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Efficient Access to Orthoquinols and Their [4 + 2] Cyclodimers via SIBX-Mediated Hydroxylative Phenol Dearomatization

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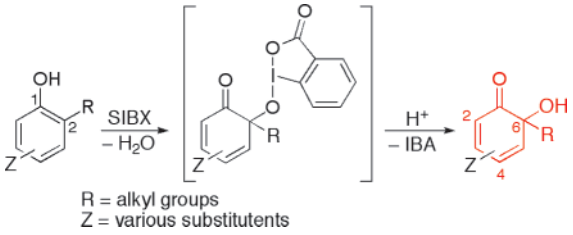

SIBX, the nonexplosive formulation of the λ^5-iodane 2-iodoxybenzioc acid (IBX), safely and efficiently mediates the hydroxylative dearomatization of various 2-alkylphenols and napthols into orthoquinols or their [4 + 2] cyclodimers. Reactions are typically run at room temperature using SIBX as a suspension in THF. Using these conditions, natural products such as the cyclodimer of the terpene carvacrol and, for the first time, the shikimate-derived (±)-grandifloracin were prepared in one step from their respective phenolic precursor.

6-Alkyl-6-hydroxycyclohexa-2,4-dienone derivatives are commonly referred to as orthoquinols, for they can be viewed as deriving from orthoquinones in which one of the two carbonyl groups is replaced by a tertiary alcohol function. Such an arrangement of a chiral carbon center adjacent to a conjugated dienone unit within a six-membered ring system makes orthoquinols attractive intermediates for the rapid construction of complex structural architectures.[1] Evidence of such a synthetic potential can be gleaned from the chemistry of several naturally occurring substances that either feature an orthoquinol moiety or biosynthetically derive from an orthoquinol intermediate (Figure 1).[1] Natural orthoquinols are not often identified as such, because of the propensity of their hydroxydienone system to undergo spontaneous [4 + 2] cyclodimerizations. Only when their substitution pattern sterically blocks their [4 + 2] cycloaddition can these species be isolated from their natural sources.[1a] The structures displayed in Figure 1 exemplify both natural nondimerizing orthoquinols [e.g., humulone (**1**),[2] wasabidienone B_1 (**2**),[3] and the epoxide scyphostatin (**3**)[4]] and orthoquinol-derived cyclodimers [e.g., aquaticol (**4**),[5] bisorbicillinol (**5**),[6] and grandifloracin (**6**)[7]].

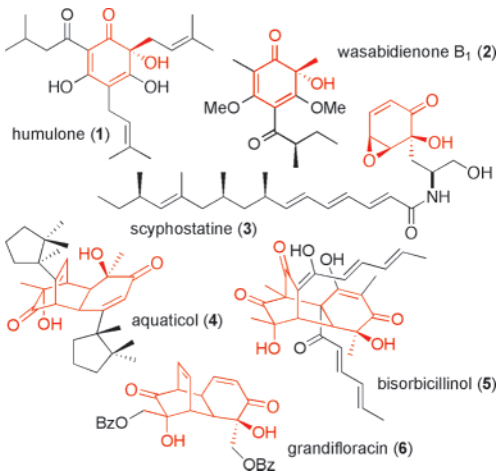

FIGURE 1. Examples of natural nondimerizing orthoquinols and orthoquinol-derived [4 + 2] cyclodimers.

Direct additions of carbon-based nucleophiles to orthoquinones are of limited synthetic value to access orthoquinols because of the difficulty in controlling the regioselectivity of this carbon−carbon bond formation, which is further complicated by the instability of most orthoquinones.[1a] A much better strategy is based on phenol dearomatization tactics that can instead promote the formation of the carbon−oxygen bond of the tertiary alcohol function. Over the last 50 years, several oxygenative dearomatizing systems have thus been examined to generate orthoquinols from 2-alkylphenols with some success.[1] More recently, the utilization of the λ^5-iodane 2-iodoxybenzoic acid (IBX) or its stabilized nonexplosive version (SIBX, i.e., 49% IBX, 22% benzoic acid, 29% isophthalic acid)[8] was explored by the Pettus group[9a] and us,[9b] and these were thus revealed as a promising general alternative to mediate hydroxylative phenol dearomatization (HPD) reactions in an ortho-selective manner. We wish to report herein our results on the

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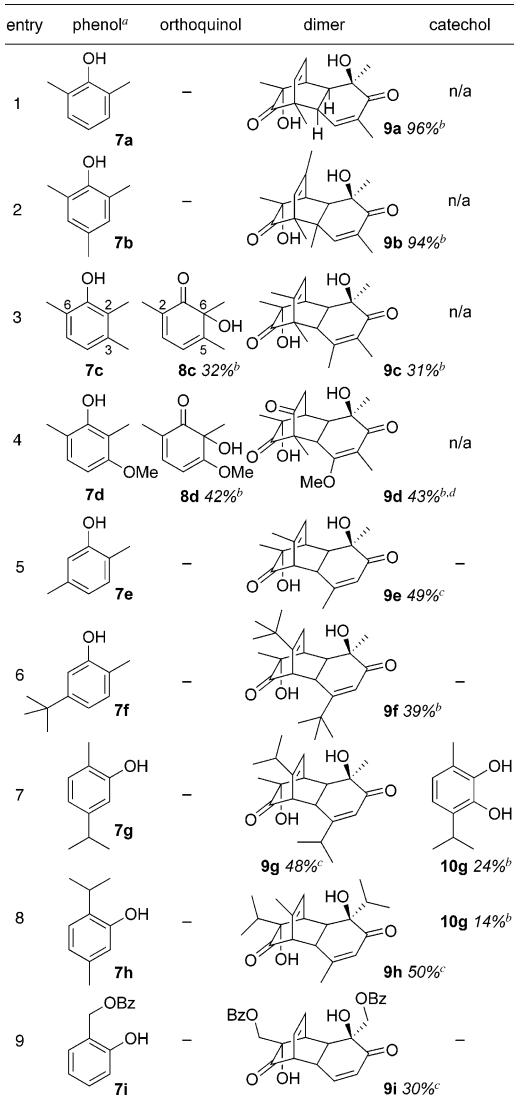
TABLE 1. SIBX-Mediated HPD of 2-Alkylphenols



[a] Reactions run in THF using SIBX (1.1 equiv) at rt for 24 h. [b] Isolated yield after chromatography. [c] Isolated yield after chromatography and crystallization. [d] The methyl enol ether of the bridge unit of the expected dimer suffered hydrolysis during processing to furnish the triketone **9d**.

use of SIBX to convert directly, cleanly, and safely 2-alkylated phenols and naphthols into orthoquinols or their corresponding [4 + 2] cyclodimers.

The first phenol that was submitted to the SIBX-mediated HPD reaction was 2,6-dimethylphenol (**7a**). The resulting orthoquinol dimerizes spontaneously to furnish the known [4 + 2] cyclodimer **9a**[10a,b,11] (Table 1). This dimer was previously obtained in 51% yield by using standard IBX in DMF, followed by a reductive ($Na_2S_2O_4$) workup.[9a] Gratifyingly, we found that treatment of **7a** with SIBX in THF furnished **9a** in 96% yield (Table 1, entry 1), after treating the reaction mixture with TFA (1.0 equiv). Similarly, the 2,4,6-trimethylated phenol **7b** was converted into dimer **9b**[10a,12] in 94% yield (Table 1, entry 2). These first two examples demonstrate the excellent level of ortho-oxygenation control brought about by the use of the stabilized IBX reagent. This regioselectivity is a consequence of the initial step of the reaction during which the hypervalent iodine(V) center of IBX probably exchanges one of its oxygen ligands with the reacting phenol through a condensation event (i.e., 1 equiv of H_2O is generated).[8a,9] The resulting phenyloxy-λ^5-iodanyl species can then rearrange in a sigmatropic-like manner by forming a single oxygen−carbon bond at either available methylated ortho-carbon center of the starting phenol, with concomitant reduction of the iodine(V) center into the iodine(III) center of a 2-iodosobenzoic acid (IBA) unit then still linked at the ortho-carbon center undergoing the $sp^2 \rightarrow sp^3$ hybridation change. In support of this sequence of events is our observation of 2,6-di-*tert*-butylphenol that remained refractory to these HPD reaction conditions, probably because the steric bulk of the two *tert*-butyl groups either masks the phenolic hydroxy group or prevents the intramolecular oxygenation of their carbon bearers.

The high yields of conversion of **7a** and **7b** into cyclodimers **9a** and **9b** were not totally unexpected, since the two ortho-positions of these symmetrically substituted phenols are equivalent. We then submitted the 2,6-dimethylphenols **7c** and **7d**, which also bear either a methyl or a methoxy group at their 3-position, to the same reaction conditions. Hydroxylation cleanly and solely occurred at both methylated ortho-positions to about the same extent. Interestingly, in each case, only the orthoquinol resulting from oxygenation at the methylated 6-position of the starting phenol dimerized to give either **9c**[13a] or **9d** (Table 1, entries 3 and 4). Indeed, the presence of a small alkyl or alkoxy group at the 5-position of an orthoquinol is known to block the Diels−Alder process.[13] Hence, when oxygenation takes place at the methylated 2-position of **7c** or **7d**, the resulting orthoquinols **8c**[13a] and **8d** are also isolated as such (Table 1, entries 3 and 4).

We then wondered about what could happen when using phenols featuring an alkyl group at only one of its two ortho-positions. Is the inductive electron release of an alkyl group enough to direct oxygenation exclusively at its carbon bearer? The answer is negative in contrast to what is observed with phenols singly ortho-substituted by a conjugating electron-releasing alkoxy group.[8a,14] Thus, treatment of 2,5-dimethylphenol (**7e**) with SIBX under the same reaction conditions furnished dimer **9e**,[10c] together with an unstable orthoquinone (not shown) resulting from oxygenation at the free ortho-position. A reductive step was then added to the workup procedure using $Na_2S_2O_4$ in the aim of isolating the corresponding catechol, but this was also found to be unstable during standard silica gel chromatography.[15] Dimer **9e** was then the sole product isolated from this reaction in 49% yield after crystallization (Table 1, entry 5). Similarly, 5-*tert*-butyl-2-methylphenol (**7f**) gave rise to the expected dimer **9f**[9b] in 39% yield (Table 1, entry 6). Again, the

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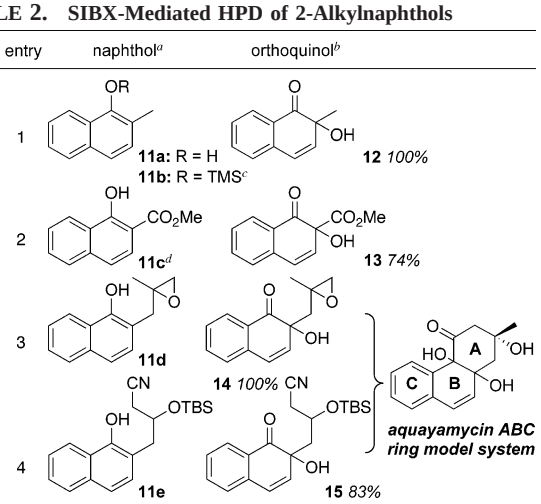
TABLE 2. SIBX-Mediated HPD of 2-Alkylnaphthols



[a] Reactions run in THF using SIBX (1.1 equiv) at rt for 14 h, unless otherwise noted. [b] Isolated yields. [c] Reaction run using SIBX (2.5 equiv) in DMSO at rt for 2 h. [d] Reaction run in EtOAc at 50 °C for 7 days.

catechol byproduct could not be isolated. Next, the terpenoid 2-alkylphenols carvacrol (**7g**) and thymol (**7h**) were efficiently converted into their corresponding dimers **9g**[16] and **9h**[17] (Table 1, entries 7 and 8) in yields much higher than those previously obtained using sodium periodate or iodic acid as the oxidizing agent (48−50% vs 12−30%).[16b,17] Of particular note is the fact that the carvacrol-derived dimer **9g** has been isolated from the heartwood of *Callitris macleayana*.[16a] In these two last runs, the catechol **10g** could be isolated in 24 and 14% yields, respectively. The last 2-alkylphenol that was submitted to our HPD reaction conditions was 2-hydroxybenzyl benzoate (**7i**), which gave rise to (±)-grandifloracin (**9i**) in 30% yield, after purification by silica gel chromatography and crystallization (Table 1, entry 9). This is the first reported synthesis of this natural product isolated from the plant *Uvaria grandiflora*.[7] Overall, considering that the maximum possible yield of orthoquinol-derived cyclodimers from nonsymmetrically substituted ortho-alkylated phenols is 50%, the yields we obtained ranging from 30 to 50%, after purification, are very satisfying (Table 1, entries 3−9). The remarkable level of regio- and stereoselectivities observed in these Diels−Alder reactions (i.e., only one dimer is in each case produced out of 16 possible dimeric racemates)[10c] has been rationalized in the context of the first total synthesis of (+)-aquaticol (**4**).[18]

Having thus established the value of our SIBX-mediated HPD reaction to generate orthoquinols from 2-alkylphenols, we turned our attention toward 2-alkylnaphthols. 2-Methylnaphthol (**11a**) was thus converted quantitatively into the orthoquinol **12** (Table 2, entry 1). It is worth noting that this HPD reaction can also be performed on the silylated 2-methylnaphthol **11b** using an excess of SIBX dissolved in DMSO instead of suspended in THF (Table 2, entry 1).[19] Also, the same reaction performed on 1-naphthol (not shown) led to the stable 1,2-naphthoquinone in 99% yield (Supporting Information). Naphthols, as well as phenols, bearing electron-withdrawing groups are usually refractory to iodane-mediated oxidative transformations.[8a,20] Nevertheless, the naphtholic ester **11c** could here be converted into orthoquinol **13** in 74% yield after 7 days in EtOAc at 50 °C (Table 2, entry 2). More complex naphthol-derived orthoquinols were then targeted in the context of our ongoing efforts toward the synthesis of natural angucyclines bearing oxygen atoms at the two AB ring fusion positions of their ABCD benz[*a*]-anthracenic ring system.[21] Orthoquinols **14** and **15** can serve as useful models to explore different tactics for the construction of angucycline AB ring systems, such as that of aquayamycin.[21,22] These two orthoquinols were obtained in high yields from naphthols **11d** and **11e** (Table 2, entries 3 and 4, and Supporting Information).

No treatment of reaction mixtures with TFA was necessary in these cases of nondimerizing naphthoid orthoquinols (Table 2). However, the advantage of treating reaction mixtures with an organic acid such as TFA in the case of dimerizing benzoid orthoquinols (Table 1) deserves additional comments. In fact, when these reactions are performed using IBX, the resulting cyclodimers still bear IBA units at their two oxygenated tetrahedral carbon centers. This was first evidenced by Pettus and co-workers, who isolated such a dimer from **7a**.[9a] It thus appears that the acidity of any unreacted IBX ($pK_a^{H_2O} = 2.4$)[23] is not strong enough to mediate in situ the hydrolytic cleavage of these IBA units. When SIBX is used, this cleavage sometimes occurs as observed for the naphthoid orthoquinols (Table 2). We suspect that this hydrolytic capability is due to some residual HCl left in the SIBX formulation after its preparation process.[8b] We then performed a series of reactions on **7a** using IBX with or without different acids, including the benzoic acids used in its stabilized formulation (Supporting Information, Table 3). We thus found that the HPD reaction proceeds at a faster rate with SIBX (12 h) than with IBX (48 h), but that the addition of a strong organic acid such as TFA ($pK_a^{H_2O} = 0.30$) to the IBX-containing reaction mixture significantly accelerates the reaction rate (1 h) to furnish directly the free dimer **9a**. Nevertheless, for safety reasons, we recommend the use of SIBX, followed by a treatment of the reaction mixture with TFA before working it up.

In conclusion, this work demonstrates the value of our SIBX-mediated HPD reaction to access safely and cleanly orthoquinols or their [4 + 2] cyclodimers, including natural products, in one step from their phenolic precursors.

Experimental Section

General Procedure A for SIBX-Mediated HPD of 2,6-Dimethylphenols. To a solution of starting 2,6-dimethylphenol (10 mmol) in THF (25 mL) was added SIBX (6.875 g, i.e., 11 mmol of IBX) as a solid in one portion. The resulting suspension was stirred at room temperature for 24 h, after which time TFA (780

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μL, 10 mmol) was added, and the mixture was further stirred for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL), then neutralized with aqueous 1 M solution of NaOH at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with aqueous 1 M NaOH (40 mL), H_2O (50 mL), and brine (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to furnish products of good to excellent purity. Further purification and/or product separation was carried out by column chromatography (Supporting Information).

General Procedure B for SIBX-Mediated HPD of 2-Alkylphenols. To a solution of 2-alkylphenol (10 mmol) in THF (25 mL) was added SIBX (6.875 g, i.e., 11 mmol of IBX) as a solid in one portion. The resulting suspension was stirred at room temperature for 24 h, after which time TFA (780 μL, 10 mmol) was added, and the mixture was further stirred for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL). An aqueous 1 M solution of NaOH was added slowly and continuously with vigorous shaking until all solid material dissolved. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with aqueous 1 M NaOH (40 mL), H_2O (50 mL), and brine (2 × 50 mL), then shaken vigorously with a saturated aqueous solution of $Na_2S_2O_4$ (100 mL), washed again with brine (50 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature to give a residue, which was then purified by column chromatography.

(±)-Grandifloracin (9i). To an ice-cooled solution of salicylic alcohol (124 mg, 1 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (144 μL, 1 mmol) and benzoyl chloride (117 μL, 1 mmol). The resulting mixture was stirred at room temperature for 24 h, after which time it was quenched with a saturated aqueous solution of NH_4Cl (20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated to give a crude brown oil (250 mg). Purification by column chromatography, eluting with hexanes/acetone from (10:1) to (3:1), gave 2-hydroxybenzyl benzoate (**7i**)[24] as a colorless oil (93 mg, 41%). This phenolic benzoate **7i** (456 mg, 2 mmol gathered from several runs) was then submitted to the SIBX-mediated HPD reaction according to the general procedure B apart from the fact that a saturated aqueous solution of Na_2CO_3 was used instead of an aqueous 1 M solution of NaOH during the workup. Purification by column chromatography, eluting with hexanes/acetone (3:1), afforded a solid residue that was then crystallized from a mixture of CH_2Cl_2 and hexanes to give pure (±)-grandifloracin (**9i**) as white fines crystals (146 mg, 30%). mp 188−188.5 °C (lit.[7] mp 161−163 °C); R_f = 0.20 [hexanes/acetone, (3:1)]; IR (NaCl, neat) 3450, 1720, 1711, 1683, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20−3.35 (m, 3H), 3.69 (d, J = 6.8 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 4.40−4.43 (m, 2H), 4.46 (d, J = 12.0 Hz, 1H), 6.00 (t, J = 6.7 Hz, 1H), 6.20 (d, J = 9.8 Hz, 1H), 6.43 (t, J = 7.2 Hz, 1H), 6.58 (dd, J = 3.6, 10.0 Hz, 1H), 7.92 (d, J = 7.3 Hz, 2H), 8.05 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.1, 198.1, 166.6, 165.8, 146.7, 135.1, 133.4, 133.3, 129.8, 129.7, 129.3, 129.2, 128.5, 128.5, 128.4, 128.0, 75.4, 74.4, 71.8, 68.1, 52.1, 41.0, 39.9, 37.3; ESIMS (MeOH) m/z (relative intensity) 511 [MNa^+, 100]; HRMS (ESIMS) calcd for $C_{28}H_{24}O_8Na^+$ 511.1369, found 511.1365.

Methyl 1,2-Dihydro-2-hydroxy-1-oxonaphthalene-2-carboxylate (13). To a solution of naphthol **11c** (50 mg, 0.25 mmol) in EtOAc (1.5 mL) was added SIBX (310 mg, 0.52 mmol) as a solid in one portion. The resulting suspension was stirred at 50 °C for 7 days, after which time it was diluted with EtOAc (20 mL), washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to give an oily residue (109 mg). This residue was then purified by column chromatography, eluting with cyclohexane/acetone (1:2), to furnish orthoquinol **13** (37 mg, 74%) as an orange oil. IR (NaCl) 3491, 1748, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 6.12 (d, J = 9.8 Hz, 1H), 6.73 (d, J = 9.8 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.39 (dt, J = 0.7, 7.5 Hz, 1H), 7.62 (dt, J = 1.1, 7.5 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 196.6, 169.7, 137.5, 135.5, 129.7, 129.0, 128.8, 128.1, 127.8, 127.5, 77.8, 53.7; EIMS m/z (relative intensity) 218 (M$^+$, 21), 159 (30), 131 (100); HRMS (EI) calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0591.

2-Hydroxy-2-[(2-methyloxiran-2-yl)methyl]naphthalen-1(2*H*)-one (14). To a solution of naphthol **11d** (60 mg, 0.28 mmol) in THF (2 mL) at 0 °C was added SIBX (176 mg, 0.31 mmol) as a solid in one portion. The resulting suspension was stirred at 0 °C for 14 h, after which time it was poured into ice-cold water (2 mL). This mixture was treated with aqueous 1 M NaOH, which was added dropwise until pH near 9 was reached, and separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with water (20 mL), dried over Na_2SO_4, and evaporated to afford orthoquinol **14** (65 mg, 100%) as a mixture (∼50:50) of two diastereoisomers: IR (NaCl, neat) 3428, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H), 1.39 (s, 3H), 1.75 (d, J = 14.2 Hz, 1H), 1.88 (d, J = 14.2 Hz, 1H), 2.00 (d, J = 14.1 Hz, 1H), 2.17 (d, J = 14.4 Hz, 1H), 2.50 (s, 2H), 2.54 (d, J = 4.6 Hz, 1H), 2.67 (d, J = 4.6 Hz, 1H), 3.62 (s, 1H), 3.62 (s, 1H), 6.31−6.38 (m, 2H), 6.48−6.51 (m, 2H), 7.19 (dd, J = 3.0, 7.1 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 2H), 7.91 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.80, 203.77, 137.5, 137.3, 136.0, 135.8, 135.1, 135.1, 128.4, 128.3, 127.5, 127.3, 127.2, 127.0, 124.8, 124.8, 74.4, 54.9, 54.6, 54.4, 54.2, 48.3, 47.9, 22.9, 22.6; EIMS m/z (relative intensity) 230.2 (M$^+$, 3), 213 (6), 131 (100); HMRS (EI) calcd for $C_{14}H_{14}O_3$ 230.0943, found 230.0951.

2-Hydroxy-2-[(2-*tert*-butyldimethylsilyloxy-3-cyano)propyl]-naphthalen-1(2*H*)-one (15). To a solution of naphthol **11e** (46 mg, 0.135 mmol) in THF (2 mL) at 0 °C was added SIBX (85 mg, 0.15 mmol) as a solid in one portion. The resulting suspension was stirred at 0 °C for 14 h, after which time it was poured into ice-cold water (2 mL). This mixture was treated with aqueous 1 M NaOH, which was added dropwise until pH near 9 was reached, and separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with water (20 mL), dried over Na_2SO_4, and evaporated to afford orthoquinol **15** as a mixture (∼60:40) of two diastereoisomers (40 mg, 83%): IR (NaCl, neat) 3461, 2252, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (bt, 1H), 7.59 (bt, 1H), 7.36 (bd, 1H), 7.20 (bd, 1H), 6.51 (d, J = 10 Hz, 1H, minor), 6.47 (d, J = 9.8 Hz, 1H, major), 6.31 (d, J = 9.8 Hz, 1H, minor), 6.27 (d, J = 9.8 Hz, 1H, major), 4.25 (m, 1H, minor), 4.11 (m, 1H, major), 2.79−2.52 (m, 2H), 2.18−1.76 (m, 1H), 0.86 (s, 9H, minor), 0.82 (s, 9H, major), 0.10 (s, 3H, minor), 0.06 (s, 3H, minor), 0.05 (s, 3H, major), −0.06 (s, 3H, major); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.7, 203.5, 137.34, 137.31, 136.3, 135.42, 135.39, 135.36, 128.55, 128.45, 128.2, 127.49, 127.45, 127.3, 125.1, 124.9, 117.7, 117.4, 65.5, 64.7, 47.4, 46.5, 27.7, 27.3, 25.6, 0.97, −4.66, −4.74, −4.85, −4.89; HMRS (ESI) calcd for $C_{20}H_{27}NO_3Si$ 357.1760, found 357.1773.

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Supporting Information Available: Additional experimental details, characterization data and ^{1}H and ^{13}C NMR spectra for all compounds, ORTEP diagrams of all new X-ray crystal structures (**9b**, **9c**, **9e**, **9h**, CCDC 640072-75), and their corresponding CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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