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FURAQUINOCINS A-G: RELATIVE AND ABSOLUTE STEREOCHEMISTRY

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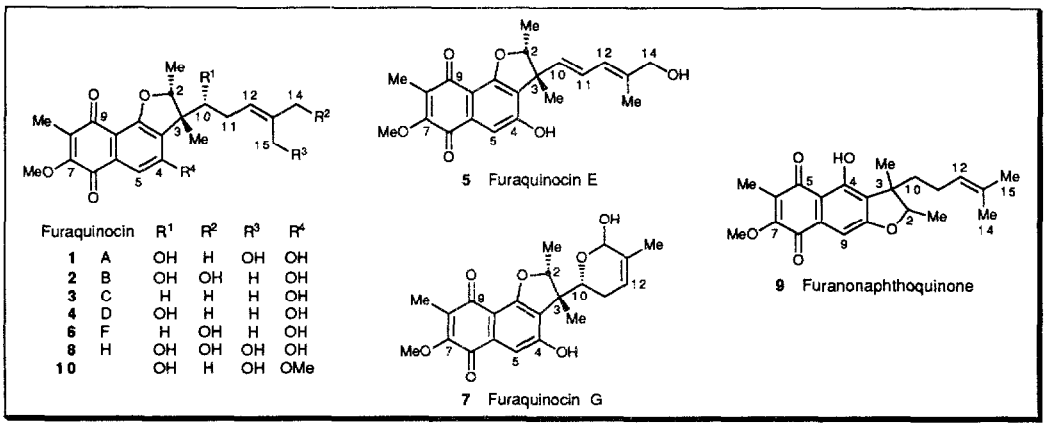
Summary: The complete relative and absolute stereochemistry of furaquinocins A-G, a family of cytotoxic antibiotics, have been assigned via a combination of X-ray crystallography, NMR analysis of the derived Mosher esters, and chemical correlation.

Komiyama et al. at the Kitasato Institute recently reported the isolation, physicochemical, and biological characteristics of furaquinocins A (**1**) and B (**2**).[1] These novel antibiotics, obtained from the fermentation broth of *Streptomyces sp.* KO-3988, exhibited strong *in vitro* cytotoxicity against HeLaS$_3$ cells at concentrations of 3.1 and 1.6 μg/mL, respectively.[1,2] Six additional congeners, furaquinocins C-H (**3-8**), were subsequently isolated from the same species.[3] More detailed biological evaluation then revealed that the furaquinocins also possess antihypertensive, anticoagulative, and antiplatelet activity.[4] A related furanonaphthoquinone (**9**) was very recently isolated from *Streptomyces cinnamonensis* ATCC 15413,[5] although no bioassay results have as yet been reported. Whereas the connectivities of the furaquinocins were deduced via extensive spectroscopic[2,3] and physicochemical analyses,[1,3] their stereostructures have remained unknown. As a prelude to total synthesis, we describe herein the complete relative and absolute stereochemistries of the furaquinocins.



Furaquinocin		R^1	R^2	R^3	R^4
1	A	OH	H	OH	OH
2	B	OH	OH	H	OH
3	C	H	H	H	OH
4	D	OH	H	H	OH
5	F	H	OH	H	OH
6	H	OH	OH	OH	OH
10		OH	H	OH	OMe

5 Furaquinocin E

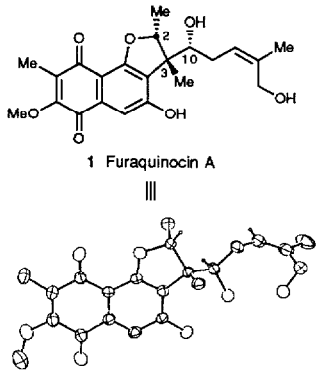
7 Furaquinocin G

9 Furanonaphthoquinone

Extensive decoupling and 2-D NMR experiments by Ōmura et al.[2] demonstrated that furaquinocins A and B differ only in the configurations of the trisubstituted olefin. In addition, the orientation of the C(2) and C(3) methyl groups was tentatively assigned as trans, based upon the observation of a 12% NOE between H(2) and the

C(3) methyl of *O*-methyl derivative **10**.[2] These conclusions, as well as the previously unassigned relative stereochemistry of the C(10) hydroxyl and C(3) methyl group, were unequivocally secured via single-crystal X-ray analysis of furaquinocin A (**1**) (plates from ethyl acetate-hexanes, mp 177-180 °C). The ORTEP plot is shown in Figure 1.[6]

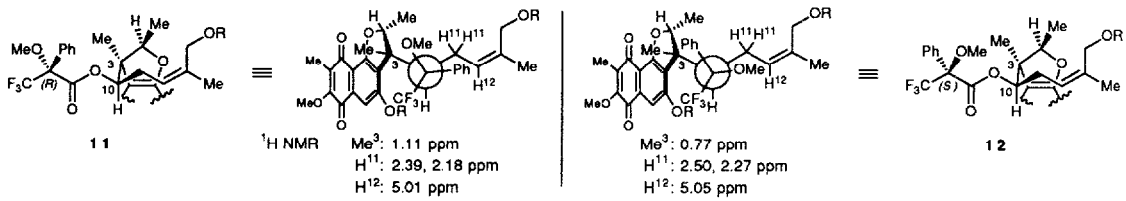
Figure 1



1 Furaquinocin A

Having established the relative configurations at the 2, 3, and 10 positions, we turned to determination of the absolute stereochemistry of furaquinocins A and B. To this end, **1** was converted to the tris *(R)*- and *(S)*-Mosher ester derivatives **11** and **12**.[7-9] NMR analysis revealed that the C(3) methyl resonated further upfield in **12** (0.77 ppm) than in **11** (1.11 ppm). Moreover, H(11), H(11'), and H(12) appeared further upfield for **11** than for **12**. Based upon the Mosher ester model,[7,10] these data permit assignment of the *R* configuration at C(10) (Figure 2). Similar analysis likewise established the 10*(R)* configuration for furaquinocin B (**2**).[7-9]

Figure 2



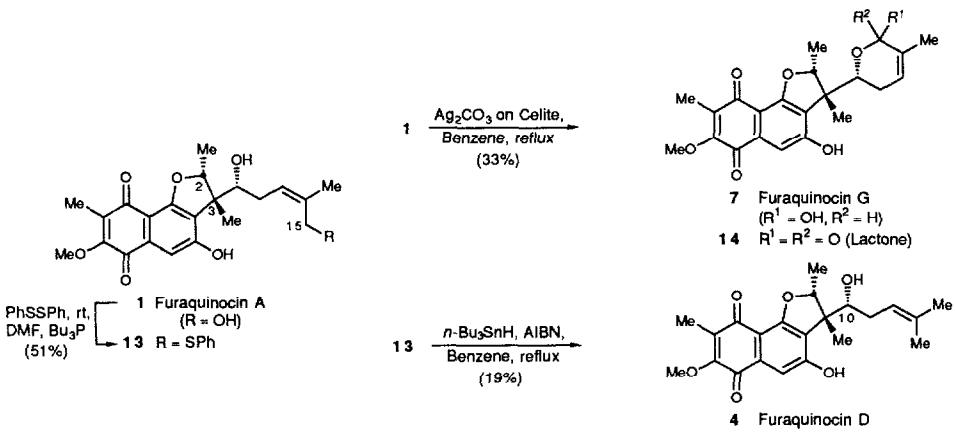
11 12

*Extended Newman projection of tris (R)-Mosher ester **11**, with the R configuration at C(10).*

*Extended Newman projection of tris (S)-Mosher ester **12**, with the R configuration at C(10).*

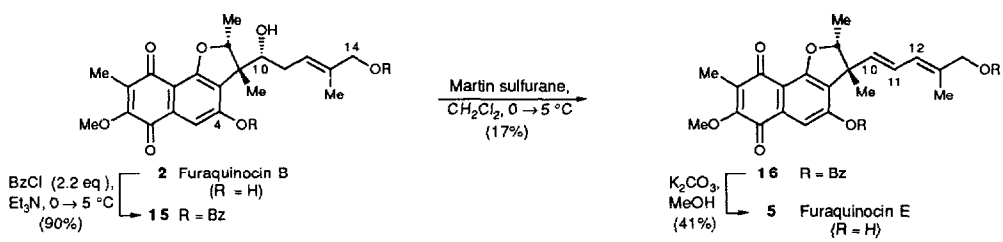
With the relative and absolute stereochemistry of furaquinocins A and B in hand, we next investigated chemical correlations of A with congeners D (**4**) and G (**7**). A was first transformed to D by removal of the C(15) allylic hydroxyl (Scheme 1). Specifically, treatment of **1** (2.2 mg) with diphenyl disulfide (9.6 equiv) and tributylphosphine (10.2 equiv) in dry DMF (0.2 mL) afforded allylic sulfide **13** as the only isolated product (yellow oil; 51% yield).[9,11] Reduction with excess tributyltin hydride[12] and AIBN (benzene, reflux) then furnished semisynthetic furaquinocin D (ca. 0.5 mg), identical with natural **4** by ^{1}H NMR (500 MHz), IR, UV, and HRMS. Although we isolated insufficient semi-synthetic material for a precise determination of the specific rotation, the sign was clearly the same as reported for the natural product {lit.[3] $[\alpha]_D^{18}$ -95° (*c* 0.53, $CHCl_3$)}. The absolute stereochemistry of natural D was then confirmed via preparation and NMR analysis of the Mosher esters.[7-9] We then sought to convert furaquinocin A (**1**) to furaquinocin G (**7**) (Scheme 1). Fetizon oxidation[13] of A (5.5 mg) gave a yellow oil identical with **7** in all respects[9] {33% yield, obs. $[\alpha]_D^{18}$ +5° (c 0.02, CH_3OH); lit.[3] $[\alpha]_D^{19}$+12° (c 0.33, CH_3OH)}, accompanied by lactone **14**. We did not attempt to optimize the latter transformation.

Scheme 1



At this juncture, we prepared furaquinocin E (**5**) from B (**2**) via a three-step protocol (Scheme 2). *Treatment of* **2** *(13.8 mg) with benzoyl chloride (2.2 equiv) and excess triethylamine in dry THF at 0-5 °C* furnished the 4,14-dibenzoyl derivative **15**[9] in ca. 90% yield. Dehydration of the latter with the Martin sulfurane[14] (4 equiv, THF, 0-5 °C) afforded exclusively the 10*(E)*,12*(E)* diene **16**[9] ($J_{10,11}$ = 15.4 Hz) (17% isolated yield). Interestingly, none of the 10*(Z)*,12*(E)* diene was observed under these conditions. Debenzoylation then led to **5**, identical in all respects with natural furaquinocin E. Thus, furaquinocin E shares both the relative configurations at C(2,3) and the absolute stereochemistry of furaquinocins A and B.

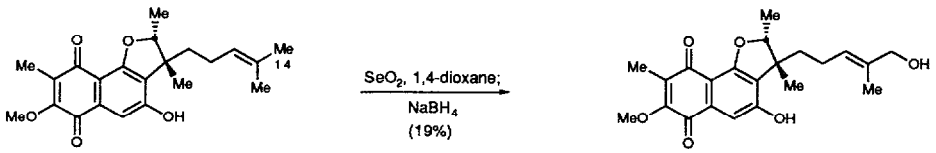
Scheme 2



All that remained was elucidation of the stereostructures of furaquinocins C (**3**) and F (**6**), via C(10) deoxygenation of D (**4**) and B (**2**), respectively. Unfortunately, several attempts to derivatize **2** and **4** for deoxygenation were unsuccessful. *We therefore devised an alternative correlation of furaquinocin C with F, via* selenium(IV) oxide-mediated allylic oxidation of the C(14) methyl group. Specifically, treatment of **3** (6.1 mg) with selenium dioxide (4 equiv) in dry 1,4-dioxane for 30 min at room temperature, followed by quenching with excess sodium borohydride and flash chromatography gave semisynthetic **6** as the major isolable product in 19% yield {$[\alpha]_D^{1.8}$ -8.3° (*c* 0.01, CH_3OH); lit.[3] $[\alpha]_D^{1.8}$ -13° (*c* 0.35, CH_3OH)}, identical with **6** by ^1H NMR (500 MHz), IR, UV, and HRMS. Although selenium oxidation afforded predominantly the *E* allylic alcohol, as expected,[15] the stereochemical features of both **3** and **6** otherwise remained undefined. A cis relationship between H(2) and the C(3) methyl of furaquinocin C was deduced from the observation of a 5.1%

NOE between these groups. Finally, C and F were assigned the same absolute configuration as A, B, and D, buttressed by the observation that furaquinocins A-F all display negative optical rotations at the sodium D line.

Scheme 3



3 Furaquinocin C

6 Furaquinocin F

Acknowledgments. Support for this work was provided by the National Institutes of Health (National Cancer Institute) through grant GM-29028 and by the University of Pennsylvania. We also acknowledge Drs. George T. Furst and Patrick J. Carroll and Mr. John Dykins for assistance in obtaining NMR, X-ray, and mass spectral data, respectively. Finally, we thank Mr. Paul Sprengeler for helpful suggestions and critical comments.

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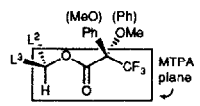
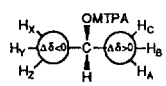
8. Typical preparation of a furaquinocin Mosher ester derivative: a solution of furaquinocin A (2.5 mg), DCC (20 equiv), *(R)*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (17 equiv), and DMAP (1 equiv) in dry dichloromethane was stirred overnight at room temperature. The mixture was filtered, the filtrate concentrated, and the resultant oil purified by flash chromatography (silica gel, 15% EtOAc-hexanes).
9. All new compounds gave ^{1}H NMR (500 MHz), IR, UV, and HRMS data consistent with the assigned structures.
10. In employing the Mosher method to ascertain the absolute stereochemistry of sterically congested secondary alcohols, Kakisawa and coworkers observed positive and negative Δδ values ($\Delta\delta=\delta_S-\delta_R$) on both sides of the MTPA plane. These irregular values, which could lead to erroneous assignment of the absolute configuration, were attributed to non-ideal conformations. According to the Kakisawa model, ideal behavior will generate only negative Δδ values on one side of the MTPA plane and exclusively positive on the other. Our Mosher ester derivatives of **1**, **2**, and, **4** uniformly displayed regular Δδ values; hence we are confident of the *R* configuration at C(10). Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147. Ohtani, I.; Kusumi, T.; Kashman, Y, Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.



Mosher model



Kakisawa model

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