A HIGHLY EFFICIENT SYNTHETIC ROUTE TO (-)-FURAQUINOCIN C

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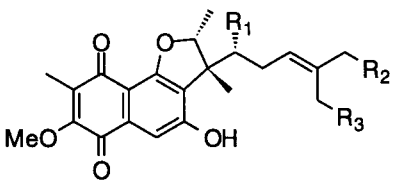
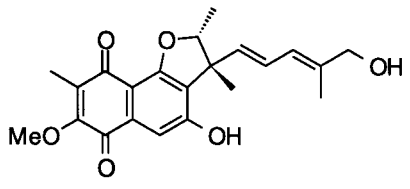
Abstract — The first total synthesis of (-)-furaquinocin C, a member of the furaquinocin family of cytotoxic antibiotics, has been achieved. Central features of the successful synthetic strategy include Diels-Alder construction of the furanonaphthoquinic skeleton and sequential cuprate-mediated conjugate additions to an α,β–unsaturated lactone. The synthetic route proved remarkably efficient requiring only six steps from (*R*)-(+)-angelicalactone, and utilizing a mere four reaction vessels. This stereospecific construction of (-)-furaquinocin C confirms earlier assignments of absolute and relative stereochemistry for the furaquinocins and also constitutes completion of a formal synthesis of (-)-furaquinocin F.

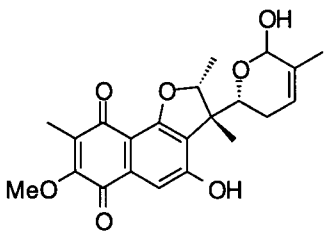
The furaquinocins A-H (**1–8**), comprise a novel family of antibiotics isolated from the culture broth of *Streptomyces* sp. KO-3988, first reported by Ōmura and coworkers[1] at the Kitasato Institute (Tokyo) in 1990. The furaquinocins display a wide range of biological effects including strong *in vitro* cytotoxicity against HeLaS$_3$ cells,[2] antihypertensive activity, and inhibition of platelet aggregation and coagulation.[3]



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



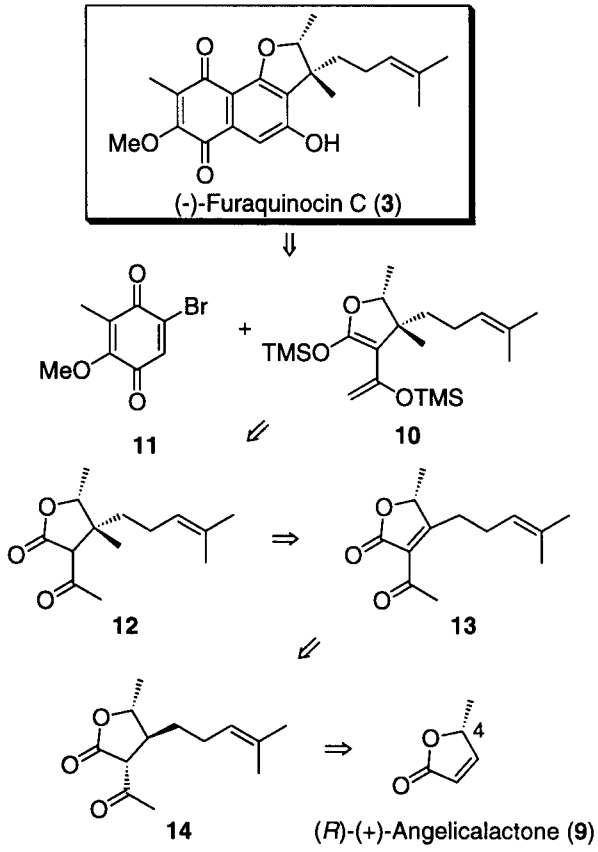
(**5**) Furaquinocin E



(**7**) Furaquinocin G

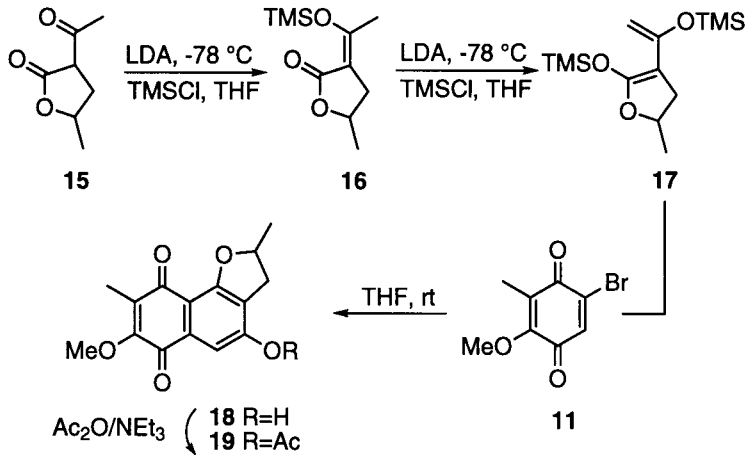
In 1992, in conjunction with Ōmura, we assigned the complete relative and absolute stereochemistries of furaquinocins A, B, D, E and G exploiting a combination of Mosher NMR data, chemical correlation, and X-Ray crystallography.[4] We also established the relative stereochemistry of furaquinocins C and F, but the absolute stereochemistry of these congeners remained undefined. Recently Saito *et al.* reported the syntheses of furaquinocins A, B, D and H,[5] elaborating on the synthesis of furaquinocin D reported earlier.[6] In this, a full account, we report the first and to date only total synthesis of (-)-furaquinocin C,[7] a formal precursor of (-)-furaquinocin F. The highly efficient synthesis proceeds in only six steps from (*R*)-(+)-angelicalactone and utilizes but four reaction vessels. Evaluation of this synthetic strategy suggests that it could readily be exploited to provide access to the entire family of furaquinocin natural products.

Analysis of the Furaquinocin Synthetic Problem. Structurally the furaquinocins are characterized by a highly substituted furanonapthoquinic skeleton bearing a functionalized isoprenoid side chain. From the retrosynthetic perspective, we envisioned synthesis of the furaquinocin skeleton *via* a regioselective Diels-Alder reaction between bromoquinone (**11**)[8] and diene (**10**), followed by HBr and TMSOH elimination and tautomerization. Literature precedent dictated that bromoquinone (**11**) would render the desired regiochemical outcome in good yield.[9] Although the synthetic utility of dienes of the Danishefsky type[10] is now widely recognized, the ability to employ effectively highly-substituted dienes, especially those wherein one of the double bonds is constrained in a ring, is rare.[11] Despite this fact, our results (*vide infra*) provide evidence that such cyclic synthons offer a viable approach for the construction of a wide variety of polycyclic natural and unnatural products.[12]

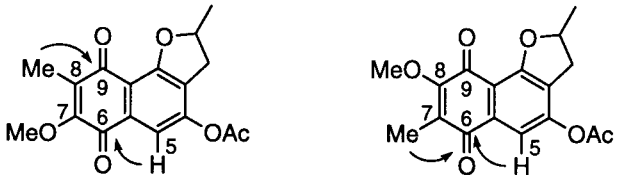


The synthesis of bistrimethylsilyl ether (**10**) starting with the known (*R*)-(+)-angelicalactone (**9**), would exploit the C(4) methyl group as the stereochemical control element for introduction of the stereogenicity at C(3). Cognizant of the expected stereochemical outcome of cuprate additions to α,β–unsaturated systems[13] we opted to introduce the isoprenoid side chain first and to append the methyl group at a later stage.

Diels-Alder Model Studies. The realization of highly efficient synthetic routes to structurally complex natural products like the furaquinocins demands transformations characterized by high regioselectivity and stereospecificity. To this end we thought it prudent to test the feasibility and confirm the predicted regiochemical outcome of the proposed Diels-Alder sequence using a model system.[4b] Model diene (**17**) was thus prepared in 47% overall yield from 3-acetyl-5-methyldihydrofuran-2(3*H*)-one (**15**)[14] *via* sequential generation of the enolate with LDA and subsequent capture with TMSCl. Interestingly, diene (**17**) proved extremely moisture-sensitive while **16** readily retained its integrity. Diels-Alder reaction of **17** with bromoquinone (**11**) in THF afforded furanonaphthoquinone (**18**) as the exclusive (by TLC) product in 50% yield. Recognizing the apparent instability of the resultant naphthol, cycloadduct (**18**) was converted into the more stable acetate (**19**) in 40% yield.



Two-dimensional NMR studies (*via* the HMBC technique optimized for $^{3}J_{H\text{-}C}$ = 7 Hz)[15] of the acetylated cycloadduct (**19**) revealed long range ^{1}H-^{13}C couplings between H(5) and C(6), and between Me(8) and C(9) that correspond only to the desired furanonaphthoquinone skeleton.[4b] Had the regioisomeric Diels-Alder adduct (**20**) formed in this sequence, long range couplings would be observed between both H(5) and Me(7) to the same carbonyl, C(6). The latter scenario was not operative.



19 (Desired) **20** (Undesired)

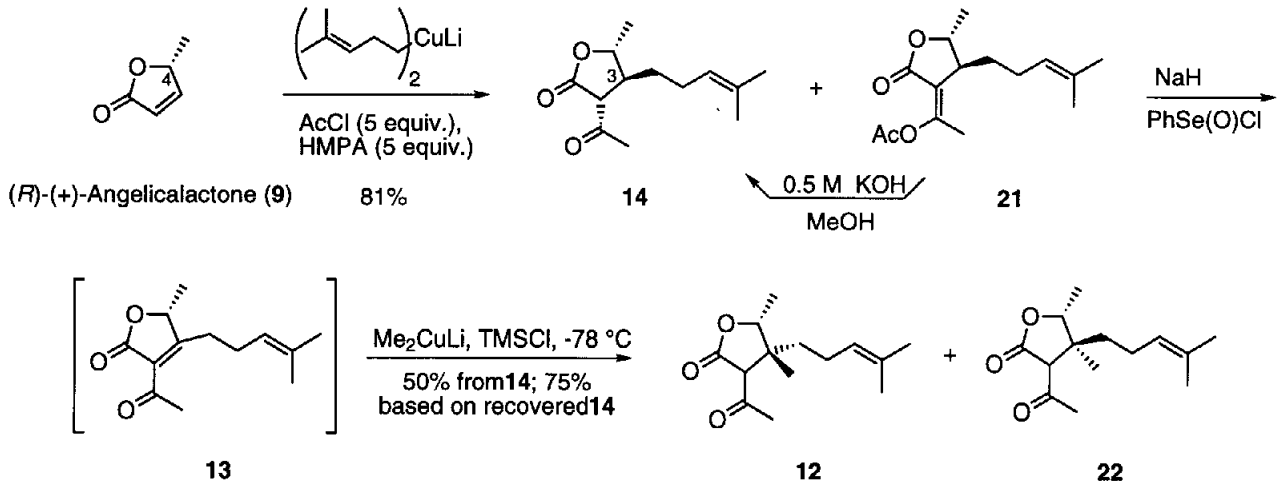
Diene Synthesis. The planned construction of diene (**10**) was based upon organocuprate conjugate additions to (*R*)-(+)-angelicalactone. However, while such cuprate-mediated additions to enones are

commonplace, the number of examples involving esters or lactones, especially those that are β-substituted, are scarce.[16] To circumvent the anticipated attenuation in reactivity, we postponed introduction of the C(2) acetyl group until after the first conjugate addition. Thus, our synthesis began with the generation of the isoprenoid cuprate derived from 5-iodo-2-methyl-2-pentene[17] by metallation with *t*-BuLi at -78 °C, addition of the CuI/$(PBu_3)_2$ complex and warming of the mixture to -50 °C. Addition of (*R*)-(+)-angelicalactone,[18] prepared in five steps from D-(+)-ribonolactone, followed by trapping of the resulting enolate with a mixture of AcCl/HMPA, afforded lactone (**14**) in 68% yield together with a moderate amount of enolacetate (**21**) (16%). Treatment of **21** with dilute methanolic KOH led to near-complete transformation to **14**, improving the overall yield of the initial sequence to 81%. To our delight, lactone (**14**) was obtained as a single stereoisomer; the stereochemistry was assigned based on coupling constants between the β and γ hydrogens (J = 8 Hz) in conjunction with the observed nuclear Overhauser enhancements between the γ-methyl and the C(3) hydrogen.[19]

Continuing with the designated approach, we sought regeneration of the α,β-unsaturation in the lactone ring. Unfortunately, all attempts to utilize the standard procedures of electrophilic attack of PhSeCl followed by oxidation with H_2O_2 or O_3 failed.[20] Although the selenenyl adduct was formed in reasonable yield (65%), oxidative elimination afforded only small amounts of the desired enone, accompanied by concomitant decomposition of the selenoxide. Undaunted, we explored alternative approaches, including bromination and β-elimination,[21] and the action of $Pd(OAc)_2$[22] or DDQ on the intermediate enol silyl ether. These tactics proved equally unproductive. Yielding to the difficulty of the oxidation step, we explored benzeneseleninyl chloride [PhSe(O)Cl] as the elecrophile.[21b] Deprotonation of the lactone (**14**) with NaH, addition of PhSe(O)Cl at -78 °C, and slow warming of the mixture to room temperature afforded the enone (**13**) as the major product, along with a small amount of phenyl selenoxide, presumbly bearing an *anti* disposition of the selenoxide and β-proton. Recognizing that enone (**13**) decomposes rapidly in the presence of oxygen, it was used in the next step without purification.

To effect the second conjugate addition, the unpurified enone (**13**) was added to an ethereal solution of Me_2CuLi at -78 °C to afford a mixture of diastereomers (**12**) and (**22**) (1:2.4) in 50% yield. We attribute the observed thirty percent of recovered dicarbonyl (**14**) to reduction of the selenoxide precursor associated with enone (**13**). Both diketones (**12**) and (**22**) appear as three-compound mixtures comprised of the C(2) acetyl epimers and an enol-lactone tautomer in ratios of 3:1:1 and 1:1:1, respectively. Silylation with TBSCl converted **12** and **22** to single TBS enol ethers differing only in the C(3) stereogenicity. Their relative stereostructures were established via nuclear Overhauser experiments.

Contrary to our expectations that the C(4) methyl of (*R*)-(+)-angelicalactone would control the stereochemical outcome of the isoprenoid conjugation by forcing an *anti* [to C(4)] approach of the organocuprate, diastereomer (**22**), rather than **12**, was the major product, presumably the result of a *syn* approach. In an attempt to define further and clarify this result, we investigated the selectivity of the addition reaction using an array of methyl organocopper reagents, solvents, temperatures and addition orders (Table 1). For example addition of methylcopper, higher order cuprates, and heterocuprates to **13**,

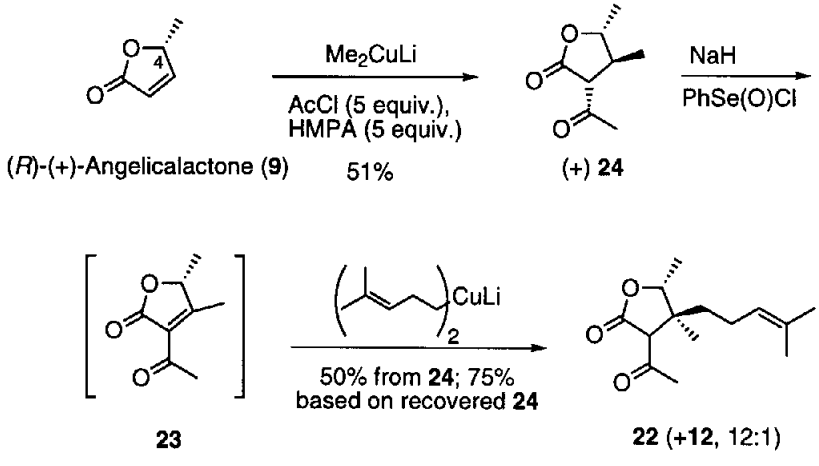


with or without Lewis acids in Et_2O or THF at different temperatures afforded **22** as the major product in similar yields. Exceptions occurred when heterocuprates (lower) or methyl organocopper (traces) were employed. The highest yield of diastereomer (**12**) was obtained when enone (**13**) was added to a solution of Me_2CuLi with TMSCl (**22**:**12**, 1.8:1).

Table 1. Cuprate additions to 13

Cuprate	Ratio (22:12)
Me_2CuLi to **13**	3.1:1
13 to Me_2CuLi	2.4:1
Me_2CuLi, TMSCl	1.8:1
$Me_2Cu(CN)Li_2$	2.3:1
$Me(PPh_2)CuLi$	2.4:1
MeCu, BF_3Et_2O	n.r.

To explore this unexpected stereochemical outcome, we examined the consequences of inverting the order of the two cuprate additions. As literature precedent would suggest, methyl cuprate addition proceeded *anti* with respect to the C(4) methyl group in **9** affording after the second cuprate addition a 12:1 mixture of **22** and **12**.



A Monte Carlo simulation of enone (**13**) with the MM2 force-field suggested that in the lowest energy conformation the side chain exists with the C(7) methylene *anti* to the C(4) methyl group, thus creating a situation where the cuprate experiences steric hindrance no matter from which direction it approaches. Apparently the isoprenoid side chain is more obtrusive than the C(4) methyl and thus diastereomer (**22**) always predominates. When the order of conjugate addition is reversed, the corresponding enone, lacking the side chain, does not present an obstacle *anti* to the C(4) methyl; the methyl then directs the facial selectivity in accord with our initial predictions.[23]

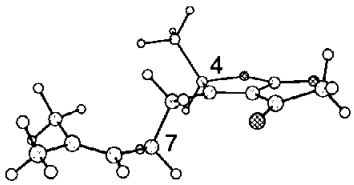
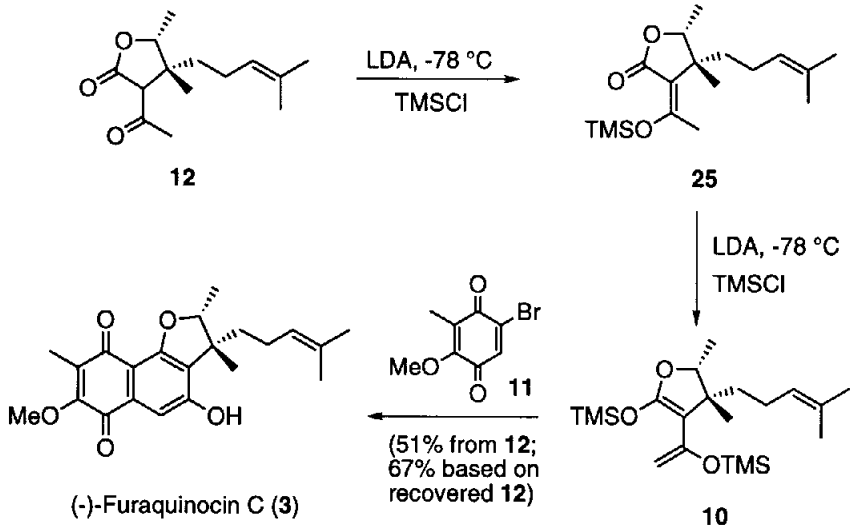


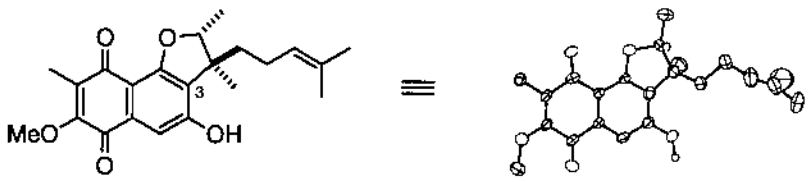
Figure 1. Lowest energy conformation (Monte Carlo) found for enone (**13**) employing the MM2 force field showing the anti disposition of the C(7) carbon of the side chain to the C(4) methyl group.

With both diastereomers in hand, we were poised to complete the synthetic venture utilizing the previously modeled Diels-Alder reaction. Towards this end, **12** was transformed to diene (**10**) by treatment with LDA and TMSCl in a two step sequence. Both trimethylsilyl ether (**25**) and bistrimethyl ether (**10**) were unstable in the presence of air and moisture, and were most advantageously used without purification. Addition of the bromoquinone (**11**) to diene (**10**) at room temperature led to the formation of (–)-furaquinocin C (**3**) as sole product in 50% yield (67% based on recovered starting material).



Synthetic and natural furaquinocin C were identical in all respects (mp, mmp, ^{1}H and ^{13}C NMR, IR, HRMS, optical rotation and TLC with three solvent systems).

Using diastereomer (**22**) and an analogous reaction sequence, (+)-epi-furaquinocin C (**26**) was prepared in 57% yield (70% based on recovered **22**); the structure of **26** was confirmed by X-Ray analysis.



(+)-3-Epi-furaquinocin C (**26**)

In summary, we have developed an extremely concise and efficient synthetic route to (-)-furaquinocin C, and in the process determined the absolute stereochemistry and that of (-)-furaquinocin F. Highlights of the synthesis include the use of a new highly-substituted Diels-Alder diene and the demonstrated utility of cuprates in conjugate additions to lactones. In addition we observed the first example of a cuprate addition that proceeds with addition *syn* to the chiral auxiliary due to the presence of an additional steric constraint.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were carried out in oven-dried glassware under an argon atmosphere using dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Benzene was distilled from sodium metal. Dichloromethane, diisopropylamine, and trimethylchlorosilane were distilled from calcium hydride. Methyllithium, *n*-butyllithium and *tert*-butyllithium were purchased from Aldrich.® All alkyllithium reagents were standardized by titration against diphenylacetic acid. Copper iodide was purified by recrystallization from saturated potassium iodide solution.[24] All other reagents were purchased from Aldrich® and used as received without further purification. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm pre-coated silica gel plates supplied by either E. Merck or Whatman. Preparative TLC was performed using 250 μm pre-coated silica gel plates (20 cm x 20 cm, E. Merck) with the indicated solvent. Flash column chromatography was performed with the solvents indicated using silica gel-60 (particle size 0.040-0.063 mm) supplied by E. Merck, ICN, or J. T. Baker. Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

All melting points were obtained on a Thomas-Hoover apparatus and are corrected. IR spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. ^{1}H and ^{13}C NMR were recorded at 500 and 125 MHz, respectively, on a Bruker AMX-500 or AMX-II-500 (the latter equipped with a digital ^{2}H lock) spectrometer with a 5-mm $^{1}H/^{13}C$ or 5 mm inverse ^{1}H/BB probe. ^{13}C-NMR multiplicities were determined *via* the distortionless enhancement by polarization transfer (DEPT) method. ^{1}H COSY, ^{13}C DEPT, and ^{1}H-^{13}C HMBC 2-dimensional spectra were acquired using standard Bruker pulse sequences (AMX-UXNMR version 930901). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent signals as internal reference. Coupling constants are given in Hz. IR, ^{1}H, and ^{13}C NMR spectra were obtained using chloroform ($CHCl_3$) and deuterochloroform ($CDCl_3$) solutions unless otherwise stated. UV absorbtion spectra were recorded in the solvent indicated. Optical rotations were obtained with a Perkin-Elmer Model 241 polarimeter in the solvent indicated. High-resolution MS

spectra were obtained at the University of Pennsylvania Mass Spectrometry Center on either a VG micromass 70/70H or a VG ZAB-E high-resolution electron-impact/chemical-ionization spectrometer.

3-Acetyl-5-methyldihydrofuran-2(3*H*)-one (15): Sodium metal (23 g, 1 mol) was added in one portion, at rt, to anhydrous ethanol (400 mL) in a 3-neck, 1 L flask equipped with a condenser, thermometer, Claisen head, and overhead stirrer. After dissolution of the sodium (4 h), ethyl acetoacetate (127 mL, 1 mol) was added dropwise to the stirred sodium ethoxide/ethanol solution, adjusting the addition rate to maintain the reaction temperature at 45-50 °C. When addition was complete, the reaction mixture was cooled to 0-5°C and then propylene oxide (70 mL, 1 mol) was added dropwise to the mixture over a 20 min period. The resultant clear, pale green solution was stirred at 0-5 °C overnight, after which it was warmed to rt and stirred for another 4 h. After removal of the solvent under reduced pressure, the residue was neutralized (50% aqueous AcOH, *ca.* 100 mL), diluted with water (100 mL), extracted with ether (6 x 150 mL), and the combined extracts dried ($MgSO_4$). After removal of the ether *in vacuo* the resultant oil was purified by distillation through a Vigreux column under high vacuum to afford impure **15** as a clear colorless oil. A second distillation then gave pure **15** (28.3 g) as a 1:1 *cis:trans* mixture: bp 94-95/1 mm Hg; IR ($CHCl_3$) 3520 (br, w), 3025 (m), 2990 (m), 2940 (m), 1760 (s),1725 (s), 1660 (m), 1390 (m), 1360 (m), 1350 (m), 1185 (br, s), 1125 (m), 1105 (m), 1055 (s), 950 (s) cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 4.16-4.02 (m, 0.5 H), 3.83-3.69 (m, 0.5 H), 2.92 (dd, J = 5.3, 10.1 Hz, 0.5 H), 2.77 (t, J = 9.6 Hz, 0.5 H), 2.37-2.28 (m, 0.5), 1.48-1.37 (m, 0.5 H), 1.04 (m, 0.5 H), 0.88 (d, J = 6.4 Hz, 1.5 Hz), 0.78 (d, J = 6.4 Hz, 1.5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.8/200.5, 172.6/172.4, 76.3/75.4, 54.3, 31.2, 29.4/28.9, 20.8/20.6.

3-[[(Trimethylsilyl)oxy]ethyl]-5-methyldihydrofuran-2-one (16): A solution of LDA was prepared *via* dropwise addition of *n*-butyllithium (2.4 M in hexanes, 7 mL, 16.8 mmol) to a stirred solution of diisopropylamine (2.6 mL, 18.55 mmol) in THF (5 mL) at 0-5 °C. After stirring the solution at 0-5 °C for 10 min, the LDA solution was cooled to –78 °C. To the LDA/THF solution was added *via* cannula a pre-cooled solution of 3-acetyl-5-methyldihydrofuran-2(3*H*)-one (**27**, 2.0 g, 14.1 mmol) in THF (10 mL + 2 mL). The resulting clear yellow solution was stirred at –78 °C for 10 min and then quenched with neat trimethylchlorosilane (4.5 mL, 35.5 mmol). The solution was then concentrated by distillation under anhydrous conditions and reduced pressure to afford a white residue. The residue was slurried in a small amount of ether and filtered through a short pad of oven-dried Celite, the pad washed with ether (3 x 5 mL), and the combined filtrates concentrated by distillation under reduced pressure, again using anhydrous conditions. The resulting oil was purified *via* high vacuum distillation through a Vigreux column yielding **16** as a clear, colorless oil (2.6 g) in 85% yield: bp 94-96°C/0.1 mm Hg; IR (CCl_4) 2970 (m), 2930 (m), 1750 (s), 1665 (s), 1380 (s), 1290 (s), 1275 (s), 1260 (s), 1015 (s), 1000 (s), 845 (s) cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 4.08-3.97 (m, 1 H), 2.64-2.53 (m, 1 H), 2.32 (t, J = 2.3 Hz, 3 H), 2.13-2.02 (m, 1 H), 0.95 (d, J = 6.3 Hz, 3 H), -0.02 (s, 9 H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 117.0, 161.3, 106.7, 72.0, 33.9, 22.2, 18.5, 0.75.

2-[(Trimethylsilyl)oxy]-3-[1'-[trimethylsilyl)oxy]ethenyl]-5-methyldihydrofurane (17): A solution of LDA was generated *via* dropwise addition of *n*-butyllithium (2.4 M in hexanes, 465 µL, 1.12

mmol) to a pre-cooled solution of diisopropylamine (180 μL, 1.28 mmol) in THF (2 mL) at 0-5 °C. This solution was stirred for 10 min and then cooled to –78 °C. To the LDA/THF solution was added *via* cannula a pre-cooled solution of **16** (197 mg, 0.92 mmol) in THF (2 mL) at –78 °C. After stirring the pale-yellow, hazy solution at –78 °C for 10 min, the reaction was quenched by addition of trimethylsilyl chloride (300 μL, 2.36 mmol), and then stirred at –78 °C for 10 min. The solvent was removed under reduced pressure while maintaining anhydrous conditions leaving a white residue. The residue was slurried in a small amount of dry ether, filtered through a short pad of oven-dried Celite, and the pad washed with ether (3 x 2 mL). Concentration of the combined filtrates gave **17** (223 mg, 84% yield) as a pale yelow oil containing *ca.* 30-40% of **16** as an impurity. As **17** is quite moisture sensitive, it was used immediately in the following reaction. ^{1}H NMR (250 MHz, C_6D_6) δ 4.26-4.17 (m, 1 H), 4.19 (s, 1 H), 4.09 (s, 1 H), 2.69 (dd, *J* = 9.5, 12.9 Hz, 1 H), 2.17 (dd, *J* = 6.5, 12.9 Hz, 1 H), 1.01 (d, *J* = 6.2 Hz, 3 H), 0.26 (s, 9 H), 0.21 (s, 9 H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 165.3, 154.1, 153.9, 87.2, 74.7, 37.8, 22.0, 0.58, 0.37.

3-Hydroxy-6-methoxy-7-methyl-2-methylfuro[2,3a]naphtho-5,8-dione (**18**): Bromoquinone (**11**) (191.4 mg, 0.83 mmol) was added to neat **17** (60% purity, 223 mg, 0.47 mmol) at rt and the flask purged with argon. A slight exotherm was observed as **11** dissolved in **17**. The reaction mixture was immediately dissolved with THF (3 mL) and the resulting orange-yellow solution stirred rt. TLC analysis (Solvent A: 1/1 ether/hexanes; Solvent B: 5% methanol/chloroform) after 5 min indicated the formation of a product more polar than either starting material (*Rf* 0.15, Solvent B). No further change in the TLC was observed after stirring the orange-yellow solution at rt for 6 days. The solvent was removed under reduced pressure and the resultant orange oil purified by flash chromatography (1% MeOH/CH_2Cl_2) to afford **18** as a reddish brown powder (64 mg) in 50% yield. [*n.b.* Cycloadduct (**18**), after prolonged exposure to air, decomposed to an uncharacterized brown insoluble material]: mp (corr.) 215-217 °C; ^{1}H NMR (250 MHz, 1:1 $CDCl_3$:CD_3OD) δ 7.06 (s, 1 H), 5.23-5.15 (m, 1 H), 3.99 (s, 3 H), 3.30 (dd, *J* = 9.1, 16.5 Hz, 1 H), 2.75 (dd, *J* = 7.1, 16.5 Hz, 1 H), 2.04 (s, 3 H), 1.55 (d, *J* = 6.3 Hz, 1 H); high resolution MS spectrum (CI, NH_3) *m/z* 274.0846 [$(M)^+$; calcd for $C_{15}H_{14}O_5$: 274.0841].

3-Acetoxy-6-methoxy-7-methyl-2-methylfuro[2,3a]naphtho-5,8-dione (**19**): Acetic anhydride (50 μL, 0.53 mmol) and triethylamine (50 μL, 0.38 mmol) were added with stirring to a brown solution of impure **18** (55.7 mg, 0.20 mmol) in dichloromethane (2 mL) at rt. After 4 h at rt, TLC (5% methanol/dichloromethane) indicated that all of **18** (*Rf* 0.28) was consumed and that a less-polar product had formed (*Rf* 0.55). The solvent was removed under reduced pressure and the resultant yellow-brown solid purified by flash chromatography (2/1 ether/hexanes) to afford **19** (25.7 mg, 40%) as a yellow powder: *Rf* 0.55 (5% methanol/dichloromethane); UV (MeOH) λ_{max} 232, 244, 284, 398 nm; IR ($CHCl_3$) 3005 (m), 1775 (s), 1665 (s), 1655 (s), 1620 (m), 1595 (m), 1425 (m), 1370 (m), 1275 (s), 1250 (s), 1190 (s), 905 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 5.23-5.17 (m, 1 H), 4.02 (s, 3 H), 3.23 (dd, *J* = 8.9, 16.7 Hz, 1 H), 2.72 (dd, *J* = 7.31, 16.7 Hz, 1 H), 2.31 (s, 3 H), 2.04 (s, 3 H), 1.54 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.91, 179.95, 167.60, 161.18, 150.22, 133.26,

133.06, 128.56, 113.70, 113.00, 82.92, 60.75, 34.03, 21.87, 20.74, 9.22; high resolution MS spectrum (CI, NH_3) *m/z* 317.1031 [$(M+H)^+$; calcd for $C_{17}H_{16}O_6$: 317.1024].

(+)-3-Acetyl-4-(2'-methylpentenyl)-5-methyldihydrofuran-2(3*H*)-one (14). A solution of *tert*-BuLi in hexanes (24.5 mmol, 1.7 M) was cooled at -78 °C and an ethereal (6 mL) solution of 5-iodo-2-methyl-2-pentene (2.57 g, 12.2 mmol) was added *via* canula. After 30 min at –78 °C a solution of $CuI(PBu_3)_2$ [generated in 20 min by rt reaction of PBu_3 (3.05 mL, 12.2 mmol) with an ethereal (5 mL) slurry of CuI (1.16 g, 6.1 mmol)] was added *via* cannula. The cloudy, light yellow mixture became clear as it was warmed slowly to –50 °C over 30 min. Introduction *via* canula of a solution of (*R*)-(+)-angelicalactone (**9**) (500 mg, 5.10 mmol) in Et_2O (3 mL + 1mL rinse) immediately gave a canary yellow solution that was warmed to –30 °C for 40 min and then cooled to -78 °C. A solution of acetyl chloride (1.8 mL, 25.5 mmol) in HMPA (3.6 mL, 25.5 mmol) was added quickly, and the reaction mixture was stirred for 40 min, quenched with saturated aqueous $NaHCO_3$ solution (2 mL), poured into Et_2O (100 mL), and washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with Et_2O (30 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (15% Et_2O/hexanes) afforded **14** (776 mg, 68%) and enol acetate(**21**) (220 mg. 16%). **21**: Colorless oil; $[\alpha]_D^{23}$ -14.7° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2930, 1760, 1690, 1360, 1280 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.06 (m, 1 H), 4.30 (br q, *J* = 6.4 Hz, 1 H), 2.60 (m, 1 H), 2.22 (s, 3 H), 1.99 (m, 2 H), 1.87 (s, 3 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.52 (m, 2 H), 1.24 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 150.6, 132.7, 128.5, 124.1, 123.1, 77.4, 45.7, 34.1, 25.6, 25.1, 23.8, 22.3, 20.1, 17.7]; high resolution MS spectrum (CI, NH_3) *m/z* 267.1607 [$(M+H)^+$; calcd for $C_{15}H_{23}O_4^+$: 267.1576].

Enol acetate [**(-)-21**] (220 mg, 0.83 mmol) was dissolved in KOH/MeOH (5 mL) and stirred for 6 h at rt, poured into Et_2O (30 mL), and washed with 1N HCl (20 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography on a short silica column (20% AcOEt/hexanes) gave **14** (185 mg, 98% yield from **21**; 82% total yield from **9**) as a colorless oil: $[\alpha]_D^{23}$ +28.72° (*c* 2.03, $CHCl_3$); IR ($CHCl_3$) 2980, 2920, 1765, 1720, 1650, 1450, 1372, 1350, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (m, 1 H), 4.18 (dq, *J* = 6.1 and 8 Hz, 1 H), 3.44 (d, *J* = 9.5 Hz, 1 H), 2.67-2.60 (m, 1 H), 2.40 (s, 3 H), 1.96-1.86 (m, 3 H), 1.65 (s, 3 H), 1.54 (s, 3 H), 1.40 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 171.7, 132.9, 122.9, 80.8, 60.5, 43.7, 32.4, 30.0, 25.9, 25.6, 20.0, 17.7; high resolution MS spectrum (CI, NH_3) *m/z* 225.1476 [$(M+H)^+$; caicd for $C_{15}H_{23}O_4^+$: 225.1490].

3-Acetyl-4,4-(2'-methylpentenyl)-methyl-5-methyldihydrofuran-2(3H)-one (12 and 22). A solution of lactone (**14**) (135 mg, 0.6 mmol) in THF (6 mL) was added to a rt slurry of NaH (17.3 mg, 95%) in THF (8 mL) *via* cannula. The resultant mixture was stirred until the evolution of H_2 ceased (1 h), at which point the enolate solution was transferred to a new flask *via* cannula and cooled to –78 °C. A solution of PhSe(O)Cl (150 mg, 0.72 mmol) in THF (2 mL) was then added *via* cannula, and the mixture was stirred for 45 min at –78 °C, slowly warmed to rt over a period of 2.5 h, poured into Et_2O (50 mL), and washed with 1N HCl (10 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined

organic solutions were dried over $MgSO_4$, filtered and concentrated. The crude material was stored under vacuum. Analysis by ^{1}H-NMR (500 MHz, $CDCl_3$) revealed the formation of enone **13** as the major product: δ 5.06 (m, 1H), 4.94 (q, *J* = 6.9 Hz, 1 H), 3.10 (m, 1 H), 2.53 (s, 3 H), 2.24 (m, 3 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.46 (d, *J* = 6.9 Hz, 3 H).

A solution of Me_2CuLi (1.02 mL, 1.44 mmol) and TMSCl (180 μL, 1.44 mmol) in Et_2O (5 mL) was cooled to –78 °C and a solution of enone (**13**) in Et_2O (3 mL) was added *via* cannula. After 5 min the canary yellow reaction was quenched with a mixture of 30% aqueous NH_4OH and saturated NH_4Cl (2:1 v/v, 2 mL), poured into Et_2O (30 mL), and washed with saturated NH_4Cl (30 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined organic solutions were dried over $MgSO_4$, filtered and concentrated. Analysis by ^{1}H-NMR showed a 1.8:1 mixture of diastereomers (**22**) and (**12**), accompanied by recovered **14**. Flash chromatography (15% Et_2O/hexanes) afforded **22** (45 mg, 32%) and a mixture of **14** and **12** (61 mg). Preparative TLC (2% AcOEt/toluene) then gave **14** (25 mg, 18%) and **12** (36 mg, 30%). Both **22** and **12** were isolated as mixtures consisting of the corresponding C(2) epimers and an enol tautomer (*ca.* 1:1:1 and 3:1:1, respectively). **22:** colorless oil; IR ($CHCl_3$) 3020, 2980, 2400, 1770, 1715, 1690, 1640, 1490, 1220 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.79 (s, 1H), 5.04-4.95 (m, 1H), 4.69, 4.39 and 4.28 (q, *J* = 6.4 Hz, 1H), 3.43 and 3.40 (s, 1 H), 2.34, 2.32 and 1.99 (s, 3 H), 2.00-1.80 (m, 3 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 1.28, 1.26 and 1.24 (d, *J* = 6.4 Hz, 3 H), 1.11, 1.04 and 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 202.2, 176.2, 172.5, 172.0, 169.6, 132.7, 132.6, 132.4, 123.3, 123.1, 123.0, 103.6, 83.5, 82.3, 81.8, 64.8, 61.4, 47.0, 46.7, 43.4, 39.4, 37.7, 32.4, 31.7, 29.7, 29.2, 25.7, 25.6,23.8, 23.3, 23.1, 21.7, 19.8, 18.4, 17.6, 15.7, 14.1, 14.0; high resolution MS spectrum (CI, NH_3) *m/z* 256.1922 [$(M+NH_4)^+$; calcd for $C_{14}H_{23}O_3^+$: 256.1913]. The three components of the mixture were converted to the TBS enol ether giving a single compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (m, 1 H), 4.22 (q, *J* = 6.5 Hz, 1 H), 2.40 (s, 3 H), 1.90 (m, 1 H), 1.80 (m, 2 H), 1.63 (s, 3 H), 1.54 (s, 3 H), 1.43 (m, 1 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 1.12 (s, 3 H), 0.95 (s, 9 H), 0.27 (s, 3 H), 0.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 164.2, 131.5, 124.0, 111.7, 78.7, 45.3, 38.0, 25.9, 25.6, 23.5, 20.0, 19.9, 18.5, 17.7, 15.7, -2.7, -2.8; high resolution MS spectrum (CI, NH_3) *m/z* 353.2511 [$(M+H)^+$; calcd for $C_{20}H_{37}O_3Si^+$: 353.2502].

(+)-12. Colorless oil; $[\alpha]_D^{23}$ +12.00° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2930, 2880, 1770, 1715, 1640, 1240 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.69 (s, 1 H), 5.02 (m, 1 H), 4.50, 4.32 and 4.18 (q, *J* = 6.6 Hz, 1 H), 3.54 and 3.25 (s, 1 H), 2.41 2.30 and 2.02 (s, 3 H), 1.95 (m, 3 H), 1.87 (m, 1 H), 1.65 (s, 3 H), 1.59 (s, 3 H), 1.37 and 1.34 (d, *J* = 6.6 Hz, 3 H), 1.27, 1.22 and 1.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) major one, δ 202.8, 172.6, 132.7, 123.0, 84.2, 62.2, 46.1, 36.2, 34.8, 32.4, 25.6, 22.8, 18.6, 13.7; high resolution MS (CI) *m/z* [$(M+NH_4)^+$; calcd for $C_{14}H_{23}O_3$]: 256.1913, found 256.1925]. The mixture was transformed to the TBS enol ether giving a single compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (m, 1 H), 4.01 (q, *J* = 6.6 Hz, 1 H), 2.40 (s, 3 H), 1.90 (m, 2 H), 1.64 (s, 3 H), 1.54 (s, 3 H), 1.50-1.40 (m, 2 H), 1.27 (d, *J* = 6.6 Hz, 3 H), 1.26 (s, 3 H), 0.96 (s, 9 H), 0.27 (s, 3 H), 0.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 163.9, 131.4, 124.3, 112.1, 81.9, 45.8, 35.0, 26.0, 25.7, 24.0, 23.0, 20.2, 18.5, 17.7, 13.3, -2.6, -2.7.

(-)-Furaquinocin C. Freshly prepared LDA in THF (1M, 62 μL, 0.06 mmol) was added to a solution of the lactone (**12**) (12 mg, 0.05 mmol) in THF (5 mL) at –78 °C. After 30 min the mixture was treated with a THF solution containing 1M TMSCl and 1M NEt_3 (150 μL, 0.15 mmol), warmed to rt over 15 min, and recooled to -78 °C. A second portion of LDA (62 μL, 0.06 mmol, 1M) was then added, and after 30 min the reaction mixture was again treated with 1 M TMSCl and 1 M NEt_3 in THF (150 μL, 0.15 mmol), warmed to rt and concentrated. The solid residue was dissolved in THF (1 mL), bromoquinone (**11**) (27 mg, 0.12 mmol) was added, and the resultant mixture was stirred at rt for 6 h and then concentrated. Flash chromatography (30% Et_2O/Hexanes) afforded 9 mg of furaquinocin C (9 mg, 51%) and unreacted lactone (**12**) (3 mg). Samples of **3** gave identical ^{1}H-NMR and ^{13}C-NMR spectra provided that the spectra were recorded using equivalent sample concentrations. In natural furaquinocin C,[25] the shifts of the H(5) and C(5) signals are concentration dependent as are those of C(4) and its attached hydroxy group. Our sample behaved similarly. When mixed together, the synthetic and natural furaquinocin C samples were indistinguishable by both ^{1}H-NMR and ^{13}C-NMR, had the same specific rotation, and bore identical MS, IR, and UV spectra.

3: Yellow solid mp: 208-210 °C; $[\alpha]_D^{23}$ -25° (*c* 0.22, $CHCl_3$); IR ($CHCl_3$)) 3260, 3020, 2940, 1660, 1620, 1580, 1300, 1200 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1 H), 6.29 (br s, 1 H), 4.96 (m, 1 H), 4.53 (q, *J* = 6.7 Hz, 1H), 3.99 (s, 3 H), 2.05 (s, 3 H), 1.93 (m, 2 H), 1.76 (m, 2 H), 1.59 (s, 3 H), 1.51 (d, *J* = 6.7 Hz, 3 H), 1.47 (s, 3 H), 1.45 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 181.1, 161.6, 157.1, 156.9, 133.9, 133.3, 131.7, 128.0, 124.1, 109.7, 109.0, 91.6, 60.7, 46.6, 35.1, 25.6, 23.8, 22.7, 17.6, 13.6, 9.4; high resolution MS spectra (CI, NH_3) *m/z* [(M-H)$^+$; calcd for $C_{22}H_{26}O_5$]: 371.1858, found 371.1853].

(+)-3-Epifuraquinocin C (26). Yellow solid mp: 233 °C; $[\alpha]_D^{23}$ +57.86° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 2990, 2349, 1631, 1590, 1488, 1352, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1 H), 6.75 (br s, 1 H), 5.09 (m, 1 H), 4.87 (q, *J* = 6.6 Hz, 1 H), 4.02 (s, 3 H), 2.10 (s, 3 H), 1.67 (s, 3 H), 1.56 (s, 3 H), 1.47 (d, *J* = 6.6 Hz, 3 H), 1.30 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 181.2, 161.2, 156.9, 133.0, 132.0, 127.9, 123.8, 109.6, 109.2, 88.1, 60.7, 46.9, 37.8, 25.6, 23.7, 19.7, 17.6, 15.4, 9.4; high resolution MS spectra (CI, NH_3) *m/z* [(M-H)$^+$; calcd for $C_{22}H_{26}O_5$]: 371.1858, found 371.1851.

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