Stereocontrolled Convergent Total Synthesis of (±)-Furaquinocin D

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Received July 18, 1995

The furaquinocins constitute a novel class of cytocidal antibiotics isolated from the fermentation broth of *Streptomyces* sp. KO-3988 by Ōmura *et al.*[1] The relative and absolute stereochemistry was established by the collaboration of Smith and Ōmura.[2] The structure of these compounds comprises two biosynthetically distinct moieties, i.e., the polyketide-derived naphthoquinone and an isoprenoid side chain,[1c] which pose synthetic challenges including (a) stereocontrol of three contiguous stereogenic centers at C-2, C-3 (*quaternary*), and C-10, (b) selective construction of the densely functionalized naphthoquinone, and (c) establishment of the sterically congested aromatic−isoprenoid hybrid structure.

Our synthetic plan (Figure 1) relied on an annulation to form the central ring from synthons **I** and **II**. We expected that **III** and **IV** would serve as their equivalents. The present communication describes the successful implementation of this strategy in the first total synthesis of furaquinocin D (**1d**).[3]

The synthesis started with the reductive 1,2-rearrangement shown in Scheme 1.[4,5] Epoxy silyl ether **2**[6] was treated with BF_3·OEt_2 (3 equiv) in the presence of Et_3SiH (5 equiv/CH_2Cl_2, −78 °C to 20 °C, 3 h) to effect 1,2-migration of the alkynyl group,[7] followed by the in situ reduction of the resulting aldol to give 1,3-diol **3** as the sole detectable isomer.[8] The success of this process was particularly gratifying for two reasons. First, the alkynyl group, usually ranked as a poor migrating group in 1,2-anionotropic rearrangements,[7] underwent a clean 1,2-shift. Second, the in situ reduction proceeded with high stereoselectivity to establish the desired C-2−C-3 stereochemical relationship.[9] Deprotection of the alkynyl group, followed by selective silylation of the primary hydroxyl, gave alcohol **4**, ready for coupling with the aromatic component.

The coupling partner, hexasubstituted benzene **7**, was prepared from the known phenol **5**[10] (Scheme 2).[5] After regioselective hydroxymethylation of **5**,[11] selective protection of the phenol, followed by Ag(I)-assisted iodination, gave alcohol **6**.[12] The aldehyde, derived from **6** by PDC oxidation, was treated with diethyl 2-lithio-1,3-dithian-2-ylphosphonate,[13] and the

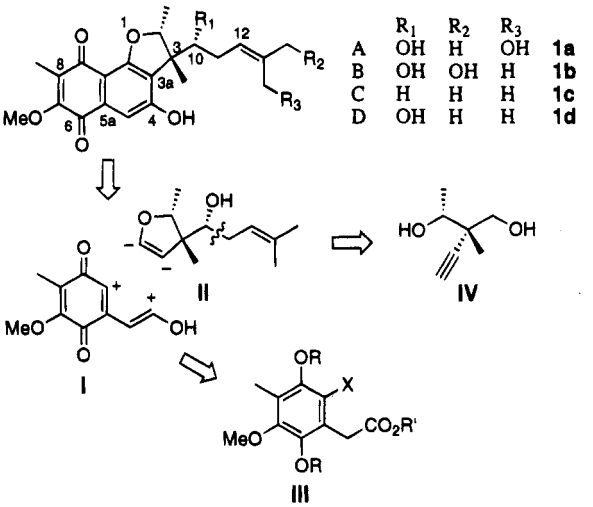
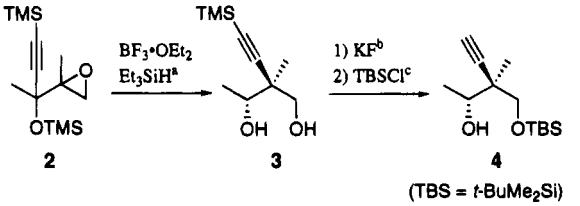


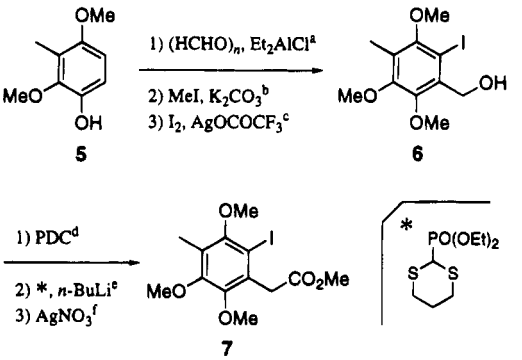
Figure 1. The furaquinocins.[1e]

Scheme 1



[a] CH_2Cl_2, −78 °C → 20 °C, 60%. [b] MeOH, 50 °C, 89%. [c] Imidazole, DMF, 98%.

Scheme 2



[a] CH_2Cl_2, 89%. [b] Acetone, reflux, quantitative. [c] $CHCl_3$, 82%. [d] Pyridine, CH_2Cl_2, 86%. [e] THF, −78 °C → 20 °C. [f] MeOH, reflux, 94% (two steps).

(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. (e) For the structures of additional congeners, furaquinocin E−H, see ref 1d.

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

(3) We learned that Prof. A. B. Smith, III, University of Pennsylvania, has achieved the total synthesis of furaquinocin C. We thank Prof. Smith for providing the information prior to publication. See the preceding communication in this issue (Smith, A. B., III; et al. *J. Am. Chem. Soc.* **1995**, *117*, 10755).

(4) For the stereospecific synthesis of α,α-disubstituted aldols via epoxy silyl ether (epoxy alcohol) rearrangements, see: Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891. For leading references and reviews, see: (a) Suzuki, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 365. (b) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (c) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515. (d) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron* **1988**, *44*, 4061.

(5) All new compounds were fully characterized by spectroscopic means (^1H and ^{13}C NMR, IR), high-resolution MS, and/or combustion analysis.

(6) Prepared from 3-methyl-3-buten-2-one in three steps: (a) LiC≡CTMS, THF (64%); (b) TBHP, $VO(acac)_2/CH_2Cl_2$ (79%); (c) TMSCl, imidazole/DMF (93%). Epoxide **2** was a mixture of diastereomers (1.5:1), both of which proved to take part in the 1,2-rearrangement.

(7) For poor migratory aptitudes of alkynyl groups in 1,2-anionotropic rearrangements, see: Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348. Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 373. Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765. For a theoretical explanation, see: Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112.

(8) The structure of **3** was confirmed by single X-ray crystallographic analysis, kindly performed by Drs. T. Tsuji and K. Ishikawa, Ajinomoto Co. See supporting information.

(9) The origin of the stereoselectivity is currently under study. For a stereochemical study on the Lewis acid-promoted addition to β-oxycarbonyl compounds, see: Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

(10) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745.

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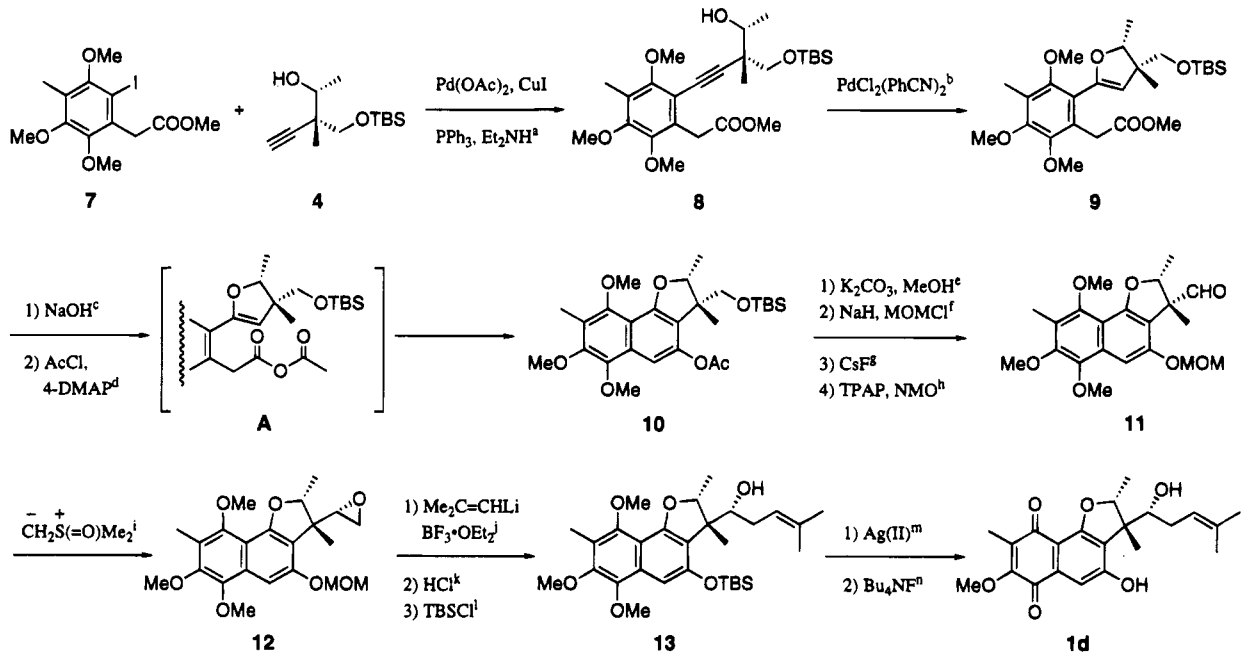
Scheme 3



[a] DMSO, 80 °C, 88%. [b] MeCN, 60 °C, 91%. [c] MeOH, H_2O, 60 °C. [d] Toluene, 100 °C, 96%. [e] 20 °C. [f] THF, −78 °C → 20 °C, 81% (from **10**). [g] DMF, 120 °C, 94%. [h] Molecular sieves 4 Å, CH_2Cl_2, CH_3CN, 86%. [i] DMSO, 72%. [j] THF, −78 °C, 70%. [k] MeOH, 60 °C. [l] Imidazole/DMF, 71% (two steps). [m] Benzene, H_2O. [n] THF, 33% (from **13**).

resulting ketene dithioacetal was subjected to solvolysis in methanol to give ester **7** in 59% overall yield from **5**.

Union of alkyne **4** with aryl iodide **7** was cleanly effected by Sonogashira reaction[14] to give alkyne **8** in 88% yield (Scheme 3). Cyclization of the hydroxyl group in **8** onto the internal alkyne was achieved by Pd(II) catalysis to yield dihydrofuran **9**.[15] The next step, construction of the naphthofuran skeleton, was one of the crucial steps in the overall synthetic plan. Considerable experimentation led to the following efficient protocol. After alkaline hydrolysis of methyl ester **9**, the resulting sodium carboxylate was extracted into chloroform.[16] After drying (K_2CO_3) and evaporation, the carboxylate was treated with acetyl chloride (3 equiv) and 4-DMAP (3 equiv), and the mixture was heated (toluene, 100 °C, 2 h) to give naphthyl acetate **10** in excellent yield. The reaction presumably proceeds via a mixed anhydride **A**, which undergoes attack by the dihydrofuran, followed by tautomerization and acetylation. An alternative explanation for the ring closure is the formation of a ketene from **A**, followed by elctrocyclization.[17] Several standard transformations led to aldehyde **11**,[18] which was treated with dimethyloxosulfonium methylide[19] (DMSO, 20 °C, 45 min) to give, gratifyingly, the desired epoxide **12** in high stereoselectivity (13:1).[20,21] After chromatographic separation, the major isomer **12** was subjected to the side chain elongation by the BF_3-promoted addition[22] of 2-methylpropen-1-yllithium, followed by oxidation with silver(II) dipicolinate[23] and removal of the silyl protecting group to afford the target, furaquinocin D (**1d**).[24]

In summary, a convergent stereoselective synthetic approach to furaquinocin D has been developed, which would have considerable promise in the syntheses of other congeners of the furaquinocins.

Acknowledgment. This work was financially supported by the Ministry of Education, Science and Culture of Japan (Grant-in-Aid for Scientific Research on a Priority Area No. 0523415).

Supporting Information Available: Experimental procedures for the key steps, complete physical and spectral data for compounds **1d**, **2**−**13**, and X-ray data for **3** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.
(16) The corresponding carboxylic acid proved to be highly unstable.
(17) We thank Prof. R. M. Coates, University of Illinois at Urbana−Champaign, for bringing this possibility to our attention and also for his kind correction of the manuscript.
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(20) Stereochemical assignment of the diastereomeric epoxides, **12** and its epimer, relies on the correlation to the natural product. While **12** was converted to **1d** as described, application of the same sequence of conversions to *epi*-**12** gave the final product obviously discernible from **1d** (see supporting information).
(21) The origin of the high stereoselectivity is currently under study. The selectivity of the corresponding reaction with dimethylsulfonium methylide (DMSO, 20 °C, 10 min) was substantially lower (2:1). For a well-known example of the stereochemical divergence in the methylenation of cyclic ketones by the sulfonium or the oxosulfonium ylides, see ref 19.
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(23) Syper, L.; Kloc, K.; Młochowski, J.; Szulc, Z. *Synthesis* **1979**, 521.
(24) Synthetic **1d**: Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.21; H, 7.08. Mp 184−186 °C (*lit.*[1d] mp 177−179 °C). We attribute the difference in the melting points to the racemic nature of the synthetic material. The spectroscopic data (^1H and ^{13}C NMR, IR, UV, and high-resolution MS) were fully identical with the natural product. We thank Prof. Omura, Kitasato Institute, for copies of ^1H NMR and IR spectra of **1d**.