Total Synthesis of the Furaquinocins

Takeshi Saito, Takao Suzuki, Munetsugu Morimoto, Chikako Akiyama, Takashi Ochiai, Kazuhiro Takeuchi, Takashi Matsumoto, and Keisuke Suzuki*

Contribution from the Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152, Japan, and Department of Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

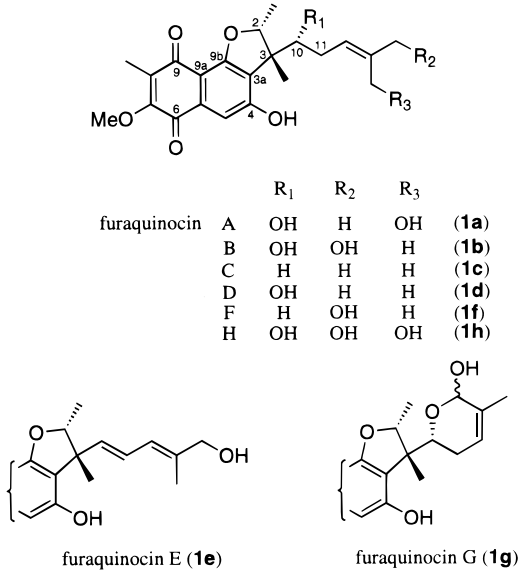
Received July 8, 1998

Abstract: A viable synthetic route to the furaquinocin-class antibiotics is described. The key steps include (1) Co-complex mediated stereospecific 1,2-shift of an alkynyl group (**9** → **6**) to establish the C(2)−C(3) stereochemical relationship, (2) efficient construction of furanonaphthalene **20** from the sodium carboxylate derived from ester **19**, and (3) stereoselective methylene transfer reaction to aldehyde **21** to establish the three contiguous stereogenic centers, C(2), C(3), and C(10). The stereodefined epoxide **23**, thus obtained, served as a versatile intermediate in divergent syntheses of four congeners of this class of natural products, furaquinocins A (**1a**), B (**1b**), D (**1d**), and H (**1h**), by changing the vinylic nucleophiles.

Introduction

The furaquinocins (**1a**−**1h**; Figure 1) constitute a new class of antibiotics isolated from the fermentation broth of *Streptomyces* sp. KO-3988 by Ōmura et al.,[1] which show cytotoxic activity against HeLa S3 and B16 melanoma cells, but no antimicrobial activity.[1b] There are several congeners that differ in the oxidation level at the isoprenoid portion, and among them the most potent cytocidal activity is exhibited by the most highly oxygenated congener, furaquinocin H (**1h**).[1c] Biosynthetic studies revealed that the naphthoquinone moiety is derived from pentaacetate, which is connected to an internal carbon of the isoprenoid chain through the C(3)−C(3a) bond.[1e,2] The relative and absolute stereochemistries were assigned by the extensive correlation of each component and by an X-ray study in the collaboration of Smith and Ōmura.[1d] So far, the synthetic efforts directed toward these natural products have culminated in the development of two total synthetic routes; one is the beautifully short synthesis of (−)-furaquinocin C (**1c**) by Smith[3a] and the other is our synthesis of (±)-furaquinocin D (**1d**).[3b]

In this full account, we detail our total synthetic route to these natural products. The improvements from our preliminary route[3b] include (1) an enantioselective synthesis enabled by exploiting the Co-complex mediated 1,2-shift of an alkynyl group, (2) suitable choice of the protecting group that realized selective oxidation of the aromatic ring at the final step of the synthesis, and (3) syntheses of four congeners, furaquinocin A, B, D, and H, by utilizing stereodefined epoxide **23** (vide infra) as the common synthetic intermediate.



		R_1	R_2	R_3	
furaquinocin	A	OH	H	OH	(**1a**)
	B	OH	OH	H	(**1b**)
	C	H	H	H	(**1c**)
	D	OH	H	H	(**1d**)
	F	H	OH	H	(**1f**)
	H	OH	OH	OH	(**1h**)

Figure 1. The furaquinocins.

Results and Discussion

In planning the synthetic approach to these natural products, the following problems were taken into consideration. First, the targets share a quaternary stereogenic center at C(3) that is surrounded by one or two additional chiral center(s) at C(2) and C(10). Such a stereocontrol *at* and *peripheral to* a quaternary stereogenic center is obviously ranked as a challenging problem in organic synthesis.[4] Second, selective construction of the highly substituted aromatic moiety is also challenging; the common naphthoquinone shared by these

(1) For the isolation and the structure elucidation of the furaquinocins, see: (a) Funayama, S.; Ishibashi, M.; Anraku, Y.; Komiyama, K.; Ōmura, S. *Tetrahedron Lett.* **1989**, *30*, 7427. (b) Komiyama, K.; Funayama, S.; Anraku, Y.; Ishibashi, M.; Takahashi, Y.; Ōmura, S. *J. Antibiot.* **1990**, *43*, 247. (c) Ishibashi, M.; Funayama, S.; Anraku, Y.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1991**, *44*, 390. (d) Dormer, P. G.; Smith, A. B., III; Funayama, S.; Ōmura, S. *Tetrahedron Lett.* **1992**, *33*, 1717. For biosynthetic study of the furaquinocins, see: (e) Funayama, S.; Ishibashi, M.; Komiyama, K.; Ōmura, S. *J. Org. Chem.* **1990**, *55*, 1132. For the isolation of related compounds, see: (f) Kagamizono, T.; Kawashima, A.; Kishimura, Y.; Yamagishi, M.; Tsuchida, Y.; Kondo, H.; Hanada, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 766. (g) Sedmera, P.; Pospísil, S.; Novák, J. *J. Nat. Prod.* **1991**, *54*, 870.

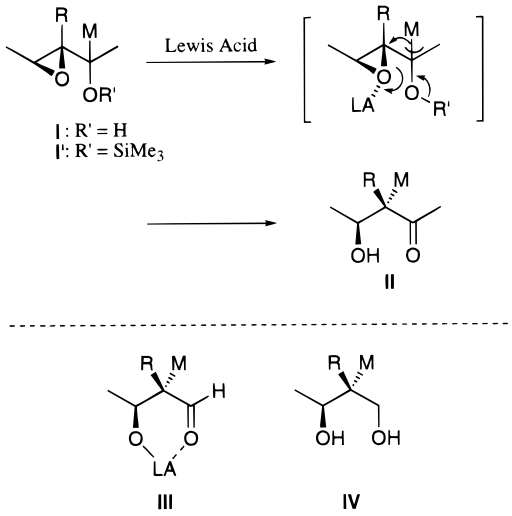
(2) The furaquinocin numbering is used throughout this paper.

(3) (a) Smith, A. B., III; Sestelo, J.; Dormer, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 10755. (b) Saito, T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757.

(4) For reviews on constructing a quaternary stereogenic center, see the following: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

10.1021/ja982403t CCC: $15.00
Published on Web 10/30/1998

Scheme 1. Epoxy Alcohol → Aldol Rearrangement

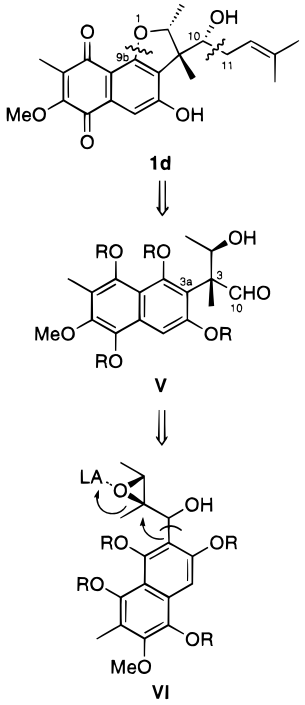


molecules is densely functionalized. The last, but not the least, problem is the steric congestion around the interface of the aromatic and the isoprenoid portions; the C(3)−C(3a) bond has an aliphatic quaternary carbon at one end, while at the other end is an *o*,*o*′-disubstituted aromatic carbon. Despite a rather small molecular framework, these issues render the total synthesis of this class of natural products highly challenging. Below, we discuss our synthetic studies, which have culminated in the development of a synthetic route which is general and flexible enough to allow the synthesis of many congeners.

The key motif of our approach was the 1,2-rearrangement of epoxy alcohol derivatives (Scheme 1).[5] Treatment of epoxy alcohol **I** or its silyl ether **I**′ with a Lewis acid induces an epoxide opening, the 1,2-shift of a group (M), and the carbonyl formation to give *β*-hydroxy carbonyl compound **II**. By the stereospecificity of the 1,2-shift, the epoxide stereochemistry is predictably transmitted into the aldol product. Essential to the present context is the construction of a quaternary stereogenic center;[5c] stereospecificity of the 1,2-shift holds even when the starting epoxide is more substituted (R ≠ H), thereby giving stereodefined α,α-disubstituted aldols **II** (R ≠ H) that are barely accessible by the usual aldol chemistry.[6] Such a starting material as **I** is readily available via the Katsuki−Sharpless reaction.[7] When the product is a *β*-hydroxy aldehyde which is prone to undergo retro-aldol reaction, a variant protocol is available; the reaction in the presence of a reducing agent as Et_3SiH leads to an in situ reduction of the formed aldolate **III** to give 1,3-diol **IV**.[5]

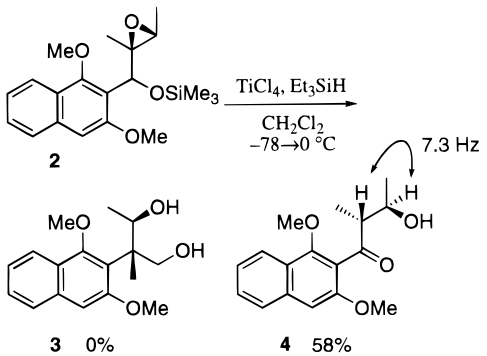
Initial Approach. On the basis of these tactics, we initially centered our attention on the strategy shown in Scheme 2. Disconnections at the C(10)−C(11) and the O(1)−C(9b) bonds suggested an aldol intermediate **V**, which, we envisioned, would be readily accessible via the 1,2-shift of a naphthyl group

Scheme 2. First Synthetic Plan



corresponding to the whole chromophore (**VI** → **V**). We surmised that such a process would work if we reductively modify the quinone chromophore as in **VI**, since an electron-rich aromatic usually behaves as a good migrating group.

However, the model study was negative: When an aryl group has two *o*-methoxy groups at the migrating center, the 1,2-shift of the aryl group does not occur as exemplified by a model reaction (eq 1). The naphthyl group did not undergo 1,2-shift at all, and instead, formation of aldol **4** was only observed.[8] This result could be ascribed to the extremely high steric demand of such an *o*,*o*′-disubstituted aryl group that would discourage its 1,2-shift. A number of trials centered on this single step turned out, unfortunately, to be unfruitful, and we were forced to abandon this plan.



(1)

Second Synthetic Plan. This juncture made us recognize that the essential problem was the steric hindrance around the aromatic−isoprenoid interface. Paying particular attention to this point, we turned to the second plan (Scheme 3), where the key is the disconnection of the C(3a)−C(4) bond in **VII**, thereby

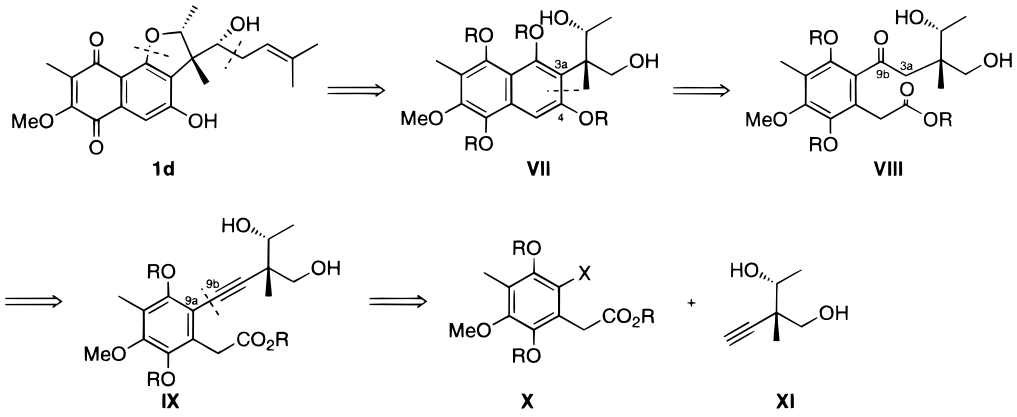
(5) (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515. (c) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891. (d) Shimazaki, M.; Morimoto, M.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 3335. (e) For a review, see: Suzuki, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 49.

(6) For reviews on aldol reaction, see: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Mukaiyama, T. *Org. React.* **1982**, *28*, 203. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111.

(7) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(8) Unexpectedly, the aldol product **4** proved to have the anti structure, based on the coupling constant (see figure) as well as derivation to a cyclic acetal [(1) $NaBH_4$, Ce^{3+}; (2) CH_2=C(OMe)Me, H^+]. This *retentive hydride shift* could be rationalized by the double inversion including the neighboring group participation of the aromatic moiety. Further study on this intriguing result is in progress, which will be disclosed elsewhere.

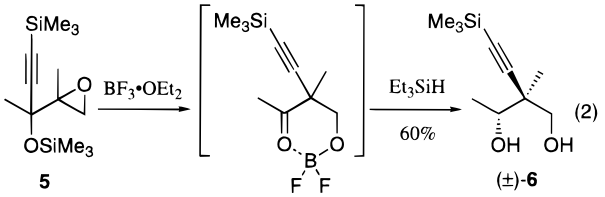
Scheme 3. Second Synthetic Plan



generating the more *relaxed* intermediate **VIII**. Implicit in the conversion, **VIII** → **VII**, is the Claisen condensation[9] of a keto ester. Then the two-carbon tether (C(9b) and C(3a)) that connects the aromatic and isoprenoid portions can be derived from an ethynyl group as in **IX**, provided that hydration of the triple bond proceeded regioselectively. Final disconnection at C(9a)−C(9b) suggests two early intermediates, that is, a hexasubstituted benzene **X** and a 1,3-diol **XI** with a quaternary stereogenic center.

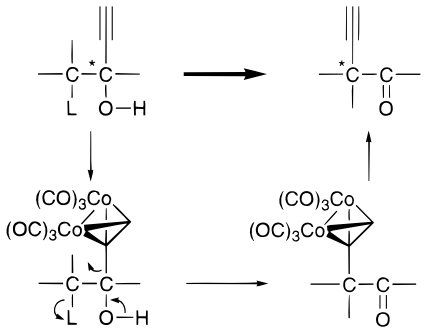
We hoped that the latter unit **XI** could be derived from the 1,2-rearrangement of an epoxy alcohol derivative as discussed. However, our major concern in this plan resided at this very beginning step as an alkynyl group is known as a poor migrating group due to its electron-poor nature (sp hybridization).[10] Another concern was the selective construction of hexasubstituted benzene **X**. With these issues in mind, we restarted the study which eventually culminated in the total synthesis as described below.

(a) Preliminary Synthesis of the 1,3-Diol Fragment as a Racemate. For the synthesis of the 1,3-diol fragment, a preliminary solution we reached is shown in eq 2. With the poor migratory aptitude of an alkynyl group in mind, we nonetheless dared to test the reaction of epoxy silyl ether **5** with Lewis acids. Gratifyingly, we found that under carefully

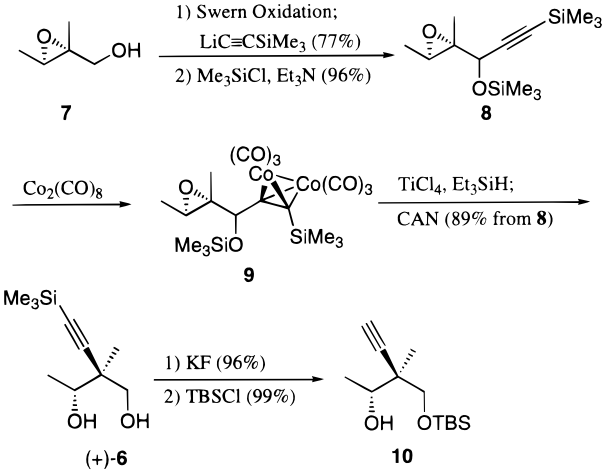


specified conditions the 1,2-shift of the $Me_3SiC{\equiv}C$ group proceeded, albeit slowly (−78 → 20 °C during 3 h, then 3 h at 20 °C). Furthermore, the in situ reduction of the aldolate by Et_3SiH was fully stereoselective, giving 1,3-diol (±)-**6** as the sole product. Although (±)-**6** helped us in the exploration of the synthetic route,[3b] the reaction (**5** → **6**) suffered from two drawbacks: (1) Asymmetric synthesis was not easy, if not impossible, due to the poor availability of **5** in an enantiopure form. (2) Careful choice of the reaction conditions was required in order to achieve even an acceptable yield of **6**, due to the

Scheme 4



Scheme 5. Synthesis of 1,3-Diol Fragment **10**



inherently poor migratory aptitude of an alkynyl group.[10] However, we recently found a clean solution to these issues by the complexation-facilitated 1,2-rearrangement.[11]

(b) Enlightenment to Asymmetric Synthesis of the 1,3-Diol Fragment. The solution was based on the finding that, upon conversion to the corresponding cobalt complex, an alkynyl group becomes an efficient migrator in the 1,2-anionotropic reactions (Scheme 4).[11] After the 1,2-shift, oxidative decomplexation readily regenerates the parent alkynyl group. Thus, a three-step protocol offered us a way to effect the 1,2-shift of an alkynyl group, which indeed worked nicely for the asymmetric synthesis of the planned key intermediate **10** (Scheme 5).

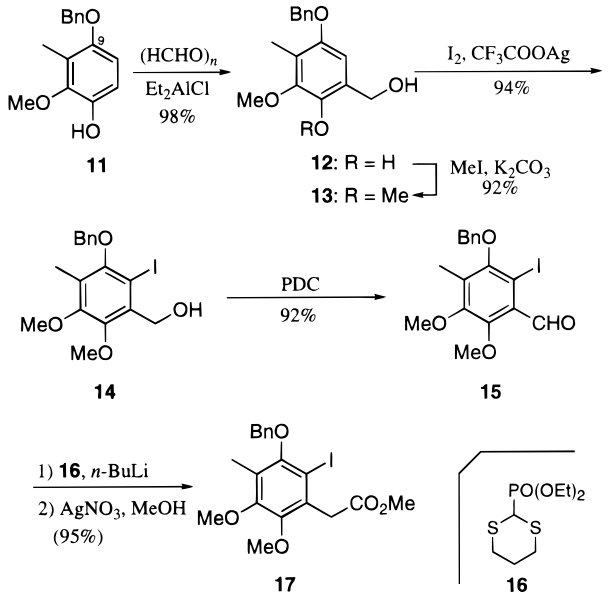
The optically active epoxy alcohol **7**, obtained by Katsuki−Sharpless reaction (97% ee),[7,12] was subjected to Swern oxida-

(9) Harris, T. M.; Harris, C. M. *Pure Appl. Chem.* **1986**, *58*, 283.

(10) (a) Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348. (b) Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 373. (c) Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; Vanduyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765. (d) For a computational study on this topic, see: Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112.

(11) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949.

Scheme 6. Synthesis of Aromatic Portion **17**



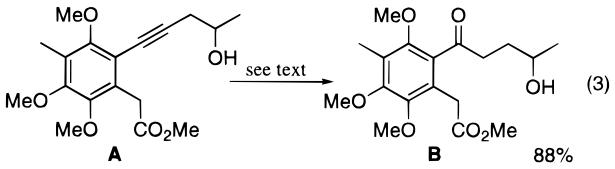
tion ($(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78 → −20 °C),[13] and the resulting aldehyde was treated in situ with $Me_3SiC{\equiv}CLi$ (THF, −78 °C, 0.5 h, 77%). The propargyl alcohol, obtained as a mixture of diastereomers (ca. 6:4, the stereochemistry unassigned), was silylated (Me_3SiCl, Et_3N/DMF, 15 min, 96%) to give silyl ether **8**, ready for the 1,2-rearrangement.

Silyl ether **8** was converted to Co-complex **9** ($Co_2(CO)_8$/hexane, 30 min), which was treated with $TiCl_4$ in the presence of Et_3SiH in CH_2Cl_2 (−78 → −20 °C). The high migrating ability of the Co-complexed alkynyl group proved valid also for this case. The rearrangement proceeded so quickly at −78 °C that we could not recognize any appreciable difference in reactivity between the diastereomers.[11] The warming of the reaction to −20 °C was only necessary for effecting the in situ reduction of the aldehyde formed. Quenching and oxidative workup (CAN/MeOH, 0 °C, 15 min) cleanly gave 1,3-diol (+)-**6** in 89% yield from **8**. The stereochemical purity of diol (+)-**6** was checked by ^{1}H NMR (for the diastereomeric purity) and ^{1}H NMR of its bis-MTPA ester (for the ee),[14] thereby showing no contamination from the other diastereomer within the detection limit and preservation of the enantiomeric purity. Thus, the stereochemical integrity of the synthetic scheme was proven, including the 1,2-shift. Removal of the TMS group (KF/MeOH, 60 °C, 1 h, 96%) followed by selective protection of the primary alcohol by a *tert*-butyldimethylsilyl group (TBSCl, imidazole/DMF, 25 °C, 0.5 h, 99%) gave alcohol **10**, ready for the coupling with the aromatic part.

(c) Synthesis of Hexasubstituted Benzene 17. Scheme 6 shows the synthesis of aryl iodide **17** starting from known phenol **11**.[15] A crucial improvement compared with our preliminary synthetic route[3b] was the choice of the C(9) phenol[2] protection; a benzyl group, rather than a methyl, was installed in order for the selective liberation of the C(9) phenol that indeed served for the selective oxidation of the aromatic ring at the final stage (vide infra). Regioselective hydroxymethylation of phenol **11** under Casiraghi conditions[16] (paraformaldehyde, Et_2AlCl/CH_2Cl_2, 25 °C, 17 h, 98%) cleanly gave benzyl alcohol **12**, and its phenol was selectively protected (MeI, K_2CO_3/acetone, reflux, 9 h, 92%) to give methyl ether **13**. Iodination of the aromatic ring was nicely achieved under the Ag(I)-promoted conditions[17] ($AgOCOCF_3$, $I_2/CHCl_3$, 0 °C, 1 h, 94%) to give iodide **14**, which was oxidized (PDC[18]/pyridine, CH_2Cl_2, 25 °C, 41 h, 92%) to give aldehyde **15**. Treatment of **15** with the lithio anion of Mikołajczyk reagent (**16**)[19] (THF, −78 → 25 °C) gave the corresponding ketene dithioacetal, which was solvolyzed under the Ag(I)-promoted conditions ($AgNO_3$/MeOH, 60 °C, 1 h) to give methyl ester **17** in 95% yield from **15**. The overall yield from phenol **11** was 70% in five steps.

(d) Union of Two Fragments. Now the stage was set for the union of alkyne **10** and aryl iodide **17**, which was nicely effected by Sonogashira reaction[20] ($Pd(OAc)_2$, PPh_3, CuI, Et_2NH/DMSO, 90 °C, 12 h) to give alkyne **18** in excellent yield (Scheme 7). Attempted hydration of the triple bond under conventional protocols, e.g., HgO, H_2SO_4,[21a] turned out to be extremely slow even under forcing conditions, presumably due to the high steric hindrance.

Model studies showed that the situation could be circumvented by use of a Pd(II) salt instead of Hg(II) salts (eq 3).[21] It



was found that a simple model alkyne **A** was cleanly hydrated by using $PdCl_2(PhCN)_2$ as a catalyst in aqueous CH_3CN at 90 °C, thereby giving hydroxy ketone **B** in 88% yield. Upon subjection to the similar conditions (Scheme 7), alkyne **18** was quickly converted to a new single material (TLC assay), which, however, was not the expected ketone but dihydrofuran **19**. The reaction similarly proceeded in the absence of water, which suggested a mechanism composed of oxypalladation and protodemetalation to give dihydrofuran **19** with the simultaneous regeneration of $PdCl_2$. The optimum procedure involved the use of 20 mol % of $PdCl_2$ (THF, 25 °C, 3.5 h) that gave dihydrofuran **19** as a single product in 96% yield.[22]

Although dihydrofuran **19** was not the planned synthetic intermediate (see Scheme 3), it offered us a nice opportunity for further elaboration to construct the naphthalene skeleton; the enol ether in **19** has the right polarity for the Claisen condensation. To exploit this feature, we pursued a way to activate the carboxylic acid function so as to facilitate the internal attack of the enol ether. However, our initial attempts along these lines met with trouble; the carboxylic acid, derived

(12) Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375.

(13) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(15) Compound **11** was prepared from commercially available 4′-benzyloxy-2′-methoxy-3′-methylacetophenone in two steps [(1) MCPBA (93%); (2) NaOH aq (94%)]. Cf. Maruyama, K.; Nagai, N.; Naruta, Y. *J. Org. Chem.* **1986**, *51*, 5083.

(16) Casiraghi, G.; Bigi, F.; Casnati, G.; Sartori, G.; Soncini, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *J. Org. Chem.* **1988**, *53*, 1779.

(17) Janssen, D. E.; Wilson, C. V. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. IV, p 547.

(18) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

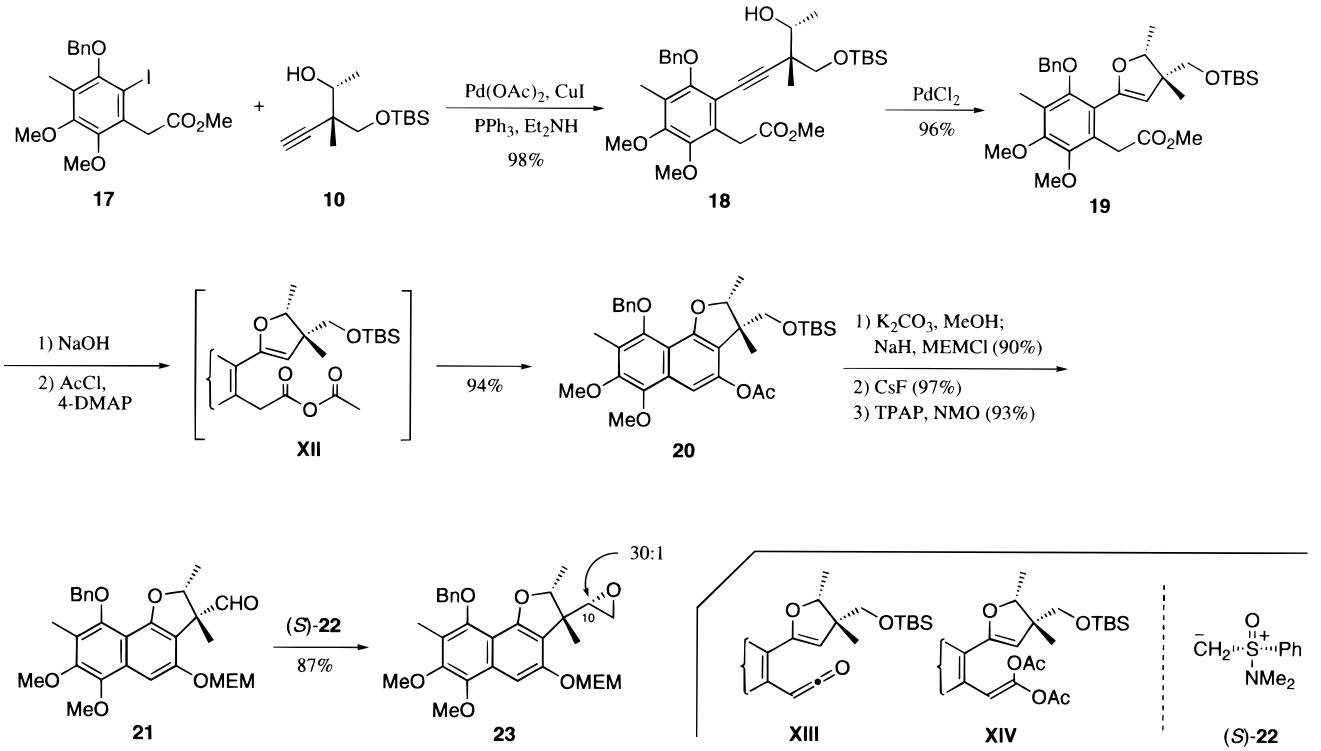
(19) Mikołajczyk, M.; Grzejszczak, S.; Zatorski, A.; Młotkowska, B.; Gross, H.; Costisella, B. *Tetrahedron* **1978**, *34*, 3081.

(20) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(21) (a) Hudrlik, P. F.; Hudrlik, A. M. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Vol. 1, p 199. (b) Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127. (c) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

(22) As for the hydration of model alkyne **A**, Hg^{2+}-based conditions also worked well, which, however, were totally ineffective for **18**. As for the mechanism, we thank Prof. E. Negishi for helpful discussion.

Scheme 7. Union of Two Fragments



by saponifying ester **19** followed by careful acidification, proved to be highly unstable, presumably because the carboxylic acid protonates the enol ether moiety to cause decomposition. After considerable experimentation, we were able to find a nice way to bypass the carboxylic acid, thereby effecting the furanonaphthalene cyclization. The key was the finding that the sodium carboxylate derived from **19** can be extracted into an organic solvent. Thus, after saponification of ester **19** (NaOH, MeOH, 60 °C, 12 h), the resulting sodium carboxylate was extracted into $CHCl_3$, dried (K_2CO_3), and concentrated. The sodium salt, thus obtained, was treated with acetyl chloride (3 equiv) and 4-(dimethylamino)pyridine (3 equiv) in toluene and heated under reflux for 5 h to give tricycle **20** in 94% yield. Concerning this highly delightful process, our initial rationale is the formation of mixed anhydride **XII**, which is attacked by the internal enol ether to give the cyclized ketone, followed by its tautomerization and acetylation. However, it is noted that two additional mechanisms may also account for the process: (1) the intermediacy of ketene **XIII** that undergoes electrocyclization followed by tautomerization and acetylation or (2) the enol acetylation to generate olefin **XIV** that undergoes electrocyclization followed by aromatization by elimination of an acetic acid.[23]

Aside from the mechanistic details, we now had a highly efficient access to the requisite furanonaphthalene structure. For further elaboration, acetate **20** was transformed to aldehyde **21** in three steps in 79% overall yield: (1) exchange of the acetyl protecting group to an MEM group[24] (K_2CO_3/MeOH, 25 °C, 25 min; NaH, MEMCl/DME, −78 → 25 °C, 90%), (2) cleavage of the silyl ether (CsF/DMF, 120 °C, 4 h, 97%), and (3) the ruthenium-catalyzed oxidation[25] of the primary alcohol (catalytic TPAP, *N*-methylmorpholine *N*-oxide/CH_2Cl_2, MeCN, 25 °C, 15 min, 93%).

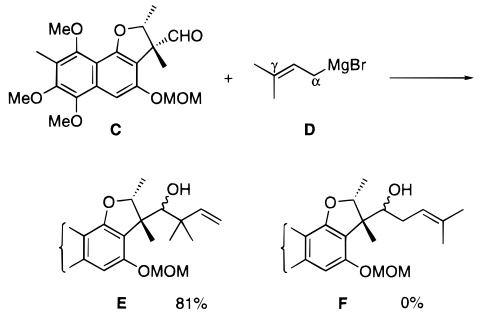
The remaining task was the construction of the side-chain moiety while controlling the third stereogenic center at the exocyclic C(10) position.[2] After initial unfruitful attempts to introduce the whole side chain,[26] we turned our attention to the methylene transfer to aldehyde **21** with the hope of obtaining epoxide **23** in a diastereoselective manner.[27] We were pleased to find that treatment of **21** with dimethyloxosulfonium methylide[28] in DMSO (25 °C, 2 h) gave a mixture of isomeric epoxides, **23** and *epi*-**23**, with the former highly predominant,

(23) We thank Prof. R. M. Coates, University of Illinois, Prof. H. Nagaoka, Meiji College of Pharmacy, and Dr. K. Tanino, Tokyo Institute of Technology, for bringing these possibilities to our attention.

(24) The MOM protecting group for the C(4) hydroxyl, used in the preliminary study (see ref 3b), caused trouble in its removal, particularly in the synthetic routes to furaquinocins A and B.

(25) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(26) We initially attempted the direct introduction of a five-carbon unit to aldehyde **21** by using γ,γ-disubstituted allylmetals. With the general γ-selectivity (S_E2' reaction) in mind, we were nonetheless intrigued by a possible emergence of the α-selectivity for such a highly sterically encumbered aldehyde as **21** (see: Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1983**, *48*, 1564), which unfortunately turned out to be not the case:

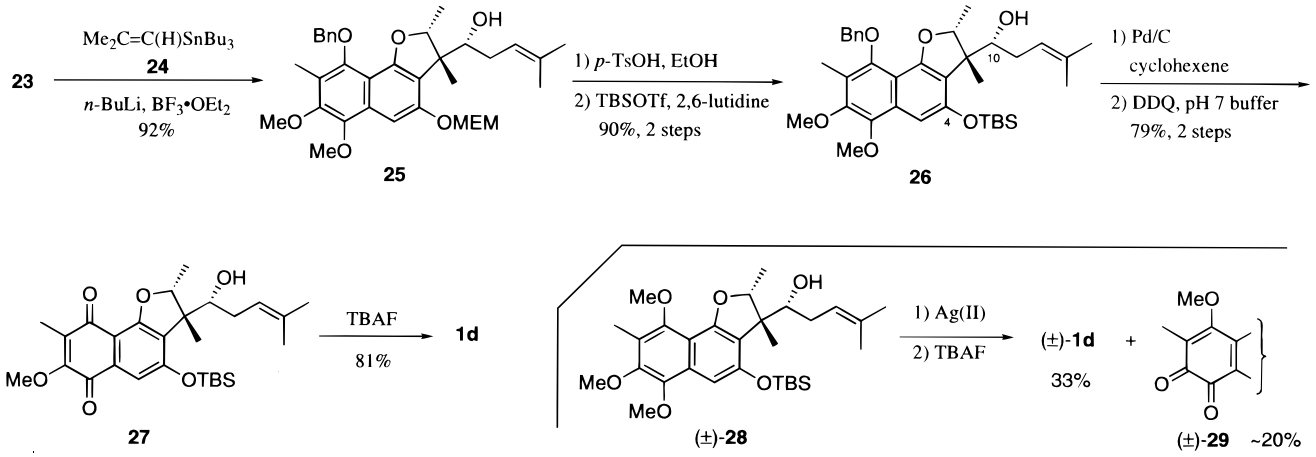


The reaction of model aldehyde **C** with Grignard reagent **D** gave **E** as a sole product. Furthermore, the allylbarium reagent, a uniquely α-selective reagent (see: Yanagisawa, A.; Habue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130) gave only a complex mixture of unidentified products in our hands.

(27) Saito, T.; Suzuki, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 3755.

(28) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

Scheme 8. Completion of Synthesis of Furaquinocin D (**1d**)



13:1. The natural 10*S* configuration[2] of **23** was verified by eventual transformation to the natural product (vide infra). Concerning this particular step, we now have several lines of evidence that the stereochemistry is determined not by the kinetic facial selectivity of the aldehyde but at a later stage of the process as reported recently.[27,29] Furthermore, the selectivity was enhanced by a double stereodifferentiation:[30] While (*S*)-**22** reacted smoothly with a high diastereoselectivity (DMSO, 25 °C, 6 days, 87%, **23**:*epi*-**23** = 30:1), (*R*)-**22** reacted much more slowly, giving a lower selectivity (5:1).[31,32]

Total Synthesis of Furaquinocin D. With the stereodefined epoxide **23** in hand, the stage was set to introduce a four-carbon unit for completing the whole carbon skeleton. Scheme 8 shows the synthesis of (−)-furaquinocin D (**1d**) with a simpler side chain. (*β*,*β*-Dimethylvinyl)lithium, generated by the tin−lithium exchange[33] of **24** (*n*-BuLi, THF, 0 °C, 10 min), was chilled to −78 °C, which was treated with epoxide **23** in the presence of BF_3•OEt_2 (1 equiv).[34] To effect a clean reaction, it was necessary to keep the reaction at low temperature (−78 °C). While the solution was stirred at −78 °C for 23 h, a slow, but clean addition occurred to give alcohol **25**. Also crucial was the choice of the precursor of the vinyllithium. The vinylstannane worked nicely as above, whereas the corresponding vinyl bromide gave poor results; the problem was the epoxide ring opening by a bromide produced by the halogen−lithium exchange with *n*- or *t*-BuLi, thereby producing only the corresponding bromohydrin.[35]

Removal of the MEM group in **25** (*p*-TsOH/EtOH, reflux, 15 h) followed by silylation of the liberated C(4)-phenol[2] (TBSOTf, 2,6-lutidine/CH_2Cl_2, −78 °C, 5 min) gave silyl ether **26** in high yield. The C(10)-hydroxy group[2] remained untouched. Under the hydrogen-transfer conditions (cyclohexene, 10% Pd−C/EtOH, reflux, 1.5 h),[36] the benzyl protection was selectively removed without saturating the C=C bond, and subsequent oxidation with DDQ (CH_2Cl_2, *t*-BuOH, pH 7 phosphate buffer, 0 °C, 15 min) gave quinone **27** in 79% yield. It should be noted here that liberation of the C(9)-hydroxy group[2] is a crucial strategy for the selective aromatic oxidation. Note that the final stage of our former synthesis of (±)-**1d**, i.e., (±)-**28** → (±)-**1d**, was low-yielding, due to the formation of the corresponding *o*-quinone (±)-**29** as a side product. In contrast, the present protocol cleanly gave *p*-quinone **27** as the sole product (Scheme 8). Final removal of the silyl protecting group (TBAF/THF, 0 °C, 20 min) gave (−)-furaquinocin D (**1d**) as yellow crystals, identical in all respects with the authentic material (mp, $[\alpha]_D$, ^1H and ^{13}C NMR, IR, UV, high-resolution MS, combustion analysis).

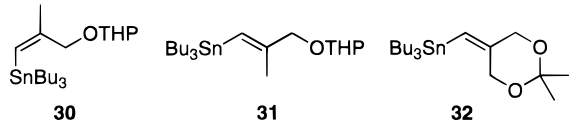


Figure 2. Vinylstannanes for furaquinocins A, B, and H.

Divergent Syntheses of Other Congeners. As discussed in the Introduction, the biological activities of the furaquinocins depend on the structure of the isoprenoid side chain. In the search for better biological activities, development of a general synthetic route to the natural/unnatural furaquinocins seemed desirable, and we became interested in examining the feasibility of preparing some other congeners with varied side chains. The specific targets we chose were the congeners with a more oxidized side chain, i.e., the monooxygenated geometrical isomers, furaquinocins A (**1a**) and B (**1b**), and the doubly oxygenated congener, furaquinocin H (**1h**), which we hoped to be accessible in a divergent manner from the stereodefined epoxide **23** as the key branching point by employing suitable vinylic nucleophiles.

Vinylstannanes **30**, **31**, and **32** were synthesized as the vinyl anion precursors and used for the syntheses of furaquinocins A (**1a**), B (**1b**), and H (**1h**), respectively (Figure 2). Table 1 summarizes the yields of the synthetic steps for each compound. The unified approach worked nicely in general, but several specific precautions are noted below.

(a) Furaquinocin A (1a). The first step was the addition of the vinyllithium derived from **30** to epoxide **23**, which turned

(29) For reviews on the stereoselective methylenation with sulfur ylides, see: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Johnson, C. R. In *Comprehensive Organic Chemistry*; Jones, N. D., Ed.; Pergamon: Oxford, U.K., 1973; Vol. 3, p 247.

(30) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(31) (a) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097. (b) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429.

(32) (a) Johnson, C. R.; Maake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418.

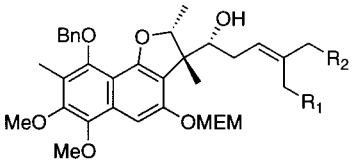
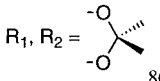
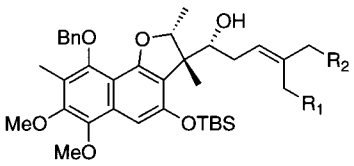
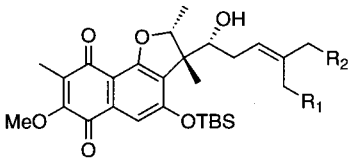
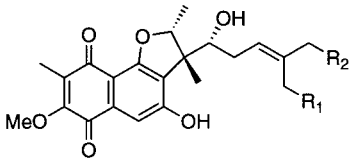
(33) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987; p 149.

(34) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(35) Such a situation never changed irrespective of the presence/absence of BF_3•OEt_2. Furthermore, transmetalation to other organometallic species such as Grignard reagent or cuprate proved unfruitful.

(36) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.

Table 1. Divergent Synthesis of Furaquinocins

	furaquinocin A	furaquinocin B	furaquinocin H
	**33a** R_1 = OTHP R_2 = H 85%	**33b** R_1 = H R_2 = OTHP 88%	**33h** R_1, R_2 =  86%
	**34a** R_1 = OTBS R_2 = H 82%	**34b** R_1 = H R_2 = OTBS 70%	**34h** R_1 = OTBS R_2 = OTBS 73%
	**35a** R_1 = OTBS R_2 = H 84%	**35b** R_1 = H R_2 = OTBS 82%	**35h** R_1 = OTBS R_2 = OTBS 84%
	**1a** R_1 = OH R_2 = H 85%	**1b** R_1 = H R_2 = OH 79%	**1h** R_1 = OH R_2 = OH 73%

out to be sluggish. An optimization study showed that the vinyllithium as well as BF_3·OEt_2 should be used in excess. Thus, (*Z*)-vinylstannane **30** (5 equiv) was treated with *n*-BuLi (5 equiv) at −78 °C in THF, and the solution was gradually warmed to −10 °C to generate the corresponding vinyllithium, to which, after being rechilled to −78 °C, was added epoxide **23** followed by BF_3·OEt_2 (5 equiv). During the gradual warming to −20 °C in 3 h, the addition went cleanly to give alcohol **33a** in 85% yield (see the left column of Table 1). Then, both MEM and THP ethers in **33a** were cleaved (catalytic *p*-TsOH, EtOH, 75 °C, 11 h), and the resulting hydroxy groups were protected by TBS groups (TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 1.5 h). The C(10) hydroxy group[2] again remained untouched. The benzyl ether in **34a** was removed under carefully controlled conditions (1,4-cyclohexadiene, 10% Pd−C, EtOH, 40 °C, 20 min); prolonged reaction caused an overreduction to remove the allylic silyloxy group, giving rise to the furaquinocin D-type side chain! Oxidation of the resulting naphthol with DDQ (CH_2Cl_2, *t*-BuOH, pH 7 phosphate buffer, 0 °C, 5 min) gave quinone **35a** in 84% yield, and finally two silyl groups were cleanly removed by using TBAF (THF, 0 °C, 1.5 h) to give (−)-furaquinocin A (**1a**) as yellow crystals, identical in all respects with the authentic material.

(b) Furaquinocin B (1b). To this geometrical isomer of **1a** at the olefinic side chain was applied a similar sequence of reactions as above, starting with the lithiation of (*E*)-vinylstannane **31** with *n*-BuLi (THF, −78 °C, 2 h). Importantly, the lithiation temperature in this particular case should be maintained at −78 °C (cf. the other cases), since the generated vinyllithium was unstable at higher temperature. To the resulting solution of the vinyllithium was added epoxide **23** followed by BF_3·OEt_2. While 5 equiv of the nucleophile was used, 2 equiv of BF_3·OEt_2 sufficed in this case. The reaction at −78 °C for 5 h cleanly gave alcohol **33b** in 88% yield (see the central column of Table 1). The next stage, acid-catalyzed removal of both MEM and THP groups, turned out to be quite sensitive to the conditions. Use of acidic EtOH, employed for the cases of **25** and **33a** (vide supra), gave the product arising from the allylic substitution by EtOH among other unidentified byproducts. After considerable experimentation, we found the optimal conditions, 1 M aqueous H_2SO_4 in DME at 75 °C for 3 h, where silyl ether **34b** was obtained in 70% yield from **33b** after silylation (TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 1.5 h). Hydrogenolysis of the benzyl ether went uneventfully (1,4-cyclohexadiene, 10% Pd−C, EtOH, 45 °C, 20 min), and oxidation of the resulting naphthol with DDQ (CH_2Cl_2, *t*-BuOH, pH 7 phosphate buffer, 0 °C, 5 min) gave quinone **35b** in 82% yield. Final removal of two silyl groups (TBAF, 4 Å sieves, THF, 0 °C, 3 h) gave (−)-furaquinocin B (**1b**) as yellow crystals, identical in all respects with the authentic material.

(c) Furaquinocin H (1h). The synthesis of the most oxygenated congener **1h** is shown in the right column of Table 1. The requisite vinyllithium was generated by treating vinylstannane **32** (5 equiv) with *n*-BuLi (5 equiv, THF, −78 °C, 4 h), to which was added epoxide **23** followed by BF_3·OEt_2 (2 equiv). Stirring at −78 °C for 3 h cleanly gave adduct **33h** in 86% yield. Acid treatment of **33h** (*p*-TsOH, EtOH, 75 °C, 11 h) detached the isopropylidene group and the MEM protection, and the crude material was silylated (TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 30 min) to give trisilyl derivative **34h** in 73% yield. Removal of the benzyl group (1,4-cyclohexadiene, 10% Pd−C, EtOH, 35 °C, 1.5 h) followed by oxidation with DDQ (CH_2Cl_2, *t*-BuOH, pH 7 phosphate buffer, 0 °C, 5 min, 84%) gave quinone **35h**. Final removal of three silyl groups (TBAF, 4 Å molecular sieves, THF, 0 °C, 1.2 h, 73%) gave (−)-furaquinocin H (**1h**) as yellow crystals, which showed fully identical spectroscopic properties (^1H and ^{13}C NMR, IR, high-resolution MS) with those of the natural product.[37]

Conclusion

A general synthetic route to the furaquinocin-class antibiotics has been developed, which depends on three significant findings: (1) an effective 1,2-shift of alkynyl group facilitated by Co-complexation, which worked nicely for asymmetric synthesis, (2) a naphthofuran cyclization technique to construct the densely functionalized furanonaphthalene tricyclic core, and (3) a highly stereoselective methylenation of an aldehyde that allowed installation of the third stereogenic center next to a quaternary center. These findings not only have contributed to the overall strategy but also are mechanistically intriguing and await further studies. The viable synthesis of four different furaquinocin congeners demonstrates the flexibility of the route, implying its further potential in preparing many related compounds for biological study.

Experimental Section

Synthesis of Epoxy Silyl Ether 8. To a solution of oxalyl chloride (3.05 g, 24.0 mmol) in CH_2Cl_2 (80 mL) was added a solution of DMSO (3.08 g, 39.4 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After 5 min, a solution of epoxy alcohol **7**[7,12] [97% ee as determined by the Mosher method[14]] (2.01 g, 19.7 mmol) in CH_2Cl_2 (20 mL) was added, and the mixture was stirred for 30 min at −78 °C. A solution of Et_3N (4.84 g, 47.8 mmol) in CH_2Cl_2 (20 mL) was added, and the mixture was gradually warmed to −20 °C. In a separate flask, a solution of $Me_3SiC{\equiv}CLi$ was prepared as follows: To a solution of trimethylsilylacetylene (5.00 g, 50.9 mmol) in THF (20 mL) was slowly added *n*-BuLi (1.60 M hexane solution, 26 mL, 41.6 mmol) at 0 °C, and after 30 min of stirring, this mixture was cooled to −78 °C. The former oxidation reaction mixture was cooled to −78 °C, to which was added THF (10 mL), to which was cannulated the solution of the lithium trimethylsilylacetylide at −78 °C. After the solution was stirred for 30 min, the reaction was quenched by adding saturated aqueous NH_4Cl, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/2) to give a diastereomeric mixture of (4*S*,5*S*)-4,5-epoxy-1-trimethylsilyl-2-hexyne-3-ol (3.00 g, 77%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.18 (s 9 H), 1.33 (d, J = 5.5 Hz) and 1.35 (d, J = 5.5 Hz) (3 H), 1.399 (s) and 1.403 (s) (3 H), 2.48−2.56 (m, 1 H), 3.20 (q, J = 5.5 Hz) and 3.30 (q, J = 5.5 Hz) (1 H), 4.17 (d, J = 7.1 Hz) and 4.33 (d, J = 3.5 Hz) (1 H); ^{13}C NMR ($CDCl_3$) δ 0.0, 12.7, 13.77 and 13.84, 56.5 and 56.6, 62.4 and 62.8, 65.7 and 66.7, 91.3 and 91.6, 102.7 and 103.0; IR (neat) 3450, 2970, 2190, 1460, 1390, 1255, 1155, 1010, 850 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15. Found: C, 60.26; H, 9.39.

To a solution of the epoxy alcohol stated above (2.60 g, 13.1 mmol) and Et_3N (2.65 g, 26.2 mmol) in DMF (39 mL) was added a solution of TMSCl (2.13 g, 19.6 mmol) in DMF (13 mL). After the solution was stirred for 15 min, the reaction was quenched by adding H_2O. The products were extracted with Et_2O, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 95/5) to give epoxy silyl ether **8** (3.42 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.167 (s, 9 H), 0.172 (s) and 0.21 (s) (9 H), 1.31 (d, 3 H, J = 5.5 Hz), 1.35 (s) and 1.36 (s) (3 H), 3.09 (q, 1 H, J = 5.5 Hz), 4.05 (s) and 4.08 (s) (1 H); ^{13}C NMR ($CDCl_3$) δ −0.26, 0.15 and 0.21, 11.9 and 12.6, 13.5 and 13.9, 56.4 and 57.7, 61.9 and 62.9, 67.9 and 68.7, 90.4 and 90.8, 103.6 and 103.8; IR (neat) 2970, 2190, 1390, 1255, 1080, 1025, 850 cm^{-1}.

Synthesis of Diol 6. *CAUTION*: The reaction should be performed in a well-ventilated hood. A suspension of epoxy silyl ether **8** (4.97 g, 18.4 mmol) and $Co_2(CO)_8$ (6.99 g, 20.4 mmol) in hexane (36 mL) was stirred at room temperature for 30 min. The mixture was filtered through a Celite pad, with Et_2O washing. After the filtrate was concentrated in vacuo, the residue was passed through a silica gel pad (eluted with hexane/EtOAc = 98/2), and the eluent was concentrated in vacuo to give crude cobalt complex **9** (10.4 g), which was dissolved in CH_2Cl_2 (90 mL). To this solution was added a solution of Et_3SiH (6.42 g, 55.2 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and $TiCl_4$ (4.0 mL neat, 36 mmol) was slowly added to this mixture at −78 °C. The temperature was then gradually raised to −20 °C, and the stirring was continued for 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was filtered through a Celite pad. The products were extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was then dissolved in MeOH (100 mL) and cooled to 0 °C, and CAN (50.3 g, 91.8 mmol) was added portionwise to this solution. After the evolution of CO gas was ceased, brine was added, the mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 65/35) to give diol **6** (3.27 g, 89%) as a colorless solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9 H), 1.17 (s, 3 H), 1.28 (d, 3 H, J = 6.4 Hz), 2.16 (s, 2 H), 3.57 (d, 1 H, J = 10.8 Hz), 3.66 (d, 1 H, J = 10.8 Hz), 3.92 (q, 1 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 0.11, 17.5, 18.5, 43.5, 68.7, 71.7, 88.7, 108.6; IR (KBr) 3350, 2960, 2170, 1250, 1090, 1050, 880, 840 cm^{-1}; $[\alpha]^{22}_D$ +10.9 (*c* 1.00, $CHCl_3$); HRMS *m*/*z* 200.1271 (200.1232 calcd for $C_{10}H_{20}O_2Si$, M^+). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.79; H, 10.00.

Synthesis of Silyl Ether 10. Diol **6** (460 mg, 2.30 mmol) was dissolved in saturated methanolic KF solution (11.5 mL), and the solution was heated at 60 °C for 1 h. After the solution was cooled to room temperature, brine was added to the mixture, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 1/1) to give the desilylated product (283 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.29 (d, 3 H, J = 6.2 Hz), 2.23 (s, 1 H), 2.98 (s, 2 H), 3.61 (d, 1 H, J = 10.8 Hz), 3.69 (d, 1 H, J = 10.8 Hz), 3.97 (q, 1 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 17.3, 18.4, 42.1, 68.7, 71.4, 71.8, 86.8; IR (neat) 3380, 2120, 1090, 1040 cm^{-1}; $[\alpha]^{25}_D$ +7.7 (*c* 1.07, $CHCl_3$); HRMS *m*/*z* 128.0814 (128.0825 calcd for $C_7H_{12}O_2$, M^+).

A mixture of the above diol (1.17 g, 9.14 mmol) and imidazole (1.24 g, 18.2 mmol) and TBSCl (1.67 g, 11.1 mmol) in DMF (18 mL) was stirred at room temperature for 30 min. The mixture was diluted with Et_2O and successively washed with H_2O (×2) and brine. The organic extracts were concentrated in vacuo, and the residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to give TBS ether **10** (2.20 g, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.24 (s, 3 H), 1.26 (d, 3 H, J = 6.6 Hz), 2.15 (s, 1 H), 3.17 (s, 1 H), 3.65 (d, 1 H, J = 9.9 Hz), 3.77 (d, 1 H, J = 9.9 Hz), 3.96 (q, 1 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ −5.68, −5.65, 17.5, 18.1, 18.4, 25.7, 41.2, 70.9, 71.3, 72.6, 86.5; IR (neat) 3470, 2120, 1260, 1100 cm^{-1}; $[\alpha]^{24}_D$ +3.1 (*c* 1.00, $CHCl_3$); HRMS *m*/*z* 242.1708 (242.1701 calcd for $C_{13}H_{26}O_2Si$, M^+).

Synthesis of Alkyne 18. To a mixture of methyl ester **17** (508 mg, 1.11 mmol), alkyne **10** (298 mg, 1.23 mmol), triphenylphosphine (58.6 mg, 0.223 mmol), $Pd(OAc)_2$ (25.1 mg, 0.112 mmol), and diethylamine (246 mg, 3.36 mmol) in DMSO (11 mL) was added CuI (2.2 mg, 0.012 mmol). The mixture was immediately subjected to a freeze−pump−thaw degassing operation for three times. The solution was heated at 90 °C for 12 h under a deoxygenated N_2 atmosphere. After the solution was cooled to room temperature, the reaction was quenched by adding H_2O, and the products were extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/2) to give alkyne **18** (622 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ −0.04 (s, 6 H), 0.88 (s, 9 H), 1.24 (d, 3 H, J = 6.2 Hz), 1.29 (s, 3 H), 2.12 (s, 3 H), 3.31 (d, 1 H, J = 4.0 Hz), 3.62 (d, 1 H, J = 9.5 Hz), 3.71 (s, 3 H), 3.77 (d, 1 H, J = 9.5 Hz), 3.808 (s, 3 H), 3.813 (s, 3 H), 3.84 (s, 2 H), 3.96 (dq, 1 H, J_1 = 4.0, J_2 = 6.2 Hz), 5.01 (s, 2 H), 7.31−7.47 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ

(37) The reported $[\alpha]_D$ value of **1h** (+52°, ref 1c) should read −52°. We thank Profs. Satoshi Ōmura and Shinji Funayama (Kitasato Institute) for the information. (Shinji Funayama is currently located at Aomori University, Japan.)

−5.66, −5.70, 9.6, 17.8, 18.1, 18.9, 25.7, 33.8, 42.6, 52.0, 60.2, 60.6, 70.9, 72.9, 74.7, 78.4, 99.5, 113.8, 125.5, 127.5, 127.9, 128.4, 128.6, 137.6, 148.0, 152.1, 154.7, 171.7; IR (neat) 3470, 2940, 2870, 1740, 1450, 1420, 1380, 1260, 1090, 1000, 840 cm^{-1}; $[\alpha]^{24}_D$ +4.1 (*c* 1.44, $CHCl_3$). Anal. Calcd for $C_{32}H_{46}O_7Si$: C, 67.34; H, 8.12. Found: C, 67.36; H, 8.12.

Synthesis of Dihydrofuran 19. A mixture of alkyne **18** (2.63 g, 4.62 mmol) and $PdCl_2$ (164 mg, 0.925 mmol) in THF (41 mL) was stirred at room temperature for 3.5 h. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to give dihydrofuran **19** (2.52 g, 96%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 3 H), −0.01 (s, 3 H), 0.87 (s, 9 H), 1.13 (s, 3 H), 1.34 (d, 3 H, *J* = 6.6 Hz), 2.17 (s, 3 H), 3.27 (d, 1 H, *J* = 9.9 Hz), 3.58 (d, 1 H, *J* = 9.9 Hz), 3.69 (s, 3 H), 3.73 (s, 2 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 4.25 (q, 1 H, *J* = 6.6 Hz), 4.79 (s, 1 H), 4.83 (d, 1 H, *J* = 11.4 Hz), 4.87 (d, 1 H, *J* = 11.4 Hz), 7.29−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.6, 9.7, 15.1, 18.2, 22.8, 25.8, 33.0, 50.3, 51.8, 60.0, 60.4, 65.4, 75.4, 86.5, 109.6, 122.7, 125.4, 126.2, 127.3, 127.7, 128.3, 137.9, 148.2, 150.6, 151.9, 152.2, 172.4; IR (neat) 2950, 2860, 1740, 1660, 1590, 1460, 1420, 1380, 1340, 1250, 1170, 1090, 1030, 840 cm^{-1}; $[\alpha]^{24}_D$ −9.1 (*c* 1.00, $CHCl_3$); HRMS *m*/*z* 570.3040 (570.3013 calcd for $C_{32}H_{46}O_7Si$, M^+).

Synthesis of Acetate 20. To dihydrofuran **19** (999 mg, 1.75 mmol) in MeOH (18 mL) was added 2 M NaOH (4.4 mL), and the mixture was heated at 60 °C for 12 h. The mixture was cooled to room temperature, and the products were extracted with $CHCl_3$ (×5) [acid-free $CHCl_3$, which was prepared by treating $CHCl_3$ with solid NaOH immediately before use, was used]. The combined organic extracts were dried (K_2CO_3) and concentrated in vacuo. The residue was dissolved in toluene (18 mL), 4-(dimethylamino)pyridine (644 mg, 5.27 mmol) and acetyl chloride (446 mg, 5.68 mmol) were added, and the mixture was heated at 110 °C for 5 h. After the solution was cooled to room temperature, brine was added to the mixture, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to give acetate **20** (955 mg, 94%) as a colorless oil, which solidified in the refrigerator: mp < room temperature; ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 3 H), 0.01 (s, 3 H), 0.82 (s, 9 H), 1.37 (s, 3 H), 1.46 (d, 3 H, *J* = 6.6 Hz), 2.28 (s, 3 H), 2.35 (s, 3 H), 3.63 (d, 1 H, *J* = 10.3 Hz), 3.75 (d, 1 H, *J* = 10.3 Hz), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.58 (q, 1 H, *J* = 6.6 Hz), 4.82 (d, 1 H, *J* = 10.3 Hz), 4.93 (d, 1 H, *J* = 10.3 Hz), 7.32 (s, 1 H), 7.34−7.58 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.8, −5.7, 9.7, 14.6, 18.1, 20.4, 21.1, 25.7, 49.4, 60.5, 60.9, 64.5, 76.5, 89.2, 106.4, 112.6, 119.2, 123.4, 127.9, 128.3, 128.5, 129.9, 137.8, 143.4, 145.7, 148.0, 149.0, 156.0, 169.3; IR (neat) 2980, 2930, 1790, 1640, 1590, 1470, 1400, 1340, 1270, 1220, 1100, 1070, 860 cm^{-1}; $[\alpha]^{24}_D$ −17.8 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{33}H_{44}O_7Si$: C, 68.25; H, 7.64. Found: C, 68.13; H, 7.86.

Synthesis of Aldehyde 21. (i) Replacement of Acetyl by MEM in 20. A mixture of acetate **20** (2.58 g, 4.44 mmol) and K_2CO_3 (123 mg, 0.889 mmol) in MeOH (44 mL) was stirred for 25 min. After the solution was cooled to 0 °C, the reaction was quenched by adding saturated aqueous NH_4Cl, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo and then dissolved in DME (30 mL). NaH (356 mg, 60% oil dispersion, ca. 8.90 mmol) was washed with hexane to remove the oil, suspended in DME (5 mL), and chilled to −78 °C. The solution of the crude phenol was added to the suspension of NaH, a solution of MEMCl (1.11 g, 8.90 mmol) in DME (10 mL) at −78 °C was added, and the temperature was gradually raised to room temperature. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 85/15) to give the MEM ether (2.52 g, 90%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ −0.10 (s, 3 H), 0.0 (s, 3 H), 0.80 (s, 9 H), 1.45 (s, 3 H), 1.58 (d, 3 H, *J* = 6.6 Hz), 2.27 (s, 3 H), 3.41 (s, 3 H), 3.61 (t, 2 H, *J* = 4.5 Hz), 3.77 (d, 1 H, *J* = 10.1 Hz), 3.82 (d, 1 H, *J* = 10.1 Hz), 3.87 (t, 2 H, *J* = 4.5 Hz), 3.92 (s, 3 H), 3.93 (s, 3 H), 4.58 (q, 1 H, *J* = 6.6 Hz), 4.79 (d, 1 H, *J* = 10.2 Hz), 4.97 (d, 1 H, *J* = 10.2 Hz), 5.39 (d, 1 H, *J* = 6.4 Hz), 5.45 (d, 1 H, *J* = 6.4 Hz), 7.18 (s, 1 H), 7.31−7.59 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.8, 9.5, 14.8, 18.0, 18.0, 20.8, 25.7, 49.6, 59.2, 60.4, 60.6, 64.1, 67.9, 71.6, 76.4, 89.1, 92.8, 95.1, 110.5, 116.9, 121.2, 127.7, 128.2, 128.5, 130.4, 137.9, 143.0, 148.0, 148.8, 152.9, 155.5; IR (neat) 2930, 2870, 1630, 1580, 1450, 1380, 1350, 1320, 1240, 1110, 1050, 740 cm^{-1}; $[\alpha]^{25}_D$ −8.1 (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{35}H_{50}O_8Si$: C, 67.06; H, 8.04. Found: C, 67.02; H, 8.34.

(ii) Detachment of TBS Group. A mixture of MEM ether (471 mg, 0.751 mmol) and CsF (1.14 g, 7.53 mmol) in DMF (12 mL) was heated at 120 °C for 14 h. After the solution was cooled to room temperature, H_2O was added to the mixture, and the products were extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 1/1) to give the alcohol (374 mg, 97%) as a pale red oil: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3 H), 1.55 (d, 3 H, *J* = 6.6 Hz), 1.91 (s, 1 H), 2.29 (s, 3 H), 3.37 (s, 3 H), 3.58 (t, 2 H, *J* = 4.7 Hz), 3.78 (d, 1 H, *J* = 11.2 Hz), 3.84 (d, 1 H, *J* = 11.2 Hz), 3.86 (t, 2 H, *J* = 4.7 Hz), 3.92 (s, 3 H), 3.94 (s, 3 H), 4.62 (q, 1 H, *J* = 6.6 Hz), 4.82 (d, 1 H, *J* = 10.3 Hz), 4.92 (d, 1 H, *J* = 10.3 Hz), 5.45 (s, 2 H), 7.24 (s, 1 H), 7.25−7.58 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.2, 21.0, 49.6, 59.0, 60.4, 60.6, 65.5, 68.1, 71.5, 76.4, 89.0, 92.8, 95.7, 110.5, 116.1, 121.7, 127.8, 128.2, 128.4, 130.5, 137.7, 143.0, 147.9, 149.1, 152.5, 155.5; IR (neat) 3500, 2930, 2860, 1630, 1580, 1450, 1380, 1090, 1050 cm^{-1}; $[\alpha]^{25}_D$ +21.2 (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 67.66; H, 7.31.

(iii) Oxidation. In the presence of powdered 4 Å molecular sieves (1.76 g), a mixture of alcohol (1.81 g, 3.53 mmol), TPAP (125 mg, 0.356 mmol), and NMO (826 mg, 7.06 mmol) in CH_2Cl_2 (35 mL) and MeCN (3.5 mL) was stirred at room temperature for 15 min. After being diluted with Et_2O, the mixture was passed through a Florisil pad with Et_2O as an eluent. The eluent was evaporated in vacuo, and the residue was purified by flash column chromatography (hexane/EtOAc = 7/3) to give aldehyde **21** (1.62 g, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 6.6 Hz), 1.56 (s, 3 H), 2.30 (s, 3 H), 3.39 (s, 3 H), 3.57 (t, 2 H, *J* = 4.6 Hz), 3.76−3.79 (m, 2 H), 3.94 (s, 6 H), 4.80 (q, 1 H, *J* = 6.6 Hz), 4.87 (d, 1 H, *J* = 10.3 Hz), 4.94 (d, 1 H, *J* = 10.3 Hz), 5.37 (s, 2 H), 7.27 (s, 1 H), 7.32−7.56 (m, 5 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.6, 16.2, 18.5, 58.5, 59.1, 60.5, 60.7, 68.0, 71.5, 76.5, 89.8, 92.8, 96.0, 110.6, 113.7, 122.1, 127.9, 128.3, 128.4, 131.5, 137.7, 143.3, 148.0, 149.7, 152.4, 156.4, 201.5; IR (neat) 2930, 1730, 1630, 1580, 1450, 1380, 1320, 1110, 1050 cm^{-1}; $[\alpha]^{25}_D$ −140 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{29}H_{34}O_8$: C, 68.22; H, 6.71. Found: C, 68.15; H, 6.61.

Methylenation of Aldehyde 21. (a) With Dimethyloxosulfonium Methylide. To NaH (116 mg, 60% oil dispersion, ca. 2.90 mmol), washed with hexane, was added DMSO (2 mL) at 20 °C, and the mixture was stirred for 15 min. To the resulting solution was added trimethyloxosulfonium iodide (635 mg, 2.89 mmol), and the mixture was stirred for 30 min at room temperature. A solution of **21** (295 mg, 0.578 mmol) in DMSO (4 mL) was added to the mixture, and the stirring was continued for 2 h. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc (×5). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/2 to 6/4, gradient elution) to give epoxide **23** (182 mg, 60%) as a colorless oil and *epi*-**23** (14.3 mg, 4.7%) as a pale yellow oil.

(b) With (*S*)-(Dimethylamino)phenyloxosulfonium Methylide. To NaH (18 mg, 60% oil dispersion, ca. 0.46 mmol), washed with hexane, was added DMSO (0.5 mL) at 20 °C, and the mixture was stirred for 45 min. To the resulting solution was added (*S*)-(dimethylamino)-methylphenyloxosulfonium tetrafluoroborate (161 mg, 0.594 mmol), and the mixture was stirred for 40 min at room temperature. A solution of **21** (122 mg, 0.238 mmol) in DMSO (2 mL) was added, and the mixture was stirred for 6 days. The reaction was quenched with pH 7 phosphate buffer, and the products were extracted with EtOAc (×5).

The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone = 9/1 for separating epoxides **23** from *N*,*N*-dimethylphenylsulfinamide) to give a mixture of epoxide **23** and *epi*-**23** (110 mg), which was subjected to HPLC analysis (Zorbax sil, 4.6 mm × 25 cm, hexane/THF = 8/2, flow rate 0.5 mL/s; **23**, 34.3 min; *epi*-**23**, 51.4 min; **23**:*epi*-**23** = 30:1). The diastereomers were separated by PTLC (hexane/EtOAc = 3/2) to give epoxide **23** (105 mg, 84%) as a colorless oil and *epi*-**23** (3.8 mg, 3%) as a pale yellow oil.

23: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3 H), 1.63 (d, 3 H, J = 6.6 Hz), 2.28 (s, 3 H), 2.44 (dd, 1 H, J_1 = 2.7, J_2 = 4.9 Hz), 2.68 (dd, 1 H, J_1 = 3.9, J_2 = 4.9 Hz), 3.02 (dd, 1 H, J_1 = 2.7, J_2 = 3.9 Hz), 3.40 (s, 3 H), 3.59−3.62 (m, 2 H), 3.86−3.89 (m, 2 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 4.60 (q, 1 H, J = 6.6 Hz), 4.79 (d, 1 H, J = 10.1 Hz), 4.97 (d, 1 H, J = 10.1 Hz), 5.41 (d, 1 H, J = 6.4 Hz), 5.44 (d, 1 H, J = 6.4 Hz), 7.22 (s, 1 H), 7.30−7.59 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.1, 19.2, 44.0, 48.0, 54.4, 59.1, 60.4, 60.6, 68.1, 71.6, 76.5, 89.4, 93.0, 95.6, 110.4, 114.5, 121.6, 127.8, 128.2, 128.6, 130.7, 137.9, 143.1, 148.1, 149.2, 153.0, 156.1; IR (neat) 2930, 1630, 1580, 1460, 1380, 1320, 1110, 1050 cm^{-1}; $[\alpha]^{21}_D$ +28.8 (*c* 1.15, $CHCl_3$); HRMS *m*/*z* 524.2386 (524.2410 calcd for $C_{30}H_{36}O_8$, M^+).

***epi*-23:** ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.64 (d, 3 H, J = 6.6 Hz), 2.29 (s, 3 H), 2.69 (dd, 1 H, J_1 = 4.0, J_2 = 4.9 Hz), 2.80 (dd, 1 H, J_1 = 2.9, J_2 = 4.9 Hz), 3.09 (dd, 1 H, J_1 = 2.9, J_2 = 4.0 Hz), 3.41 (s, 3 H), 3.58−3.61 (m, 2 H), 3.83−3.86 (m, 2 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 4.65 (q, 1 H, J = 6.6 Hz), 4.86 (d, 1 H, J = 10.3 Hz), 4.91 (d, 1 H, J = 10.3 Hz), 5.39 (d, 1 H, J = 6.5 Hz), 5.42 (d, 1 H, J = 6.5 Hz), 7.23 (s, 1 H), 7.32−7.58 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.7, 16.6, 43.5, 47.8, 52.7, 59.0, 60.4, 60.6, 67.9, 71.5, 76.5, 90.0, 92.9, 95.9, 110.4, 115.7, 121.7, 127.9, 128.3, 128.5, 130.3, 137.7, 143.1, 147.9, 149.2, 153.0, 155.4; IR (neat) 2920, 2850, 1630, 1450, 1380, 1100, 1050 cm^{-1}; $[\alpha]^{24}_D$ −34.2 (*c* 1.15, $CHCl_3$); HRMS *m*/*z* 524.2391 (524.2410 calcd for $C_{30}H_{36}O_8$, M^+).

Synthesis of Alcohol 25. To a solution of vinylstannane **24** (251 mg, 0.728 mmol) in THF (1 mL) was added *n*-BuLi (0.45 mL, 1.63 M hexane solution, 0.73 mmol) at 0 °C, and the mixture was stirred for 10 min. The mixture was cooled to −78 °C, to which was added a solution of epoxide **23** (74.6 mg, 0.142 mmol) in THF (2.5 mL) followed by a freshly prepared solution of BF_3·OEt_2 (0.20 mL, 0.70 M solution in THF, 0.14 mmol), and the mixture was stirred for 23 h at −78 °C. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 7/3) to give alcohol **25** (76.1 mg, 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6 H), 1.67 (d, 3 H, J = 6.8 Hz), 1.68 (s, 3 H), 1.73 (d, 1 H, J = 5.3 Hz), 2.29 (s, 3 H), 2.24−2.30 (m, 2 H), 3.41 (s, 3 H), 3.60 (t, 2 H, J = 4.6 Hz), 3.78−3.84 (m, 1 H), 3.87 (t, 2 H, J = 4.6 Hz), 3.93 (s, 3 H), 3.95 (s, 3 H), 4.57 (q, 1 H, J = 6.8 Hz), 4.78 (d, 1 H, J = 10.0 Hz), 4.91 (d, 1 H, J = 10.0 Hz), 5.15 (t, 1 H, J = 6.7 Hz), 5.41 (d, 1 H, J = 6.5 Hz), 5.47 (d, 1 H, J = 6.5 Hz), 7.28 (s, 1 H), 7.31−7.59 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.1, 18.0, 21.0, 25.8, 31.9, 51.9, 59.1, 60.4, 60.6, 68.0, 71.5, 75.7, 76.5, 90.3, 93.1, 95.9, 110.4, 115.8, 121.57, 121.65, 127.8, 128.2, 128.6, 130.5, 134.4, 137.7, 143.0, 148.0, 149.1, 153.1, 156.0; IR (neat) 2960, 2920, 2870, 2850, 1460, 1440, 1380, 1200, 1130, 1120, 1080, 1020, 910, 870 cm^{-1}; $[\alpha]^{25}_D$ −10 (*c* 0.91, $CHCl_3$); HRMS *m*/*z* 580.3016 (580.3036 calcd for $C_{34}H_{44}O_8$, M^+).

Synthesis of Silyl Ether 26. A mixture of alcohol **25** (13.9 mg, 23.9 μmol) and *p*-TsOH·H_2O (0.9 mg, 5 μmol) in EtOH (2 mL) was gently refluxed for 15 h. After the solution was cooled to 0 °C, the reaction was quenched by adding saturated aqueous $NaHCO_3$, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude material (16 mg) was dissolved in CH_2Cl_2 (1 mL), to which was added 2,6-lutidine (26.1 mg, 0.24 mmol) and TBSOTf (38.1 mg, 0.14 mmol) at −78 °C. After the solution was stirred for 5 min, the reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 7/3) to give silyl ether **26** (13.0 mg, 90%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 3 H), 0.41 (s, 3 H), 1.07 (s, 9 H), 1.53 (s, 3 H), 1.55 (s, 3 H), 1.59−1.62 (m, 1 H), 1.66 (d, J = 6.8 Hz, 3 H), 1.67 (s, 3 H), 2.21 (s, 3 H), 2.17−2.36 (m, 2 H), 3.78−3.83 (m, 1 H), 3.926 (s, 3 H) 3.931 (s, 3 H), 4.53 (q, J = 6.8 Hz, 1 H), 4.79 (d, J = 10.1 Hz, 1 H), 4.91 (d, J = 10.1 Hz, 1 H), 5.11 (t, J = 7.0 Hz, 1 H), 7.05 (s, 1 H), 7.32−7.58 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.7, 9.5, 14.2, 18.1, 18.6, 21.2, 25.9, 26.2, 32.0, 51.6, 60.5, 60.7, 75.9, 76.7, 90.1, 100.7, 110.0, 117.7, 121.1, 121.6, 127.8, 128.3, 128.7, 130.4, 134.5, 137.8, 142.5, 148.1, 149.0, 151.8, 156.4; IR (neat) 3550, 2940, 2850, 1620, 1600, 1570, 1450, 1390, 1330, 1270, 1100, 1050, 860 cm^{-1}; $[\alpha]^{29}_D$ −12.7 (*c* 1.02, $CHCl_3$); HRMS *m*/*z* 606.3369 (606.3377 calcd for $C_{36}H_{50}O_6Si$, M^+).

Synthesis of Quinone 27. A mixture of silyl ether **26** (30.1 mg, 49.6 μmol), cyclohexene (1.0 mL), and 10% Pd−C (30 mg) in EtOH (2 mL) was refluxed for 1.5 h. After being cooled to room temperature, the mixture was filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated in vacuo to give crude naphthol (38 mg), which was dissolved in CH_2Cl_2 (1 mL). To the solution were added *t*-BuOH (0.1 mL) and pH 7 phosphate buffer (0.1 mL), and the mixture was cooled at 0 °C. DDQ (23 mg, 0.10 mmol) was added to the mixture, which was stirred for 15 min. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc (×5). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 75/25) to give quinone **27** (19.6 mg, 79%, 2 steps) as a bright yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.38 (s, 3 H), 0.39 (s, 3 H), 1.03 (s, 9 H), 1.50 (s, 3 H), 1.53 (s, 3 H), 1.69 (s, 3 H), 1.75 (d, J = 6.9 Hz, 3 H), 2.05 (s, 3 H), 2.08−2.15 (m, 1 H), 2.26−2.37 (m, 1 H), 3.74−3.78 (m, 1 H), 4.02 (s, 3 H), 4.56 (q, J = 6.9 Hz, 1 H), 5.04 (t, J = 7.3 Hz, 1 H), 7.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.7, 9.3, 14.1, 18.1, 18.5, 20.4, 22.4, 25.9, 32.0, 50.7, 60.7, 75.1, 91.4, 109.7, 110.9, 120.5, 128.3, 133.4, 133.6, 136.1, 156.7, 157.0, 162.4, 180.7, 183.8; IR (neat) 3520, 2960, 2930, 2860, 1660, 1590, 1470, 1390, 1290, 1170, 1100, 1060, 870 cm^{-1}; $[\alpha]^{26}_D$ −21.8 (*c* 1.21, $CHCl_3$); HRMS *m*/*z* 500.2589 (500.2594 calcd for $C_{28}H_{40}O_6Si$, M^+).

(−)-Furaquinocin D (1d). To a solution of quinone **27** (18.0 mg, 35.9 μmol) in THF (1.5 mL) was added a solution of TBAF (1.0 M in THF, 0.05 mL, 50 μmol) at 0 °C. After the mixture was stirred for 20 min at 0 °C, the reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with $CHCl_3$ (×5). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$/MeOH = 95/5) to give (−)-furaquinocin D (**1d**) (11.3 mg, 81%). Reprecipitation from $CHCl_3$ (+hexane) gave analytically pure **1d** as bright yellow solids: mp 176−179 °C (lit.[1c] mp 177−179 °C); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6.4 Hz), 1.36 (s, 3 H), 1.73 (s, 3 H), 1.81 (s, 3 H), 2.05 (s, 3 H), 2.14−2.19 (m, 1 H), 2.52 (ddd, 1 H, J_1 = 14.7, J_2 = J_3 = 9.9 Hz), 3.20−3.27 (broad, 1 H), 4.01 (s, 3 H), 4.03−4.05 (m, 1 H), 4.67 (q, 1 H, J = 6.4 Hz), 5.16−5.20 (m, 1 H), 7.17 (s, 1 H), 10.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.6, 180.7, 160.4, 158.4, 156.9, 139.2, 134.1, 133.7, 124.5, 118.4, 110.5, 109.2, 88.8, 73.0, 60.7, 52.1, 32.0, 26.1, 18.9, 18.3, 16.1, 9.33; IR (neat) 3500, 2930, 1660, 1630, 1575, 1400, 1380, 1300, 1275, 1160 cm^{-1}; UV (ν_{max}, MeOH) 270, 295, 405 nm; $[\alpha]^{24}_D$ −94 (*c* 0.75, $CHCl_3$) (lit.[1c] $[\alpha]^{19}_D$ −95 (*c* 0.53, $CHCl_3$)); HRMS *m*/*z* 386.1737 (386.1728 calcd for $C_{22}H_{26}O_6$, M^+). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.21; H, 7.08.

Total Synthesis of (−)-Furaquinocin A. (a) Synthesis of Alcohol 33a. To a solution of vinylstannane **30** (174 mg, 0.391 mmol) in THF (1 mL) was added *n*-BuLi (0.24 mL, 1.64 M hexane solution, 0.39 mmol) at −78 °C, and the mixture was gradually warmed to −10 °C. After the mixture was cooled to −78 °C, a solution of epoxide **23** (40.9 mg, 0.0781 mmol) in THF (2 mL) was added followed by a freshly prepared solution of BF_3·OEt_2 (0.20 mL, 1.86 M solution in THF, 0.37 mmol), and the temperature was gradually raised to −20 °C for 3 h. The reaction was quenched by adding pH 7 phosphate buffer, and the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 6/4) to give alcohol **33a** (45.1 mg, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$)

δ 1.16−1.45 (m, 6 H), 1.45 (s, 3 H), 1.60 (d, J = 6.7 Hz) and 1.61 (d, J = 6.7 Hz) (3 H), 1.65 (s) and 1.71 (s) (3 H), 2.17−2.43 (m, 1 H), 2.22 (s, 3 H), 2.27−2.42 (m, 2 H), 2.82−2.88 (m) and 3.10−3.18 (m) (2 H), 3.34 (s, 3 H), 3.36−3.46 (m, 1 H), 3.54 (t, J = 4.6 Hz, 2 H), 3.64 (d, J = 11.2 Hz) and 3.93 (d, J = 11.1 Hz) (1 H), 3.72 (d, J = 11.2 Hz) and 4.08 (d, J = 11.1 Hz) (1 H), 3.79 (t, J = 4.6 Hz, 2 H), 3.84 (s, 3 H), 3.85 (s) and 3.87 (s) (3 H), 4.34 (s) and 4.41 (s) (2 H), 4.48 (q, J = 6.7 Hz, 1 H), 4.63 (d, J = 10.0 Hz) and 4.64 (d, J = 10.0 Hz) (1 H), 4.85 (d, J = 10.0 Hz) and 4.87 (d, J = 10.0 Hz) (1 H), 5.34 (t, J = 6.3 Hz, 1 H), 5.37 (t, J = 6.3 Hz) and 5.38 (t, J = 6.6 Hz) (1 H), 7.18 (s) and 7.19 (s) (1 H) 7.27−7.53 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.4, 13.9 and 14.0, 18.4 and 18.9, 20.9, 22.3 and 22.8, 25.0, 29.6 and 30.3, 31.6 and 31.9, 52.0 and 52.4, 59.1, 60.4 and 60.5, 60.6 and 60.7, 61.7, 64.2 and 66.0, 68.0 and 68.1, 71.6, 74.9 and 75.1, 76.5, 90.5, 93.1 and 94.8, 95.5 and 95.7, 98.3, 110.4, 115.6, 121.3 and 121.4, 127.2 and 127.8, 128.2, 128.7 and 128.8, 129.0, 130.5, 133.4 and 134.7, 137.6 and 137.7, 142.9 and 143.0, 148.0, 149.0, 153.2 and 153.3, 156.4 and 156.5; IR (neat) 3470, 2940, 2870, 1630, 1570, 1360, 1320, 1120, 1080, 1050, 1020 cm^{-1}; HRMS *m*/*z* 680.3535 (680.3577 calcd for $C_{39}H_{52}O_{10}$, M^+).

(b) (−)-Furaquinocin A (1a). To a suspension of powdered, well-dried 4 Å molecular sieves in THF (0.3 mL) was added a solution of TBAF (1.0 M in THF, 0.30 mL, 0.30 mmol) at 0 °C, and the suspension was stirred for 5 min. To this mixture was added a solution of quinone **35a** (27.3 mg, 43.3 μmol) in THF (2 mL), and the mixture was stirred for 3 h. The reaction was quenched by adding pH 7 phosphate buffer, the mixture was filtered, and the filtrate was washed with Et_2O. After brine was added, the products were extracted with Et_2O (×5), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$/MeOH = 9/1) to give (−)-furaquinocin A (**1a**) (14.8 mg, 85%). Concentration from a $CHCl_3$ solution gave **1a** as bright yellow solids: mp 178−180 °C (lit.[1b] mp 182−183 °C); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 3.1 Hz, 3 H), 1.32 (s, 3 H), 1.88 (s, 3 H), 2.05 (s, 3 H), 2.14 (dd, J_1 = J_2 = 6.0 Hz, 1 H), 2.61 (ddd, J_1 = 4.0, J_2 = 6.0, J_3 = 10.6 Hz, 1 H), 3.95 (d, J = 4.0 Hz, 1 H), 4.00 (s, 3 H), 4.01 (d, J = 10.8 Hz, 1 H), 4.44 (d, J = 10.8 Hz, 1 H), 4.68 (q, J = 6.4 Hz, 1 H), 5.52 (dd, J_1 = 6.0, J_2 = 10.6 Hz, 1 H), 6.05−6.40 (broad, 1 H), 7.15 (s, 1 H), 11.3 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.3, 16.1, 19.0, 23.3, 32.5, 52.8, 60.6, 61.5, 71.4, 88.8, 109.0, 111.0, 124.6, 125.1, 133.6, 134.0, 138.3, 157.0, 158.9, 160.6, 180.8, 183.8; IR (neat) 3450, 2920, 2850, 1640, 1580, 1400, 1280, 1170, 1030 cm^{-1}; $[\alpha]^{27}_D$ −48 (*c* 0.37, $CHCl_3$) (lit.[1b] $[\alpha]^{19}_D$ −46 (*c* 0.58, $CHCl_3$)); HRMS *m*/*z* 404.1805 (404.1835 calcd for $C_{22}H_{28}O_7$, M^+ + 2). Anal. Calcd for $C_{22}H_{26}O_7 \cdot 0.5H_2O$: C, 64.22; H, 6.61. Found: C, 64.16; H, 6.35.

Total Synthesis of (−)-Furaquinocin B. (a) Synthesis of Alcohol 33b. To a solution of vinylstannane **31** (273 mg, 0.613 mmol) in THF (2 mL) was added *n*-BuLi (0.35 mL, 1.64 M in hexane, 0.58 mmol) at −78 °C, and the mixture was stirred for 3 h at −78 °C. To the mixture was added a solution of epoxide **23** (65.6 mg, 0.125 mmol) in THF (2 mL) and a freshly prepared solution of $BF_3 \cdot OEt_2$ (0.20 mL, 1.25 M in THF, 0.25 mmol), and the mixture was stirred for 5 h at −78 °C. The reaction was quenched by adding MeOH (1 mL), to this mixture was added pH 7 phosphate buffer, and the products were extracted with EtOAc (×5). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 6/4) to give alcohol **33b** (75.1 mg, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.46−1.84 (m, 7 H), 1.54 (s, 3 H), 1.61 (s, 3 H), 1.67 (d, J = 6.6 Hz, 3 H), 2.29 (s, 3 H), 2.29−2.36 (m, 2 H), 3.41 (s) and 3.89 (s) (3 H), 3.44−3.51 (m, 1 H), 3.59−3.62 (m, 2 H), 3.80−3.89 (m, 5 H), 3.93 (s) and 3.94 (s) (3 H), 3.95 (s, 3 H), 4.05−4.11 (m, 1 H), 4.53−4.60 (m, 1 H), 4.57 (q, J = 6.6 Hz, 1 H), 4.79 (d, J = 10.1 Hz, 1 H), 4.91 (d, J = 10.1 Hz, 1 H), 5.41 (d, J = 6.5 Hz, 1 H), 5.46−5.55 (m, 1 H), 5.48 (d, J = 10.1 Hz, 1 H), 7.28 (s, 1 H), 7.31−7.59 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.1 and 14.2, 14.3 and 14.4, 19.37 and 19.43, 21.0 and 21.2, 25.4, 30.55 and 30.57, 31.6, 51.9 and 52.0, 59.1, 60.4 and 60.6, 62.07 and 62.13, 68.06 and 68.07, 71.54, 72.8, 73.0, 75.50 and 75.53, 76.5, 90.32 and 90.34, 93.2, 96.0, 97.7, 110.4, 115.7 and 115.8, 121.6, 125.1 and 125.2, 127.8, 128.2, 128.6, 130.6, 134.4 and 134.7, 137.7, 143.0, 148.0, 149.1, 153.0 and 153.1, 156.0 and 156.1; IR (neat) 3480, 2940, 2870, 1630, 1570, 1450, 1380, 1120, 1050, 870 cm^{-1}; HRMS *m*/*z* 681.3629 (681.3639 calcd for $C_{39}H_{53}O_{10}$, M^+ + 1). Anal. Calcd for $C_{39}H_{52}O_{10}$: C, 68.80; H, 7.70. Found: C, 68.97; H, 7.90.

(b) (−)-Furaquinocin B (1b). To a suspension of powdered, well-dried 4 Å molecular sieves in THF (0.3 mL) was added a solution of TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) at 0 °C, and the suspension was stirred for 5 min. To this mixture was added a solution of quinone **35b** (61.6 mg, 97.6 μmol) in THF (2 mL), and the mixture was stirred for 2.5 h. The reaction was quenched by adding pH 7 phosphate buffer, the mixture was filtered, and the filtrate was washed with EtOAc. After the addition of brine, the products were extracted with EtOAc (×5), and the combined organic extracts were successively washed with 0.13 M H_2SO_4 (×2) and brine (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone = 6/4) followed by chromatography on a Sephadex LH-20 column (MeOH) to give (−)-furaquinocin B (**1b**) (30.1 mg, 79%) as a bright yellow solid. Analytically pure material was obtained after recrystallization (hexanes−EtOAc): mp 101−103 °C (lit.[1b] mp 101−104 °C); ^{1}H NMR ($CDCl_3$) δ 0.86−0.90 (m, 1 H), 1.26 (s, 1 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.38 (s, 3 H), 1.75 (s, 3 H), 2.05 (s, 3 H), 2.20 (dd, J_1 = 14.0, J_2 = 5.0 Hz, 1 H), 2.57 (ddd, J_1 = 14.0, J_2 = J_3 = 9.7 Hz, 1 H), 4.01 (s, 3 H), 4.04−4.10 (m, 1 H), 4.10 (s, 2 H), 4.69 (q, J = 6.4 Hz, 1 H), 5.53 (dd, J_1 = 5.0, J_2 = 9.7 Hz, 1 H), 7.15 (s, 1 H), 10.67 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.3, 14.3, 16.2, 18.9, 31.8, 52.4, 60.7, 67.9, 73.1, 88.9, 109.2, 110.7, 120.1, 124.5, 133.6, 134.2, 139.9, 156.9, 158.4, 160.5, 180.7, 183.7; IR (neat) 3430, 2920, 1670, 1640, 1580, 1410, 1300, 1280, 1170, 1030, 900 cm^{-1}; $[\alpha]^{27}_D$ −135 (*c* 0.34, $CHCl_3$) (lit.[1b] $[\alpha]^{19}_D$ −132 (*c* 0.57, $CHCl_3$)); HRMS *m*/*z* 402.1698 (402.1679 calcd for $C_{22}H_{26}O_7$, M^+). Anal. Calcd for $C_{22}H_{26}O_7 \cdot 0.25H_2O$: C, 63.53; H, 6.66. Found: C, 63.51; H, 6.69.

Total Synthesis of (−)-Furaquinocin H. (a) Synthesis of Alcohol 33h. To a solution of vinylstannane **32** (501 mg, 1.20 mmol) in THF (2 mL) was added *n*-BuLi (0.70 mL, 1.64 M hexane solution, 1.1 mmol) at −78 °C, and the mixture was stirred for 4 h at −78 °C. To the mixture were added a solution of epoxide **23** (112 mg, 0.213 mmol) in THF (3 mL) and a freshly prepared solution of $BF_3 \cdot OEt_2$ (0.20 mL, 2.12 M solution in THF, 0.42 mmol), and the mixture was stirred for 2.5 h at −78 °C. The reaction was quenched by adding MeOH (1 mL), to this mixture was added pH 7 phosphate buffer, and the products were extracted with EtOAc (×5). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 5/5) to give alcohol **33h** (120 mg, 86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6 H), 1.52 (s, 3 H), 1.64 (d, J = 6.7 Hz, 3 H), 1.76−1.82 (broad, 1 H), 2.14−2.26 (m, 2 H), 2.29 (s, 3 H), 3.40 (s, 3 H), 3.60 (t, J = 4.5 Hz, 2 H), 3.80−3.82 (m, 1 H), 3.86 (t, J = 4.5 Hz, 2 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 4.16 (d, J = 13.4 Hz, 1 H), 4.22 (d, J = 13.4 Hz, 1 H), 4.29 (s, 2 H), 4.55 (q, J = 6.7 Hz, 1 H), 4.84 (d, J = 10.1 Hz, 1 H), 4.89 (d, J = 10.1 Hz, 1 H), 5.30 (t, J = 7.0 Hz, 1 H), 5.39 (d, J = 6.4 Hz, 1 H), 5.47 (d, J = 6.4 Hz, 1 H), 7.28 (s, 1 H), 7.32−7.57 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.1, 21.0, 23.7, 24.2, 30.7, 52.0, 59.1, 59.9, 60.4, 60.7, 64.5, 68.2, 71.6, 75.6, 76.5, 90.4, 93.2, 96.2, 99.0, 110.5, 115.5, 120.9, 121.9, 127.9, 128.3, 128.6, 130.9, 133.9, 137.7, 143.1, 148.0, 149.3, 153.0, 156.1; IR (neat) 3480, 2940, 2870, 1630, 1600, 1570, 1450, 1380, 1320, 1050, 830 cm^{-1}; $[\alpha]^{25}_D$ −29.6 (*c* 1.00, $CHCl_3$); HRMS *m*/*z* 652.3246 (652.3247 calcd for $C_{37}H_{48}O_{10}$, M^+).

(b) (−)-Furaquinocin H (1h). To a suspension of powdered, well-dried 4 Å molecular sieves in THF (1 mL) was added a solution of TBAF (1.0 M in THF, 1.1 mL, 1.1 mmol) at 0 °C, and the suspension was stirred for 5 min. To this mixture was added a solution of quinone **35h** (83.8 mg, 110 μmol) in THF (2 mL), and the mixture was stirred for 1.5 h. The reaction was quenched by adding pH 7 phosphate buffer, the mixture was filtered, and the filtrate was washed with EtOAc. After addition of brine, the products were extracted with EtOAc (×5), and the combined organic extracts were successively washed with 0.13 M H_2SO_4 (×2) and brine (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone = 4/6) followed by Sephadex LH-20 column (MeOH) to give (−)-furaquinocin H (**1h**) (33.7 mg, 73%) as a yellow oil. Analytically pure material was obtained after recrystalization (EtOAc): mp 172−175 °C (lit.[1c] mp 75−78 °C); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.39 (d, J = 6.3 Hz, 3 H), 2.05 (s,

3 H), 2.22 (dd, $J_1 = 13.5$, $J_2 = 5.8$ Hz, 1 H), 2.62 (ddd, $J_1 = 13.5$, $J_2 = J_3 = 9.3$ Hz, 1 H), 3.98 (d, $J = 10.1$ Hz, 1 H), 4.00 (s, 3 H), 4.08 (d, $J = 12.1$ Hz, 1 H), 4.12−4.17 (m, 1 H), 4.16 (d, $J = 10.1$ Hz, 1 H), 4.25 (d, $J = 12.1$ Hz, 1 H), 4.68 (q, $J = 6.3$ Hz, 1 H), 5.66 (dd, $J_1 = 9.3$, $J_2 = 5.8$ Hz, 1 H), 7.13 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.4, 15.8, 19.3, 31.9, 53.0, 57.9, 60.8, 65.5, 72.3, 89.8, 109.0, 110.8, 125.0, 126.1, 134.0, 134.1, 141.3, 157.3, 159.2, 161.2, 181.2, 184.2; IR (neat) 3420, 2940, 1670, 1640, 1580, 1410, 1300, 1280, 1030, 890 cm^{-1}; $[\alpha]^{27}_D$ −51 (*c* 0.77, MeOH) (lit.[1c,37] $[\alpha]^{19}_D$ −52 (*c* 0.25, MeOH)); HRMS *m*/*z* 420.1793 (420.1785 calcd for $C_{22}H_{28}O_8$, $M^+ + 2$). Anal. Calcd for $C_{22}H_{26}O_8 \cdot 0.5H_2O$: C, 61.82; H, 6.37. Found: C, 62.07; H, 6.30.

Acknowledgment. The authors are grateful to Prof. Satoshi Ōmura for providing us with valuable authentic samples and/or spectra of the furaquinocins. Financial support from the Ministry of Education, Science, Sports and Culture of the Japanese Government [Grant-in-Aid for Scientific Research (No. 09554045)] and from Toray Science Foundation is gratefully acknowledged. T.S. thanks JSPS for a predoctoral fellowship.

Supporting Information Available: General experimental procedures, synthetic schemes for **30**−**32**, details of experimental procedures and characterization data for **12**−**17**, **34a**−**h**, and **35a**−**h** (11 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA982403T