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Synthetic Studies on Lactonamycins: Synthesis of the Model BCDEF Aglycon

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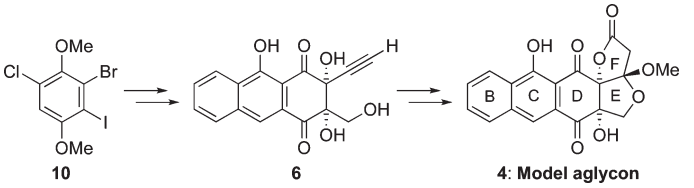

The lactonamycin model aglycon **4** was synthesized from the trihalogenated benzene derivative **10**. Ethynyltetraol **6** was prepared from **10** via carbon elongations, oxidative demethylation, a cycloaddition reaction with the diene derived from homophthalic anhydride, and dihydroxylation. Final E- and F-ring constructions from **6** were realized via a palladium-catalyzed cyclization−methoxycarbonylation, a stereoselective methanol addition, and lactonization, leading to the production of **4**.

Introduction

Lactonamycin (**1**) (Figure 1) was isolated in 1996 by Matsumoto and co-workers from a culture broth of *Streptomyces rishiriensis* MJ773-88K4 collected at Yokohama, Japan.[1] Lactonamycin (**1**) shows potent antimicrobial activities against Gram-positive bacteria (MIC 0.20−0.78 μg/mL) including methicillin-resistant *Staphylococcus aureus* (MRSA, MIC 0.39−1.56 μg/mL) and vancomycin-resistant *Enterococcus* (VRE, MIC 0.20−0.78 μg/mL).[1] Furthermore, lactonamycin (**1**) shows cytotoxicity against various tumor cell lines (IC_{50} 0.06−3.3 μg/mL).[1] The relative stereochemistry of **1** was determined by spectroscopic studies and X-ray crystallographic analysis.[1] The absolute configuration of **1** was determined by a degradation study; the acidic treatment of **1** afforded the aglycon, lactonamycinone (**3**), and L-rhodinose (Figure 1).[1] The structure of **1** is characterized by its hexacyclic, densely oxygenated aglycon (A−F-ring) portion. Lactonamycin Z (**2**) (Figure 1) was later isolated in 2003 by Fiedler and coworkers from a culture broth of *Streptomyces sanglieri* AK 623 collected at Hamsterley Forest, Country Durham, UK.[2] Lactonamycin Z (**2**), having a different sugar moiety from **1**, is less potent against Gram-positive bacteria.[2] Recently, biosynthetic investigations of lactonamycins have been reported.[3]

The combination of the unique hexacyclic core structure including a densely oxygenated hydrofuran−hydrofuranone ring system and significant biological properties of lactonamycin (**1**) has inspired synthetic efforts in several laboratories. Cox and Danishefsky initiated the synthetic studies on lactonamycin (**1**), describing two routes to the model CDEF-ring system using oxidative dearomatization[4a] and diastereoselective dihydroxylation.[4b] Deville and Behar reported the synthesis of the model ABCD-ring system using a tandem conjugate cyanide addition−Dieckmann condensation.[5] Kelly et al. reported the synthesis of the model ABCD-ring system using a Diels−Alder reaction between the B- and D-rings.[6a] Kelly's group also reported the asymmetric synthesis of the EF-ring system starting from dimethyl

(1) (a) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Sawa, R.; Kinoshita, N.; Homma, Y.; Takahashi, Y.; Iinuma, H.; Naganawa, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 953–954. (b) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 269–275. (c) Matsumoto, N.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276–280.

(2) Höltzel, A.; Dieter, A.; Schmid, D. G.; Brown, R.; Goodfellow, M.; Beil, W.; Jung, G.; Fiedler, H.-P. *J. Antibiot.* **2003**, *56*, 1058–1061.

(3) Zhang, X.; Alemany, L. B.; Fiedler, H.-P.; Goodfellow, M.; Parry, R. J. *Antimicrob. Agents Chemother.* **2008**, *52*, 574–585.

(4) (a) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493–3496. (b) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899–2902.

(5) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403–1405.

(6) (a) Kelly, T. R.; Xu, D.; Martínez, G.; Wang, H. *Org. Lett.* **2002**, *4*, 1527–1529. (b) Kelly, T. R.; Cai, X.; Tu, B.; Elliott, E. L.; Grossmann, G.; Laurent, P. *Org. Lett.* **2004**, *6*, 4953–4956.

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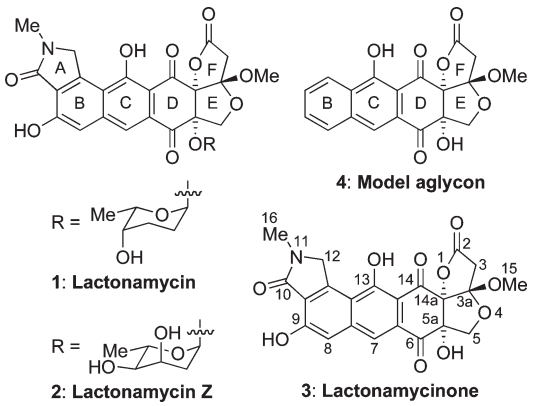


FIGURE 1. Structures of lactonamycins, lactonamycinone, and model aglycon.

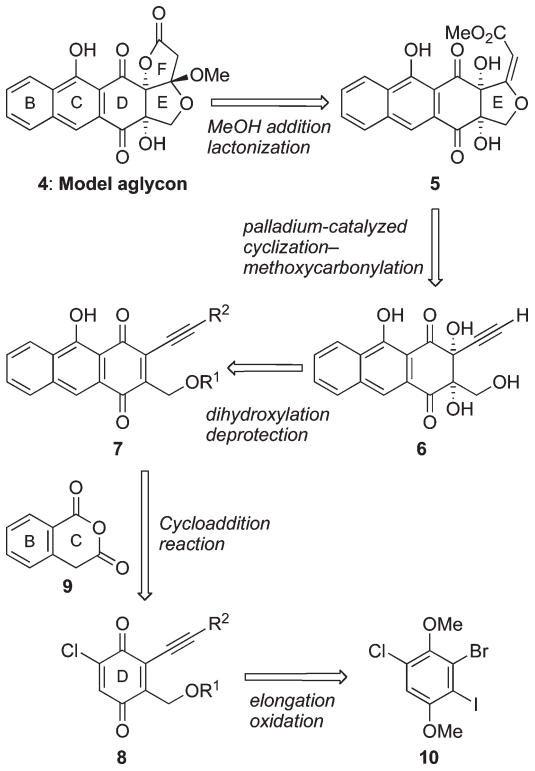
D-tartrate.[6b] The Barrett group synthesized the model CDEF and ABCD-ring systems.[7] Parsons and co-workers reported the synthesis of the model ABC-ring system using a cascade cyclization reaction.[8] To date, the most advanced accomplishment is the Danishefsky total synthesis of (±)-lactonamycinone (**3**).[9]

We report herein the synthesis of the model BCDEF aglycon **4** (Figure 1, racemate) by a new and conceptually different route.

Results and Discussion

Retrosynthetic Analysis. Retrosynthetic analysis of the lactonamycin model aglycon **4** is shown in Scheme 1. The F-ring lactone in **4** was expected to be constructed via a stereoselective methanol addition to α,β-unsaturated ester **5** followed by lactonization. We anticipated that the tetrahydropyran ring (E-ring) in **5** would be regio- and stereoselectively secured via a palladium-catalyzed cyclization−methoxycarbonylation of ethynyltetraol **6**. These mild reaction conditions were developed by Kato, Akita, and co-workers.[10] Our synthetic method for EF-ring formation is distinct from others.[6b,7a,9b] Ethynyltetraol **6** would be obtained by dihydroxylation of ethynylanthraquinone **7**, which in turn would regioselectively arise via a cycloaddition reaction between ethynylchloroquinone **8** and the enolate derived from homophthalic anhydride (**9**). This cycloaddition reaction was developed by Tamura and co-workers.[11] Finally, ethynylchloroquinone **8** would be obtained from the trihalogenated benzene derivative **10** via sequential carbon-elongations and oxidative demethylation. The starting material **10** was used as a key intermediate in our total synthesis of A-80915G.[12]

SCHEME 1. Retrosynthetic Analysis for Model Aglycon 4



Synthesis of Silylethynylbenzenes 16. The synthesis of the lactonamycin model aglycon **4** commenced with the efficient preparation of silylethynylbenzenes **16** (Scheme 2), the precursor of ethynylchloroquinone **8**. Our previously synthesized trihalogenated benzene derivative **10**[12] (see the Supporting Information) was first treated with *n*-BuLi in toluene[13] at −78 °C to lithiate the iodine substituent in preference to the bromine and chlorine substituents; to the resulting anion was added HCO_2Me, giving aldehyde **11** in 87% yield. $NaBH_4$ reduction of **11** followed by MOM protection afforded **12** (98%, two steps), which was again lithiated (*t*-BuLi in THF) and the resulting anion treated with HCO_2Me to afford aldehyde **13** in 90% yield. In this second formylation, the quick addition of HCO_2Me after lithiation was important for obtaining a reproducibly good yield. Treatment of aldehyde **13** in methanol with the Ohira reagent **14**[14] in the presence of K_2CO_3 afforded ethynylbenzene **15** in 70% yield. Silylation of the alkyne terminus in **15** was realized with *n*-BuLi and TMSCl, giving silylethynylbenzene (TMS acetylene) **16a** in 96% yield. By the same procedure, three other silylethynylbenzenes (TES acetylene **16b**, TBS acetylene **16c**, and TIPS acetylene **16d**) were derived from **15** in good yield.

(7) (a) Henderson, D. A.; Collier, P. N.; Pavé, G.; Rzepa, P.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 2434–2444. (b) Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pavé, G.; Roulland, E.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 8151–8158. (c) Vézouët, R. L.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *Tetrahedron* **2006**, *62*, 12252–12263.

(8) (a) Parsons, P. J.; Board, J.; Waters, A. J.; Hitchcock, P. B.; Wakenhut, F.; Walter, D. S. *Synlett* **2006**, 3243–03246. (b) Parsons, P. J.; Waters, A. J.; Walter, D. S.; Board, J. *J. Org. Chem.* **2007**, *72*, 1395–1398.

(9) (a) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5625–5629. (b) Siu, T.; Cox, C. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5629–5634.

(10) (a) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203–4205. (b) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 643–645. (c) Kato, K.; Sasaki, T.; Takayama, H.; Akita, H. *Tetrahedron* **2003**, *59*, 2679–2685.

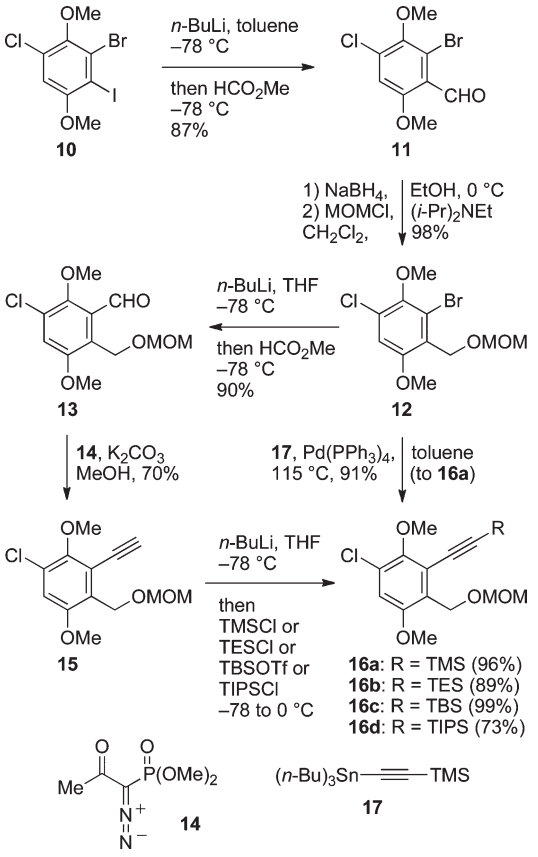
(11) Tamura, Y.; Fukata, F.; Sasho, M.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 2273–2277. and references cited therein.

(12) Takemura, S.; Hirayama, A.; Tokunaga, J.; Kawamura, F.; Inagaki, K.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **1999**, *40*, 7501–7505.

(13) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630–6631.

(14) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522. (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.

SCHEME 2. Synthesis of Silylethynylbenzenes 16



Alternatively, TMS acetylene **16a** could be directly prepared from **12** by Stille coupling[15] with commercially available **17** in 91% yield.

Cycloaddition Reaction of Silylethynylchloroquinones 8. With silylethynylbenzenes **16a**−**d** in hand, we next turned our attention to the regioselective cycloaddition reaction between the B- and D-rings (Scheme 3). We selected homophthalic anhydride (**9**) as the diene precursor with which silylethynylchloroquinones **8a**−**d** were expected to react under Tamura's conditions.[11] Indeed, TMS acetylene **16a** was subjected to CAN oxidation[16] in aqueous acetonitrile to afford the corresponding silylethynylchloroquinone **8a** (92% yield), which was then exposed to the enolate derived from **9** (LDA in THF) to afford the expected cycloaddition product **7a** in 51% yield together with the reduced hydroquinone **18a** (11% yield).[17] This hydroquinone **18a** could be reused after oxidation with CAN to the corresponding silylethynylchloroquinone **8a**. From various cycloaddition experiments, we learned that the best results, in terms of both yield and reproducibility, were secured when the reaction partners were used in precisely an equimolar amount. In analogy to the above two steps, the other silylethynylbenzenes **16b**−**d** were also converted into cycloaddition products **7b**−**d** through **8b**−**d** accompanied by the reduced hydroquinones **18b**−**d**. All quinones **8a**−**d** could be used without purification and the total yields turned out to be the same as the step-by-step yields. The TBS-protected quinone **8c** was the most suitable for this cycloaddition, whereas the TIPS-protected quinone **8d** gave the corresponding adduct **7d** in poor yield.

SCHEME 3. Cycloaddition Reaction of Silylethynylchloroquinones 8

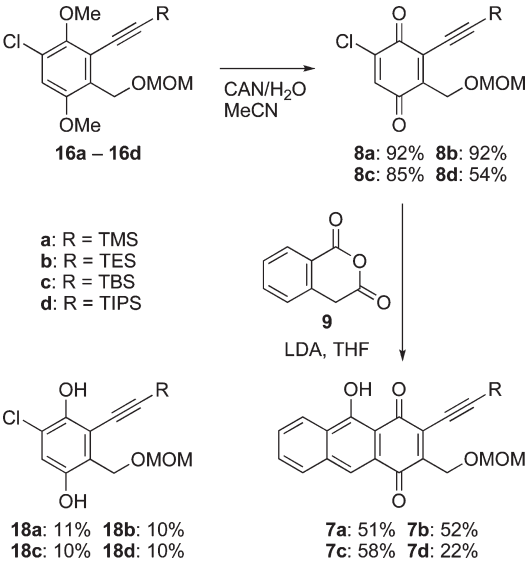
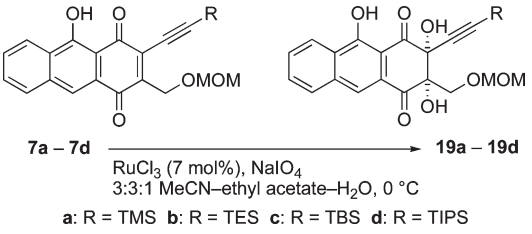


TABLE 1. Dihydroxylation of Silylethynylanthraquinones 7



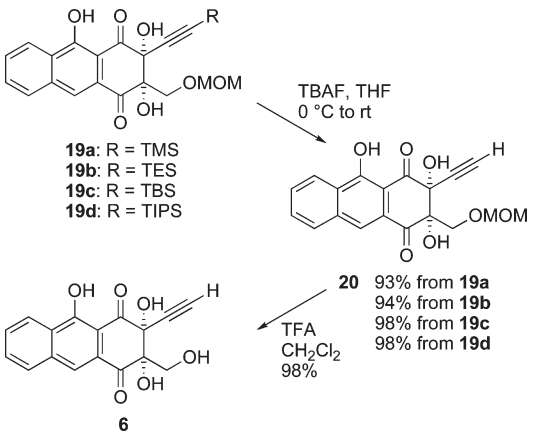
				yield (%)	
entry	substrate	equiv of $NaIO_4$	time (min)	**19**	**7**
1	**7a**	1.5	30	13	64
2	**7a**	3.0	15	18	20
3	**7b**	1.5	30	11	58
4	**7b**	3.0	15	16	22
5	**7c**	1.5	30	17	54
6	**7c**	3.0	15	33	22
7	**7d**	3.0	30	35	29

Dihydroxylation of Silylethynylanthraquinones 7. Dihydroxylation of silylethynylanthraquinones **7a**−**d** proved to be a challenging task. Even in the presence of excess (3 molar amounts) OsO_4, dihydroxylation of the quinone moiety in **7a** afforded only a trace amount of the desired **19a**; instead, **7a** was almost completely recovered. Addition of pyridine to the reaction mixture caused immediate decomposition. We next tried $RuCl_3$−$NaIO_4$ dihydroxylation (Table 1).[7a,18] When **7a** was treated with a catalytic amount of $RuCl_3$ and 1.5 molar amounts of $NaIO_4$ in 3:3:1 acetonitrile−ethyl acetate−water

(15) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866.
(16) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629.
(17) In preliminary experiments, cycloaddition of the ethynylchloroquinone derived from ethynylbenzene **15** was attempted; however, decomposition occurred probably due to the instability of ethynylchloroquinone under the basic conditions.

(18) (a) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312–2313. (b) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem.—Eur. J.* **1996**, *2*, 50–57.

SCHEME 4. Synthesis of Ethynyltetraol 6



at 0 °C, the desired dihydroxylated product **19a** was obtained in 13% yield accompanied by a 64% yield of the starting quinone **7a** (entry 1). Addition of a catalytic amount of H_2SO_4[19a,b] or $CeCl_3$[19c] to the reaction mixture gave no improvement. When 3 molar amounts of $NaIO_4$ was used, the yield of **19a** slightly increased to 18%, but the recovery yield of **7a** decreased to 20% (entry 2). The low yield of **19a** led us to consider other silyl protecting groups. The results with TES ethynylanthraquinone **7b** (entries 3 and 4) resembled those of **7a**. In contrast, in the case of TBS ethynylanthraquinone **7c**, the yield of **19c** doubled (33%) with the increased amount of $NaIO_4$ (entries 5 and 6). Unlike the aforementioned cycloaddition case, TIPS ethynylanthraquinone **7d** gave the best yield of **19d** (35%, entry 7). From the viewpoint of the overall yield from silylethynylbenzenes **16** to the dihydroxylated products **19**, the TBS-series compounds gave the best result (16% three-step overall yield from **16c** to **19c**).

Synthesis of Ethynyltetraol 6. All of the obtained **19a**−**d** were converted to the desilylated product **20** in comparably good yields by treatment with TBAF in THF (Scheme 4). Finally, **20** was subjected to TFA in CH_2Cl_2 to afford ethynyltetraol **6** in 98% yield.

E- and F-Ring Formation. At this point, our synthesis of the model BCDEF aglycon **4** reached the crucial E- and F-ring formation stage. Ethynyltetraol **6** was treated in methanol with a catalytic amount of $PdCl_2$ and 1,4-benzoquinone in the presence of an atmospheric pressure of CO (balloon) at rt to afford the E-ring compound **5** in 62% yield as a single stereoisomer (Scheme 5). The double-bond configuration of the α,β-unsaturated ester portion in **5** was not strictly determined but was presumed to be the one depicted in Scheme 5 based on the proposed reaction mechanism.[10]

The final stereoselective methanol addition to the E-ring compound **5** followed by lactonization to make the F-ring was then realized. Compound **5** was treated in methanol with 1 molar amount of CSA at 80 °C to afford the model aglycon **4**, the methanol adduct **21**, and the starting compound **5** in 28%, 14%, and 50% yield, respectively (Table 2, entry 1). When excess CSA was used, the amount of the recovered starting material **5** decreased (entries 2 and 3). It is likely that

(19) (a) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353–3356. (b) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116–1124. (c) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402–2405.

SCHEME 5. E- and F-Ring Formation

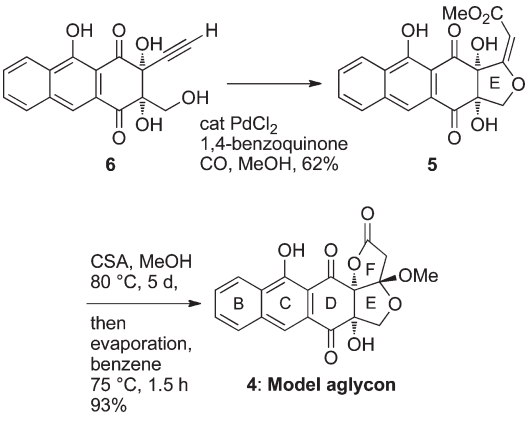
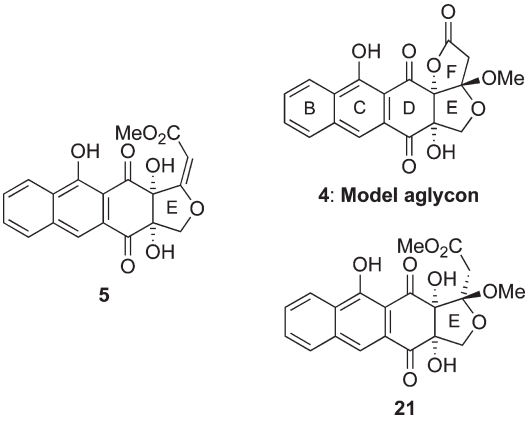


TABLE 2. F-Ring Formation



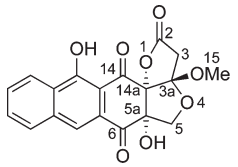
				yield (%)		
entry	substrate	mol amt of CSA	time (d)	**4**	**21**	**5**
1	**5**	1.0	9	28	14	50
2	**5**	3.0	3	42	50	trace
3	**5**	5.0	4	50	37	0
4	**4**	3.0	1	(**4**:**21** = 3:1)[a]		
5	**21**	3.0	5	(**4**:**21** = 5:3)[a]		

[a]The ratio of **4**:**21** was determined by ^{1}H NMR analysis of the crude products.

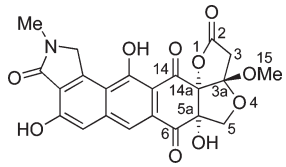
compounds **4** and **21** are in equilibrium under the reaction conditions. Indeed, when **4** and **21** were each treated separately with 3 molar amounts of CSA in methanol at 80 °C, a 3:1 and 5:3 mixture of **4**:**21** was obtained, respectively (entries 4 and 5); the E-ring compound **5** could not be detected under the reaction conditions. It is reasonable to assume that the equilibrium between **4** and **21** would be driven toward **4** if methanol was removed from the reaction mixture. This theory was tested by evaporating the reaction mixture following the complete disappearance of the E-ring compound **5** when treated with CSA in methanol at 80 °C for 5 d. Dissolution of the residue in benzene with heating at 75 °C for 1.5 h gave the model BCDEF aglycon **4** in 93% yield as the only detectable product (Scheme 5).

The structure of **4** was initially deduced by comparing its ^{1}H and ^{13}C NMR spectra with those of lactonamycinone (**3**)[3] (Table 3), as the two compounds are very similar to one

TABLE 3. Representative ^1H and ^{13}C NMR Data for 3 and 4[a]



4: Model aglycon



3: Lactonamycinone

	4			3		
position	$^1H^b$	J (Hz)	$^{13}C^b$	$^1H^{b,c}$	J (Hz)^c	$^{13}C^{b,c}$
2			170.5			170.6
3	3.02	17.0	37.7	2.99	17.0	37.7
3	3.10	17.0		3.09	17.0	
3a			112.6			112.4
5	4.09	9.8	74.1	4.10	9.6	73.8
5	4.88	9.8		4.91	9.6	
5a			82.6			82.6
6			189.8			189.5
14			192.7			192.2
14a			90.7			90.6
15	3.20		52.6	3.20		52.7

[a]Lactonamycin numbering system applied to this table. [b]Chemical shifts in ppm. [c]Reference 3.

another. X-ray crystallographic analysis then confirmed the structure of **4** (see the Supporting Information).

The structure of the methanol adduct **21** was determined as follows. When lactone **4** was treated with sodium methoxide in methanol at 0 °C for 2 h, a small amount (ca. 10%) of ester **21** was obtained together with the starting lactone **4** (ca. 30%). In addition, when lactone **4** was treated with sodium methoxide-d_3 in methanol-d_4 at 0 °C for 10 min, a small amount (ca. 10%) of the methyl-d_3 ester of **21** was obtained together with **4** (67%). No methyl-d_3 acetal (at C3a) of **21** was detected. Furthermore, lactone **4** was treated in methanol-d_4 with 3 molar amounts of CSA at 80 °C for 3 d, affording the methyl-d_3 ester of **21** and the starting lactone **4** in ca. a 1.5:1.0 ratio. In this case also, the methyl acetal at C3a was intact. If the methanol adduct obtained from **5** were the C3a-epimer of **21**, the deuterium would be incorporated into both the ester and acetal positions via the esterification and the elimination/reinstallation of methanol. These results indicate that the methanol adduct is **21** and the methanol addition at C3a is irreversible under the reaction conditions. The high stereoselectivity of the methanol addition can be rationalized by the steric hindrance around the C3a position caused by the C14a hydroxy group.

Conclusion

The lactonamycin model aglycon **4** was synthesized from the trihalogenated benzene derivative **10**. By selective utilization of three kinds of halogen substituents, **10** was transformed into silylethynylbenzene **16**, which was further converted to ethynyltetraol **6** through a cycloaddition reaction with homophthalic anhydride followed by dihydroxylation. Palladium-catalyzed cyclization−methoxycarbonylation of **6** to form the E-ring followed by stereoselective methanol addition and lactonization to form the F-ring are not only distinct routes compared to those taken by other groups but also provided **4** in good yield. Total synthesis of lactonamycin is now underway with this approach.

Experimental Section

2-Bromo-4-chloro-3,6-dimethoxybenzaldehyde (11). To a stirred solution of **10** (16.6 g, 42.8 mmol) in dry toluene (428 mL) was added at −78 °C a 1.60 M hexane solution of *n*-BuLi (40.1 mL, 64.2 mmol). After 10 min at −78 °C, to this solution was slowly added HCO_2Me (26.4 mL, 0.428 mol). After 0.5 h at −78 °C, the reaction mixture was warmed to 0 °C and to this was added a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc and the extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (1.2 kg, 10:1 hexane−acetone) to afford **11** (10.5 g, 87%) as pale yellow crystals: R_f 0.31 (10:1 hexane−acetone); mp 110−111 °C (not recrystallized); IR (KBr, cm^{-1}) 1690, 1580, 1470, 1380, 1290, 1250, 1220, 1030, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 10.33 (1H, s), 7.02 (1H, s), 3.90 (3H, s), 3.87 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 60.8, 112.8, 121.3, 123.0, 134.6, 147.6, 157.6, 189.4; HRMS (EI) m/z calcd for $C_9H_8O_3{}^{35}Cl^{81}Br$ (M^+) 279.9325, found 279.9323. Anal. Calcd for $C_9H_8O_3ClBr$: C 38.67, H 2.88. Found: C 38.77, H 2.87.

3-Bromo-1-chloro-2,5-dimethoxy-4-((methoxymethoxy)methyl)-benzene (12). To a stirred solution of **11** (1.11 g, 3.97 mmol) in EtOH (79.4 mL) was added at 0 °C $NaBH_4$ (150 mg, 3.97 mmol). After 0.5 h at 0 °C, saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residual pale yellow crystals (1.10 g, 98%), 2-bromo-4-chloro-3,6-dimethoxybenzyl alcohol [R_f 0.42 (3:1 hexane−EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, s), 4.86 (2H, d, J = 6.8 Hz), 3.86 (3H, s), 3.84 (3H, s), 2.30 (1H, t, J = 6.8 Hz)], were used for the next step without purification. To a stirred solution of 2-bromo-4-chloro-3,6-dimethoxybenzyl alcohol (1.09 g, 3.87 mmol) in dry CH_2Cl_2 (48.4 mL) were successively added at 0 °C $(i\text{-Pr})_2NEt$ (4.72 mL, 27.1 mmol) and MOMCl (1.47 mL, 19.4 mmol). After 12 h at rt, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (62.5 g, 3:1 hexane−EtOAc) to afford **12** (1.25 g, 100%) as colorless crystals: R_f 0.57 (3:1 hexane−EtOAc); mp 43−45 °C (not recrystallized); IR (KBr, cm^{-1}) 1590, 1480, 1390, 1220, 1150, 1100, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, s), 4.76 (2H, s), 4.74 (2H, s), 3.84 (3H, s), 3.83 (3H, s), 3.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.4, 60.6, 63.3, 96.3, 111.8, 123.2, 125.8, 128.9, 147.1, 155.1; HRMS (EI) m/z calcd for $C_{11}H_{14}O_4{}^{35}Cl^{79}Br$ 323.9764 (M^+), found 323.9780. Anal. Calcd for $C_{11}H_{14}O_4ClBr$: C 40.58, H 4.33. Found: C 40.79, H 4.33.

3-Chloro-2,5-dimethoxy-6-((methoxymethoxy)methyl)benzaldehyde (13). To a stirred solution of **12** (3.00 g, 9.26 mmol) in dry THF (185 mL) was added at −78 °C a 1.59 M pentane solution of *t*-BuLi (12.8 mL, 20.4 mmol). After 1 min at −78 °C, to this solution was quickly added HCO_2Me (5.71 mL, 92.6 mmol). After 0.5 h at −78 °C, the reaction mixture was warmed to rt and to this was added a 1 M aqueous HCl solution. The mixture was extracted with EtOAc and the extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (250 g, 3:1 hexane−EtOAc) to afford **13** (4.28 g, 90%) as colorless crystals: R_f 0.31 (3:1 hexane−EtOAc); mp 45−46 °C (not recrystallized); IR (KBr, cm^{-1}) 2940, 1700, 1580, 1480, 1390, 1300, 1250, 1100, 1050, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 10.41 (1H, s), 7.10 (1H, s), 4.81 (2H, s), 4.66 (2H, s), 3.84 (3H, s), 3.81 (3H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2, 56.4, 58.7, 62.8, 96.5, 117.3, 125.7, 128.8, 130.9, 151.8, 154.5, 191.5; HRMS (EI) m/z calcd

for $C_{12}H_{15}O_5{}^{35}Cl$ 274.0608 (M^+), found 274.0600. Anal. Calcd for $C_{12}H_{15}O_5Cl$: C 52.47, H 5.50. Found: C 52.29, H 5.35.

1-Chloro-3-ethynyl-2,5-dimethoxy-4-((methoxymethoxy)methyl)-benzene (15). To a stirred solution of **13** (1.69 g, 6.15 mmol) in dry MeOH (87.9 mL) were successively added at rt K_2CO_3 (2.13 g, 15.4 mmol) and a solution of the Ohira's reagent **14** (1.77 g, 9.23 mmol) in dry MeOH (29.3 mL). After 20 h at rt, 5% aqueous $NaHCO_3$ solution was added at 0 °C and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (180 g, 3:1 hexane−EtOAc) to afford **15** (1.17 g, 70%) as colorless crystals: R_f 0.34 (3:1 hexane−EtOAc); mp 87−90 °C (not recrystallized); IR (KBr, cm^{-1}) 1580, 1480, 1300, 1240, 1150, 1100, 1030, 920; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (1H, s), 4.73 (2H, s), 4.72 (2H, s), 3.88 (3H, s), 3.82 (3H, s), 3.52 (1H, s), 3.41 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2, 56.3, 61.1, 61.7, 76.8, 85.9, 96.3, 113.5, 120.0, 128.1, 128.3, 151.4, 154.5; HRMS (EI) m/z calcd for $C_{13}H_{15}O_4{}^{35}Cl$ 270.0659 (M^+), found 270.0651. Anal. Calcd for $C_{13}H_{15}O_4Cl$: C 57.68, H 5.59. Found: C 57.67, H 5.47.

3-((*tert*-Butyldimethylsilyl)ethynyl)-1-chloro-2,5-dimethoxy-4-((methoxymethoxy)methyl)benzene (16c). To a stirred solution of **15** (1.55 g, 5.73 mmol) in dry THF (95.5 mL) was added at −78 °C a 1.59 M hexane solution of *n*-BuLi (4.69 mL, 7.46 mmol). After 10 min at −78 °C, TBSOTf (1.58 mL, 6.88 mmol) was added and the mixture was stirred at −78 °C for 1 h. The reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc and the extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (60 g, 5:1 hexane−EtOAc) to afford **16c** (2.18 g, 99%) as a colorless syrup: R_f 0.74 (3:1 hexane−EtOAc); IR (neat, cm^{-1}) 1570, 1470, 1400, 1250, 1120, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, s), 4.73 (4H, s), 3.88 (3H, s), 3.82 (3H, s), 3.42 (3H, s), 1.00 (9H, s), 0.22 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, 16.7, 26.1, 55.2, 56.3, 60.9, 62.3, 96.5, 98.4, 102.5, 113.1, 121.1, 127.8, 128.2, 151.2, 154.6; HRMS (EI) m/z calcd for $C_{19}H_{29}O_4Si^{35}Cl$ 384.1524 (M^+), found 384.1518.

3-((*tert*-Butyldimethylsilyl)ethynyl)-5-hydroxy-2-((methoxymethoxy)methyl)-1,4-anthraquinone (7c) and 3-((*tert*-Butyldimethylsilyl)ethynyl)-1-chloro-2,5-dihydroxy-4-((methoxymethoxy)methyl)benzene (18c). To a stirred solution of **16c** (91.5 mg, 0.238 mmol) in MeCN (3.40 mL) was added at 0 °C a solution of CAN (547 mg, 0.998 mmol) in water (2.00 mL). The reaction mixture was stirred at 0 °C for 15 min. CAN (547 mg, 0.998 mmol) in water (2.00 mL) was added at intervals of 15 min (three times). Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (3.5 g, 5:1 hexane−EtOAc) to afford **8c** (71.4 mg, 85%) as a yellow syrup [R_f 0.89 (2:1 hexane−EtOAc); IR (neat, cm^{-1}) 1680, 1650, 1580, 1250, 1150, 1100, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, s), 4.68 (2H, s), 4.56 (2H, s), 3.36 (3H, s), 0.99 (9H, s), 0.20 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 16.7, 26.0, 55.4, 61.8, 95.8, 96.9, 115.5, 130.4, 134.1, 143.3, 144.3, 176.1, 183.5]. To a stirred solution of $(i\text{-Pr})_2NH$ (0.0266 mL, 0.190 mmol) in dry THF (0.950 mL) was added at 0 °C a 1.55 M hexane solution of *n*-BuLi (0.123 mL, 0.190 mmol). After 0.5 h at 0 °C, homophthalic anhydride (**9**) (30.8 mg, 0.190 mmol) was added and the mixture was warmed to rt. To this was added at rt **8c** (67.3 mg, 0.190 mmol) in dry THF (2.72 mL). After 5 min at rt, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (10 g, 2:1 hexane−EtOAc) to afford **7c** (48.5 mg, 58%) as red-brown solids and **18c** (6.9 mg, 10%) as red-brown solids. **7c**: R_f 0.70 (2:1 hexane−EtOAc); IR (KBr, cm^{-1}) 3450, 1660, 1630, 1580, 1460, 1310, 1250, 1150, 1040, 980; ^1H NMR (300 MHz, $CDCl_3$) δ 13.80 (1H, s), 8.48 (1H, br d, J = 7.8 Hz), 8.13 (1H, s), 7.96 (1H, br d, J = 7.8 Hz), 7.71 (2H, m), 4.77 (2H, s), 4.76 (2H, s), 3.42 (3H, s), 1.05 (9H, s), 0.27 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, 16.8, 26.1, 55.5, 62.6, 96.7, 97.0, 108.6, 114.8, 122.1, 125.0, 127.3, 127.5, 129.2, 130.5, 131.4, 133.8, 136.1, 148.7, 162.8, 182.5, 185.5; HRMS (EI) m/z calcd for $C_{25}H_{28}O_5Si$ 436.1706 (M^+), found 436.1717. **18c**: R_f 0.43 (2:1 hexane−EtOAc); IR (neat, cm^{-1}) 3400, 1590, 1460, 1320, 1250, 1150, 1000, 930; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, s), 6.93 (1H, s), 5.72 (1H, s), 4.93 (2H, s), 4.73 (2H, s), 3.42 (3H, s), 1.00 (9H, s), 0.22 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, 16.6, 26.1, 55.9, 66.1, 96.0, 96.9, 105.8, 110.0, 119.2, 120.0, 122.2, 147.0, 149.5; HRMS (EI) m/z calcd for $C_{17}H_{25}O_4Si^{35}Cl$ 356.1211 (M^+), found 356.1203.

3-Ethynyl-2,3-dihydro-2,3,5-trihydroxy-2-((methoxymethoxy)-methyl)-1,4-anthraquinone (20) from 7c. To a stirred solution of **7c** (24.2 mg, 0.0554 mmol) in a mixture of MeCN (0.33 mL), EtOAc (0.33 mL), and water (0.11 mL) were added at 0 °C a 0.1 M aqueous solution of $RuCl_3$ (0.0388 mL, 0.00388 mmol) and $NaIO_4$ (35.6 mg, 0.166 mmol). After 15 min at 0 °C, saturated aqueous $Na_2S_2O_3$ solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (2.0 g, 2:1 hexane−EtOAc) to afford **19c** (8.7 mg, 33%) as pale yellow solids and **7c** (5.4 mg, 22%) [**19c**: R_f 0.56 (2:1 hexane−EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 12.65 (1H, br s), 8.51 (1H, br d, J = 7.8 Hz), 8.11 (1H, s), 7.97 (1H, br d, J = 7.8 Hz), 7.74 (2H, m), 4.63 (2H, br s), 4.41 (1H, s), 3.96−4.40 (3H, m), 3.30 (3H, br s), 0.82 (9H, s), 0.08 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 16.6, 25.8, 55.7, 60.4, 68.1, 81.0, 95.9, 97.3, 99.5, 108.1, 120.9, 124.7, 127.4, 128.3, 128.9, 130.0, 131.3, 136.3, 162.2, 193.4, 194.7]. To a stirred solution of **19c** (8.7 mg, 0.0185 mmol) in dry THF (0.924 mL) was added at 0 °C a 1.0 M THF solution of TBAF (0.0370 mL, 0.0370 mmol). After 15 min at rt, saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (1.0 g, 1:2 hexane−EtOAc) to afford **20** (6.5 mg, 98%) as pale yellow solids: R_f 0.19 (2:1 hexane−EtOAc); mp 160−164 °C (not recrystallized); IR (KBr, cm^{-1}) 3400, 1690, 1650, 1460, 1380, 1260, 1150, 1100, 1000, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 12.74 (1H, br s), 8.50 (1H, br d, J = 7.8 Hz), 8.12 (1H, s), 7.97 (1H, br d, J = 7.8 Hz), 7.74 (2H, m), 4.56 (1H, br s), 4.52 (2H, br s), 4.18 (1H, br d, J = 10.0 Hz), 4.05 (1H, br s), 3.94 (1H, br d, J = 10.0 Hz), 3.21 (3H, s), 2.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 68.8, 77.2, 77.8, 78.9, 81.2, 97.0, 108.4, 121.0, 124.8, 127.6, 127.7, 129.1, 130.1, 131.5, 136.2, 162.6, 193.7, 195.2; HRMS (EI) m/z calcd for $C_{19}H_{16}O_7$ 356.0896 (M^+), found 356.0908. Anal. Calcd for $C_{19}H_{16}O_7$: C 64.04, H 4.53. Found: C 63.76, H 4.51.

3-Ethynyl-2,3-dihydro-2,3,5-trihydroxy-2-(hydroxymethyl)-1,4-anthraquinone (6). To a stirred solution of **20** (13.8 mg, 0.0387 mmol) in CH_2Cl_2 (0.775 mL) was added at 0 °C TFA (0.194 mL, 1.84 mmol). After 3 h at rt, saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (2.0 g, 1:1 hexane−EtOAc) to afford **6** (11.8 mg, 98%) as pale yellow solids: R_f 0.40 (1:1 hexane−EtOAc); IR (KBr, cm^{-1}) 3490, 1700, 1640, 1380, 1260, 1150, 1070, 970; ^1H NMR (300 MHz, $CDCl_3$) δ 12.34 (1H, br s), 8.52 (1H, br d, J =

7.8 Hz), 8.14 (1H, br s), 7.99 (1H, br d, J = 7.8 Hz), 7.76 (2H, m), 4.42 (1H, br dd, J = 12.0 Hz, 7.0 Hz), 4.34 (1H, br s), 4.24 (1H, br dd, J = 12.0 Hz, 7.0 Hz), 4.13 (1H, br s), 2.68 (1H, br s), 2.59 (1H, br t, J = 7.0 Hz); ^{1}H NMR (300 MHz, $(CD_3)_2CO$, the solvent residual peak = 2.05) δ 12.95 (1H, br s), 8.47 (1H, br d, J = 7.8 Hz), 8.18 (1H, br d, J = 7.8 Hz), 8.12 (1H, s), 7.83 (2H, m), 6.25 (1H, s), 5.15 (1H, br s), 4.23 (1H, br s), 4.13 (1H, m), 3.97 (1H, m), 3.34 (1H, s); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, the solvent peak = 29.8) δ 64.7, 78.4, 79.5, 79.8, 83.5, 110.0, 120.7, 124.8, 128.0, 129.77, 129.80, 131.0, 132.1, 137.0, 162.4, 196.4, 196.8; HRMS (EI) m/z calcd for $C_{17}H_{12}O_6$ 312.0634 (M^+), found 312.0645.

E-Ring Compound 5. To a mixture of 1,4-benzoquinone (2.9 mg, 0.027 mmol) and $PdCl_2$ (0.4 mg, ca. 0.002 mmol) in dry MeOH (0.14 mL) was added at 0 °C **6** (7.7 mg, 0.025 mmol) in dry MeOH (1.23 mL) under CO atmosphere (balloon). After 8 h at rt, CO was replaced with Ar and saturated aqueous NH_4Cl solution was added. The mixture was extracted with $CHCl_3$ and the extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (1.0 g, 10:1 $CHCl_3$−acetone) to afford **5** (5.6 mg, 62%) as pale yellow solids: R_f 0.70 (1:2 $CHCl_3$−acetone); mp 232−245 °C (not recrystallized); IR (KBr, cm^{-1}) 3490, 1700, 1680, 1650, 1460, 1360, 1260, 1140, 1080; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.55 (1H, br s), 9.57 (1H, s), 8.55 (1H, br d, J = 7.8 Hz), 8.17 (1H, s), 8.00 (1H, br d, J = 7.8 Hz), 7.82 (1H, ddd, J = 7.8 Hz, 7.0 Hz, 1.4 Hz), 7.76 (1H, ddd, J = 7.8 Hz, 7.0 Hz, 1.4 Hz), 5.84 (1H, s), 4.45 (2H, s), 4.11 (1H, br s), 3.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 83.4, 87.1, 97.48, 97.51, 107.9, 121.6, 125.1, 126.4, 127.8, 129.5, 130.2, 132.2, 136.5, 164.8, 171.5, 171.7, 191.9, 195.2; HRMS (EI) m/z calcd for $C_{19}H_{14}O_8$ 370.0688 (M^+), found 370.0689. Anal. Calcd for $C_{19}H_{14}O_8$: C 61.62, H 3.81. Found: C 61.40, H 3.81.

Model Aglycon 4 and Methanol Adduct 21 (Table 2, Entry 2). A mixture of **5** (2.6 mg, 0.0070 mmol) and CSA (4.9 mg, 0.021 mmol) in MeOH (0.47 mL) was refluxed for 3 d. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (1.0 g, 2:1 hexane−EtOAc) to afford **21** (1.4 mg, 50%) as pale yellow solids and **4** contaminated with a small amount of **5**. The latter mixture was purified with silica gel column chromatography (1.0 g, 10:1 $CHCl_3$−acetone) to afford **4** (1.1 mg, 42%) as pale yellow solids. **4**: R_f 0.42 (10:1 $CHCl_3$−acetone), 0.72 (1:1 hexane−EtOAc); mp 239−240 °C (pale yellow needles recrystallized from CH_2Cl_2−hexane); IR (KBr, cm^{-1}) 3480, 1790, 1680, 1640, 1460, 1390, 1250, 1140, 980; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.39 (1H, s, OH), 8.55 (1H, br d, J = 7.8 Hz, ArH), 8.20 (1H, s, ArH), 8.01 (1H, br d, J = 7.8 Hz, ArH), 7.81 (1H, ddd, J = 7.8 Hz, 7.0 Hz, 1.4 Hz, ArH), 7.75 (1H, ddd, J = 7.8 Hz, 7.0 Hz, 1.4 Hz, ArH), 4.88 (1H, d, J = 9.8 Hz, one of OCH_2), 4.09 (1H, d, J = 9.8 Hz, one of OCH_2), 3.20 (3H, s, OMe), 3.10 (1H, d, J = 17.0 Hz, one of CH_2CO), 3.05 (1H, br s, OH), 3.02 (1H, d, J = 17.0 Hz, one of CH_2CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.7, 52.6, 74.1, 82.6, 90.7, 110.1, 112.6, 122.2, 125.1, 127.4, 128.1, 129.4, 130.1, 132.0, 136.8, 163.3, 170.5, 189.8, 192.7; HRMS (EI) m/z calcd for $C_{19}H_{14}O_8$ 370.0688 (M^+), found 370.0696. **21**: R_f 0.27 (10:1 $CHCl_3$−acetone), 0.28 (1:1 hexane−EtOAc); IR (KBr, cm^{-1}) 3440, 1740, 1700, 1620, 1460, 1280, 1070, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.36 (1H, br s), 8.50 (1H, br d, J = 7.8 Hz), 8.14 (1H, br s), 7.96 (1H, br d, J = 7.8 Hz), 7.72 (2H, m), 5.92 (1H, br s), 4.95 (1H, d, J = 9.4 Hz), 3.94 (1H, d, J = 9.4 Hz), 3.76 (3H, s), 3.34 (1H, br s), 3.00 (5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 48.1, 52.5, 71.0, 82.8, 83.5, 107.3, 110.6, 121.0, 124.9, 127.0, 128.6, 129.8, 130.3, 131.5, 136.8, 162.9, 170.2, 188.3, 198.0; HRMS (EI) m/z calcd for $C_{20}H_{18}O_9$ 402.0951 (M^+), found 402.0948.

One-Pot Formation of 4. A mixture of **5** (1.4 mg, 0.0038 mmol) and CSA (2.6 mg, 0.011 mmol) in MeOH (0.25 mL) was refluxed for 5 d. The reaction mixture was concentrated and to the residue was added dry benzene (0.25 mL). After 75 °C for 1.5 h, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (1.0 g, 10:1 $CHCl_3$−acetone) to afford **4** (1.3 mg, 93%).

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Supporting Information Available: Experimental procedures for compounds except for those described in the Experimantal Section, copies of the ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.