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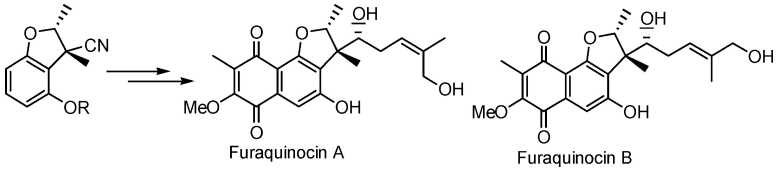

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Total Syntheses of Furaquinocin A, B, and E

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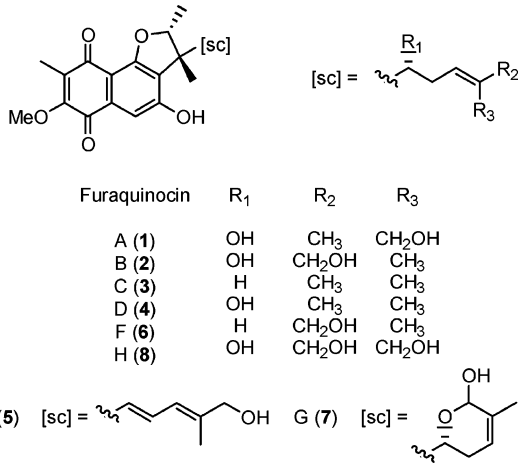
Abstract: A modular approach to the total synthesis of furaquinocins culminated in the total syntheses of furaquinocin A, B, and E. A Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) on carbonates derived from Baylis−Hillman adducts, followed by a reductive Heck cyclization allows the enantio- and diastereoselective construction of dihydrobenzofuran **32**. Introduction of a double unsatured side chain via Horner−Wadsworth−Emmons reaction and assembly of the naphthoquinone with squaric acid based methodology leads to furaquinocin E. The use of differentially substituted squaric acid derivatives allows the synthesis of three analogues of furaquinocin E. The additional stereocenters in furaquinocin A and B can be introduced with a diastereoselective Sakurai allylation. The stereoselective elongation of the side chain is possible using cross metathesis or ring closing metathesis. The obtained late-stage intermediates were successfully transformed to furaquinocin A and B.

Introduction

The furaquinocins (**1**−**8**; Figure 1) are a class of antibiotics isolated from the fermentation broth of *Streptomyces* sp. KO-3998 by Ōmura.[1] They show a wide range of biological effects including in vitro cytotoxicity against HeLa S3 and B16 melanoma cells, antihypertensive activity, and inhibition of platelet aggregation and coagulation. All members of the furaquinocins share a densely functionalized naphthoquinone core, differing only in the degree of oxidation of the isoprenoid side chain. The relative and absolute stereochemistry was assigned by extensive correlations between the members of the family and by a single-crystal X-ray analysis of furaquinocin A (**1**).[2] The biological activity, as well as the challenging structural features, make this class of compounds prime targets for synthesis. Smith reported a short chiral-pool based synthesis of furaquinocin C (**3**)[3] and Suzuki prepared furaquinocin A (**1**), B (**2**), D (**4**), and H (**8**).[4] We recently described a concise total synthesis of furaquinocin E (**5**), based on a dynamic asymmetric kinetic transformation (DYKAT) process.[5] In this full account, we present the development of our synthetic approach in greater detail. The flexibility of this strategy allows easy variations of the side chain as demonstrated by the synthesis of additional furaquinocins A (**1**) and B (**2**) as well as variations of the substituents on the naphthoquinone moiety.



Furaquinocin	R_1	R_2	R_3
A (**1**)	OH	CH_3	CH_2OH
B (**2**)	OH	CH_2OH	CH_3
C (**3**)	H	CH_3	CH_3
D (**4**)	OH	CH_3	CH_3
F (**6**)	H	CH_2OH	CH_3
H (**8**)	OH	CH_2OH	CH_2OH

Figure 1. Furaquinocins.

Results and Discussion

Despite some recent progress in the development of an asymmetric Baylis−Hillman reaction, the present methods for this type of transformation still have serious drawbacks, which preclude their use in asymmetric synthesis.[6−8] We developed an efficient alternative to the asymmetric Baylis−Hillman

(1) (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) Funayama, S.; Ishibashi, M.; Komiyama, K.; Ōmura, S. *J. Org. Chem.* **1990**, *55*, 1132. (d) Ishibashi, M.; Funayama, S.; Anraku, Y.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1991**, *44*, 390.
(2) (a) Dormer, P. G.; Smith, A. B., III; Funayama, S.; Ōmura, S. *Tetrahedron Lett.* **1992**, *33*, 1717.
(3) (a) Smith, A. B., III.; Sestelo, J. P.; Dormer, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 10 755. (b) Smith, A. B., III.; Sestelo, J. P.; Dormer, P. G. *Heterocycles* **2000**, *52*, 1315.
(4) (a) Saito, T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10 757. (b) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11 633.
(5) Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2002**, *114*, 11 616.
(6) For a recent review on the Baylis-Hillman reaction, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(7) (a) Yang, K.; Lee, W.; Pan, J.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915. (b) Shi, M.; Jiang, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1941. (c) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatekeyama, S. *Chem. Commun.* **2001**, 2030. (d) Iwabuchi, Y.; Nakatami, M.; Yokoyama, N.; Hatekayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10 219. (e) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (f) Hayase, T.; Shibata, T.; Soai, K.; Wakalsuki, Y. *Chem. Commun.* **1998**, 1271. (g) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015. (h) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.

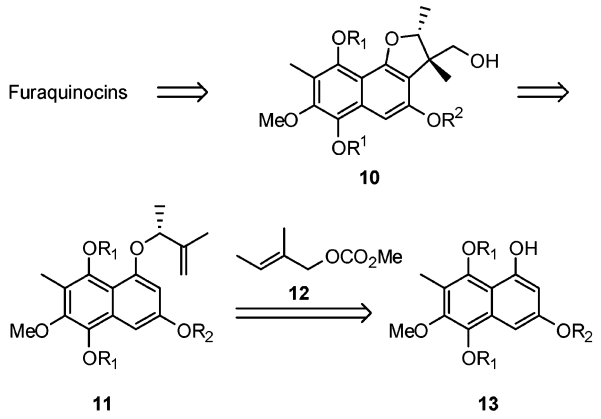
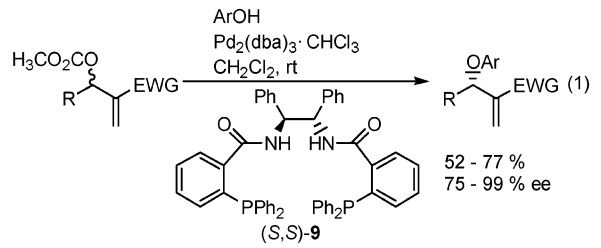


Figure 2. Initial retrosynthetic analysis.

reaction. The carbonates of Baylis−Hillman adducts can be used as substrates in the Pd-catalyzed allylic alkylation with phenols as nucleophiles (eq 1).[9]A dynamic kinetic asymmetric transformation (DYKAT)[10] leads to the corresponding products in good yields and high enantioselectivity.



Initial Approach. Our initial retrosynthetic approach is depicted in Figure 2. All furaquinocins should be available from the common intermediate **10**, by late-stage introduction of the appropriate side chains. This intermediate **10** should be obtained via diastereoselective epoxidation and subsequent electrophilic cyclization of substrate **11**. Allylic alkylation of carbonate **12** with the phenolic nucleophile **13** should establish the absolute stereochemistry.

To test the feasibility of our strategy, we prepared naphthoquinone **16** through a Diels−Alder reaction of bromoquinone **14** with diene **15** (Scheme 1).[11] The diol **16** was monoprotected to afford naphthoquinone **17**. The palladium-catalyzed reaction of allylic carbonate **12** with this nucleophile failed. This failure can be attributed to an incompatibility between the palladium(0) catalyst and the oxidizing naphthoquinone moiety and to the decreased nucleophilicity of the phenol due to a strong hydrogen bond with the adjacent carbonyl moiety. To circumvent these problems, the naphthoquinone **16** was protected as the diacetate, reduced to the dihydronaphthoquinone, and protected as the bismethoxymethyl ether. Saponification of the acetates and monosilylation afforded the phenol **19**. To our surprise, this compound was also not a reactive nucleophile in the allylic alkylation of carbonate **12**.

Revised Approach. Since the introduction of the naphthoquinone as a nucleophile in the allylic alkylation reaction failed, we had to revise our retrosynthetic strategy (Figure 3). We chose furaquinocin E (**5**) as the initial target molecule. Late stage construction of the naphthoquinone should be possible from intermediate **21** using the squaric acid based methodology developed earlier by Moore and Liebeskind.[12] Disconnection of the doubly unsaturated side chain leads to aldehyde **22**. This aldehyde could be obtained from benzofuran **23**. We thought that we could establish the absolute and relative stereochemistry of this key intermediate with a sequence of Pd-catalyzed allylic alkylation and diastereoselective reductive Heck cyclization.

Construction of the Benzofuran. Initially we investigated the monoalkylation of 2-iodoresorcinol **24**[13] with carbonates **25**−**27** (Scheme 2).[14] In agreement with our previous results concerning the DYKAT on similar substrates, we observed the best results with nitrile derivative **25**.[8] Use of the corresponding methyl and ethyl ester derivatives **26** and **27** resulted in diminished enantioselectivity. Unfortunately, we were not able to obtain high yields of the monoalkylated product. Even in the presence of an excess of the nucleophile (1.5 equiv), the isolated yield of compound **28** was only 63%. Nonetheless, we investigated **28**−**30** as substrates in the reductive Heck cyclization.[15] The reaction of the methyl ester **29** under conditions reported previously in the literature (different palladium sources such as $PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$, $Pd(CF_3CO_2)_2$, or $PdCl_2(PPh_3)_2$, $NaCO_2H$, K_2CO_3, DMF, 50 °C)[15a,b] led to the predominant formation of the 6-endo-cyclization product. Whereas the use of the ethyl ester **30** led to similar results, switching to the nitrile **28** as substrate led to a reversal in selectivity. The 5-exo-cyclization was now the major reaction pathway. Using the conditions that we applied successfully in the synthesis of aflatoxin B_1 ($PdCl_2(CH_3CN)_2$, HCOOH, TEA, DMF, 50 °C)[15c,d] we could obtain a 40% yield of product **32**, after acetylization of the free phenol. The use of phenol **28** as substrate in the reductive Heck cyclization revealed that the allylic ether moiety was rather labile under the reaction conditions, simple cleavage of the allyl ether was a major competing pathway. While we contemplated the possibility of utilizing a protecting group for the phenol to improve the yield in the allylic alkylation and to minimize the side reactions, a more attractive alternative that might improve both palladium-catalyzed reactions arose.

The alternate envisions a dialkylation approach, which should give higher yields in both the allylic alkylation and the reductive Heck cyclization (Scheme 3). Reaction of 2-iodoresorcinol **24** with allylic carbonate **25** (2.85 equiv) in the presence of $Pd_2(dba)_3$·$CHCl_3$ (1 mol %) and (*R*,*R*)-ligand **10** (3 mol %) gave the desired product **31** in excellent yield (97%) and good diastereoselectivity (dr 92/8).[16] In contrast to our previously

(8) For use of chiral auxiliaries in Baylis-Hillman reactions, see: (a) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888. (b) Radha Krishna, P.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, *12*, 829. (c) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (d) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16 423.

(9) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

(10) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. For a recent review: Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(11) Botha, M. E.; Giles, R. G. F.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 85.

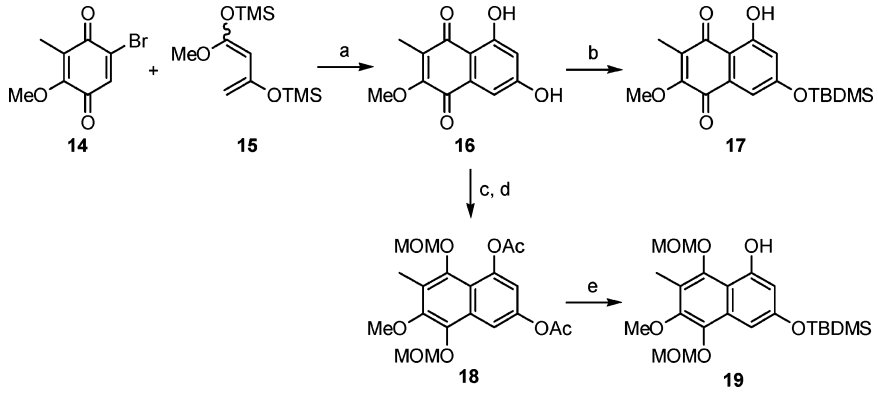
(12) (a) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996. (b) Perri, S. T.; Foland, S. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (c) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065. (d) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053.

(13) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1991**, *45*, 539.

(14) The carbonates were obtained from the corresponding Baylis-Hillman adducts in good yields by reaction with methylchloroformate/potassium carbonate.

(15) (a) Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357. (b) Hoffmann, H. M. R.; Schmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6113. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.

Scheme 1. Synthesis of Nucleophiles **17** and **19**[a]



[a] Conditions: (a) toluene, TEA, 65%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, reflux, 75%. (d) (i) Pd/C, H_2, CH_2Cl_2; (ii) MOMCl, DIPEA, CH_2Cl_2, 72%. (e) (i) $LiAlH_4$, THF; (ii) TBDMSCl, imidazole, CH_2Cl_2, 57%.

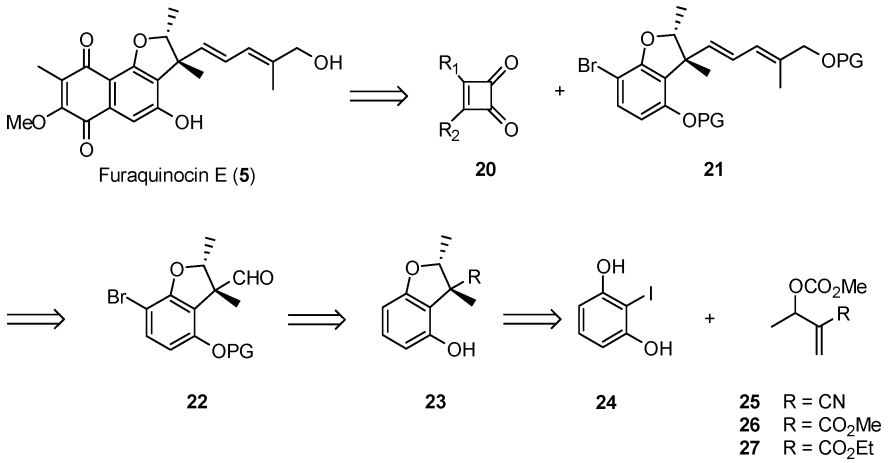
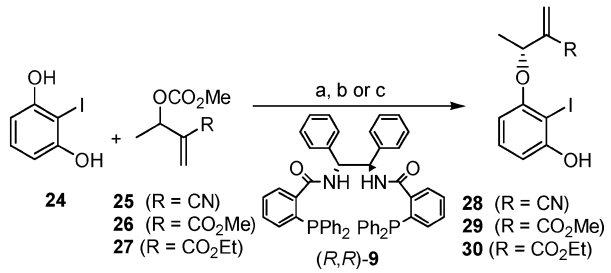


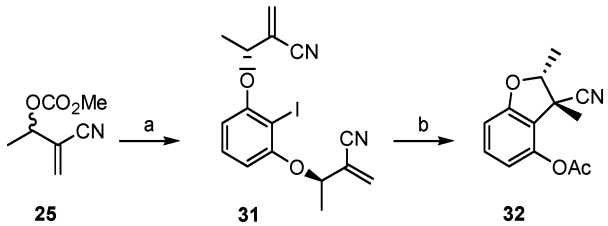
Figure 3. Revised retrosynthetic analysis.

Scheme 2. Monoalkylation of **24**[a]



[a] Conditions: (a) **24** (1.5 equiv), $Pd_2(dba)_3$·$CHCl_3$ (1 mol %), (*R*,*R*)-**9** (3 mol %), CH_2Cl_2, room temperature; **28** (R= CN), 64%, 91% ee; **29** (R= CO_2Me), 62%, 74% ee; **30** (R= CO_2Et), 52%, 71% ee.

Scheme 3. Two-Step Construction of the Furaquinocin Core[a]



[a] Conditions: (a) **24**, $Pd_2(dba)_3$·$CHCl_3$ (1 mol %), ligand (*R*,*R*)-**9** (2.65 mol %), CH_2Cl_2, room temperature, 97%, (dr 92/8). (b) (i) $PdCl_2(CH_3CN)_2$ (10 mol %), HCOOH, PMP, DMF, 50 °C; (ii) Ac_2O, TEA, DMAP, CH_2Cl_2, room temperature, 81%, 87% ee (99% ee after recrystallization).

reported examples, no formation of the regioisomer resulting from the attack of the phenol at the terminal position was observed.[9] No attempts were made at this stage to assign the absolute stereochemistry of **31**. Based upon our previous experience we believed that the use of (*R*,*R*)-**10** as ligand in the allylic alkylation led to the formation of (*R*,*R*)-**31** as major stereoisomer. This assumption was confirmed by the conversion of this intermediate to the natural enantiomers of the furaquinocins. Ionization of the carbonate **25** leads to the two diastereomeric syn-π-allylpalladium complexes **I** and **II** (Figure 4). These two complexes are in equilibrium via a π-σ-π-isomerization. The nucleophile attacks the allyl complex in an exo mode. The matched reaction pathway leads to the *R*-configured product.

Since we were not able to separate the diastereomers of **31** using crystallization or column chromatography, the mixture was subjected to the next reaction. Reductive Heck cyclization under the same conditions we used for the cyclization of **28** ($PdCl_2(CH_3CN)_2$, HCOOH, TEA, DMF, 50 °C) showed poor reproducibility. Significant competing pathways were the 6-endo-cyclization and reionization of the substrate. Switching to the sterically hindered base pentamethylpiperidine (PMP) led to a great improvement in yield and reproducibility.[17] The reaction proceeded with good regio- and diastereoselectivity and the

(16) This diastereomeric ratio reflects the ratio of (*R*,*R*)-**31** and *meso*-**31**. No (*S*,*S*)-**31** was formed.

(17) For the beneficial use of PMP as base in Heck reactions, see, for example: (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

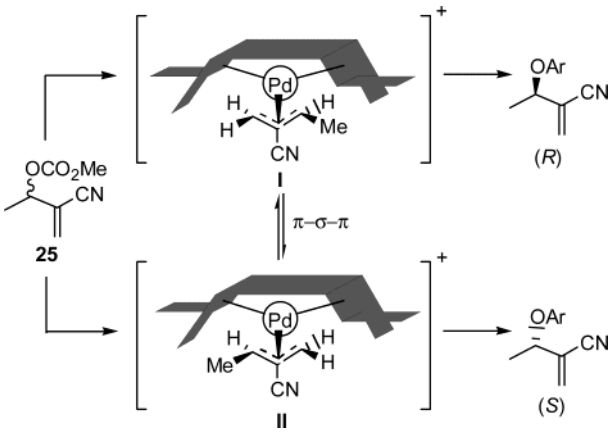


Figure 4. Rationale for asymmetric induction in the allylic alkylation.

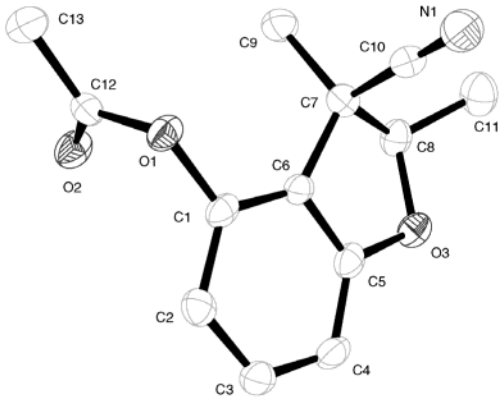
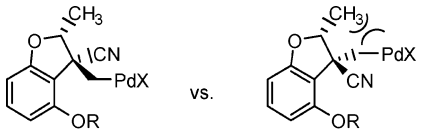


Figure 5. Crystal structure of **32**.

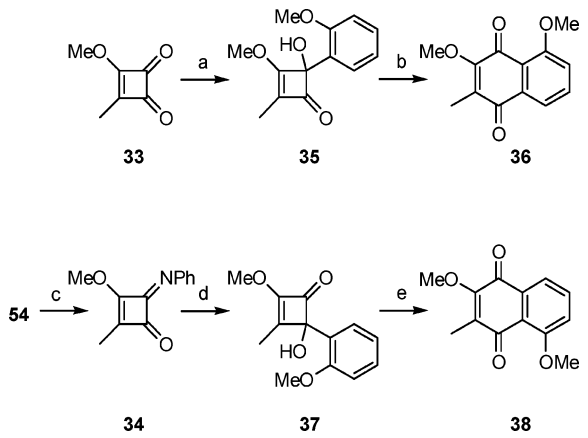


III **IV**

Figure 6. Possible diastereomeric intermediates in the reductive Heck cyclization.

second allyl moiety was cleaved under the reaction conditions. After acetylization of the free phenol, the desired diastereomer **32** was obtained in very good yield. A strong NOE between the methyl C-3 and the hydrogen at C-2 established their cis relationship. The relative stereochemistry was finally confirmed by single-crystal X-ray analysis (Figure 5). This stereochemical outcome is expected based on minimization of steric strain in the transition state for the intramolecular carbapalladation step (Figure 6). The reaction pathway leading to the major diastereomer leads to intermediate III, in which the methyl group and the bulky palladium-bearing methylene group are oriented trans to each other. The diastereoselectivity of the reductive Heck cyclization was diminished in the case of the substrates **29** and **30**. The ester substituents are bulkier than the nitrile and therefore intermediate **IV** becomes a more accessible pathway. The enantiomeric excess obtained in the allylic alkylation was determined to be 87%. Recrystallization of acetate **32** led to enantiopure material (85% recovery). With this strategy, the absolute and relative stereochemistry of the benzofuran was established using two Pd-catalyzed steps. Thus a simple two-step protocol provided the dihydrobenzofuran core enantiomerically pure in 67% yield from two simple building blocks **24** and **25**. This compound serves as the pivotal intermediate which provides access to several furaquinocins and their analogues.

Scheme 4. Model Study for Naphthoquinone Assembly[a]



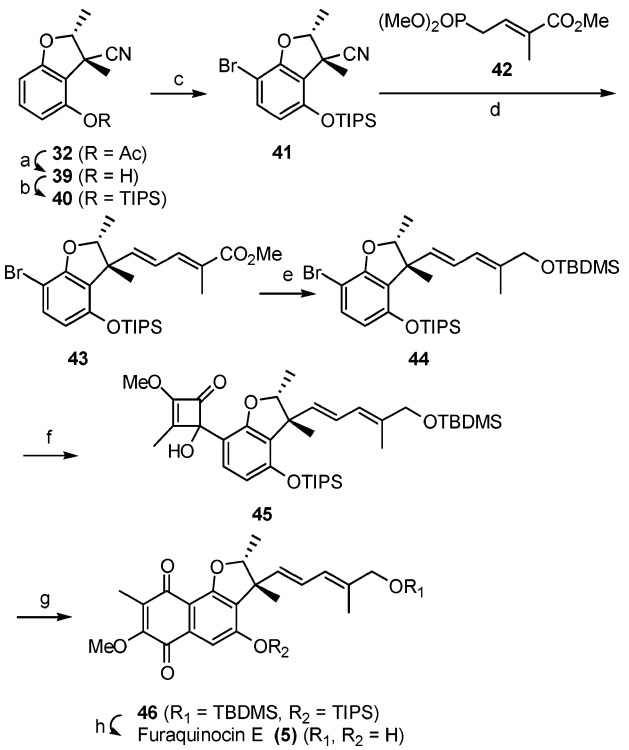
[a] Conditions: (a) 2-lithioanisole, THF, −78 °C, 33%. (b) (i) toluene, 110 °C; (ii) Ag_2O, K_2CO_3, room temperature, 66%. (c) (i) MeLi, THF, −100 °C; (ii) trifluoroacetic anhydride, −78 °C; (iii) aniline, −78 to −15 °C (53%). (d) (i) 2-lithioanisole, THF, −78 °C; (ii) oxalic acid, THF/H_2O, 53%. (e) (i) toluene, 110 °C; (ii) Ag_2O, K_2CO_3, room temperature, 79%.

Studies Directed Toward the Synthesis of Regioisomeric Naphthoquinones. Squaric acid based methodology is available for the construction of naphthoquinones.[12] To examine selectivity issues as well as to establish reaction conditions, we employed the addition of 2-lithioanisole to the squaric acid derivatives **33** and **34** as a model system for the furaquinocin synthesis. Use of the derivative **33** leads to nucleophilic attack of an organometallic compound on the more reactive carbonyl group adjacent to the methoxy group (Scheme 4). After rearrangement and oxidation this furnishes naphthoquinone **36,** which is regioisomeric to the furaquinocins with regard to the substituents on the quinone.[12d] To reverse the chemoselectivity, a temporary protecting group was introduced.[18] Taking advantage of the higher reactivity of the C-2 carbonyl group, the imine **34** could be obtained from dimethyl squarate **54** in good yield through a one-pot procedure. Addition of 2-lithioanisole to imine **34** followed by hydrolysis of the imine under mild acidic conditions afforded regioisomer **37**. This compound could be rearranged and oxidized to provide naphthoquinone **38**. Thus, both positional isomers are readily accessible.

Completion of the Furaquinocin E Synthesis. Having established the two stereogenic centers of **32** in an efficient manner and with a selective naphthoquinone synthesis available, we were confident that we could sucessfully complete the total synthesis of furaquinocin E (**5**). The formation of the required aryllithium required access to an aryl bromide precursor. Direct bromination of the free phenol **39** with tetra-*n*-butylammonium perbromide gave an 84% yield of monobromide, but as a 1:1 mixture of the ortho and para (with respect to the phenolic OH) products. To direct the reaction to form the desired para bromide, a bulky triisopropylsilyl group was placed on the free phenol. Indeed, bromination with NBS proceeded regioselectively to form monobromide **41** (Scheme 5).[19] For installation of the side chain, the nitrile was reduced with DIBAL and the resultant

(18) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572.
(19) Bromination of acetate **32**, the free phenol **33,** or the corresponding TBDMS-ether were unselective.

Scheme 5. Conversion of **32** to Furaquinocin E (**5**)[a]



[a] Conditions: (a) NaOMe, MeOH, room temperature, 94%. (b) TIPSOTf, TEA, CH_2Cl_2, 96%. (c) NBS, THF, room temperature, 92%. (d) (i) DIBAL, CH_2Cl_2, −78 °C; (ii) **42**, LHMDS, THF, 0 °C, 89%. (e) (i) DIBAL, CH_2Cl_2, −78 °C; (ii) TBDMSCl, imidazole, CH_2Cl_2, reflux, 89% (2 steps). (f) (i) *n*-BuLi, THF, −78 °C; (ii) **34**, THF, −78 °C; (iii) oxalic acid, THF/H_2O, 50%. (g) (i) toluene, 110 °C; (ii) air, room temperature, 64%. (h) TBAF, THF, 0 °C, 65%.

aldehyde was subjected to a Horner−Wadsworth−Emmons reaction with phosphonate **42**[20] to yield the desired (*E*,*E*)-diene **43** exclusively. Reduction of the methyl ester to the alcohol followed by TBDMS protection completed the elaboration of the side chain. The stage was now set to inspect the scope of the naphthoquinone synthesis on a more elaborate substrate. Halogen−metal exchange on bromide **44** and addition of the generated organolithium to imine **34** followed by hydrolysis of the resulting imine under mild acidic conditions led to the addition product **45** in acceptable yield. All efforts to improve the yield by using cerium- or magnesium-derived organometallics failed. Thermal rearrangement followed by oxidation in air delivered the desired naphthoquinone **46**. Furaquinocin E (**5**) was obtained upon deprotection of the silyl ethers with TBAF in THF. The spectroscopic data are in full agreement with those published for the natural product,[1d] thereby confirming the chemoselectivity in the attack of the protected squaric acid derivative.

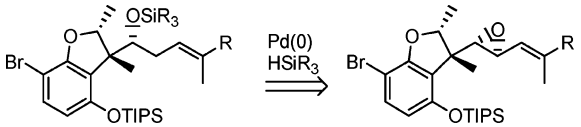
Synthesis of Furaquinocin E Analogues. Although we were initially disappointed that our original retrosynthetic approach had failed, we realized that our revised approach was more modular in nature. It should enable us to access analogues of furaquinocin E with different substitution patterns on the naphthoquinone very easily. We therefore used the intermediate **44** to prepare several analogues. The reactions leading to the analogues proceeded in analogy to the synthesis of furaquinocin E (Scheme 6). Using the squaric acid derivative **33**, the regioisomer **49** of furaquinocin E could be obtained. The use of compound **50** gave rise to the dimethylnaphthoquinone **53,** and employment of compound **54** resulted in the dimethoxynaphthoquinone **57**. The thermal rearrangement of compound **55** under the relatively mild conditions that were successfully applied to all other furaquinocins (toluene, 110 °C) led to incomplete conversions. Hence the reaction was performed under microwave irradiation (toluene, 180 °C, 30 min), affording an acceptable yield of 58% after oxidation to the naphthoquinone. The analogues **49**, **53,** and **57** were submitted to biological testing, but unfortunately no cytotoxicity against HEK293T, LnCAP, and A2780 cell lines was observed in the micromolar range.[21]

Syntheses of Furaquinocin A and B. Our modular approach allowed easy access to several analogues of furaquinocin E. We were also interested in the synthesis of other members of the furaquinocin family that would bear more complicated side chains. We chose furaquinocins A (**1**) and B (**2**) as additional targets. Compared to furaquinocin E, they have an additional stereogenic center bearing a hydroxyl group in the side chain. Furaquinocins A and B only differ in the stereochemistry of the double bond in the side chain. We envisioned that we could introduce the side chain by addition of organometallic reagents to aldehyde **58**, which we already obtained from the reduction of nitrile **41** (Scheme 7). Since the introduction of the side chain as a whole failed in earlier approaches,[4b] we only briefly investigated this possibility.[22] As our efforts in this direction were only met with limited success, we concentrated on the allylation of the aldehyde. Such a strategy would postpone the elaboration of the complete side chain toward subsequent stages. Addition of allylmagnesium bromide to aldehyde **58** proceeded in good yield (65% from **41**), but no diastereoselectivity (dr 1:1) was observed. The Lewis acid (BF_3 or $TiCl_4$) mediated addition of allyltributylstannane afforded the corresponding alcohols with better selectivity (dr 4:1). The best results were obtained with the addition of allyltrimethylsilane mediated by $TiCl_4$ (9:1).[23] The desired homoallylic alcohol **59** could be obtained in pure form after purification by column chromatography (67% from **41**).[24] Attempts to perform the allylation with allyltrimethylsilane in the presence of a Lewis acidic catalyst ($FeCl_3$[25] or $Sc(OTf)_3$[26]) led to no conversion. The activation of the allylating reagent with TBAF[27] only led to cleavage of the TIPS group of aldehyde **58**. The observed diastereoselectivity

(20) Evans, D. A.; Miller, S. J.; Ennis, S. D. *J. Org. Chem.* **1993**, *58*, 471.

(21) Cytotoxicity of the compounds was evaluated in HEK293T, LnCAP and A2780 cell lines using viable stainin with Alamar Blue (O'Brien, J.; Wilson, I.; Orton, T.; Pognan, F. *Eur. J. Biochem.* **2000**, *267*, 5421.

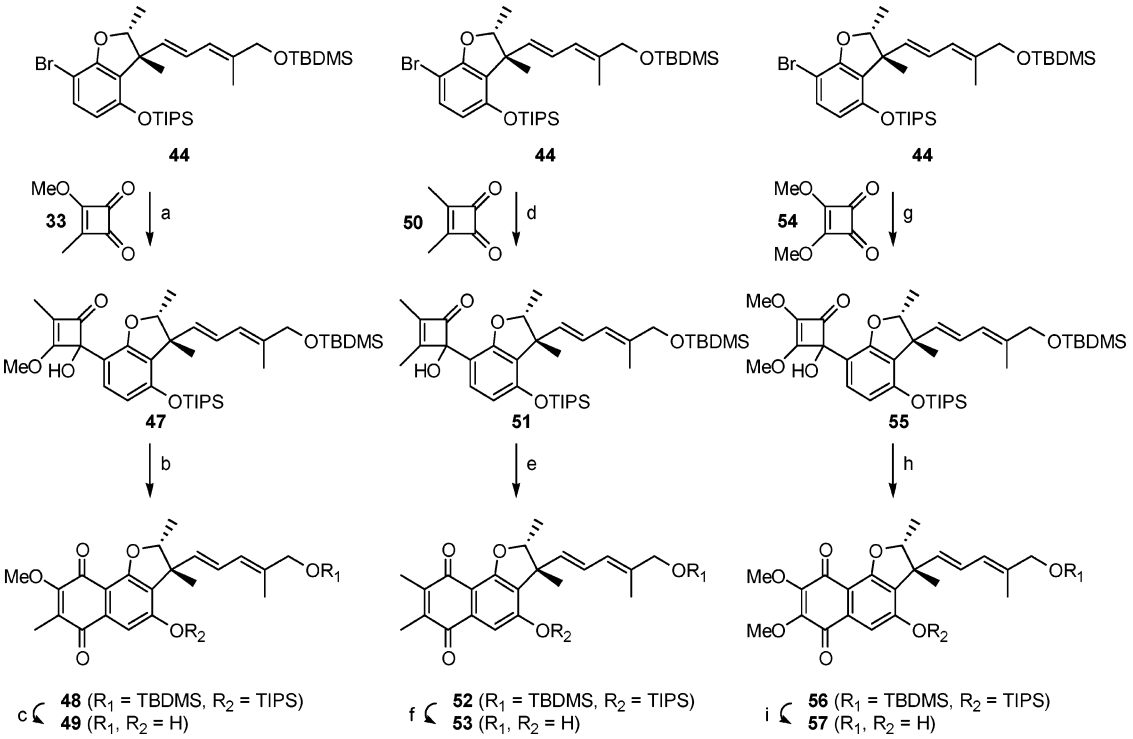
(22) We believed that we could access the secondary alcohol **53** by palladium-catalyzed reductive opening of the vinyl epoxide **54**. Attempts to selectively epoxidize the disubstituted double bond of dienes **43** and **44** failed. An alternative approach toward the epoxide **53** would be the addition of sulfur ylides to the aldehyde **58**. Initial attempts in this directions were not successful, and this route was therefore abandoned.



53a (R = CH_2OTBS) **54a** (R = CH_2OTBS)
53b (R = CO_2Me) **54b** (R = CO_2Me)

(23) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295. (b) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

Scheme 6. Synthesis of Furaquinocin E Analogues[a]

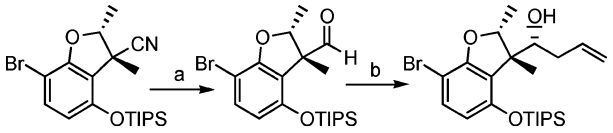


[a] Conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) **33**, THF, −78 °C, 74%. (b) (i) toluene, 110 °C; (ii) air, room temperature, 92%. **(**c) TBAF, THF, 0 °C, 93%. (d) (i) *n*-BuLi, THF, −78 °C; (ii) **50**, THF, −78 °C, 61%. (e) (i) toluene, 110 °C; (ii) Ag_2O, K_2CO_3, room temperature, 55%. **(**f) TBAF, THF, 0 °C, 77%. (g) (i) *n*-BuLi, THF, −78 °C; (ii) **54**, THF, −78 °C, 81%. (h) (i) toluene, microwave, 180 °C; (ii) air, room temperature, 58%. **(**i) TBAF, THF, 0 °C, 94%.

in the Lewis acid mediated allylation can be explained by the polar model proposed by Evans (Figure 7).[28] The extended Newman projection depicts the conformation that minimizes the dipole moment. The bottom face of the aldehyde is blocked toward the attack of nucleophiles by the β-methyl substituent.

Homoallylic alcohol **59** served as a common intermediate toward both furaquinocin A and B by using olefin metathesis chemistry.[28] Grubbs reported on the use of methacrolein in the cross metathesis using new NHC-substituted ruthenium complexes.[30] This reaction proceeds stereoselectively to give the thermodynamically favored (*E*) double bond isomer. We therefore subjected acetate **60**, derived from alcohol **59**, to the cross metathesis (Scheme 8).[31] Alkene **60** was reacted with methacrolein in the presence of complex **61** as precatalyst[32] to

Scheme 7. Diastereoselctive Allylation[a]



[a] Conditions: (a) DIBAL, CH_2Cl_2, −78 °C. (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, room temperature, 67% (isolated yield of **59** based on **41**).

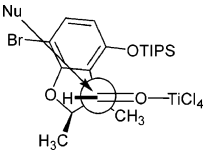
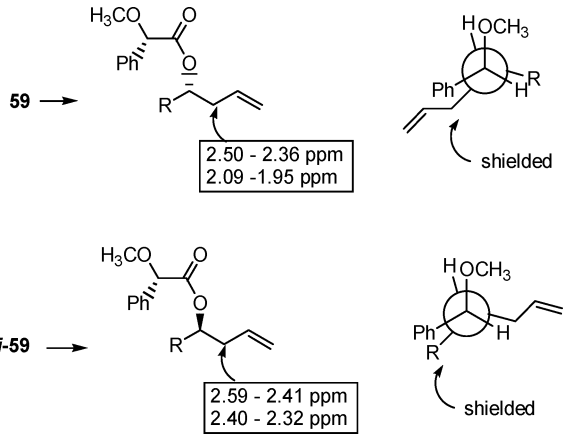


Figure 7. Rationalization of the diastereoselectivity in the allylation.

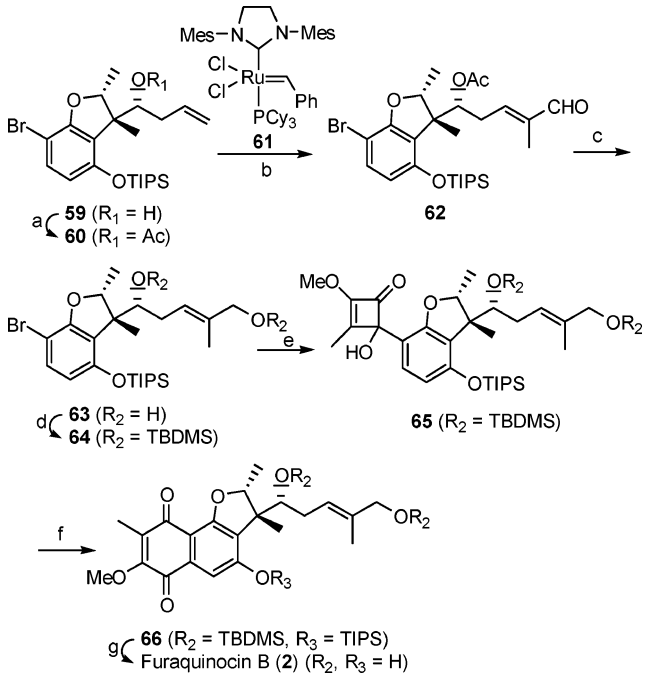
(24) The configuration of the newly formed stereogenic center of **59** was deduced from the ^{1}H NMR spectra of the *O*-methylmandelate derivatives of the major and minor diastereomer. See: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. Final proof of this assignment was possible by transformation of **59** to the natural products.



(25) Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2002**, *43*, 8959.
(26) Aggarwal, V. K.; Vennall, G. P. *Tetrahedron Lett.* **1996**, *37*, 3745.
(27) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *18*, 3043.
(28) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *116*, 4322.

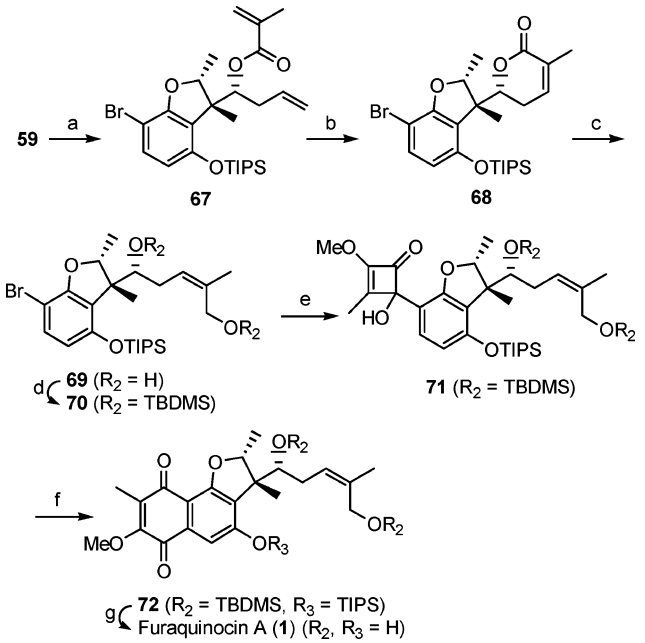
(29) For leading reviews, see: (a) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.*. **2001**, *34*, 18. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900.
(30) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
(31) The free alcohol **53** or the TBDMS-protected derivative led to inferior results in the cross metathesis.
(32) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.

Scheme 8. Synthesis of Furaquinocin B (**2**)[a]



[a] Conditions: (a) Ac_2O (5 equiv), DMAP (0.5 equiv), pyridine, 91%. (b) methacrolein (10 equiv.), **61** (10 mol %), CH_2Cl_2, reflux, 89%. (c) DIBAL, CH_2Cl_2, room temperature, 94%. (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 4 h, 81%. (e) (i) *n*-BuLi, THF, −78 °C; (ii) **34**, THF, −78 °C, (iii) oxalic acid, THF/H_2O, 56%. (f) (i) toluene, 110 °C, 2 h; (ii) air, room temperature, 70%. (g) HF, acetonitrile, 20 h, room temperature, 61%.

Scheme 9. Synthesis of Furaquinocin A[a]



[a] Conditions: (a) methacroyl chloride, TEA, DMAP, CH_2Cl_2, room temperature, 14 h, 78%. (b) **61** (5 mol %), CH_2Cl_2, reflux, 16 h, 66%. (c) (i) DIBAL, CH_2Cl_2, room temperature, 2 h; (ii) $NaBH_4$, MeOH, 62%. (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 5 h, 86%. (e) (i) *n*-BuLi, THF, −78 °C; (ii) **34**, THF, −78 °C; (iii) oxalic acid, THF/H_2O, 59%. (f) (i) toluene, 110 °C, 2 h; (ii) air, room temperature, 81%. (g) HF, acetonitrile, 18 h, room temperature, 70%.

construct the trisubstituted double bond. The large excess of methacrolein was needed, due to the propensity of this reagent to polymerize under the reaction conditions. Reduction of the α,β-unsaturated aldehyde **62** and cleavage of the acetate group with DIBAL proceeded uneventfully to afford diol **63**. Use of TBDMSOTf/2,6-lutidine was necessary for the bis-TBDMS protection because of the sterically hindered nature of the secondary alcohol. Intermediate **64** was transformed to furaquinocin B via the already established synthetic strategy (vide supra). Bromine−lithium exchange and addition of the resulting lithium anion to imine **34** led to compound **65** in good yield. Thermal rearrangement and oxidation with air afforded naphthoquinone **66**. Deprotection of the silyl ethers was first attempted under the conditions that were successfully applied in the synthesis of furaquinocin E (TBAF/THF). Unfortunately the silyl group on the secondary alcohol was resistant to these conditions. However, the use of aqueous HF in acetonitrile afforded furaquinocin B (**2**) in good yield. The analytical data for synthetic **2** was identical with the data reported for the natural product.[1d]

A stereoselective crossmetathesis was used to control the geometry of the double bond in the synthesis of furaquinocin B. It was envisioned that the opposite double bond isomer should be obtained via a ring-closing metathesis approach (Scheme 9). Esterification with methacroyl chloride afforded methacrylate **67**. Ring-closing metathesis of the methyacrylate **67** proceeded well with NHC-substituted ruthenium complexes.[30,33] Reduction of lactone **68** afforded the advanced diol **69** with the (*Z*)-alkene. This reduction proceeded well with DIBAL on small scale (0.035 mmol). On a larger scale (0.5 mmol), the reduction with DIBAL stopped partially at the stage of the lactol and the crude mixture could then be reduced with $NaBH_4$ in MeOH. Protection of the diol **69** with TBDMSOTf/2,6-lutidine afforded intermediate **70**. The synthesis of furaquinocin A (**1**) was completed by the same route as for furaquinocin B and E. Addition of the lithium anion generated by bromine−lithium exchange of intermediate **70** to the imine **34** led to **71** in good yield. Thermal rearrangement and oxidation in air afforded the fully protected naphthoquinone **72**. The final deprotection with HF in acetonitrile gave furaquinocin A (**1**). The analytical data for synthetic **1** were determined to be identical with the data reported for the natural product.[1d]

Conclusion

Asymmetric syntheses of furaquinocin A, B, and E are described. This work highlights the ability to use racemic Baylis−Hillman adducts for asymmetric synthesis. A Pd-catalyzed DYKAT, followed by a reductive Heck cyclization was used to establish the absolute and relative stereochemistry of the common benzohydrofuran core. A diastereoselective Sakurai reaction set the third stereogenic center in furaquinocin A and B. All stereogenic centers are therefore derived from the use of a catalytic amount of ligand **10** in the allylic alkylation step. The control over the olefin geometry in the construction of the side chain is possible using olefin metathesis reactions. Ring-closing metathesis gave the (*Z*)-olefin **69** needed for the synthesis of furaquinocin A. Cross metathesis with methacrolein led to the (*E*)-olefin **63** which was further transformed to furaquinocin B. The naphthoquinone part of the furaquinocins could be constructed regioselectively using the protected squaric acid derivative **34**. The preparation of furaquinocin analogues

(33) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

was easily achieved by using other squaric acid derivatives. Thus, a modular strategy emerges wherein both the naphthoquinone and the side chain moieties can be readily varied from a simply available common intermediate.

Experimental Section

(*R*)-3-[3-((R)-2-Cyano-1-methylallyloxy)-2-iodophenoxy]-2-methylenebutyronitrile (31). $Pd_2(dba)_3$·$CHCl_3$ (72.5 mg, 0.0700 mmol), ligand (*R*,*R*)-**9** (146.8 mg, 0.1860 mmol), and 2-iodoresorcinol (**24**) (1.65 g, 7.00 mmol) were weighed into a flask directly. The flask was put under vacuum, refilled with argon (repeated 3 times), and cooled to 0 °C. Allylic carbonate **25** (3.10 g, 20.0 mmol) was weighed into another flask and CH_2Cl_2 (200 mL) was added. The solution was purged with argon for 30 min, cooled to 0 °C, and then cannulated into the other flask. The mixture was allowed to stir at room temperature for 4 h. Solvents were removed in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 2:1 → 1:1) gave bisallylic ether **31** (2.66 g, 97%) as a colorless solid. mp = 65−66 °C. IR (film): 2985, 2935, 2227, 1912, 1586, 1456, 1409, 1378, 1285, 1247, 1095, 1022, 954, 853, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 8.3 Hz, 1 H), 6.46 (d, J = 8.3 Hz, 2 H), 6.13 (d, J = 1.3 Hz, 2 H), 6.05 (d, J = 1.3 Hz, 2 H), 4.92 (q, J = 6.3 Hz, 2 H), 1.66 (d, J = 6.3 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 131.2, 129.7, 124.0, 116.5, 108.2, 81.8, 74.9, 20.4. HRMS m/z $C_{16}H_{15}N_2O_2I$ (M^+). Calcd: 394.0178. Found: 394.0182. Stereoisomers were separated by HPLC on chiral cel OD eluting with heptane/2-propanol 97:3 (1 mL/min): *R*,*R* 29.51, *R*,*S* 32.45, *S*,*S* 34.47. The prepared sample showed the diasteremeric ratio 92:8 ((*R*,*R*):(*S*,*S*)).

Acetic Acid (2*R*,3*S*)-3-Cyano-2,3-dimethyl-2,3-dihydrobenzofuran-4-yl Ester (32). Bisallylic ether **31** (2.64 g, 6.70 mmol) and $PdCl_2(CH_3CN)_2$ (173 mg, 0.670 mmol) were dissolved in dry DMF (150 mL) at room temperature. 1,2,2,6,6-Pentamethylpiperidine (7.26 mL, 40.1 mmol) and formic acid (1.01 mL, 26.8 mmol) were added. The mixture was heated at 50 °C for 6 h. After being cooled to room temperature, the mixture was diluted with ether (50 mL). The organic phase was washed with brine (2 × 20 mL), dried over $MgSO_4$, and filtered. Evaporation of the solvents and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 4:1 → 2:1) gives crude benzofuran **39**, which is used directly in the next step. The crude product is dissolved in CH_2Cl_2 (20 mL) and triethylamine (3.42 mL, 25.7 mmol); acetic anhydride (1.54 mL, 16.3 mmol) and a catalytic amount of DMAP were added. After being stirred at room temperature for 1 h, the mixture is quenched with water (5 mL) and diluted with ether (10 mL). Layers were separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Solvents were removed in a vacuum and flash chromatography (SiO_2, petroleum ether/ether 10:1) gave benzofuran **32** (1.26 g, 81%) as a colorless oil. ee = 87% (determined by chiral HPLC). Enantiomerically pure material (ee = 99%) can obtained by recrystallization from petroleum ether/ether as colorless needles. mp = 63−64 °C. $[\alpha]^{25}D$ +139.7° [*c* 1.06, CH_2Cl_2]. IR (film): 2985, 2937, 1771, 1617, 1601, 1456, 1386, 1261, 1196, 1175, 1091 1032, 867, 862, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.26 (dd, J = 8.3 Hz, J = 8.1 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 6.71 (d, J = 8.1 Hz, 1 H), 4.55 (q, J = 6.3 Hz, 1 H), 2.34 (s, 3 H), 1.73 (s, 3 H), 1.63 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 159.7, 147.5, 131.3, 118.7, 118.6, 115.7, 108.3, 87.3, 44.5, 24.2, 20.8, 17.6. HRMS m/z $C_{13}H_{13}NO_3$ (M^+). Calcd: 231.0895. Found: 231.0891. Enantiomers were separated by HPLC on chiralcel OD eluting with heptane/2-propanol 99:1 (1 mL/min); 2*R*,3*S* 15.73, 2*S*,3*R* 17.95.

3-Methoxy-2-methyl-4-phenyliminocyclobut-2-enone (34). Methyllithium (6.25 mL, 10.0 mmol, 1.6 M in ether) is added slowly to a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (1.42 g, 10.0 mmol) in THF (50 mL) at − 100 °C (N_2/ether). After stirring for 30 min at this temperature the reaction mixture is warmed to −78 °C and trifluoroacetic anhydride (1.41 mL, 10.0 mmol) was added. After stirring for 15 min, aniline (1.00 mL, 11.0 mmol) was added. The reaction mixture was warmed to −15 °C, before being quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 3:2) gave **34** (1.07 g, 53%) as a yellow solid. mp = 60−62 °C. IR (film): 3062, 2996, 1772, 1682, 1583, 1487, 1463, 1387, 1354, 1090, 1027, 962, 905, 771, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.31 (m, 4 H), 7.20−7.14 (m, 1 H), 4.45 (s, 3 H), 2.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.1, 188.6, 168.0, 156.5, 145.5, 128.6, 128.4, 126.1, 123.5, 60.3, 8.6. HRMS m/z $C_{12}H_{11}NO_2$ (M^+). Calcd: 201.0790. Found: 201.0799.

(2*R*,3*R*)-3-[(1E,3E)-(tert-Butyldimethylsilanyloxy)methylpenta-1,3-dienyl]-7-methoxy-2,3,8-trimethyl-4-triisopropylsilanyloxy-2,3-dihydronaphtho[1,2-*b*]furan-6,9-dione (46). *n*-BuLi (197 μL, 0.315 mmol, 1.6 M in hexanes) was added at −78 °C to a solution of aryl bromide **44** (183 mg, 0.300 mmol) in THF (3 mL). After stirring for 30 min, a solution of imine **34** (91 mg, 0.450 mmol) in THF (3 mL) was added dropwise at −78 °C. After stirring for 60 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), extracted with ether (3 × 25 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the crude imine. The crude product is dissolved in THF (20 mL); a solution of oxalic acid (100 mg) in H_2O (5 mL) is added. The reaction mixture was stirred for 10 min before being quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 4:1 → 2:1) afforded **45** (98 mg, 50%) as a colorless oil.

A solution of **45** (98 mg, 0.149 mmol) in toluene (5 mL) was heated to 110 °C for 3.5 h. After cooling to room temperature the reaction mixture was stirred in air for an additional 2 h. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 10:1 → 4:1) afforded **46** (62 mg, 64%) as a yellow foam. $[\alpha]^{24}_D$ −24.6° (*c* 0.66, CH_2Cl_2). IR (film): 2949, 2868, 1666, 1651, 1619, 1589, 1463, 1413, 1392, 1295, 1257, 1204, 1167, 1112, 1089, 1064, 1018, 882, 838, 776, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.08 (s, 1 H), 6.08−5.99 (2 H, m), 5.58−5.51 (m, 1 H), 4.62 (q, J = 6.6 Hz, 1 H), 4.04 (s, 3 H), 4.02 (s, 2 H), 2.06 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.39 (d, J = 6.6 Hz, 3 H), 1.35 (sept, J = 7.3 Hz, 3 H), 1.09 (d, J = 7.3 Hz, 9 H), 1.08 (d, J = 7.3 Hz, 9 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.9, 180.9, 161.2, 157.2, 156.7, 136.9, 133.5, 133.4, 132.3, 130.3, 126.4, 122.8, 110.9, 109.7, 91.9, 67.8, 60.7, 49.0, 25.9, 22.3, 18.4, 17.95, 17.9, 15.6, 13.8, 13.1, 9.3, −5.4. HRMS m/z $C_{37}H_{58}O_6Si_2$ (M^+). Calcd: 654.3772. Found: 654.3774.

Furaquinocin E (5). To a suspension of dried 4-Å molecular sieves (20 mg) and quinone **46** (12.6 mg, 0.019 mmol) in THF (2 mL) is added TBAF (115 μL, 0.115 mmol, 1M in THF) and the reaction mixture was stirred at 0 °C for 30 min. Then a ph 7.4 buffer solution (2 mL) was added, the mixture extracted with ether (3 × 10 mL), and the combined organic layers dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by flash chromatography (SiO_2, $CHCl_3$/MeOH 98:2) afforded **5** (4.8 mg, 65%) as a bright yellow solid. mp = 183−185 °C (lit. mp 184−186 °C). $[\alpha]^{24}_D$ −76.5° [*c* 0.22, MeOH] (lit. $[\alpha]^{18}_D$ −79° [*c* 0.26, MeOH]). IR (film): 3312, 2924, 2853, 1667, 1637, 1628, 1574, 1433, 1410, 1383, 1293, 1261, 1203, 1162, 1112, 1080, 1052, 1012, 742 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 7.08 (s, 1 H), 6.09−6.03 (m, 2 H), 5.63−5.57 (m, 1 H), 4.57 (q, J = 6.5 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 2 H), 2.00 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.36 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (126 MHz, CD_3OD) δ: 185.4, 182.0, 162.5, 160.6, 158.4, 138.2, 135.0, 134.0, 133.8, 127.5, 127.4, 125.3, 109.8, 109.6, 93.1, 68.4, 61.1, 50.2, 22.5, 15.5, 14.1, 9.3. The analytic data match the data reported for the natural product.[1d]

(*R*)-1-((2*R*,3*S*)-2,3-Dimethyl-4-triisopropylsilanyloxy-2,3-dihydrobenzofuran-3-yl)but-3-en-1-ol (59). DIBAL-H (8.40 mL, 8.40 mmol, 1 M in CH_2Cl_2) was added dropwise to a solution of nitrile **41** (2.03 g, 4.80 mmol) in CH_2Cl_2 (150 mL) at −78 °C. Stirring was continued for 60 min at this temperature and then the reaction quenched by addition of ethyl acetate. After being warmed to room temperature, saturated aqueous NH_4Cl (20 mL) was added. The reaction mixture was diluted with a saturated solution of potassium sodium tartrate (100 mL) and ether (100 mL) and stirred for 1 h. Extraction with ether (3 × 50 mL), drying over $MgSO_4$, filtration, evaporation of the solvents under reduced pressure, and filtration through a plug of silica gel (petroleum ether/ether 20:1) gave the crude aldehyde **58**, which was directly used in the next reaction. $TiCl_4$ (2.40 mL, 4.80 mmol, 2 M in CH_2Cl_2) was added at room temperature to a solution of the crude aldehyde **58** in CH_2Cl_2 (50 mL). After stirring for 5 min, allyltrimethylsilane (1.15 mL, 7.20 mmol) was added. Stirring is continued at room temperature for an additional 5 min. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 10:1) afforded **59** (1.50 g, 67%) as a colorless oil. Diastereomeric ratio: 9:1 (determined by integration of ^{1}H NMR of the crude product, *q* at 4.42 and 4.48 ppm). Major diastereomer in the allylation: $[\alpha]^{25}_D$ +35.0° [*c* 3.57, CH_2Cl_2]. IR (film): 3568, 2946, 2869, 1590, 1477, 1419, 1386, 1283, 1224, 1079, 1045, 1016, 993, 917, 883, 830, 787, 689 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10 (d, J = 8.8 Hz, 1H), 6.24 (d, J = 8.8 Hz, 1 H), 5.80−5.64 (m, 1 H), 5.08−4.98 (m, 2 H), 4.42 (q, J = 6.8 Hz, 1 H), 3.84−3.76 (m, 1 H), 2.34−2.20 (m, 2 H), 1.63 (d, J = 6.8 Hz, 3 H), 1.48 (s, 3 H), 1.32 (sept, J = 6.8 Hz, 3 H), 1.11 (d, J = 7.3 Hz, 9 H), 1.10 (d, J = 7.3 Hz, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.3, 153.1, 135.8, 131.8, 121.2, 117.9, 112.6, 94.6, 89.9, 74.5, 52.8, 37.8, 20.7, 18.0, 14.1, 13.4. Anal. Calcd for $C_{23}H_{37}BrO_3Si$: C, 58.83; H, 7.94. Found: C, 59.04; H, 7.55. Minor diastereomer in the allylation: $[\alpha]^{25}_D$ +0.3° [*c* 4.56, CH_2Cl_2]. IR (film): 3528, 2947, 2870, 1641, 1586, 1476, 1418, 1386, 1279, 1266, 1224, 1178, 1079, 1053, 1018, 918, 883, 846, 829, 800, 752, 689 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10 (d, J = 8.8 Hz, 1 H), 6.27 (d, J = 8.8 Hz, 1 H), 5.89−5.74 (m, 1 H), 5.04−4.94 (m, 2 H), 4.48 (q, J = 6.8 Hz, 1 H), 3.64−3.55 (m, 1 H), 2.42 (d, J = 9.1 Hz, 1 H), 2.24 (d, J = 9.1, 6.1 Hz, 1 H), 1.54 (s, 3 H), 1.48 (d, J = 6.8 Hz, 3 H), 1.33 (sept, J = 6.8 Hz, 3 H), 1.12 (d, J = 7.3 Hz, 9 H), 1.10 (d, J = 7.3 Hz, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 152.7, 136.6, 131.8, 122.0, 116.8, 112.5, 95.1, 89.3, 74.9, 53.5, 39.2, 20.8, 18.0, 17.9, 13.8, 13.3.

Acetic Acid (*R*)-(*E*)-1-((2*R*,3*R*)-7-Bromo-2,3-dimethyl-4-triisopropylsilanyloxy-2,3-dihydrobenzofuran-3-yl)-4-methyl-5-oxopent-3-enyl Ester (62). Ruthenium complex **61** (9.2 mg, 0.011 mmol, 10 mol %) was added to a solution of olefin **60** (60.6 mg, 0.110 mmol) and methacrolein (91 μL, 1.1 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was heated at reflux for 5 h and then quenched by addition of ethyl vinyl ether. Evaporation of the solvents under reduced pressure and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 10:1 to 4:1) afforded **62** (54.0 mg, 89%) as a colorless solid. mp = 117−119 °C. $[\alpha]^{23}_D$ −84.4° [*c* 0.54, CH_2Cl_2]. IR (film): 2947, 2869, 2713, 1746, 1693, 1646, 1585, 1479, 1419, 1386, 1372, 1284, 1226, 1150, 1082, 1047, 1024, 922, 882, 827, 793, 751, 715 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.14 (s, 1 H), 7.11 (d, J = 8.8 Hz, 1 H), 6.25 (d, J = 8.8 Hz, 1 H), 6.08−6.03 (m, 1 H), 5.49 (dd, J = 8.0, 6.5 Hz, 1 H), 4.48 (q, J = 7.1 Hz, 1 H), 2.74−2.66 (m, 1 H), 2.62−2.54 (m, 1 H), 2.06 (s, 3 H), 1.73 (d, J = 7.1 Hz, 3 H), 1.58 (s, 3 H), 1.49 (s, 3 H), 1.35 (sept, J = 7.4 Hz, 3 H), 1.14 (d, J = 7.4 Hz, 9 H), 1.13 (d, J = 7.4 Hz, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 194.7, 170.2, 158.0, 153.2, 149.2, 139.8, 132.6, 121.2, 112.6, 94.6, 88.9, 74.9, 51.7, 31.3, 21.8, 20.9, 18.0, 17.9, 14.9, 13.3, 9.2. HRMS *m/z* $C_{27}H_{41}BrO_5Si$ (M^+). Calcd: 552.1907. Found: 552.1900. Anal. Calcd for $C_{27}H_{41}BrO_5Si$: C, 58.58; H, 7.46. Found: C, 58.70; H, 7.53.

(2*R*,3*R*)-3-[(*R*)-(*E*)-Bis(tert-butyldimethylsilanyloxy)methylpent-3-enyl]-7-methoxy-2,3,8-trimethyl-4-triisopropylsilanyloxy-2,3-dihydronaphtho[1,2-*b*]furan-6,9-dione (66). *n*-Butyllithium (142 μL, 0.200 mmol, 1.4 M in hexanes) was added at −78 °C to a solution of aryl bromide **64** (148.4 mg, 0.200 mmol) in THF (2 mL). After stirring for 5 min, a solution of **34** (60.0 mg, 0.300 mmol) in THF (2 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (3 × 10 mL). After drying of the combined organic layers over $MgSO_4$ and filtration, evaporation of the solvents in vacuo afforded the crude imine. The crude product was dissolved in THF (10 mL) and a solution of oxalic acid (80 mg) in water (4 mL) was added. The reaction mixture was stirred for 10 min before being quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 4:1 → 2:1) afforded **65** (89.0 mg, 56%) as a colorless oil.

A solution of **65** (38.7 mg, 0.049 mmol) in toluene (2 mL) was heated to 120 °C for 2 h. After cooling to room temperature, the reaction mixture was stirred in air overnight. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 4:1) afforded **66** (26.9 mg, 70%) as a yellow foam. $[\alpha]^{24}_D$ −39.1° [*c* 1.65, CH_2Cl_2]. IR (film): 2929, 2857, 1667, 1652, 1622, 1589, 1463, 1415, 1392, 1292, 1255, 1204, 1174, 1099, 1056, 882, 836, 775, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (s, 1 H), 5.03 (t, J = 6.5 Hz, 1 H), 4.56 (q, J = 7.0 Hz, 1 H), 4.13 (dd, J = 6.5, 5.0 Hz, 1 H), 4.03 (s, 3 H), 3.76−3.67 (m, 2 H), 2.40−2.31 (m, 1 H), 2.26−2.17 (m, 1 H), 2.05 (s, 3 H), 1.81 (d, J = 7.0 Hz, 3 H), 1.54 (s, 3 H), 1.43 (sept, J = 7.3 Hz, 3 H), 1.32 (s, 3 H), 1.17 (d, J = 7.3 Hz, 9 H), 1.16 (d, J = 7.3 Hz, 9 H), 0.90 (s, 9 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.02 (s, 3 H), −0.03 (s, 3 H), −0.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.7, 180.8, 161.9, 157.0, 156.6, 134.7, 133.5, 133.4, 130.0, 122.8, 110.6, 109.7, 91.4, 76.8, 68.3, 60.7, 51.3, 33.0, 29.7, 26.0, 25.9, 23.9, 18.3, 18.2, 18.1, 18.0, 15.9, 13.3, 9.3, −3.9, −4.0, −5.5. Anal. Calcd for $C_{43}H_{74}O_7Si_3$: C, 65.60; H, 9.47. Found: C, 65.47; H, 9.29.

Furaquinocin B (2). HF (48 wt % in water, 0.5 mL) was added to a solution of **66** (33.0 mg, 0.0420 mmol) in acetonitrile (3 mL). After stirring for 14 h at room temperature, additional HF (48 wt % in water, 0.3 mL) was added and stirring was continued for 6 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by preparative thin-layer chromatography (SiO_2, $CHCl_3$/MeOH 20:1) afforded **2** (10.2 mg, 61%) as a bright yellow solid. mp = 102−104 °C (lit. mp 101−104 °C). $[\alpha]^{25}_D$ −133.6° [*c* 0.33, $CHCl_3$] (lit. $[\alpha]^{19}_D$ −132° [*c* 0.57, $CHCl_3$]). IR (film): 3374, 2925, 2859, 1666, 1641, 1582, 1433, 1408, 1302, 1277, 1202, 1168, 1111, 1071, 1021, 985, 897, 772, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (s, 1 H), 5.56−5.49 (m, 1 H), 4.70 (q, J = 6.4 Hz, 1 H), 4.10 (s, 2 H), 4.07 (d, J = 1.2 Hz, 1 H), 4.01 (s, 3H), 2.63−2.53 (m, 1 H), 2.23−2.17 (m, 1 H), 2.05 (s, 3 H), 1.74 (s, 3 H), 1.37 (s, 3 H), 1.32 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.6, 180.7, 160.4, 158.4, 156.9, 140.1, 134.1, 133.7, 124.4, 119.9, 110.7, 109.2, 88.8, 73.0, 67.9, 60.7, 52.3, 31.8, 18.9, 16.1, 14.3, 9.3. The analytic data match the data reported for the natural product.[1d]

(*R*)-6-((2*R*,3*R*)-7-Bromo-2,3-dimethyl-4-triisopropylsilanyloxy-2,3-dihydrobenzofuran-3-yl)-3-methyl-5,6-dihydropyran-2-one (68). Ruthenium complex **61** (47 mg, 0.056 mmol, 5 mol %) was added to a solution of methacrylate **67** (600 mg, 1.12 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was heated at reflux for 16 h and then quenched by addition of ethyl vinyl ether. Evaporation of the solvents under reduced pressure and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 20:1) afforded **68** (413 mg, 66%) as a colorless oil. $[\alpha]^{25}_D$ +29.3° [*c* 0.49, CH_2Cl_2]. IR (film): 2946, 2869, 1728, 1586, 1478, 1418, 1387, 1281, 1243, 1224, 1126, 1082,

1046, 1021, 883, 831, 744, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J = 8.8 Hz, 1 H), 6.48−6.43 (m, 1 H), 6.25 (d, J = 8.8 Hz, 1 H), 4.69 (dd, J = 13.9, 4.0 Hz, 1 H), 4.53 (q, J = 7.0 Hz, 1 H), 2.78−2.68 (m, 1 H), 1.90 (s, 3 H), 1.87−1.78 (m, 1 H), 1.67 (d, J = 7.0 Hz, 3 H), 1.66 (s, 3 H), 1.32 (sept, J = 7.4 Hz, 3 H), 1.10 (d, J = 7.4 Hz, 9 H), 1.09 (d, J = 7.4 Hz, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 157.9, 152.9, 139.3, 132.4, 128.0, 121.0, 112.5, 94.5, 89.1, 79.9, 51.0, 25.8, 21.8, 18.0, 17.1, 15.4, 13.3. HRMS m/z $C_{25}H_{37}BrO_4Si$ (M^+). Calcd: 508.1644. Found: 508.1641. Anal. Calcd for $C_{25}H_{37}BrO_4Si$: C, 58.93; H, 7.32. Found: C, 58.85; H, 7.44.

(2*R*,3*R*)-3-[(*R*)-(*E*)-Bis(tert-butyldimethylsilanyloxy)methylpent-3-enyl]-7-methoxy-2,3,8-trimethyl-4-triisopropylsilanyloxy-2,3-dihydronaphtho[1,2-*b*]furan-6,9-dione (72). *n*-Butyllithium (71 μL, 0.10 mmol, 1.4 M in hexanes) was added at −78 °C to a solution of aryl bromide **70** (74.2 mg, 0.100 mmol) in THF (1 mL). After stirring for 5 min a solution of **6** (30.0 mg, 0.15 mmol) in THF (1 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Evaporation of the solvents under reduced pressure afforded the crude imine. The crude product was dissolved in THF (5 mL) and a solution of oxalic acid (40 mg) in water (2 mL) was added. The reaction mixture was stirred for 10 min before being quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 4:1) afforded **71** (46.5 mg, 59%) as a colorless oil.

A solution of **71** (46.5 mg, 0.0590 mmol) in toluene (2 mL) was heated to 120 °C for 2 h. After cooling to room temperature the reaction mixture was stirred in air for 2 h. Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (SiO_2, petroleum ether/ether 10:1) afforded **72** (37.8 mg, 81%) as a yellow foam. $[\alpha]^{24}_D$ −26.2° [*c* 1.01, CH_2Cl_2]. IR (film): 2929, 2857, 1667, 1652, 1622, 1589, 1463, 1414, 1392, 1292, 1252, 1204, 1181, 1098, 1076, 1056, 1024, 882, 836, 776, 744 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.05 (s, 1 H), 4.78 (t, J = 6.6 Hz, 1 H), 4.56 (q, J = 7.1 Hz, 1 H), 4.08 (7, J = 5.8 Hz, 1 H), 4.02 (s, 3 H), 3.93 (d, J = 11.8 Hz, 1 H), 3.62 (d, J = 11.8 Hz, 1 H), 2.40−2.33 (m, 1 H), 2.31−2.23 (m, 1 H), 2.05 (s, 3 H), 1.79 (d, J = 7.1 Hz, 3 H), 1.53 (s, 3 H), 1.45 (s, 3 H), 1.43 (sept, J = 7.3 Hz, 3 H), 1.18 (d, J = 7.3 Hz, 9 H), 1.17 (d, J = 7.3 Hz, 9 H), 0.91 (s, 9 H), 0.82 (s, 9 H), 0.09 (s, 3 H), 0.03 (s, 3 H), −0.05 (s, 3 H), −0.06 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 183.5, 180.7, 161.9, 157.1, 156.6, 134.8, 133.6, 133.4, 129.7, 124.5, 110.6, 109.7, 91.3, 76.8, 61.6, 60.7, 51.1, 33.3, 25.9, 25.8, 24.0, 21.1, 18.3, 18.1, 18.0, 15.9, 13.3, 9.2, −4.0, −4.1, −5.4, −5.5. Anal. Calcd for $C_{43}H_{74}O_7Si_3$: C, 65.60; H, 9.47. Found: C, 65.31; H, 9.35.

Furaquinocin A (1). HF (48 wt % in water, 0.5 mL) was added to a solution of **72** (32.1 mg, 0.0410 mmol) in acetonitrile (3 mL). After stirring for 14 h at room temperature, additional HF (48 wt % in water, 0.3 mL) was added and stirring was continued for 6 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases layers were dried over $MgSO_4$ and then evaporated in vacuo. Purification of the residue by flash chromatography (SiO_2, $CHCl_3$/MeOH 50:1) afforded **1** (11.5 mg, 70%) as a bright yellow solid. Mp = 181−183 °C (lit. mp 182−183 °C). $[\alpha]^{25}_D$ −46.9° [*c* 0.36, $CHCl_3$] (lit. $[\alpha]^{19}_D$ −46.7° [*c* 0.58, $CHCl_3$]). IR (film): 3402, 2924, 2850, 1668, 1636, 1582, 1433, 1408, 1433, 1408, 1297, 1278, 1198, 1168, 1111, 1026, 999, 899, 772, 732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.15 (s, 1 H), 5.54−5.50 (m, 1 H), 4.69 (q, J = 6.4 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.01 (d, J = 11.3 Hz, 1 H), 4.00 (s, 3 H), 3.95 (dd, J = 9.5, 1.1 Hz, 1 H), 2.65−2.57 (m, 1 H), 2.14 (dd, J = 15.8, 6.0 Hz, 1 H), 2.05 (s, 3 H), 1.88 (s, 3 H), 1.32 (s, 3 H), 1.31 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 183.7, 180.8, 160.5, 158.8, 156.9, 138.1, 134.0, 133.6, 125.1, 124.8, 111.0, 108.9, 88.8, 71.2, 61.5, 60.6, 52.7, 32.5, 23.4, 18.9, 16.1, 9.3. The analytic data match the data reported for the natural product.[1d]

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Supporting Information Available: Full experimental details and characterization data for compounds **28**−**30**, **35**−**41**, **43**, **44**, **48, 49**, **52, 53**, **56, 57**, **60**, **63**, **64**, **67**, **69**, **and 70**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic (CIF) data for **32** can be found in the supporting information of ref 5.

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