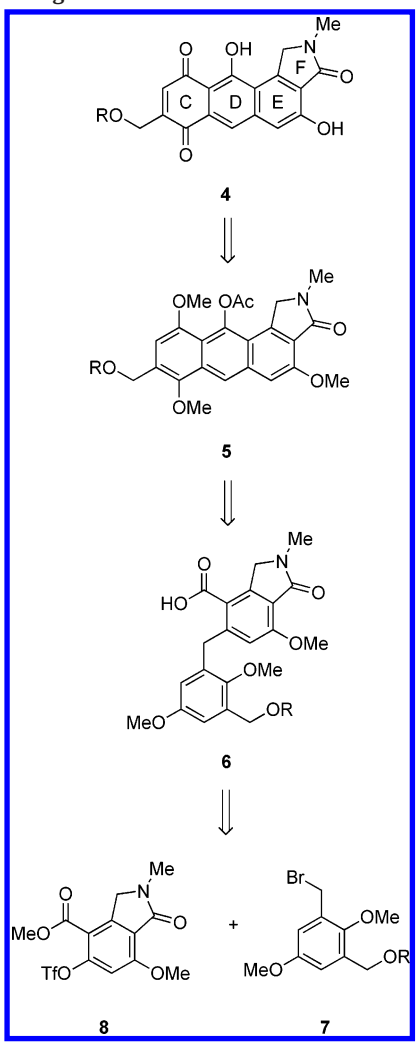
10.1021/jo0613378 CCC: $33.50
Published on Web 09/19/2006

SCHEME 1. Retrosynthetic Analysis of the Model CDEF Tetracyclic Target 4



ring system.[6] More recently the Kelly group has described a model asymmetric synthesis of the AB ring system.[8] Recently, we reported model studies on the synthesis of the ABCD ring system of lactonamycin.[9] This study highlighted the use of several iterative Michael addition reactions and oxidations to construct the oxygenated lactone entity. Retrosynthetically, we considered that the CDEF ring system **4** should be available using an intramolecular Friedel−Crafts acylation approach (Scheme 1). In this analysis, we considered that tetracycle **4** should be obtained by oxidation of hydroquinone **5**, which in turn should be available from carboxylic acid **6**. Acid **6** should be derived from triflate **8** using a Pd(0)-catalyzed Negishi coupling with benzyl bromide **7**. We considered that triflate **8** should be accessible from 2,4,6-trihydroxybenzoic acid, whereas bromide **7** should be easily available from *p*-methoxyphenol.

Results and Discussion

Synthesis of Lactam 8. Triflate **8** was synthesized on multigram scale from commercially available trihydroxy acid **9** in 11 steps (Scheme 2). Permethylation of acid **9** using dimethyl sulfate followed by a boron trichloride induced monodeprotection of the *o*-methyl ether afforded phenol **10** (77% over two steps).[10] Subsequent Vilsmeier−Haack formylation gave aldehyde **11** (75%), which was oxidized to produce ester **12** using an excess of sodium cyanide and manganese dioxide (87%).[11] Scale-up of the oxidation reaction was problematic and only a low yield (45%) of **12** was obtained. Alternatively, a two-step oxidation sequence was used to convert aldehyde **11** into diester **12** using sodium chlorite as the oxidizing agent in the presence of sulfamic acid. This reaction required care in execution to prevent formation of the chlorinated phenol **16**, which was formed in 37% yield when the reaction was carried out at 0−5 °C (Figure 2). Addition of the chlorine scavenger 2-methylbutene suppressed the formation of chloride **16** and afforded diester **12** in excellent yield (94% on a 10-g scale).

Condensation of phenol **12** with triflic anhydride followed by a palladium-catalyzed cross-coupling reaction with zinc cyanide[12] successfully gave nitrile **13** (90%). Cobalt chloride and sodium borohydride reductions of nitrile **13** resulted in the formation of lactam **14**. However, yields of this reaction were only good (66%) on a small scale (500 mg) of nitrile **13**, but were significantly reduced (30%) on a multigram scale. Conducting the reduction with sodium borohydride in the presence of trifluoroacetic acid (TFA)[13] gave lactam **14** in slightly improved yield (41%). Neither the replacement of TFA by 2,2-difluoroacetic acid or acetic acid itself nor the replacement of cobalt by nickel[14] or copper[15] resulted in formation of the desired lactam **14** in acceptable yields. Alternatively, hydrogenation of nitrile **13** was investigated, and equimolar amounts of Adams catalyst[16] in acetic acid and THF was found to result in a clean conversion to lactam **14** (94%). Notwithstanding this expense, the platinum was easily recycled in high yield and used repeatedly.[17] Attempts to reduce the amount of the platinum catalyst to catalytic amounts were unsuccessful as were reductions with Raney nickel,[18] palladium,[19] and rhodium.[20] In these less successful reactions, the conversion of nitrile **13** to lactam **14** was very slow and side products, such as succinimide **17** and the mixed aminal **18**, were formed (Figure 2).

Methylation of lactam **14** using iodomethane and sodium hydride in degassed DMF gave ether **15** (91%). This reaction also required care in execution to prevent the formation of succinimide **19a** (Figure 2), a product formed through benzylic oxidation during prolonged reaction times in the presence of

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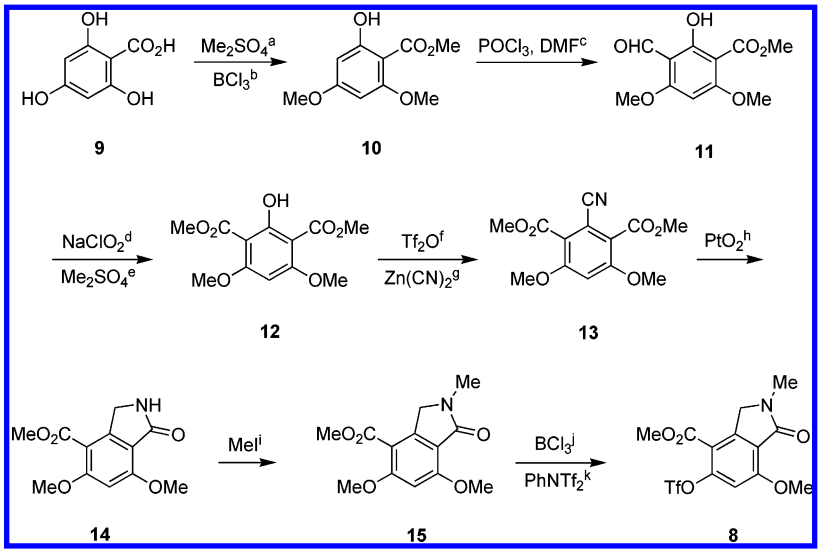
(20) Galan, A.; Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 452.

SCHEME 2. Synthesis of Triflate 8[a]



[a] Reagents and conditions: (a) Me_2SO_4, K_2CO_3, Me_2CO (84%). (b) BCl_3, CH_2Cl_2, −78 °C (91%). (c) $POCl_3$, DMF, 0 to 25 °C (75%). (d) $NaClO_2$, NH_2SO_3H, 2-methylbutene, THF, H_2O and DMSO. (e) DMF, $KHCO_3$, Me_2SO_4 (94% over two steps). (f) Tf_2O, pyridine, CH_2Cl_2 (95%). (g) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 60 °C (95%). (h) PtO_2, THF, AcOH, H_2, 70 psi (94%). (i) NaH, MeI, DMF, 0 °C (91%). (j) BCl_3, CH_2Cl_2, −78 °C (82%). (k) $PhNTf_2$, NEt_3, CH_2Cl_2, reflux (92%).

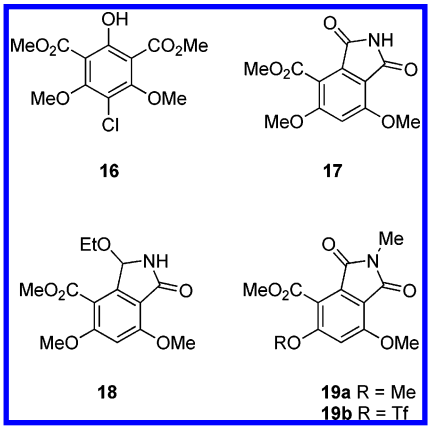


FIGURE 2. Structures of minor side products formed in Scheme 2.

oxygen. Reaction of amide **15** with boron trichloride[21] at −78 °C gave the corresponding phenol (82%) remarkably as a single regioisomer, the structure of which was consistent with the low field position of the phenolic proton in the ^1H NMR spectrum [11.42 (s, 1H)] and was confirmed by the X-ray structure of imide **19b** (vide infra). It is likely that the origin of this regioselectivity is the result of the closer proximity of the ester carbonyl−boron trichloride Lewis base−acid complex to the adjacent methyl ether than the corresponding lactam−boron trichloride complex due to the bicyclic ring fusion. Alternatively, the lactam−boron trichloride complex should be less Lewis acidic and therefore less reactive. Triflation of the phenol using *N*,*N*-ditriflylaniline and triethylamine in dichloromethane gave triflate **8** (92%). It is germane to mention that the success of this reaction was largely dependent on the concentration of the reaction mixture (0.3 M). In contrast, reaction at higher dilution was significantly slower and accompanied by extensive decomposition. In addition, attempted triflation using trifluoromethanesulfonic anhydride was complicated by benzylic oxidation to provide the fluorescent phthalimide derivative **19b**, the structure of which was confirmed by X-ray crystallography (see Supporting Information).

Construction of the CDEF Model Ring System. With triflate **8** in hand, the synthesis of the CDEF model ring system **25** was investigated (Scheme 3). Following the standard protocol for Negishi coupling,[22] triflate **8** was allowed to react with 2,5-dimethoxybenzylzinc chloride (**20**) to give methyl ester **21** (94%). The methyl ester **21** was alternatively obtained in 65% unoptimized yield, when the organozinc compound **20** was prepared from the corresponding chloride using lithium naphthalenide and zinc chloride.[23] Saponification of ester **21** with lithium hydroxide gave carboxylic acid **22** in 37−64% yield. The poor and varying yield was due to loss of material during purification by column chromatography and the low solubility of **22** in most common solvents.

With acid **22** in hand, the intramolecular Friedel−Crafts acylation was investigated. Attempted cyclization of acid **22** to produce tetracycle **23** using trifluoroacetic anhydride[24] was unsuccessful, resulting in the recovery of starting material. Attempts to achieve the intramolecular acylation using oxalyl chloride[25] or triflic anhydride in chloroform with or without pyridine also led to the formation of intractable mixtures of products along with recovered starting material. In contrast to these frustrating failures, polyphosphoric acid[26] (PPA) catalyzed intramolecular Friedel−Crafts acylation of acid **22** gave tetracycle **23** as a single product. Since phenol **23** was oxidatively unstable in air due to anthraquinone formation on the central

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(23) 2,5-Dimethoxybenzylzinc chloride (**20**) was prepared as described in the literature for other organic zinc reagents: Zhu, L.; Wehmeyer, R. M.; Riecke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

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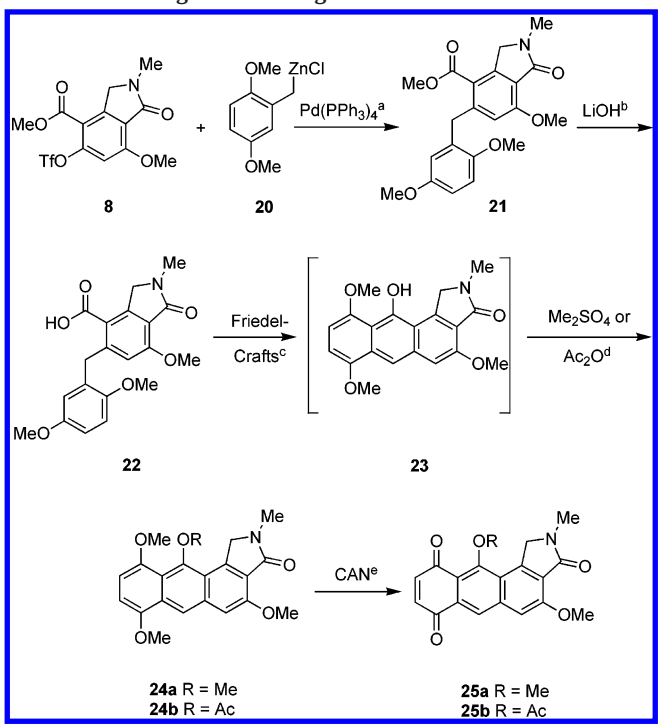
SCHEME 3. Model Negishi Coupling of Triflate 8 with Commercial Organozinc Reagent 20[a]



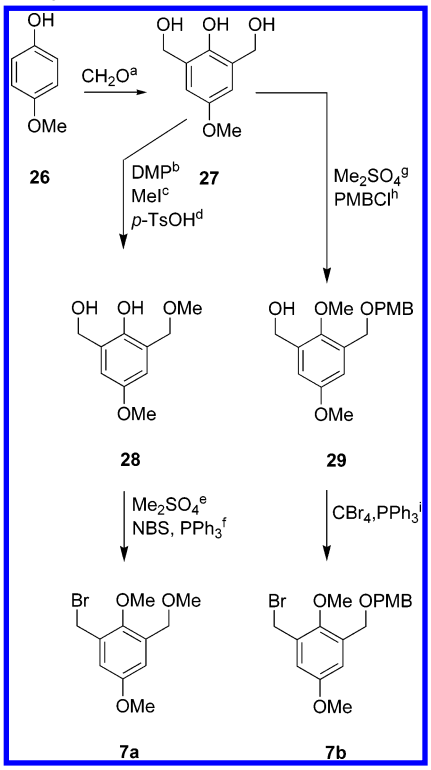
[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, THF (94%). (b) LiOH, THF, MeOH, H_2O 2:1:1 (37−64%). (c) **24a:** PPA, 110 °C, 5 h. **24b:** $Me_2C{=}C(Cl)NMe_2$, CH_2Cl_2, $ZnCl_2$. (d) **24a**: K_2CO_3, Me_2SO_4, acetone, 50 °C, 3 h (<30% over two steps). **24b**: Ac_2O, pyridine, DMAP (80% over two steps). (e) **25b**: CAN, MeCN, and H_2O (65%).

aromatic ring, it was further methylated by reaction with dimethyl sulfate and potassium carbonate in acetone to give ether **24a** (<30% over the last two steps).

Unfortunately, attempted selective oxidation of **24a** to produce quinone **25a** using iodobenzene bis-trifluoroacetate gave only intractable mixtures of polar products, presumably resulting from the oxidation of the central aromatic ring of the anthracene system, which according to Behar should be favored under these conditions.[27] In consequence, phenol **23** was converted into acetate **24b** under standard conditions (vide infra).[28] In contrast and consistent with the Behar studies, ceric ammonium nitrate (CAN) oxidation of acetate **24b** finally afforded the desired quinone **25b** in 65% yield.

Synthesis of Ethers 7a,b. Having established the synthetic strategy for the preparation of the CDE-anthraquinone system of lactonamycin on model compound **25b**, we sought to prepare the tetracyclic ring system **4** with a protected hydroxymethyl side chain attached to the quinone C-ring. This C_1-side chain should allow for elaboration of the highly oxygenated furan−furanone ring system.[9] The required bromide **7a** was synthesized from triol **27**, which was easily prepared from 4-methoxyphenol (**26**) via double hydromethylation using formaldehyde in the presence of calcium oxide (Scheme 4).[29] Ketal formation with dimethoxypropane, *O*-methylation, and acid-promoted cleavage of the acetal group gave diol **28**. Selective methylation of the

SCHEME 4. Synthesis of Bromides 7a,b[a]



[a] Reagents and conditions: (a) CaO, CH_2O, H_2O.[29] (b) $Me_2C(OMe)_2$, *p*-TsOH, Me_2CO (93%). (c) MeI, NaH, THF. (d) *p*-TsOH, THF, H_2O (98% over two steps). (e) Me_2SO_4, K_2CO_3, Me_2CO. (f) NBS, Ph_3P, THF (76% over two steps). (g) K_2CO_3, Me_2SO_4, Me_2CO (70%). (h) NaH, 4-$MeOC_6H_4$-CH_2Br, Bu_4NI, THF:DMF 5:1 (64% based on recovered starting material). (i) PPh_3, CBr_4, THF (73%).

phenol followed by reaction of the benzylic alcohol with *N*-bromosuccinimide and triphenylphosphine gave bromide **7a** (76% over two steps).

In parallel, we decided to examine a more easily cleavable protecting group[30] for the benzyl alcohol, and we chose the 4-methoxybenzyl (PMB) group. In contrast to the synthesis of bromide **7a**, a more direct approach was chosen for the introduction of the PMB protecting group. Selective phenolic methylation of triol **27** followed by mono-4-methoxybenzylation gave alcohol **29** (45% over two steps). To avoid double 4-methoxybenzylation, substoichiometric amounts of the base and 4-methoxybenzyl chloride were used, and the recovered starting material was (33%) recycled. The primary alcohol **29** was converted into bromide **7b** by reaction with carbon tetrabromide and triphenylphosphine (73%).

Synthesis of Tetracyclic CDEF Ring Units 33. With the bromides **7a,b** in hand, the Negishi coupling with triflate **8** was investigated (Scheme 5). Bromides **7a,b** (2.2 equiv) were first transformed into the corresponding organozinc reagents by reaction with zinc-dust and dibromoethane and subsequently coupled with triflate **8** (1 equiv) using palladium(0) catalysis.[31] The coupling products **30a,b** were obtained in excellent yields

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(28) In consequence of the poor yield in the polyphosphoric acid-mediated Friedel−Crafts acylation of acid **22**, phenol **23** was prepared from acid **22** using the Ghosez reagent, analogous to the synthesis of **5a,b**. Phenol **23** was directly acetylated to provide the corresponding acetate **24b** in superior overall yield (80%).

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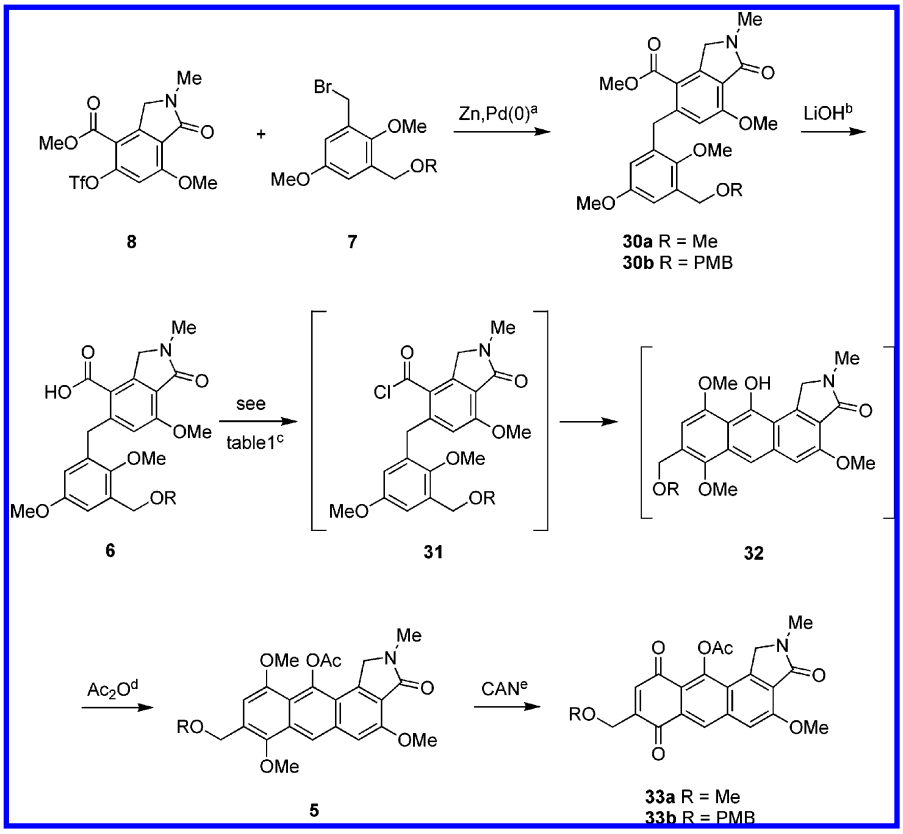
SCHEME 5. Synthesis of the CDEF-Components of Lactonamycin[a]



[a] Reagents and conditions: (a) **7** (2.2 equiv), Zn, $(BrCH_2)_2$, THF, $Pd(PPh_3)_4$ (85% for **30a**, 92% for **30b** both based on **8**). (b) LiOH, THF, MeOH, and H_2O (100% for both **6a,b**). (c) see Table 1. (d) Pyridine, Ac_2O, DMAP. (e) CAN, MeCN, H_2O (61% for **33a**, 71% for **33b**).

TABLE 1. Intramolecular Friedel−Crafts Acylation of Carboxylic Acid 6

entry	starting material	reagents	product	yield (%)
1	**6a**	PPA	**5a**	–
2	**6a**	$(COCl)_2$ (10 equiv)	**5a**	13
3	**6a**	NaH (1.1 equiv), $(COCl)_2$ (1.2 equiv)	**5a**	24[a]
4	**6a**	$Me_2C{=}C(Cl)NMe_2$ (2 equiv)	**5a**	30
5	**6a**	$Me_2C{=}C(Cl)NMe_2$ (5 equiv), $Bi(OTf)_3$ (2 equiv)	**5a**	–
6	**6a**	$Me_2C{=}C(Cl)NMe_2$ (5 equiv), DMAP (1-5 equiv)	**5a**	30
7	**6a**	$Me_2C{=}C(Cl)NMe_2$ (5 equiv), $FeCl_3$ (2 equiv)	**5a**	30
8	**6a**	$Me_2C{=}C(Cl)NMe_2$ (5 equiv), $ZnCl_2$ (2 equiv)	**5a**	82
9	**6b**	$Me_2C{=}C(Cl)NMe_2$ (5 equiv), $ZnCl_2$ (2 equiv)	**5b**	92

[a] 55% of starting material **6a** was recovered.

(85 and 92%) and directly hydrolyzed with lithium hydroxide to provide carboxylic acids **6a,b** in quantitative yields.

Unfortunately, subsequent intramolecular Friedel−Crafts acylation reaction of acid **6a** with polyphosphoric acid resulted in its complete decomposition. We considered that this was probably the result of the acid lability of the benzylic ether entity. We therefore chose to examine more selective conditions for the intramolecular Friedel−Crafts acylation (see Table 1). We found that the tetracycle **5a** could be isolated in 13% yield when oxalyl chloride in triflic acid was used to generate the acid chloride **31** (entry 2). Prior conversion of the carboxylic acid **6a** into the sodium salt using sodium hydride, reaction with oxalyl chloride, and cyclization gave the tetracycle **5a** (24%) along with recovered starting material **6a** (55%) (entry 3). As an alternative, the reaction was carried out under nearly neutral conditions using the Ghosez reagent (1-chloro-*N*,*N*,2-trimethyl-1-propylenamine).[32] This gave acetate **5a** in slightly improved 30% yield (entry 4). To enhance the rate of formation of the acid chloride **31** and its subsequent intramolecular Friedel−Crafts acylation reaction, the addition of Lewis acids and DMAP was investigated. Whereas the addition of bismuth triflate resulted in decomposition (entry 5), DMAP and iron(III) chloride gave tetracycle **5a** in comparable yields to the unpromoted reaction (entries 6 and 7). Pleasingly, however, reaction of acid **6a** with 1-chloro-*N*,*N*,2-trimethyl-1-propylenamine and 2 equiv of zinc chloride finally gave the cyclization product **32**, essentially in quantitative yield, which after direct protection using acetic anhydride and DMAP in pyridine gave acetate **5a** in excellent yield (82%) (entry 8). These optimized reaction conditions also proved to be highly effective for the PMB-protected acid **6b** and gave the desired tetracycle **5b** in excellent yield (92%) (entry 9).

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Smooth conversion of acetate **5a** into quinone **33a** (61%) was carried out by oxidation with CAN.[27] Again, it is germane to comment on the isolation of a side product in this reaction. As expected, the oxidation of acetate **5a** was accompanied by partial D-ring anthraquinone formation (10%). For the oxidation of the 4-methoxybenzyl-protected acetate **5b**, iodobenzene bis-difluoroacetate was used, since we were concerned that CAN would bring about 4-methoxybenzyl ether cleavage.[30] This oxidation reaction gave quinone **33b** in disappointing yield (35%). However, in an act of desperation, the CAN oxidation of **5b** was examined and found to produce quinone **33b** in superior yield (71%). It is appropriate to mention that neither cleavage of the 4-methoxybenzyl protecting group nor oxidation of the central aromatic ring was observed.

Conclusion

The use of a zinc chloride-catalyzed, intramolecular Friedel−Crafts acylation has been shown to be useful for the synthesis of the CDEF ring system of lactonamycin (**1**). Of particular note is the multigram synthesis of triflate **8**, which was allowed to react using an efficient and high-yielding Negishi coupling with the 4-methoxybenzyl-protected bromide **7b**.

Experimental Section

Dimethyl 2-Hydroxy-4,6-dimethoxy-1,3-benzenedicarboxylate (12).[33] 2-Methylbutene (80 mL, 0.75 mol) and amidosulfonic acid (12.4 g, 127 mmol) were added successively to aldehyde **11** (9.00 g, 37.5 mmol) in THF (280 mL), H_2O (220 mL), and DMSO (22 mL) at 15 °C. $NaClO_2$ (13.5 g, 0.12 mmol) in H_2O (36 mL) was added dropwise, so that the internal solution temperature remained <30 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (150 mL). The colorless solution was extracted with EtOAc (1 × 500 mL, 5 × 100 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (150 mL), dried (Na_2SO_4), and rotary evaporated. The residue was dissolved in anhydrous DMF (100 mL), and $KHCO_3$ (4.51 g, 45.0 mmol) and Me_2SO_4 (3.9 mL, 41 mmol) were added successively. After 2 h of stirring at room temperature, saturated aqueous NH_3:saturated aqueous NH_4Cl (1:4, 25 mL) was added, stirring was continued for 30 min, H_2O (350 mL) was added, and the solid was filtered off and washed with H_2O (150 mL). The solid was suspended in EtOAc (60 mL), stirred for 10 min at 50 °C, and precipitated by addition of pentane (60 mL). The solid was filtered off, washed with EtOAc:pentane (1:1, ∼100 mL) and pentane to give **12** (8.8 g, 84%) as a white solid. The deep yellow mother liquid was rotary evaporated and recrystallized to give **12** (1.06 g, 10%) as a white solid: IR (film) 3417, 1718, 1621, 1570, 1439, 1417, 1302, 1274, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 6H), 3.85 (s, 6H), 5.95 (s, 1H), 12.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.3, 56.0, 86.9, 100.7, 162.3, 163.0, 168.7; MS (Cl, NH_3) *m/z* 271 $[M + H]^+$; HRMS *m/z* calcd for $C_{12}H_{15}O_7$ $[M + H]^+$ 271.0819, found $[M + H]^+$ 271.0818. The spectroscopic data were consistent with those reported in the literature.[33]

Dimethyl 2-Cyano-4,6-dimethoxy-1,3-benzenedicarboxylate (13). Pyridine (4.1 mL, 50.0 mmol) and Tf_2O (11.5 mL, 43.4 mmol) were added successively with stirring at 0 °C to phenol **12** (9.0 g, 33.4 mmol) in CH_2Cl_2 (250 mL). After 4 h at room temperature, H_2O (200 mL) was added and the aqueous layer extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), rotary evaporated, and crystallized (cyclohexane:EtOAc 2:1) to give the corresponding triflate (12.8 g, 95%) as a white solid: mp 87−90 °C (EtOAc); R_f 0.27 (hexanes:EtOAc 1:1); IR (film) 1743, 1727, 1568, 1567, 1400, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 6H), 3.91 (s, 6H), 6.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.7, 56.6, 95.2, 110.3, 118.3 (q, J = 318.1 Hz), 144.6, 160.6, 162.9; MS (CI, NH_3)-*m/z* 420 $[M + NH_4]^+$; HRMS (CI) *m/z* calcd for $C_{13}H_{17}F_3NO_9S$ $[M + NH_4]^+$ 420.0576, found $[M + NH_4]^+$ 420.0572. Dppf (5.4 g, 9.8 mmol) and Pd_2dba_3 (2.2 g, 2.5 mmol) were added with stirring to previously degassed triflate (19.8 g, 49.2 mmol) in DMF (150 mL) and heated to 60 °C. $Zn(CN)_2$ (17.3 g, 148 mmol) was added in portions over 6 h and stirring continued overnight at 60 °C. The mixture was cooled to room temperature, when saturated aqueous NH_3:saturated aqueous NH_4Cl (1:9, 600 mL), H_2O (400 mL), and EtOAc (1.5 L) were added, and the mixture was heated to 30−40 °C, giving two clear yellow phases. The aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with H_2O (2 × 150 mL) and brine (200 mL), dried ($MgSO_4$), and rotary evaporated. The dark residue was suspended in CH_2Cl_2 (100 mL), heated at 40 °C, filtrated, and washed with pentane and EtOAc to obtain nitrile **13** (13.1 g, 95%) as a white microcrystalline solid: mp 169−172 °C (pentane); R_f 0.20 (hexanes:EtOAc 1:1); IR (film) 2233, 1720, 1576, 1455, 1426, 1328, 1316, 1116, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.94 (s, 6H), 3.96 (s, 6H), 6.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.0, 56.6, 99.5, 112.8, 114.6, 118.7, 160.2, 164.3; MS *m/z* (CI, NH_3) 297 $[M + NH_4]^+$; HRMS (CI) *m/z* calcd for $C_{13}H_{17}N_2O_6$ $[M + NH_4]^+$ 297.1084, found $[M + NH_4]^+$ 297.1087. Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 55.89; H, 4.75; N, 5.01.

Methyl 5,7-Dimethoxy-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylate (14). PtO_2 (2.5 g, 11 mmol) was added under N_2 to nitrile **13** (3.0 g, 10.7 mmol) in THF (160 mL) and glacial AcOH (80 mL) (Parr apparatus) and heated with stirring to 40−50 °C. After cooling to room temperature under N_2 flow, the apparatus was flushed four times with H_2 and shaken for 6 h under H_2 (70 psi) until a white solid had formed. After having removed the excess of H_2 with N_2, a CH_2Cl_2:MeOH mixture (3:1, 160 mL) was added, and the mixture was heated with stirring until complete dissolution of **14**. Pt was allowed to settle and the mixture filtered through a glass microfiber disk. The catalyst was washed with CH_2Cl_2:MeOH (3:1, 100 mL) and the filtrate rotary evaporated and the residue dissolved in PhMe (100 mL) and re-evaporated. The crude product was combined with material from four separate experiments (from **13** (15.4 g in total) and crystallized from EtOAc and traces of MeOH to obtain lactam **14** (13.0 g, 94%) as a white solid: mp 228−235 °C (pentane); R_f 0.39 (CH_2Cl_2:MeOH 10:1); IR (film) 3354, 1699, 1661, 1596, 1402, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H), 4.00 (s, 3H), 4.04 (s, 3H), 4.59 (s, 2H), 6.47 (s, 1H), 7.33 (bs, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.0, 51.7, 56.7, 57.5, 94.9, 98.4, 107.6, 151.2, 161.4, 164.8, 165.2; MS (CI, NH_3) *m/z* 252 $[M + H]^+$; HRMS (CI) *m/z* calcd for $C_{12}H_{14}NO_5$ $[M + H]^+$ 252.0872, found $[M + H]^+$ 252.0872.

Methyl 5,7-Dimethoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylate (15). NaH (2.49 g, 62.3 mmol, 60% in mineral oil) was added portionwise at 0 °C to a previously degassed solution of lactam **14** (13.0 g, 51.9 mmol) in DMF (500 mL). After 15 min at room temperature, MeI (3.9 mL, 62.3 mmol) was added and the reaction mixture stirred for 15 min, warmed to room temperature, and stirred for a further 2.5 h. Half-saturated aqueous NH_4Cl (300 mL) and EtOAc (500 mL) were added. The aqueous layer was extracted with $CHCl_3$ (300 mL) and $CHCl_3$:*i*PrOH (5:1, 3 × 100 mL). The combined organic layers were rotary evaporated, and DMF was distilled off under reduced pressure. H_2O (100 mL), saturated aqueous $Na_2S_2O_3$ (100 mL), and $CHCl_3$:*i*PrOH (5:1, 600 mL) were added, the mixture was stirred for 30 min, the phases were separated, and the aqueous layer was extracted with $CHCl_3$:*i*PrOH (5:1, 2 × 100 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated, and crystallized (EtOAc and traces of MeOH) to give lactam **15** (12.5 g, 91%) as a white solid: mp 196−201 °C (pentane); R_f 0.48 (CH_2Cl_2:MeOH 10:1); IR (film)

(33) Smalberger, T. M.; Vleggaar, R.; De Wall, H. L. *J. Soc. Afr. Chem. Inst.* **1971**, *24*, 1.

1713, 1672, 1596, 1467, 1431, 1336, 1271, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.11 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 4.47 (s, 2H), 6.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.0, 51.7, 53.2, 56.1, 56.6, 95.0, 107.2, 113.8, 148.4, 160.9, 164.2, 165.3, 166.3; MS (CI, NH_3) *m*/*z* 266 $[M + H]^+$; HRMS (CI) *m*/*z* calcd for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1033, found $[M + H]^+$ 266.1028. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.80; N, 5.26.

Methyl 7-Methoxy-2-methyl-1-oxo-5-trifluoromethanesulfonyloxy-2,3-dihydro-1*H*-isoindole-4-carboxylate (8). BCl_3 (95 mL, 95 mmol, 1.0 M in CH_2Cl_2) was added dropwise with stirring under N_2 to amide **15** (11.5 g, 43.3 mmol) so that the inside temperature remained below −72 °C. After 3 h at −78 °C, 10% aqueous HCl (150 mL) was added and the mixture allowed to warm to room temperature and transferred to 10% aqueous HCl (1.3 L) and CH_2Cl_2 (500 mL). After stirring for 2 h, the aqueous layer was extracted with CH_2Cl_2 and $CHCl_3$ (3 × 250 mL) and $CHCl_3$:*i*PrOH (5:1, 2 × 250 mL), and the combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), rotary evaporated, and crystallized to give the corresponding phenol (8.9 g, 82%) as a white solid: mp 198−203 °C (pentane); R_f 0.44 (CH_2Cl_2:MeOH 15:1); IR (film) 1713, 1672, 1596, 1467, 1431, 1336, 1271, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.14 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 4.47 (s, 2H), 6.47 (s, 1H), 11.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.0, 52.3, 53.4, 56.2, 99.3, 100.9, 114.0, 147.4, 162.4, 166.4, 167.2, 170.0; MS (CI, NH_3) *m*/*z* 252 $[M + H]^+$; HRMS (CI) *m*/*z* calcd for $C_{12}H_{14}NO_5$ $[M + H]^+$ 252.0872, found $[M + H]^+$ 252.0871. The phenol (9.5 g, 38.0 mmol) was dissolved with heating in dry CH_2Cl_2 (130 mL). After cooling to room temperature, Et_3N (8.0 mL, 56.0 mmol) and $PhNTf_2$ (16.3 g, 45.6 mmol) were added. The mixture was heated at reflux for 72 h and cooled to room temperature, when H_2O (80 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layers were washed with brine (80 mL), dried ($MgSO_4$), and rotary evaporated. The residue was crystallized from Et_2O to give triflate **8** (11.5 g, 79%) as a white solid. The mother liquid was concentrated and filtered through silica (100 g, EtOAc to EtOAc:MeOH 15:1) to give, after recrystallization, triflate **8** (1.9 g, 13%): mp 152−157 °C (Et_2O); R_f 0.49 (CH_2Cl_2:MeOH 15:1); R_f 0.40 (EtOAc:MeOH 20:1); IR (film) 3061, 2960, 1727, 1694, 1632, 1423, 1287, 1206, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.17 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 4.65 (s, 2H), 6.78 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 29.2, 52.4, 53.2, 56.8, 105.9, 114.2 (q, J = 362.9), 120.8, 121.1, 148.6, 151.6, 160.5, 163.1, 164.9; MS (CI, NH_3) *m*/*z* 384 $[M + H]^+$; HRMS (CI) *m*/*z* calcd for $C_{13}H_{13}NSO_7F_3$ $[M + H]^+$ 384.0365, found $[M + H]^+$ 384.0367; Anal. Calcd for $C_{13}H_{12}F_3NO_7S$: C, 40.74; H, 3.16; N, 3.65. Found: C, 40.79; H, 3.14; N, 3.57.

Methyl 5-(2,5-Dimethoxy-3-methoxymethylbenzyl)-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylate (30a). Zn dust (3.8 g, 58.2 mmol) was placed in a Schlenk tube and heated in a vacuum. After cooling, the tube was flushed with N_2, THF (2 mL) and 1,2-dibromoethane (0.17 mL, 2.0 mmol) were added, and the mixture was heated to reflux for 3 min and cooled to 0 °C. Bromide **7a** (1.6 g, 5.82 mmol) in THF (5 mL) was added within 90 min at 0 °C and the mixture stirred for 1 h at 0 °C. The resultant organozinc compound was added via a filter cannula to the previously freeze−thaw degassed triflate **8** (767 mg, 2.0 mmol) in THF (20 mL) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) at room temperature. After 2.5 h at reflux, saturated aqueous NH_4Cl (10 mL) and H_2O (10 mL) were added, the aqueous layer was extracted with EtOAc (4 × 25 mL), and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), rotary evaporated, and purified by chromatography (EtOAc to EtOAc:MeOH 15:1) to yield **30a** (730 mg, 85%) as a white solid: mp 108−111 °C (EtOAc); R_f 0.14 (EtOAc); IR (film) 1689, 1596, 1478, 1432, 1277, 1160, 1058, 1009, 858, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.31 (s, 3H), 3.42 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 4.42 (s, 2H), 4.49 (s, 2H), 4.52 (s, 2H), 6.33 (s, 1H), 6.70 (s, 1H), 6.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.0, 34.6, 51.6, 53.3, 55.3, 55.9, 58.3, 61.6, 69.6, 111.7, 113.8, 115.5, 117.3, 119.3, 132.0, 134.6, 146.9, 148.4, 149.9, 155.7, 159.0, 166.26, 166.33; MS (CI, NH_3) *m*/*z* 430 $[M + H]^+$; HRMS (CI) *m*/*z* calcd for $C_{23}H_{27}NO_7H$ $[M + H]^+$ 430.1866, found $[M + H]^+$ 430.1866. Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.37; H, 6.42; N, 3.26.

5-(2,5-Dimethoxy-3-(methoxymethyl)benzyl)-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (6a). $LiOH·H_2O$ (662 mg, 27.6 mmol) was added at room temperature to methyl ester **30a** (663 mg, 1.54 mmol) in THF (14 mL), MeOH (7 mL), and H_2O (7 mL). After stirring for 24 h, saturated aqueous NH_4Cl (6 mL), 2 M HCl (2 mL), and H_2O (5 mL) were added, and the aqueous layer was extracted with $CHCl_3$:*i*PrOH (4:1, 1 × 50 mL, 5 × 30 mL). The combined organic layers were dried (Na_2SO_4) and rotary evaporated to give crude acid **6a** (660 mg) as a white solid: mp 153−155 °C ($CHCl_3$:*i*PrOH 4:1); R_f 0.15 ($CHCl_3$:MeOH 10:1); IR (film) 1702, 1655, 1597, 1478, 1422, 1265, 1169, 1061, 895, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.14 (s, 3H), 3.43 (s, 3H), 3.68 (2s, 6H), 3.82 (s, 3H), 4.49 (s, 2H), 4.51 (s, 2H), 4.61 (s, 2H), 6.40 (s, 1H), 6.68 (s, 1H), 6.81 (s, 1H), 6.53−6.99 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.1, 34.6, 53.9, 55.4, 55.8, 58.4, 61.7, 69.6, 111.9, 113.7, 115.9, 116.7, 119.4, 132.0, 134.6, 147.9, 149.8, 150.1, 155.8, 159.5, 166.5, 169.9; MS (CI, NH_3) *m*/*z* 416 $[M + H]^+$; HRMS (CI) *m*/*z* calcd for $C_{22}H_{26}NO_7$ $[M + H]^+$ 416.1709, found $[M + H]^+$ 416.1706. Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.52; H, 6.14; N, 3.27.

11-Acetoxy-8-methoxymethyl-2-methyl-4,7,10-trimethoxy-1,2-dihydronaphtho[2,3-*e*]isoindol-3-one (5a). $Me_2C{=}C(Cl)NMe_2$ (32 μL, 0.24 mmol) was added with stirring to acid **6a** (24 mg, 0.058 mmol) in CH_2Cl_2 (1.2 mL). After 3 h at room temperature, the deep yellow mixture was cooled to 0 °C, $ZnCl_2$ in Et_2O (1.0 M; 100 μL) added, and the reaction mixture stirred for 30 min by which time a color change to orange was observed. Pyridine (3 mL), Ac_2O (1 mL), and DMAP (cat.) were added, and after 15 h, the reaction was quenched with H_2O (2 mL) and 5 M HCl (6 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (EtOAc to EtOAc:MeOH 15:1) to yield acetate **5a** (21 mg, 82%) as a deep yellow to greenish oil: R_f 0.44 (EtOAc:MeOH 10:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3H), 3.21 (s, 3H), 3.46 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 4.54 (bs, 1H), 4.68 (s, 2H), 4.82 (bs, 1H), 6.77 (s, 1H), 7.17 (s, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.4, 29.2, 53.4, 55.8, 56.1, 58.4, 62.6, 68.8, 103.9, 105.0, 116.6, 116.9, 118.0, 123.9, 126.3, 129.7, 134.8, 141.5, 143.1, 146.7, 151.6, 154.4, 166.8, 169.5; MS (CI, NH_3) *m*/*z* 440 $[M + H]^+$ 382, 288, 269, 162; HRMS (CI) *m*/*z* calcd for $C_{24}H_{26}NO_7$ $[M + H]^+$ 440.1709, found $[M + H]^+$ 440.1705.

11-Acetoxy-4-methoxy-8-methoxymethyl-2-methyl-3,7,10-trioxo-2,3,7,10-tetrahydro-1*H*-naphtho[2,3-*e*]isoindole (33a). CAN (94 mg, 0.17 mmol) in H_2O (0.75 mL) was slowly added with stirring to acetate **5a** (25 mg, 0.057 mmol) in MeCN (4 mL) at 0 °C. After 10 min, stirring was continued for 20 h at room temperature. H_2O (5 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (EtOAc to EtOAc:MeOH 20:1) to yield quinone **33a** (13 mg, 61%) as a yellow oil: R_f 0.51 (EtOAc:MeOH 10:1); IR (film) 1771, 1706, 1659, 1604, 1586, 1456, 1427, 1246, 1181, 1111, 899, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H), 3.25 (s, 3H), 3.51 (s, 3H), 4.09 (s, 3H), 4.46 (s, 2H), 4.59 (bs, 1H), 4.83 (bs, 1H), 6.97 (s, 1H), 7.29 (s, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$; 75.5 MHz) δ 22.2, 29.8, 53.2, 56.7, 59.7, 68.3, 109.0, 117.4, 121.0, 126.0, 126.2, 130.8, 136.8, 139.9, 143.0, 147.8, 148.4, 158.1, 166.1, 169.1, 183.2, 183.9.

Methyl 5-(2,5-Dimethoxy-3-((4-methoxybenzyloxy)methyl)-benzyl)-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylate (30b). Zn dust (2.9 g, 44.0 mmol) was placed in a Schlenk tube and heated in vacuo. After cooling, the tube was flushed with N_2, dry THF (2 mL) followed by dibromoethane (0.17 mL, 2.0 mmol) was added, and the mixture heated to reflux for 3 min. Dry bromide **7b** (1.4 g, 4.4 mmol) in THF (5 mL) was added within 90 min at 0 °C and stirring continued for 1 h at 0 °C. The resultant benzylzinc compound was added via filter cannula to triflate **8** (767 mg, 2.0 mmol) in THF (20 mL) (degassed four times by freeze−thaw process) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) at room temperature. After 14 h at reflux, the reaction mixture was allowed to cool to room temperature when saturated aqueous NH_4Cl (10 mL), aqueous HCl (6 M, 5 mL), and H_2O (10 mL) were added. The aqueous layer was extracted with EtOAc (4 × 25 mL), the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and rotary evaporated. The residue was dissolved in $CHCl_3$ and MeOH and silica gel (8 g) added, the solvents were evaporated, and the residue was chromatographed (CH_2Cl_2:MeOH 25:1 to 10:1) to yield methyl ester **30b** (980 mg, 92%) as a colorless oil: R_f 0.13 (EtOAc); IR (film) 1689, 1597, 1513, 1465, 1432, 1277, 1252, 1160, 1057; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (s, 3H), 3.65 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 4.41 (s, 2H), 4.50 (s, 2H), 4.51 (s, 2H), 4.56 (s, 2H), 6.33 (d, J = 2.6 Hz, 1H), 6.70 (s, 1H), 6.78−6.90 (m, 3H), 7.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.9, 34.6, 51.5, 53.2, 55.1, 55.3, 55.8, 61.5, 67.3, 72.6, 112.0, 113.6, 113.7, 115.2, 117.2, 119.2, 129.3, 130.0, 132.1, 134.5, 146.8, 148.3, 149.9, 155.6, 159.0, 159.1, 166.1, 166.2; MS (CI, NH_3) m/z 536 $[M + H]^+$ 444, 430, 414, 400, 154; HRMS (CI) m/z calcd for $C_{30}H_{34}NO_8$ $[M + H]^+$ 536.2284, found $[M + H]^+$ 536.2292.

5-(2,5-Dimethoxy-3-((4-methoxybenzyloxy)methyl)benzyl)-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (6b). $LiOH\cdot H_2O$ (778 mg, 18.1 mmol) was added to methyl ester **30b** (970 mg, 1.81 mmol) in THF (16 mL), MeOH (8 mL), and H_2O (8 mL) at 0 °C. After 1 h, the mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), HCl (2 M, 2 mL), and H_2O (5 mL). $CHCl_3$:*i*PrOH (4:1, 100 mL) was added and the suspension heated to 60 °C for 20 min until two layers had formed. The aqueous layer was extracted with $CHCl_3$ (4 × 100 mL) at 60 °C, and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to give crude acid **6b** (990 mg) as a white solid: mp 101−103 °C ($CHCl_3$:*i*PrOH 4:1); R_f 0.29 ($CHCl_3$:MeOH 10:1); IR (film) 3148, 1667, 1598, 1424, 1514, 1468, 1249, 1058, 853, 822, 758 cm^{-1}; ^{1}H NMR (MeOH-d_4:$CDCl_3$ 2:1, 300 MHz,) δ 3.12 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 3.78 (s, 6H), 4.46 (s, 2H), 4.51 (s, 2H), 4.55 (s, 2H), 4.60 (s, 2H), 6.54 (d, J = 2.6 Hz, 1H), 6.72 (s, 1H), 6.82 (d, J = 3.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75.5 MHz,) δ 28.6, 33.6, 52.6, 55.07, 55.13, 55.6, 61.2, 66.4, 71.4, 111.5, 113.7, 115.0, 118.2, 129.3, 130.2, 132.0, 135.3, 145.8, 146.1, 149.6, 155.1, 157.1, 158.8, 165.4, 168.0; MS (FAB) m/z 522, HRMS (FAB) m/z calcd for $C_{29}H_{32}NO_8$ $[M + H]^+$ 522.2128, found $[M + H]^+$ 522.2129.

11-Acetoxy-8-((4-methoxybenzyloxy)methyl)-2-methyl-4,7,10-trimethoxy-1,2-dihydronaphtho[2,3-*e*]isoindol-3-one (5b). $Me_2C{=}C(Cl)NMe_2$ (33 μL, 0.25 mmol) was added dropwise to acid **6b** (26 mg, 0.050 mmol) in dry CH_2Cl_2 (2 mL). After 3 h, the deep yellow mixture was cooled to 0 °C, $ZnCl_2$ (100 μL, 1.0 M in Et_2O) was added, and the mixture was stirred for 15 min, resulting in a color change to orange. Pyridine (1.5 mL), Ac_2O (0.75 mL), and DMAP (6 mg, 0.050 mmol) were added and stirring continued for a further 15 h. H_2O (2 mL) and HCl (6 M, 5 mL) were added, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (EtOAc to EtOAc:MeOH 15:1) to yield acetate **5b** (25 mg, 92%) as a deep yellow-greenish solid: mp 208−212 °C (EtOAc); R_f 0.53 (EtOAc:MeOH 10:1); IR (film) 1768, 1689, 1619, 1513, 1464, 1347, 1248, 1198, 1169, 1059, 883, 823, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (s, 3H), 3.23 (s, 3H), 3.81 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 4.06 (s, 3H), 4.56 (s, 3H), 4.30−4.87 (bs, 2H), 4.76 (s, 2H), 6.81 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.20 (s, 1H), 7.32 (d, J = 8.6 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 29.1, 53.2, 55.1, 55.6, 56.0, 62.5, 66.1, 72.1, 104.0, 104.8, 113.7 (2C), 116.4, 116.7, 117.8, 123.6, 126.3, 129.4 (2C), 129.5, 130.0, 134.6, 141.3, 142.9, 146.7, 151.4, 154.2, 159.2, 166.6, 169.4; MS (FAB) m/z 546 $[M + H]^+$.

11-Acetoxy-4-methoxy-8-((4-methoxybenzyloxy)methyl)-2-methyl-3,7,10-trioxo-2,3,7,10-tetrahydro-*1H*-naphtho[2,3-*e*]isoindole (33b). CAN (166 mg, 0.300 mmol) in H_2O (0.14 mL) was slowly added to acetate **5b** (75 mg, 0.14 mmol) in MeCN (5.5 mL) at 0 °C. After 10 min, the yellow mixture was stirred for 20 h at room temperature. H_2O (5 mL) was added, the mixture was extracted with $CHCl_3$:*i*PrOH (4:1, 4 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed ($CHCl_3$) to yield quinone **33b** (50 mg, 71%) as a yellow/orange solid: mp 260−265 °C (MeOH); R_f 0.55 (EtOAc:MeOH 10:1); IR (film) 1772, 1702, 1657, 1607, 1514, 1428, 1377, 1246, 1165, 1101, 921, 898, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H,), 3.25 (s, 3H), 3.82 (s, 3H), 4.10 (s, 3H), 4.53 (s, 2H), 4.62 (2s, 2H), 4.47−4.73 (bs, 1H), 4.79−5.03 (bs, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.07 (s, 1H), 7.25 (s, 1H), 7.31 (d, J = 8.9 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz,) δ 21.8, 29.4, 52.9, 55.3, 56.3, 65.1, 73.0, 108.6, 113.9, 117.1, 120.6, 125.6, 125.9, 129.4, 130.5, 136.5, 139.4, 142.6, 147.7, 148.0, 157.8, 159.5, 158.1, 165.8, 168.7, 183.0, 183.5; MS (FAB) m/z 516 $[M + H]^+$; HRMS (CI) m/z calcd for $C_{29}H_{26}NO_8$ $[M + H]^+$ 516.1658, found $[M + H]^+$ 516.1655. Anal. Calcd for $C_{29}H_{25}NO_8$: C, 67.57; H, 4.89; N, 2.72. Found: C, 67.58; H, 4.82; N, 2.69.

Acknowledgment. We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Sciences at Imperial College, the Engineering and Physical Sciences Research Council and AstraZeneca for generous support of our studies, FWF for an Erwin Schrödinger Fellowship (E.J.), the European Commission for a Marie Curie Intra-European Fellowship (G.P.), and the Deutsche Forschungsgemeinschaft [for a PostDoctoral Fellowship (H.W.)]. We additionally thank Peter R. Haycock and Richard N. Sheppard for the high-resolution NMR spectroscopy.

Supporting Information Available: Additional experimental procedures and structural data for all new compounds, copies of ^{1}H NMR and ^{13}C NMR spectra for selected new compounds, and X-ray crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org

JO0613378