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Strategies for the Synthesis of the Halenaquinol and Xestoquinol Families of Natural Products

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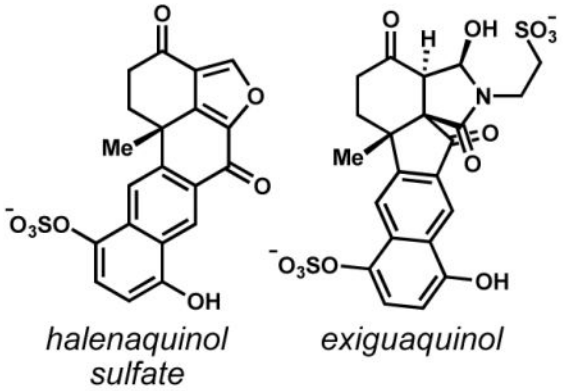
Abstract

The halenaquinol family of naphthoquinol natural products includes a few closely related polycyclic compounds that feature an activated, electrophilic furan ring. This motif is likely responsible for the rich biological activity attributed to these secondary metabolites. Their interesting structures—related via their electrophilic furan to the biologically important furanosteroids—and their activities prompted significant efforts by organic chemists that resulted in many strategically compelling laboratory syntheses of these targets. These different strategies are compared and contrasted in this Microreview, and the authors' recent work on the structurally different but biogenetically related natural product exiguaquinol is put into the context of the previous studies on halenaquinol-type targets.

Graphical Abstract

The wealth of different strategies for the chemical synthesis of the halenaquinol/xestoquinol family of natural products is discussed. Similar themes throughout the different achievements are highlighted, and a discussion of the recently discovered relative exiguaquinol is included.



Keywords

natural products; total synthesis; Diels–Alder; Heck reactions; electrophilic compounds; Cycloaddition; Heterocyclic chemistry

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1. Introduction to the Halenaquinol and Xestoquinol Families of Natural Products

The furanosteroid class of fungus-derived natural products includes wortmannin (**1**, Figure 1) and viridin (**2**). These bioactive compounds have long been known to be electrophilic natural products by virtue of their doubly activated (acylated) furans, which can undergo addition/elimination reactions with biologically relevant nucleophiles.[1–4] In an interesting example of possible convergent evolution, the halenaquinol/xestoquinol family (see halenaquinol sulfate and xestoquinol sulfate, **3** and **4**, respectively) also feature the activated furan incorporated into a structurally complex secondary metabolite; the structural origins of these natural products are thought to be polyketide biosynthesis.[5] The halenaquinol and xestoquinol family members, which are the primary focus of this review, have demonstrated antibiotic,[5a] cardiotonic,[6] cytotoxic,[7] antifungal,[7] and protein tyrosine kinase inhibitory activity,[5b] among others. Recently, this famiy has expanded, with the addition of exiguaquinol (**5**), a probable biosynthetic descendant of halenaquinol, and a possible antibiotic.[8]

Halenaquinone (**7**) was isolated in 1983 by the Clardy group from the marine sponge *Xestospongia exigua* (Figure 2).[5a] Its chemical structure and relative stereochemistry were determined by X-ray diffraction, but its absolute configuration could not be confirmed at that time. In 1985, the Kitagawa group reported the isolation of two related natural products, halenaquinol (**9**) and halenaquinol sulfate (**4**), from *Xestospongia sapra* and confirmed their absolute stereochemistry by total synthesis.[9] In the same year, xestoquinone (**6**), a structurally similar furanosteroid lacking a C3 ketone, was isolated from *Xestospongia sapra* by the Nakamura group.[6] Xestoquinol (**8**) and xestoquinol sulfate (**3**) were also identified from the same organism several years later.[10]

To date, there have been four syntheses of halenaquinone or halenaquinol (three asymmetric) and four syntheses of xestoquinone or xestoquinol (two asymmetric). In addition, several approaches have been reported to access the core structural features of halenaquinol and xestoquinol. The following sections will highlight the synthetic efforts towards the halenaquinol and xestoquinol classes of natural products and will conclude with some work towards exiguaquinol.

2. Total Syntheses of Halenaquinol, Xestoquinol, and Thiohalenaquinol

2.1. Common Approaches to the Syntheses of Halenaquinol and Xestoquinol

Since 1988, there have been eight reported syntheses of halenaquinol or xestoquinol and one synthesis of a related analogue, thiohalenaquinol. In two instances, the successful strategy to access halenaquinol was applied to xestoquinol with little perturbation to the overall approach. While each group's approach was unique, there appear to be four main C–C bond disconnections used in the seven distinct strategies (Figure 3). The groups of Harada,[11,12] Kanematsu,[13] and Rodrigo[14,15] based their syntheses on a similar disconnection in which the naphthalene portion of the molecule is formed by a [4+2] cycloaddition (red). Although

their tricyclic dienophiles were different in each case, all three groups utilized a stable *o*-quinodimethane precursor to annulate the naphthalene moiety.

The second most common strategic bond disconnection involved scission of the C–C bond between the C6 quaternary center and the naphthalene group (blue, Figure 3). The Keay[16] and Wipf[17] groups noticed that this bond could be constructed through an intramolecular Heck reaction of an aryl halide and a pendant alkene. Using a chiral ligand, the Keay group was able to perform their transformation enantioselectively, highlighting the power of this tactical disconnection.

The Shibasaki group completed their synthesis of halenaquinol using a late-stage assembly of the furan ring (grey, Figure 3).[18,19] This strategy was unlike previous approaches in that it first formed the CDE-ring tricycle and postponed construction of the A and B rings. This approach resulted in the longest linear synthesis of halenaquinol and perhaps suggests the greater step economy of the alternative routes.

The most recent synthesis of halenaquinol was disclosed by the Trauner group and took advantage of a previously unexplored [4+2] cycloaddition to assemble the naphthalene portion of the molecule (green, Figure 3).[20] Their strategy centered on the early functionalization of the furan ring and a late-stage intramolecular Diels–Alder reaction of a vinyl quinone diene. This interesting strategy enabled a concise synthesis of halenaquinol in a high overall yield.

2.2 Harada's Syntheses of Halenaquinol, Xestoquinol, and Adociaquinones A & B

The first total syntheses of (+)-halenaquinone (**7**) and (+)-halenaquinol (**9**) were performed by the Harada group in 1988 (Scheme 1).[11] Using their π-electron SCF-CI-dipole velocity MO method to calculate the CD spectrum,[21] they were able to predict the natural configuration of the C6 methyl quaternary stereogenic center to be (*S*), and then complete the first enantioselective syntheses of halenaquinone and halenaquinol (Scheme 1).[22] This achievement required 15 steps in the longest linear sequence for halenaquinone and one additional transformation to access halenaquinol. Their approach features a benzocyclobutene ring-opening/*o*-quinodimethane Diels–Alder cycloaddition to stitch together the molecule.

Starting from (−)-Wieland–Miescher ketone (**10**), the Harada group accessed enone **11** in nine steps (Scheme 1). Dienophile **11** underwent an *o*-quinodimethane Diels–Alder cycloaddition with benzocyclobutene **12** upon heating to temperatures above 200 °C to generate **13** in 33% yield. DDQ was used to aromatize **13** to the corresponding naphthalene, which was then treated with O_2 and *t*-BuOK in *t*BuOH to provide diosphenol **14** in 90% yield. To forge the furan ring, the Harada group developed a modified Pfitzner–Moffatt oxidation protocol that utilized DCC, DMSO and trifluoroacetic acid.[11,23] After ketal deprotection, the 1,3-diol was oxidized to the β-ketoaldehyde and underwent spontaneous cyclization to reveal furan **15**. Finally, pentacycle **15** can be converted to halenaquinone (**7**) by oxidative deprotection with CAN; subsequent reduction with sodium dithionite affords halenaquinol (**9**). Owing to the high instability of **9** to light, air, and heat, the final reduction to halenaquinol was performed in the dark. With synthetic samples of enantiopure

halenaquinone and halenaquinol, the Harada group was able to verify that the CD spectrum of the synthetic sample matched the spectrum calculated by their SCF-CI-DV MO method, indicating that the enantiomer synthesized was identical to the one isolated by Kitagawa.[11,21]

Using a nearly identical route, Harada and coworkers were able to complete a synthesis of xestoquinone (**6**)[12] and adociaquinones A and B (**17–18**)[24] starting from enone **16** (Scheme 2). Overall, Harada's syntheses provided halenaquinone in 15 steps and 2% overall yield and xestoquinone in 17 steps and 1% overall yield from **10**.

2.3 Kanematsu's Synthesis of Xestoquinone

In 1991, the Kanematsu group published the second synthesis of xestoquinone based on a furan ring transfer strategy developed previously in their lab (Scheme 3).[25,13] This reaction rearranges a propargyl furfuryl ether (**19**) into a dihydroisobenzofuran (**22**) by a base-mediated isomerization to the allene (**20**) followed by an intramolecular Diels–Alder/ring-opening cascade (Scheme 3). Other furfuryl ethers, bearing alkyl substituents on the furan or linker, were found to participate in this transformation, affording substituted dihydroisobenzofurans in excellent yields.[25]

Starting with furfuryl alcohol (**23**), a four-step sequence involving furan ring transfer produced **24**,[26] which can engage methyl acrylate in a conjugate addition followed by regioselective methylation to afford **25** (Scheme 4). The ketone in **25** was reduced via the tosylhydrazone and the methyl ester was saponified and cyclized to **27** through a Friedel–Crafts acylation. Oxidation of the cyclohexanone provided enone **28**, which served as the dienophile in the subsequent Cr-mediated *o*-quinodimethane Diels–Alder reaction between **28** and **29**. To complete their formal synthesis of xestoquinone, the Diels–Alder adduct was aromatized to generate **30**, which can be converted to xestoquinone (**6**) by oxidation with CAN.[12]

The Kanematsu synthesis completed xestoquinone in 14 steps from furfuryl alcohol with an overall yield of 0.8%. The key transformations included a furan ring transfer reaction and an *o*-quinodimethane Diels–Alder cycloaddition originating from the Cr-mediated reductive metallation of an *o*-bis(bromomethyl)arene.

2.4. Rodrigo's Syntheses of Halenaquinone and Xestoquinone

In 2001, the Rodrigo group disclosed a short formal synthesis of racemic halenaquinone in which they rapidly assemble the ABC tricycle using an intramolecular Diels–Alder cycloaddition that was previously discovered in their lab (Scheme 5).[14,27,28] Afterwards, the naphthalene portion was appended through the cycloaddition of an electron-rich isobenzofuran.

Diene **32** was prepared from propargyl alcohol in four steps[29–31] and subjected to the Rodrigo group's optimal conditions for *o*-benzoquinone monoketalization/IMDA with methylguaiacol **31** and PIFA (Scheme 5). Adducts **33** and **34** were obtained as an inseparable mixture; however, heating this mixture to reflux in 1,2,4-trimethylbenzene converted **33** into **34** by means of a Cope rearrangement, and **34** was obtained in 36%

overall yield. Treatment of enone **34** with dimethoxyisobenzofuran **35** afforded pentacycle **36** in high yield. Naphthalene **37** was formed after base-mediated aromatization and acid-mediated elimination of the ketal. To complete their formal synthesis, **37** was aromatized to the furan with *p*-chloranil and the vinyl sulfide was converted into ketone **15** by heating with $TiCl_4$ in wet acetic acid. **15** can be transformed into halenaquinone using the previously disclosed methods.[11] This sequence provided **7** in 12 steps (longest linear) from commercially available materials and with roughly 3% overall yield.

Prior to their synthesis of halenaquinol, the Rodrigo group completed a formal synthesis of xestoquinone using a similar strategy (Scheme 6).[27] In this case, their dienol fragment (**38**) was lacking the thiophenyl ether group and required a late-stage hydrogenation of the cyclohexene to afford xestoquinone (**6**). This route efficiently provided **6** in eight steps and 7% overall yield from **31**. Following their synthesis, several methoxy-substituted congeners of xestoquinone were synthesized to validate their proposed structures and substitution patterns.[15]

2.5. Keay's Synthesis of Xestoquinone

The Keay group disclosed an asymmetric formal synthesis of xestoquinone in 1996 that took advantage of a Pd-catalyzed polyene cyclization to assemble the pentacyclic scaffold (Scheme 7).[16,32] This work constituted the third synthesis of xestoquinone and the second asymmetric synthesis. Their convergent strategy relied on joining two key fragments: one containing the furan and another bearing the naphthalene.

The naphthalene segment was prepared in 11 steps from 2,5-dimethoxybenzoic acid (**41**, Scheme 7). According to the procedure developed by Wallace, **41** can be transformed into 1,3,6-trimethoxybenzocyclobutene (**42**) in seven steps and 49% yield utilizing a [2+2] cycloaddition of an *in situ* generated benzyne.[33] With heating, **42** can rearrange to the *o*-quinodimethane and undergo a Diels–Alder reaction with ethyl 3-bromopropiolate (**43**) to generate **44**.[34] With three additional steps, **44** was converted into acid chloride **45**.

Trisubstituted furan building block **46** was assembled in a straightforward manner, and it was united with naphthoyl chloride **45** by lithiation of the unsubsituted furan position and nucleophilic addition to afford **47** in 54% yield. Formation of aryl triflate **48** followed by their pivotal asymmetric Heck bicyclization with catalytic $Pd_2(dba)_3$ and (*S*)-BINAP produced pentacycle **49** in 82% yield over two steps and up to 68% ee. Finally, **49** was hydrogenated and demethylated to provide xestoquinone (**6**).[12]

In their synthesis of xestoquinone, the Keay group demonstrated the importance of Pd catalysis in asymmetric total synthesis. Although the syntheses of their two key fragments (**45** and **46**) were fairly lengthy, the steps following their combination rapidly produced xestoquinone (**6**). Overall, the Keay group's enantioselective synthesis afforded xestoquinone in 17 steps (longest linear) and 4% overall yield.

2.6. Wipf's Synthesis of Thiohalenaquinone

The activated furan is believed to play a significant role in the biological activity of the furanosteroids,[1–4] as well as the xestoquinone/halenaquinone family. However, as a potent electrophile, this group is also likely responsible for its poor target specificity and *in vivo* toxicity.[17,35] In order to probe the biological significance of the furan present in halenaquinone (**7**), the Wipf group synthesized thiohalenaquinone (**56**, Scheme 8), an analogue containing a thiophene ring in place of the typical furan. They reasoned that the reduced strain energy due to the longer C–S bonds in the thiophene and the increased resonance stabilization energy should make thiohalenaquinone less prone to nucleophilic addition compared to halenaquinone, thus making the sulfur variant a more selective inhibitor for its target enzymes.[17] Their strategy initially revolved around functionalization of the thiophene ring. The naphthalene portion was installed via an *o*-quinodimethane Diels–Alder reaction and the carbon framework was assembled with a Heck reaction followed by a late-stage RCM.

Conversion of 3,4-dibromothiophene (**50**) into highly substituted thiophene **51**, bearing a bromo-ynone dienophile, was accomplished through a 12-step protocol. Treatment of **51** with benzocyclobutene **46** at 220 °C afforded aryl bromide **52**, which was then subjected to a Pd-catalyzed 6-*exo* Heck reaction under microwave irradiation to forge the cyclohexanone ring of **53** in 10% yield over four steps. To form the final 6-membered ring, the protected alcohol was converted to the aldehyde and allylated with allyltributyltin and $BF_3{\cdot}OEt_2$ to give **54**. Ru-catalyzed isomerization to the internal olefin and RCM with Hoveyda–Grubbs catalyst produced pentacycle **55** in 56% yield over the two steps. Interestingly, RCM of the vinylated compound (not shown) proceeded in poor yield; fortunately, their allylation/isomerization sequence was shown to work significantly better. Finally, the synthesis of thiohalenaquinone was completed in three steps by Dess–Martin oxidation, conjugate reduction, and CAN oxidation to unveil the naphthoquinone in **56**. In the end, the Wipf synthesis of thiohalenaquinone was accomplished in 22 linear steps and 0.4% overall yield and utilized a convergent Diels–Alder/Heck sequence to assemble the majority of the carbon framework of **56**. Biological evaluations of these potentially interesting halenaquinone analogues have yet to be reported.

2.7. Shibasaki's Synthesis of Halenaquinone

In 1996, Shibasaki and coworkers disclosed the second total synthesis and the first catalytic asymmetric synthesis of halenaquinone (Scheme 9).[18,19] Their strategy revolved around the naphthalene portion of the molecule while the remaining three rings were annulated sequentially. Their key enantiodetermining Suzuki cross-coupling/Heck cyclization was the first example of this type of cascade. Although their Pd-cascade forges the same C–C bond as the Keay and Wipf strategies, the Shibasaki group performed this step much earlier in their synthesis and relied on additional key steps to complete their synthesis.

The synthesis of the tricyclic motif of **60** began with a five-step protocol to access naphthalene **58** from commercially available tetralone **57**. Double triflation of **58** followed by the remarkable one-pot Suzuki cross-coupling/asymmetric Heck cascade using $Pd(OAc)_2$

and (*S*)-BINAP directly provided **60** in 85% ee, although in low yield. Alternative stepwise pathways afforded **60** with improved yields (not shown).

Tetrahydroanthracene **60** was converted over ten steps to ynone/vinyl iodide **61**. Finally, Pd-catalyzed furan formation forged the fused pentacyclic scaffold of halenaquinol (**15**) after desilylation with TBAF. Naphthoquinol demethylation/oxidation following Harada's protocol[11] yielded halenaquinone (**7**).

Although the Shibasaki synthesis accessed halenaquinone in the greatest number of steps (18 longest linear steps using their most direct route, 1% overall yield), it constituted the first catalytic asymmetric synthesis of halenaquinone. Key features included their Pd-catalyzed Suzuki cross-coupling/Heck reaction cascade and the metal-mediated furan formation.

2.8. Trauner's Synthesis of Halenaquinone

To showcase their methodology involving the inverse-electron-demand Diels–Alder reaction of vinyl quinones,[36,37] the Trauner group developed a concise asymmetric total synthesis of (−)-halenaquinone (Scheme 10).[20] First, 3,4-diiodofuran (**62**) was converted in a five step sequence to enantioenriched Heck precursor **63**. The 6-*exo* Heck reaction using $Pd(OAc)_2$ and TBAB closed the cyclohexane ring of **64** with good diastereoselectivity (*dr* = 7:1). Nucleophilic addition of the stannate of **65** to aldehyde **64** produced an inconsequential mixture of carbinol diastereomers (**66**) in high yield. Next, deprotection and Ley–Griffith oxidation of both secondary alcohols yielded a chalcone-type intermediate, which was oxidized to vinyl quinone **67** with AgO and HNO_3. The desired inverse-electron-demand Diels–Alder cycloaddition was performed under high pressure, and the immediate product was aromatized with MnO_2 to afford *ent*-halenaquinone (*ent*-**7**).[20]

The Trauner group accomplished their asymmetric synthesis of the unnatural enantiomer of halenaquinone in 12 linear steps and 8% overall yield from diiodofuran **62**. The route features a diastereoselective intramolecular Heck cyclization and a Diels–Alder cycloaddition of a vinyl-substituted benzoquinone to assemble the furanosteroid pentacyclic scaffold.

3. Syntheses of Halenaquinol and Xestoquinol Analogues and Model Systems

A number of studies toward the xestoquinol/halenaquinol natural products culminated in the syntheses of the complex tetracyclic core structure of these targets. In most cases, the *o*-quinodimethane Diels–Alder cycloaddition plays a key role, as it did in some of the total syntheses described above.

3.1. Crews's Syntheses of Halenaquinone and Xestoquinone Analogues

During their studies on the protein tyrosine kinase activity associated with various furanosteroids and naphthalene-derived structures, the Crews group synthesized several complex halenaquinone and xestoquinone analogues.[38] The structures most relevant to halenaquinone and xestoquinone include those in which the furan is replaced with a benzene

ring (**73**–**74**, Scheme 11) or those lacking the fused aromatic ring altogether (**75**). While no yields are reported throughout their syntheses, enough of each analogue was isolated for biological evaluation. Their strategy appears to take inspiration from the work of both the Harada and the Kanematsu groups.[11,13] Readily available tricyclic intermediate **68** was oxidized with PCC to obtain diketone **69**. Heating either **68** or **69** in the presence of sulfone **70** effected a cheletropic extrusion/*o*-quinodimethane Diels–Alder cycloaddition with the enones to provide pentacyclic compounds **71** and **72**. Finally, aromatization to the naphthalene was accomplished with DDQ and oxidative demethylation with CAN led to xestoquinone analogue **73** and halenaquinone analogue **74**, each containing a fused benzene ring in place of the furan.

The synthesis of the tetracyclic analogue **75**, lacking the furan ring altogether, started from Wieland–Miescher ketone (synthesis not shown). Protein tyrosine kinase inhibition assays indicated that each analogue was less active (IC_{50} = 27 μM for **73**, 9 μM for **74**, and 10 μM for **75**) compared to halenaquinone (**7**) and halenaquinol (**9**) (IC_{50} = 1.5 and 0.6 μM, respectively).[38] However, the fact that any activity remained likely points to a non-covalent mechanism of action in these cases

3.2. Nemoto's Synthesis of the Halenaquinone Core

In 2001, the Nemoto group described their strategy for accessing the tetracyclic core of halenaquinol (**79**, Scheme 12).[39,40] They planned to access a fused tetracycle resembling halenaquinol through an intramolecular *o*-quinodimethane Diels–Alder cycloaddition. Benzocyclobutene **76** was heated to reflux in *o*-dichlorobenzene to unveil the *o*-quinodimethane, which underwent facile intramolecular cycloaddition with the furan to afford *endo* product **77** exclusively. Formation of an intermediate phenylselenide by alkoxyselenenylation, followed by oxidation and elimination provided dihydrofuran **78**. Finally, treatment with acid generated furan **79** with loss of methanol.

The halenaquinone core synthesis by the Nemoto group provided tetracycle **79** in nine steps and 8% overall yield from 3-furoyl chloride. Although their target still lacks a ketone and an additional aryl ring, it remains a unique and concise strategy in the halenaquinone synthesis literature.

3.3. Ahn's Synthesis of the Xestoquinone Core

In 2003, the Ahn group published a racemic synthesis of the tetracyclic core of xestoquinone (**85**, Scheme 13).[41] Their approach focused on the early formation of the quaternary center and postponed construction of the fused ring scaffold until a later stage. Using a [4+2] cycloaddition of a propargyl aldehyde, the 6,5-ring system was assembled in a single step, although with poor conversion.

Reactive ynal/ynoate **81** was obtained by oxidation of **80** with Dess–Martin periodinane. Upon heating in toluene, **81** underwent the intended proposed cascade, involving a tetradehydro-hetero-Diels–Alder reaction followed by a ring rearrangement and hydride shift, and provided **84**.[41] Although this reaction proceeded in only 5% yield, enough of **84** was obtained to evaluate the final step. Methyl ester **84** was treated with BBr_3 to effect a

one-pot demethylation/Friedel–Crafts acylation to afford the tetracyclic core of xestoquinone (**85**) in 42% yield.

The Ahn synthesis provided the tetracyclic core of xestoquinone (**85**) in 15 linear steps and 0.3% overall yield. While they demonstrated that their thermal cascade can yield furan **84**, significant optimization of this step is needed increase the efficiency of the Ahn group's overall approach.

4. Exiguaquinol. Proposed Origin from Halenaquinol Sulfate and Synthetic Studies

4.1. Likely Biogenesis of Exiguaquinol

Exiguaquinol (**5**) was isolated by the Quinn group from the methanolic extracts of the Australian sponge *Neopetrosia exigua*.[8] It was identified in a high-throughput screen for *H. pylori* MurI inhibition (IC_{50} = 361 μM) and postulated to bind the same cryptic allosteric site as AstraZeneca's pyrazolopyrimidinedione inhibitors.[42] In their report, the Quinn group proposed a biogenesis of exiguaquinol (**5**) starting from halenaquinol sulfate (**4**) (Scheme 14). First, an oxidative ring opening of the furan group in **4** is proposed, generating tetracarbonyl intermediate **87**. A molecule of taurine (**88**) can then condense with the aldehyde and cyclize onto the nearby ketone, forming hemiaminal **90**. Finally, the tertiary alcohol can undergo a semipinacol rearrangement to afford the fused 5-6-5 ring system present in **5**.[8] This plausible biogenetic connection converts a largely planar polycyclic natural product to one with a dense array of four stereogenic centers and more significant challenges for synthesis.

Besides exiguaquinol, other halenaquinol-derived natural products have been isolated that contain the addition of a taurine moiety (Figure 4). In 1988, a regioisomeric mixture of hypotaurine adducts of both xestoquinone and halenaquinone, named adociaquinone A–B (**17**–**18**) and ketoadociaquinone A–B (**91**–**92**) respectively, were isolated from a South Pacific marine sponge, *Adocia* sp.[43] Semi-syntheses from xestoquinone (**6**) and halenaquinone (**7**) were performed in order to confirm their structural assignment, while also supporting the likely biosyntheses of adociaquinones and ketoadociaquinones from their respective natural product precursors.[24,43]

According to reports by Harada and Kitagawa, the unprotected dihydroxynaphthalene groups of xestoquinol (**8**) and halenaquinol (**9**) are unstable to air, moisture, and light, and they readily oxidize back to the corresponding naphthoquinones (Figure 2).[9,11] Therefore, we hypothesized that the sulfated alcohols in xestoquinol sulfate (**3**), halenaquinol sulfate (**4**), and exiguaquinol (**5**) could serve as protecting groups for the hydroquinone forms of the natural products. With the proper sulfatase enzyme, **3**, **4**, and **5** would likely be converted to the unprotected dihydroxynaphthalene analogue, which will spontaneously oxidize to the naphthoquinone under aerobic conditions; this form might contribute to the observed bioactivity of this family of natural products.

4.2. A Synthesis of the Tetracyclic Core of Exiguaquinol and Exiguaquinol Dessulfate by the Vanderwal Group

Besides the incorporation of exogenous taurine, exiguaquinol (**5**) contains several features that distinguish it from halenaquinol sulfate (**4,** Figure 1). Most notably, exiguaquinol contains a rearranged pentacyclic carbon skeleton that lacks the furan moiety present in the furanosteroid framework.

In 2014, the Vanderwal group disclosed a strategy to access the tetracyclic framework of exiguaquinol (**93**, Figure 5),[44] which was subsequently followed up by a synthesis of exiguaquinol dessulfate.[45] This work relied on an aldol reaction to append the aryl fragment and a late-stage reductive Heck reaction to forge the C-ring cyclopentanone. This latter step is inspired by the work of the Keay and Wipf groups and can be classified in the same category of C–C bond disconnections.

Through a synthesis of the C-2 hemiaminal epimer of **93**, the Vanderwal group demonstrated the feasibility of their C–C bond forming strategy; however, the C2 hemiaminal did not equilibrate as expected to the natural configuration as found in exiguaquinol.[44] Ground state computational analysis of **93** and its unnatural epimer, as performed by the Houk group, suggested the presence of favorable internal hydrogen bonding in the observed (undesired) tetracycle epimer. Conversely, in the ground state analysis of fully-functionalized exiguaquinol, there exists a thermodynamic preference for the natural hemiaminal epimer (**5**), owing to a different arrangement of intramolecular hydrogen bonding, in this case involving the sulfonate.[44]

With this computational support, the Vanderwal group set out to apply their strategy to a synthesis of **5**.[45] Diene **95** and maleimide (**96**) were converted via a Diels–Alder reaction, subsequent *N*-alkylation with TBS-protected 2-bromoethanol, and alkene hydrogenation to generate *meso*-imide **97**. $BF_3{\cdot}OEt_2$-assisted aldolization of the lithium enolate of **97** with naphthaldehyde **94** (itself made by an interesting sequence from 3,4-dibromothiophene) gave adduct **98** in high yield with complete diastereoselectivity. Alcohol protection, oxidation to the bis(sulfoxide), and thermal elimination delivered diene **99**. Regioselective reduction of the imide provided the unnatural C2 hemiaminal epimer, which was carried through the reductive Heck cyclization to give **100**. Subsequent deprotection and oxidation yielded the naphthyl ketone, and the exocyclic alkene was oxidatively cleaved to afford **101**. Sulfonate **102** was then accessed via a high-yielding Mitsunobu reaction followed by direct thioester oxidation with *m*-CPBA. With the alkyl sulfonate installed, the stereochemical inversion of the hemiaminal was carried out in two steps to form the naturally-occurring (*R*)-epimer (**103**), which could be demethylated using CAN and sodium dithionite to afford exiguaquinol dessulfate (**104**). Unfortunately, **104** was unstable and readily decomposed under ambient conditions, thereby preventing the regioselective sulfation to exiguaquinol (**5**) under the myriad conditions attempted.

While exiguaquinol dessulfate has not been isolated as a natural product, it is possible that **104** or its quinone form might be secondary metabolites that remain undiscovered. **104** bears clear familial resemblance to halenaquinol (**9**) and xestoquinol (**8**), and is plagued by the same instability issues reported for these two known natural products. Through synthesis,

exiguaquinol dessulfate (**104**) was accessed by the Vanderwal group in a longest linear sequence of 19 steps and 1% overall yield.

5. Conclusions and Outlook

The synthetic work discussed in this review takes advantage of several key disconnections to access the natural products halenaquinol and xestoquinol, as well as several of their derivatives and analogues. Recurring approaches include Diels–Alder cycloadditions of an *in situ* generated *o*-quinodimethanes to assemble the naphthalene ring structures, highlighting the power of this transformation; and intramolecular Heck reactions, which illustrated the utility of palladium catalysis in accessing the natural product scaffolds in both asymmetric and diastereoselective fashions. While it remains unclear what future directions await in terms of biological applications of these natural products, it is clear that synthesis should be able to address the needs of both material supply and analogue production, when needed. The exception, of course, is exiguaquinol, which has yet to succumb to a complete synthesis.

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References

1. Baggiolini M, Dewald B, Schnyder J, Ruch W, Cooper PH, Payne TG. Exp Cell Res. 1987; 169:408–418. [PubMed: 3556425]
2. a) Haefliger W, Kis Z, Hauser D. Helv Chim Acta. 1975; 58:1620–1633.b) Norman BH, Paschal J, Vlahos CJ. Bioorg Med Chem Lett. 1995; 5:1183–1186.c) Viswanathan K, Ononye SN, Cooper HD, Hadden MK, Anderson AC, Wright DL. Bioorg Med Chem Lett. 2012; 22:6919–6922. [PubMed: 23040731]
3. a) Powis G, Bonjouklian R, Berggren MM, Gallegos A, Abraham R, Ashendel C, Zalkow L, Matter WF, Dodge J, Grindey G, Vlahos CJ. Cancer Res. 1994; 54:2419–2423. [PubMed: 8162590] b) Norman BH, Shih C, Toth JE, Ray JE, Dodge JA, Johnson DW, Rutherford PG, Schultz RM, Worzalla JF, Vlahos CJ. J Med Chem. 1996; 39:1106–1111. [PubMed: 8676346] c) Wymann MP, Bulgarelli-Leva G, Zvelebil MJ, Pirola L, Vanhaesebroeck B, Waterfield MD, Panayotou G. Mol Cell Biol. 1996; 16:1722–1733. [PubMed: 8657148] d) Walker EH, Pacold ME, Perisic O, Stephens L, Hawkins PT, Wymann MP, Williams RL. Mol Cell. 2000; 6:909–919. [PubMed: 11090628]
4. a) Drahl C, Cravatt BF, Sorensen EJ. Angew Chem Int Ed. 2005; 44:5788–5809.b) Hanson JR. Nat Prod Rep. 1995; 12:381–384. [PubMed: 7666979] c) Wipf P, Halter RJ. Org Biomol Chem. 2005; 3:2053–2061. [PubMed: 15917886]
5. (a) Roll DM, Scheuer PJ, Matsumoto GK, Clardy J. J Am Chem Soc. 1983; 105:6177–6178.(b) Lee RH, Slate DL, Moretti R, Alvi KA, Crews P. Biochem Biophys Res Commun. 1992; 184:765–772. [PubMed: 1315532] (c) Longeon A, Copp BR, Roué M, Dubois J, Valentin A, Petek S, Debitus C, Bourguet-Kondracki ML. Bioorg Med Chem Lett. 2010; 18:6006–6011.
6. Nakamura H, Kobayashi J, Kobayashi M, Ohizumi Y, Hirata Y. Chem Lett. 1985:713–716.
7. Nakamura M, Kakuda T, Qi J, Hirata M, Shintani T, Yoshioka Y, Okamoto T, Oba Y, Nakamura H, Ojika M. Biosci Biotechnol Biochem. 2005; 69:1749–1752. [PubMed: 16195594]
8. de Almeida Leone P, Carroll AR, Towerzey L, King G, McArdle BM, Kern G, Fisher S, Hooper JNA, Quinn RJ. Org Lett. 2008; 10:2585–2588. [PubMed: 18489104]
9. Kobayashi M, Shimizu N, Kyogoku Y, Kitagawa I. Chem Pharm Bull. 1985; 33:1305–1308.
10. Kobayashi J, Hirase T, Shigemori H, Ishibashi M, Bae M-A, Tsuji T, Sasaki T. J Nat Prod. 1992; 55:994–998.
11. Harada N, Sugioka T, Ando Y, Uda H, Kuriki T. J Am Chem Soc. 1988; 110:8483–8487.

12. Harada N, Sugioka T, Uda H, Kuriki T. J Org Chem. 1990; 55:3158–3163.
13. Kanematsu K, Soejima S, Wang G. Tetrahedron Lett. 1991; 32:4761–4764.
14. Sutherland HS, Souza FES, Rodrigo RGA. J Org Chem. 2001; 66:3639–3641. [PubMed: 11348164]
15. Sutherland HS, Higgs KC, Taylor NJ, Rodrigo R. Tetrahedron. 2001; 57:309–317.
16. Maddaford SP, Andersen NG, Cristofoli WA, Keay BA. J Am Chem Soc. 1996; 118:10766–10773.
17. Wakefield B, Halter RJ, Wipf P. Org Lett. 2007; 9:3121–3124. [PubMed: 17630756]
18. Kojima A, Takemoto T, Sodeoka M, Shibasaki M. J Org Chem. 1996; 61:4876–4877.
19. Kojima A, Takemoto T, Sodeoka M, Shibasaki M. Synthesis. 1998:581–589.
20. Kienzler MA, Suseno S, Trauner D. J Am Chem Soc. 2008; 130:8604–8605. [PubMed: 18549215]
21. Kobayashi M, Shimizu N, Kitagawa I, Kyogoku Y, Harada N, Uda H. Tetrahedron Lett. 1985; 26:3833–3836.
22. Harada N, Sugioka T. Stud Nat Prod Chem. 1995; 17:33–72.
23. Harada N, Sugioka T, Uda H, Kuriki T, Kobayashi M, Kitagawa I. J Org Chem. 1994; 59:6606–6613.
24. Harada N, Sugioka T, Soutome T, Hiyoshi N, Uda H, Kuriki T. Tetrahedron: Asymmetry. 1995; 6:375–376.
25. Hayakawa K, Yamaguchi Y, Kanematsu K. Tetrahedron Lett. 1985; 26:2689–2692.
26. Yamaguchi Y, Tatsuta N, Soejima S, Hayakawa K, Kanematsu K. Heterocycles. 1990; 30:223–226.
27. Carlini R, Higgs K, Older C, Randhawa S, Rodrigo R. J Org Chem. 1997; 62:2330–2331. [PubMed: 11671562]
28. Souza FES, Rodrigo R. Chem Commun. 1999:1947–1948.
29. Grieco PA, May SA, Kaufman MD. Tetrahedron Lett. 1998; 39:7047–7050.
30. Magriotis PA, Brown JT, Scott ME. Tetrahedron Lett. 1991; 32:5047–5050.
31. Kabanyane ST, MaGee DI. Can J Chem. 1992; 70:2758–2763.
32. Cristofoli WA, Keay BA. Synlett. 1994:625–627.
33. a) Azadi-Ardakani M, Hayes R, Wallace TW. Tetrahedron. 1990; 46:6851–6858.b) Azadi-Ardakani M, Wallace TW. Tetrahedron. 1988; 44:5939–5952.
34. Andersen NG, Maddaford SP, Keay BA. J Org Chem. 1996; 61:2885–2887. [PubMed: 11667129]
35. Wipf P, Minion DJ, Halter RJ, Berggren MI, Ho CB, Chiang GG, Kirkpatrick L, Abraham R, Powis G. Org Biomol Chem. 2004; 2:1911–1920. [PubMed: 15227545]
36. Löbermann F, Mayer P, Trauner D. Angew Chem Int Ed. 2010; 49:6199–6202.
37. Löbermann F, Weisheit L, Trauner D. Org Lett. 2013; 15:4324–4326. [PubMed: 23962323]
38. Alvi KA, Rodriguez J, Diaz MC, Moretti R, Wilhelm RS, Lee RH, Slate DL, Crews P. J Org Chem. 1993; 58:4871–4880.
39. Toyooka N, Nagaoka M, Kakuda H, Nemoto H. Synlett. 2001:1123–1124.
40. Toyooka N, Nagaoka M, Sasaki E, Qin H, Kakuda H, Nemoto H. Tetrahedron. 2002; 58:6097–6101.
41. Ahn CM, Woo HB. J Korean Chem Soc. 2003; 47:354–362.
42. a) de Jonge BLM, Kutschke A, Uria-Nickelsen M, Kamp HD, Mills SD. Antimicrob Agents Chemother. 2009; 53:3331–3336. [PubMed: 19433553] b) Basarab GS, Hill P, Eyermann CJ, Gowravaram M, Käck H, Osimoni E. Bioorg Med Chem Lett. 2012; 22:5600–5607. [PubMed: 22877632]
43. Schmitz FJ, Bloor SJ. J Org Chem. 1988; 53:3922–3925.
44. Schwarzwalder GM, Steinhardt SE, Pham HV, Houk KN, Vanderwal CD. Org Lett. 2013; 15:6014–6017. [PubMed: 24219829]
45. Schwarzwalder GM, Scott DR, Vanderwal CD. Chem Eur J. 2016:22. ####–####.

Biographies

Gregg Schwarzwalder grew up in Glen Rock, New Jersey, USA. He received his B.A. degree in Chemistry from Cornell University where he worked in the group of Professor Jon T. Njardarson. In 2010, he moved to the University of California, Irvine to pursue his doctoral studies under the direction of Professor Christopher D. Vanderwal. As an NIH Predoctoral Fellow, his research focused on the synthesis of bioactive natural products. After obtaining his Ph.D. in 2015, Gregg moved to the California Institute of Technology, where he is currently an NIH Postdoctoral Fellow in the laboratory of Professor Gregory C. Fu.

Christopher Vanderwal received a B.Sc. degree in Biochemistry (1995) and an M.Sc. degree in Chemistry (1998) from the University of Ottawa. He then moved to the Scripps Research Institute for doctoral studies in the group of Professor Erik Sorensen. After obtaining his Ph.D. in 2003, Chris joined the group of Professor Eric Jacobsen at Harvard University as a Jane Coffin Childs postdoctoral associate. In 2005, Chris began his independent academic career at the University of California, Irvine, where he is currently Professor of Chemistry.

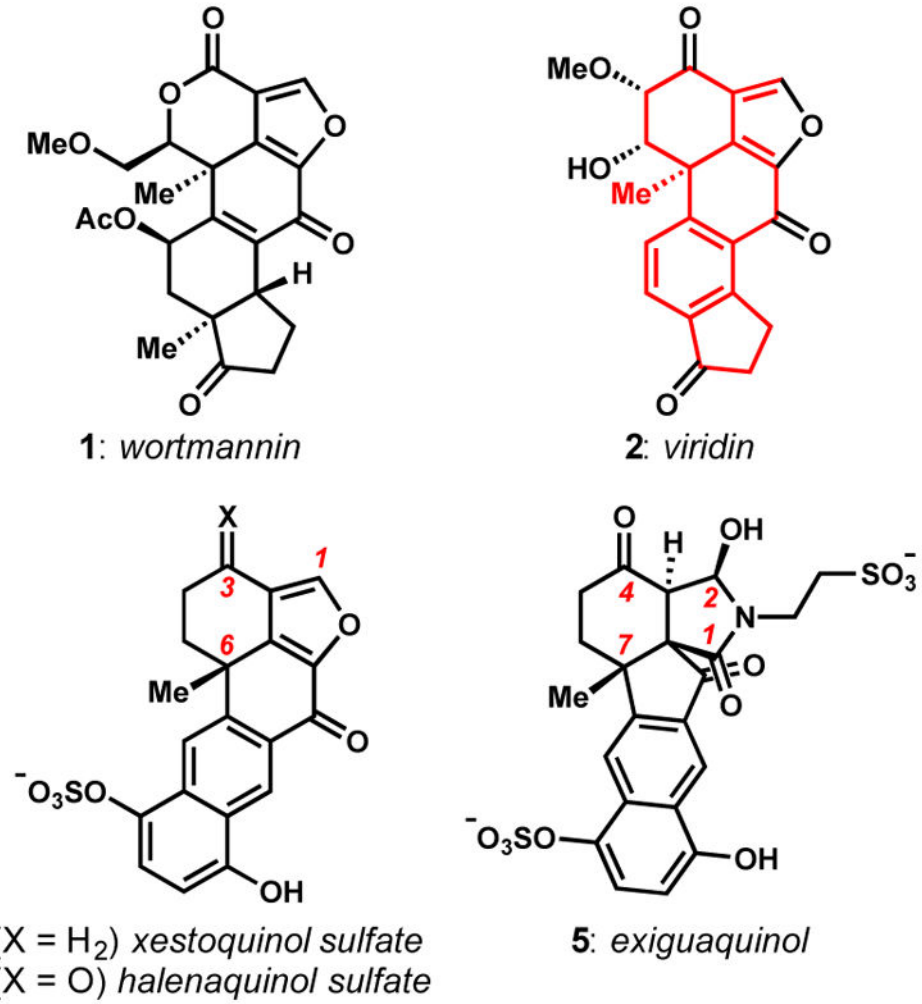
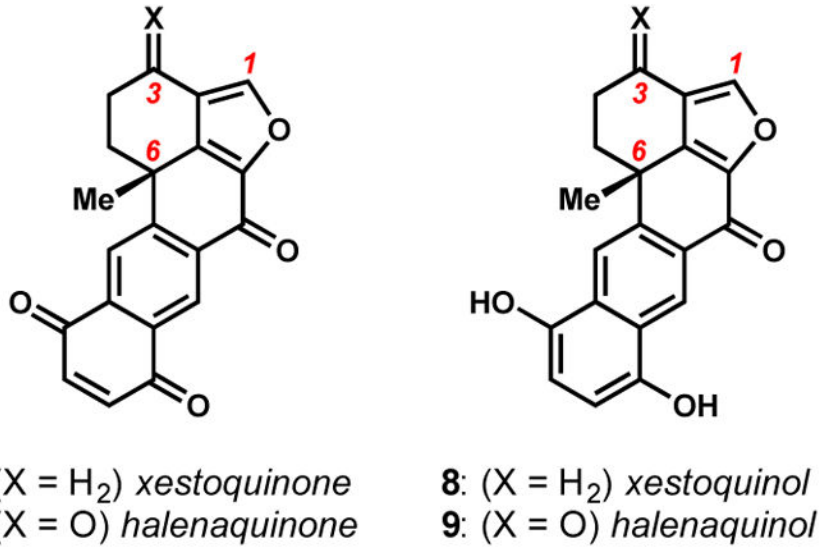


Figure 1.

Structures of representative furanosteroid natural products (steroid nucleus highlighted in red in viridin), halenaquinol-type secondary metabolites, and exiguaquinol



6: (X = H_2) *xestoquinone*
7: (X = O) *halenaquinone*
8: (X = H_2) *xestoquinol*
9: (X = O) *halenaquinol*

Figure 2.
Additional members of the xestoquinol and halenaquinol families

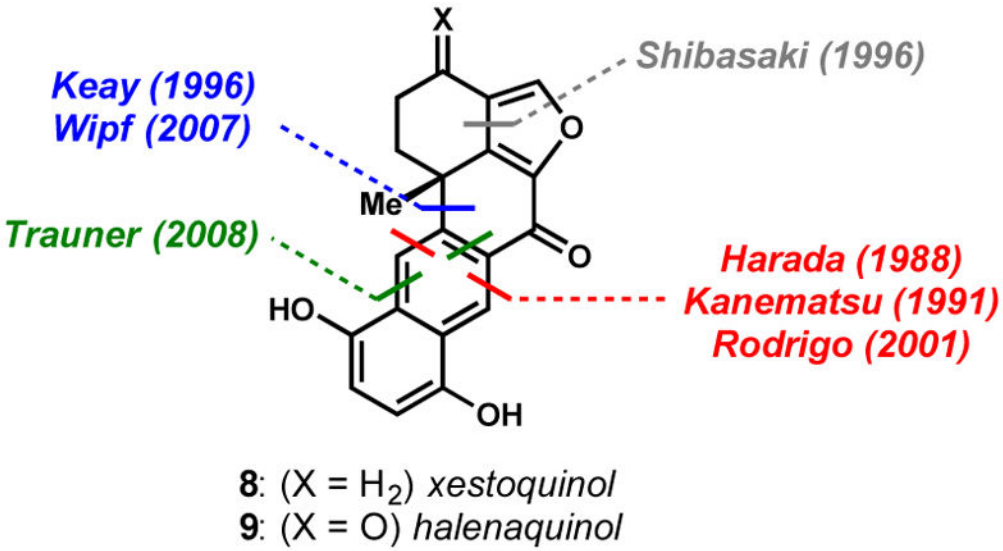


Figure 3.
Four unique approaches to xestoquinol/halenaquinol

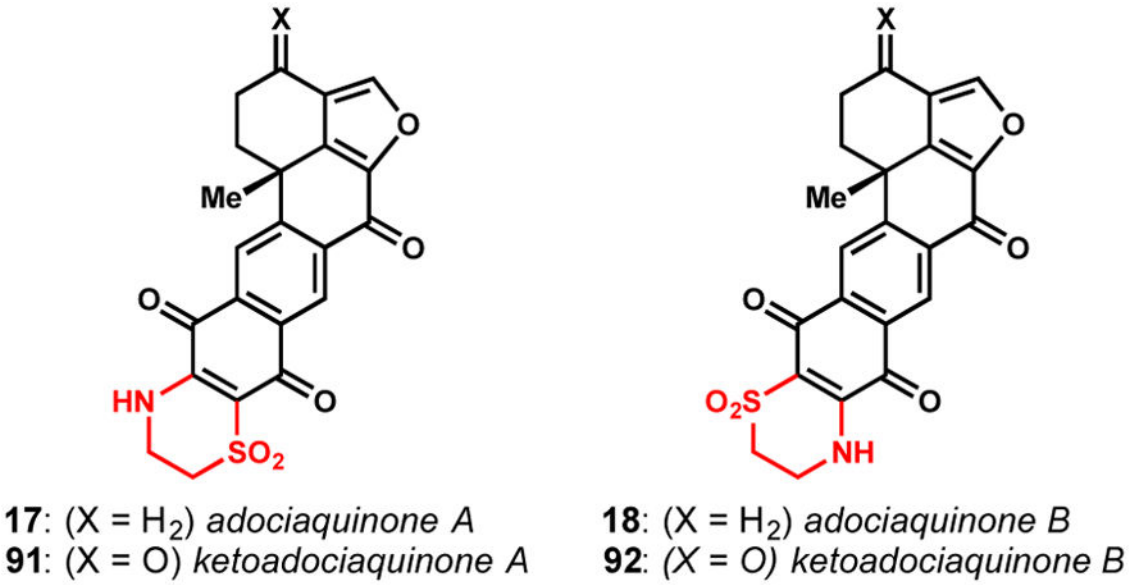


Figure 4.
Other taurine-containing members of the xestoquinone/halenaquinone family

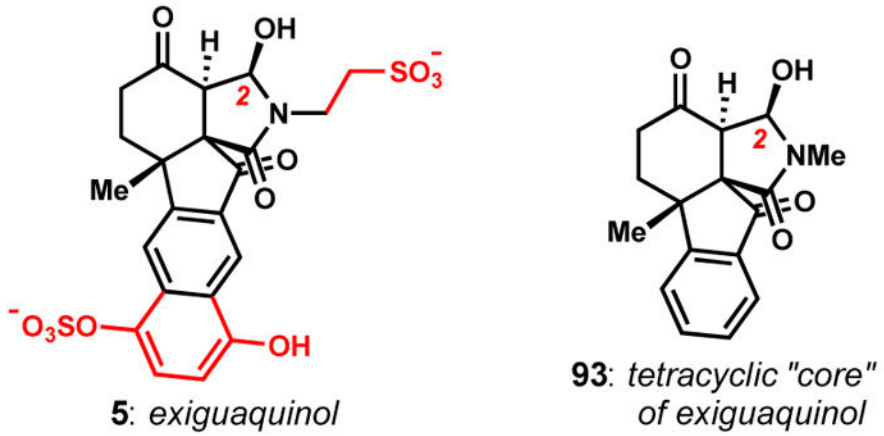
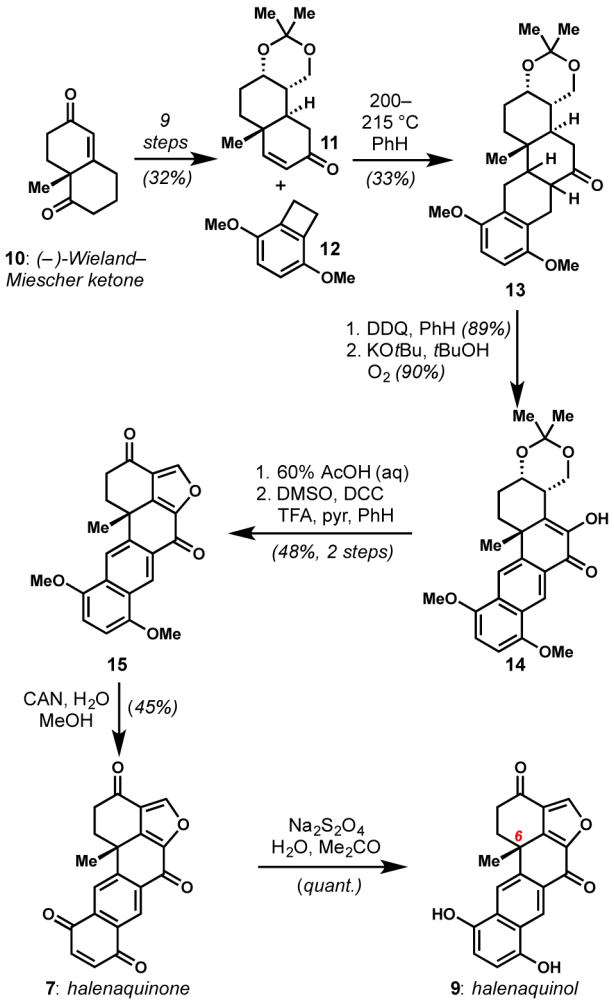
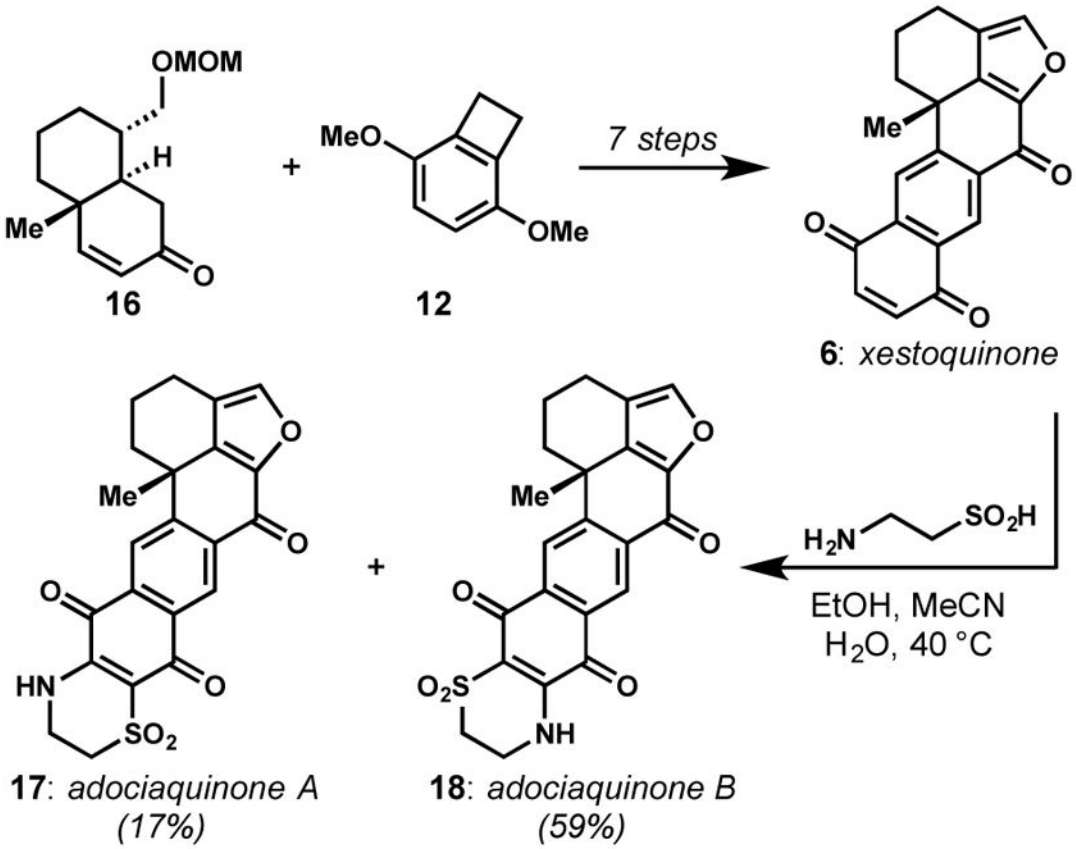


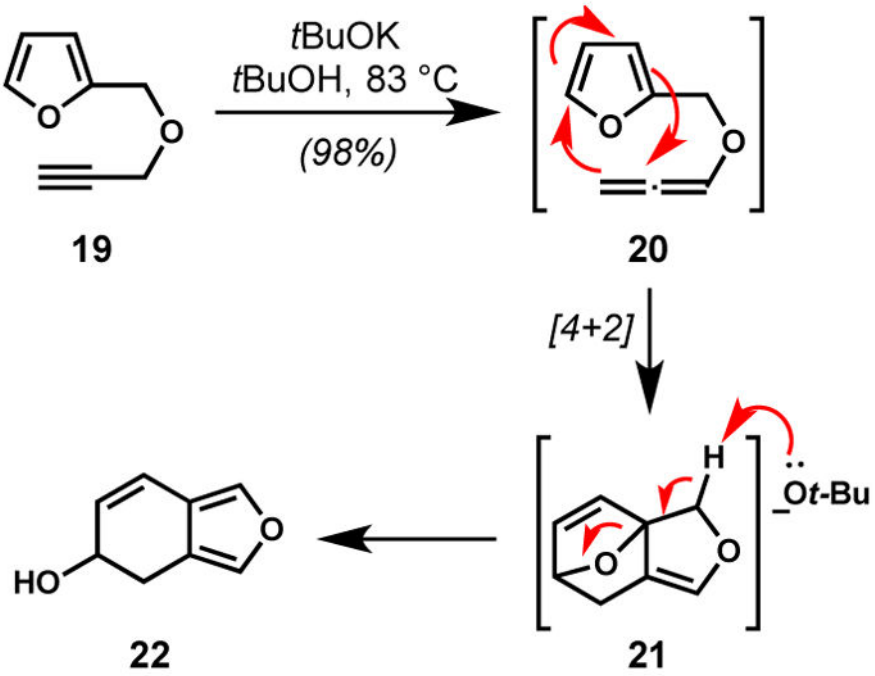
Figure 5.
Exiguaquinol and the tetracyclic model system first targeted by Vanderwal and co-workers.



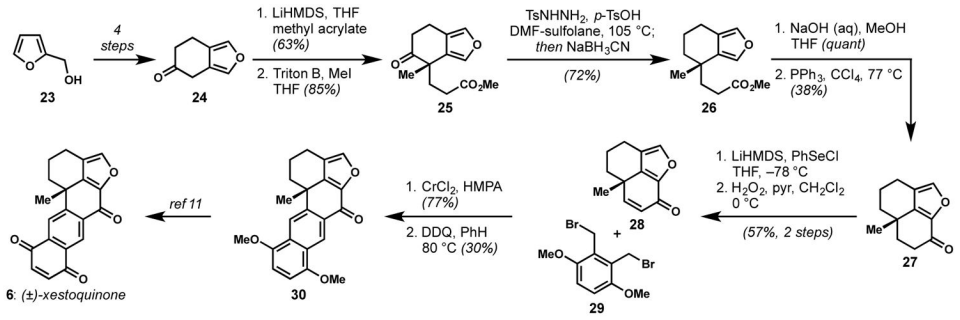
Scheme 1.
Synthesis of halenaquinol by the Harada group



Scheme 2.
Synthesis of xestoquinone and adociaquinones A and B by the Harada group

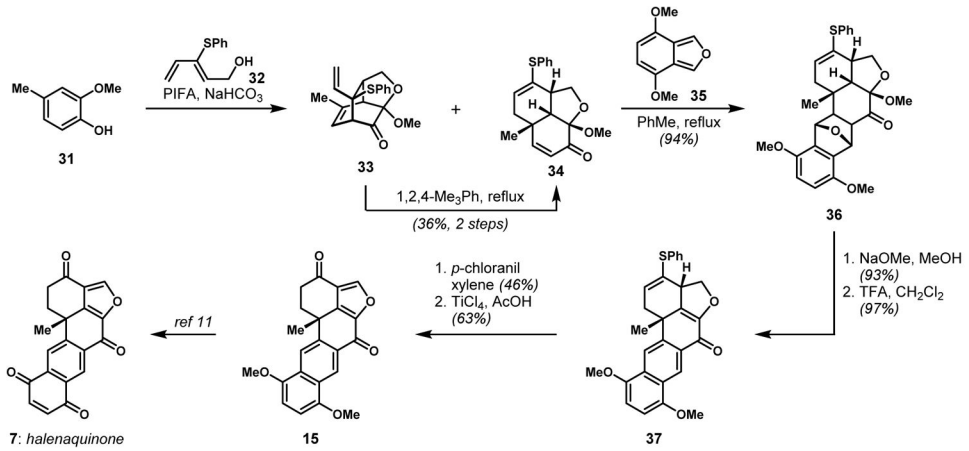


Scheme 3.
Kanematsu's furan ring transfer method

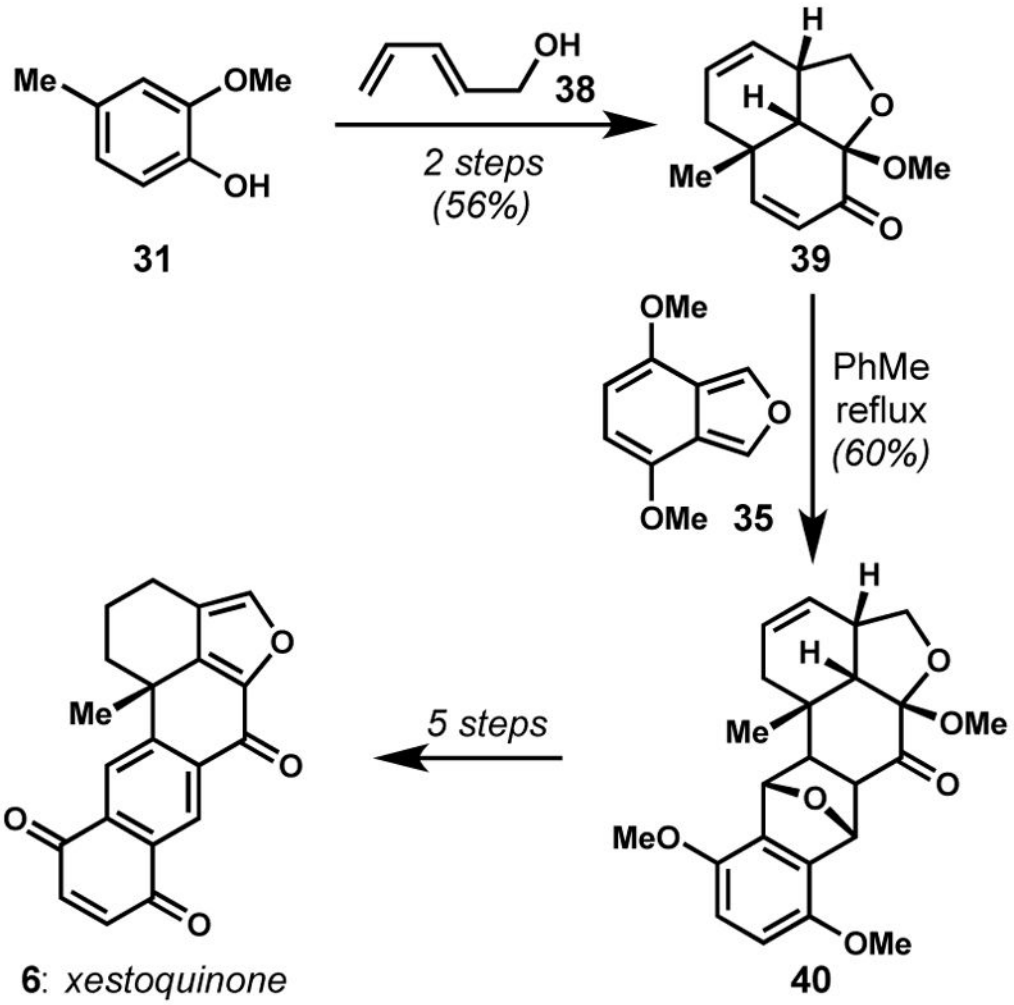


Scheme 4.

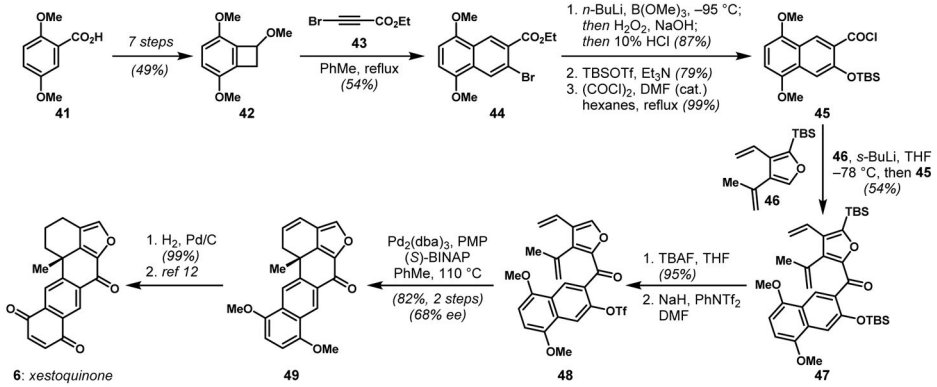
Formal synthesis of (±)-xestoquinone by the Kanematsu group



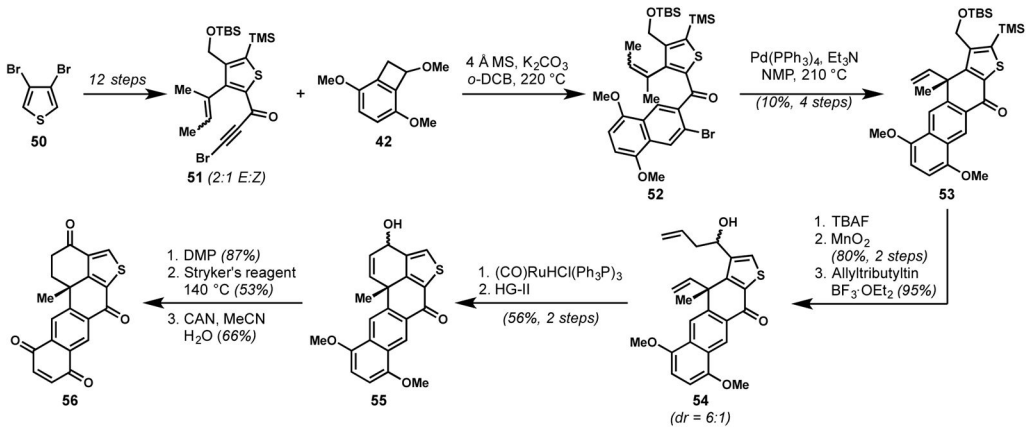
Scheme 5.
Synthesis of halenaquinone by the Rodrigo group



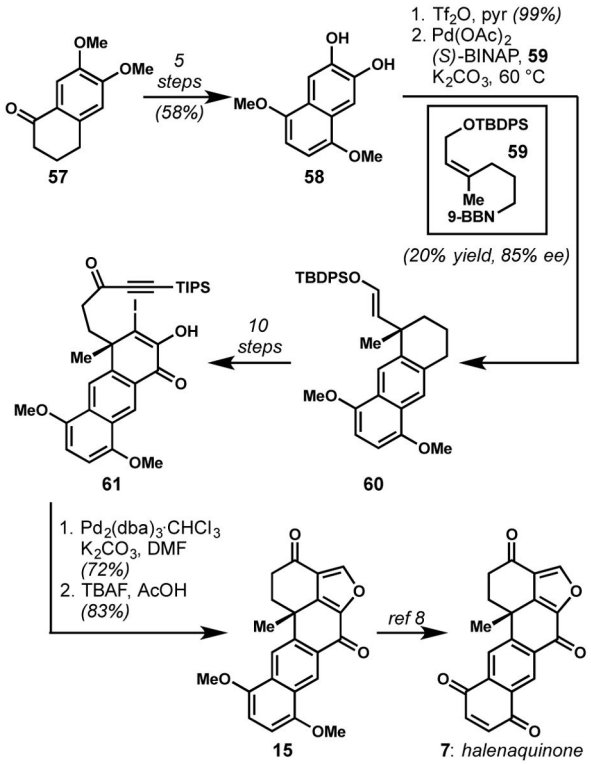
Scheme 6.
Rodrigo's synthesis of xestoquinone



Scheme 7.
Synthesis of xestoquinone by the Keay group

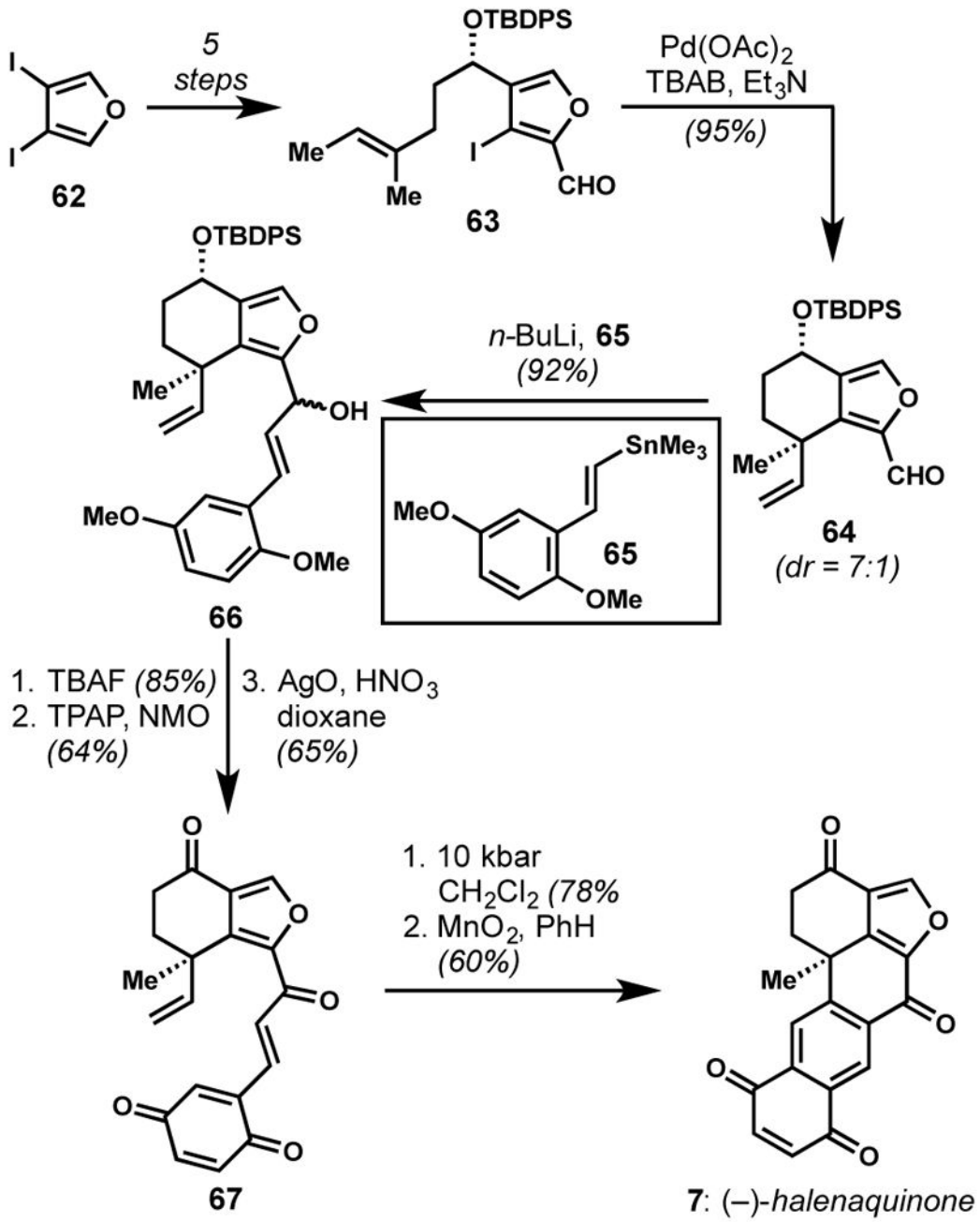


Scheme 8.
Wipf's synthesis of thiohalenaquinone (**56**)



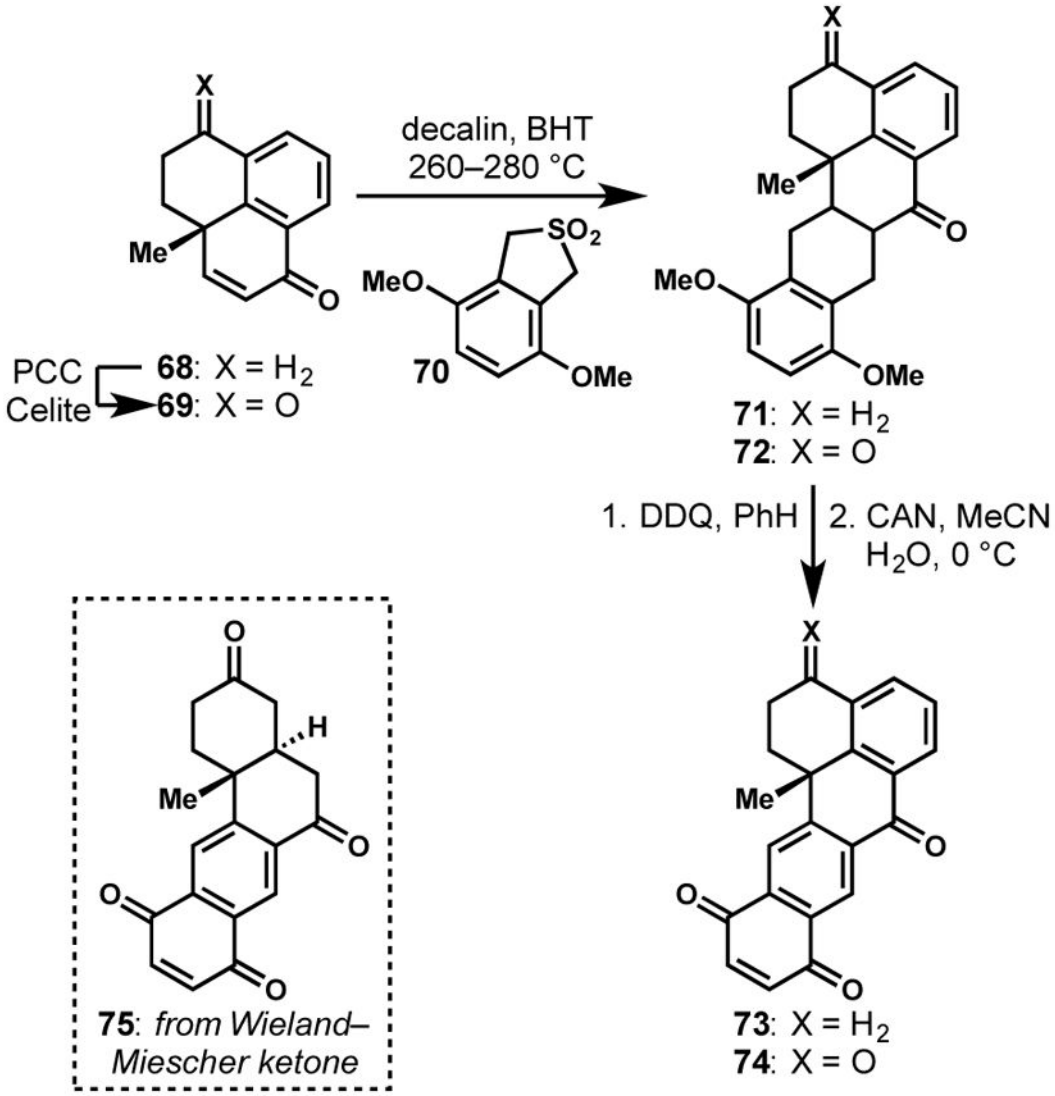
Scheme 9.

Shibasaki's synthesis of halenaquinone featuring a cascade of Suzuki–Miyaura coupling and asymmetric Heck cyclization



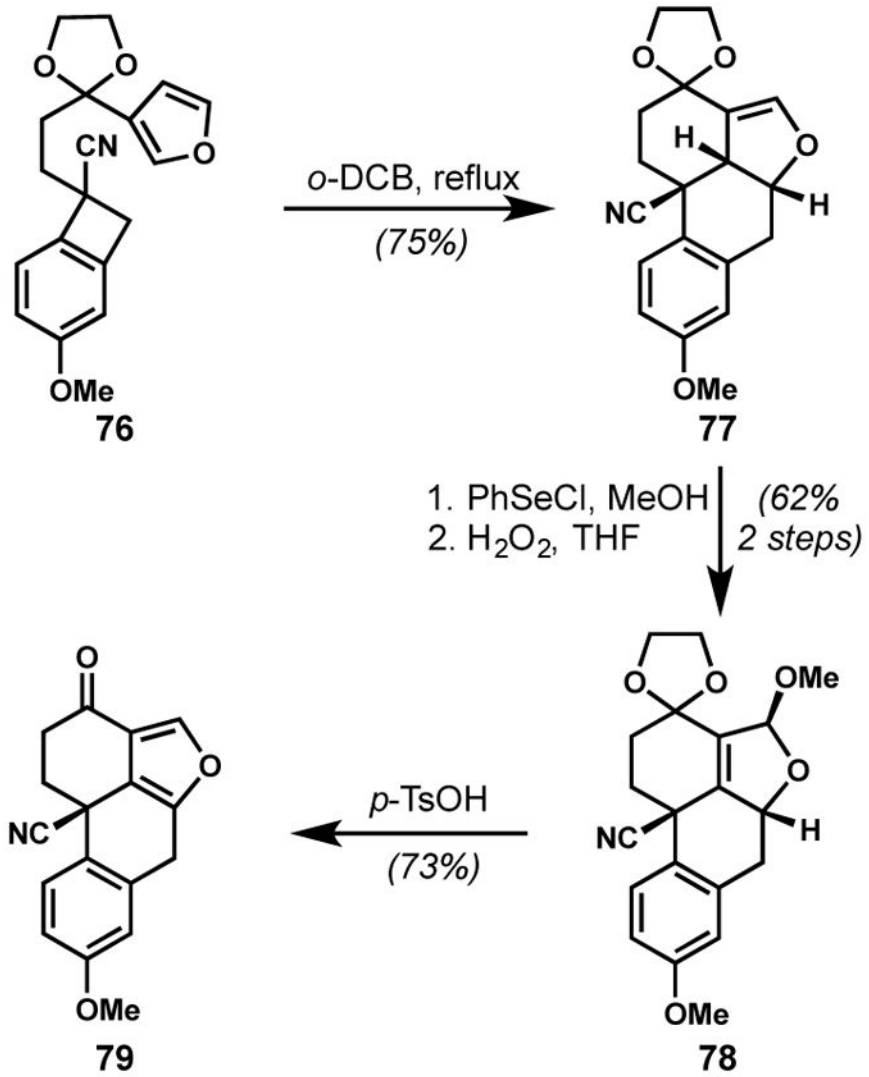
Scheme 10.

Trauner's synthesis of halenaquinone featuring an intramolecular vinylquinone Diels–Alder cycloaddition

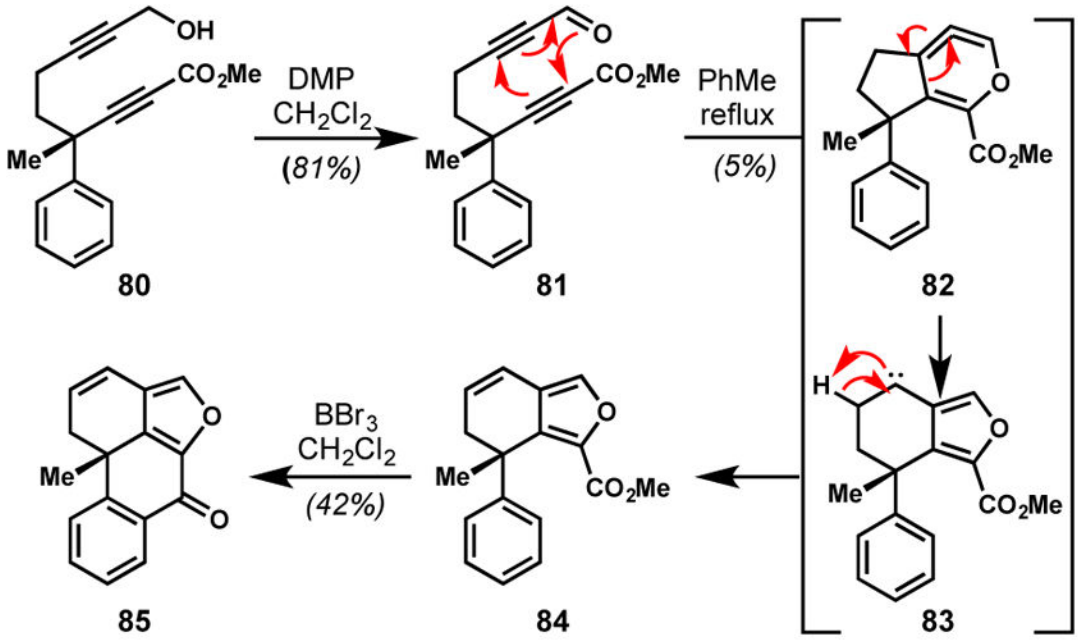


Scheme 11.

Halenaquinone and xestoquinone analogues made by the Crews group

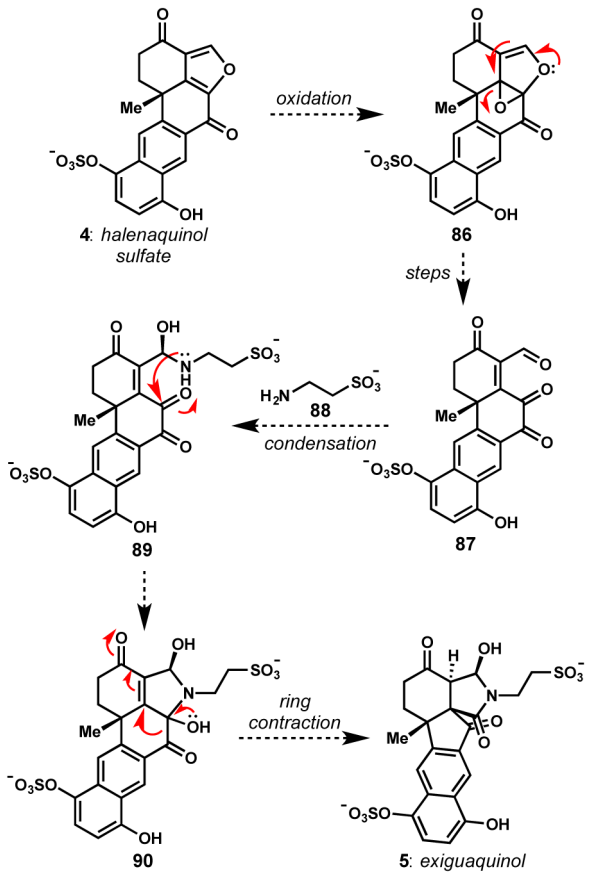


Scheme 12.
Nemoto's IMDA approach to the halenaquinone tetracycle



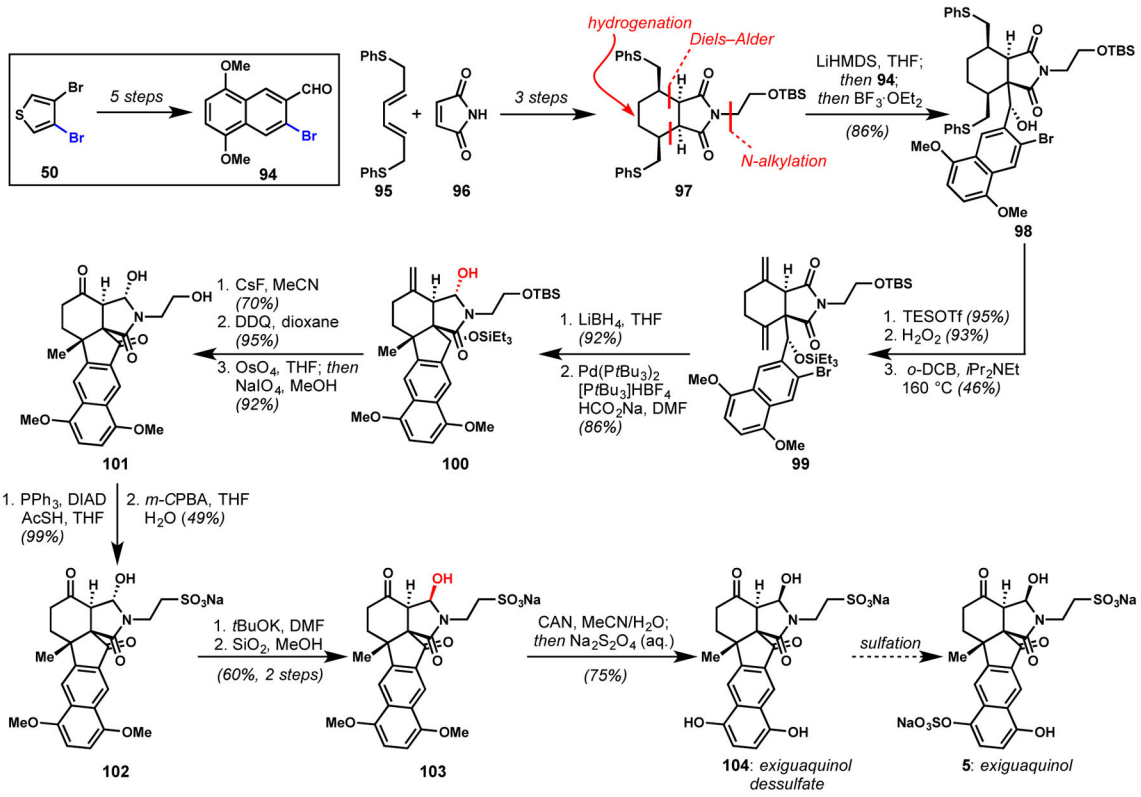
Scheme 13.

Ahn's unusual synthesis of tetracyclic furanyl ketone **85**



Scheme 14.

Plausible biogenesis of exiguaquinol from halenaquinol sulfate as proposed by Quinn and co-workers



Scheme 15.

The Vanderwal group's synthesis of exiguaquinol dessulfate using desymmetrization of *meso*-imide **97** as a key strategic ideal