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Toward an Asymmetric Synthesis of the Dimeric Pyranonaphthoquinone Antibiotic Crisamicin A

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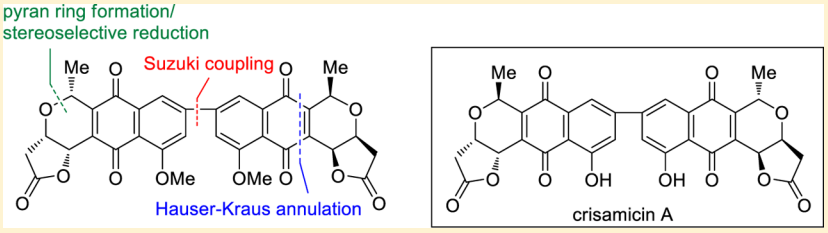
Supporting Information



ABSTRACT: A full account of our efforts toward an asymmetric synthesis of crisamicin A are presented. The key steps include a Hauser−Kraus annulation of a cyanophthalide with a chiral enone-lactone, a stereoselective cyclization−reduction to install the pyran unit, and a Suzuki homocoupling to forge the key biaryl bond. This work has culminated in the asymmetric synthesis of a dimer bearing the complete carbon skeleton of the dimeric pyranonaphthoquinone natural product crisamicin A.

INTRODUCTION

The pyranonaphthoquinones[1] are a large group of natural products that have attracted the attention of our research group.[2] While we have successfully synthesized the simpler monomeric structures of this family of natural products, of significant interest to us are the more complex dimeric pyranonaphthoquinones such as crisamicin A **1**,[3] actinorhodin **2**[4] and cardinalin 3 **3**[5] (Figure 1). These natural products are characterized by a C8−C8′ biaryl linkage with various substitution around the pyranonaphthoquinone ring system.

The dimeric pyranonaphthoquinone crisamicin A **1** was isolated in 1985 from a *Micromonospora* bacterium[6] and displayed spectral properties similar to monomeric pyranonaphthoquinone kalafungin **4** and its enantiomer nanaomycin D **5**, which both contain a fused γ-lactone ring and methyl substitution at C-1 (Figure 1). The structure of crisamicin A **1** was determined to be a dimer with the same substitution and stereochemistry around the pyran ring as nanaomycin D **5** and a naphthol group at C-6/C-6′. Crisamicin A **1** exhibits activity against Gram-positive bacteria, B16 murine melanoma cells and the herpes simplex, vaccinia and vesicular stomatitis viruses.[7] The pyranonaphthoquinone family have been proposed to act as bioreductive alkylating agents[8] and more recently have been shown to exhibit selective inhibitory activity against the serine/threonine AKT enzyme,[9] hence they have significant importance for the development of new anticancer agents.

To date, only a solitary racemic total synthesis of crisamicin A **1** has been reported, by Yang et al. in 2008.[10] The 19-step synthesis employed a palladium-catalyzed carbonylative lactonization and a Diels−Alder reaction to construct the monomeric pyranonaphthoquinone-lactone. The key step involved a palladium-catalyzed homocoupling reaction of a racemic boronate to form the racemic biaryl intermediate. Subsequent deprotection and oxidation gave racemic crisamicin A **1**.

Our earlier synthetic work toward crisamicin A **1** focused on the use of a Suzuki coupling to construct the dimeric framework followed by a double furonaphthofuran rearrangement to form the pyranonaphthoquinone; however, this strategy only afforded regioisomers of crisamicin A **1**.[3,4,11] A later attempt probed the use of a double Hauser−Kraus (HK) annulation using a bis-cyanophthalide to afford a dimeric naphthalene intermediate that was not able to be further elaborated to crisamicin A **1**.[3a] However, this HK annulation approach was successfully used to construct the core of the related dimeric pyranonaphthoquinones, the cardinalins.[5] Additionally, we have recently reported[12] a formal synthesis[13] of the monomer nanaomycin A **5** using a HK annulation of a cyanophthalide with an enone **8** bearing a preformed lactone ring, followed by a one-pot cyclization−stereoselective reduction (Scheme 1). The lactone in monomeric nanaomycin A **5** bears the same (*S*,*S*) stereochemistry as the dimer crisamicin A **1**.

In the current research, it was thought to combine the two previous approaches making use of an early HK annulation step and a late stage Suzuki coupling (Scheme 2). It was therefore envisaged that crisamicin A **1** could be formed by pyran ring formation, stereoselective reduction, oxidative demethylation and epimerization of dimeric trimethoxynaphthalene **6**. The

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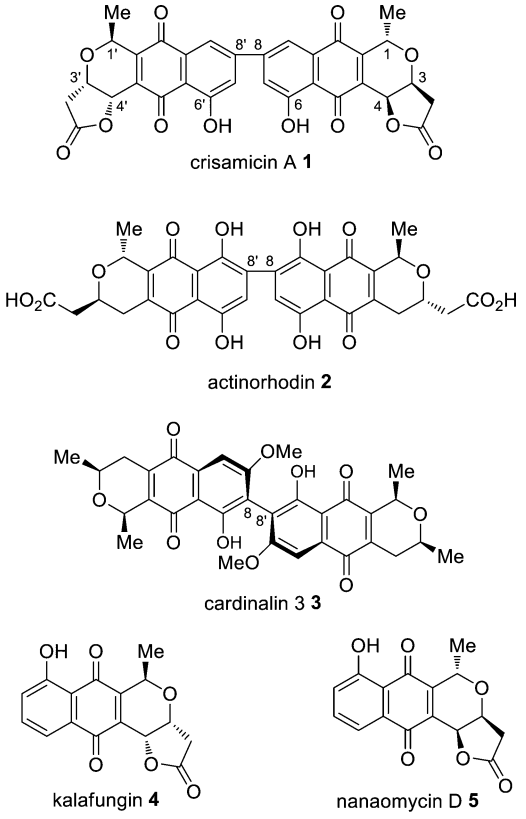


Figure 1. Dimeric pyranonaphthoquinones and related monomeric pyranonaphthoquinones.

dimeric structure **6** could be accessed via Suzuki homocoupling of triflate **7**, itself available from HK annulation of novel cyanophthalide **9** with previously synthesized enone-lactone **8**.[12] In turn, cyanophthalide **9** could be accessed from readily available *o*-formylbenzamide **10**.

RESULTS AND DISCUSSION

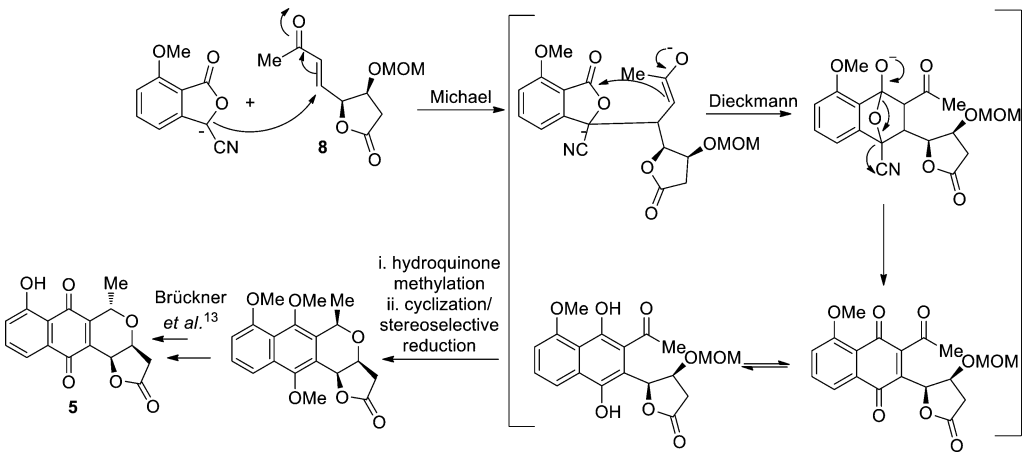
Our synthetic endeavors focused on the key Hauser–Kraus annulation of cyanophthalide **9** with previously synthesized enone-lactone **8**. Initial attention thus concentrated on the synthesis of cyanophthalide **9**. In an analogous sequence to that previously employed for the synthesis of a similar cyanophthalide,[2a] 3,5-dimethoxybenzoic acid **11** was converted to *N*-diethylbenzamide **12** in a one-pot procedure involving activation as the *N*-hydroxysuccinimide ester followed by substitution with diethylamine (Scheme 3). Directed *ortho*-formylation of amide **12** delivered aldehyde **13**, which underwent a deprotection/protection sequence to furnish orthogonally protected aldehyde **10**. Following double methyl ether deprotection of **13** with aluminum trichloride, the C5-phenol was selectively protected as a benzyl ether due to the lower reactivity of the C3-phenol resulting from hydrogen bonding of the adjacent formyl group. Reprotection of the C3-phenol group as its methyl ether was achieved using methyl iodide in dimethylformamide affording aldehyde **10** in good yield over three steps. Finally, phthalide **9** was generated via the corresponding trimethylsilyl-cyanohydrin intermediate using a well-established one-pot literature procedure.[2b]

Upon preparation of cyanophthalide **9**, attention next turned to its use in an HK annulation with enantiopure enone-lactone **8**, which was prepared from D-mannitol as described previously.[12] The HK annulation involves Michael addition of a phthalide anion to a Michael acceptor, followed by Dieckmann-like condensation and elimination of a leaving group to form a bicyclic system.[14] The annulation products are known to interconvert between the hydroquinone and quinone forms; therefore, the hydroquinone is often trapped as the dimethyl ether derivative. Thus, cyanophthalide **9** was deprotonated using freshly prepared lithium diisopropylamide (LDA) and reacted with enone **8**. After workup, the crude mixture was subjected to reductive methylation using sodium dithionite, cesium carbonate and methyl iodide in dimethylformamide. However, the product isolated was not the desired trimethoxynaphthalene **14** but rather the *C*-alkylated product **15** (Scheme 4).

Repetition of the HK annulation as described in Scheme 4, but omitting the methylation step did not result in formation of the desired quinone **16**, instead the nonaromatized compound **17** was isolated (Scheme 5). Attempts to effect the HK annulation using alternative bases *t*-BuOK or *t*-BuOLi also resulted in formation of **17**.

This undesired outcome was overcome using the alkylation conditions reported by Kraus (Scheme 6).[15] HK annulation with *t*-BuOLi followed by immediate methylation using dimethyl sulfate and potassium carbonate in refluxing acetone afforded the desired trimethoxynaphthalene **18** in 35% yield over two steps. In order to prepare for the biaryl coupling, HK

Scheme 1. Formal Synthesis of Nanaomycin A (5) Using a HK Annulation (Mechanism Shown)[12]



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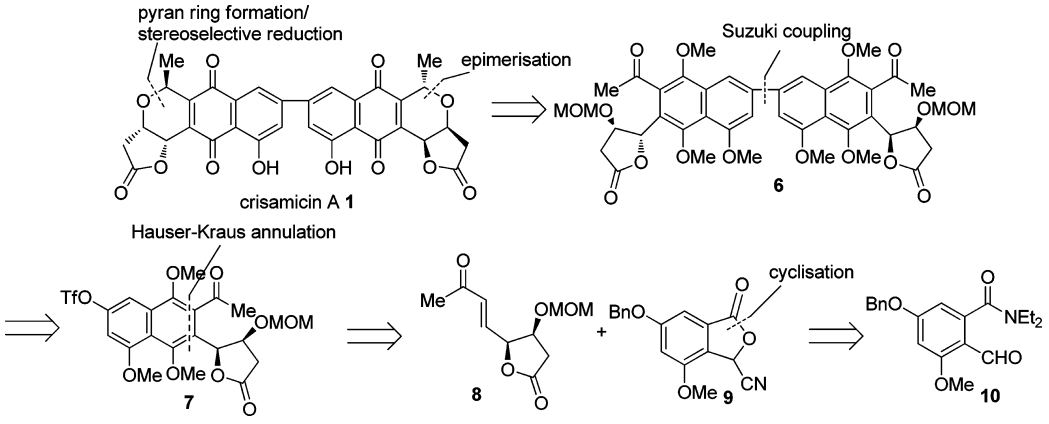
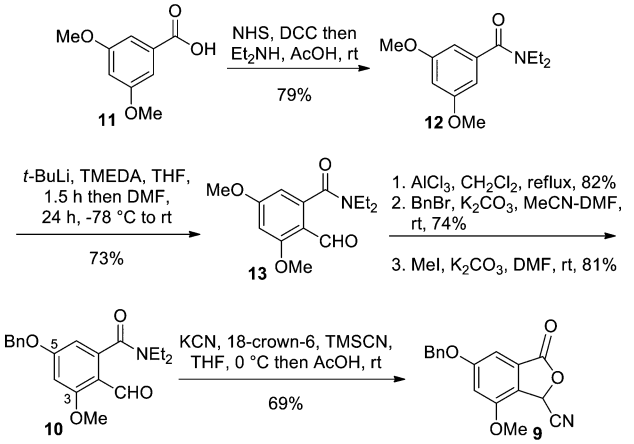
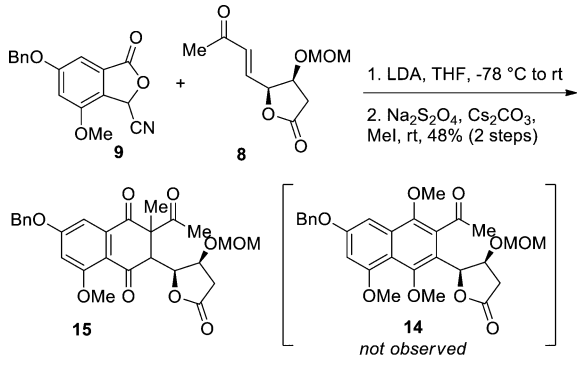
Scheme 2. Retrosynthesis of Crisamicin 1



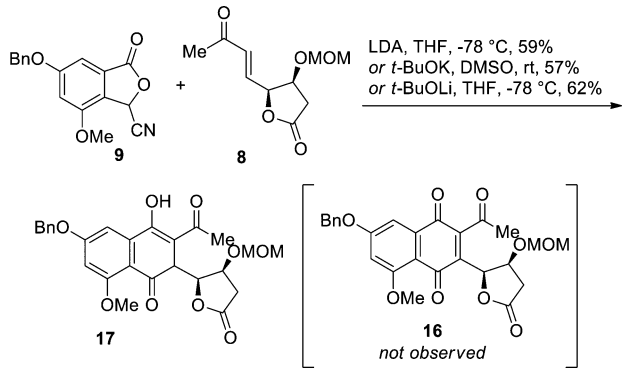
Scheme 3. Synthesis of Cyanophthalide 9



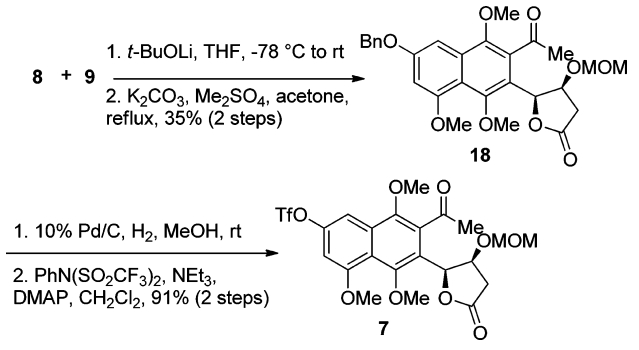
Scheme 4. Formation of Undesired *C*-Alkylation Product 15



Scheme 5. Synthesis of Nonaromatized Annulation Product 17



Scheme 6. Synthesis of Triflate 7



annulation product **18** was next converted to triflate **7** (Scheme 6). Hydrogenolysis of the benzyl ether using 10% palladium on carbon and triflation of the resulting naphthol with *N*-phenyl-bis(trifluoromethanesulfonimide) afforded triflate **7** in 91% yield over two steps.

Upon preparation of triflate **7**, the key Suzuki homocoupling could be attempted. Using conditions previously employed by our group,[5] potassium carbonate and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were added to a solution of triflate **7** in dioxane before the addition of $PdCl_2$(dppf) catalyst and bis(pinacolato)diboron (Scheme 7). The degassed reaction mixture was heated at 85 °C in a sealed tube to afford a moderate 55% yield of the desired dimer **19**. A second attempt using microwave irradiation gave only a 48% yield of dimer **19**. In both cases no starting material remained, with the rest of the reaction mixture containing only degradation products. The first procedure was found to give reliable yields when carried out on up to 100 mg scale.

With dimer **19** in hand, double MOM deprotection was effected using anhydrous hydrochloric acid in dioxane to give diol **20**. As with our previous nanaomycin D synthesis,[12] diol **20** did not spontaneously cyclize to the lactol **21** as hoped. Alternative attempts at concomitant deprotection-lactol formation were performed using Amberlyst 15, trimethylsilyl bromide and DOWEX 50; however, none of these conditions promoted lactol formation, and all gave lower yields of diol **20** than the initially attempted conditions.

Double lactol formation and stereoselective reduction was attempted using the successful conditions employed during our earlier synthesis of the monomer nanaomycin D **5** (boron

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Scheme 7. Suzuki Homocoupling of Triflate 7 to Dimer 20

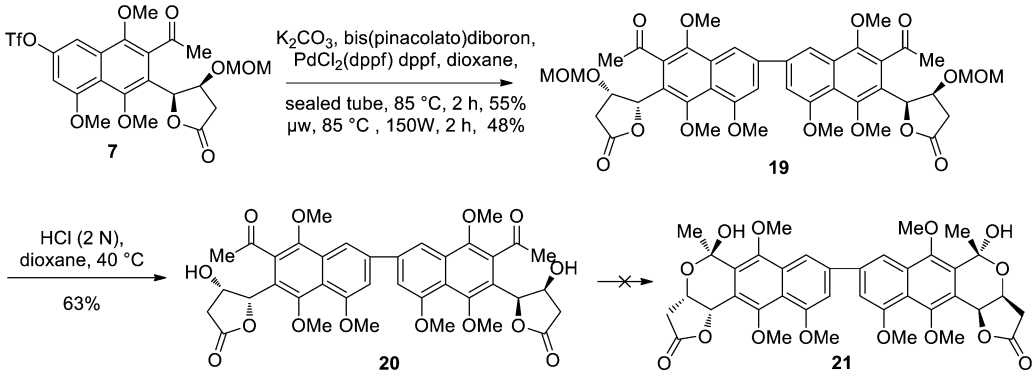
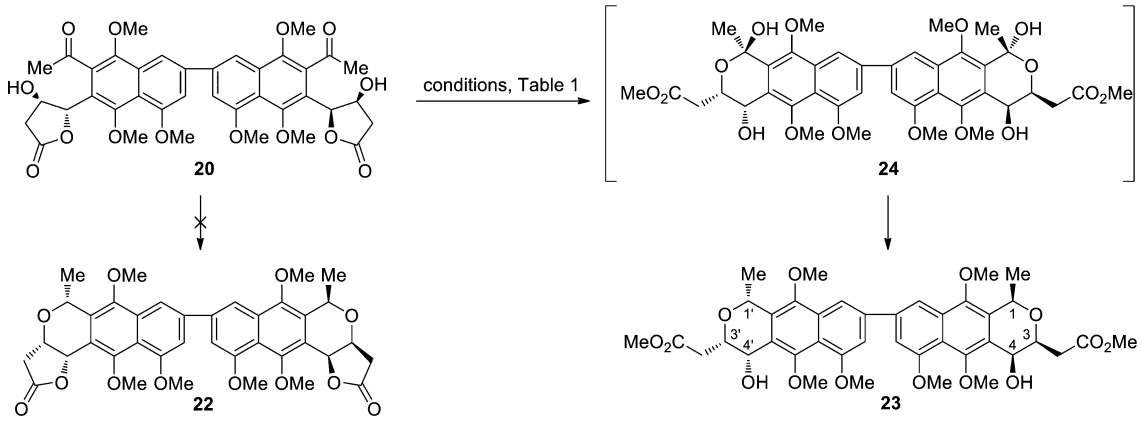
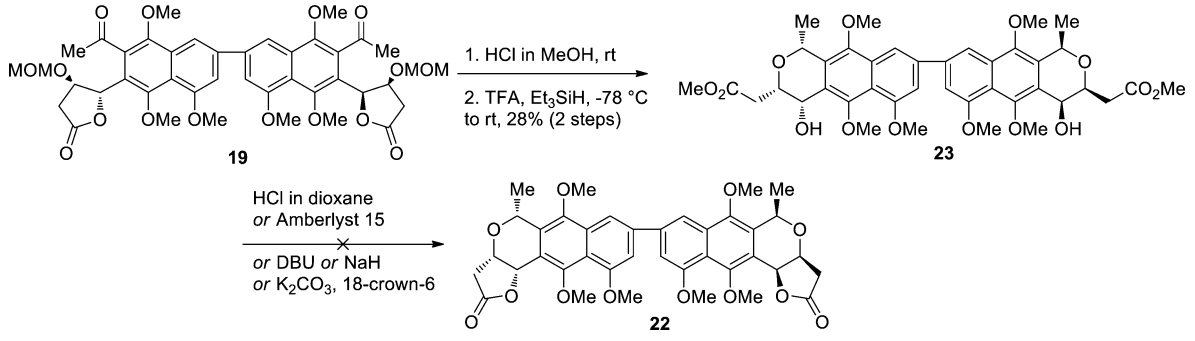


Table 1. Attempted Double Pyran Ring Formation from Diol 20



entry	reagents	solvent	temperature (°C)	result
1	$BF_3{\cdot}Et_2O$ then Et_3SiH	CH_2Cl_2	−78 to rt	recovered **20**
2	Et_3SiH then $BF_3{\cdot}Et_2O$	CH_2Cl_2	−78 to rt	recovered **20**
3	Et_3SiH then $BF_3{\cdot}Et_2O$	CH_2Cl_2	−78 to 50	degradation
4	*p*-TsOH	toluene	rt to −60	degradation
5	*p*-TsOH	CH_2Cl_2	rt to −60	degradation
6	*p*-TsOH	THF	rt to −60	degradation
7	*p*-TsOH then Et_3SiH, TFA	$MeOH/CH_2Cl_2$	rt to −78 to rt	11% **23**

Scheme 8. Two-Step Formation of Pyranonaphthalene 23 from MOM-Protected Dimer 19



trifluoride diethyl etherate and triethylsilane).[12] Unfortunately, only starting material was returned when these conditions were applied to diol **20** (Table 1, entry 1). Altering the order of addition of the reagents only afforded recovered starting material (entry 2), while increasing the reaction temperature to 50 °C resulted in degradation (entry 3). Stirring diol **20** with *p*-toluenesulfonic acid[16] in toluene, dichloromethane or tetrahydrofuran at room temperature showed no change by TLC analysis; subsequent heating to 60 °C again resulted in degradation (entries 4−6). However, stirring **20** with *p*-toluenesulfonic acid in methanol gave a new product, as observed by TLC analysis. Subsequent reduction with triethylsilane and trifluoroacetic acid revealed the product to be pyranonaphthalene **23**, obtained in a poor 11% yield. Although we were pleased to see that cyclization-stereoselective reduction had successfully occurred, it was clear that the lactone

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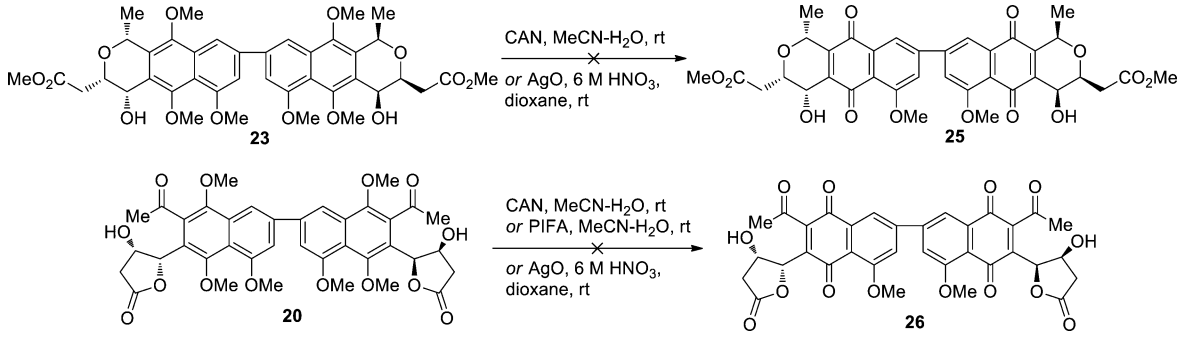
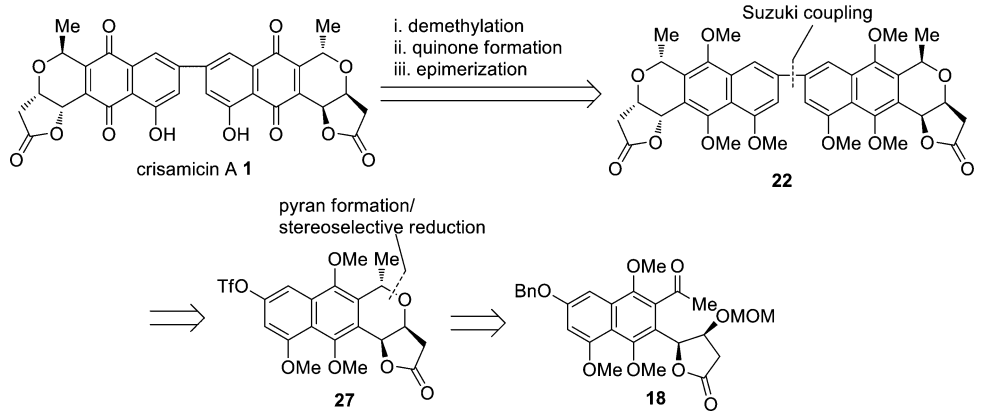
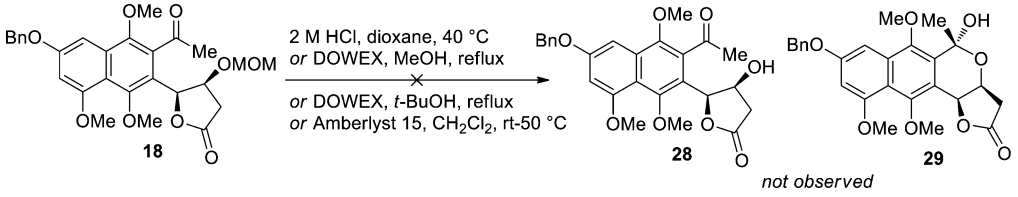
Scheme 9. Attempted Oxidative Demethylation of 23 and 20



Scheme 10. Revised Retrosynthesis of Crisamicin A (1)



Scheme 11. Attempted Deprotection of MOM Ether 18



ring had undergone methanolysis in the presence of methanol. Pyranonaphthalene **23** likely arose from methanolysis of the lactone prior to cyclization to lactol **24** as the cyclization only took place when methanol was used as the solvent.

Despite providing an undesired product, the methanolysis-lactone opening-pyran ring formation-reduction sequence furnished a single isomer of **23**. The *cis*-relationship of the H-3/H-3′ and H-4/H-4′ protons was confirmed by a clear NOE correlation. Additionally, the cyclization−reduction was stereoselective, providing the (*R*)-configuration of the 1-methyl group as verified by a NOE correlation between H-3/H-3′ and H-5/H-5′ (see Supporting Information for full details).

It was next thought that subjecting dimer **19** to a one-pot deprotection−methanolysis−cyclization−reduction sequence would afford pyranonaphthalene **23** in higher yield than the route already described (Scheme 8). Dimer **19** was stirred with methanolic hydrochloric acid to presumably give the lactol intermediate **24**, which upon reduction with triethylsilane and trifluoroacetic acid furnished pyranonaphthalene **23** in a slightly higher 28% yield over two steps. Attention next focused on reinstallation of the two γ-lactone rings to form the desired pyranonaphthalene-lactone **22** (Scheme 8). Lactonization was attempted under both acidic and basic conditions. Reaction of **23** with anhydrous hydrochloric acid, Amberlyst 15, DBU, sodium hydride or potassium carbonate with 18-crown-6 only resulted in recovery of the starting material or degradation.

At this point, it was thought that oxidation of the ring-opened pyranonaphthalene **23** to the less sterically demanding pyranonaphthoquinone **25** might facilitate lactonization (Scheme 9). Oxidative demethylation of **23** was attempted using ceric ammonium nitrate (CAN) or silver(II) oxide/nitric acid. While both of these reactions gave a yellow spot on TLC indicative of quinone formation, no product could be isolated inferring that the bis-quinone **25** was unstable and degraded upon work up. Similarly, it was thought that oxidative demethylation of naphthalene-lactone **20** to quinone **26** may promote pyran ring formation (Scheme 9). However, oxidative demethylation of **20** using CAN, silver(II) oxide/nitric acid or phenyliodine bis(trifluoroacetate) (PIFA) all afforded an unstable product that rapidly degraded upon workup.

At this stage, it was clear that the dimer **20** behaved very differently to the previously synthesized nanaomycin D monomer (Scheme 1), which successfully underwent concomitant lactol formation and stereoselective reduction using boron trifluoride diethyl etherate-triethylsilane.[12] It was therefore decided to alter the synthetic route to effect pyran ring

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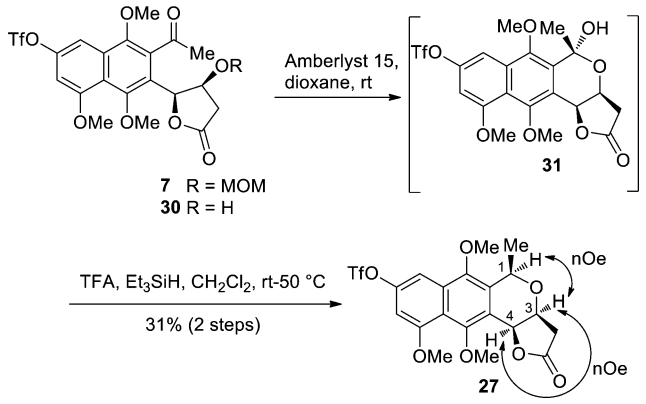
formation prior to Suzuki coupling (Scheme 10). It was envisaged that oxidative demethylation, deprotection and epimerization of enantiopure dimer **22** would afford the natural product crisamicin A **1**. Dimer **22** would be accessed by Suzuki homocoupling of pyranonaphthalene-triflate monomer **27**, itself available via pyran ring formation and stereoselective reduction of previously synthesized HK annulation product **18**.

Our new synthetic plan began with investigations into the key pyran ring forming step on trimethoxynaphthalene **18**. Frustratingly, all conditions attempted to effect deprotection of the methyoxymethyl ether in **18** to facilitate pyran ring formation resulted in degradation or recovery of the starting material (Scheme 11).

Attention next turned to the deprotection of triflate **7** instead of benzyl ether **18** (Scheme 12). Upon treatment of triflate **7** with Amberlyst 15, two spots were observed by TLC, presumed to be a mixture of alcohol **30** and lactol **31**. Subsequent stereoselective reduction of the crude mixture with TFA and triethylsilane gratifyingly afforded a single diastereomer of the desired pyranonaphthalene **27** in 31% yield over two steps. The *cis*-stereochemistry of the γ-lactone was confirmed by a clear NOE correlation between H-3 and H-4. Additionally, the (*R*)-configuration of the 1-methyl group in **27** was also confirmed by a NOE correlation between H-3 and H-1 (see Supporting Information for full details).

Scheme 12. Synthesis of Pyranonaphthalene 27



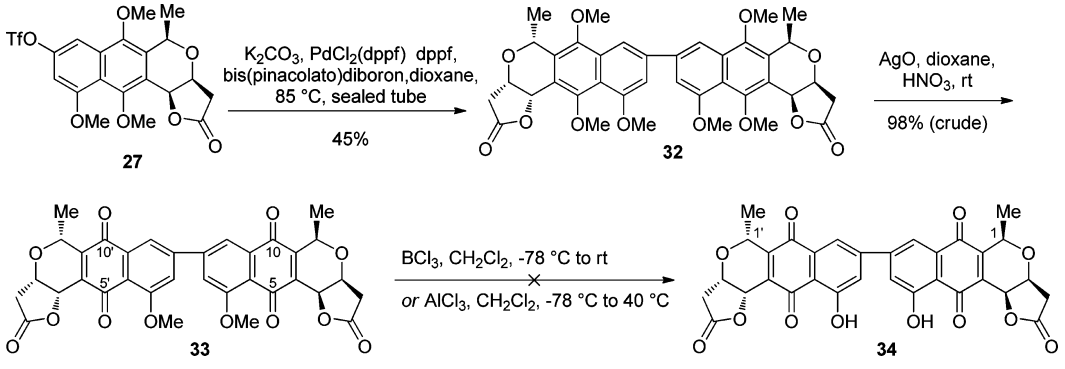
Having successfully synthesized triflate **27**, the key Suzuki homocoupling reaction was next investigated. Homocoupling of triflate **27** using the same conditions as the successful Suzuki homocoupling of monomer **7** to dimer **18** (Scheme 7) gave the dimeric naphthopyran **32** in a pleasing 45% yield (Scheme 13). The NOE correlations previously observed in the monomeric triflate **27** (H-3 correlated with H-1 and H-4) were all still evident, indicating that the stereochemical integrity of the monomer **27** had been preserved in dimer **32**.

With the full carbon framework of crisamicin A fully assembled, quinone formation, demethylation and epimerization at C-1/C-1′ would complete the total synthesis. Oxidative demethylation was unsuccessful with CAN or PIFA; however, reaction with AgO/HNO_3 gave a yellow spot on TLC indicative of quinone formation (Scheme 12). Unfortunately, all purification attempts resulted in degradation of the product. Analysis of the ^1H NMR spectrum of the crude product confirmed the formation of the quinone **33** by disappearance of the C-5, C-5′, C-10 and C-10′ methoxy resonances. Additionally, the mass spectrum of the crude product confirmed the molecular formula $C_{34}H_{26}O_{12}$ by observation of the $[M + Na]^+$ molecular ion at m/z 649.1316. As bis-quinone **33** could not be purified, the subsequent demethylation step was attempted on the crude material. Unfortunately, demethylation with boron trichloride or aluminum trichloride resulted in a complex mixture of products. This result was highly disappointing considering the closely related example reported by Wang et. al,[10] who reported a successful demethylation using boron trichloride on the racemic dimeric pyranonaphthoquinone where the C1 and C1′ methyl groups are epimeric.[10] Nevertheless, a successful asymmetric synthesis of the bis-pyranonaphthoquinone-lactone **33** bearing the complete carbon skeleton of the dimeric pyranonaphthoquinone natural product crisamicin A (**1**) has been achieved.

■ CONCLUSION

In summary, we have completed an asymmetric synthesis of the dimeric pyranonaphthoquinone **33** bearing the full carbon skeleton of crisamicin A **1**. Using an efficient HK annulation–Suzuki homocoupling sequence, the synthesis of bis-quinone **33** was completed in a longest linear sequence of 17 steps. As attempted pyran ring formation of dimer **20** also resulted in opening of the γ-lactone ring, it was necessary to reorder the synthesis and form the pyran ring prior to Suzuki coupling. Frustratingly, the penultimate demethylation step was unsuccessful using conditions previously used for a closely related racemic dimer.[10] Future work is geared toward conducting the final de-etherification step on the corresponding diisopropyl ether, known to be more readily cleaved than their methyl counterparts.[17]

Scheme 13. Homocoupling of Triflate 27, Subsequent Oxidative Demethylation, and Attempted Demethylation



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EXPERIMENTAL SECTION

General Methods. THF and dioxane were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 was freshly distilled from CaH_2. Reactions were monitored by thin-layer chromatography (TLC) using Kieselgel F254 0.2 mm (Merck) silica plates with visualization by ultraviolet irradiation (254 nm) followed by staining with vanillin or potassium permanganate. Optical rotations were measured at a wavelength of 589 nm, with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded as thin films on an ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei, as stated. Chemical shifts were referenced to δ_H 7.26 and δ_C 77.0 ppm from tetramethylsilane for chloroform for ^1H and ^{13}C, respectively. All coupling constants, J are reported in Hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode, and assignments were determined using DEPT135, DEPT90, COSY, HSQC and NOESY experiments where required. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.

Compound **8** was synthesized as described previously.[12]

***N,N*-Diethyl 3,5-dimethoxybenzamide (12).** 3,5-Dimethoxybenzoic acid **11** (4.00 g, 21.9 mmol) and *N*-hydroxysuccinimide (3.04 g, 26.4 mmol) were taken up in EtOAc (200 mL). A solution of DCC (5.43 g, 26.4 mmol) in EtOAc (50 mL) was added, and the reaction mixture was stirred at room temperature for 4 h. Et_2NH (20 mL) was added, and the reaction mixture was stirred at room temperature for a further 18 h. AcOH (15 mL) was then added, the reaction mixture was filtered, and the filtrate concentrated to ∼100 mL and then filtered again. The filtrate was concentrated under reduced pressure and taken up in EtOAc (100 mL) and washed with aq. NaOH (2 × 100 mL, 1 M). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 7:3) to give the title compound **12** (4.10 g, 17.3 mmol, 79%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (br s, 3H), 1.21 (br s, 3H), 3.27 (br s, 2H), 3.54 (br s, 2H), 3.80 (s, 6H), 6.47 (t, J = 2.2, 1H), 6.49 (d, J = 2.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 14.2, 39.1, 43.2, 55.4 (2C), 101.2, 104.1 (2C), 139.1, 160.8 (2C), 170.8. Spectroscopic data was in agreement with the literature values.[18]

***N,N*-Diethyl 2-formyl-3,5-dimethoxybenzamide (13).** Benzamide **12** (2.00 g, 8.43 mmol) was dissolved in distilled THF (40 mL) and cooled to −78 °C. TMEDA (1.65 mL, 9.00 mmol) and *t*-BuLi (7.31 mL, 1.5 M in pentane, 10.9 mmol) were added, and the reaction mixture stirred at −78 °C for 1.5 h. DMF (6 mL) was added dropwise, and the reaction mixture was warmed to room temperature overnight. Sat. aq. NH_4Cl (50 mL) was added, and the resulting layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 2:1) to give the title compound **13** (1.62 g, 6.11 mmol, 73%) as a colorless solid: mp 108−110 °C (lit[19] 114−116 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1, 3H), 1.32 (t, J = 7.1, 3H), 3.07 (q, J = 7.1, 2H), 3.58 (br s, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 6.36 (d, J = 2.3, 1H), 6.45 (d, J = 2.3, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 13.5, 38.6, 42.3, 55.7, 55.9, 98.0, 104.4, 115.2, 141.4, 164.0, 165.5, 169.6, 187.5. Spectroscopic data was in agreement with the literature values.[19]

***N,N*-Diethyl 2-formyl-3,5-dihydroxybenzamide.** To a solution of benzaldehyde **13** (1.50 g, 5.60 mmol) in distilled CH_2Cl_2 (80 mL) was added $AlCl_3$ (4.53 g, 33.6 mmol), and the reaction mixture heated at reflux for 24 h. Upon cooling to 0 °C, HCl (2 M, 40 mL) was added slowly. The layers were separated, and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 1:1) to give the title compound (1.10 g, 4.64 mmol, 82%) as a colorless solid: mp 162−164 °C; IR (neat, cm^{-1}) 2975, 2933, 2793, 2612, 1593, 1556, 1497, 1455, 1439, 1385, 1360, 1315, 1288, 1257, 1222, 1177; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J = 7.2, 3H), 1.28 (t, J = 7.2, 3H), 3.21 (q, J = 7.2, 2H), 3.45 (br s, 1H), 3.75 (br s, 1H), 6.20 (d, J = 2.2, 1H), 6.28 (d, J = 2.2, 1H), 9.64 (br s, 1H), 9.64 (s, 1H), 11.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 14.0, 39.7, 43.7, 104.3, 107.2, 110.5, 141.9, 164.8, 165.4, 168.7, 191.7; HRMS (EI) m/z $[M]^+$ calcd for $C_{12}H_{15}NO_4$ 237.10011, found 237.1007.

***N,N*-Diethyl 5-(benzyloxy)-2-formyl-3-hydroxybenzamide.** To a solution of *N,N*-diethyl 2-formyl-3,5-dihydroxybenzamide (1.00 g, 4.21 mmol) in acetonitrile (20 mL) and DMF (2 mL), K_2CO_3 (641 mg, 4.64 mmol) was added followed by BnBr (0.55 mL, 4.64 mmol), and the reaction mixture stirred at room temperature for 48 h. Sat. aq. NH_4Cl (40 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 1:1) to give the title compound (1.02 g, 3.1 mmol, 74%) as an oil that solidified on standing: mp 46−48 °C; IR (neat, cm^{-1}) 3066, 3034, 2975, 2936, 2875, 1626, 1573, 1497, 1455, 1441, 1423, 1384, 1368, 1297, 1269, 1222; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.1, 3H), 1.26 (t, J = 7.1, 3H), 3.19 (q, J = 7.1, 2H), 3.47 (br s, 1H), 3.69 (br s, 1H), 5.12 (s, 2H), 6.44 (d, J = 2.3, 1H), 6.50 (d, J = 2.2, 1H), 7.34−7.41 (m, 5H), 9.73 (d, J = 0.4, 1H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.2, 39.2, 43.2, 70.6, 101.9, 106.7, 111.3, 127.5 (2C), 128.5, 128.8 (2C), 135.3, 143.4, 165.4, 165.6, 167.2, 192.9; HRMS (EI) m/z $[M]^+$ calcd for $C_{19}H_{21}NO_4$ 327.147106, found 327.14768.

***N,N*-Diethyl 5-(benzyloxy)-2-formyl-3-methoxybenzamide (10).** To a solution of *N,N*-diethyl 5-(benzyloxy)-2-formyl-3-hydroxybenzamide (800 mg, 2.44 mmol) in DMF (10 mL) was added K_2CO_3 (1.01 g, 7.36 mmol) followed by MeI (0.45 mL, 7.36 mmol), and the reaction mixture was stirred at room temperature for 24 h. Sat. aq. NH_4Cl (40 mL) was added, followed by EtOAc (50 mL). The resulting layers were separated, and the aqueous layer extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 2:1) to give the title compound **10** (676 mg, 1.98 mmol, 81%) as an oil that solidified upon standing: mp 38−40 °C; IR (neat, cm^{-1}) 3091, 3066, 3034, 2978, 2936, 2873, 1674, 1633, 1595, 1455, 1380, 1327, 1237, 1201; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.1, 3H), 1.31 (t, J = 7.1, 3H), 3.03 (q, J = 7.1, 2H), 3.57 (br s, 2H), 3.89 (s, 3H), 5.13 (s, 2H), 6.42 (d, J = 2.0, 1H), 6.53 (d, J = 2.0, 1H), 7.34−7.41 (m, 5H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 13.4, 38.5, 42.3, 55.9, 70.5, 98.9, 105.2, 115.2, 127.5 (2C), 128.4, 128.7 (2C), 135.6, 141.4, 163.9, 164.5, 169.6, 187.6; HRMS (EI) m/z $[M]^+$ calcd for $C_{20}H_{23}NO_4$ 341.16271, found 341.16300.

6-(Benzyloxy)-3-cyano-4-methoxy-1(3*H*)-dihydroisobenzofuranone (9). A solution of *N,N*-diethyl 5-(benzyloxy)2-formyl-3-methoxybenzamide **10** (670 mg, 1.96 mmol) in distilled CH_2Cl_2 (5 mL) was cooled to 0 °C. TMS-CN (0.29 mL, 2.16 mmol) was added followed by KCN (12.0 mg, 0.196 mmol) and 18-crown-6 (13 mg, 0.049 mmol, 2.5 mol %). The reaction mixture was stirred at 0 °C for 1.5 h, concentrated under reduced pressure, the residue taken up in AcOH (5 mL) and stirred at room temperature for 4 h. Aq. NaOH (10 mL, 1 M) was added, followed by EtOAc (20 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 2:1) to give the title compound **9** (400 mg, 69%) as a beige solid: mp 121−122 °C; IR (neat, cm^{-1}) 2930, 1793, 1778, 1613, 1504, 1444, 1428, 1348, 1324, 1277; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 5.13 (s, 2H), 5.92 (s, 1H), 6.86 (d, J = 1.9, 1H), 7.03 (d, J = 1.9, 1H), 7.34−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 60.1, 70.9, 100.5, 106.5, 113.3, 122.5, 127.0, 127.6 (2C), 128.5, 128.8 (2C), 135.4, 155.2,

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163.3, 167.7; HRMS (EI) m/z $[M]^+$ calcd for $C_{17}H_{13}NO_4$ 295.08446, found 295.0839.

***C*-Alkylated naphthoquinone-lactone 15.** A solution of phthalide **9** (27.57 mg, 0.093 mmol) in distilled THF (2 mL) was added slowly to freshly prepared solution of LDA (0.14 mmol) in distilled THF (1 mL) at −78 °C [prepared from *n*-BuLi (1.6 M in hexanes, 0.09 mL, 0.14 mmoL) and diisopropylamine (0.02 mL, 0.14 mmoL) at 0 °C], and the reaction mixture was stirred for 15 min. To the resulting bright yellow solution was added enone **8** (10 mg, 0.047 mmol) in distilled THF (1 mL) and stirred for 1 h. Sat. aq. NH_4Cl (10 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Then, the resulting residue was taken up in DMF (5 mL) and $Na_2S_2O_4$ (65.0 mg, 0.37 mmol) was added. After stirring for 30 min, Cs_2CO_3 (121.7 mg, 0.37 mmol) was added followed by MeI (0.023 mL, 0.0376 mmol). The reaction mixture was stirred for 15 h under an atmosphere of N_2. Sat. aq. NH_4Cl (5 mL) and CH_2Cl_2 (10 mL) were added, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with H_2O (3 × 10 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 1:1) to afford the title compound **15** (11.2 mg, 0.02 mmol, 48% over 2 steps) as a dark oil: $[\alpha]_D^{22}$ +28.3 (*c* 0.10, CH_3OH); IR (neat, cm^{-1}) 2923, 2852, 1779, 1685, 1592, 1460, 1310; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.19 (s, 3H), 2.68 (d, J = 17.6, 1H), 2.75 (dd, J = 4.9, 17.9, 1H), 3.28 (s, 3H), 3.59 (d, J = 8.7, 1H), 3.89 (s, 3H), 4.58 (d, J = 6.9, 1H), 4.63 (d, J = 6.9, 1H), 4.88 (m, 1H), 5.17 (s, 2H), 5.31 (dd, J = 3.8, 8.7, 1H), 6.82 (d, J = 2.4, 1H), 7.23 (d, J = 2.4, 1H), 7.35−7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 26.3, 36.3, 52.5, 55.9, 56.5, 68.4, 70.7, 75.7, 81.4, 96.5, 103.5, 106.2, 118.6, 127.7 (2C), 128.6 (2C), 128.8, 135.4, 136.6, 160.9, 163.6, 174.4, 191.2, 193.7, 205.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{28}NaO_9$ 519.1626, found 519.1630.

Hydroxynaphthalenone-lactone 17. To a solution of *t*-BuOLi (4.10 mg, 0.052 mmol) in distilled THF (1 mL) was added a solution of phthalide **9** (15.3 mg, 0.05 mmol) in distilled THF (1 mL) at −78 °C, and the mixture stirred for 10 min. A solution of enone **8** (10.0 mg, 0.047 mmol) in distilled THF (1 mL) was added, and the resulting mixture was stirred for 15 min, warmed to room temperature and stirred for another 15 min. The dark red solution was quenched by addition of sat. aq. NH_4Cl (5 mL). The resulting mixture was partitioned between CH_2Cl_2 (10 mL) and sat. aq. NH_4Cl (5 mL), and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 7:3) to afford the title compound **17** (14.1 mg, 0.032 mmol, 62%) as a yellow oil: $[\alpha]_D^{21}$ −68.3 (*c* 0.67, $CHCl_3$); IR (neat, cm^{-1}) 3202, 3002, 2930, 2824, 1787, 1672, 1658, 1594, 1584, 1454, 1388, 1340; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.60 (dd, J = 17.6, 1H), 2.73 (d, J = 17.5, 1H), 3.48 (s, 3H), 3.89 (s, 3H), 4.23 (m, 1H), 4.33 (d, J = 10.3, 1H), 4.36 (dd, J = 2.9, 10.3, 1H), 4.81 (d, J = 7.2, 1H), 4.89 (d, J = 7.2, 1H) 5.20 (d, J = 11.3, 1H), 5.23 (d, J = 11.5, 1H), 6.71 (d, J = 2.3, 1H), 7.35 (d, J = 2.3, 1H), 7.35−7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 37.8, 48.3, 56.3 (2C), 70.7, 74.1, 84.3, 97.2, 102.9, 103.6, 106.3, 114.8, 127.7 (2C), 128.6, 128.8 (2C), 135.4, 138.2, 161.0, 164.4, 170.6, 173.7, 193.0, 199.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{26}NaO_9$ 505.1469, found 505.1460.

Benzoxy-trimethoxynaphthalene-lactone 18. To a solution of *t*-BuOLi (86.7 mg, 1.08 mmol) in distilled THF (2 mL) was added a solution of phthalide **9** (320 mg, 1.08 mmol) in distilled THF (5 mL), and the solution stirred for 5 min at −78 °C. A solution of enone **8** (211 mg, 0.99 mmol) in distilled THF (3 mL) was added, and the resulting mixture was stirred for 15 min then warmed to room temperature and stirred for another 15 min. The dark red solution was quenched upon addition of sat. aq. NH_4Cl (10 mL). The resulting mixture was partitioned between CH_2Cl_2 (15 mL) and sat. aq. NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was taken up in acetone (25 mL) and K_2CO_3 (816.8 mg, 5.91 mmol) was added followed by Me_2SO_4 (0.56 mL, 5.91 mmol). The reaction mixture was heated at reflux for 8 h. Sat. aq. NH_4Cl (15 mL) and CH_2Cl_2 (50 mL) were added, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 7:3) to afford the title compound **18** (177 mg, 0.35 mmol, 35% over 2 steps) as a dark oil: $[\alpha]_D^{26}$ −17.4 (c 0.10, $CHCl_3$); IR (neat, cm^{-1}) 2923, 2846, 1784, 1695, 1615, 1452, 1340; ^1H NMR (400 MHz, $CDCl_3$) δ 2.63 (dd, J = 5.4, 18.1, 1H), 2.62 (s, 3H), 3.14 (dd, J = 8.2, 18.1, 1H), 3.31 (s, 3H), 3.73 (s, 3H), 3.81 (s, 3H), 3.99 (s, 3H), 4.63 (d, J = 6.9, 1H), 4.67 (d, J = 6.9, 1H), 4.74 (ddd, J = 5.2, 5.2, 8.2, 1H), 5.20 (d, J = 11.9, 1H), 5.23 (d, J = 11.9, 1H), 5.71 (d, J = 4.9, 1H), 6.71 (d, J = 2.2, 1H), 7.04 (d, J = 2.2, 1H), 7.26−7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 36.6, 55.7, 56.2, 62.9, 63.6, 70.2, 79.2, 81.7, 94.5, 96.3, 100.9, 116.5, 121.4, 127.6 (2C), 128.2, 128.7 (2C), 132.2, 132.4, 136.4, 147.6, 152.1, 157.7, 158.6, 174.9, 206.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{31}O_9$ 511.196, found 511.1965.

Hydroxy-trimethoxynaphthalene-lactone. To a solution of trimethoxynaphthalene **18** (110 mg, 0.22 mmol) in MeOH (10 mL) was added Pd/C (10%, 50.0 mg), and the reaction mixture stirred under an atmosphere of H_2 for 3 h. The reaction mixture was filtered through Celite then concentrated under reduced pressure to give the naphthol as black oil that was used directly in the next step without further purification. The crude naphthol material was purified for characterization purposes using flash chromatography (hexanes−EtOAc, 1:1) to afford the title compound (82.0 mg, 0.195 mmol, 88%) as a dark oil: $[\alpha]_D^{22}$ −35.7 (*c* 0.70, $CHCl_3$); IR (neat, cm^{-1}) 3386, 2934, 2846, 1740, 1782, 1695, 1616, 1583, 1467, 1458, 1410, 1335; ^1H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.66 (dd, J = 5.2, 18.2, 1H), 3.17 (dd, J = 8.2, 18.2, 1H), 3.32 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 3.96 (s, 3H), 4.63 (d, J = 6.9, 1H), 4.68 (d, J = 6.9, 1H), 4.76 (ddd, J = 5.2, 5.2, 8.2, 1H), 5.73 (d, J = 4.8, 1H), 6.61 (d, J = 2.1, 1H), 6.85 (s, 1H), 6.99 (d, J = 2.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 36.7, 55.7, 56.2, 63.0, 63.5, 79.2, 82.1, 96.3, 97.1, 100.2, 115.9, 120.5, 132.0, 132.5, 147.5, 152.1, 156.4, 158.0, 175.7, 206.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}NaO_9$ 443.1313, found 443.1307.

Trimethoxynaphthalene triflate 7. To a solution of crude naphthol in distilled CH_2Cl_2 (5 mL) was added DMAP (5.27 mg, 0.043 mmol), *N*-phenyl-bis(trifluoromethanesulfonimide) (115.5 mg, 0.32 mmol) and freshly distilled Et_3N (0.06 mL, 0.043 mmol). The reaction mixture was stirred at room temperature for 2 h then quenched with sat. aq. NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes−EtOAc, 7:3) to afford the title compound **7** (111 mg, 0.201 mmol, 91% over 2 steps) as a dark oil: $[\alpha]_D^{20}$ −34.3 (*c* 0.90, $CHCl_3$); IR (neat, cm^{-1}) 3549, 2953, 2915, 2850, 1790, 1698, 1583, 1506, 1465, 1401, 1354, 1285; ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (s, 3H), 2.65 (dd, J = 5.6, 18.2, 1H), 3.13 (dd, J = 8.2, 18.2, 1H), 3.33 (s, 3H), 3.84 (s, 6H), 4.06 (s, 3H), 4.65 (d, J = 6.9, 1H), 4.68 (d, J = 6.9, 1H), 4.73 (ddd, J = 5.4, 5.4, 8.1, 1H), 5.77 (d, J = 5.0, 1H), 6.82 (d, J = 2.2, 1H), 7.58 (d, J = 2.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 36.4, 55.8, 56.7, 63.8 (2C), 79.1, 81.1, 96.4, 101.6, 106.3, 118.7 (d, J_{CF} = 118.7), 120.9, 125.7, 131.1, 133.5, 148.6, 148.7, 151.9, 158.5, 174.5, 205.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{24}F_3O_{11}S$ 553.0986, found 553.1001.

MOM-Protected Dimer 19. *Use of Sealed Tube.* A solution of triflate **7** (76.0 mg, 0.14 mmol) in distilled dioxane (4 mL) was placed in a sealed tube. K_2CO_3 (57.0 mg, 0.41 mmol), bis(pinacolato)diboron (17.5 mg, 0.07 mmol) and dppf (26.7 mg, 0.05 mmol) were added to the above solution. The resulting suspension was degassed by bubbling Ar through the mixture for 15 min. $PdCl_2$(dppf) (35.2 mg, 0.05 mmol)

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was added, and the suspension degassed for a further 15 min. The reaction mixture was heated to 85 °C for 2 h. After cooling to room temperature, the suspension was diluted with EtOAc (10 mL) and washed with H_2O (25 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (hexanes−EtOAc, 1:1) to yield the title compound **19** (31.0 mg, 0.04 mmol, 55%) as a dark oil.

Use of Microwave Irradiation. A solution of triflate **7** (20.0 mg, 0.036 mmol) in dioxane (2 mL) was placed in a sealed tube. K_2CO_3 (15.0 mg, 0.109 mmol), bis(pinacolato)diboron (4.60 mg, 0.0181 mmol) and dppf (5.02 mg, 0.009 mmol) were added to the above solution. The suspension then degassed by bubbling Ar through the mixture for 15 min. $PdCl_2$(dppf) (6.62 mg, 0.009 mmol) was added, and the suspension was degassed for a further 15 min. The reaction mixture was heated under microwave irradiation (150 W, 85 °C) for 2 h. After cooling to room temperature, the suspension was diluted with EtOAc (5 mL) and washed with H_2O (15 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes−EtOAc, 1:1) to yield the title compound **19** (6.96 mg, 0.0086 mmol, 48%) as a dark oil: $[\alpha]_D^{23}$ −23.8 (*c* 0.60, $CHCl_3$); IR (neat, cm^{-1}) 2930, 2851, 1786, 1732, 1697, 1615, 1584, 1561, 1452, 1335; ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 5.5, 18.2, 2H), 2.67 (s, 6H), 3.16 (dd, *J* = 8.2, 18.2, 2H), 3.34 (s, 6H), 3.89 (s, 6H), 3.90 (s, 6H), 4.14 (s, 6H), 4.67 (d, *J* = 6.9, 2H), 4.70 (d, *J* = 6.9, 2H), 4.80 (ddd, *J* = 5.4, 5.4, 8.2, 2H), 5.80 (d, *J* = 5.1, 2H), 7.27 (d, *J* = 1.6, 2H), 7.97 (d, *J* = 1.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8 (2C), 36.6 (2C), 55.8 (2C), 56.4 (2C), 63.7 (2C), 63.8 (2C), 79.2 (2C), 81.5 (2C), 96.4 (2C), 107.4 (2C), 113.4 (2C), 120.1 (2C), 124.5 (2C), 131.6 (2C), 132.6 (2C), 140.4 (2C), 149.0 (2C), 151.9 (2C), 157.0 (2C), 174.8 (2C), 205.9 (2C); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{42}H_{47}O_{16}$ 807.2859, found 807.2862.

Dihydroxy Dimer 20. To a solution of dimer **19** (30.5 mg, 0.038 mmol) in distilled dioxane (2 mL) was added anhydrous HCl in dioxane (2 mL, 4 M), and the resulting solution stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure then purified by flash chromatography (hexanes−EtOAc, 3:7) to yield the title compound **20** (17.0 mg, 0.024 mmol, 63%) as a yellow oil: $[\alpha]_D^{20}$+41.9 (*c* 0.80, $CHCl_3$); IR (neat, cm^{-1}) 3376, 2926, 2855, 1782, 1703, 1601, 1458, 1397, 1353, 1267; ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 6.2, 18.1, 2H), 2.72 (s, 6H), 2.82 (br s, 2H), 3.12 (dd, *J* = 8.4, 18.1, 2H), 3.89 (s, 6H), 3.92 (s, 6H), 4.15 (s, 6H), 4.87 (m, 2H), 5.69 (d, *J* = 5.2, 2H), 7.27 (m, 2H), 7.96 (d, *J* = 1.1, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7 (2C), 37.4 (2C), 56.4 (2C), 63.4 (2C), 63.6 (2C), 74.3 (2C), 83.7 (2C), 107.2 (2C), 113.5 (2C), 120.1 (2C), 125.0 (2C), 131.4 (2C), 132.2 (2C), 140.2 (2C), 149.4 (2C), 151.1 (2C), 156.8 (2C), 174.4 (2C), 206.2 (2C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{38}NaO_{14}$ 741.2154, found 741.2135.

Bis-trimethoxypyranonaphthalene 23. *Method 1.* To a solution of diol **20** (4.50 mg, 0.0063 mmol) in MeOH(1 mL) was added, *p*-TsOH (27.0 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 4 h. H_2O (10 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was taken up in distilled CH_2Cl_2 (2 mL) and cooled to −78 °C. Trifluoroacetic acid (0.07 mL, 0.076 mmol) was added followed by Et_3SiH (0.12 mL, 0.076 mmol). The reaction mixture was stirred at −78 °C for 15 min then allowed to warm to room temperature over 15 h. H_2O (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (hexanes−EtOAc, 1:9) provided the title compound **23** (0.5 mg, 0.0007, 11% over 2 steps) as a red oil.

Method 2. To a solution of dimer **19** (30 mg, 0.037 mmol) in MeOH (1 mL) was added HCl in MeOH [1 mL, 2 M (prepared from addition of 0.16 mL acetyl chloride in 1 mL HPLC grade MeOH at 0 °C)], and the reaction mixture stirred for 1 h. H_2O (5 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was taken up in distilled CH_2Cl_2 (10 mL) and cooled to −78 °C. Trifluoroacetic acid (0.02 mL, 0.223 mmol) was added followed by Et_3SiH (0.03 mL, 0.223 mmol). The solution was stirred at −78 °C for 15 min then allowed to reach room temperature over 3 h. H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (hexanes−EtOAc, 1:9) provided the title compound **23** (7.7 mg, 0.0103 mmol, 28% over 2 steps) as a red oil: $[\alpha]_D^{20}$ −20.0 (*c* 0.25, $CHCl_3$); IR (neat, cm^{-1}) 3428, 2926, 2852, 1733, 1605, 1438, 1364, 1340, 1256; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6.4, 6H), 2.53 (dd, *J* = 3.3, 15.7, 2H), 2.65 (dd, *J* = 8.9, 15.9, 2H) 3.69 (s, 6H), 3.89 (s, 6H), 3.91 (s, 6H), 4.12 (s, 6H), 4.66 (m, 2H), 5.53 (d, *J* = 5.2, 2H), 5.58 (q, *J* = 6.4, 2H), 7.23 (d, *J* = 1.5, 2H), 8.03 (d, *J* = 1.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (2C), 37.2 (2C), 51.7 (2C), 56.5 (2C), 61.1 (2C), 61.9 (2C), 71.1 (2C), 76.6 (2C), 78.5 (2C), 84.8 (2C), 106.4 (2C), 113.2 (2C), 120.4 (2C), 130.6 (2C), 132.6 (2C), 133.7 (2C), 139.4 (2C), 146.5 (2C), 157.0 (2C), 173.1 (2C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{40}H_{46}NaO_{14}$ 773.2780, found 773.2766.

Trimethoxypyranonaphthalene triflate 27. To a solution of triflate **7** (22.5 mg, 0.044 mmol) in distilled dioxane (5 mL), Amberlyst 15 (100 mg) was added and stirred at room temperature for 8 h. Another portion of Amberlyst 15 (100 mg) was added and stirring was continued for further 8 h. The third portion of Amberlyst 15 (100 mg) was added, and the reaction mixture was stirred for another 8 h. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue taken up in distilled CH_2Cl_2 (3 mL) and cooled to 0 °C. Trifluoroacetic acid (0.03 mL, 0.41 mmol) was added and after stirring for 5 min, Et_3SiH (0.065 mL, 0.41 mmol) was added and further stirred for 1 h then warmed to room temperature over 16 h. H_2O (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexanes−EtOAc, 7:3) provided the title compound **27** (6.7 mg, 0.014 mmol, 31% over 2 steps) as a pale yellow oil: $[\alpha]_D^{20}$ +127.1 (*c* 0.43, $CHCl_3$); IR (neat, cm^{-1}) 2929, 2858, 1797, 1656, 1601, 1581, 1422, 1375, 1344, 1202; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.4, 3H), 2.82 (dd, *J* = 11.8, 15.8, 1H), 2.89 (dd, *J* = 7.2, 15.8, 1H) 3.87 (s, 3H), 3.89 (s, 3H), 4.06 (s, 3H), 4.08−4.11 (m, 1H), 5.12 (d, *J* = 9.0, 1H), 5.47 (q, *J* = 6.5, 1H), 6.75 (d, *J* = 2.4, 1H), 7.52 (d, *J* = 2.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 35.5, 56.7, 61.5, 63.9, 73.4, 76.2, 77.3, 100.6, 106.1, 118.8 (d, J_{CF} = 319), 119.5, 125.4, 130.3, 130.6, 148.2, 148.4, 150.0, 158.8, 173.1; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}F_3NaO_9S$ 515.0594, found 515.0575.

Bis-trimethoxypyranonaphthalene 32. A solution of triflate **27** (25.8 mg, 0.052 mmol) in distilled dioxane (2 mL) was placed in a sealed tube. K_2CO_3 (21.7 mg, 0.16 mmol), bis(pinacolato)diboron (6.7 mg, 0.026 mmol) and dppf (7.3 mg, 0.013 mmol) were added to the above solution. The resulting suspension was degassed by bubbling Ar through the mixture for 15 min. $PdCl_2$(dppf) (9.6 mg, 0.013 mmol) was added and further degassed for 15 min. The reaction mixture was heated to 85 °C for 2 h. After cooling to room temperature, the suspension was diluted with EtOAc (5 mL) and washed with H_2O (15 mL). The aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes−EtOAc, 3:7) to yield the title compound **32** (8 mg, 0.012 mmol, 45%) as a dark oil: $[\alpha]_D^{20}$+137 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2923, 2852, 1794, 1735, 1598, 1449, 1368, 1338, 1247, 1201; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (d, *J* = 6.4, 6H), 2.83 (dd, *J* = 11.7, 15.7, 2H), 2.89 (dd, *J* = 7.4, 15.8, 2H),

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3.92 (s, 6H), 3.95 (s, 6H), 4.10 (m, 2H), 4.12 (s, 6H), 5.17 (d, J = 8.9, 2H), 5.52 (q, J = 6.5, 2H), 7.23 (d, J = 1.5, 2H), 7.92 (d, J = 1.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (2C), 35.6 (2C), 56.6 (2C), 61.5 (2C), 63.9 (2C), 73.6 (2C), 76.3 (2C), 77.2 (2C), 106.8 (2C), 113.1 (2C), 119.7 (2C), 124.1 (2C), 128.9 (2C), 131.3 (2C), 140.0 (2C), 148.6 (2C), 150.0 (2C), 157.3 (2C), 173.4 (2C); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{38}H_{38}NaO_{12}$ 709.2255, found 709.2219.

1,1′-*epi*,6,6′-Dimethyl-crisamicin A (33). To a solution of dimer **32** (9 mg, 0.013 mmol) in distilled dioxane (2 mL) was added AgO (16.2 mg, 0.13 mmol) followed by HNO_3 (6 M, 0.02 mL). The reaction mixture was stirred at room temperature for 20 min. H_2O (10 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was removed under pressure to give the crude bis-quinone **33** (8.0 mg, 0.013 mmol, 98%) as a bright yellow solid: $[\alpha]_D^{24}$+136 (c 0.23, $CHCl_3$); IR (neat, cm^{-1}) 2926, 2853, 1797, 1660, 1592, 1458, 1266, 1290, 1204; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, J = 6.7, 6H), 2.77−2.91 (m, 4H), 4.09 (s, 6H), 3.96−4.06 (m, 2H), 4.84−4.87 (m, 2H), 5.16−5.18 (m, 2H), 7.47 (d, J = 1.6, 2H), 7.92 (d, J = 1.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (2C), 35.3 (2C), 56.8 (2C), 73.1 (2C), 74.1 (2C), 75.3 (2C), 116.4 (2C), 117.8 (2C), 119.4 (2C), 134.4 (2C), 144.4 (2C), 145.5 (2C), 145.5 (2C), 160.3 (2C), 171.9 (2C), 179.5 (2C), 182.7 (2C); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{34}H_{26}NaO_{12}$ 649.1316, found 649.1304.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H, ^{13}C NMR and selected NOESY spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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