Protein Tyrosine Kinase Inhibitory Properties of Planar Polycyclics Obtained from the Marine Sponge *Xestospongia* cf. *carbonaria* and from Total Synthesis

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Nine related polycyclic quinones and hydroquinones of the halenaquinone class were isolated from two Indo-Pacific collections of the sponge *Xestospongia* cf. *carbonaria*. The halenaquinone family appears not to be of polyketide origin but can be biogenetically derived by the union of a sesquiterpene and a quinone. Four new metabolites were characterized including tetrahydrohalenaquinone B (**8a**), 14-methoxyhalenaquinone (**9**), xestoquinolide A (**10**), and xestoquinolide B (**11**). These were accompanied by five known compounds, halenaquinone (**3**), halenaquinol (**4**), halenaquinol sulfate (**5**), xestoquinone (**6**), and tetrahydrohalenaquinone A (**7a**). The new structures were established from 2D NMR data, and the absolute stereochemistry of the chiral centers in **7** and **8** was determined by the formation of **7b** and **7c**, the bis esters of *O*-methylmandelic acid. A series of polycyclic models of natural products **3** and **6** were synthesized and included **16–23**. The more complex members of this group were assembled via a 4 + 2 cycloaddition between an *o*-quinodimethane and a functionalized enone. The marine natural products plus two known fungal metabolites, viridin (**13**) and wortmannin (**14**), along with halenaquinone synthetic model compounds, were each tested for their ability to inhibit the activity of $pp60^{v\text{-}src}$ protein tyrosine kinase (PTK). Halenaquinone and 14-methoxyhalenaquinone were the most potent with IC_{50} values <10 μM. The other compounds were either less potent or inactive, and a rationalization for this SAR (structure activity relationship) pattern is presented.

Introduction

Enhanced protein tyrosine kinase (PTK) activity has been associated with proliferative diseases such as cancer[1a] and psoriasis.[1b] Examples can be found in the literature showing that both the receptor types and the cytoplasmic types of PTKs are associated with human cancers.[2] In addition, this family of enzymes is intimately involved in the regulation of cell growth and signaling; consequently, we believe that the discovery of PTK antagonists ought to be important in the development of new chemotherapeutic agents. To date, only four marine natural products have been found to inhibit PTKs; these are aeroplysinin (**1**),[3] melemeleone B (**2**),[4] halenaquinone (**3**),[5] and halenaquinol (**4**).[5] The effectiveness of the latter two compounds as potent PTK inhibitors was disclosed in a recent paper from our laboratories.[5] Halenaquinone (**3**)[6-9] was effective against both the $pp60^{v\text{-}src}$ and epidermal growth factor (EGF) receptor PTKs. Similar potency was observed with **4**[9] as it is undoubtedly oxidized to **3** during assay. Four other related compounds, halenaquinol sulfate (**5**), xestoquinone (**6**),[7] tetrahydrohalenaquinone A (**7a**)[5] and tetrahydrohalenaquinone B (**8a**),[5] were also evaluated in the PTK assay, and all were inactive.

After this initial disclosure our investigation was continued on a large (8 kg) Fijian recollection of *Xestospongia* cf. *carbonaria*, and another new study was begun on a different collection obtained from Vanuatu. A parallel program was also begun to synthesize analogs of halenaquionone to explore their effects against PTK. Presented in this report are the details of the structure elucidations of **8a** along with those of new compounds **9–11**. Also outlined are schemes for the synthesis of bicyclic to pentacyclic halenaquinone model compounds **16–23**. Further PTK testing data have also been accumulated on the sponge products, on structurally related fungal natural products **13–14**, and on the synthetic model compounds. The collective bioactivity trends can now be interpreted to define the features of the halenaquinone structure which are needed for inhibition of PTK.

Results and Discussion

Three compounds, halenaquinone (**3**), halenaquinol (**4**), and xestoquinone (**6**), were isolated as major components from the CH_2Cl_2 solvent partition fraction of the Fijian material, and the fourth compound, halenaquinol sulfate

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(2) Chang, C. J.; Geahlen, R. L. *J. Nat. Prod.* **1992**, *55*, 1529–1560.
(3) Kreuter, M.-H; Leake, R. E.; Rinaldi, F.; Muller-Klieser, W.; Maidohf, A.; Muller, W. E. G.; Schroder, H. C. *Comp. Biochem. Physiol.* **1990**, *97B*, 151–158.
(4) Alvi, K. A.; Diaz, M. C.; Crews, P.; Slate, D. L.; Lee, R. H.; Moretti, R. *J. Org. Chem.* **1992**, *57*, 6604–6607.
(5) Lee, R. H., Slate, D. L., Moretti, R., Alvi, K. A. and Crews, P. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 765–772.
(6) (a) First report of structure for **3**: Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 6177–6178. (b) Absolute stereochemistry of **3** via total synthesis: ref 17.
(7) Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y; Hirata, Y. *Chem. Lett.* **1985**, 713–716.
(8) Schmitz, F. J.; Bloor, S. J. *J. Org. Chem.* **1988**, *53*, 3922–3925.
(9) Kobayashi, M.; Shimizu, N.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1985**, *33*, 1305–1308.

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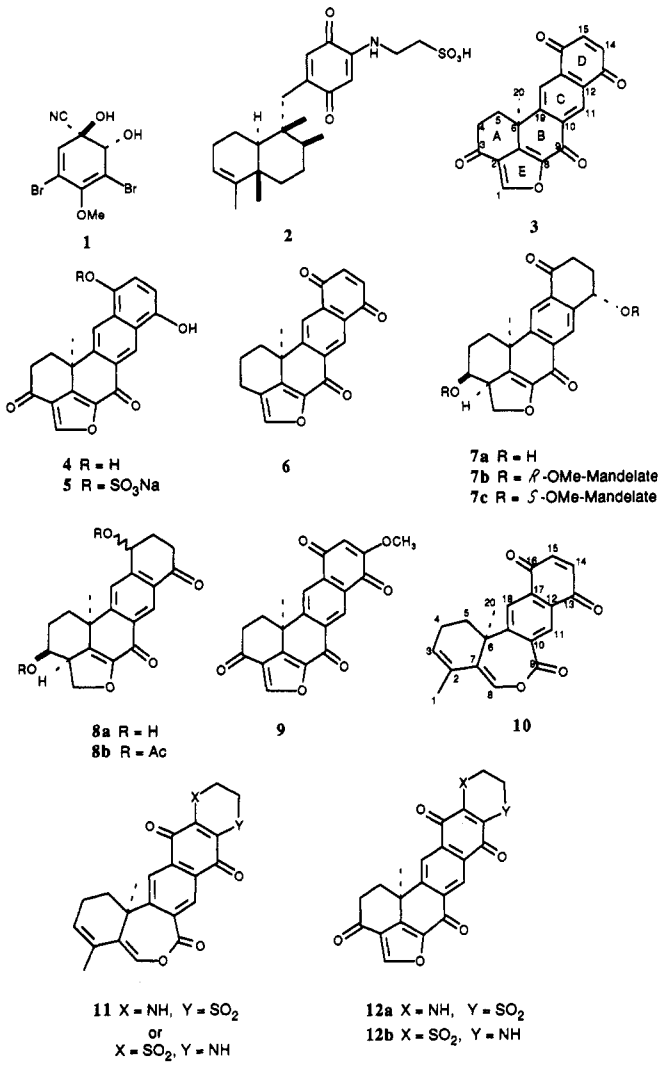


(5), was isolated from the BuOH solvent partition. During the process of comparing the spectral properties of **3–6** to the literature[6–9] it became apparent that the least number of signature NMR resonances diagnostic of the structural elements present in this family of pentacyclic quinones and hydroquinones could be defined as ^{13}C NMR resonances for carbonyls at δ 191 (A-ring), δ 170 (B-ring), and δ 183 and δ 184 (D-ring) and ^1H NMR peaks for vinyl protons of the quinones and hydroquinones at δ 8.3–9.1 (C-ring) and δ 7.6 or 8.8 (E-ring) 7.49–6.29 (D-ring).

Our work on new compounds related to **3–6** began with a mixture obtained from the Fijian collection. Their NMR spectra lacked many of the above ^{13}C or ^1H diagnostic signals, but displayed carbonyls, as clusters of two peaks near δ 193 and 173, accompanied by aromatic ring protons as singlets restricted to the region between δ 8.1–8.5. Extensive chromatography work on this mixture eventually yielded two isomeric compounds, tetrahydrohalenaquinone A (**7a**) and tetrahydrohalenaquinone B (**8a**), both of formula $C_{20}H_{20}O_5$. The structure of the less polar compound (**7a**) was assigned (HREIMS $[M]^+$ 340.1315) by comparing its NMR data to those of a compound, reported by Schmitz,[8] with the same overall structure but without description of hydroxy stereochemistry at C-13. Our material was concluded to be identical to the compound reported by Schmitz because all the ^{13}C NMR shifts were within 2 ppm of one another (see Table I). Both the ^1H and ^{13}C NMR shifts of the more polar **8a**[10] (HREIMS $[M]^+$ 340.1315) were nearly identical to those of **7a** with

Table I. ^{13}C NMR Data

C no.	3[a]	7a[b,d]	8a[b]	9[c]	10[a]
1	149.4	72.6	72.7	150.2	23.3
2	122.6	47.3	47.2	122.8	133.1
3	191.1	68.3	68.3	192.1	131.8
4	33.4	29.4	29.6	33.4	23.6
5	36.5	35.2	35.1	36.6	33.6
6	36.8	39.9	40.3	37.2	39.5
7	147.5	143.3	142.0	148.3	142.5
8	145.0	148.8	148.6	145.1	139.5
9	170.9	176.8	177.0	170.9	179.3
10	137.2	134.3	132.8	137.0	130.3
11	127.4	126.7	126.2	127.7	126.0
12	130.8	145.9	130.6	130.2	133.8
13	183.5	67.8	198.9	179.2	183.7
14	138.8	32.8	36.8	161.5	139.1
15	139.5	36.3	33.0	110.5	139.1
16	184.4	199.2	68.4	184.5	184.5
17	133.8	136.8	151.1	134.5	133.1
18	124.0	125.6	127.2	124.0	125.2
19	154.1	152.3	158.2	155.1	156.3
20	30.8	24.8	25.3	29.9	27.5
OCH_3				57.0	

[a] Recorded in $CDCl_3$ at 75 MHz. [b] Recorded in CD_3OD at 62.5 MHz. [c] Recorded in $CDCl_3$ at 125 MHz. [d] We have been informed of revisions to the literature ^{13}C NMR shifts of **7a** (Prof. F. J. Schmitz, personal communication): C-6 δ 38.3, C-15 δ 35.7.

the exception that the net differences in shift of the resonances assignable to C-12/17 of **7a** and **8a** were 5 and 6 ppm, respectively. This effect was quickly ascribed to differing D-ring regiochemistry between this pair. Additional evidence in support of the structures we show here was established from two-dimensional NMR data including ^1H–^1H COSY, ^1H–^{13}C COSY (J = 140 Hz), and long-range ^1H–^{13}C COSY (J = 9 Hz) and by NOEDS measurements. Chemical verification was provided by acetylation of **8a** to afford **8b**, and the latter exhibited NOEs both from the acetate signal at δ 2.12 to the resonance at δ 7.88 (H-18) and from the latter signal to the Me-20 singlet at δ 1.52.

The absolute stereochemistry of **7a** at C-3 and C-13 was determined by ^1H NMR analysis[11] of the bis-(+)-(*R*)-*O*-(methyl mandelate) (**7b**) and bis-(−)-(*S*)-*O*-(methyl mandelate) (**7c**). The key observations are summarized in

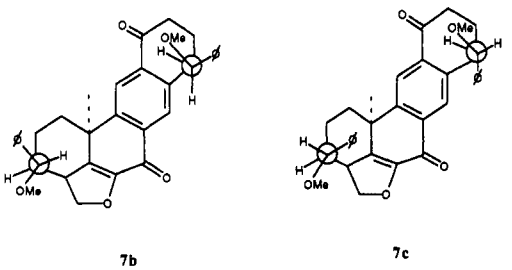


Table II. In particular, the protons H-1 and H-11 of **7b** were deshielded as compared to the corresponding protons of **7c** due to the anisotropic effect of the benzene rings while signals of H-14, H-15, H-18, and H-20 in **7c** were deshielded as compared to those of **7b**. Consequently, the absolute configurations of 3*S* and 13*S* can be assigned. Using the relative stereochemistry previously assigned for

(10) After our paper (ref 5) was published compound **8a** was reported without details of the D-ring stereochemistry: Kobayashi, J.; Hirase, T.; Shigemori, H.; Ishibashi, M. *J. Nat. Prod.* **1992**, *55*, 994–998.

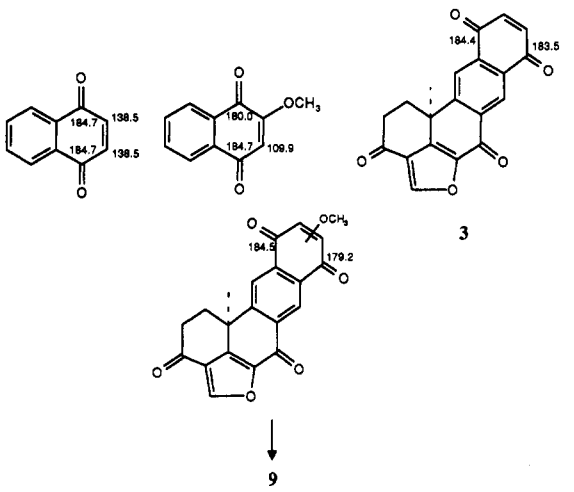
(11) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 4929–4932. (c) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370–2374. (d) Adamczeski, M.; Quiñoá, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240–242. (e) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

Table II. Comparison of the ^1H NMR Data for the Bis(methoxy mandelate) Esters 7b and 7c[a]

H no.	bis-(+)-(*R*)-*O*-(methyl mandelate) (7b)	bis-(−)-(*S*)-*O*-(methyl mandelate) (7c)	Δδ(*S*–*R*)
1	4.40 (dd)	3.76 (dd)	−1.36
	4.64 (dd)	4.39 (dd)	0.25
2	3.51 (m)	3.51 (m)	0.00
3	5.12 (brs)	5.12 (brs)	0.00
4	1.90 (m)	1.90 (m)	0.00
5	1.85 (m)	1.85 (m)	0.00
11	8.39 (s)	8.16 (m)	−0.23
14	2.15 (m)	2.32 (m)	+0.17
14′	2.25 (m)	2.50 (m)	+0.25
15	2.53 (m)	2.86 (m)	+0.33
15′	2.25 (m)	2.76 (m)	+0.51
18	8.02 (s)	8.08 (s)	+0.06
20	1.48 (s)	1.52 (s)	+0.04

[a] Recorded in $CDCl_3$ at 250.13 MHz.

Chart I. ^{13}C Additivity Effects[12,13]



7a allows the additional stereocenters to be denoted as 2*S* and 6*S*. Assuming that **7a** and **8a** have the same absolute configurations at C-3 and a parallel stereochemistry in the A-ring allows a provisional absolute stereochemistry to be assigned for **8a** as 2*S*, 3*S*, 6*S*.

The Fijian recollection of *X.* cf. *carbonaria* afforded 14-methoxyhalenaquinone (**9**) as a reddish yellow solid. Its mass spectrum showed a molecular ion at *m/z* 362.0790 corresponding to the molecular formula $C_{21}H_{14}O_6$. The ^{13}C NMR spectrum of **9** (Table I) contained all of the signals indicative of **3** plus one additional OMe (δ 57.0) group. Also, the upfield shifts of the vinyl proton (δ 6.30) and its associated carbon (δ 110.5), as compared to the corresponding data of halenaquinone (**3**), indicated that this CH residue was β to the $-OCH_3$. The regiochemistry of the new OMe was assigned from ^{13}C NMR shift additivity effects. Important bench marks were the data for napthoquinone and 2-methoxynapthoquinone (see Chart I)[12,13] which illustrate that only the quinone C=O α to an OMe is shifted when this substituent is added to the chromophore. The D-ring C=O shifts of **9** were unambiguously assigned from a long range ^{13}C–^1H COSY spectrum, and adding the quinone OMe substituent increment to these base shifts indicated that the OMe was best placed at C-14 in **9**.[12,13]

Another new compound, xestoquinolide A (**10**), a yellow crystalline solid, was also isolated from the Fijian recollection. It displayed six vinyl proton resonances rather than the five observed for **3**–**6**. The molecular formula of $C_{20}H_{16}O_4$ was determined by HREIMS $[M]^+$ 320.1049, and this indicated 13 degrees of unsaturation rather than the 14 or 15 associated with **6** or **3**, respectively. Extended conjugation was apparent from the UV spectrum of **10** [λ_{max} = 216, 234 sh, 245, 325 nm], and key ^1H (see Experimental Section) and ^{13}C NMR (Table I) resonances could be assigned for CH-11, CH-14, CH-15, and CH-18 indicating the presence of halenaquinone type C/D-rings. The new features could then be summarized as a conjugated carbonyl vinyl ester based on ^{13}C NMR resonances at δ 179.3 (s), 142.5 (s), 139.5 (d) and an IR λ_{max} 1672 cm^{-1}. ^1H NMR resonances could be identified for an additional trisubstituted double bond at δ 5.90 (bs), a vinyl Me at δ 2.28 (s), and a quaternary Me at δ 1.48 (s). At this point with six double bonds and three C=O's identified it was evident that a tetracyclic structure was required. Definitive assignment of each of the proton-bearing carbons was provided by a ^1H-detected ^1H–^{13}C COSY NMR experiment (HMQC).[14] Important additional atom connectivities were derived from a ^1H–^1H COSY NMR spectrum and were further confirmed by an HMBC (heteronuclear multiple bond correlation spectroscopy) experiment.[15] These data confirmed the presence of halenaquinone type CD-rings as substructure **A** (Figure 1) plus the vinyl ester containing substructure **B**. A ^1H–^1H COSY NMR spectrum showed cross peaks from H-3 to Me-1 and H_2-4, while H_2-4 also showed a correlation to H_2-5. The remaining ring could finally be assembled by joining C-10/C-19 to C-6/C-10 (see Figure 1), and the proper way to make these connections was guided by HMBC correlations from H-11 to C-9 and from H-18 to C-6.

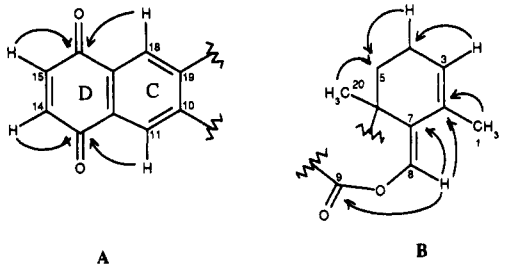


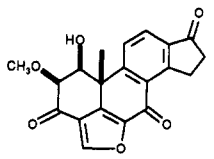
Figure 1. Partial structures of **10** from ^1H–^1H COSY and ^1H–^{13}C HMBC (see arrows) data.

The investigation of a Vanuatu collection of *X.* cf. *carbonaria* yielded **9**, accompanied by an additional new lactone, xestoquinolide B (**11**), as a yellow powder. A molecular formula for **11** of $C_{22}H_{19}O_6NS$ was established by HRFABMS, and the NMR data of **11** which was similar to that of **10** revealed two substructures consisting of the tetracyclic ring core of **10** and a $-NHCH_2CH_2SO_2-$ (taurine) moiety. No quinone ring protons were observed and other new proton resonances were those assigned to the taurine at δ 3.40 (m, 2H), and 4.18 (m, 2H). The two substructures could be joined as shown in **11**. Unfortunately, comparison of the C=O shifts of **11** to those in the literature[8] for **12a** and **12b** did not provide a way to establish the taurine annulation regiochemistry.

At first glance the structural frameworks present in quinones or hydroquinones such as **3**–**6** or **7a** plus nine related known derivatives seem quite unique.[16] Inter-

(12) Hoofle, G. *Tetrahedron* **1977**, *33*, 1963–1970.
(13) Neidlein, R.; Kramer, W.; Leidholdt, R. *Helv. Chim. Acta* **1983**, 2285–2293.
(14) Klenar, V. S.; Bax, A. *J. Magn. Res.* **1987**, *71*, 379–383.
(15) Bax, A.; Subramanian S., *J. Magn. Res.* **1986**, *67*, 565–569.
(16) For a recent review see: Thomson, R. H. *Naturally Occurring Quinones III. Recent Advances*; Chapman and Hall: New York, 1987.

estingly, an analogy can be drawn between these structures, which have been the subject of recent total syntheses,[17] and two families of polycyclic fungal metabolites exemplified by viridin (13)[18] and wortmannin (14).[19] Not



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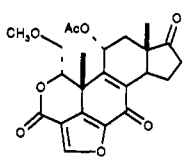

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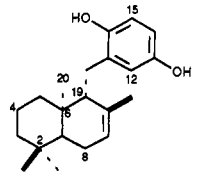

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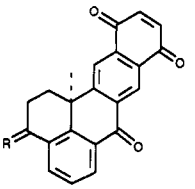
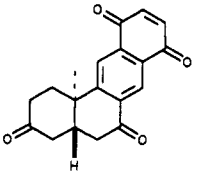
surprisingly, these fungal metabolites have been shown experimentally to be of steroid biosynthesis origin,[20] and the parallel nature between 3, 13, and 14 becomes readily apparent when their structures are drawn from the same perspective (see structures in refs 5–10). Also, our recent summary of the phyletic origins and structures of such metabolites known from marine sponges and algae provides valuable background information.[21] Consequently, we proposed that the halenaquinone family of compounds is comprised of a sesquiterpene plus a triketide. A tidy biosynthetic link to 3 is provided by isozonarol (15),[22a] and the transformation to the former would involve A-ring demethylation, bond formation between C-11/12, ether ring formation from C-1 to C-8, and finally oxidation of the hydroquinol ring. Hypothetical tricyclic sesquiterpenequinones with appended taurine residues analogous to 2 are likely biosynthetic precursors to penta- and hexacyclics such as 11 or 12. A parallel biogenetic relationship to that proposed above can also be seen for sesterterpenehydroquinols, toxislyide A, and disidenin.[22b] A separate, important point is that the members of the halenaquinone family have been previously reported from tropical Pacific sponges identified as members of the *Xestospongia*[6,7,9,10] or *Adocia*[8] genera. However, this structural family can now be considered to be an exclusive taxonomic marker for the less massive members of the *Xestospongia* genus because our reexamination of the *Adocia* voucher[8] specimens previously shown to yield nine halenaquinone metabolites shows that they are actually identical to the taxa studied here and were misidentified.

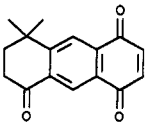
Total synthetic chemistry work was initiated once the initial PTK data for 3 and 6 were in hand, and it continued in parallel with the structure elucidation studies described above. One goal was to better understand the differences in the keto furan region in 3 versus 6 which markedly influences their relative inhibition of PTK. The synthetic efforts which provided new compounds 16–23 proceeded as shown in Schemes I and II, and the preparation of the pentacyclic and tetracyclic compounds (±)-16, (±)-17, and (±)-18 presented the biggest challenge. Compounds 16



(±) 16 R = H_2
17 R = O



(±) 18



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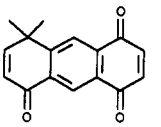

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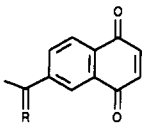
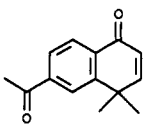


21 R = O
22 R = H_2



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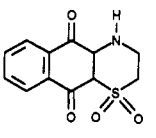

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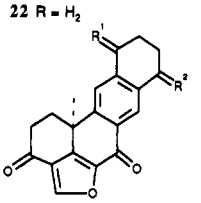

25 R^1 = H,OH R^2 = O
26 R^1 = R^2 = H,OH
27 R^1 = O R^2 = H,OH

and 17 have the furan ring of, respectively, 3 and 6 replaced by a fused benzene ring while in 18 the furan ring is absent. Our retrosynthetic strategy was built on the convergent methodology developed by the Harada[17] group who completed a scalemic synthesis of (+)-halenaquinone using a Diels–Alder coupling. Thus, a 4 + 2 cycloaddition between *o*-quinodimethide, derived *in situ* by thermal extrusion of SO_2 from 32 and, respectively, 30 or 31, prepared from 28[23] as shown in Scheme I, afforded analogs 16 and 17. Likewise, cycloaddition of 40, prepared from 35 with 32, gave the cycloadduct 41 which was aromatized and oxidized (see Scheme I) to the desfuran halenaquinone 18. The sulfone 32 also served as a precursor for construction of model compounds 19 and 20 which possess just the halenaquinone BCD rings. This route involved cyclization of 4,4-dimethylcyclohexenone with 32, and the resultant cycloadduct 43 was converted separately to 19 and 20 as shown in Scheme II.

Conveniently, the dibromide 44 prepared by Harada[17] served as the precursor to the model compounds 21 and 22 which both have only the halenaquinone CD rings. Reductive debromination of 44 with chromium dichloride[24] and trapping of the reactive *o*-quinodimethide with methyl vinyl ketone generated cycloadduct 45. Aromatization of this product afforded 46 which was smoothly transformed to, respectively, 21 and 22 as shown in Scheme II. Another model compound, 23, containing modified halenaquinone CD rings, was prepared in an efficient manner from the known tetralone 48[25] as shown in Scheme II.

An interesting array of cytotoxic activities has been noted in the literature for the halenaquinone family of polyketides. Schmitz showed that 3 and a synthetic model compound 24 were active against PS cells whereas 6 was inactive.[8] By contrast, Kobayashi found that both 3 and 6 were potent against both L1210 and KB cells.[10] In addition, 26 was noted as active against L1210 only, and

(17) (a) Harada, N.; Sugioka, T.; Ando, Y.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1988**, *110*, 8483–8487. (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *J. Org. Chem.* **1990**, *55*, 3158–3163.

(18) Cole, R. J.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*; Academic Press: New York, 1981.

(19) (a) Petcher, T. J.; Weber, H. -P.; Kis, Z. *J. Chem. Soc., Chem. Commun.* **1972**, 1061–1062. (b) MacMillan, J.; Simpson, T. J.; Yeboah, S. K. *J. Chem. Soc., Chem. Commun.* **1972**, 1062–1063. (c) Broka, C. A; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888–4894.

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(21) Rodríguez, J.; Quiñoá, E.; Riguera, R.; Peters, B. M.; Abrell, L. M.; Crews, P. *Tetrahedron* **1992**, *48*, 6667–6680.

(22) (a) Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. J. *J. Org. Chem.* **1973**, *38*, 2383–2386. (b) Crews, P.; Naylor, S. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 203–269.

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(24) Stephan, D.; Gorgues, A.; Le Coq, A. *Tetrahedron Lett.* **1984**, *25*, 5649–52.

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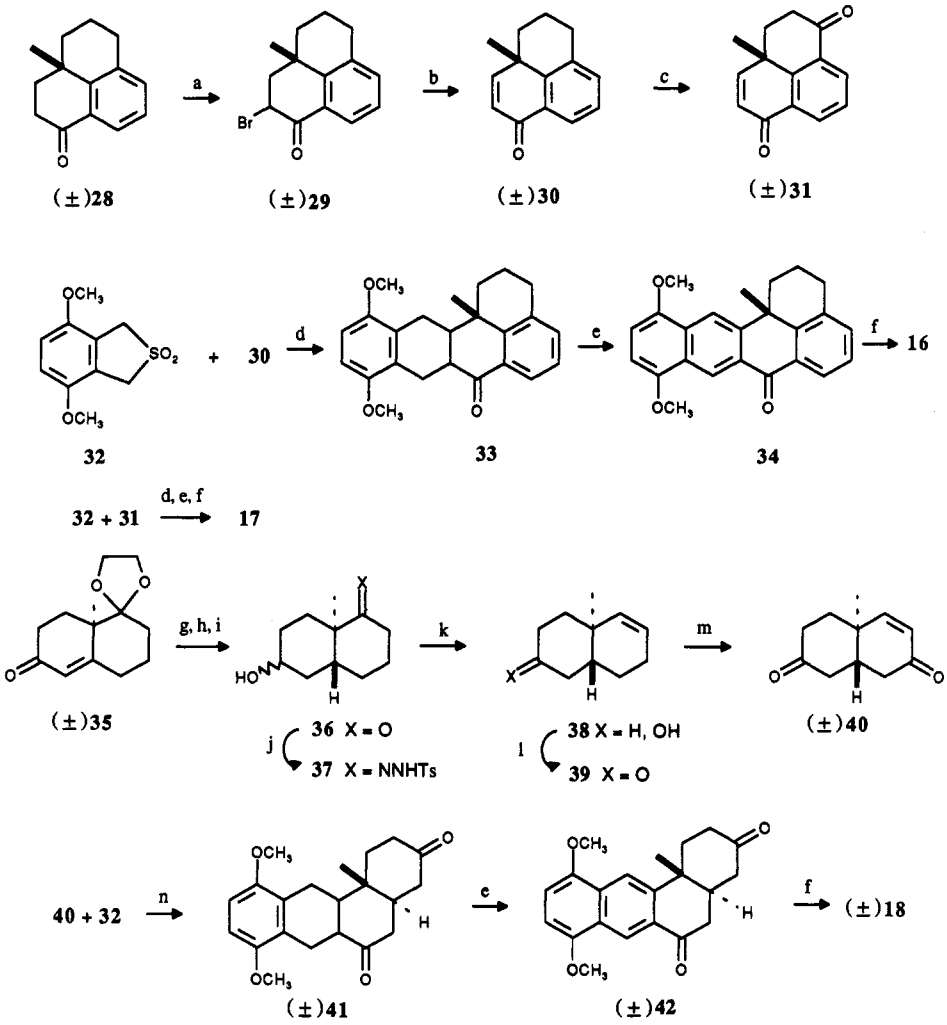
Scheme I.[a] Preparation of Halenaquinone Model Compounds 16–18



[a] Key: (a) Compound **28** prepared by a modified procedure as described in ref 23 then treated with Br_2, Et_2O, 0 °C; (b) *s*-collidine, rt; (c) PCC, Celite, benzene; (d) decalin, 260–280 °C, (cat.) BHT; (e) DDQ, benzene, rt; (f) CAN, CH_3CN (aq), 0 °C; (g) **35** prepared according to ref 17 then tested with Li/NH_3; (h) $NaBH_4$; (i) TsOH; (j) $TsNHNH_2$; (k) CH_3Li; (l) oxalyl chloride, −78 °C, then Et_3N; (m) CrO_3; (n) decaline 260–280 °C, (cat) BHT.

5, **25**, and **27** were all inactive against both cell lines.[10] We submitted both **3** and **6** for evaluation in the NCI-DTP *in vitro* multicell line screen.[26] Both compounds were potent growth inhibitors but ineffective as cytotoxins in assay against 50–58[27] different types of tumor cells from a panel which included leukemia, non-small cell lung, small cell lung, colon, CNS, melanoma, ovarian, and renal cancers. Antiproliferative activity shown in Figure 2[27,28] was observed against only four cell lines which included leukemia, CCRF-CEM, MOLT-4, and HL-60, and colon, DLD-1, and full dose response curves appear in the supplementary material (Charts S1–S4).

While halenaquinone (**3**) is a potent inhibitor of both the $pp60^{v\text{-}src}$ (IC_{50} = 1.5 μM) and of the EGF receptor (IC_{50} = 19 μM) kinase,[5] it is not active against protein kinase C. This interesting observation intimates that **3** is not a general kinase inhibitor. That **3** is an irreversible inhibitor of $pp60^{v\text{-}src}$ is relevant and is analagous to the behavior of herbimycin A which irreversibly inactivates $pp60^{v\text{-}src}$.[29] A Michael addition by PTK at C-1, C-14, or C-15 on the halenaquinone (**3**) frame provides the simplest rationalization of the enzyme inhibition mechanism. Furthermore, the weak activity of **6** against PTK (Table III) lends some support this idea. Unfortunately, such a straightforward explanation does not accommodate the additional data shown in Table III. This broad base of structure–activity results was obtained for halenaquinone analogs which included both simple and complex halenaquinone model compounds, along with both marine and nonmarine natural products. None of the synthetic compounds inhibited $pp60^{v\text{-}src}$ as potently as **3**; **19–22** are moderate (IC_{50}s = 9–20 μM) PTK inhibitors, while **23** is inactive. A parallel trend of weak or no activity is represented in the results for the marine natural products **7a** and **8a** (both inactive)

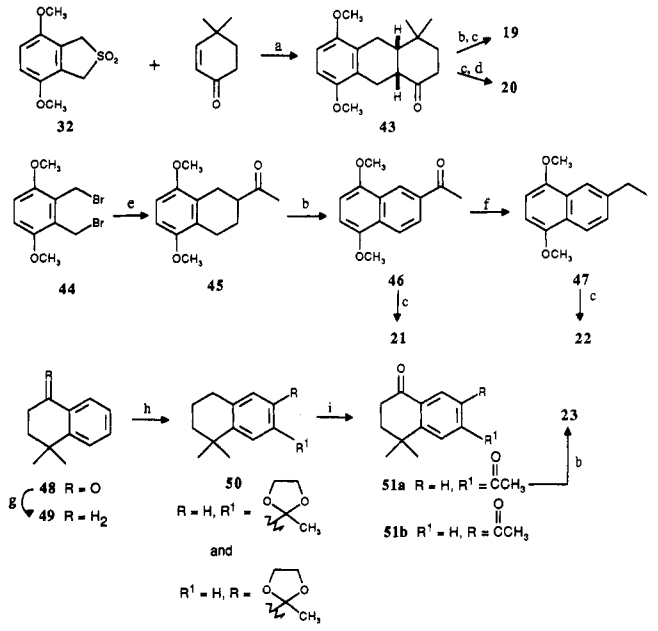
(26) Boyd, M. R. In *Cancer Principles & Practice of Oncology. Update Series*; DeVita, V. T., Jr., Hellman, S., Rosenberg, S. A., Eds.; Lippincott: Philadelphia, 1989; Vol. 3, No. 10, pp 1–12.

(27) The screening was conducted by the NCI Developmental Therapeutics Program against 58 (**3**) or 50 (**6**) cell lines, respectively, divided into groups which included leukemia cell lines plus six different families of solid cancer tumor types. The GI_{100}'s under 10 μM were: **3** leukemia CCRF-CEM = 5.4, HL-60(TB) = 5.5, and **6** leukemia CCRF-CEM = 7.7, MOLT-4 = 6.2, colon DLD-1 = 6.1.

(28) For an overview of the NCI's screening see: (a) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Visitca, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766. (b) Boyd, M. R.; Paull, K. D.; Rubinstein, L. R. Data Display and Analysis Strategies for the NCI Disease-oriented *In Vitro* Antitumor Drug Screen. In *Antitumor Drug Discovery and Development*; Valeriote, F. A., Corbett, T., Baker, L., Eds.; Kluwer Academic Publishers: Amsterdam, 1992; pp 11–34.

(29) (a) Fukazawa, H.; Mizuno, S.; Uehara, Y. *Biochem. Biophys. Res. Commun.* **1990**, *172*, 276–282. (b) Uehara, Y, Fukazawa, H.; Murakami, Y.; Mizuno, S. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 803–809.

Scheme II.[a] Preparation of Halenaquinone Model Compounds 19–23



[a] Key: (a) decalin (cat.) BHT, 260–280 °C; (b) DDQ, benzene, rt; (c) CAN, CH_3CN; (d) TMS–OTf, NEt_3, CH_2Cl_2 then $PPd(OAc)_4$, CH_3CN, rt; (e) $CrCl_2$, excess methyl vinyl ketone, THF, rt; (f) H_2 (1 atm), Pd/C, EtOH, HCl (aq); (g) compound **48** prepared according to ref 25 first treated with H_2 Pd/C 60 psi to givd **49**, then treated with $AlCl_3$, CH_3COCl in CH_2Cl_2; (h) glycerol, TsOH (cat.), benzene, DME; (i) CrO_3 (cat), *t*-BuOOH, CH_2Cl_2, rt.

and the fungal natural products **13** (IC_{50} = 30 μM) and **14** (inactive). The activity data of the three other new natural products isolated in this study provide additional relevant information. The potency of **9** (IC_{50} = 5 μM) indicates limited halenaquinone D-ring substitution can be tolerated as long as an enone chromophore is present at C-1/C-2/C-3. Apparently, neither compound **10** (IC_{50} = 80 μM) nor **11** (inactive) contains the optimum structural features for activity against PTK. Collectively, the data of Table III suggest that one minimum structural requirement for strong PTK inhibitory activity of a halenaquinone derivative is the presence of a pentacyclic skeleton with electrophilic sites at each end (e.g., the A/E- and D-rings of **3**). In addition, a planar polyunsaturated framework with a quinone end ring is a necessary but not a sufficient condition for PTK activity.

Experimental Section

The NMR spectra were recorded at 250, 300, or 500 MHz for ^1H and 62.5 or 125 MHz for ^{13}C. Multiplicities of ^{13}C NMR resonances were determined from APT data, DEPT data, or COSY experiments (300 MHz). Low- and high-resolution electron impact mass spectrometry data were obtained on a magnetic sector instrument. High-performance liquid chromatography (HPLC) was done using columns that included 10 μm ODS or 10 μm silica gel. All solvents were distilled and dried for HPLC use and were spectral grade for spectroscopy.

Collection and Identification. The sponges, collected from Fiji (coll. nos. 89109 and 91007) or Vanuatu (coll. no. 90033) were identified as *Xestospongia* cf. *carbonaria* (Order Haplosclerida,[30] Family Petrosiidae) by M. C. Diaz and Dr. R. W. M. van Soest (Institute of Taxonomic Zoology, University of Amsterdam). The Fijian sponges (recollection) were obtained at a depth of 80–110 feet from the outer reefs of the Benga Lagoon in January of 1991,

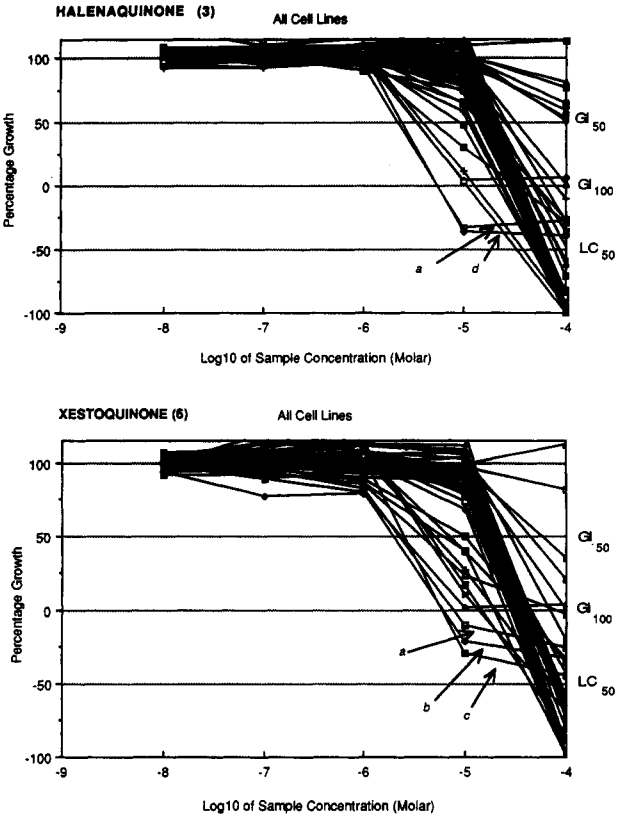


Figure 2. Composite dose–response curves for the testing of **3** and **6** against NCI-DTP library of leukemia and human tumor cells lines. The codes for the cell lines most sensitive to **3** and **6** are as follows: (a) CCRF–CED; (b) MOLT-4; (c) DLD-1; and (d) HL-60 (TB).

Table III. PTK Inhibition Activity Data[a]

compd	IC_{50} against $pp60^{v\text{-}src}$ (μM)
halenaquinone (**3**)	1.5[b]
halenaquinol (**4**)	0.6[b]
halenaquinol sulfate (**5**)	28[b]
xestoquinone (**6**)	60[b]
tetrahydrohalenaquinone A (**7a**)	≫200[b]
tetrahydrohalenaquinone B (**8a**)	≫200[b]
14-methoxyhalenaquinone (**9**)	5
xestoquinolide A (**10**)	80
xestoquinolide B (**11**)	≫200
viridin (**13**)	30
wortmannin (**14**)	≫200
16	9[b]
17	27[b]
18	10[b]
19	18[b]
20	≈200[b]
21	15[b]
22	14[b]
23	≫200[b]

[a] Compounds were solubilized in DMSO and preincubated with the enzyme for 15 min before the addition of [val[5]]-angiotensin II and ATP. The IC_{50} is defined as the concentration of compound which reduces the enzyme activity by 50% as compared to vehicle alone; final DMSO concentration was 3%. All compounds, except **13** and **14**, were assayed in the absence of 2-mercaptoethanol. [b] Values are from ref 5.

(30) At varying times taxonomists have placed the genus *Xestospongia* in three different orders, Haplosclerida, Nephelosclerida, or Petrosida. We have used the taxonomic placement suggested by Van Soest (1980). For a summary of this seemingly ever changing classification see: Fromont, J. *The Beagle, Records Northern Territory Museum Arts Sciences* **1991**, *8*, 73–96.

(31) Several synonyms have been used for *X. carbonaria*. For a comprehensive summary and references to prior literature see discussions under *Pellina carbonaria* (Lamarck, 1814) in: Zea, S. *Esponjas del Caribe Colombiano*; Editorial Catálogo Cientfífico: Santa Marta, Colombia, 1987.

while the Vanuatu samples were gathered in March of 1990 from Melne Bay. All three sponges are very similar to the Caribbean sponge *Xestospongia carbonaria* (Lamarck, 1814);[31] however, a definitive species can not be assigned until comparative histological and reproductive studies are undertaken. The morphology of both the Fijian and Vanuatuan sponges was massive amorphous to thick encrustations. Oscules which ranged in diameter from 1 to 5 mm were irregularly dispersed. Live specimens ranged in color from brown to dark green to black, and the color was the same throughout the sponge. The surface was microhispid. The sponge consistency was slightly compressible, easy to break, and crumbly. A brown (or green or black) sticky exudate was present in live specimens which when touched or broken underwater stained the hands with the color of the exudate noted above. The ectosomal skeleton was a nondetachable uni- to plurispicular reticulation of oxeas, oriented tangentially to the surface. The choanosomal skeleton consisted of plurispicular primary columns running toward surface, connected by confused unispicular tracts. A clear isotropic reticulation was not observed. The spicules were fusiform oxeas of one size class (180–230) × (6–8) μM.

Prof. F. J. Schmitz, University of Oklahoma (UO), kindly provided voucher specimens of his sponges (coll. nos. 6-T-91 and 57-T-84) which were previously identified as *Adocia* sp. and were a source of **3**, **6**, and **12** plus six other related compounds.[8] We reexamined the taxonomy of these vouchers and concluded that they are more properly classified as *Xestospongia* cf. *carbonaria*. These specimens were brown in color, and their overall morphology and spicule types were similar to that of the University of California at Santa Cruz (UCSC) samples. Both the UCSC and the UO specimens present a skeletal arrangement somewhere in between that typical of *Xestospongia* and *Adocia* (Family Halichlonidae). However, the best match is with the genus *Xestospongia* because *Adocia* has mainly unispicular isotropic reticules which are absent from the UCSC and UO specimens.

Extraction and Isolation. Sponges were preserved by being immersed in a 45:55 MeOH/H_2O solution. After approximately 24 h this solution was decanted and discarded. The damp organisms were placed in nalgene bottles and shipped back to the home lab at ambient temperature. Next, 100% MeOH was added, and the organisms were soaked for 24 h. This procedure was repeated two more times. The crude oil was then successively partitioned between equal volumes of aqueous MeOH, percent adjusted to produce a biphasic solution, and a solvent series of hexanes, CCl_4 and CH_2Cl_2. The remaining water solubles were extracted with BuOH. The workup of coll. no. 91007 was as follows. Its CH_2Cl_2 fraction was subjected to flash chromatography using a gradient elution of hexane/EtOAc increasing in EtOAc (1:0–0:1), and 10 fractions were collected. Flash chromatography fractions 2–5 were combined together and subjected to HPLC (SiO_2 column, EtOAc–hexane (1:1)) and afforded **3** (200 mg), **9** (7 mg), and **6** (185 mg) while compound **4** (198 mg) was isolated from flash chromatography fractions 8–10 using normal phase HPLC (EtOAc–hexane (1:1)). Compound **5** (20 mg) was isolated from the BuOH fraction. Compounds **7a** (15 mg) and **8a** (15 mg) were isolated from flash chromatography fractions 6 and 7 after they were further subjected to circular plate chromatography (chromatotron) using MeOH–CH_2Cl_2 (0.5:9.5). Flash chromatogrpahy fraction 1, which contained compound **10** (10 mg), was further purified by circular plate chromatography (chromatotron) using hexane–EtOAc (9:1). The other specimen collected from the Vanuatu Islands was treated as above. Its CH_2Cl_2 solvent partition fraction (0.1 g) was subjected to silica gel flash chromatography using a solvent gradient of CH_2Cl_2/MeOH, and eight fractions were collected. The first fraction afforded **9** (12.1 mg). The second fraction, purified by HPLC (reversed phase, MeOH/H_2O 30% aq), gave two different peaks, which included **11** (0.7 mg) and a mixture of quinones which could not be completely characterized.

Enzyme Assays. The assay for inhibition of $pp60^{v\text{-}src}$ PTK was performed as described in the experimental section of ref 5. All incubations were carried out with or without 2-mercaptoethanol as indicated in Table III.

3,13-Dideoxo-1,2,14,15-tetrahydro-3,13-dihydroxyhalenaquinone (7a): white solid (15 mg); mp 234 °C, $[\alpha]_D$ = +12°; UV (MeOH) λ_{max} 216, 258.2, 334.2 nm; ^{1}H NMR (250 MHz, CD_3OD) δ 4.55 (dd, *J* = 9.8, 7.2 Hz, H-1), 3.52 (ddd, *J* = 9.5, 7.5, 4.0 Hz, H-2), 3.98 (brs, H-3), 1.80 (m, H-4), 1.94 (m, H-4), 1.68 (dd, *J* = 13.5, 4.0 Hz, H-5), 1.94 (m, H-5), 8.39 (s, H-11), 4.92 (dd, *J* = 8.2, 3.9 Hz, H-13), 2.31 (m, H-14), 2.10 (m, H-14′), 2.82 (ddd, *J* = 16.4, 8.3, 5.0 Hz, H-15), 2.62 (ddd, *J* = 16.4, 8.3, 5.0 Hz, H-15′), 8.15 (s, H-18) and 1.49 (s, H-20); LREIMS, positive, *m/z* (rel int) 340 (M^+, 100), 325 (30), 307 (18), 283 (65), 265 (80), 165 (30) and 85 (69); HREIMS M^+ 340.1315 ($C_{20}H_{20}H_5$, Δ 0.9 mmu of calcd).

Preparation of Bis(methoxy mandelates) (7b) and (7c). The standard procedure for the preparation of all *O*-methyl mandelates is as follows. A catalytic amount of DMAP was added to a solution of the title alcohol (0.01 mM) with *O*-methylmandelic acid (0.01 mM) and DCC (0.01 mM) in CH_2Cl_2 (3 mL). After 24 hr the dicyclohexylurea was removed by filtration, and the solvent was removed in vacuo. The filter cake was washed with hexane (3 × 3 mL), and the combined filtrates were washed with cold 1 N HCl (2 × 1 mL), 10% aqueous $NaHCO_3$ (2 × 1 mL), and saturated aqueous NaCl (2 × 3 mL). The organic phase was filtered and the solvent concentrated *in vacuo*. The pure compounds were obtained by chromatography.

3,16-Dideoxo-1,2,14,15-tetrahydro-3,16-dihydroxyhalenaquinone (8a): white solid (15 mg); mp 234 °C, [α] = +24°; UV (MeOH) λ_{max} 216, 238, 245, 352 nm; ^{1}H NMR (250 MHz, CD_3OD) δ 4.55 (dd, *J* = 9.8, 7.2 Hz, H-1), 3.50 (ddd, *J* = 9.5, 7.4, 4.0 Hz, H-2), 3.99 (brs, H-3), 1.88 (m, H-4), 1.81 (m, H-5), 1.95 (m, H-5′), 8.69 (s, H-11), 2.62 (ddd, *J* =16.2, 8.3, 5.0 Hz, H-14), 2.80 (ddd, *J* = 16.4, 8.3, 5.0 Hz, H-14′), 2.14 (m, H-15), 2.34 (m, H-15′), 4.92 (dd, *J* = 10.0, 4.7 Hz, H-16), 7.88 (s, H-18) 1.52 (s, H-20); LREIMS, positive, *m/z* (rel int) 340 (H^+, 100), 325 (30), 307 (18), 283 (65), 265 (80), 165 (30), 85 (69); HREIMS M^+ 340.1315 ($C_{20}H_{20}H_5$ Δ 0.03 mmu of calcd).

14-Methoxyhalenaquinone (9): reddish yellow solid; UV (MeOH) λ_{max} 351, 246, 237, 216 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, H-1), 2.27 (ddd, H-4), 2.87 (m, H-4′), 2.80 (m, H-5), 3.12 (ddd, H-5′), 8.38 (s, H-11), 6.29 (s, H-15), 8.33 (s, H-18), 1.68 (s, H-20), 3.91 (s, OCH_3); LREIMS, positive, *m/z* (rel int) 362 (M^+, 40), 347 (100), 332 (11), 263 (30), 179 (10), 151 (10); HREIMS M^+ 362.0790 ($C_{21}H_{14}O_6$, Δ 0.4 mmu of calcd).

Xestoquinolide A (10): yellow powder (5 mg); $[\alpha]_D$ = +32; UV (MeOH) λ_{max} 216, 234 sh, 245, 325 nm; IR (KBr) 2929, 2854, 1679, 1640, 1624 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.28 (3H, brs, H-1), 5.90 (1H, brs, H-3), 2.49 (2H, m, H-4), 2.45 (1H, m, H-5), 1.70 (1H, m, H-5′), 7.09 (1H, s, H-8), 8.92 (1H, s, H-11), 7.06 (2H, s, H-14 and 15), 8.34 (1H, s, H-18) and 1.48 (3H, s, H-20); LREIMS, positive, *m/z* (rel int) 320 (M^+, 100), 305 (10), 292 (15), 278 (19), 238 (6), 175 (2); HREIMS M^+ 320.1049 ($C_{20}H_{16}O_4$, Δ 0.3 mmu of calcd).

Xestoquinolide B (11): yellow powder; UV (MeOH) λ_{max} 211, 242 , 272, 304 nm; IR 3400, 1698, 1647, 1604, 1462, 1352, 1289, 1238 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.28 (3H, brs, H-1), 5.90 (1H, brs, H-3), 2.49 (2H, m, H-4), 2.45 (1H, m, H-5), 1.70 (1H, m, H-5′), 8.99 (1H, s, H-11), 8.33 (1H, s, H-18), 1.47 (3H, s, H-20), 3.40 (2H, m, H-21), 4.18 (2H, m, H-22); no ^{13}C NMR data could be obtained because of the small amount (0.7 mg) of material that was isolated; HRFABMS *m/z* $(M + Na]^+$; 448.3496 ($C_{22}H_{19}O_6$ NSNa, Δ 0.2 mmu of calcd).

Preparation of (±)-16. Bromine (3.9 mL, 75.4 mM) was added dropwise to a cold (0 °C) solution of ketone (±)-**28** (15.1 g, 75.4 mM) in dry ether. The reaction mixture was warmed to rt and then refluxed for 30 min. The solvent was evaporated, the residue dried under vacuum, and the crude **29** was used without further purification.

Compound **29** was taken up in *s*-collidine (60 mL), heated to reflux for 1 h, and then cooled to rt. Ether (300 mL) was added, and the mixture was stirred for 10 min and filtered through Celite. The filtrate was washed with 1 N HCl (2 × 300 mL), 1 N NaOH (300 mL), and brine (300 mL). Each aqueous phase was extracted again with EtOAc (300 mL). The organics were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was chromatographed (hexanes/EtOAc (4:1)) to give (±)-**30** 12.57 g (63.4 mM, 84% over two steps), and the following physical properties were observed: IR (neat) 3067, 1661, 1622, 1591, 1580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 1H), 7.29 (m, 2H), 7.03 (d, *J* = 10.0 Hz, 1H), 6.33 (d, *J* = 10.0 Hz, 1H), 3.03 (m, 1H), 2.85 (m, 1H), 2.20 (m, 1H), 1.93 (m, 2H), 1.71 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.74, 26.35, 29.08, 31.90, 37.09, 124.50, 126.45, 126.73, 130.79, 132.68, 136.25, 146.20, 157.24, 185.65; LREIMS *m/z* (rel int) 198 (M^+).

The enone (±)-30 (300 mg, 1.51 mM), the sulfone 32 (330 mg, 1.45 mM), and BHT (20 mg) were placed in a sealed tube with decaline. An argon atmosphere was established, and the mixture was heated at 280 °C for 20 h and then cooled to rt. Chromatography (hexanes/EtOAc (5:1)) gave 330 mg of (±)-33 as an impure product which was used directly in the next step without further purification.

Compound 33 (~330 mg) was dissolved in dry benzene (20 mL), DDQ (500 mg, 2.2 mM) was added, and the mixture was refluxed for 4 h. The reaction was cooled to rt and filtered through basic alumina (EtOAc as eluent) and the solvent evaporated. The residue was chromatographed (hexanes/EtOAc (1:1 → 3:5) gradient elution) to give 34 (124 mg, 0.37 mM, 25% yield over two steps), and the following physical properties were observed: IR (neat) 3440, 2987, 1662, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.37 (s, 1H), 8.08 (m, 1H), 7.30 (m, 2H), 6.80/6.68 (AB system, J = 8.3 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.07–2.78 (m, 3H), 2.21 (m, 3H), 1.47 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.73, 28.69 (two signals), 32.85, 37.68, 38.77, 55.72, 103.15, 105.97, 116.36, 123.58, 125.03, 125.69, 126.30, 128.32, 129.67, 133.12, 133.78, 146.62, 147.31, 148.32, 151.13, 184.23; LREIMS 358 (M^+).

CAN (470 mg, 0.85 mM) in 3 mL of H_2O was added dropwise to 34 (120 mg, 0.33 mM) in 7 mL of acetonitrile at 0 °C. After 10 min, the solution was diluted with CH_2Cl_2 (40 mL). The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (hexanes/EtOAc (5:1)) giving 86 mg of (±)-16 (0.26 mM, 78%), and the following physical properties were observed: IR (KBr) 3677, 3440, 2952, 1669, 1602, 1468, 1338, 1290, 1228, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.29 (s, 1H) 8.00 (d, J = 7.1 Hz, 1H) 7.30 (m, 2H), 6.99 (s, 2H), 3.07–2.70 (m, 3H), 2.30–2.00 (m, 3H), 1.4 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.36, 28.02, 32.19, 37.58, 38.25, 122.68, 125.89, 126.46, 126.90, 130.21, 131.16, 133.94, 134.56, 135.77, 135.97, 138.74, 139.30, 144.98, 156.57, 183.80, 183.83, 184.65; HREIMS M^+ 328.1097 ($C_{22}H_{16}O_3$ Δ 0.2 mmu of calcd).

Preparation of (±)-17. PCC (45 mM) was finely powdered and homogenized with Celite (25 g). This mixture was added to a solution of (±)-30 (1.87 g, 9 mM) in dry benzene (120 mL). The reaction mixture was refluxed overnight. After being cooled to rt it was poured into Et_2O (800 mL), stirred for 15 min, and then filtered through Celite and $MgSO_4$. The solvent was removed, the crude product was chromatographed to give 31 (530 mg, 2.5 mM, 28%), and the following physical properties were observed: ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, J = 7.7, 1.3 Hz, 1H), 8.21 (dd, J = 7.7, 1.6 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 10.0 Hz, 1H), 6.45 (d, J = 10.0 Hz, 1H), 2.25 (m, 4H), 1.46 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 29.39 (q), 31.93 (t), 34.02 (t), 36.62 (s), 127.46 (d), 127.52 (d), 130.5 (s) 131.0 (s), 131.72 (d), 132.30 (d), 151.0 (s) 155.51 (d), 183.84 (s), 196.25 (s).

The diketone 31 (690 mg, 1.95 mM) and sulfone 32 (640 mg, 2.8 mM) were coreacted analogously to the procedure used above for 31, and workup of the reaction mixture yielded a cycloadduct (710 mg, 2.0 mM, 87%). This product was aromatized and oxidized analogous to the procedure above to yield 17 (245 mg, 0.72 mM, 41% yield for two steps), and the following physical properties were observed: IR (KBr) 3440, 1672, 1603, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.51 (dd, J = 7.7, 1.7 Hz, 1H), 8.41 (s, 1H), 8.37 (dd, J = 7.6, 1.7 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.08 (s, 2H), 2.5–3.2 (m, 4H), 1.62 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 31.86 (t), 34.09 (t), 34.58 (q), 37.68 (s), 123.42 (d), 127.15 (d), 128.08 (d), 130.49 (s), 130.70 (s), 131.24 (s), 133.46 (d), 133.53 (d), 134.52 (s), 134.65 (s), 138.87 (d), 139.50 (d), 150.35 (s), 154.23 (s), 182.20 (s), 183.61 (s), 184.38 (s), 195.64 (s); HREIMS M^+ 342.8893 ($C_{22}H_{14}O_4$ Δ 0.1 mmu of calcd).

Preparation of (±)-18. Li wire (1.0 g, 143 mM, cut in small pieces) was added to cold (−78 °C) NH_3 (200 mL) while stirring. The cooling bath was removed, and the blue solution was stirred for 30 min. The enone (±)-35[17] (5.3 g, 23.8 mM) and 2-methyl-2-propanol (4.5 mL, 47.6 mM) in dry THF (35 mL) were added over 30 min. The mixture was stirred an additional 30 min, and isoprene (3 mL) was added to quench the excess Li, followed by solid NH_4Cl (30 g), and then saturated $NaHCO_3$ (100 mL) was added, the ammonia was evaporated, and the residue was extracted with Et_2O (500 mL). The organic phase was washed with water (200 mL) and brine (200 mL). Each aqueous phase was extracted again with EtOAc (200 mL). The organics were combined and dried over Na_2SO_4. After filtration and evaporation of solvent, the residue was chromatographed (hexanes/EtOAc (2:1)), giving 4.45 g of ketone, and the following physical properties were observed: IR (neat) 2949, 2880, 1713, 1458, 1448, 1335, 1276, 1184, 1155, 1142, 1125 cm^{-1}; ^1H NMR (300 MHz) 3.98–3.84 (m, 4H) 2.4–1.5 (m, 11H), 1.3–1.2 (m, 2H) 1.1 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) d 13.01 (q), 22.72 (t), 28.07 (t), 30.12 (t), 30.38 (t), 37.75 (t), 41.32 (d), 41.35 (s), 44.13 (t), 64.97 (t), 65.17 (t), 112.32 (s), 211.32 (s); LREIMS 224 (M^+).

To a solution of the above ketone (4.40 g, 19.8 mM) in THF/MeOH (4:1) (100 mL) at 0 °C was added $NaBH_4$ (756 mg, 20 mM). After 1 h at 0 °C the cooling bath was removed and the mixture stirred at rt for 30 min. Water (50 mL) was added and stirring continued for 10 min. The reaction was then saturated with NaCl and extracted with EtOAc (2 × 200 mL). The organics were washed with brine (2 × 100 mL) and dried (Na_2SO_4). After filtration and removal of solvent the residue was chromatographed (hexanes/EtOAc (1:1–1:2) gradient elution) to give a quantitative yield of the expected ketal alcohol (4.40 g, 19.8 mM, 100%). Capillary GC indicated a 6.7:1 ratio of stereoisomers, and the following physical properties were observed: IR (neat) 3360, 2981, 2931, 2867, 1457, 1438, 1379, 1289, 1187, 1168; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97–3.81 (m, H) 1.83–1.14 (m, H) 0.97/0.94 (s, 3H); LREIMS 226 (M^+).

$TsOH·H_2O$ (250 mg, 1.32 mM) was added to a solution of the above ketal alcohol (19.6 mM) in H_2O/acetone (4:1) (250 mL). The reaction was stirred at rt overnight and then worked up with saturated with NaCl and extracted with EtOAc (2 × 300 mL). The organics were dried over Na_2SO_4. After filtration and removal of solvent a quantitative yield of 36, LREIMS 182 (M^+), was obtained (3.57 g, 19.6 mM), and it was used below without further purification.

Compound 36 (3.57 g, 19.6 mM) and tosylhydrazide (4.52 g, 24.3 mM) were refluxed in ethanol (300 mL) for 4 h, during which time the ethanol was gradually distilled. The reaction mixture was evaporated to dryness and the residue dissolved in hot EtOAc (1 L) and treated with activated charcoal (2 g). Filtration and evaporation of solvent left a white solid 37, LREIMS 350 (M^+), which was used directly in the next step.

CH_3Li/Et_2O (56 mL, 1.4 M; 78.4 mM) was added to a solution of 37 (~19.6 mM) in dry THF (170 mL) at 0 °C. After the addition was complete, the cooling bath was removed, and the orange mixture was stirred at rt for 1 h. The reaction mixture was then poured onto ice–water (400 mL) and extracted with EtOAc (2 × 400 mL). Each organic phase was washed with 10% aqueous Na_2CO_3 (200 mL) and brine (200 mL). The combined organics were dried over $MgSO_4$. After filtration and removal of solvent the residue was chromatoghraphed (hexanes/EtOAc (2:1)) to give 38 (2.93 g, 17.62 mM, 90% over three steps) as a mixture of diasteromers, and the following physical properties were observed: IR (neat) 3329, 3009, 2928, 2860, 1647, 1467, 1453, 1431, 1369, 1303, 1268, 1180, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (2H) 4.09/3.66 (1H, 1:5) 2.09–2.00 (m, 2H), 1.88–1.20 (m, 11H), 0.91/0.88 (3H, 1:5); ^{13}C NMR (75.4 MHz, $CDCl_3$) d 18.95, 24.90, 25.16, 25.88, 31.29, 34.04, 36.95, 37.72, 40.57, 71.56, 124.41, 138.41; LREIMS 166 (M^+).

DMSO (2.0 mL, 28.14 mM) in CH_2Cl_2 (4 mL) was added dropwise to a cold (−78 °C) solution of oxalyl chloride (1.25 mL, 14.07 mM) in CH_2Cl_2 (35 mL). After 5 min, a solution of 38 (1.95 g, 11.73 mM) in CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was stirred for 30 min, and then Et_3N (8.2 mL, 58.7 mM) was added. The cooling bath was removed and the reaction mixture stirred for 30 min. Water (100 mL) was added to dissolve the precipitate which had formed. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). Each organic phase was washed with 1 N HCl (100 mL) and 10% Na_2CO_3 (100 mL). The organic extracts were dried over $MgSO_4$. After filtration and removal of solvent, the residue was chromatographed (hexanes/EtOAc (5:2)) to give 39 (1.75 g, 10.65 mM, 91%), and the following physical properties were observed: mp 52–53.5 °C; IR (KBr) 3010, 2974, 2964, 2948, 2928, 2867, 2856, 2836, 1703, 1646, 1455, 1430, 1414, 1239, 1228, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (s, 2H), 2.49–2.06 (m, 6H), 1.82–1.41 (m, 5H), 1.08 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.11, 25.15, 25.34, 34.04, 37.81, 38.21, 41.87, 44.57, 125.18, 136.67, 211.35; LREIMS 164 (M^+).

3,5-Dimethylpyrazole (19.8 g, 206 mM) was added in one portion to a cold (−20 °C) suspension of CrO_3 (20.6 g, 206 mM; powdered and dried over P_2O_5) in dry CH_2Cl_2 (100 mL). After stirring for 20 min at −20 °C, a solution of **39** (1.69 g, 10.3 mM) in dry CH_2Cl_2 (100 mL) was added over a 20-min period. The reaction was stirred at −10 to −20 °C for 3 h, and then 5 N NaOH (85 mL) was added and the reaction stirred for 1 h at 0 °C. The phases were separated. The organic phase was washed with 1 N HCl (2 × 100 mL), H_2O (100 mL), and brine (100 mL). Each aqueous phase was extracted again with CH_2Cl_2 (2 × 100 mL). The organic phases were combined and treated with Celite (100 g) to absorb chromium salts and then filtered. The filtrate was dried over Na_2SO_4. After filtration and evaporation of solvent the residue was chromatographed (hexanes/EtOAc (3:2 → 1:1) gradient elution) to give a product which was recrystallized from hexane/Et_2O/THF to provide (±)-**40** as white crystals (1.00 g, 5.61 mM, 54%), and the following physical properties were observed: IR (KBr) 3200, 1706, 1681, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 9.96, 1H), 5.93 (d, J = 9.97, 1H), 2.4–2.6 (m, 2H), 1.2–2.35 (m, 5H), 1.23 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.53 (q) 35.17 (s), 36.41 (t), 37.36 (t), 40.12 (t), 41.00(t), 43.01 (d), 127.54 (d), 158.14 (d), 197.65 (s), 208.03 (s); LREIMS 178 (M^+).

The enedione (±)-**40**[32] (590 mg, 3.3 mM), the sulfone **32** (1.14 g, 5 mM), and BHT (30 mg) were heated in decalin (3 mL) in a sealed tube under an argon atmosphere at 260–280 °C for 5 h. The residue was chromatographed (hexanes/EtOAc (2:1)) to give impure (±)-**41** which was used directly in the next step. Compound **41** (810 mg, 2.4 mM) was dissolved in benzene (30 mL), and DDQ (1.3 g, 5.7 mM) was added. The mixture was heated at reflux for 4 h and then cooled to rt and filtered through basic alumina (eluent = EtOAc). The residue was chromatographed (hexanes/EtOAc (1:1 → 3:5) gradient elution) to give (±)-**42** (176 mg, 0.52 mM, 16% over two steps), and the following physical properties were observed: IR (neat) 2941, 1715, 1685, 1627,1590, 1465, 1270, 1239 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.46 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.90 (m, 1H), 2.83–2.40 (m, 5H), 2.10 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.42, 36.52, 37.05, 38.02, 41.21, 41.80, 43.71, 55.70, 103.42, 106.44, 117.45, 124.38, 124.38, 128.96, 147.08, 148.81, 150.99, 196.70, 209.25; LREIMS 338 (M^+).

A solution of CAN (650 mg, 1.18 mM) in H_2O (5 mL) was added over a 10-min period to (±)-**42** (165 mg, 0.49 mM) in CH_3CN (15 mL). After the solution was stirred an additional 10 min at 0 °C, more solvent, CH_2Cl_2 (100 mL), was added and the organic phase washed with H_2O (50 mL) and brine (50 mL). Each aqueous phase was extracted again with CH_2Cl_2 (2 × 30 mL). The organics were combined and dried (Na_2SO_4). After filtering and removal of solvent, the residue was chromatographed (hexanes /EtOAc (2:3)) to give a quantitative yield of **18**, and the following physical properties were observed: mp 204–206.5 °C; IR (KBr) 3439, 1693, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.18 (s, 1H), 7.05 (s, 2H), 2.86–2.40 (m, 8H), 2.08–1.97 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.74, 194.70, 184.42, 183.60, 156.43, 139.43, 138.79, 134.95, 134.75, 130.56, 127.10, 123.58, 43.33, 41.14, 40.67, 37.67, 37.23, 36.42, 19.78; HREIMS M^+ 308.1050 ($C_{19}H_{16}O_4$ Δ 0.2 mmu of calcd).

Preparation of 19. 4,4-Dimethyl-2-cyclohexen-1-one (621 mg, 5 mM) and the sulfone **32** (228 mg, 1 mM) were combined with decalin (1.2 mL) and 2,6-di-*tert*-butyl-4-methylphenol (~5 mg) in a sealed tube under argon. The mixture was heated at 250 °C for 3 h. After being cooled to rt, the residue was chromatographed (hexanes/EtOAc (6:1 → 3:1) gradient elution) to give 147 mg of desired product (±)-**43** (0.51 mM, 51%) and the following physical properties were observed: ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.21–2.97 (m, 2H), 2.64–2.33 (m, 4H), 1.82 - 1.61 (m, 4H), 1.11 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.45, 23.89, 25.43, 29.14, 32.74, 38.31, 41.49, 45.28, 47.09, 55.53, 55.56, 106.64, 106.79, 125.53, 125.77, 150.99, 151.47, 212.19; LREIMS 288 (M^+).

Compound **43** (147 mg, 0.51 mM) and DDQ (278 mg, 1.22 mM) were refluxed in benzene under N_2. After 1 h additional DDQ (100 mg) was added, and after 2 h the solvent was evaporated and the residue was filtered through basic alumina (EtOAc/hexanes (1:1)) to give the aromatized product (117 mg, 0.41 mM, 81%) which was next dissolved in CH_3CN (5 mL) and then cooled to 5 °C. A solution of CAN (550 mg, 1.0 mM) in CH_3CN/H_2O (1:1, 5 mL) was added dropwise over 10 min to the aromatized product above. After being stirred for an additional 10 min, the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 60 mL). The organics were dried over Na_2SO_4 and filtered and solvent removed. Chromatography of the residue (hexanes/EtOAc (3:1)) gave **19** (85 mg, 0.33 mM, 82%), and the following physical properties were observed: IR (KBr) 2966, 1691, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.7 (s, 1H), 8.15 (s, 1H), 7.01 (s, 2H), 2.8 (t, J = 7 Hz, 2H), 2.6 (t, J = 7 Hz, 2H) 1.47 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 29.52 (2 × q), 34.83 (t), 34.97 (t), 36.38 (s), 124.79 (d), 126.51 (d), 130.03 (s), 134.56 (s), 134.98 (s), 138.76 (d), 139.42 (d), 157.83 (s), 183.85 (s), 184.67 (s), 196.64(s); HREIMS M^+ 254.0942 ($C_{16}H_{14}O_3$ Δ 0.1 mmu of calcd).

Preparation of 20. The aromatized product (284 mg, 1 mM) from treatment of **43** plus DDQ was dissolved in CH_2Cl_2 (30 mL) containing Et_3N (2.80 mL, 20 mM), and it was cooled to 0 °C. The reagent TMS–OTf (2.22 g, 1.93 mL, 10 mM) was added dropwise to this solution. The reaction mixture was maintained at 0 °C for 30 min, and then cold pentane (50 mL) was added. Next, the solution was washed with cold satd $NaHCO_3$ (2 × 50 mL). Each aqueous phase was reextracted with cold pentane (20 mL). The combined organics were dried (K_2CO_3), filtered, and concentrated to give an oily residue used directly in the next step. The silyl enol ether was dissolved in dry CH_3CN (30 mL), $Pd(OAc)_4$ was added, and the mixture was stirred at rt overnight. The solution was concentrated to a brown residue which was chromatographed to give an aromatic enone (229 mg, 0.82 mM, 81% over four steps) as a yellow solid. This material (225 mg, 8 mM) was oxidized with CAN according to the procedure above to yield **20** in quantative yield, and the following physical properties were observed: ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.27 (s, 1H), 7.05 (s, 2H), 7.01 (d, J = 10.4 Hz, 1H), 6.46 (d, J = 10.3 Hz, 1H) 1.57 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 29.48 (2 × q), 38.36 (s), 125.28 (d), 126.27 (d), 126.43 (d), 130.28 (s), 133.76 (s), 134.52 (s), 138.82 (d), 139.55 (d), 154.87 (s), 157.79 (d), 183.20 (s), 183.76 (s), 184.60 (s); HREIMS M^+ 252.0784 ($C_{16}H_{12}O_3$ Δ 0.2 mmu of calcd).

Preparation of 21. A solution of **44**[17] (1.62 g, 5 mM) in dry THF (15 mL) was added dropwise to a mixture of $CrCl_2$ (25 mM) and methyl vinyl ketone (4.1 mL, 50 mM) in refluxing THF (20 mL). The mixture was stirred for an additional 20 min and then cooled to rt, diluted with EtOAc (100 mL), and washed with water (2 × 100 mL) and brine (100 mL). Each aqueous phase was extracted again with EtOAc (100 mL). The organics were combined, dried (Na_2SO_4), and chromatographed (hexanes/EtOAc (3:1)) to afford **45** (1.15 g, 4.9 mM, 98%), and the following physical properties were observed: mp 70–73.5 °C; IR (KBr) 2937, 2834, 1708, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.07–2.90 (m, 2H), 2.67–2.47 (m, 3H), 2.25 (s, 3H), 2.10 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.15, 24.4, 25.40, 28.12, 47.28, 55.60, 106.89, 106.92, 125.45, 126.26, 151.23, 151.34, 211.49.

Compound **45** (347 mg, 1.48 mM) and DDQ (807 mg, 3.55 mM) were taken up in 15 mL of benzene under a N_2 atmosphere. The solution was refluxed for 5 h and then cooled to rt and filtered through a column of basic alumina (EtOAc eluent). The solvent was then evaporated to give **46** (212 mg, 0.92 mM, 62%) and the following physical properties were observed: IR (KBr) 1670, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 1.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.72, 55.72, 55.83, 104.00, 106.18, 122.45, 123.80, 124.32, 125.42, 128.31, 134.28, 149.26, 150.34, 198.44.

A solution of CAN (1.21 g, 2.2 mM) in water (12 mL) was added dropwise over 15 min to a solution of **46** (210 mg, 0.91 mM) in CH_3CN (12 mL) at 0 °C. The mixture was stirred an additional 15 min and then diluted with $CHCl_3$ (100 mL) and H_2O (100 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The organics were combined, dried (Na_2SO_4), filtered, and evaporated. Chromatography (hexanes/EtOAc (3:1)) gave **21** (167 mg, 0.83 mM, 92%), and the following physical properties were observed: mp 109.5–111.5 °C; IR (KBr) 1687, 1670, 1636, 1602, 1369, 1360, 1331, 1312, 1281, 1246, 1144 cm^{-1}; ^1H NMR ($CDCl_3$,

(32) The *cis* isomer **40** is known (Wenkert, E.; Haviv, F.; Zeitlin, A. *J. Am. Chem. Soc.* **1969**, *91*, 2299–2307) whereas **40** itself is unknown and our synthesis of this intermediate is shown in Scheme I.

300 MHz) δ 8.59 (d, J = 1.8 Hz, 1H), 8.32 (dd, J = 1.8, 8.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.05 (s, 2H), 2.71 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.01, 126.50, 127.07, 132.15, 132.86, 134.36, 138.88, 139.03, 140.93, 184.24, 196.56. Anal. Calcd for $C_{12}H_8O_3$: C, 71.99; H, 4.03. Found: C, 72.23.

Preparation of 22. Compound **45** (1.2 g, 5.12 mM) and DDQ (2.8 g, 12.3 mM) were taken up in 40 mL of benzene under N_2 atmosphere, and the solution was refluxed for 5 h. After the solution was brought to rt it was filtered through basic alumina (eluent EtOAc). Evaporating the solvent gave an oil that was dissolved in EtOH (100 mL), H_2O (10 mL), and concd HCl (2 mL). The solution was stirred under H_2 at rt in the presence of 10% Pd/C (280 mg) overnight. The mixture was filtered and rinsed with ethanol. The concentrated residue was diluted with EtOAc (100 mL), washed with H_2O (30 mL) and brine (30 mL), and dried (anhydrous Na_2SO_4). The product was chromatographed (hexanes/EtOAc (10:1)) to give **47** (458 mg, 2.12 mM, 41% over two steps), and the following physical properties were observed: IR (neat) 2963, 2936, 2833, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.6 Hz, 1H), 8.00 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 6.66 (m, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.83 (m, 2H) 1.33 (t, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.68, 29.26, 55.71, 102.35, 103.26, 119.56, 121.82, 124.75, 126.51, 126.89, 141.98, 149.24, 149.64; LREIMS 216 (M^+).

Using the same procedure as above, compound **47** was treated with CAN, the crude product was chromatographed (hexane/EtOAc (3:1)) affording **22** (352 mg, 1.89 mM, 90%), and the following physical properties were observed: mp 53.5–55 °C; IR (KBr) 3050, 2968, 2937, 1664, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.58 (dd J = 1.7 Hz, 8 Hz, 1H), 6.94 (s, 2H), 2.79 (t, 2H), 1.42 (t, 3H). Anal. Calcd $C_{12}H_{10}O_2$: C, 77.40, H, 5.41. Found: C, 77.06; H, 5.51.

Preparation of 23. Dimethyltetralone (**48**)[25] (4.79 g, 27.5 mM) was hydrogenated (60 psi) for 5 hr at rt in MeOH (50 mL), H_2O (5 mL), and concd HCl (2 mL) with 10% Pd/C (800 mg). The reaction mixture was filtered through Celite, which was rinsed with MeOH (30 mL) and pentane (300 mL), followed by the addition of H_2O (5 mL) to the filtrate. The organic phase was separated and washed with brine (200 mL). Each aqueous phase was reextracted with pentane (200 mL). The combined organic phases were dried over Na_2SO_4. Filtration and removal of solvent yielded **49** (4.07 g, 25.4 mM, 92%), and the following physical properties were observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 1H), 7.1 (m, 3), 2.79 (t, J = 6.2 Hz, 2H), 1.84 (p, J = 6.2 Hz, 2H), 1.71 (m, 2H), 1.31 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 19.67 (t), 30.70 (t), 31.82 (2 × q), 33.78 (s), 39.27 (t), 125.18 (d), 125.74 (d), 126.57 (d), 128.99 (d), 136.07 (s), 145.76 (s).

A solution of **49** (5 mM) and acetyl chloride (471 mg, 6 mM) in dry CH_2Cl_2 (5 mL) was quickly added to a slurry of $AlCl_3$ (800 mg, 6 mM) in dry CH_2Cl_2 (5 mL) at −20 °C. The reaction was warmed to rt, stirred for 3 h, and then poured into a mixture of ice/1 N HCl (1:1, 100 mL). The mixture was extracted with dry CH_2Cl_2 (2 × 100 mL). The organic phase was washed with 1 N HCl (100 mL) and saturated $NaHCO_3$ (100 mL). The organics were dried over Na_2SO_4. Flash chromatography gave a mixture of acetyl regioisomers (944 mg, 4.67 mM, 93%), LREIMS 202 (M^+), which were converted to the corresponding ketal as follows. The preceeding reaction product (4.5 mM) with DEG (2.80 g, 45 mM) was refluxed in dry benzene (60 mL) under N_2 containing *p*-TsOH (50 mg) in a vessel fitted with a Dean-Stark trap. After 5 h, 2-ethyl-2-methyl-1,3-dioxolane (5 mL) was added, and the mixture was refluxed overnight. After being cooled to rt, the reaction mixture was diluted with Et_2O (100 mL), washed with saturatedd $NaHCO_3$ (100 mL), and brine (100 mL), and then dried over Na_2SO_4. Flash chromatography (hexanes/Et_2O (10:1)) gave the mixture of regioisomers **50** (895 mg, 3.63 mM, 81%), and the following physical properties were observed for the isomer mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (bd, J = 1.8 Hz, 2H), 7.41 (m, 2H), 7.31 (m, 2H), 7.18 (bd, J = 7.9 Hz, 2H), 4.17 (m, 4H), 3.95 (m, 4H), 2.90 (m, 4H), 1.95 (m, 4H), 1.82 (m, 4H), 1.80 (s, 6H), 1.43 (s, 6H), 1.42 (s 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 19.70 (t), 19.77 (t), 27.56 (q), 27.74 (q), 30.54 (t), 30.90 (t), 31.87 (4 × q), 33.73 (s), 33.98 (s), 39.33 (2 × t), 64.39 (2 × t), 64.49 (2 × t), 108.91 (s), 109.02 (s), 122.37 (d), 122.72 (d), 123.33 (d), 125.66 (d), 126.51 (d), 128.91 (d), 135.76 (s), 135.85 (s), 139.97 (s), 140.62 (s), 145.37 (s), 145.68 (s).

To a stirred suspension of CrO_3 (18 mg, 0.18 mM) in CH_2Cl_2 (3 mL) were successively added 70% *t*-BuOOH (aq) (3.5 mL, 25.4 mM), and the isomer mixture **50** (896 mg, 3.63 mM) was dissolved in CH_2Cl_2. The stoppered flask was stirred at rt for 8 h and then cooled to 0 °C and diluted with CH_2Cl_2 (50 mL). Next, 10% $Na_2S_2O_5$ was slowly added to the mixture which was then warmed to rt and stirred for 2 h. The organic phase was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). Each aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The organics were combined and dried over Na_2SO_4. After filtration and removal of solvent the residue was chromatographed (hexanes/Et_2O (5:1 → 2:1) gradient) to separate the pair of isomeric diketones **51a** (273 mg) and **52b** (155 mg) in a total yield of 55% (1.98 mM). These isomers were distinguished based on the following physical properties. **51a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.82 (dd, J = 8.1, 1.7 Hz, 1H), 2.77 (t, J = 6.8 Hz, 2H), 2.64 (s, 3H), 2.06 (t, J = 6.8 Hz, 2H), 1.43 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 26.96 (q), 29.70 (2 × q), 34.19 (s),35.12 (t), 35.84 (t), 125.80 (d), 126.09 (d), 127.83 (d), 134.11 (s), 140.74 (s), 154.54 (s), 197.84 (s), 197.90 (s). **51b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 2.0 Hz, 1H), 8.14 (dd, J = 8.3, 1.9 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 2.78 (t J = 6.8 Hz, 2H), 2.64 (s, 3H), 2.06 (t, J = 6.8 Hz, 2H), 1.43 (s, 6H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 26.95 (q), 29.51 (2 × q), 34.38 (s), 35.00 (t), 36.91 (t), 126.61 (d), 127.81 (d), 131.16 (s), 132.58 (d), 135.31 (s), 157.19 (s), 197.32 (s), 197.55 (s).

Isomer **51a** (273 mg, 1.26 mM) was aromatized with DDQ (375 mg, 1.65 mM) as above to afford **23** (30 mg) plus unreacted **51a** (182 mg) after chromatography (hexane/Et_2O gradient from 5:1 to 2:1 to 1:1) of the crude reaction product. The resultant solid was recrystallized from hexane/EtOAc, and the following physical properties were observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 8.1, 1.6 Hz, 1H), 6.99 (d, J = 10.0 Hz, 1H), 6.43 (d, J = 10.4 Hz, 1H), 2.67 (s, 3H), 1.53 (s, 6H); HREIMS M^+ 214.0996 ($C_{14}H_{14}O_2$ 0.2 mmu of calcd).

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Supplementary Material Available: Charts S1–S4 plus NMR spectra of **7a**, **8a**, **9–11**, and **16–23** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.