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Synthesis of (±)-Thiohalenaquinone by Iterative Metalations of Thiophene

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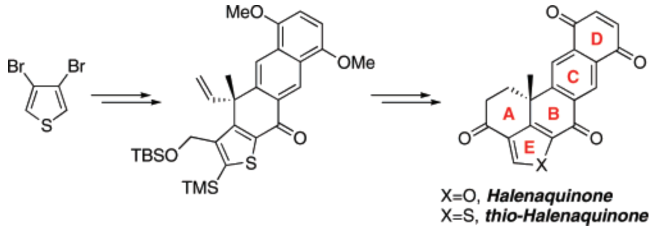
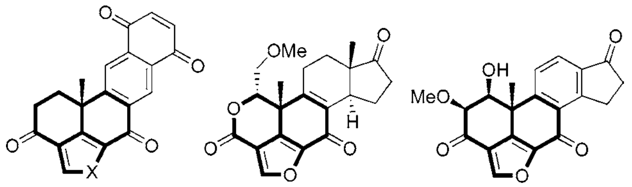
ABSTRACT



The synthesis of a thiophene-containing analogue of halenaquinone was realized. Key steps include an alkynyl ketone–benzocyclobutane Diels–Alder reaction to construct the C,D-ring naphthalene subunit, a Heck cyclization to form the quaternary carbon, and a ring closing metathesis to add the A-ring.

Halenaquinone (**1**) was isolated in 1983 from the Pacific sponge *Xestosongia exigua*.[1] Biological assays revealed a wide array of activities including antibiotic,[1] cardiotonic,[2] cytotoxic,[3] and antifungal[3a] properties as well as inhibition of protein tyrosine kinase,[4] phosphatidylinositol 3 (PI-3) kinase,[5] and Cdc25B dual specificity phosphatase.[6] Several partial and total syntheses of **1** and related compounds have been reported,[7] and while halenaquinone and the closely related xestoquinone have not yet reached the significance of other chemical standards for kinase characterization, such as wortmannin and staurosporine,[8] readily available synthetic derivatives of halenaquinone would represent valuable probe molecules for fundamental biological studies.

A key structural feature of **1**, wortmannin (**3**), and viridin (**4**) is the strained tricyclic furanodecaline core (Figure 1).



1 (X=O)
2 (X=S)

3

4

Figure 1. Structures of halenaquinone (**1**), thiohalenaquinone (**2**), wortmannin (**3**), and viridin (**4**).

This moiety is responsible for the irreversible conjugation of wortmannin to PI-3 kinase,[9] and we hypothesized that its reactivity could also account for low kinase subtype selectivity, in vivo toxicity, and poor bioavailability of wortmannin.[8d] The strain energy of the 1,8a-dihydrofuro[4,3,2-*de*]isochromene ring system in wortmannin was calculated to be

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12.1 kcal/mol.[8a] Replacement of the furan with a thiophene decreases the relative energy of hydrogenation of the tricycle **6** versus **5** by 2.6 kcal/mol (Figure 2). This is mainly due to a decrease in the angle strain of the fused ring systems. Isoelectronic replacement of the furan with a thiophene should therefore significantly decrease the electrophilic, alkylating properties of the heterocycle and increase the biological target selectivity. In order to investigate this hypothesis and to gain access to natural product analogues with an improved kinase selectivity profile, we embarked on the preparation of the thiophene analogue **2** of halenaquinone.

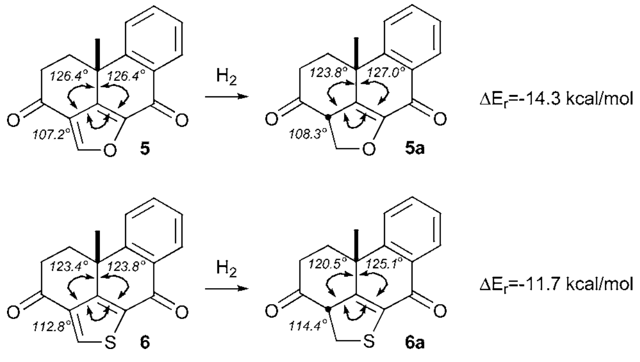


Figure 2. Selected bond angles of furanodecaline (**5**) and thiophenodecaline (**6**), and approximate reaction enthalpies for hydrogenations determined at the B3LYP/6-31G* level in Spartan 04.

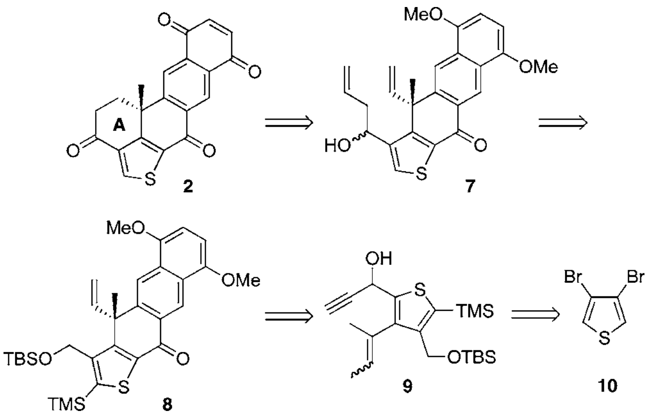
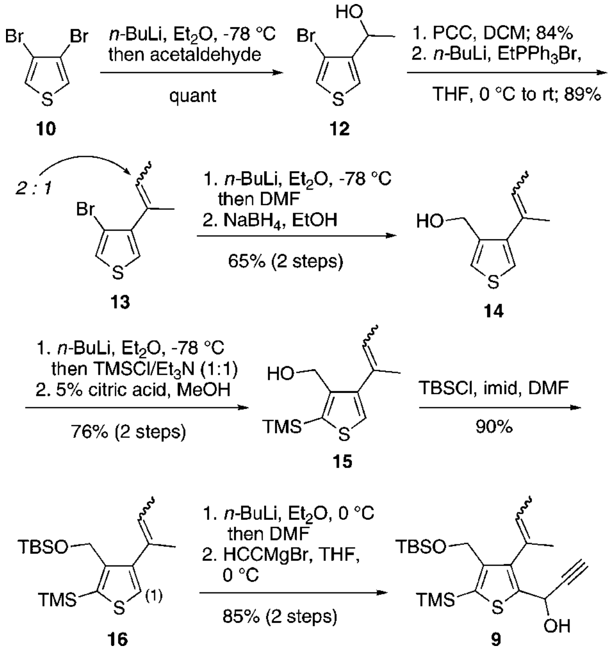


Figure 3. Retrosynthetic analysis of thiohalenaquinone (**2**).

A retrosynthetic analysis of **2** is shown in Figure 3. We envisioned installing the A-ring of thiohalenaquinone through an alkene isomerization[10] and ring closing metathesis[11] of **7**. The key intermediate tetracycle **8** would arise from a Diels–Alder cycloaddition followed by a Heck cyclization[12] to install the quaternary center. Sequential metalations of commercially available 3,4-dibromothiophene (**10**) were envisioned to lead to alkynyl ketone **9**. Recently, heterocycle metalations have been used with considerable success for the preparation of polyfunctionalized heteroaromatic systems.[13]

Treatment of 3,4-dibromothiophene with *n*-BuLi and quenching with acetaldehyde gave alcohol **12** in quantitative yield (Scheme 1). PCC oxidation and Wittig olefination of the methyl ketone[14] afforded the trisubstituted olefin **13** as a 2:1 mixture of alkene isomers which were carried on without separation. The thiophene ring was further modified by a bromine–lithium exchange reaction followed by quenching with DMF and a subsequent sodium borohydride reduction of the intermediate aldehyde to give 65% of alcohol **14**. The remaining two ring substituents were installed by

Scheme 1. Synthesis of Tetrasubstituted Thiophene **9**



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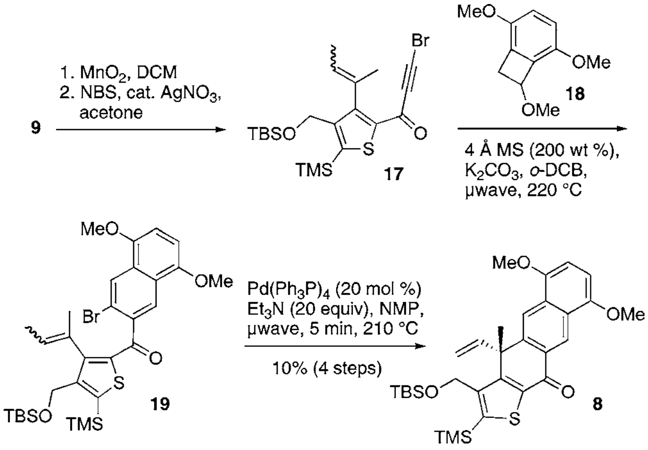
selective deprotonations. Alcohol-directed metalation[15] at the 5-position of thiophene **14** was followed by trapping with TMSCl. The resulting bis-TMS-protected compound was treated with citric acid to yield the primary alcohol **15**. Protection of the hydroxyl group with the more robust TBS-ether proceeded in excellent yield to afford trisubstituted thiophene **16**. Finally, metalation at C(1) and introduction of the aldehyde (*n*-BuLi, then DMF) was followed by addition of ethynyl Grignard reagent to give the desired thiophene **9** in 85% yield from **16**.

Oxidation of thiophene **9** with manganese dioxide and bromination of the alkynyl ketone with NBS in the presence of catalytic silver nitrate[16] provided the Diels−Alder dienophile **17** (Scheme 2). Microwave irradiation in *ortho*-dichlorobenzene (*o*-DCB) was used to mediate the cycloaddition of **17** and benzocyclobutane **18**,[17] and 4 Å molecular sieves and K_2CO_3 were present to quench methanol and hydrobromic acid formed during the process. After removal of solvent and other volatiles by distillation, further microwave irradiation of a solution of crude **19** in NMP in the presence of 20 mol % of $Pd(Ph_3P)_4$ and 20 equiv of Et_3N for 5 min at 210 °C gave the desired tetracyclic product **8** in 10% overall yield from **9**. In contrast, under conventional heating in NMP at reflux, a reaction time of 36 h was necessary for the Heck reaction to go to completion, and an inferior yield of **8** was obtained.

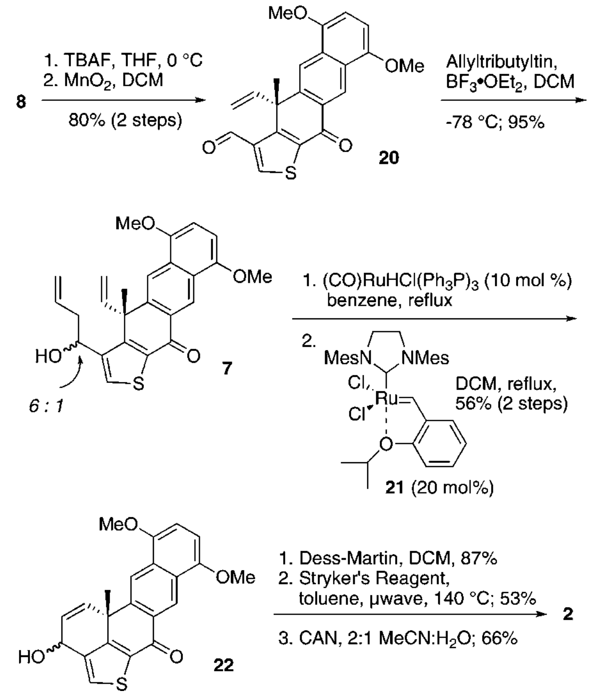
Scheme 2. Diels−Alder−Heck Cyclization Sequence to Give Tetracycle **8**



After the successful realization of the sequential Diels−Alder−Heck cyclization strategy for the formation of B-, C-, and E-rings of thiohalenaquinone, formation of ring A by ring closing metathesis required installing at least an additional vinyl side chain onto intermediate **8**. However, we found that a higher overall yield of cyclohexene product could be achieved if an allyl group was added instead of a terminal vinyl function.

Removal of the silyl-protecting group in **8** with TBAF and oxidation of the primary alcohol gave aldehyde **20** (Scheme 3). This aldehyde was treated with a variety of vinyl organometallics, but product mixtures that were difficult to separate were obtained in all cases, and the desired allylic alcohol could not be isolated in satisfactory yield. Fortunately, treatment with tributylallylstannane in the presence of $BF_3 \cdot OEt_2$[18] gave the homoallylic alcohol **7** in 95% yield and a surprisingly high 6:1 diastereoselectivity. The major isomer was not assigned, and since the formation of stereoisomers at the secondary alcohol carbon was inconsequential, the mixture was carried on without separation. The terminal alkene moiety was readily isomerized in the presence of a Ru hydride catalyst[19] to give the allylic alcohol. Ring closing metathesis with ruthenium catalyst **21**[20] afforded cyclohexenol **22** in 56% yield. Oxidation with Dess−Martin periodinane and treatment of the resulting enone with

Scheme 3. Alkene Isomerization−RCM Reaction and Completion of the Synthesis of Thiohalenaquinone



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Stryker's reagent[21] led to the conjugate reduction product. Finally, oxidation of the dimethoxyarene moiety with CAN[22] afforded thiohalenaquinone **2**.

In summary, we completed a synthesis of (±)-thiohalenaquinone in 22 steps and 0.3% overall yield from 3,4-dibromothiophene. Key transformations of this sequence include multiple selective metalations of thiophene heterocycles to install four different substituents, the Diels−Alder reaction of the highly functionalized alkynyl ketone **17** with benzocyclobutane **18** followed by a Heck cyclization to form the tetracyclic B,C,D,E-ring system, and an alkene isomerization−ring closing metathesis reaction to introduce the remaining cyclohexanone moiety. We are presently extending this synthetic strategy to gain access to additional substrates for biological evaluations. The kinase inhibitory profile of this sulfur-containing series of natural product analogues will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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