Total Synthesis of (−)-Furaquinocin C

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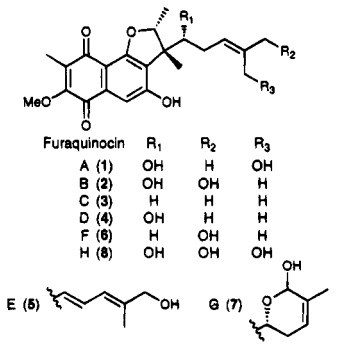
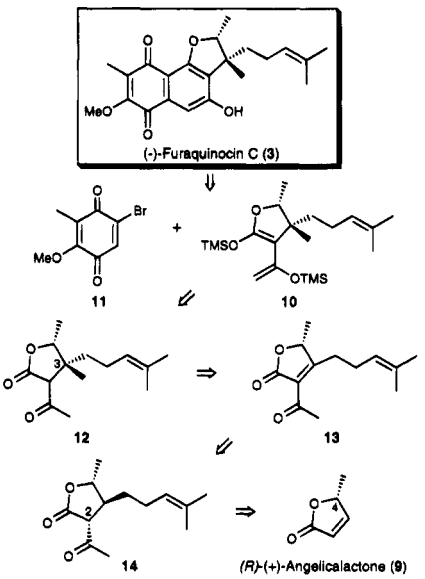
The furaquinocins (A−H, **1**−**8**), isolated by Ōmura and co-workers[1] at the Kitasato Institute (Tokyo) from the fermentation broth of *Streptomyces* sp. KO-3988, manifest wide-ranging biological effects, including in vitro cytotoxicity against $HeLaS_3$ cells,[2] antihypertensive activity, and inhibition of platelet aggregation and coagulation.[3] In 1992, as a prelude to total



synthesis, we collaborated with Ōmura in the assignment of complete relative and absolute stereochemistries for the furaquinocins, employing Mosher NMR analysis and chemical correlation in conjunction with X-ray crystallography.[4] Herein we report the first total synthesis of (−)-furaquinocin C (**3**).[5] The successful strategy proved highly concise, requiring only six steps from (*R*)-(+)-angelicalactone (**9**).

From the retrosynthetic perspective, we envisioned an efficient construction of the natural product via regioselective[6,7] Diels−Alder reaction of the bis(silyl enol ether) **10** with bromoquinone **11**[6] (Scheme 1). Although the synthetic utility of the original Danishefsky diene and its progeny is now well established,[8] few examples have incorporated cyclic olefins

Scheme 1



within the diene moiety. As demonstrated herein, the latter synthons hold considerable promise for the construction of polycyclic natural and unnatural products.

Lactone **12**, the precursor to diene **10**, would in turn derive from **9** via a series of conjugate additions, exploiting the C(4) methyl group as the stereochemical control element for creation of the C(3) quaternary center. To circumvent the low reactivity of β-substituted α,β-unsaturated lactones toward cuprates,[9] we planned to incorporate the C(2) acetyl moiety prior to the second conjugate addition. Considerable precedent[10] indicated that this scenario would require introduction of the C(3) unsaturated side chain first, followed by conversion to α,β-unsaturated acetyl lactone **13** and conjugate addition of the C(3) methyl group. Bis(enol silyl ether) generation would then furnish **10**.

As our point of departure, addition of the cuprate derived from 5-iodo-2-methyl-2-pentene[11] [*t*-BuLi, CuI(P-*n*-Bu_3)$_2$] to **9**, prepared from D-ribonolactone,[12] and enolate trapping with acetyl chloride and HMPA afforded lactone (+)-**14** and enol acetate (+)-**15** in 68% and 16% yields, respectively (Scheme 2). Treatment of the mixture (or purified **15**) with 0.5 M methanolic KOH (6 h, room temperature) effected enol acetate hydrolysis, increasing the yield of **14** to 81%. Lactone **14** was formed as a single diasteroisomer, within the limits of NMR detection; the assignment of relative stereochemistry derived from the coupling constants between the β and γ protons[13] as well as nuclear Overhauser experiments.

Unsaturated lactone **13**, the substrate for the second conjugate addition, was readily obtained by treatment of **14** with NaH and PhSe(O)Cl.[14,15] Without purification, **13** was added to an

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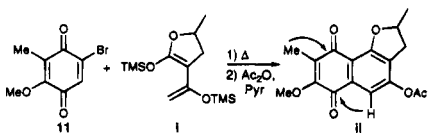
(4) Dormer, P. G.; Smith, A. B., III; Funayama, S.; Ōmura, S. *Tetrahedron Lett.* **1992**, *33*, 1717.

(5) Professor K. Suzuki and co-workers, Keio University (Yokohama, Japan), have completed a total synthesis of furaquinocin D. We thank Prof. Suzuki for informing us of his work prior to publication. See the following communication in this issue (Saito, T.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 10757).

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

(7) We modeled the proposed Diels−Alder reaction with bromoquinone **11** and diene **i**, prepared from the corresponding acetyl butenolide. 2D-NMR experiments revealed the adduct regiochemistry shown in **ii**.



Long-range ^1H-^{13}C correlations observed in an HMBC experiment are indicated by arrows.

(8) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996. (c) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. (d) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392. (e) Danishefsky, S.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2455.

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(12) Chen, S. Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2186.

(13) Jaime, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946.

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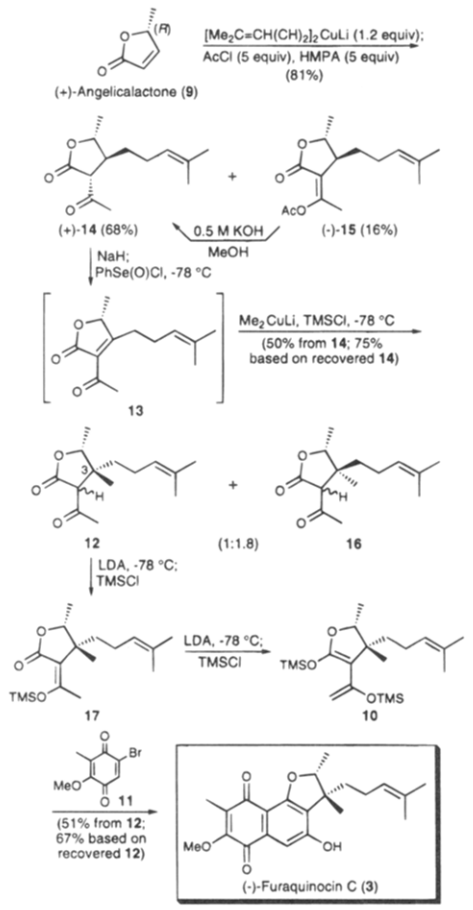
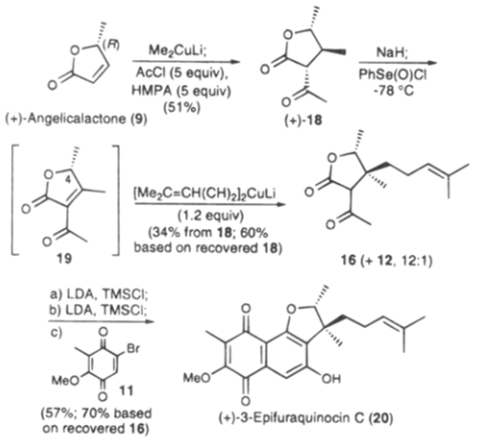
Scheme 2



ethereal solution of Me_2CuLi and TMSCl (1:1) at −78 °C; lactone **12** and its C(3) epimer **16** were isolated as chromatographically separable mixtures, each consisting of the corresponding C(2) acetyl epimers and an enol lactone tautomer (ca. 3:1:1 and 1:1:1, respectively). Upon silylation with NaH and TBSCl, each mixture furnished a single TBS enol ether; the latter species differed only in the relative stereochemistry at C(3), which was assigned via nuclear Overhauser experiments. The diastereoselectivity (i.e., the **12**:**16** ratio) proved to be 1:1.8; surprisingly, conjugate addition syn to the C(4) methyl substituent predominated. A variety of related organometallics including methylcopper, heterocuprates, and higher-order cuprates, in the absence or presence of Lewis acids, all afforded similar selectivities.

Scheme 3



To further investigate the unexpected stereochemical outcome, we inverted the order of the cuprate additions (Scheme 3); as anticipated,[10] the ratio of **16** to **12** increased to 12:1. A plausible rationale for these results derives from the ground-state conformation of lactone **13**. A Monte Carlo simulation with the MM2 force field generated a lowest-energy conformer wherein the C(7) methylene group is oriented anti to the methyl substituent at C(4) (Figure 1); an unfavorable transition-state interaction of the methylene with the cuprate would inhibit the formation of **12**. When the order of conjugate addition is reversed, the intermediate enone **19** lacks the C(7) methylene, and reaction occurs anti to the C(4) methyl with good diastereoselectivity.

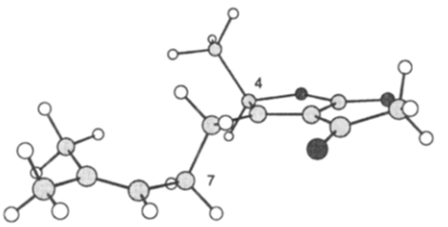


Figure 1. Monte Carlo lowest-energy conformation for enone **13**, computed with the MM2 force field ($CHCl_3$).

With **12** and **16** in hand, we turned to the critical Diels−Alder cycloaddition. Following the stepwise one-flask conversion of **12** to the enol silyl ether **17** and then to the bis(silyl ether) **10** (LDA, TMSCl; Scheme 2), partial concentration in vacuo and reaction with bromoquinone **11** (room temperature, 6 h) furnished (−)-furaquinocin C (**3**) in 51% yield after flash chromatography (67% based on recovered **12**). Synthetic **3** was identical in all respects (mp, mmp, ^1H and ^{13}C NMR, IR, HRMS, optical rotation, and TLC with three solvent systems) with a sample of the natural product.[16] An analogous sequence (Scheme 3) transformed **16** to a new congener, (+)-3-epifuraquinocin C (**20**), in 54% yield (70% based on recovered starting material). The latter structure was confirmed via single-crystal X-ray analysis.[17]

In summary, we have developed a concise Diels−Alder approach to the furaquinocin family of cytotoxic antibiotics, exemplified by a six-step construction of (−)-furaquinocin C from *(R)*-(+)-angelicalactone. The total synthesis of furaquinocin C confirms our earlier assignments of relative and absolute stereochemistry for the furaquinocins and also constitutes a formal synthesis of (−)-furaquinocin F.[4]

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Supporting Information Available: Spectroscopic and analytical data for **3**, **12**, **14**, **15**, **16**, and **20**, as well as selected experimental procedures (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) The epimeric selenoxide, incapable of syn elimination, was also formed and was subsequently converted to **14** and recovered (~30%) upon treatment of the mixture with Me_2CuLi.

(16) We thank Prof. Ōmura for a generous sample of authentic (−)-furaquinocin C.

(17) Carroll, P. J., University of Pennsylvania, unpublished results.