Total Synthesis of (+)-Xestoquinone Using an Asymmetric Palladium-Catalyzed Polyene Cyclization

Shawn P. Maddaford, Neil G. Andersen, Walter A. Cristofoli, and Brian A. Keay*

Contribution from the Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

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Abstract: The first total asymmetric synthesis of (+)-xestoquinone (**1**) has been accomplished in 68% ee by a palladium(0)-catalyzed polyene cyclization of naphthyl triflate **44** using (*S*)-(+)-BINAP as the chiral ligand. Attempts at an asymmetric polyene cyclization using the corresponding naphthyl bromide **41** gave poor enantioselectivities even in the presence of silver salts, thus exemplifying the effect of the coordination state of palladium on the enantioselectivity. A new method for the preparation of 6,7-dihydroisobenzofurans is also described using a [1,2]-Wittig rearrangement on a seven-membered cyclic ether precursor.

(+)-Xestoquinone (**1**) and (+)-halenaquinone (**2**) are pentacyclic polyketides isolated from the Pacific sponges *Xestospongia sapra* and *Xestospongia exigua*, respectively.[1,2] Both **1** and **2** exhibit important biological activities. These compounds, especially **2**, are potent irreversible inhibitors of both the oncogenic protein tyrosine kinase $pp60^{v-src}$ encoded by the Rous sarcoma virus[3] and the human epidermal growth factor kinase (EGF). In addition to its antiproliferative activity, xestoquinone is a potent cardiotonic agent resulting from its unique positive inotropic effect on cardiac muscle.[1,4] More recently, xestoquinone has been used as a specific biochemical probe for the elucidation of structure and function of muscle contractile machinery.[5]

A diastereoselective synthesis of (+)-xestoquinone was reported by Harada *et al.*[6] starting from the optically pure Wieland−Miescher ketone, and a formal total racemic synthesis, via a furan ring transfer reaction, has been reported by Kanematsu *et al.*[7] An examination of the structures of **1** and **2** suggested that the chiral quaternary center could readily be introduced by an asymmetric Heck or polyene cyclization.[8] The intramolecular Heck reaction is a powerful method for construction of complex polycyclic systems as demonstrated by its application to the asymmetric synthesis of important natural products,[9] including (+)-halenaquinone.[6d] The power of the asymmetric palladium-catalyzed polyene cyclization for the construction of polycyclic ring structures has been demonstrated only once, by Overman;[8b] however, it has not been applied to an enantioselective synthesis of a natural product. We report herein a full account on our enantioselective total synthesis of (+)-xestoquinone (68% ee). The first section describes our initial strategy using a Heck reaction to attempt to create ring C and the quaternary carbon center (Path A, Scheme 1). Although this approach was unsuccessful, it led us to design a route using an asymmetric palladium-catalyzed polyene cyclization which forms both rings C and D while simultaneously introducing the asymmetric center in a single step (path B, Scheme 1).

Heck Reaction Approach

In our first approach toward **1**, we envisaged performing a Heck reaction on **3** to form ring C and the quaternary carbon center of xestoquinone (**1**; path A, Scheme 1). Disconnection of **3** led to the previously reported naphthalene **5** ($R = R^1 = H$)[10] and furan **6**. We felt that **6** could be prepared from furan **8** via introduction of a suitable group at C-4 of **8** using our previously reported methodology for the preparation of such compounds[11] followed by an intramolecular closure.

We first investigated the feasibility of using an intramolecular Barbier[12] cyclization of **14** to form dihydroisobenzofuran **18**

* Corresponding author. Phone: 1-403-220-5354. Fax: 1-403-284-1372. E-mail: keay@acs.ucalgary.ca.

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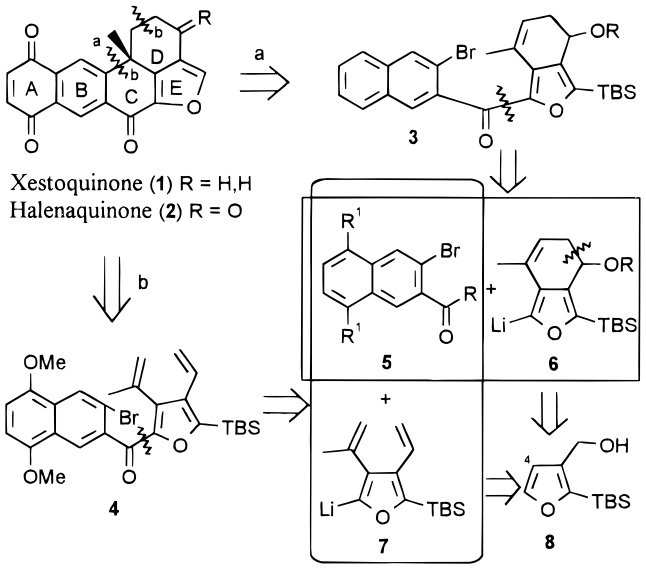
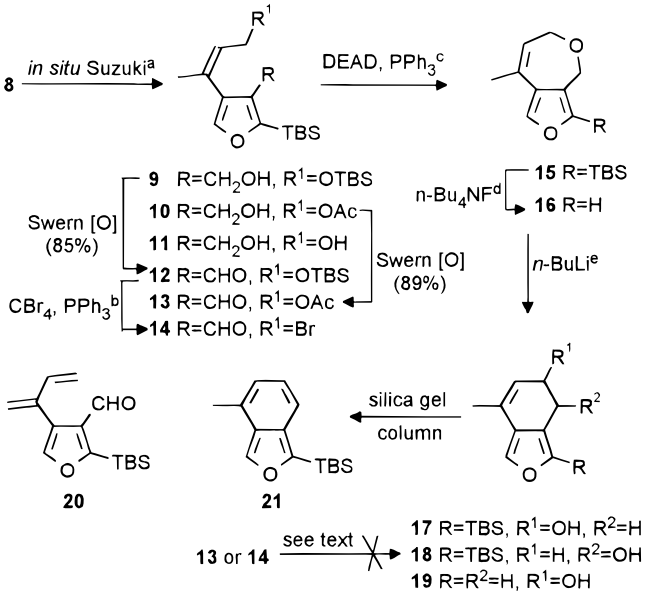
Scheme 1



Scheme 2[a]



[a] Reagents: (a) 2.2 equiv of *n*-BuLi, DME, 0 °C, 1 h; then add $(MeO)_3B$, 0 °C, 1 h; then add $Pd(PPh_3)_4$, 10% Na_2CO_3, 80 °C, 4 h, and (i) (*Z*)-1-(TBSoxy)-3-iodo-2-butene (96%) or (ii) (*Z*)-1-acetoxy-3-iodo-2-butene (88%) or (iii) (*Z*)-3-iodo-2-buten-1-ol (86%); (b) acetone/acetonitrile, 0 °C (50-60%); (c) THF, 20 °C (86%); (d) THF, 0 °C (84%); (e) ether, −78 °C, 5 min; then 0 °C 1 h (92%, 17).

(Scheme 2). Bromide **14** was prepared in four steps starting from 2-(*tert*-butyldimethylsilyl)-3-(hydroxymethyl)furan (**8**).[11d] The four-carbon substituent was introduced using our modified *in situ* variant of the Suzuki reaction.[11a,13] Treatment of **8** with 2.2 equiv of *n*-butyllithium in DME resulted in a regiospecific lithiation at C-4,[11c] which was quenched with trimethyl borate. After the mixture was stirred for 1 h at 0 °C, $Pd(PPh_3)_4$ (10 mol %), 10% aqueous Na_2CO_3, and (*Z*)-3-iodo-1-((*tert*-butyldimethylsilyl)oxy)-2-butene[14] (1.5 equiv) were added followed by heating the reaction to 80 °C for 4h. A standard workup provided **9** in 96% yield. Swern oxidation[15] of **9** yielded aldehyde **12**, which, when treated with carbon tetrabromide and PPh_3 in a mixture of acetone/acetonitrile,[16] provided a mixture of geometrical isomers **14** and a small amount of diene **20** (5%). Although **14** was a mixture of inseparable geometrical isomers, we attempted a Barbier cyclization under a variety of reaction conditions (using Li, Mg, and Zn).[12,17] Complex mixtures were always obtained, and the desired product **18** was never detected in the reaction mixture. A final attempt using $CrCl_2$ (generated *in situ*)[18] also provided a complex mixture even though allylic chromium species have been reported to react with aldehydes.[19]

Since Barbier type closures did not provide any of the desired product **18**, we investigated using transition metals to form the six-membered ring. Tabuchi and co-workers[20] have reported that allylic acetates react with aldehydes in the presence of Pd(0) and SmI_2. Acetate **10** was prepared as previously described[11a,13] and the hydroxymethyl group oxidized to provide aldehyde **13** (Scheme 2). Treatment of **13** with 10 mol % $Pd_2(dba)_3$ and SmI_2 in the presence of PPh_3 in THF at 0 °C provided only unreacted starting material; changing the reaction conditions and amounts of reagents used did not provide any of the expected product **18**. Since the aldehyde was not reduced in the presence of the SmI_2, it must be sterically hindered by the two large groups at the adjacent positions; thus, we attempted a method which did not require an initial reaction with the aldehyde. Although Semmelhack and co-workers[21] have reported that allylic halides and sulfonate esters react with aldehydes in the presence of Ni(0), we found that acetate **13** did not react under similar conditions.

Although the above methods and others[22] did not provide the required precursor **18**, we ultimately found that dihydroisobenzofurans could be easily prepared via a [1,2]-Wittig rearrangement of a cyclic ether precursor. Yadav and Ravishankar[23] have used this intramolecular rearrangement to construct the carbon framework of taxol by contracting a nine-membered cyclic ether to an eight-membered carbocycle. The use of this strategy for the preparation of **18** required a synthesis of ether **15** (Scheme 2). This was accomplished by treatment of **11**, prepared by our modified *in situ* Suzuki reaction,[11a,13] with DEAD and PPh_3 (86%).[24]

Normally, the precursor for a [1,2]-Wittig rearrangement has one of the two methylene groups (adjacent to the ether oxygen) in an allylic or benzylic position. Treatment of the ether with *n*-butyllithium results in the removal of a proton from the allylic methylene resulting in a regiospecific rearrangement.[25] Since both methylene groups in **15** are adjacent to double bonds, two products, **17** and **18**, were possible from this rearrangement (Scheme 2). Treatment of **15** with 2.5 equiv of *n*-butyllithium in ether afforded only compound **17** in 92% yield. Since **17**

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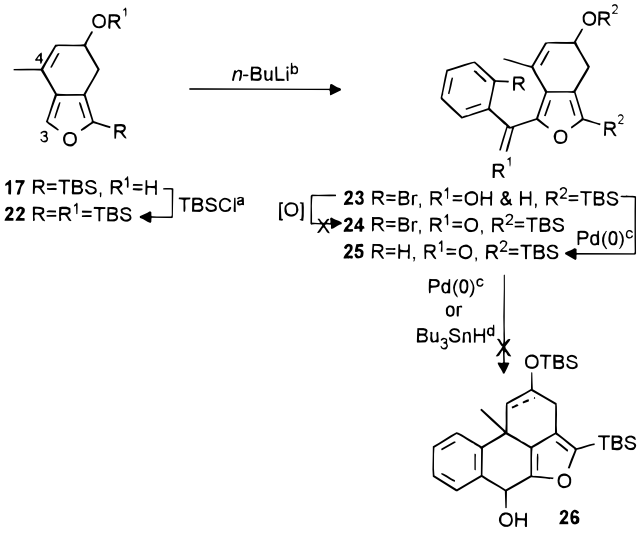
Scheme 3[a]



[a] Reagents: (a) imidazole, DMF (68%); (b) TMEDA, THF, −78 °C, 1 h; then 2-bromobenzaldehyde (73%); (c) $Pd(PPh_3)_4$, Ag_2CO_3, toluene, 110 °C; (d) AIBN, benzene, reflux.

was the wrong isomer required for the synthesis of xestoquinone (**1**), we investigated whether the bulky silane was responsible for sterically blocking attack of the *n*-butyllithium at the furylic position. The silyl group in **15** was removed (*n*-Bu_4NF, THF) to provide **16** and subjected to the same reaction conditions. Furan **19** was isolated, indicating that the methylene protons on the carbon adjacent to the double bond in the seven-membered ring must be more acidic than those at the furylic position. Changing the type of base, solvent, and/or temperature did not result in the formation of the desired dihydroisobenzofuran.

Compound **17** could be isolated if appropriate precautions were taken to prevent dehydration to form isobenzofuran **21**. Purification of **17** using silica gel resulted in the formation of a small amount of **21** (∼14%); however, the addition of 10% (w/w) potassium carbonate to the silica gel prior to the preparation of the column suppressed the dehydration, and **17** could be isolated in 92% yield. Surprisingly, isobenzofuran **21** was relatively stable at room temperature for approximately 2 h which allowed us to obtain a ^{1}H NMR spectrum. This unusual stability at room temperature is in contrast to the literature which states that isobenzofurans are difficult to isolate at room temperature unless electron-withdrawing groups or bulky aromatic rings are present in the C-1 or C-3 position.[26] Presumably the presence of the bulky silane at C-1 reduces the tendency of **21** to polymerize at higher temperatures. We are currently investigating the use of systems like **21** as intermediates in natural product syntheses. Although the [1,2]-Wittig reaction provided the wrong isomer, we decided to use **17** as a model to determine if an aromatic ring could be attached to the furan ring and if the Heck cyclization would work.

The hydroxy group in **17** was protected under standard conditions to yield silyl ether **22** (68%; Scheme 3), which upon treatment with 2.5 equiv of *n*-butyllithium in the presence of TMEDA (THF, −78 °C, 1 h) lithiated exclusively at C-3. The addition of 2-bromobenzaldehyde provided alcohol **23** in 73% yield. Compound **23** was used as a model system to study the Heck cyclization. Treatment of **23** with $Pd(PPh_3)_4$ in the presence of Ag_2CO_3 provided a 61% yield of **25** in which **23** had undergone an oxidative debromination;[27,28] the expected **26** (with a double bond) was not detected by either ^{1}H NMR or GC-MS analysis. To avoid this oxidative debromination problem, we attempted to oxidize the alcohol in **23** prior to performing the Heck reaction.[29] Surprisingly, every oxidation method tried to date (*e.g.*, Swern oxidation, MnO_2, PDC, PCC, DDQ, Fétizon's reagent, etc.) provided either unreacted starting material or decomposed material. In our hands, ketone **24** could not be prepared via the oxidation of alcohol **23**. Finally, we tried to close ring C by a free radical cyclization,[30] but treatment of **23** with *n*-Bu_3SnH and AIBN in refluxing benzene did not provide any of furan **26** (without a double bond).

With the failure of the Heck reaction, we turned our attention toward designing an alternative route which would allow us to prepare xestoquinone asymmetrically. The next section describes (1) how we overcame the problems associated with the Heck reaction approach and (2) the asymmetric synthesis of xestoquinone (**1**).

Asymmetric Palladium-Catalyzed Polyene Cyclization Approach

In our second approach toward xestoquinone (**1**), we envisaged performing an asymmetric palladium-catalyzed polyene cyclization[8] of dienyl bromide **4** (Scheme 1), which would create the C and D rings and also allow for the introduction of the stereogenic center in the later stages of the synthesis. Disconnection of **4** gave naphthalene **5** (R = Cl, R^1 = H or OMe) and furan **7**, which could be prepared using our previously reported method for synthesis of 2,3,4-trisubstituted furan rings.[11,13] We initially chose to use naphthalene **5** (R = Cl, R^1 = H) in our synthetic approach since it was readily available from 3-bromo-2-naphthaldehyde,[10] and we felt that after the palladium-catalyzed cyclization, ring A of the pentacyclic intermediate could be oxidized to a quinone using literature methods.[31]

Furan **8** was regioselectively lithiated[11c] with 2.2 equiv of *n*-BuLi in DME at −78 °C and trapped with $B(O\text{-}i\text{-}Pr)_3$[13,32] (Scheme 4). *In situ* treatment of the borate with water or 2 M Na_2CO_3[33] followed by a Pd(0) cross-coupling with 2-bromopropene afforded 3-isopropenylfuran **27** in 95% yield. Subse-

(25) The mechanism of a [1,2]-Wittig rearrangement is believed to be radical in nature, in which the two radicals arise from the carbon−oxygen homolysis of an α-anionic intermediate followed by the recombination of the radical and radical−anion fragments; see: (a) Marshall, J. A. In *The Wittig Rearrangement*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 975. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763.

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(27) A search of the literature revealed that Tamaru *et al*. have reported that alcohols can be oxidized to ketones or acids in the presence of $Pd(OAc)_2$ and bromobenzene. Thus, the conversion of **23** into **25** must be an intramolecular variant of this type of oxidation. (a) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z.-I. *J. Org. Chem.* **1983**, *48*, 1286. (b) Tamaru, Y.; Inoue, K.; Yamada, Y.; Yoshida, Z.-I. *Tetrahedron Lett.* **1981**, *22*, 1801. (c) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z.-I. *Tetrahedron Lett.* **1979**, *20*, 1401.

(28) We have recently reported a new one-pot desilylation−oxidation procedure using catalytic amounts of $PdCl_2$ in the presence of bromomesitylene; see: Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918.

(29) We felt the presence of ketone would also make the Heck reaction more facile, since it has been reported that Heck reactions proceed in higher yield and at lower temperatures when the aromatic ring containing the halide is substituted with electron-withdrawing groups; see: Heck, R. F. *Org. React.* **1982**, *27*, 345.

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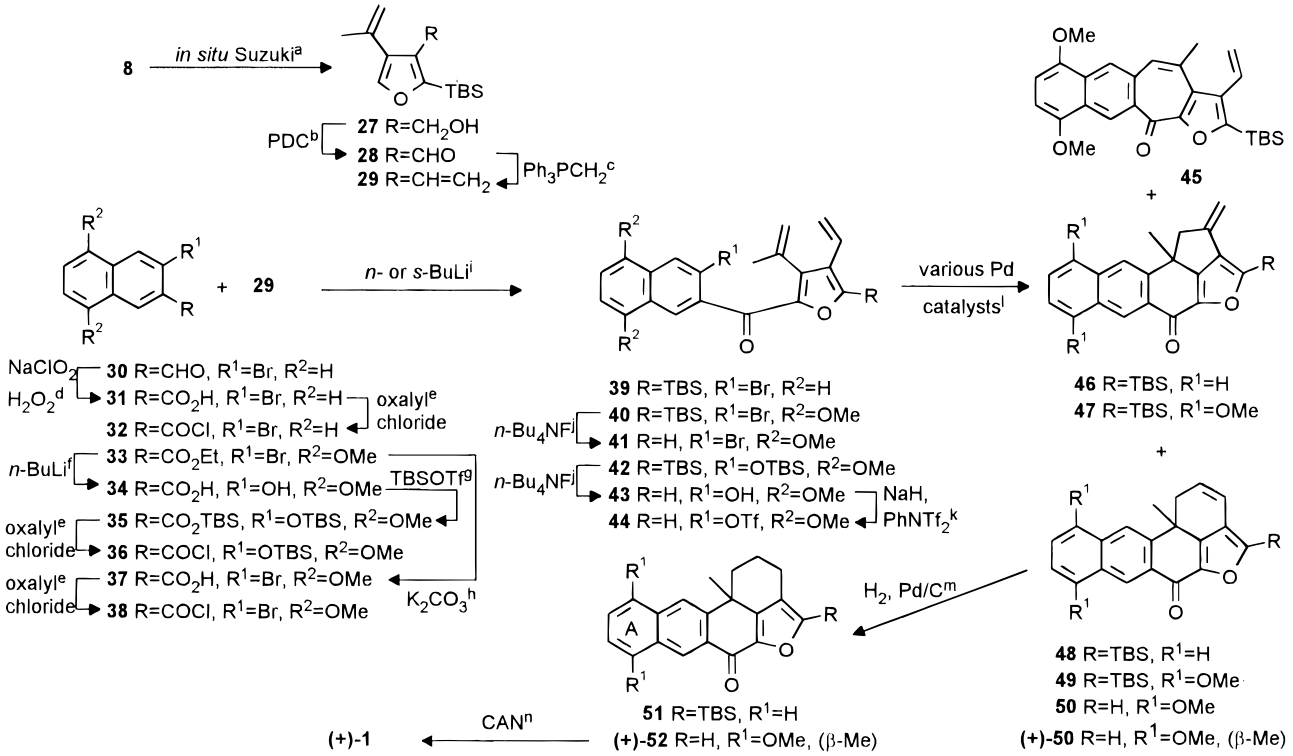
Scheme 4[a]



[a] Reagents: (a) *n*-BuLi (2.2 equiv), DME; then $B(O\text{-}i\text{-}Pr)_3$, −78 °C to room temperature, 1 h; then 2 M Na_2CO_3, 3 mol % $Pd(PPh_3)_4$, 2-bromopropene, 13 h, reflux (95%); (b) CH_2Cl_2, room temperature (85%); (c) THF, 1 h, reflux (95%); (d) Na_2HPO_4, MeOH, 10 °C, 6 h (90%); (e) hexanes, reflux (**32**, 77%), 1 drop of DMF (**36** and **38**, 99%); (f) −95 °C; then add $B(OMe)_3$; then add H_2O_2, NaOH; then 10% HCl (87%); (g) NEt_3 (79%); (h) MeOH:H_2O (9:1), reflux (95%); (i) i. **29** with 1.5 equiv of *n*-BuLi, 1.2 equiv of HMPA, THF, −78 °C, 1 h; then **32**, −78 °C, 1 h (79%); ii. **29** + s-BuLi, −78 °C, THF, 20 min; then add **36** (42% from **34**, three steps) or **38** (70% from **37**); (j) THF, 0 °C (95%); (k) DMF, room temperature, used immediately; (l) i. **39** or **40** with 10 mol % $Pd(PPh_3)_4$, NEt_3, toluene, reflux, 12 h, (74-79%); ii. **41** with 10 mol % $Pd(PPh_3)_4$, or $Pd_2(dba)_3$, Et_3N, NMP, reflux (82%); iii. **44** with $Pd_2(dba)_3$ (2.5 mol %), *S*-(+)-BINAP (10 mol %), PMP (8 equiv), 22 h (82% from **43**) (68% ee with **44**); (m) 1 atm, 4 h (99%); (n) CH_3CN/H_2O, 0 °C, 5 min.

quent PDC oxidation of **27** provided aldehyde **28**, which was converted into dienylfuran **29** by a standard Wittig reaction.

Since a ketone was necessary between the naphthalene and furan rings in **4** (Scheme 1), we investigated the direct condensation of the anion of **29** with 3-bromo-2-naphthoyl chloride (**32**). Acid chlorides[34a] and nitriles[34b] have been reported to react well with furyl anions for the preparation of ketones in one step. 3-Bromo-2-naphthoyl chloride (**32**) was prepared in two steps from the readily available 3-bromo-2-naphthaldehyde[10] (**30**; Scheme 4). Naphthaldehyde **30** was oxidized to the corresponding acid **31** by a $NaClO_2/H_2O_2$ oxidation in 90% yield, which, when treated with oxalyl chloride in hexane, provided the required acid chloride **32** in 77% yield. Acid chloride **32** was distilled and used immediately in the coupling reaction with the anion of furan **29**. Treatment of **29** with 1.5 equiv of *n*-BuLi in the presence of 1.2 equiv of HMPA (THF, −78 °C) followed by the addition of acid chloride **32** provided ketone **39** in 79% yield. With ketone **39** in hand, we investigated the palladium-catalyzed polyene cyclization reaction.

Treatment of **39** with 10 mol % $Pd(PPh_3)_4$ in toluene (NEt_3, 12 h, reflux) provided a 1:2 mixture of **46** and **48** in 74% yield. The formation of the highly strained **46** was initially surprising since AM1 level semiempirical calculations indicated that **48** was 25.1 kcal/mol more stable than **46**. Since the final step involved in the formation of furans **46** and **48** is a *syn* elimination of H-Pd-Br, which has been reported to be a fast process,[35] we conclude that the 1:2 ratio of **46**:**48** is a kinetic ratio. Adjusting the reaction conditions (type of catalyst, solvent, time, and temperature) did not noticeably change the ratio. Furans **46** and **48** were separated by column chromatography, and **48** was used to attempt a synthesis of (±)-xestoquinone (**1**). The double bond in **48** was reduced by catalytic hydrogenation to provide **51** in 65% yield. A variety of methods[31] were used to oxidize the A ring of **51** into a quinone (CrO_3−AcOH, ceric ammonium sulfate/H_2SO_4, Mn_2-SO_4, and electrochemistry); however, complex mixtures were obtained, and the quinone ring was never detected by ^1H NMR analysis. Furan rings are easily oxidized under similar conditions,[36] and presumably this was the reason for the complex mixtures.

Since the A ring of **51** could not be oxidized without destroying the molecule, we decided to develop a synthesis of 3-bromo-5,8-dimethoxy-2-naphthoyl chloride (**38**). If **38** could

(32) Trapping of the lithio anion at low temperatures with the more sterically hindered triisopropyl borate minimizes the possibility of double addition to the borate. Di- or triaryl species do not undergo Suzuki cross coupling with aryl halides; see: Thompson, W. J.; Guadino, J. *J. Org. Chem.* **1984**, *49*, 5237 and references therein.

(33) It has been shown that the transmetalation of boron with the Pd(II) species in Suzuki cross couplings is enhanced by the addition of bases like Na_2CO_3 or methoxide; see: (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457 and references therein. However, as 1 equiv of methoxide is liberated in the *in situ* method, the addition of external base makes no improvement in the yield; see ref 11a.

(34) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Petrini, P. *J. Org. Chem.* **1988**, *53*, 1748. (b) Siemanowski, W.; Witzel, H. *Liebigs. Ann. Chim.* **1984**, 1731.

(35) Heck, R. F. Vinyl Substitutions with Organopalladium Intermediates. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 833.

(36) (a) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167. (b) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *31*, 237.

be successfully coupled with furan **29** and subsequently ring closed, then the oxidation of the *para*-oriented methoxy groups into a quinone would not be a problem since Harada oxidized a similar intermediate into xestoquinone.[6]

Naphthalene **33** was prepared as previously described[37] and hydrolyzed with K_2CO_3 in refluxing methanol/water solution to give acid **37**. Treatment of **37** with oxalyl chloride in methylene chloride at room temperature in the presence of a catalytic amount of DMF provided acid chloride **38**. Deprotonation of **29** with 1.3 equiv of *s*-BuLi[38] and reaction with **38** gave the polyene precursor **40** in 70% yield from **37**.

The polyene cyclization of **40** was first investigated with an achiral Pd(0) catalyst. Treatment of **40** with $Pd(PPh_3)_4$ and triethylamine (TEA) in refluxing toluene gave a 1:2 mixture of products consistent with structures **47** and **49** (Scheme 4), consonant with our previous findings.[8a] It was hoped that conditions could be found that would preclude the formation of the 6,5-ring system. Changing the solvent from toluene to NMP resulted in a 1:2.5 mixture of **45** and **49**. Similar results were obtained in NMP using $Pd_2(dba)_3$ without added phosphine. In light of the strong preference for *exo* selectivity,[39] the formation of even small amounts of the seven-membered ring product **45** derived from an *endo* mode of cyclization is unusual. Recently, Rigby *et al.* have shown that the Jeffery conditions (10 mol % $Pd(OAc)_2$, *n*-Bu_4NCl (2 equiv), KOAc, DMF, 100 °C) give exclusively *endo* cyclization, whereas standard Heck conditions afforded mostly *exo* addition.[39] This unusual regioselectivity was attributed to a reduced coordination sphere around the palladium capable of accommodating the more substituted alkene site during the migratory insertion. This may suggest a similar effect when NMP was used, where a smaller solvent-coordinated palladium may be formed upon displacement of phosphine ligands.

The formation of the highly strained five-membered ring, likely formed under kinetic control,[8a] could be precluded if the polyene cyclization was performed after removal of the silyl group from **40** (Scheme 4). Thus, the polyene cyclization of **41**, prepared by treatment of **40** with TBAF, afforded only pentacycle (±)-**50** in 87% yield in which a 6-*exo* ring closure in the first step was followed by a rare 6-*endo* ring closure in the subsequent step.

With the successful preparation of (±)-**50**, we attempted to perform the cyclization in the presence of a chiral influence. Asymmetric polyene cyclizations of **41** were examined using a variety of chiral palladium catalysts; however, the enantioselectivities were poor at best ((i) $Pd_2(dba)_3$((*R*)-BINAP)$_2$/Et_3N (5% ee); (ii) $Pd_2(dba)_3$((*R*)-BINAP)$_2$/PMP (13% ee); (iii) $Pd_2(dba)_3$((2*R*,3*R*)-chiraphos)$_2$/PMP (7% ee)) and could not be improved by the addition of silver salts like Ag_3PO_4 or AgOTf.[40] In hopes of improving the enantioselectivity, we investigated the polyene cyclization of the corresponding triflate **44**.[41] Naphthyl bromide **33** was the starting point in the synthesis of **44**. Halogen metal exchange of **33**, trapping with $B(OMe)_3$, and subsequent oxidation/*in situ* hydrolysis afforded naphthol acid **34**. Compound **34** was treated with TfOSi(*tert*-Bu)Me_2 (2.2 equiv) to give **35** which was subsequently converted to acid chloride **36** (oxalyl chloride, DMF). Reaction of the anion of **29** with **36** at −78 °C provided **42** in good yield (42% from **34**, three steps). Both silyl groups in **42** were removed with TBAF to give naphthol **43** which was converted to the triflate **44** by treatment with NaH and $PhNTf_2$ in DMF.

Initially, the asymmetric polyene cyclization was performed with $Pd_2(dba)_3$((*R*)-(−)-BINAP)$_4$, which provided **50** in 68% ee (78% yield). To determine if **50** had the correct absolute stereochemistry needed for (+)-xestoquinone (**1**), it was converted into xestoquinone by a catalytic hydrogenation to provide **52** followed by a ceric ammonium nitrate (CAN) oxidation (Scheme 4).[6,7] Comparison of the CD spectrum (run in CH_3CN) of our synthetic sample with a CD spectrum of (+)-**1** supplied to us by Professor Harada[6] indicated synthetic **1** (and thus **52** and **50**) had the wrong absolute stereochemistry. Repeating the polyene cyclization on **44** using $Pd_2(dba)_3$((*S*)-(+)-BINAP)$_4$ gave the pentacyclic product (+)-**50** with high yield and enantioselectivity (82% from **43**, 68% ee).[42] Finally, (+)-xestoquinone (**1**) was prepared by a catalytic hydrogenation of (+)-**50** over 5% Pd/C (100%) followed by a CAN oxidation[6] of (+)-**52**. The ^{1}H NMR and CD spectra of synthetic (+)-xestoquinone (**1**) prepared using $Pd_2(dba)_3$((*S*)-(+)-BINAP)$_4$ was identical with those provided by Prof. Harada.[6]

Thus, we have developed the first asymmetric synthesis of (+)-xestoquinone which represents the first application of an asymmetric palladium-catalyzed polyene cyclization directed toward the synthesis of a natural product. We are currently investigating the use of the polyene cyclization toward other natural products and developing conditions to improve the enantioselectivity of the reaction.

Experimental Section

Methods and Materials. Compound **8**,[11b] (*Z*)-3-iodo-2-buten-1-ol,[14] 3-bromo-2-naphthaldedhyde (**30**),[10] ethyl 3-bromo-5,8-dimethoxy-2-naphthoate (**33**),[36] and the CAN oxidation of **52**[6] were prepared or carried out according to literature procedures. All NMR spectra were run in $CDCl_3$ unless otherwise stated. All melting points are uncorrected. Elemental analyses and HRMS spectra were obtained by Dorthy Fox at The University of Calgary.

2-((1,1-Dimethylethyl)dimethylsilyl)-4-(propen-2-yl)-3-(hydroxymethyl)furan (27). Furan **8** (0.71 g, 3.35 mmol) in DME (13 mL) at −78 °C under N_2 was treated with *n*-butyllithium (2.5 M in hexane, 2.29 mL, 7.37 mmol). The solution was warmed to 0 °C and stirred for 1 h. $B(OMe)_3$ (0.96 mL, 6.70 mmol) was added and the mixture stirred for 1 h. Into a second flask were placed $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), 2-bromopropene (0.45 mL, 5.03 mmol), and DME (6 mL). The contents of the first flask were transferred by syringe into the second flask followed by the addition of water (3 mL). The flask was immersed into a preheated oil bath at 70 °C. After 1 h ether was added, the organic layer separated and dried (Na_2SO_4), and the solvent removed. The crude product was purified by flash chromatography on silica gel using hexane:ethyl acetate (8:1) to provide **27** as a colorless white solid (0.50 g, 59%) which was recrystallized from ethyl acetate: mp 46−47 °C; IR (neat) 3297, 1471, 1251 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.60 (s, 1H), 5.41 (br s, 1H), 5.07 (br s, 1H), 4.63 (s, 2H), 2.07 (dd, 3H, J = 1.4, 0.7 Hz), 1.50 (br s, 1H, O*H*), 0.93 (s, 9H), 0.33 (s, 6H); ^{13}C NMR (50 MHz) δ 157.9, 144.7, 135.2, 133.1, 126.7, 112.9, 55.6, 26.3, 23.5, 17.1, −5.5; MS (EI, *m/z*) 252 (5, M^+), 237 (18, $M^+ - 15$), 195 (100, $M^+ - 57$). Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.55; H, 9.85.

3-Formyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)-furan (28). To a flask containing CH_2Cl_2 (25 mL) at −78 °C was

(37) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2885.

(38) Previously, the anion of **29** was generated by treatment with 1.5 equiv of *n*-BuLi in the presence of HMPA; see ref 8a.

(39) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834.

(40) For a discussion of the role of silver salts, see: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953. (b) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (c) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371.

(41) Higher asymmetric induction can be achieved when triflates are used as the leaving group in the Heck reaction. This has been ascribed to an increase in the liability of the Pd−OTf bond in the oxidative addition complex and allows bidentate coordination of the chiral ligand; see ref 9b.

(42) Enantiomeric excess was determined by HPLC: Chiralcel OJ, 85:15 hexanes:ethanol, λ = 350 nm. The absolute stereochemistry of (+)-**50** was extrapolated by comparing the CD spectrum of synthetic (+)-xestoquinone with a copy of the original CD spectrum sent to us by Prof. N. Harada.[6a]

added oxalyl chloride (1.1 equiv). DMSO (2.2 equiv) was added slowly and the mixture stirred for 2 min. Furan **27** (0.30 g, 1.19 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. After 15 min Et_3N (5 equiv) was added and the mixture warmed to room temperature. Water (50 mL) was added and the aqueous layer extracted with CH_2Cl_2 (5 × 25 mL). The organic layer was washed with 5% HCl (15 mL), 5% Na_2CO_3 (15 mL), and water (15 mL) and dried (Na_2SO_4) and the solvent removed to provide **28** as a colorless liquid (0.23 g, 77%): bp 56−70 °C/0.06 Torr; IR (neat) 1690, 1471, 1253 cm^{-1}; ^1H NMR (200 MHz) δ 10.10 (s, 1H), 7.57 (s, 1H), 5.25 (br s, 1H), 5.13 (br s, 1H), 2.06 (d, 3H, J = 0.8 Hz), 0.95 (s, 9H), 0.37 (s, 6H); ^{13}C NMR (50 MHz) δ 186.6, 171.9, 144.6, 135.9, 134.7, 127.1, 115.8, 26.3, 23.3, 17.4, −5.5; MS (EI, *m/z*) 250 (1, M^+), 235 (8, $M^+ - 15$), 193 (100, $M^+ - 57$). Anal. Calcd for $C_{14}H_{22}O_2Si$: C, 67.15; H, 8.86. Found: C, 66.83; H, 8.93.

3-Ethenyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)-furan (29). Methyltriphenylphosphonium bromide was purified by washing numerous times with hot toluene followed by drying under high vacuum for 8 h. In a nitrogen-purged 3-necked flask, the purified phosphonium salt (0.28 g, 0.77 mmol) was suspended in THF (10 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexane, 0.14 mL, 0.33 mmol) was added slowly via a syringe and the reaction mixture warmed to room temperature and allowed to stir for 20 min. A solution of aldehyde **28** (77.6 mg, 0.31 mmol) was dissolved in THF (5 mL) in an addition funnel and added to the orange-yellow solution of the ylide. After refluxing the mixture for 3 h, it was cooled to room temperature, poured into ether (20 mL), and allowed to stir overnight. The solvent was evaporated *in vacuo* to leave a yellow solid which was purified by flash chromatography on silica gel using hexane:ethyl acetate (100:1) to yield **29** as a colorless liquid (66.6 mg, 87%): bp 38−50 °C/0.06 Torr; IR (neat) 1633, 1251 cm^{-1}; ^1H NMR (200 MHz) δ 7.48 (s, 1H), 6.67 (dd, 1H, J = 17.9, 11.2 Hz), 5.46 (dd, 1H, J = 17.9, 2.1 Hz), 5.25 (dd, 1H, J = 11.2, 2.1 Hz), 5.15 (br s, 1H), 5.02 (br s, 1H), 2.02 (dd, 3H, J = 1.4, 1.0 Hz), 0.93 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (50 MHz) δ 156.4, 143.7, 136.5, 135.0, 129.1, 126.7, 117.3, 114.0, 26.5, 23.2, 17.7, −5.2; MS (EI, *m/z*) 248 (40, M^+), 191 (100, $M^+ - 57$). Anal. Calcd for $C_{15}H_{24}OSi$: C, 72.52; H, 9.74. Found: C, 72.46; H, 9.86.

3-Bromo-2-naphthoic Acid (31). Naphthaldehyde **30**[10] (10.55 g, 2.34 mmol) was dissolved in methanol (8.8 mL). NaH_2PO_4 (0.16 g) in water (2 mL), two portions of $NaClO_2$ (0.69 g, 6 mL), and 30% H_2O_2 (0.6 mL) were added 3h apart while keeping the temperature at 10 °C. After 6.5 h, Na_2SO_3 (0.4 g) was added followed by the addition of 10% aqueous HCl. The reaction mixture was stored in the refrigerator overnight, and the next morning the solid white fluffy precipitate was filtered to provide acid **31** (0.54 g, 92%) which was recrystallized from $CHCl_3$: mp 222−223 °C (lit.[43] mp 220 °C); IR (Nujol) 3200−2920 (br s), 1701, 1460 cm^{-1}; ^1H NMR (200 MHz) δ 8.58 (s, 1H), 8.22 (s, 1H), 7.95 (dd, 1H, J = 8.0, 1.1 Hz), 7.72 (d, 1H, J = 7.8, 1.0 Hz), 7.61 (m, 2H); ^{13}C NMR (50 Mz) ($(CD_3)_2CO$) δ 167.4, 136.1, 133.8, 132.8, 132.3, 131.4, 130.8, 129.8, 128.2, 127.8, 117.4; MS (EI, *m/z*) 252, 250 (100, M^+), 235, 233 (50, $M^+ - 17$). Anal. Calcd for $C_{11}H_7O_2Br$: C, 52.62; H, 2.81. Found: C, 52.12; H, 2.65. HRMS: calcd for $C_{11}H_7O_2{}^{81}Br$, 251.9610; found, 251.9597.

3-Bromo-2-naphthoyl Chloride (32). Acid **31** (0.91 g, 3.62 mmol) and dry hexane (25 mL) were added to a nitrogen-purged single-necked round bottom flask. The reaction flask was cooled to 0 °C, and oxalyl chloride (1.15 mL, 13.2 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min. A condenser was attached, and the reaction flask was immersed in a preheated oil bath at 65 °C and allowed to reflux gently overnight. After 12 h the flask was cooled to room temperature, the solvent removed *in vacuo*, and the flask back-purged with nitrogen. The crude material was distilled and used immediately in the next reaction. Acid chloride **32** was obtained as a colorless liquid (0.75 g, 72%): bp 100 °C/0.06 Torr; IR (neat) 1776, 1433 cm^{-1}; ^1H NMR (200 MHz) δ 8.64 (s, 1H), 8.11 (s, 1H), 7.93 (dd, 1H, J = 6.6, 1.0 Hz), 7.71−7.52 (m, 3H); ^{13}C NMR (50 MHz) δ 165.5, 135.9, 135.8, 133.6, 131.5, 130.7, 130.4, 129.3, 127.7, 126.7, 115.8.

2-Hydroxy-5,8-dimethoxy-2-naphthoic Acid (34). Bromonaphthalene **33**[36] (63.2 mg, 0.191 mmol) was dissolved in dry THF (1.6 mL). The solution was placed under N_2 and cooled to −95 °C (hexanes/liquid N_2) and *n*-BuLi (80 μL of 2.5 M in hexanes, 0.20 mmol, 1.05 equiv) added. The solution was stirred for 3 min followed by the addition of $B(OMe)_3$ (3 equiv, 0.57 mmol, 65 μL), subsequently warmed to room temperature over a period of 2 h, and stirred for an additional 15 h. The resulting solution, containing a white precipitate, was cooled to 0 °C, 2 N aqueous NaOH (4 equiv, 0.76 mmol, 0.25 mL) and 30% H_2O_2 (4 equiv, 87 μL) were added, and the mixture was stirred overnight at room temperature. The solid was dissolved in water and the solution extracted with CH_2Cl_2 until the organic phase was colorless. The aqueous phase was acidified (10% HCl), resulting in a bright yellow precipitate which was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered, and evaporated to provide **34** as a yellow solid (41.2 mg, 87%) which was recrystallized from CH_2Cl_2: mp 266−268 °C; IR (KBr) 3275, 1668, 1463, 1289, 1194 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.40 (s, 1H), 6.87 (d, 1H, J = 8.4 Hz), 6.65 (d, 1H, J = 8.4 Hz), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 171.3, 156.5, 149.6, 147.1, 130.0, 126.3, 119.1, 114.5, 107.0, 105.5, 101.3, 55.7, 55.5; MS (EI, *m/z*) 248 (52.4, M^+), 231 (16.1), 230 (100), 216 (12.4), 215 (97.1), 187 (33.6), 115 (17.3). HRMS: calcd for $C_{13}H_{12}O_5$, 248.0685; found, 248.0679.

(1,1-Dimethylethyl)dimethylsilyl 5,8-Dimethoxy-3-((1,1-dimethylethyl)dimethylsiloxy)-2-naphthoate (35). The acid **34** (70 mg, 0.28 mmol) was partially dissolved in dry CH_2Cl_2 (3 mL). Triethylamine (236 μL, 1.69 mmol, 3 equiv) was added followed by TfOSi(*tert*-Bu)-Me_2 (136 μL, 0.59 mmol, 2.1 equiv). The resulting solution was stirred at room temperature for 21 h. The solution was filtered through silica gel using hexanes:ethyl acetate (8:1) containing a few drops of TEA. The solvent was evaporated to give an oil (106 mg, 79%). The crude product **35** was used in the acid chloride reaction without further purification. An analytical sample was purified by radial chromatography (15:1 hexanes:ethyl acetate): ^1H NMR (200 Hz) δ 8.65 (s, 1H), 7.58 (s, 1H), 6.72 (d, 1H, J = 8.1 Hz), 6.56 (d, 1H, J = 8.1 Hz), 3.95 (s, 3H), 3.94 (s, 3H), 1.06 (s, 9H), 1.05 (s, 9H), 0.42 (s, 6H), 0.28 (s, 6H); ^{13}C NMR (50 Mz) δ 165.9, 152.6, 150.3, 148.4, 129.3, 126.9, 125.2, 121.0, 111.4, 105.8, 101.7, 56.0, 55.9, 26.1, 26.0, 18.7, 18.1, −4.1, −4.4.

5,8-Dimethoxy-3-((1,1-dimethylethyl)dimethylsiloxy)-2-naphthoyl Chloride (36). The silyl ester **35** (0.106 g, 0.223 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL). Oxalyl chloride (2.5 equiv, 0.56 mmol, 48 μL) and DMF (1 μL) were added resulting in a vigorous release of CO gas. The yellow solution was stirred for 19 h at room temperature and the solvent evaporated to give a yellow solid which was used in the next reaction without further purification. The reaction appeared quantitative by ^1H NMR analysis: ^1H NMR (200 MHz) δ 8.99 (s, 1H), 7.56 (s, 1H), 6.80 (d, 1H, J = 8.4 Hz), 6.60 (d, 1H, J = 8.4 Hz), 3.98 (s, 3H), 3.95 (s, 3H), 1.06 (s, 9H), 0.32 (s, 6H).

3-Bromo-5,8-dimethoxy-2-naphthoic Acid (37). The ester **33**[36] (176 mg, 0.53 mmol) was dissolved in 9:1 methanol:H_2O (10 mL). Solid K_2CO_3 monohydrate (290 mg, 3.3 equiv) was added and the solution refluxed for 4 h under N_2. The solution was cooled and the methanol evaporated to give a solid. Dilute HCl (10%, 10 mL) was added to the solid resulting in a bright yellow precipitate. Ethyl acetate (10 mL) was added and the mixture transferred to a separatory funnel. The layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give a yellow solid (158 mg, 95%): mp 242−243 °C; IR (KBr) 2943 (br), 1699 cm^{-1}; ^1H NMR (200 MHz) δ 8.92 (s, 1H), 8.54 (s, 1H), 6.86 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 8.4 Hz), 3.98 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (acetone-d_6) δ 167.7, 151.0, 149.3, 130.8, 128.5, 127.6, 124.4, 118.5, 108.5, 56.8, 56.7; MS (EI, *m/z*) 312, 310 (85.2, M^+), 297, 295 (100, $M^+ - 15$), 269 (13.4), 267 (13.5), 217 (40.1). HRMS: calcd for $C_{12}H_8O_4Br$, 309.9841; found, 309.9870.

5-((3-Bromonaphth-2-yl)carbonyl)-3-ethenyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)furan (39). To a mixture of divinylfuran **29** (0.22 g, 0.89 mmol) and HMPA (0.18 mL, 1.06 mmol) in THF (5 mL) at −78 °C was added *n*-butyllithium (2.5 M solution in hexane, 0.43 mL, 1.33 mmol), and the solution was stirred for 1 h. In a second flask, acid chloride **32** (0.35 g, 1.30 mmol) was dissolved in THF (4 mL) and cooled to −78 °C. The contents of the first flask were transferred via a cannula to the second flask and the mixture stirred

(43) Young, S. D.; Wiggins, J. M.; Huff, J. R. *J. Org. Chem.* **1988**, *53*, 1114.

for 1 h. Saturated aqueous NH_4Cl was added at −78 °C, and after the mixture stirred for 10 min the dry ice bath was removed and the reaction mixture was allowed to come to room temperature. The aqueous layer was extracted with ether (5 × 5 mL), the combined extracts were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The crude product was purified on a Chromatotron using hexane:ethyl acetate (100:1) to provide **39** as a white powder (0.34 g, 79%) which was recrystallized from $CHCl_3$: mp 94.5−96 °C; IR (KBr) 1657, 1554, 1255, 754 cm^{-1}; ^1H NMR (200 MHz) δ 8.09 (s, 1H), 7.91 (s, 1H), 7.91−7.70 (m, 2H), 7.61−7.45 (m, 2H), 6.61 (dd, 1H, J = 17.8, 11.5 Hz), 5.64 (dd, 1H, J = 17.8, 1.6 Hz), 5.24 (dd, 1H, J = 11.5, 1.6 Hz), 5.18 (br s, 1H), 5.07 (br s, 1H), 2.05 (t, 3H, J = 1.3 Hz), 0.85 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (50 MHz) δ 183.6, 161.8, 150.4, 137.9, 136.7, 135.4, 135.2, 134.5, 131.4, 131.2, 129.2, 128.3, 127.9, 127.1, 127.0, 126.9, 117.9, 117.4, 116.8, 26.3, 22.6, 17.4, −5.6; MS (EI, *m/z*) 482, 480 (82, M^+), 425, 423 (54, $M^+ - 57$), 401 (12, $M^+ - Br$). Anal. Calcd for $C_{26}H_{29}O_2BrSi$: C, 64.85; H, 6.07. Found: C, 65.04; H, 6.16.

5-((3-Bromo-5,8-dimethoxynaphth-2-yl)carbonyl)-3-ethenyl-2-((1,1-dimethylethyl)dimethylsilyl)-4-(propen-2-yl)furan (40). The bromo acid **37** was distilled at high vacuum (bp 130−180 °C/0.1 Torr) and dissolved in dry CH_2Cl_2 (3 mL). Oxalyl chloride (30.2 μL, 0.35 mmol, 1.2 equiv) was added followed by the addition of DMF (1 μL) resulting in the evolution of gas. The solution was stirred for 6 h at room temperature and the solvent removed *in vacuo* to provide acid chloride **38** as a yellow solid. This material was used without further purification.

Furan **29** was dissolved in dry THF (2 mL) and cooled to −78 °C under N_2. *s*-BuLi (0.23 mL of 1.28 M in cyclohexane, 0.289 mmol) was added to the furan solution and the resulting yellowish solution stirred for 15 min. The furyl−anion solution (−78 °C) was cannulated into a solution of acid chloride **38** in THF (−78 °C) and stirred for 50 min. The cold solution was quenched with saturated NH_4Cl (10 mL) and then warmed to room temperature. The solution was extracted with ethyl acetate, dried (Na_2SO_4), filtered, and evaporated. ^1H NMR of the crude revealed a 71% yield (based on starting furan). The oil was purified by radial chromatography (4:1 hexanes:ethyl acetate) to give a yellowish oil (109 mg, 70%): IR (film) 1768, 1657, 1583, 1461, 1108 cm^{-1}; ^1H NMR (200 MHz) δ 8.48 (s, 1H), 8.29 (s, 1H), 6.77 (d, 1H, J = 8.4 Hz), 6.70 (d, 1H, J = 8.4 Hz), 6.61 (dd, 1H, J = 11.5, 17.8 Hz), 5.64 (dd, 1H, J = 1.7, 17.9 Hz), 5.26 (dd, 1H, J = 1.7, 11.5 Hz), 5.14 (t, 1H, J = 1.6 Hz), 5.05 (dd, 1H, J = 1.0, 1.8 Hz), 3.95 (s, 3H), 3.90 (s, 3H), 2.03 (t, 1H, J = 1.0 Hz), 0.87 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (50 MHz) δ 184.0, 162.0, 150.2, 148.6, 137.8, 137.1, 135.8, 127.8, 127.4, 126.3, 124.5, 124.3, 118.1, 117.0, 67.0, 105.9, 104.4, 56.1, 55.9, 26.6, 23.0, 17.8; MS (EI, *m/z*) 542, 540 (39, M^+), 485, 483 (23, $M^+ - 57$). HRMS: calcd for $C_{28}H_{33}O_4BrSi$, 542.1320; found, 542.1299.

5-((3-Bromo-5,8-dimethoxynaphth-2-yl)carbonyl)-3-ethenyl-4-(propen-2-yl)furan (41). Silane **40** (109 mg, 0.20 mmol) was dissolved in THF (3 mL) and cooled to 0 °C under N_2. Tetra-*n*-butylammonium fluoride (0.22 mL, 1 M in THF, 1.1 equiv) was added dropwise and the solution stirred for 15 min. The reaction was quenched with saturated NH_4Cl (0.5 mL), the mixture was passed through a short silica gel column (ethyl acetate eluent), and the solvent was evaporated. The solid was purified by radial chromatography (4:1 hexanes:ethyl acetate) to give a bright yellow solid (82 mg, 0.19 mmol, 95%) which was recrystallized from ethyl acetate: mp 107−112 °C; IR (film) 1653, 1461, 1267, 1107 cm^{-1}; ^1H NMR (200 MHz) δ 8.45 (s, 1H), 8.25 (s, 1H), 7.65 (d, 1H, J = 0.4 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.74 (d, 1H, J = 8.4 Hz), 6.38 (dd, 1H, J = 5.9, 17 Hz), 5.61 (dd, 1H, J = 1.3, 17 Hz), 5.25 (dd, 1H, J = 1.3, 11.2 Hz), 5.10 (t, 1H, J = 1.6 Hz), 4.97 (dd, 1H, J = 1, 1.7 Hz), 3.97 (s, 3H), 3.93 (s, 3H), 1.95 (t, 3H, J = 1.0 Hz); ^{13}C NMR (50 MHz) δ 184.0, 150.1, 148.6, 147.8, 143.1, 137.5, 136.3, 135.9, 127.9, 126.6, 126.5, 125.4, 124.4, 124.0, 118.6, 117.4, 116.6, 106.1, 104.6, 56.1, 56.0, 23.00; MS (EI, *m/z*) 428, 426 (65, M^+). HRMS: calcd for $C_{22}O_4H_{19}Br$, 428.0451; found, 428.0478.

5-((3-((1,1-Dimethylethyl)dimethylsilyl)-5,8-dimethoxynaphth-2-yl)carbonyl)-3-ethenyl-2-((1,1-dimethylethyl)dimethylsiloxy)-4-(propen-2-yl)furan (42). Furan **29** (59 mg, 0.25 mmol, 1.1 equiv) was dissolved in dry THF and cooled to −78 °C under N_2. *s*-BuLi (0.23 mL of a 1.22 M solution in cyclohexane, 0.29 mmol, 1.3 equiv) was added. After 20 min the mixture was cannulated into a solution of the crude acid chloride **36** (0.22 mmol) in THF (6 mL) at −78 °C. The resulting solution was stirred for 50 min and the reaction quenched with saturated NH_4Cl (9 mL). The mixture was warmed to room temperature and partitioned with ethyl acetate (2 × 25 mL). The combined layers were dried (Na_2SO_4), filtered, and evaporated. The product was purified by radial chromatography on silica gel (20:1 hexanes:ethyl acetate) to provide **42** as a yellow oil (70 mg, 42% from **34**, three steps): IR (film) 1632, 1463, 1263 cm^{-1}; ^1H NMR (200 MHz) δ 8.24 (s, 1H), 7.50 (s, 1H), 6.72 (d, 1H, J = 8.3 Hz), 6.59 (dd, 1H, J = 11.5, 17.8 Hz), 6.56 (d, 1H, J = 8.3 Hz), 5.61 (dd, 1H, J = 1.7, 17.8), 5.22 (dd, 1H, J = 1.7, 11.5 Hz), 5.13 (m, 1H), 4.96 (m, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.05 (br s, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.20 (s, 6H), 0.18 (s, 6H); ^{13}C NMR (50 MHz) δ 184.9, 160.9, 151.5, 150.6, 148.6, 137.3, 135.3, 134.5, 133.3, 128.6, 127.6, 124.3, 121.4, 117.6, 117.3, 109.5, 105.2, 101.6, 56.1, 55.8, 26.6, 25.8, 23.1, 18.3, 17.7; MS (EI, *m/z*) 592 (1, M^+), 535 (100). HRMS: calcd for $C_{30}H_{39}O_5Si_2$ ($M^+ - C_4H_9$), 535.2336; found, 535.2317.

5-((3-Hydroxy-5,8-dimethoxynaphth-2-yl)carbonyl)-3-ethenyl-4-(propen-2-yl)furan (43). Disilane **42** (53.9 mg, 0.091 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C under N_2. Tetrabutylammonium fluoride (186 μL of a 1 M solution in THF, 0.186 mmol, 2.05 equiv) was added resulting in a red solution. After 5 min, the reaction was quenched with saturated NH_4Cl (6 mL) and the mixture extracted with CH_2Cl_2 (3 × 6 mL). The fractions were combined, dried (Na_2SO_4), filtered, and evaporated to give a red oil which was purified by radial chromatography (4:1 hexanes:ethyl acetate) to provide **43** as a red oil (33.1 mg, 0.091 mmol, 99%): IR (film) 1642 cm^{-1}; ^1H NMR (200 MHz) δ 10.34 (s, 1H, OH), 9.10 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 6.75 (d, 1H, J = 8.3 Hz), 6.51 (d, 1H, J = 8.3 Hz), 6.49 (ddd, 1H, J = 0.7, 11.2, 17.8 Hz), 5.68 (dd, 1H, J = 1.3, 17.8 Hz), 5.34−5.28 (7 line m, 2H), 5.02 (dd, 1H, J = 0.89, 1.7 Hz), 3.95 (s, 3H), 3.94 (s, 3H), 2.08 (t, 3H, J = 1.3 Hz); ^{13}C NMR (50 Mz) δ 219.2, 216.3, 158.2, 151.0, 148.4, 142.6, 136.7, 129.7, 126.5, 125.5, 117.9, 116.7, 111.0, 110.0, 107.4, 107.3, 100.9, 56.1, 55.8, 23.1; MS (EI, *m/z*) 364 (2, M^+). HRMS: calcd for $C_{22}H_{20}O_5$, 364.1311; found, 364.1288.

5-((5,8-Dimethoxy-3-((trifluoromethyl)sulfonyl)naphth-2-yl)carbonyl)-3-ethenyl-4-(propen-2-yl)furan (44). A solution of naphthol **43** (14.4 mg, 0.039 mmol) in dry DMF (2 mL) was cannulated into an ice-cooled flask containing solid sodium hydride (3.8 mg, 4 equiv). The resulting dark red solution was stirred at 0 °C for 15 min under N_2 followed by the addition of *N*-phenyltriflimide ($PhNTf_2$) (56 mg, 4 equiv) which rapidly decolorized the solution. The resultant colorless solution was stirred for 3.5 h, diluted with CH_2Cl_2 (20 mL), and extracted with saturated NaCl (3 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated. Excess DMF and $PhNTf_2$ were removed by heating under vacuum (0.1 Torr, 40 °C) to give the crude triflate **44**. The crude triflate was used in the polyene cyclization without further purification.

12b-Methyl-4-((1,1-dimethylethyl)dimethylsilyl)-1*H*-benzo[6,7]-phenanthro[10,1-*bc*]furan-6(12b*H*)-one (48) and 3-((1,1-Dimethylethyl)dimethylsilyl)-11b-methyl-2-methylidene-1*H*-naphth[2′,3′:4,5]-indeno[7,1-*bc*]furan-5(11b*H*)-one (46). A flask containing a mixture of compound **39** (0.22 g, 0.46 mmol), toluene (4 mL), $Pd(PPh_3)_4$ (52 mg, 0.045 mmol), and triethylamine (2 mL) was immersed into a preheated oil bath (100 °C). After 12 h, the reaction was complete by GC−MS, and the mixture was filtered through Celite and the solvent removed *in vacuo*. The crude mixture was purified by flash chromatography on silica gel using hexane:ethyl acetate (30:1) to provide a 2:1 mixture of **48**:**46**.

Compound 48: bp 136−140 °C/0.07 Torr; IR (neat) 1672, 1624, 1462 cm^{-1}; ^1H NMR (200 MHz) δ 8.95 (s, 1H), 8.04 (br d, 1H, J = 7.8 Hz), 7.90 (s, 1H), 7.87 (br d, 1H, J = 7.2 Hz), 7.62−7.48 (m, 2H), 6.71 (dd, 1H, J = 9.7, 2.7 Hz), 6.11 (ddd, 1H, J = 9.7, 6.3, 2.7 Hz), 3.80 (dd, 1H, J = 16.7, 6.3 Hz), 2.67 (dt, 1H, J = 16.7, 2.7 Hz), 1.52 (s, 3H), 0.98 (s, 9H), 0.40 (s, 6H); ^{13}C NMR (50 MHz) δ 172.5, 160.8, 147.3, 145.7, 144.0, 134.6, 131.9, 130.9, 129.5, 128.3, 127.9, 127.2, 126.3, 123.8, 123.6, 123.6, 119.3, 39.7, 35.2, 32.3, 26.3, 17.3, −5.9, −6.0; MS (EI, *m/z*) 400 (20, M^+), 385 (2, $M^+ - 15$), 343 (100, $M^+ - 57$). Anal. Calcd for $C_{26}H_{28}O_2Si$: C, 77.95; H, 7.04. Found: C, 77.58; H, 6.87. HRMS: calcd for $C_{26}H_{28}O_2Si$, 400.1859; found, 400.1851.

Compound 46: 69 mg, 39%; bp 130−138 °C/0.07 Torr; IR (neat) 1685, 1660, 1464, 1253 cm^{-1}; ^1H NMR (200 MHz) δ 8.90 (s, 1H),

7.99 (dd, 1H, $J = 7.9, 1.2$ Hz), 7.85 (dd, 1H, $J = 8.0, 1.3$ Hz), 7.79 (s, 1H), 7.62−7.45 (m, 2H), 5.48 (m, 1H), 5.36 (m, 1H), 3.51 and 3.38 (complex ABq, 1H each), 1.65 (s, 3H), 0.99 (s, 9H), 0.41 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (50 MHz) δ 172.8, 163.4, 162.5, 145.8, 145.4, 141.5, 139.7, 134.5, 134.3, 131.7, 130.8, 129.7, 128.4, 127.1, 126.4, 125.5, 110.5, 55.6, 41.5, 32.2, 26.4, 15.2, −6.0, −6.7); MS (EI, *m/z*) 400 (40, M^+), 343 (100, $M^+ - 57$). Anal. Calcd for $C_{26}H_{28}O_2Si$: C, 77.95; H, 7.04. Found: C, 77.72; H, 7.09.

(12b*S*)-8,11-Dimethoxy-12b-methyl-1*H*-benzo[6,7]phenanthro-[10,1-*bc*]furan-6(12b*H*)-one ((+)-50). The crude triflate **44** (∼0.039 mmol) was dissolved in dry toluene (2 mL). Pentamethylpiperidine (29 μL, 4 equiv) and a toluene solution of Pd((*S*)-BINAP)$_2$ (99 μL, 2.5 mol %; prepared by dissolving (*S*)-(+)-BINAP (13.9 mg) and $Pd_2(dba)_3$ (5.1 mg) in toluene (1 mL), 0.01 mmol/mL) were added. The solution was heated at 110 °C for 10 h under N_2. TLC (9:1 ether:CH_2Cl_2) indicated the presence of unreacted triflate. An additional aliquot of the catalyst solution (99 μL, 2.5 mol %) and PMP (29 μL) were added, and the solution was heated for a further 12 h. The crude reaction mixture was filtered through a pad of silica gel (2:1 hexanes:ethyl acetate) and purified by radial chromatography (8:1 hexanes:ethyl acetate) to afford a yellow solid (10.7 mg, 0.032 mmol, 82% from naphthol **43**). The enantiopurity was assessed by dissolving the sample in CH_2Cl_2/hexanes/ethanol and separating the enantiomers by chiral HPLC (85:15 hexanes:ethanol; Chiralcel OJ, $\lambda = 350$ nm, flow rate = 1.3 mL/min). The relative peak areas (12 and 15.5 min) indicated an ee of 68%. For comparison, racemic **50**, prepared from dienyl bromide **41** and $Pd(PPh_3)_4$, was injected and gave two peaks of equal intensity at 12 and 15.5 min: IR (film) 1727, 1672, 1622 cm^{-1}; ^{1}H NMR (200 MHz) δ 9.30 (s, 1H), 8.26 (s, 1H), 7.57 (s, 1H), 6.82 (d, 1H, $J = 8.4$ Hz), 6.71 (d, 1H, $J = 8.4$ Hz), 6.62 (dd, 1H, $J = 2.4, 9.7$ Hz), 6.11 (ddd, 1H, $J = 2.4, 6.2, 9.7$ Hz), 3.99 (s, 6H), 3.15 (dd, 1H, $J = 6.2, 17$ Hz), 2.67 (br d, 1H, $J = 17$ Hz); ^{13}C NMR (50 MHz) δ 172.9, 151.2, 149.0, 146.0, 144.6, 144.4, 141.6, 131.6, 129.0, 127.8, 125.1, 124.5, 118.5, 117.8, 106.4, 103.8, 56.0, 35.7, 32.4, 29.9; MS (EI, *m/z*) 346 (21, M^+). HRMS: calcd for $C_{22}H_{18}O_4$, 346.1205; found, 346.1207.

2,3-Dihydro-12b-methyl-4-((1,1-dimethylethyl)dimethylsilyl)-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6(12b*H*)-one (51). A mixture of compound **48** (76 mg, 0.19 mmol), ethanol (1 mL), and 5% Pd/C (15 mg, 20% by weight) was stirred vigorously under an atmosphere of H_2 (1 atm). After 12 h a second batch of 5% Pd/C (15 mg) was added. After 24h the mixture was filtered through Celite and washed with ethyl acetate (3 × 5 mL). The solvent was removed and the crude product purified by flash chromatography with silica gel using hexane: ethyl acetate (20:1) to provide **51** as a yellow viscous liquid (50 mg, 65%): bp 130−140 °C/0.07 Torr; IR (neat) 1666 cm^{-1}; ^{1}H NMR (200 MHz) δ 8.92 (s, 1H), 7.99 (d, 1H, $J = 7.7$ Hz), 7.90 (s, 1H), 7.88 (d, 1H, $J = 8.1$ Hz), 7.54 (m, 2H), 2.93 (ddd, 1H, $J = 9.4, 7.3, 2.3$ Hz), 2.69 (m, 1H), 2.58 (dt, 1H, $J = 9.2, 3.4$ Hz), 2.40−2.10 (m, 2H), 1.81 (dt, 1H, $J = 12.7, 4.6$ Hz), 1.53 (s, 3H), 0.97 (s, 9H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (50 MHz) δ 172.6, 162.0, 148.2, 146.8, 146.1, 134.6, 132.2, 131.6, 131.5, 129.6, 129.5, 128.2, 127.3, 126.2, 123.1, 36.3, 34.3, 31.9, 26.4, 19.4, 19.2, 17.7, −6.1, −6.2; MS (EI, *m/z*) 402 (20, M^+), 387 (2, $M^+ - 15$), 359 (2, $M^+ - 28$), 345 (100, $M^+ - 57$). HRMS: calcd for $C_{26}H_{30}O_2Si$, 402.2016; found, 402.2028. Anal. Calcd for $C_{26}H_{30}O_2Si$: C, 77.56; H, 7.51. Found: C, 77.04; H, 7.69.

(12b*S*)-2,3-Dihydro-8,11-dimethoxy-12b-methyl-1*H*-benzo[6,7]-phenanthro[10,1-*bc*]furan-6(12b*H*)-one ((+)-52). The alkene (+)-**50** (5 mg) was dissolved in ethyl acetate (1.0 mL) and hydrogenated (1 atm of H_2) at room temperature over Pd/C (5%, 1 mg) for 6.5 h. The solution was filtered through silica gel and the solvent evaporated. The product was purified by radial chromatography on silica gel (4:1 hexanes:ethyl acetate) to give xestoquinol dimethyl ether (5 mg, 100%). The ^{1}H NMR spectrum of (+)-**52** was identical with the literature spectrum:[6a] ^{1}H NMR (200 MHz) δ 9.28 (s, 1H), 8.27 (s, 1H), 7.48 (t, 1H, $J = 1.4$ Hz), 6.82 (d, 1H, $J = 8.4$ Hz), 6.70 (d, 1H, $J = 8.4$ Hz), 3.98 (s, 6H), 2.88 (dd, 2H, $J = 16.7, 7.7$ Hz), 2.70−2.58 (m, 2H), 1.83 (ddd, 2H, $J = 13.2, 13.2, 4.1$ Hz), 1.53 (s, 3H).

(+)-Xestoquinone (1). The (+)-dimethoxynaphthalene **52** (3 mg, 0.009 mmol) was dissolved in acetonitrile (1 mL) and treated with a solution of ceric ammonium nitrate (12 mg, 0.022 mmol, 3 equiv) in H_2O (0.5 mL). The solution was stirred for 10 min at 0 °C and subsequently filtered through a silica plug using ethyl acetate (eluent). The solvent was evaporated to provide (+)-xestoquinone (**1**): ^{1}H NMR (200 MHz) δ 9.08 (s, 1H), 8.25 (s, 1H), 7.55 (br t, 1H), 7.06 (s, 2H), 3.0−2.8 (m, 1H), 2.70−2.54 (m, 2H), 2.28−2.08 (m, 2H), 1.84−1.76 (m, 1H), 1.56 (s, 3H).

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Supporting Information Available: Experimental procedures and characterization data for (*Z*)-3-iodo-1-((methylcarbonyl)oxy)-2-butene, (*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-3-iodo-2-butene, (*Z*)-3-iodo-2-buten-1-ol, and compounds **9**−**17**, **19**−**23**, **25**, **49**, **47**, and **45**; ^{1}H and ^{13}C NMR spectra for compounds **36** (^{1}H NMR only), **34**, **35**, **37**, **40**−**43**, and (+)-**50**; and HPLC trace used to determine the ee of (+)- and (−)-**50** (30 pages). See any current masthead page for ordering and Internet access instructions.

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