A Facile Entry into Naphthopyran Quinones via an Annelation Reaction of Levoglucosenone. The Total Synthesis of (−)-Hongconin[1]

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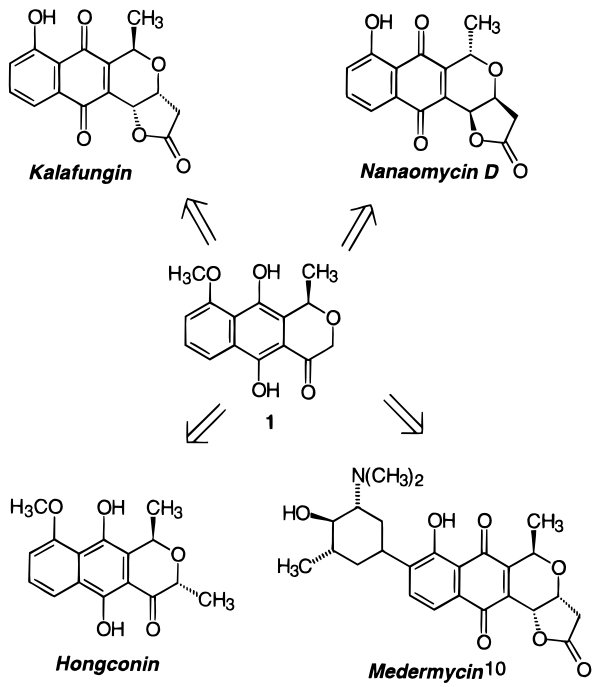
The annelation reactions of levoglucosenone, prepared by pyrolysis of paper, with 3-cyano-1(3*H*)-isobenzofuranone and 3-cyano-5-methoxy-1(3*H*)-isobenzofuranone have been studied. Reductive ring-opening of the annelation products with zinc/copper couple and subsequent chemical transformations provide a facile entry into the naphthopyran quinone ring system. Standard chemical transformations of the annelation product from 3-cyano-5-methoxy-1(3*H*)-isobenzofuranone and levoglucosenone afforded (1*R*)-5,9,10-trimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-4(3*H*)-one. The lithium enolate of this compound undergoes an interesting and potentially useful reaction with oxygen to afford (3*R*)-4,5,9-trimethoxy-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one. When oxygen is rigorously excluded, methylation of the enolate could be performed in good yield using 10 equiv of methyl iodide in the presence of 10 equiv of DMPU. This chemistry culminated in a total synthesis of (−)-hongconin in six steps from levoglucosenone.

Naphthopyran natural products are an interesting class of compounds which have as a common structural feature a pyran ring fused to a naphthoquinone nucleus[2] (see Scheme 1 for some examples). The biosynthetic origins of some of the higher molecular weight dimeric products[3] have been of interest to biochemists, and the biological activity of some of the compounds has inspired interest in their synthesis. Several years ago we envisioned a chiral approach to these compounds via **1** (see Scheme 1).[4] Ketone **1** was envisioned to be available via an annelation reaction of levoglucosenone, a compound available in chiral form by pyrolysis of paper.[5] The eventual product derived from **1** would have the proper stereochemistry for natural products having the configuration of kalafungin,[6] and epimerization of the benzylic center would give natural products having the absolute stereochemistry of nanaomycin D.[7] Although unknown at the time the work was initiated,[4] methylation of this annelation product would directly afford (−)-hongconin.[7,8,9b]

We report herein studies on the annelation chemistry of levoglucosenone, associated chemistry of the annelation products, and the application of this chemistry to the preparation of hongconin having the natural configuration. Hongconin had been prepared earlier in racemic form,[9a] and very recently a chiral synthesis of the unnatural configuration was reported.[9b,11]

Scheme 1. Synthetic Approach to Naphthopyran Quinone Natural Products



The key step in our strategy was the annelation of levoglucosenone with a cyanophthalide, an annelation reaction that had proved useful in our syntheses of anthracyclinones.[12] To examine the feasibility of this approach, the chemistry was studied first with the readily

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(1) Abstracted in part from the Ph.D. Thesis of John N. Freskos, The Ohio State University, 1985.

(2) For leading references, see: (a) Schmid, H.; Ebnother, A. *Helv. Chim. Acta* **1951**, *64*, 1041. (b) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454. (c) Zeeck, A.; Zahrer, H.; Mardin, M. *Justus Liebigs Ann. Chem.* **1974**, 1101. (d) Omura, S.; Tanaka, H.; Koyama, Y.; Oiwa, R.; Awaya, J.; Nagai, T.; Tata, H. *J. Antibiot.* **1974**, *27*, 263. (e) Tanaka, H.; Koyama, Y.; Awaya, J.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *J. Antibiot.* **1975**, *28*, 860. (f) Tanaka, H.; Koyama, Y.; Nagai, T.; Maruma, H.; Omura, S. *J. Antibiot.* **1975**, *28*, 868. (g) Omura, S.; Tanaka, H.; Okada, Y.; Maruyama, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320.

(3) Krone, B.; Zeeck, A.; Floss, H. G. *J. Org. Chem.* **1982**, *47*, 4721.

(4) Freskos, J. N.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1985**, 658.

(5) Shafizadeh, F.; Chin, P. *Carbohydr. Res.* **1977**, *58*, 79. See also: Halpern, Y.; Riffer, R.; Broido, A. *J. Org. Chem.* **1973**, *38*, 204.

(6) For a chiral synthesis of nanomycin D and kalafungin, see: Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *J. Antiobiot.* **1985**, *38*, 680; *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.

(7) Structure of hongconin: Zhengxiong, C.; Huizhu, H.; Chengrui, W.; Yuhui, L.; Jianmi, D.; Sankawa, U.; Noguchi, H.; Iitaka, Y. *Heterocycles* **1984**, *22*, 691; *Chem. Pharm. Bull.* **1986**, *14*, 2743.

(8) Biological activity of hongconin: Hainan-Renmin Hospital Guanxinbin-Keyan-Xiaozu, *Hainan-Weisheng* **1977**, 43. See also ref 9b.

(9) (a) Kraus, G. A.; Li, J. *Synlett* **1993**, 525. Li, J.; Kraus, G. A.; Gordon, M.; Jensen, J. H. *J. Org. Chem.* **1994**, *59*, 2219. (b) Deshpande, P. P.; Price, K. N.; Baker, D. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1059.

(10) Hopwood, D. A.; Malpartida, F.; Kieser, H. M.; Ikeda, H.; Duncan, J.; Fujii, I.; Rudd, B. A. M.; Floss, H. G.; Omura, A. *Nature* **1985**, *314*, 642.

(11) These workers[9b] have also prepared (−)-hongconin, and this is being published in the accompanying article: Deshpande, P. P.; Price, K. N.; Baker, D. C. *J. Org. Chem.* **1996**, *61*, 455−458. We thank these authors for agreeing to joint publication of these results.

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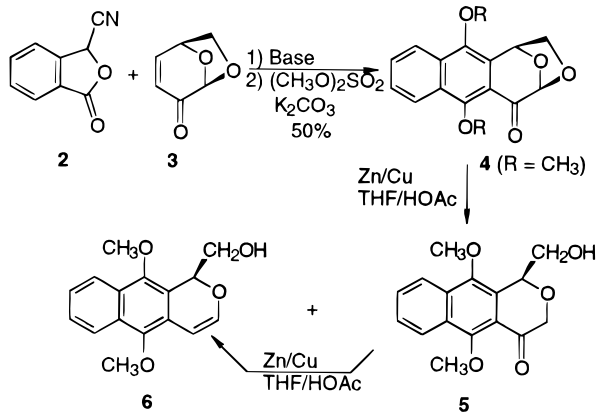
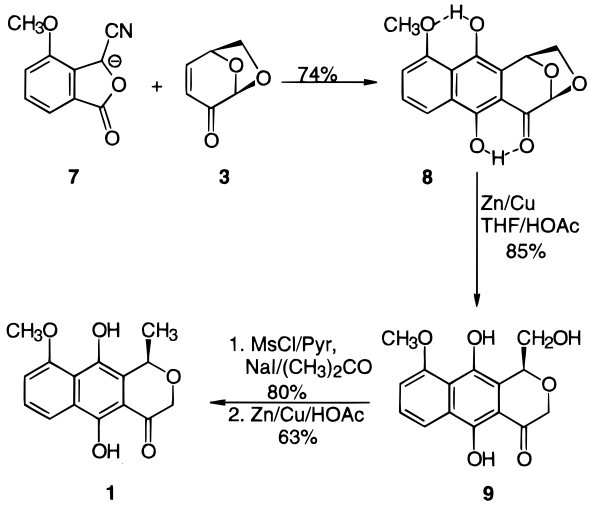
available cyanophthalide, **2**.[13] The annelation reaction of levoglucosenone gave a crude hydroquinone which was somewhat unstable, so this was directly methylated to give **4** (50% overall). Reaction of **4** with zinc/copper couple for a short reaction time gave a mixture of **5** and starting ketone. If the reaction was allowed to proceed until all of the starting material had reacted, a second product accompanied the desired **5**. The structure of the second product is assigned as **6** on the basis of analytical and spectroscopic data. Besides showing an exact mass in agreement with the formula of **6**, the IR spectrum showed a hydroxyl absorption at 3300 cm^{-1} (br, s) and the absence of a carbonyl absorption. The ^1H NMR (300 MHz) spectrum was especially informative, showing the following: the aromatic hydrogens at δ 8.0 (m, 2 H) and δ 7.5 (m, 2 H); two vinyl hydrogens as an AB quartet (δ 6.25, $\Delta\nu = 34$ Hz, $J = 6$ Hz, 2 H); the methine hydrogen as a doublet of doublets ($J = 8.5$, 3.5 Hz, 1 H); in addition to two methoxyl groups overlapping the methylene hydrogens.

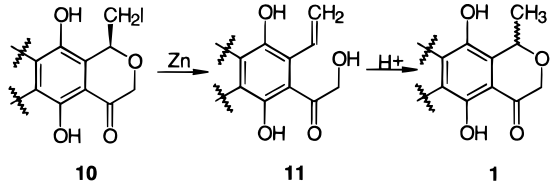


This deoxygenation (**5** → **6**) was unusual and unexpected, so additional experiments were performed to establish the actual intermediate in the reaction. The alcohol formed from reduction of **4** with lithium aluminum hydride is unreactive under the reaction conditions, so it is not an intermediate. However, the ketone **5** is converted to the vinyl ether **6** under the reaction conditions. Perhaps, a zinc enolate formed by reaction of the ketone with zinc undergoes loss of zinc oxide to afford the vinyl ether.

These preliminary studies showed the annelation reaction of levoglucosenone with the cyanophthalide to be viable. The lability of the hydroquinone from this annelation reaction and the side reaction in the **4** → **5** conversion led us to discontinue work on this model system. Instead, we proceeded to study the annealation of levoglucosenone with the methoxyl-substituted cyanophthalide, **7**, because this would lead to compounds having the oxygenation pattern in the natural products. Interestingly, the complications noted in the model studies above were absent in the **7** → **9** conversion. The annealation furnished a crystalline, stable naphthohydroquinone, and the reductive ring opening gave only **9** even at extended reaction times. The increased stability of the naphthohydroquinone may relate to hydrogen bonding between the hydroxyl groups of the hydroquinone and the methoxyl and carbonyl groups, respectively. Thus, whereas **8** shows resonance for the hydrogens of the hydroxyl groups at δ 12.65 and 9.12, the annelation product **4** (R = H) shows only one hydrogen-bonded hydroxyl group at δ 11.90. The vinyl ether formation in the zinc/copper couple reductive ring opening appears to occur only when the phenolic hydroxyl groups are converted to methoxyl groups.



For preparation of **1**, there remained the reductive removal of the primary alcohol functionality in **9** to afford the methyl group in **1**. Conversion of the primary alcohol to the mesylate followed by reaction with sodium iodide in acetone gave the iodide in good overall yield. Early attempts to reduce the iodide with tri-*n*-butyltin hydride under free radical conditions gave a complex mixture of products. We surmised that the phenolic hydroxyl groups could be complicating free radical processes, so the zinc reduction of the iodide was examined. We were concerned with a possible reductive elimination reaction of the β-alkoxy iodide under these conditions, **10** → **11**; however, no olefin was detected and the rotation of the product, $[\alpha]^{20}_D$ +26° ($CHCl_3$, $c = 0.1$), was not unusually low. An even more serious consideration was that reductive elimination was occurring to some degree, and the product was reclosing under the acidic conditions (**10** → **11** → **1**) to give partially racemized **1**. In an attempt to establish if racemization was occurring in the **9** → **1** conversion, a 500 MHz chiral shift study was done on **1** using $Eu(dcm)_3$[14] in concentrations from 0.2 to 1.75 equiv relative to **1**. Although these studies gave no evidence for any racemization, partial racemization in this step could not be rigorously excluded.



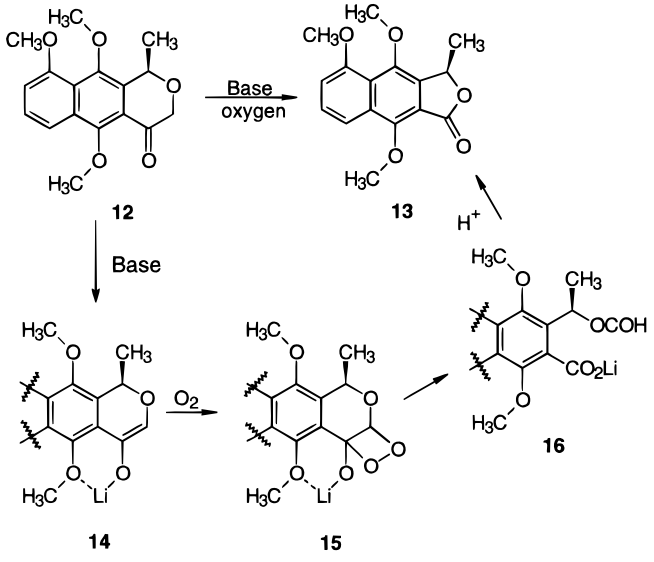
There remained only to introduce a carbon side chain α to the carbonyl moiety to afford compounds which could be elaborated to the naphthopyran natural products. This

(12) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625. Morrow, G. W.; Swenton, J. S.; Filppi, Joyce, A.; Wolgemuth, R. L. *J. Org. Chem*., **1987**, *52*, 713 and references cited therein.

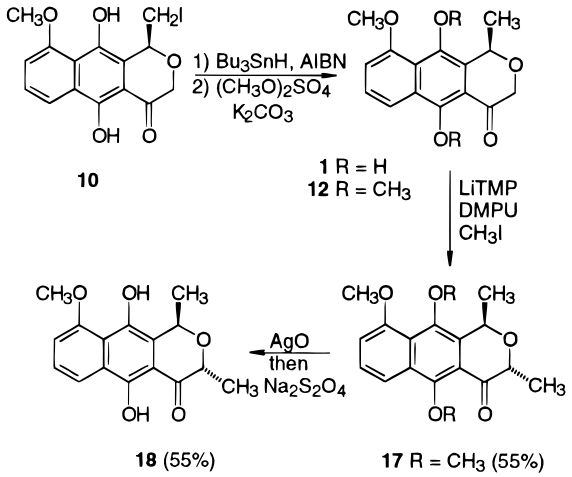
(13) For a general route to cyanophthalides (3-cyano-1(3*H*)-isobenzofuranones), see: Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem*. **1985**, *50*, 805.

(14) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

would not only provide a total synthesis of these natural products but also establish the optical purity of **1**. The hydroquinone **1** was first methylated with dimethyl sulfate to form its dimethyl ether **12**. The seemingly trivial alkylation α to the carbonyl of **12** with a variety of alkylating agents (methyl iodide, allyl bromide, ethyl bromoacetate) was in fact never adequately accomplished in our initial studies. Formation of the enolate with either lithium diisopropylamide or lithium dicyclohexylamide in tetrahydrofuran with and without added HMPA and addition of large excesses of either methyl iodide or allyl bromide gave trace amounts of alkylation products. However, at extended reaction times a highly fluorescent product was formed, which is assigned as **13**. The enolate of **12** is especially unreactive toward alkylation, perhaps because of internal coordination of the lithium enolate as illustrated in **14**. However, even using the potassium enolate, the alkylation reaction could not be performed. Although the enolate reacts very slowly in alkylation reactions, it must react rapidly with trace amounts of oxygen either in the reaction vessel or during exposure to oxygen in the workup. The structure of the highly fluorescent product is assigned as **13**, and a possible mechanism for its formation is shown below. The structural assignment is supported by a high-resolution mass spectrum which indicates the formula $C_{16}H_{16}O_5$. The IR spectrum showed a strong carbonyl absorption at 1765 cm^{-1}, and the ^{13}C NMR spectrum exhibited an absorption at δ 167.7; both absorptions are characteristic of a 5-membered lactone. The ^1H NMR spectrum was especially informative because it showed, in addition to the expected aromatic and methoxyl resonances, the methine hydrogen resonance at δ 5.69 (q, J = 6.5 Hz) and a methyl group resonance at δ 1.75 (d, J = 6.5 Hz).



Although difficulties associated with the alkylation chemistry caused temporary abandonment of the project, Kraus' [9a] recent synthesis of racemic hongconin revived interest in the research since a methylation of **12** followed by demethylation would afford hongconin. In this reinvestigation, 1,3-dimethyl-3,4,5,6-tetrahydro-2(H)-pyrimidinone, DMPU,[15] was used instead of HMPA in an attempt to promote the alkylation reaction of **12**. Indeed, formation of the lithium enolate of **12** with lithium tetramethylpiperidide followed by addition of methyl iodide (10 equiv) in the presence of DMPU (10 equiv) gave a ca. 4:1 mixture of **17** and its *cis*-isomer.[16] Careful chromatography on silica gel gave pure **17**, which was oxidatively demethylated[9a,17] with silver oxide, and then the product was reduced with dithionate to give hongconin. However, the highest obtainable rotation of the product was $[\alpha]^{20}_D$−10° ($CHCl_3$, c = 0.1). Although the synthesis led to the correct absolute configuration of hongconin,[9b] the reported value[7] for the natural product, $[\alpha]^{20}_D$−26° ($CHCl_3$, c = 0.1), indicated that partial racemization had occurred. The most probable step for racemization was the zinc reduction of the iodide, **10** → **1**, as noted earlier.



Although, the tri-*n*-butylstannane reduction of the iodide **10** was unsuccessful in an earlier attempt, this reaction was reexamined.[18] Apparently, the previous unsuccessful attempts were complicated by tri-*n*-butyltin contamination of the product from the reaction. Chromatography of the product mixture from the stannane reduction gave an 89% yield of **1** contaminated with a ca. 10% tin residue. Further treatment with potassium fluoride, chromatography, or crystallization did not lead to a pure product. However, methylation of this material with dimethyl sulfate afforded **12**, which was easily purified by chromatography. The rotation of **12** obtained via the stannane reduction was $[\alpha]^{20}_D$−149° ($CHCl_3$, c = 1.6), whereas **12** obtained via the zinc/copper route had $[\alpha]^{20}_D$−24° ($CHCl_3$, c = 1.3). Obviously, some racemization occurs in the latter reaction. When the product via the stannane reduction was then carried through the methylation/demethylation sequence,[9a,17] optically pure hongconin was obtained, $[\alpha]^{20}_D$−26.7° ($CHCl_3$, c = 2.0). In the latest studies, the alcohol-to-iodide conversion **9** → **10** was effected in one step using iodine and triphenylphosphine (88%).[19] Although the overall yield for the reaction is comparable with that of the mesylate/NaI two-step procedure employed earlier, the entire reaction and

(15) Seebach, R.; Henning, T.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705. Mukhopadhay, T.; Seeback, D. *Helv. Chim. Acta* **1982**, *65*, 385.

(16) The minor product is assigned as the *cis*-isomer, but was not obtained pure. However, the ^1H NMR spectrum of this material showed absorptions similar to the ^1H NMR of **12**. The ^1H NMR spectrum was also similar to the spectrum of the "*cis*-isomer of (+)-hongconin", (1*S*,3*R*)-9-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4,5,10(3*H*)-trione, supplied by Professor David Baker.

(17) Synder, C. D.; Rappoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

(18) We thank Professor V. Rawal for suggesting we reexamine this reaction.

(19) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 979; *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

isolation could be done in less than 4 h. However, for large-scale reactions, the mesylate/NaI procedure would be preferred since the chromatographic separations involve essentially a filtration through silica gel.

Summary. The chemistry described herein presents a convenient synthesis of chiral hongconin from readily available levoglucosenone. Furthermore, analogues of hongconin having a different substitution pattern in the aromatic ring would be available by performing the annelation reaction with the appropriate cyanophthalide. Now that reliable conditions for the alkylation have been developed, natural products such as kalafungin could be prepared from **12** using functionalized alkylating agents (e.g., ethyl bromoacetate for kalafungin). Finally, the lactone **13**, available from the oxygenation of **1**, may be a valuable starting material for preparation of related natural products.

Experimental Section

General Procedures. Melting points were determined in capillaries and are uncorrected. Only strong absorptions are reported for IR spectra unless otherwise noted. ^{1}H NMR spectra were measured at the indicated frequency in $CDCl_3$ unless noted otherwise. All reagents or compounds not explicitly referenced were obtained from commercial sources. Alumina and silica gel (Kieselgel 60 230−400 mesh) were obtained from E. Merck Co. TLC was done using Merck silica gel 60 F_{254} precoated aluminum-backed plates, 0.2-mm thickness. All organometallic reactions were done under Ar. Visualization was by UV or by spraying with 5% ethanolic phosphomolybdic acid and then heating. THF was purified by distillation from benzophenone ketyl. Extractive workup refers to extraction of the material into the indicated solvent, washing the organic layer with brine solution, drying over Drierite ($CaSO_4$), concentration in vacuo, and drying to constant weight under vacuum (1−2 Torr).

Preparation of Levoglucosenone (3). Levoglucosenone used in this work was prepared via a modification of the reported procedure.[5,20] Newspaper (3.5 lb) was finely shredded and soaked for 24 h in a solution of 1.5% H_3PO_4. The paper was then removed from the acid solution, spread out, and allowed to dry for 5 days. This paper was tightly stuffed in a cylindrical tube (1.2 m × 4.8 cm, heated zone 0.8 m × 4.8 cm), and the tube was placed in a Lindberg Hevi-Duty Furnace preheated to 300 °C. The top of the tube was fitted with a nitrogen inlet and the bottom of the tube fit into a two-necked 3-L flask. The flask, which was immersed in an ice bath, contained a ca. 1:1 mixture of chloroform/water (ca. 500 mL). Nitrogen was passed through the system at such a rate that 10−20 bubbles/min were observed in a gas washing bottle attached to the exit of the collecting flask. The pyrolysis was run for 20−30 min, after which time the drip rate into the collecting flask notably slowed. Nine such runs were made, and the contents of the collecting flask were transferred to a separatory funnel with $CHCl_3$. Distillation through a 3 in. Vigreux column afforded a forerun of furfural (15 g) and a major faction of levoglucosenone [20.43 g, bp 75−82 °C/0.6 Torr (lit.[5] bp 55−60 °C/1.5 Torr)]. The product was a clear yellow liquid with a "burnt wood" smell. VPC analysis (1.4% OV-101 on 120−140 mesh Chrom G at 150 °C) showed the product to be a 95:5 mixture of levoglucosenone and furfural. This material was used for the studies described below.

Annelation of Levoglucosenone with 3-Cyano-1(3*H*)-isobenzofuranone (4). A solution of THF (20 mL) and dry DMSO (7 mL) was cooled to 0 °C, and a 1.4 M methyllithium solution (3.0 mL, 4.2 mmol) was added dropwise to form dimsyllithium. To this solution was added the 3-cyano-1(3*H*)-isobenzofuranone[13] [0.66 g, 4.2 mmol, in DMSO (5 mL)]. After 1 min, levoglucosenone (0.51 g, 4.0 mmol) in THF (2 mL) was added. The reaction mixture turned dark red and was stirred for 3 h at 0 °C. After addition of cold 5% aqueous HCl (10 mL) to the reaction mixture, extractive workup with $CHCl_3$ (65 mL, then 2 × 25 mL) was followed by washing the $CHCl_3$ solution with 5% aqueous sodium dithionite (50 mL). Concentration in vacuo gave a dark oil that was filtered through silica gel (6 in. × 0.5 in. column, CH_2Cl_2 as eluant) to afford after concentration an orange oil which was dissolved in $(CH_3)_2CO$ (50 mL); K_2CO_3 (1.5 g) and dimethyl sulfate (1.0 mL) were added, and the solution was heated at reflux for 12 h. After concentration in vacuo, the residue was dissolved in CH_3OH (20 mL), and to the rapidly stirred solution was added 20% KOH (20 mL). A solid crystallized, and after the solution was cooled to 0 °C, the yellow crystals were filtered (0.68 g, 62% overall), mp 95−97 °C. Recrystallization gave material: mp 99−100 °C; $[\alpha]^{20}_D$ −200° ($CHCl_3$, c = 1.03); IR (KBr) 1710, 1355, 1110, 1085 cm^{-1}; ^{1}H NMR (80 MHz) δ 8.5−8.3 (m, 1 H), 8.2−8.0 (m, 1 H), 7.8−7.5 (m, 2 H), 6.03 (d, J = 6 Hz, 1 H), 5.50 (s, 1 H), 4.25−3.8 (m, 2 H), 4.0 (s, 3 H), 3.9 (s, 3 H); ^{13}C NMR (20 MHz) δ 187.2, 157.3, 146.4, 131.3, 129.7, 128.7, 127.1, 124.8, 122.2, 115.0, 101.8, 71.3, 69.3, 62.8, 62.6, one carbon not observed; HRMS , exact mass calcd for $C_{16}H_{14}O_5$ *m/e* 286.0851, obsd *m/e* 286.0846.

LiAlH$_4$ Reduction of 4. A solution of the ketone **4** (100 mg, 0.35 mmol) in THF (4 mL) was cooled to 0 °C, and $LiAlH_4$ (30 mg, 0.78 mmol) was cautiously added. After the reaction mixture had stirred for 45 min, H_2O (2 mL) was cautiously added. After filtration of the salts, extractive workup with Et_2O (2 × 20 mL) and crystallization of the residue from Et_2O/CH_3OH gave clear plates (60 mg, 60%): mp 126−127 °C; $[\alpha]^{20}_D$ −11° ($CHCl_3$, c = 0.45); IR (KBr) 3475, 1355, 1340, 1130, 1070, 1050, 1010, 960, 765 cm^{-1}; ^{1}H NMR (80 MHz) δ 8.0−7.9 (m, 2 H), 7.7−7.4 (m, 2 H), 5.9−5.7 (m, 2 H), 5.23 (dd, J = 3.5, 7 Hz, 1 H, collapses to d with D_2O wash), 4.2−4.0 (obscured m, 2 H), 4.02 (s, 3 H), 3.91 (s, 3 H), 3.28 (d, J = 7 Hz, 1 H) disappears with D_2O wash); HRMS, exact mass calcd for $C_{16}H_{16}O_5$ *m/e* 288.1020, obsd *m/e* 288.1009.

The residue (40 mg) from the crystallization solidified and was a mixture of alcohol isomers as shown by ^{1}H NMR spectroscopy.

Zn/Cu Reduction of 4. A solution of the ketone **4** (250 mg, 0.92 mmol), THF (25 mL), and Zn/Cu couple[21] (0.5 g) was heated at reflux for 30 min, then glacial HOAc (50 mL) was added, and the reaction mixture was heated an additional 10 min. After filtration and concentration of the filtrate to ca. $^2/_3$ the original volume, the solution was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was separated, washed with water (2 × 75 mL), and concentrated to give a mixture of vinyl ether and alcohol. The ratio of starting material:ketone:vinyl ether (**4**:**5**:**6**) varied depending upon the run. The crude reaction mixture was chromatographed on silica gel (9 in. × 0.5 in. column using 30% EtOAc/hexane as eluant). The vinyl ether eluted first, 65 mg: mp 98−100 °C; $[\alpha]^{20}_D$ −581° ($CHCl_3$, c = 0.16); IR (KBr) 1625 (m), 1350, 1075 cm^{-1}; ^{1}H NMR (80 MHz) δ 8.1−7.9 (m, 2 H), 7.6−7.4 (m, 2 H), 6.25 (AB q, J = 6 Hz, $\Delta\nu$ = 34 Hz, 2 H), 5.6 (dd, J = 3.5, 8.5 Hz, 1 H), 4.0−3.7 (m, 2 H) overlapping with the OCH_3 absorptions, 3.95 (s, 3 H), 3.85 (s, 3 H); ^{13}C NMR (20 MHz) 147.9, 145.7, 143.2, 129.2, 127.9, 126.5, 125.5, 122.4 (2 C), 118.5, 118.4, 99.2, 74.3, 63.2, 62.1 (2 C); HRMS, exact mass calcd for $C_{16}H_{16}O_4$ *m/e* 272.1099, obsd *m/e* 272.1074.

The second main fraction yielded the ketone **5** (70 mg) as an oil: $[\alpha]^{20}_D$ −144° ($CHCl_3$, c = 0.20); IR (neat) 3500−3400, 1690, 1350, 1075 cm^{-1}; ^{1}H NMR (200 MHz) δ 8.32 (dd, J = 9, 1 Hz), 8.00 (d, J = 8 Hz, 1 H), 7.68−7.50 (complex m, 2 H), 5.33 (dd, J = 7, 5 Hz, 1 H), 4.45 (AB q, J = 17 Hz, $\Delta\nu$ = 53 Hz, 2 H), 4.1−3.9 (partially obscured m, 2 H), 4.00 (s, 3 H), 3.92 (s, 3 H), 2.75 (br s, 1 H); HRMS, exact mass calcd for $C_{16}H_{16}O_5$ *m/e* 228.0986, obsd *m/e* 228.0992.

Annelation of Levoglucosenone with 3-Cyano-4-methoxy-1(3*H*)-isobenzofuranone (8). A solution of THF (35 mL) and dry DMSO (35 mL) was cooled to 0 °C, and a 1.5 M

(20) The material used in this work was prepared in an advanced organic laboratory class, and the Experimental Section was adapted from a report of Mr. Michael Capperelli. We thank the class for preparing over 100 g of material and Mr. Capperelli for the use of his report.

(21) Blankenship, R. M.; Burdett, K. A.; Swenton, J. S. *J. Org. Chem.* **1974**, *39*, 2300.

methyllithium solution (5.7 mL, 8.5 mmol) was added dropwise to form dimsyllithium. To this solution was added the 3-cyano-4-methoxy-1(3*H*)-isobenzofuranone[13] [1.52 g, 8.1 mmol, in DMSO (10 mL)]. After 1 min, levoglucosenone (1.0 g, 7.95 mmol) in THF (8 mL) was added, and the reaction mixture turned dark red and was stirred for 2 h at 0 °C and then for 12 h at room temperature. After addition of cold 5% aqueous HCl (40 mL) to the reaction mixture, extractive workup with CH_2Cl_2 (100 mL, then 2 × 60 mL) gave a dark yellow-orange semisolid. The residual DMSO was removed in vacuo, and the resulting solid was recrystallized from CH_2Cl_2/CH_3OH to give yellow needles, (1.3 g, 58%, mp 144−145 °C). The mother liquors were concentrated to a dark oily solid that was chromatographed on silica gel (8 in. × 0.5 in. column, 1:3 ethyl acetate/hexane as eluant). The yellow band was collected and concentrated in vacuo to yield an additional product (0.40 g, combined yield 1.7 g, 74%): mp 144−145 °C; $[\alpha]^{20}_D$ −282° ($CHCl_3$, $c = 1.0$); IR (KBr) 3380, 1660, 1635, 1610, 1590, 1460, 1385, 1250, 1235, 1110, 1050, 950, 815, 805, 795, 775, 570 cm^{-1}; ^1H NMR (200 MHz) δ 11.51 (s, 1 H), 9.06 (s, 1 H), 8.05 (dd, $J = 8$, 1 Hz, 1 H), 7.45 (t, $J = 8$ Hz, 1 H), 7.06 (dd, $J = 8$, 1 Hz, 1 H), 6.04 (d, $J = 4.6$ Hz, 1 H), 5.52 (s, 1 H), 4.10 (s, 3 H), 4.25−3.85 (m, 2 H); ^{13}C NMR (50.3 MHz) δ 194.2, 156.0, 154.5, 140.5, 126.5, 126.1, 119.0, 117.8, 116.8, 109.5, 106.6, 100.5, 70.9, 69.4, 56.4; HRMS, exact mass calcd for $C_{15}H_{12}O_6$ *m/e* 288.0634, obsd *m/e* 288.0651.

Preparation of 9 from 8. A mixture of the hydroquinone **8** (1.5 g, 5.2 mmol), Zn/Cu couple (3.06 g, 47 mmol), THF (100 mL), and HOAc (20 mL) was heated at reflux for 4 h. The cooled mixture was filtered through Celite and concentrated in vacuo. Extractive workup with CH_2Cl_2 (100 mL) gave a yellow solid. Trituration of this material with cold CH_3OH gave the primary alcohol **9** (1.196 g, 85%): mp 191−193 °C; $[\alpha]^{20}_D$ +20.7° (dioxane, $c = 0.42$); IR (KBr) 3390, 1640, 1630, 1605, 1450, 1385, 1245, 1230, 1150, 1045 cm^{-1}; ^1H NMR (80 MHz) δ 12.65 (s, 1 H), 9.12 (s, 1 H), 8.04 (dd, $J = 8.3$, 1.0 Hz, 1 H), 7.42 (t, $J = 8.3$ Hz, 1 H), 7.05 (dd, $J = 8.3$, 1.0 Hz, 1 H), 5.42 (t, $J = 5.8$ Hz, 1 H), 4.52 (AB q, $J = 17.7$ Hz, $\Delta\nu = 30.5$ Hz, 2 H), 4.04 (s, 3 H), 4.0−3.94 (obscured 2 H); ^{13}C NMR (50.3 MHz) δ 198.8, 155.7, 154.4, 140.5, 126.4, 126.0, 119.6, 118.2, 114.3, 109.6, 108.7, 72.6, 66.6, 61.4, 56.5; HRMS, exact mass calcd for $C_{15}H_{14}O_6$ *m/e* 270.0790, obsd *m/e* 270.0771.

Mesylate Formation from 9. A slurry of the primary alcohol **9** (1.2 g, 4.2 mmol) in CH_2Cl_2 (45 mL) was cooled to 0 °C, pyridine (6 mL) was added; and then methanesulfonyl chloride (3.5 mL, 42.0 mmol) was added dropwise. The reaction mixture slowly became heterogeneous and was stirred for 3 h, after which time TLC indicated no starting material. After the reaction mixture was poured into 5% aqueous HCl (150 mL), extractive workup with CH_2Cl_2 (2 × 40 mL) gave an oil which upon addition of CH_3OH (35 mL) crystallized to give a bright yellow fibrous solid which was used directly in the next step. An analytical sample was obtained by recrystallization from CH_2Cl_2/CH_3OH: mp 163−165 °C with decomposition; $[\alpha]^{20}_D$ +32.5° ($CHCl_3$, $c = 0.23$); IR (KBr) 3380, 1650, 1630, 1610, 1580, 1460, 1390, 1355, 1170 cm^{-1}; ^1H NMR (80 MHz) δ 12.57 (s, 1 H), 9.15 (s, 1 H), 8.01 (dd, $J = 8$, 2 Hz, 1 H), 7.43 (t, $J = 8$ Hz, 1 H), 7.05 (dd, $J = 8$, 1 Hz, 1 H), 5.52 (dd, $J = 8.0$, 3.5 Hz, 1 H), 4.8−4.5 (m, 4 H), 4.1 (s, 3 H), 3.0 (s, 3 H); HRMS, exact mass calcd for $C_{16}H_{16}SO_8$ *m/e* 368.0566, obsd *m/e* 368.0565.

Formation of Primary Iodide from Mesylate. A heterogenous mixture of the crude mesylate (1.35 g) from above, sodium iodide (12 g), sodium dithionate (1 g), and acetone (90 mL) was heated at reflux for 45 h, after which time TLC analysis indicated no remaining starting material. The reaction mixture was cooled and concentrated in vacuo to a solid residue that was dissolved in hot $CHCl_3$ (50 mL). Filtration of this material through silica gel (7 in. × 1.5 in. column, $CHCl_3$ as eluant) and collection of the yellow band gave after concentration yellow fibers (1.35 g, 80% over two steps): mp 158−159 °C; $[\alpha]^{20}_D$ +81.6 ° ($CHCl_3$, $c = 0.18$); IR (KBr) 3410, 1660 (br), 1610, 1585, 1385 cm^{-1}; ^1H NMR (200 MHz) δ 12.65 (s, 1 H), 9.13 (s, 1 H), 8.05 (dd, $J = 8$, 2 Hz, 1 H), 7.40 (t, $J = 8$ Hz, 1 H), 7.05 (dd, $J = 8$, 1 Hz, 1 H), 5.40 (dd, $J = 9$, 3 Hz, 1 H), 4.44 (AB q, $J = 17$ Hz, $\Delta\nu = 19.5$ Hz, 2 H), 4.04 (s, 3 H), 3.70 (dd, $J = 8$, 3 Hz, 1 H), 3.52 (t, $J = 8$ Hz, 1 H); HRMS, exact mass calcd for $C_{15}H_{13}IO_5$ *m/e* 399.9809, obsd *m/e* 399.9796.

Conversion of 9 to Primary Iodide with Ph_3P/I_2. To a solution of the primary alcohol **9** (1.45 g, 5.36 mmol), Ph_3P (2.80 g, 10.7 mmol), and imidazole (0.75 g, 11 mmol) in THF (100 mL) at 0 °C was added iodine (2.04 g, 8.04 mmol).[19] The brown reaction mixture was maintained at 0 °C for 1.5 h, and then the reaction was quenched by addition of H_2O (30 mL). Extractive workup with Et_2O (3 × 50 mL) gave a yellow solid. Chromatography of this material on silica gel (4 × 15 cm column, CH_2Cl_2 as eluant) gave the iodide as a yellow solid (1.89 g, 88%). This material showed spectroscopic properties identical with those obtained from the mesylate/sodium iodide route.

Formation of 1 from Iodide with Zn/Cu.[22] To a mixture of the iodide (625 mg) from above, Zn/Cu couple (625 mg), and THF (55 mL) was added glacial acetic acid (15 mL), and this mixture was then heated at reflux for 1.5 h. After this period TLC analysis indicated disappearance of the iodide. The reaction mixture was filtered through Celite, and the Celite was washed with copious amounts of $CHCl_3$. Extractive workup gave an orange-yellow semisolid. The residue was dissolved in $CHCl_3$ (20 mL) and chromatographed on silica gel (10 × 0.5 column, $CHCl_3$ eluant). Careful chromatography yielded **1** (270 mg, 63%) as a yellow solid. The compound was difficult to recrystallize but yellow crystalline material was obtained from acetone: mp 152−154 °C; $[\alpha]^{20}_D$ +26° ($CHCl_3$, $c = 0.1$); IR (KBr) 3400, 1645, 1635, 1609, 1455, 1390, 1235, 1160, 1085, 1060, 790, 755 cm^{-1}; ^1H NMR (200 MHz) δ 12.62 (s, 1 H), 9.02 (s, 1 H), 8.06 (dd, $J = 8$, 1 Hz, 1 H), 7.40 (t, $J = 8$ Hz, 1 H), 7.02 (dd, $J = 8$, 1 Hz, 1 H), 5.51 (q, $J = 7$ Hz, 1 H), 4.45 (AB q, $J = 18$ Hz, $\Delta\nu = 31$ Hz, 2 H), 4.02 (s, 3 H), 1.60 (d, $J = 5$ Hz, 3 H); ^{13}C NMR δ 208.3, 155.0, 153.0, 138.4, 124.8, 124.6, 119.0, 117.4, 116.9, 108.1, 106.9, 66.3, 64.3, 55.1, 15.9; HRMS, exact mass calcd for $C_{15}H_{14}O_5$ *m/e* 274.0841, obsd *m/e* 274.0842.

Formation of 12 from Iodide via Tri-*n*-butylstannane Reduction. To a solution of the primary iodide (1.67 g, 4.18 mmol) in benzene (50 mL) heated at reflux was added *n*-Bu_3SnH (1.35 mL, 5.02 mmol) followed by AIBN (30 mg). The resulting solution was heated at reflux for 12 h, after which time TLC (20% EtOAc/hexane as eluant) indicated the reaction to be complete. The reaction mixture was cooled to rt, concentrated in vacuo, and diluted with Et_2O (100 mL). The ethereal solution was stirred with 1 M aqueous KF (50 mL)[23] for 1 h, forming a white precipitate which was separated by filtration. The organic phase was washed with brine (1 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo to afford an oily yellow residue. Silica gel chromatography [4 × 10 cm column, hexane (150 mL) followed by CH_2Cl_2 as eluant] afforded the product as a crude yellow solid (0.930 g, 89%). In spite of repeated chromatography and attempted crystallization, small amounts (ca. 10% by ^1H NMR) of a tri-*n*-butyltin compound contaminated the material. Thus, this compound was used as obtained from the column for the next step. Spectral and analytical data are reported for the partially racemized product obtained from the zinc/copper reduction in the previous experimental.

A solution of the crude hydroquinone **1** (0.930 g, 3.08 mmol), dimethyl sulfate (1.75 mL, 18.5 mmol), and potassium carbonate (2.55 g, 18.5 mmol) in acetone (75 mL) was heated at reflux overnight. After 14 h, TLC (20% EtOAc/hexane as eluant) showed no hydroquinone, and the reaction solution was then filtered through Celite and concentrated in vacuo to afford a yellow oil. Residual dimethyl sulfate was removed in vacuo, and the oil was purified by silica gel chromatography [2 × 9 cm column, hexane (150 mL) 10% EtOAc/hexane (200 mL), 30% EtOAc/hexane as eluants] to afford the methylated hydroquinone **12** as a yellow oil (0.865 g, 93%): $[\alpha]^{20}_D$ −149° ($CHCl_3$, $c = 1.56$); IR 1695, 1360, 1330, 1065 cm^{-1}; ^1H NMR δ 7.96 (dd, $J = 8$, 1 Hz, 1 H), 7.44 (t, $J = 8$ Hz, 1 H), 7.02

(22) Note that this material is extensively racemized from the zinc/copper reduction step so the rotation value is low.

(23) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1977**, *44*, 449.

(dd, $J = 8.0$, 1 Hz, 1 H), 5.51 (q, $J = 7$ Hz, 1 H), 4.42 (AB q, $J = 18$ Hz, $\Delta\nu = 25.5$ Hz, 2 H), 4.02 (s, 3 H), 3.94 (s, 3 H), 3.82 (s, 3 H), 1.62 (d, $J = 7$ Hz, 3 H); HRMS, exact mass calcd for $C_{17}H_{18}O_5$ *m/e* 302.1154, obsd *m/e* 302.1154, obsd *m/e* 302.1126.

Methylation of 12 To Form 17. A flame-dried flask equipped with a stirring bar and vacuum adapter was charged with dry THF (15 mL), and the solvent was degassed using two freeze−thaw cycles. To the flask was then added degassed 2,2,5,5-tetramethylpiperidine (0.142 mL, 0.84 mmol), and the resulting solution was cooled to −78 °C prior to addition of 2.5 M *n*-BuLi (0.34 mL, 0.85 mmol). To the resulting 2,2,5,5-tetramethylpiperidine anion was added the ketone (250 mg, 0.83 mmol) as a solution in THF (5 mL) followed immediately by DMPU (0.484 mL, 4 mmol). The resulting reddish-orange solution was stirred for 15 min prior to addition of methyl iodide (0.516 mL, 8.3 mmol) and additional DMPU (0.484 mL, 4 mmol). The resulting solution was allowed to gradually warm to rt. After 4 h at room temperature, the reaction was quenched by addition of 5% HOAc (5 mL). Extractive workup with Et_2O (3 × 25 mL) afforded a dark yellow oil which was purified by silica gel chromatography [2 × 35 cm column, hexane (200 mL), 1% EtOAc/hexane (300 mL), 2% EtOAc/hexane (400 mL), 5% EtOAc/hexane (300 mL) as eluants] to give the *trans* product as an oil [140 mg, 55% (corrected for recovered ketone)] and recovered starting material contaminated with *cis*-alkylated naphthoquinone in a 1:2 ratio (50 mg). The product showed the following: $[\alpha]^{20}_D$ −135° ($CHCl_3$, $c = 0.26$); IR (KBr) 1765, 1610, 1400, 1385, 1370, 1270, 1120, 1060, 1000 cm^{-1}; ^1H NMR (200 MHz) δ 7.93 (dd, $J = 8$, 1 Hz, 1 H), 7.44 (t, $J = 8$ Hz, 1 H), 7.02 (dd, $J = 8$, 1 Hz, 1 H), 5.58 (q, $J = 6.5$ Hz, 1 H), 4.57 (q, $J = 6.7$ Hz, 1 H), 4.02 (s, 3 H), 3.98 (s, 3 H), 3.86 (s, 3 H), 1.67 (d, $J = 6.8$ Hz, 3 H), 1.51 (d, $J = 6.6$ Hz, 3 H); HRMS, exact mass calcd for $C_{18}H_{20}O_5$ *m/e* 316.1312, obsd *m/e* 316.1308.

Preparation of Hongconin. To a suspension of the alkylated ketone **17** (134 mg, 0.46 mmol) and AgO[24] (230 mg, 1.86 mmol) in THF (10 mL) at rt was added 6 N HNO_3 (0.47 mL). After 15 min TLC (20% EtOAc/hexane as eluant) indicated the reaction to be complete and the reaction was quenched by addition of water (3 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the organic phase was dried over Na_2SO_4 prior to concentration in vacuo. The crude product was then dissolved in THF/H_2O (2 mL:1 mL) and cooled to 0 °C before treatment with $Na_2S_2O_4$ (97 mg, 0.59 mmol) for 15 min. The mixture was then extracted with Et_2O (3 × 10 mL), and the organic phase was washed with brine (1 × 5 mL) and dried over Na_2SO_4. Solvent was removed in vacuo to afford the crude product which was carefully chromatographed on silica gel [2 × 20 cm column, hexane (200 mL), 1% EtOAc/hexane (200 mL), 2% EtOAc/hexane (200 mL), 10% EtOAc/hexane (200 mL) as eluants] to afford hongconin (69 mg, 57%). The material showed an ^1H NMR ($CDCl_3$)[25] identical with those previously reported: mp 128−129 °C (lit.[7] mp 135 °C): $[\alpha]^{20}_D$ −26.7° ($CHCl_3$, $c = 2.0$) (lit.[7] $[\alpha]^{20}_D$ −26° ($CHCl_3$, $c = 1.94$)); ^1H NMR (200 MHz, C_6D_6) δ 13.42 (s, 1 H), 8.90 (s, 1 H), 8.22 (dd, $J = 8.3$, 1 Hz, 1 H), 6.95 (t, $J = 8.3$ Hz, 1 H), 6.18 (dd, $J = 9.8$, 0.8 Hz, 1 H), 5.74 (q, $J = 6.7$ Hz, 1 H), 4.41 (q, $J = 6.5$ Hz, 1 H), 2.93 (s, 3 H), 1.59 (d, $J = 6.7$ Hz, 3 H), 1.51 (d, $J = 6.6$ Hz, 3 H).

The later fractions from the column were a mixture of hongconin contaminated with *cis*-isomer[16] (0.01 g).

13 from Oxygenation of 12. A solution of diisopropylcyclohexyl amine (70 μL, 0.49 mmol) in THF (4 mL) was cooled to 0 °C, and *n*-BuLi (250 μL of a 1.55 M solution in hexane, 0.4 mmol) was added. To this mixture was added a solution of the **12** (100 mg, 0.33 mol). The yellow solution was warmed to rt, and dry oxygen was bubbled through the mixture for 30 min. Workup gave a light yellow oil which was dissolved in CH_3OH (5 mL)/20% KOH (8 mL). The basic solution was extracted with $CHCl_3$ (2 × 8 mL), and then the aqueous layer was acidified with HCl [concd HCl (3 mL)/ice (5 g)]. Extractive workup with ethyl acetate (3 × 7 mL) gave an off-white solid, 62 mg (63%), which was recrystallized from Et_2O to give clear needles: mp 133.0−133.5 °C; $[\alpha]^{20}_D$ +45.7° ($CHCl_3$, $c = 0.50$); IR (KBr) 1765, 1610, 1400, 1385, 1370, 1270, 1120, 1060 (br), 1000 cm^{-1}; ^1H NMR (80 MHz) δ 7.99 (dd, $J = 8$, 1 Hz, 1 H), 7.45 (t, $J = 8$ Hz, 1 H), 7.03 (dd, $J = 8$, 1 Hz, 1 H), 5.68 (q, $J = 6.5$ Hz, 1 H), 4.26 (s, 3 H), 4.01 (s, 3 H), 3.62 (s, 3 H), 1.75 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (20 MHz) δ 166.7, 156.2, 153.1, 146.0, 136.5, 132.5, 126.7, 124.5, 117.0, 112.7, 109.2, 76.4, 63.6, 63.4, 56.3, 20.2; HRMS, exact mass calcd for $C_{16}H_{16}O_5$ *m/e* 288.1017, obsd *m/e* 288.1007.

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Supporting Information Available: ^1H NMR spectra for all compounds reported in the paper (13 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.

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(24) Hammer, R. N.; Kleinberg, J. *Inorg. Synth.* **1953**, *4*, 12.

(25) We noted that chloroform solutions of hongconin sometimes showed decomposition products after standing. Although we have verified the spectroscopic data in chloroform, the supporting information presents the ^1H NMR spectrum in benzene for the benefit of future investigators.

(26) In some runs small amounts (ca. 1−3%) of a compound having the chemical shifts of the "*cis*-isomer" [16] were detected in the ^1H NMR spectrum of late fractions from the column. This material was not present in starting **17** so in these runs a small amount of isomerization accompanies this step.