A Short Synthesis of (±)-Halenaquinone

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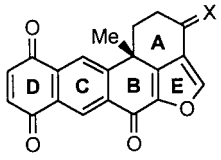
Introduction

Halenaquinone **1**, first reported[1] in 1983, was the initial member of an expanding family of pentacyclic metabolites isolated from tropical sponges of the genus *Xestospongia*. The 1*H*-benzo[6,7]phenanthro[10,1-*bc*]-furan ring system,[2] methylated as it is at C-12b in all members of the group, contains 20 carbon atoms and is believed to originate from sesquiterpene (rings A, B, C, and E) and triketide (ring D) precursors. Many of these compounds possess potentially valuable pharmacological properties[3] and have attracted much attention from synthetic chemists.[4] (+)-Halenaquinone has been synthesized twice before; in 15 steps from (−)-Wieland−Miescher ketone[5a] which was itself prepared from 2-methylcyclohexanedione,[5b] optically pure in 50% yield, and subsequently[6] in 21 steps from 6,7-dimethoxytetralone. The ABE segment, a common feature of all these marine quinones, also occurs in the viridin (**2**) family[7] of furanosteroidal antibiotics and constitutes three rings of the morphinan alkaloids.



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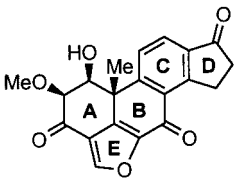
4: X = H, H



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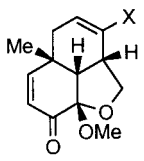
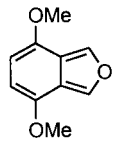
Results and Discussion

Our laboratory has concentrated its recent efforts on the development of a rapid, general route[8] to naphthofuranones such as **3** to serve as synthons for the eventual preparation of all these compounds. These investigations have recently culminated[4] in the synthesis of xestoquinone **4** and two of its methoxylated derivatives as well as of advanced intermediates for viridin[9a] and morphine.[9b] The convergent ABE (naphthofuranone, **3**) + CD (isobenzofuran,[10] **5**) plan led[4] to the pentacycle **6**, but we were unable to introduce the oxygen atom at C-3, required for the synthesis of halenaquinone from this intermediate or others similar to it, despite many attempts to do so. It thus became evident that if the synthesis of **1** (and subsequently of **2**) was to be attained by this common strategy, a correctly placed oxygen or "potential oxygen" substituent had to be incorporated in the ABE naphthofuranone and therefore in the dienol that precedes it. We now report the successful implementation of this plan, a further example of the value of *o*-benzoquinone monoketals,[11] and we illustrate this with a very short synthesis of (±)-halenaquinone.



3: X = H
9: X = SPh



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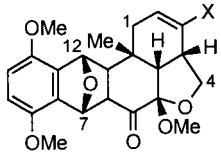
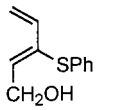


6: X = H
11: X = SPh



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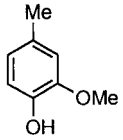

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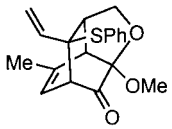

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The known[12] dienol **7** prepared from propargylic alcohol in four steps and 63% yield was subjected to our *o*-benzoquinone monoketal, Diels−Alder protocol[8] with methylguaiacol **8** and [bis(trifluoroacetoxy)iodo]benzene to provide a mixture of adducts **9** and **10** which were not easily separated from each other. The mixture was therefore refluxed in 1,2,4-trimethylbenzene for 48 h to convert **10** to **9** by means of the Cope rearrangement. In this manner **7** and **8** were combined by a sequence of three reactions (oxidative ketalization, intramolecular Diels−Alder addition, Cope rearrangement) to yield **9** (36% overall) in two steps without the isolation of any intermediates. Although a recent report[13] recorded the use of phenyl vinyl sulfide as a dienophile in the intermolecular Diels−Alder reactions with some *o*-benzoquinone dimethyl ketals, this is the first time a heterosubstituted dienol has been employed in our three-reaction sequence. We were gratified therefore with the

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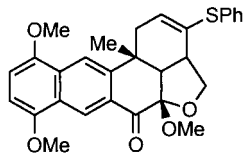
36% yield of **9**, though somewhat lower than **3** (56%),[8] and pleased that the steric and electronic effects of the thiophenyl substituent in **7** do not significantly compromise the synthetic utility of the double annulation sequence.



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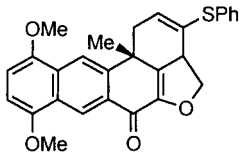

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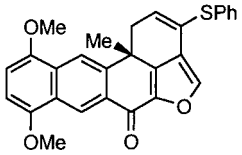

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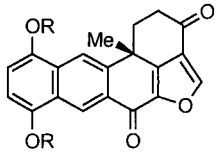

15: R = Me
16: R = H

Naphthofuranone **9** produced the expected bridged adduct **11** (94%) when refluxed in toluene with 4,7-dimethoxyisobenzofuran **5**. This was aromatized by refluxing with sodium methoxide in methanol (93%) and the product **12** treated briefly with trifluoroacetic acid in dichloromethane at ambient temperature to generate the enone **13** (97%). After aromatization of the dihydrofuran with *p*-chloranil in refluxing xylene (**14**, 46%), the thiophenyl group was hydrolyzed by heating with titanium tetrachloride in moist acetic acid to produce the known[5a] pentacyclic precursor **15** to halenaquinone in 63% yield. This compound had been previously oxidized to (+)-halenaquinone (45%) and the latter reduced[5a] to halenaquinol **16** quantitatively. Our synthesis of **15** therefore provides (±)-**1** and (±)-**16** in eight or nine steps, respectively, in ca. 4% overall yield from **7** and **8**. Furthermore, this work extends the utility of the *o*-benzoquinone monoketal methodology and promises a similar solution to the problem of functionalizing the highly oxygenated ring A of viridin (**2**).

Experimental Section[14]

8a-Methoxy-5a-methyl-3-phenylthio-2,2a,5,5a,8a,8b-hexahydronaphtho[1,8-*bc*]furan-8-one (9). To a cooled (0 °C) solution of methylguaiacol (**8**) (100 mg, 0.72 mmol), 3-phenylthiopenta-2,4-dien-1-ol (**7**) (500 mg, 2.60 mmol), and BHT (1 crystal, aproximately 2 mg) in THF (15 mL) was added [bis(trifluoroacetoxy)iodo]benzene (375 mg, 0.87 mmol), and the resulting solution was stirred for 5 min, after which solid $NaHCO_3$ (150 mg, 1.79 mmol) was also added. After the reaction mixture was allowed to warm to room temperature and stir overnight, it was partitioned between water and ether. The aqueous phase was extracted twice more with ether, and the combined organic layers were dried over $MgSO_4$ and filtered through a plug of silica gel. After removal of the solvent under reduced pressure, the resulting dark orange oil was dissolved in 1,2,4-trimethylbenzene and refluxed for 2 days. Removal of the solvent under vacuum followed by flash chromatography (30% ether in hexane) gave naphthofuranone **9** as a light yellow oil (86 mg, 0.26 mmol, 36% yield).

IR (neat): 2940, 1691, 1477, 1439, 1063, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22 (s, 3H, R-CH_3), 1.95 (br d, J = 16.2 Hz, 1H, H-5), 2.14 (dd, J = 6.7, 16.2 Hz, 1H, H-5), 2.57 (dd, J = 1.7, 9.3 Hz, 1H, H-8b), 3.08 (m, 1H, H-2a), 3.29 (s, 3H, R-OCH_3), 4.02 (dd, J = 7.5, 8.8 Hz, 1H, H-2), 4.09 (dd, J = 3.4, 8.8 Hz, 1H, H-2), 6.94 (dd, J = 3.1, 6.7 Hz, 1H, H-4), 6.05 (d, J = 10.1 Hz, 1H, H-7), 6.76 (d, J = 10.1 Hz, 1H, H-6), 7.25−7.40 (m, 5H, R-SC_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 27.7, 35.0, 38.9, 40.8, 50.2, 54.4, 73.3, 102.8, 127.1, 127.5, 127.6, 129.2, 131.9, 133.0, 135.5, 158.5, 190.5. Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14. Found: C, 69.30; H, 6.05.

7,12-Epoxy-5a,8,11-trimethoxy-12b-methyl-3-phenylthio-3a,4,5a,6a,7,12,12a-heptahydro-1*H*-benzo[6,7]phenanthro-[10,1-*bc*]furan-6-(12b*H*)-one (11). A solution of naphthofuranone **9** (204 mg, 0.62 mmol) and isobenzofuran **5** (250 mg, 1.40 mmol) in toluene (20 mL) was refluxed for 21 h, after which the solvent was removed under reduced pressure and the residue purified by flash chromatography (50% ether in hexane) to give adduct **11** as a white powder (295 mg, 0.58 mmol, 94% yield).

Mp: 155−6 °C. IR (NaCl): 2942, 1736, 1500, 1439, 1260, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): compound **11** is a fluxional molecule, and the proton NMR at room temperature consists of several very broad signals[4] with a few diagnostic peaks; 1.59 (s, R-CH_3), 3.32 (s, R-OCH_3), 3.78 (s, Ar-OCH_3), 3.80 (s, Ar-OCH_3), 6.64, 6.68 (both d, J = 9.0 Hz, H-9, H-10), 7.23−7.37 (m, 5H, R-SC_6H_5). Anal. Calcd for $C_{29}H_{30}O_6S$: C, 68.75; H, 5.97. Found: C, 68.68; H, 6.13.

5a,8,11-Trimethoxy-12b-methyl-3-phenylthio-3a,4,5a,12c-tetrahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12b*H*)-one (12). A solution of adduct **11** (403 mg, 0.80 mmol) and NaOMe (4.00 g, 74 mol) in MeOH (100 mL) was refluxed for 3 h, after which the solvent was removed under reduced pressure and the residue partitioned between ether and dilute HCl (3 M). The organic phase was washed once with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure and flash chromatography of the residue (35% EtOAc in hexane) gave the pentacycle **12** as a bright yellow solid (361 mg, 0.74 mmol, 93% yield).

Mp: 165−166 °C. IR (NaCl): 2938, 1704, 1628, 1471, 1267, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.65 (s, 3H, R-CH_3), 2.02 (br dd, J = 6.4, 17.8 Hz, 1H, H-1), 2.18 (br d, J = 17.8 Hz, 1H, H-1), 2.79 (dd, J = 1.8, 8.4 Hz, 1H, H-12c), 3.07 (m, 1H, H-3a), 3.20 (s, 3H, R-OCH_3), 3.95 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3), 4.05 (dd, J = 6.1, 8.8 Hz, 1H, H-4), 4.39 (d, J = 8.8 Hz, 1H, H-4), 6.06 (dd, J = 1.7, 6.4 Hz, 1H, H-2), 6.71, 6.82 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.24−7.44 (m, 5H, R-SC_6H_5), 8.22 (s, 1H, H-12), 8.73 (s, 1H, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 24.6, 35.4, 41.4, 41.5, 49.9, 55.5, 55.7, 55.8, 71.7, 103.8, 104.7, 106.3, 117.5, 123.4, 124.8, 127.3, 128.4, 129.2, 131.1, 131.3, 131.6, 132.7, 133.6, 145.0, 149.1, 150.7, 192.6. Anal. Calcd for $C_{29}H_{28}O_5S$: C, 71.29; H, 5.78. Found: C, 71.30; H, 5.63.

8,11-Dimethoxy-12b-methyl-3-phenylthio-3a,4 -dihydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12b*H*)-one (13). To a solution of compound **12** (153 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.5 mL). The resulting solution was stirred for 15 min, after which the reaction mixture was diluted with CH_2Cl_2 and quenched with an aqueous $NaHCO_3$ solution. The organic layer was washed with water and dried ($MgSO_4$) and the solvent removed under reduced pressure to give pentacycle **13** as a bright yellow solid (138 mg, 0.30 mmol, 97% yield) that was used without further purification.

Mp: 202−204 °C. IR (NaCl): 2934, 1664, 1627, 1464, 1268, 1091 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.66 (s, 3H, R-CH_3), 2.36 (br d, J = 17.5 Hz, 1H, H-1), 3.06 (dd, J = 5.4, 17.5 Hz, 1H, H-1), 3.97 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 4.07 (m, 1H, H-3a), 4.33 (dd, J = 9.1, 10.6 Hz, 1H, H-4), 4.67 (dd, J = 9.1, 10.2 Hz, 1H, H-4), 6.08 (m, 1H, H-2), 6.70, 6.81 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.29−7.48 (m, 5H, R-SC_6H_5), 8.35 (s, 1H, H-12), 9.22 (s, 1H, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.4, 36.6, 43.6, 44.2, 55.6, 55.7, 75.3, 103.3, 105.8, 119.3, 123.1, 124.8, 127.6, 127.9, 129.3, 129.6, 129.7, 131.8, 132.2, 132.9, 139.2, 145.0, 146.9, 148.6, 150.7, 176.2. Anal. Calcd for $C_{28}H_{24}O_4S$: C, 73.66; H, 5.30. Found: C, 73.85; H, 5.50.

8,11-Dimethoxy-12b-methyl-3-phenylthio-1*H*-benzo[6,7]-phenanthro[10,1-*bc*]furan-6-(12b*H*)-one (14). A solution of pentacycle **13** (108 mg, 0.24 mmol) and *p*-chloranil (249 mg, 1.01 mmol) in xylenes was refluxed for 2 days, after which the solvent was removed under vacuum and the residue purified by flash

(14) For general experimental details, see ref 4. Assignments of ^1H NMR signals were made with the aid of 2D and decoupling methods and by comparison with spectra of similar compounds prepared earlier[4] in our laboratory.

chromatography (50% EtOAc/hexane) to give furan **14** as a bright fluorescent yellow-green solution that provided an amorphous solid (50 mg, 46% yield) which could not be obtained in more than 85% purity in spite of repeated chromatography. It was used as such for the next step.

IR (NaCl): 2932, 1674, 1625, 1464, 1433, 1091, 724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.59 (s, 3H, R-CH_3), 2.79 (broad d, J = 16.8 Hz, 1H, H-1), 3.27 (dd, J = 6.4, 16.8 Hz, 1H, H-1), 3.97 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3), 6.34 (m, 1H, H-2), 6.70, 6.81 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.20−7.44 (m, 6H, H-4, R−SC_6H_5), 8.24 (s, 1H, H-12), 9.27 (s, 1H, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 32.2, 35.3, 37.5, 55.68, 55.70, 103.5, 106.2, 118.4, 121.7, 124.2, 124.3, 124.8, 127.2, 127.5, 128.7, 129.2, 130.2, 131.1, 131.8, 133.5, 142.5, 144.1, 144.9, 148.6, 150.8, 172.6. HRMS: calcd for $C_{28}H_{22}O_4S$ 454.1239; found 454.1249.

Halenaquinol Dimethyl Ether (15). To a solution of sulfide **14** (15 mg, 0.033 mmol) in glacial acetic acid (2 mL) were added neat $TiCl_4$ (1 mL) and water (50 μL), and the resulting mixture was refluxed overnight. After being diluted with CH_2Cl_2, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (50% Et_2O/hexane) gave known pentacycle **15** (8 mg, 0.021 mmol, 63% yield), whose NMR spectrum was identical with the previously published data for (+)-**15**.[5a]

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