# Regiocontrol by Remote Substituents. A Direct Total Synthesis of Racemic Hongconin

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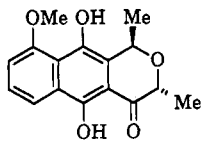
The total synthesis of hongconin (1) has been completed. Key steps include the metalation of a benzylic alcohol, the formation of a six-membered ring ether via a mercury-mediated cyclization, and the regioselective installation of the naphthalene ring by way of a Diels–Alder reaction.

Hongconin (1) is a novel naphthohydroquinone whose structure was determined in 1986. It was isolated from the rhizome of *Eleutherine americana* Merr. et Heyne (Iridaceae), a herbal plant from southern China which has been used as a medicine.[1] Hongconin has been shown to exhibit cardioprotective activity against angina pectoris in limited clinical trials.[2] The natural occurence of 1 is

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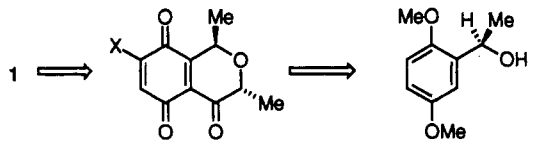
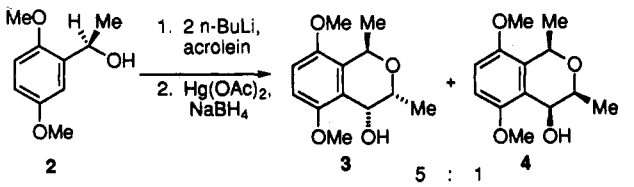
low; therefore, the availability of quantities for more definitive testing is likely dependent on the development of a direct synthetic route. We recently reported a total synthesis of hongconin.[3] This paper presents a full account of our synthetic efforts.

A retrosynthetic analysis is illustrated below. The synthesis starts from a readily available benzylic alcohol onto which a pyran ring is appended. The benzopyran is converted by oxidation into a quinone which undergoes a Diels–Alder reaction to afford hongconin. Generally, the regioselective cycloaddition reactions of quinones can be controlled by way of a substituent X such as a halogen or sulfoxide.[4] As part of a program to evaluate the




influence of functional groups not directly attached to the atoms undergoing cycloaddition,[5] we decided to determine whether the carbonyl group in the pyranone ring could control the regioselectivity of the Diels–Alder reaction.

The synthesis of benzopyranol 3 is illustrated below. Alcohol 2 was prepared in quantitative yield by the reaction of 2,5-dimethoxybenzaldehyde with methylmagnesium bromide at 0 °C. Alcohol 2 could be converted into its dianion with 2 equiv of *n*-butyllithium at ambient temperature for 24 h in 1:3 ether:pentane. After reaction with acrolein at −78 °C followed by acidification, an inseparable mixture of diols was isolated in 41% yield. A byproduct was also formed in 13% yield.[6]




2 3 5 : 1 4

Interestingly, the reaction of 2,5-dimethoxybenzyl alcohol with 2 equiv of *n*-BuLi in THF provided only the intermediate wherein metalation took place ortho to the hydroxymethyl group. Apparently, the lithium alkoxide of the secondary carbinol is a less-effective directing group for ortho metalation. This observation might be rationalized by the development of $A^{1,3}$ strain between the *o*-methoxyl group and the benzylic methyl group as the alkoxide adopts the requisite orientation to best direct ortho metalation. The inseparable mixture of diols was treated with mercuric acetate in aqueous THF according to the method of Maruyama.[7] The resulting mercurials were reduced with sodium borohydride to provide a 5:1 ratio of alcohols 3 and 4 in 59% isolated yield. The major product 3 was readily separated from 4. The structure of 3 was tentatively assigned based on NMR coupling constants (particularly the absence of an axial–axial coupling constant) and literature precedent.

Alcohol 3 was oxidized to 5 using PCC and Celite in quantitative yield. Ketone 5 was oxidized using the method of Rapoport ($AgO/HNO_3$)[8] to afford a 94% yield

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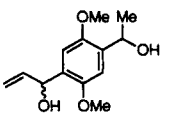
(5) Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283.

(6) The exact structure is not clear. We believe that it has the structure shown below:




(7) Naruta, Y.; Uno, H.; Maruyama, K. *J.Chem. Soc. Chem. Commun.* **1981**, 1277.

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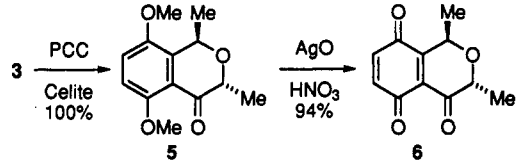
of benzoquinone 6. Unexpectedly, alcohol 4, the minor

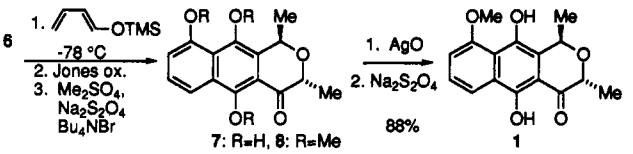



isomer formed by the oxymercuration reaction, could not be converted into ketone 6 by oxidation and epimerization. The oxidation of alcohol 4 with PCC and Celite produced the corresponding ketone, but this ketone resisted epimerization using triethylamine. We had assumed that the pyran ring existed in a chair conformation and that the benzylic methyl group was axial due to $A^{1,3}$ strain. However, RHF/6-31G(d) calculations by Gordon and Jensen suggest that the pyran ring may be in a boat conformation.

With benzoquinone 6 now readily available, we reacted 6 with 1-[(trimethylsilyl)oxy]butadiene in methylene chloride at −78 °C for 24 h followed by treatment of the unpurified adduct with Jones reagent in acetone at 0 °C and quenching excess Jones reagent with 2-propanol. A Diels–Alder reaction could have taken place at either double bond; however, given our previous research results, we expected the reaction to occur at the unsubstituted double bond.[9] We isolated only compound 7 in 51% yield. There were no isomeric byproducts or products arising from elimination of the trimethylsilyloxy group.

The rationale for this remarkably regioselective cycloaddition reaction is not clear. Although the carbonyl group was expected to exert some influence on the regioselectivity, the magnitude of the influence observed here was unexpected.

Selective methylation would have furnished hongconin in one step. Unfortunately we had to resort to a three-




step alternative because direct methylation produced a complex mixture of compounds. Methylation using conditions that we had developed for the reductive methylation of hydroxy quinones[10] cleanly generated a triether. Oxidation of the hydroquinone dimethyl ether with AgO followed immediately by reduction with $Na_2S_2O_4$ under neutral conditions provided hongconin 1 in 38% overall yield from 7. In this reduction, control of pH is very important. The reaction with $Na_2S_2O_4$ under basic conditions afforded only decomposition products.

Earlier studies[11] have successfully used molecular electrostatic potentials to explain the regioselectivity of Diels–Alder reactions, and a similar approach is taken here. All structures were optimized in $C_1$ symmetry at the AM1[12] level of theory and verified as minima by calculating the Hessian matrix numerically. All structures were then reoptimized at the RHF/6-31G(d)[13] level of theory, but no vibrational analyses were performed at this level of theory due to computational expense. In all cases the changes in structure on going from semiempirical to ab initio theory were small.

All molecular electrostatic potentials[14] (MEPs) were evaluated at the RHF/6-31G(d) level of theory. Here, a MEP is defined as the potential felt by a positive test charge due to the molecular charge density, evaluated over a grid of points in a given plane of the molecule. The contour map thus generated identifies relative positively and negatively charged regions of the molecule and can be used, for example, to indicate likely sites for electrophilic and nucleophilic attack.

All calculations were performed with the electronic structure program GAMESS.[15] Most ab initio calculations were performed with a parallel version of GAMESS on a 16-node Intel iPSC/860.

Figure 1 shows two MEPs of 6 evaluated in planes 2 Å below (Figure 1a) and 2 Å above (Figure 1c) and parallel with the dienophile (DP) plane. Figure 1b schematically depicts the orientation of 6 in the MEPs. Both MEPs show a positively charged center region (solid lines) with negatively charged regions (dotted lines) at either side. The plane below the ring shows an almost equal negative charge distribution on either side, due to the quinone oxygens. The plane above the ring shows considerable negative charge on one side, presumably due mostly to the carbonyl group on the pyran ring, but little negative buildup on the other side. Thus these MEPs indicate that an incoming diene with one electronegative substituent should prefer to react with 6 from above the DP plane with the substituent oriented away from the carbonyl group.

The observed regioselectivity thus appears to be dictated by the unequal charge distribution and the molecular geometry. The most important geometrical feature of 6 is the nonplanar quinone group. Figure 2a shows that the quinone ring is puckered such that the two quinone oxygens are bent below the DP plane, disfavoring attack from below (Figure 1a). The degree of puckering can be gauged by the dihedral angles between the oxygens and the alkene carbons, defined as $\tau$ and $\tau'$ in Figure 2: both would be 180° for a planar ring. For 6, $\tau$ and $\tau'$ are −169° and 168°, respectively—a roughly 10° deviation from planarity (negative and positive dihedral angles refer to clockwise and counter-clockwise rotation around the center bond, respectively; cf. Figure 2b). A similar parameter, $\omega$ in Figure 2b, can be defined for the carbonyl group. For 6, $\omega$ = 164° and this 16° deviation from planarity contributes to the negative contours in the plane 2 Å above the DP plane in Figure 1c.

The cause of the quinone ring puckering may be investigated by monitoring $\tau$, $\tau'$, and $\omega$ as substituents are added to the pyran ring. The intermediate structures investigated (9–12) are displayed in Figure 3. Removing all the substituents from 6 (resulting in 9) results in a flat quinone ring. Adding either the carbonyl (10) or the

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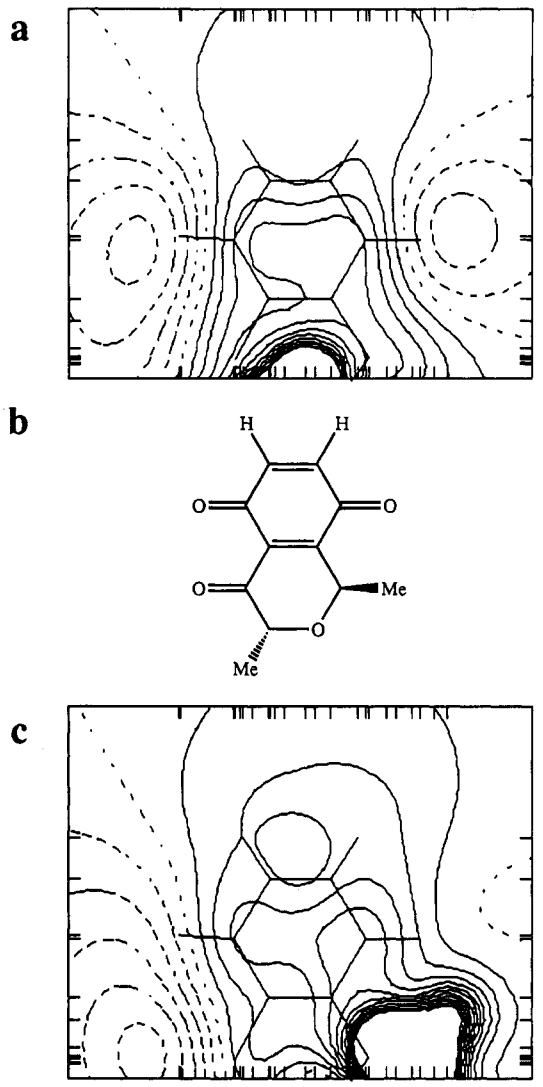


**Figure 1.** MEPs of 6 evaluated in planes 2 Å below (a) and above (c) the HC=CH plane. The contour spacing is 5 kcal/mol·e. (b) Schematic orientation of 6 in the MEPs.

methyl group (11) to 9 affects only the quinone oxygen that is closest to the respective substituent. In both cases the oxygen has moved 7° out of plane. Note that $\tau$ and $\omega$ have opposite signs for 10 and 6 because the quinone ring is puckered in opposite directions in the two structures. Adding both the methyl and carbonyl group to 9 (resulting in 12) causes a slightly larger distortion from planarity than adding just one of the two, and the dihedral angles in 12 are virtually identical to those in 6. Therefore, it appears that the two pyran ring substituents neighboring the quinone ring induce the quinone ring-puckering that contributes to the regioselectivity.

A total synthesis of racemic hongconin has been completed in eight steps from alcohol 2. Our synthetic route features a benzylic alcohol metalation and a remarkably regioselective Diels–Alder reaction. This synthetic route is flexible and direct. Additional biological evaluation of this interesting but rare natural product will soon be forthcoming.

## Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes–ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR and/or elemental analysis.

**3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-1*H*-2-benzopyran-4-ols 3 and 4.** To a solution of alcohol 2 (9.6 g, 53.0 mmol) in ether–pentane (1:3, 400 mL) at 0 °C was added *n*-butyllithium in hexane (48.6 mL, 110 mmol) dropwise with vigorous stirring. The solution was allowed to warm to rt and was stirred for 24 h. The solution was then cooled to −78 °C and acrolein (7.82 mL, 62.6 mmol) was added. After the reaction had stirred for 2 h at −78 °C, it was quenched with saturated ammonium chloride solution and extracted three times with ethyl acetate. The organic layers were dried with sodium sulfate and concentrated in vacuo. The residue was purified by sgc using 4:1 H:EA to afford 5.1 g (41% yield) of an inseparable mixture of diols, 4.1 g of starting material, and an unidentified compound (see ref 6).

To a solution of the inseparable mixture of diols (2.87 g, 12.0 mmol) in THF–$H_2O$ (2:1, 150 mL) was added mercuric acetate (4.0 g, 12.6 mmol) and the solution was stirred for 5 h at rt. The reduction of the resulting mercurial intermediate was achieved by adding 0.23 g of $NaBH_4$ dissolved in 24 mL of 2 M NaOH. The mixture was allowed to stir for 10 h. The solution was then neutralized with 3 N HCl and extracted with ether. The organic layer was washed with brine and dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was purified by sgc (H:EA = 4:1) to afford 1.4 g (49% yield) of 3 and 0.28 g (10% yield) of 4. Both compounds were viscous light yellow oils.

3: $^1$H NMR ($CDCl_3$) $\delta$ 1.39 (d, $J$ = 6.3 Hz, 3 H), 1.48 (d, $J$ = 6.6 Hz, 3 H), 2.09 (d, $J$ = 7.2 Hz, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 4.03–4.10 (m, 1 H), 4.52 (dd, $J$ = 7.5, 1.8 Hz, 1 H), 5.08 (q, $J$ = 6.6 Hz, 1 H), 6.73 (s, 2 H); IR ($CDCl_3$) 3578, 3423, 1259, 980 cm$^{-1}$; MS $m/z$ 77, 91, 121, 133, 161, 179, 194, 205, 220, 238; HRMS $m/z$ for $C_{13}H_{18}O_4$ calcd 238.12051, measured 238.12042; CMR ($CDCl_3$) $\delta$ 16.8, 17.9, 55.4, 55.7, 62.4, 66.0, 68.4, 108.4, 109.5, 125.4, 128.8, 149.0, 151.2; TLC (H:EA = 2:1) $R_f$ = 0.40.

4: $^1$H NMR ($CDCl_3$) $\delta$ 1.39 (d, $J$ = 6.6 Hz, 3 H), 1.58 (d, $J$ = 6.3 Hz, 3 H), 2.02 (d, $J$ = 9.0 Hz, 1 H), 3.63–3.69 (m, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 4.57 (d, $J$ = 9.0 Hz, 1 H), 4.92 (q, $J$ = 6.3 Hz, 1 H), 6.72–6.78 (m, 2 H); IR ($CDCl_3$) 3578, 3423, 1380, 939 cm$^{-1}$; MS $m/z$ 77, 91, 103, 121, 133, 161, 179, 194, 205, 223, 238; HRMS $m/z$ for $C_{13}H_{18}O_4$ calcd 238.12051, measured 238.12042; CMR ($CDCl_3$) $\delta$ 16.8, 17.9, 55.4, 55.7, 62.4, 66.0, 68.4, 108.4, 109.5, 125.4, 128.8, 149.0, 151.2; TLC (H:EA = 2:1) $R_f$ = 0.44.

**3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-1*H*-2-benzopyran-4-one (5).** To a suspension of PCC (0.72 g, 3.74 mmol) and Celite (1.0 g) in $CH_2Cl_2$ (10 mL) at 0 °C was added 3 (0.20 g, 0.84 mmol) in 10 mL of $CH_2Cl_2$. The mixture was warmed to rt and stirred overnight. The solvent was removed *in vacuo* and the residue was purified by sgc (H:EA = 2:1) to afford 198 mg (100% yield) of 5, an oil.

5: $^1$H NMR ($CDCl_3$) $\delta$ 1.47 (d, $J$ = 6.6 Hz, 3 H), 1.55 (d, $J$ = 6.6 Hz, 3 H), 3.82 (s, 3 H), 3.88 (s, 3 H), 4.54 (q, $J$ = 6.6 Hz, 1 H), 5.31 (q, $J$ = 6.6 Hz, 1 H), 6.94 (dd, $J$ = 9.3, 55.5 Hz, 2 H); IR ($CDCl_3$) 1683, 1435, 1266, 990 cm$^{-1}$; MS $m/z$ 77, 91, 121, 134, 149, 163, 177, 192, 221, 236; HRMS $m/z$ for $C_{13}H_{16}O_4$ calcd 236.10486, measured 236.10467; CMR ($CDCl_3$) $\delta$ 17.4, 17.7, 55.8, 56.1, 66.7, 71.3, 110.6, 116.6, 117.7, 136.9, 147.4, 153.6, 195.8; TLC (H:EA = 2:1) $R_f$ = 0.42.

**3,4,5,8-Tetrahydro-1,3-dimethyl-1*H*-2-benzopyran-4,5,8-trione (6).** To a suspension of 5 (138 mg, 0.585 mmol) and AgO (363 mg, 2.92 mmol) in 15 mL of THF at rt was added 0.59 mL of 6 N $HNO_3$. After 1 h, the reaction was quenched by the addition of 3 mL of water. The mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by sgc (H:EA = 2:1) to afford 114 mg (94% yield) of 6.

6: $^1$H NMR ($CDCl_3$) $\delta$ 1.42 (d, $J$ = 6.6 Hz, 3 H), 1.60 (d, $J$ = 6.9 Hz, 3 H), 4.45 (q, $J$ = 6.6 Hz, 1 H), 5.03 (q, $J$ = 6.9 Hz, 1 H), 6.79 (dd, $J$ = 10.2, 27.3 Hz, 2 H); IR ($CDCl_3$) 1714, 1666, 1286 cm$^{-1}$; MS $m/z$ 78, 106, 134, 162, 206; HRMS $m/z$ for $C_{11}H_{10}O_4$ calcd 206.05791, measured 206.05832; CMR ($CDCl_3$) $\delta$ 16.3, 17.3, 66.1, 71.2, 124.3, 135.5, 136.8, 152.8, 183.4, 187.4, 194.4; TLC (H:EA = 3:1) $R_f$ = 0.40.

**3,4-Dihydro-5,9,10-trihydroxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (7).** To a solution of 6 (720 mg, 3.5 mmol) in $CH_2Cl_2$ (25 mL) at −25 °C was added dropwise 1-[(trimeth-

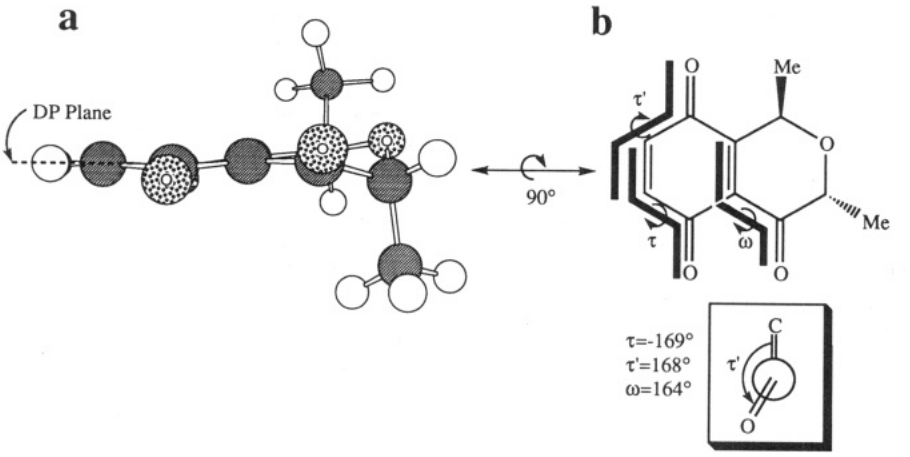


**Figure 2.** (a) Side view of the RHF/6-31G(d) optimized structure of **6** showing the puckering of the quinone ring. (b) Definitions of the three dihedral angles used to quantify the deviation from planarity for the quinone and carbonyl oxygens.

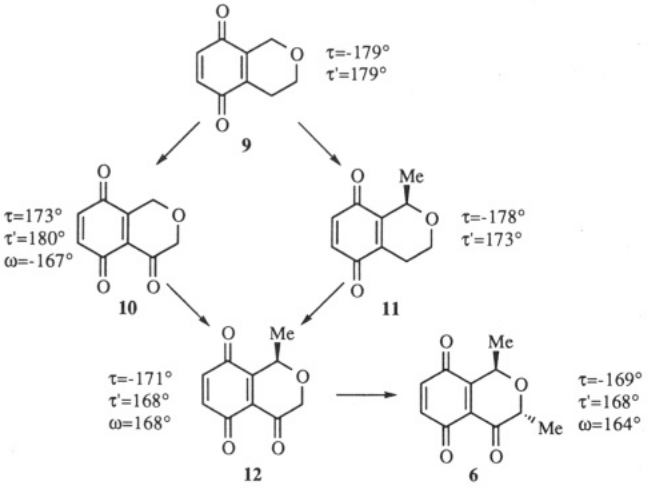


**Figure 3.** RHF/6-31G(d) values for $\tau$, $\tau'$, and $\omega$ as a function of pyran ring substituents.

ylsilyl)oxy]butadiene (2.45 mL, 14.0 mmol). The mixture was stirred at −25 °C for 5 h and then allowed to slowly warm to rt overnight. After the solvent was removed *in vacuo*, the residue was dissolved in 10 mL of acetone and 2.7 M Jones reagent (3.1 mL, 8.39 mL) was added at 0 °C. The reaction was then quenched with 2-propanol (5 mL) and stirred for 5 h at rt. The mixture was filtered and solvent was removed *in vacuo*. The residue was partitioned between saturated ammonium chloride solution (10 mL) and ether (3 × 50 mL). The organic extracts were washed with brine and dried over sodium sulfate. The solvent was concentrated *in vacuo* and the residue was purified by sgc (H:EA = 5:1) to afford 490 mg (51% yield) of **7**.

**7**: $^1$H NMR ($CD_3OD$) $\delta$ 1.29 (d, $J$ = 6.6 Hz, 3 H), 1.43 (d, $J$ = 6.6 Hz, 3 H), 4.50 (q, $J$ = 6.6 Hz, 1 H), 5.20 (q, $J$ = 6.6 Hz, 3 H), 6.76 (d, $J$ = 7.2 Hz, 1 H), 7.07 (t, $J$ = 8.2 Hz, 3 H), 7.61 (d, $J$ = 8.4 Hz, 1 H), 12.63 (s, 1 H); IR ($CDCl_3$) 1647, 1614,1291,921 cm$^{-1}$; MS $m/z$ 121, 172, 203, 213, 228, 241, 259, 274; HRMS $m/z$ for $C_{15}H_{14}O_5$ calcd 274.08412, measured 274.08349; CMR ($CD_3OD$) $\delta$ 16.4, 17.6, 68.6, 70.5, 108.2, 114.3, 117.2, 120.2, 120.3, 126.9, 127.1, 141.1, 154.4, 155.3, 203.8; TLC (H:EA = 2:1) $R_f$ = 0.37.

**3,4-Dihydro-5,9,10-trimethoxy-1,3-dimethyl-1*H*-naphtho-[2,3-*c*]pyran-4-one (8).** To a solution of **7** (100 mg, 0.365 mmol) and tetrabutylammonium bromide (30 mg, 0.091 mmol) in 5 mL of THF and 2 mL of water was added 2 mL of aqueous sodium dithionite (640 mg, 3.65 mmol). After 15 min at rt, 1 mL of aqueous KOH (1.02 g, 18.3 mmol) was added. After 2 min, 4 mL of dimethyl sulfate was added and the mixture was stirred for 12 h. The crude product was extracted by partitioning between water (5 mL) and ether (3 × 20 mL). The organic layer was mixed with 5 mL of triethylamine to remove any remaining dimethyl sulfate. The sovent was concentrated *in vacuo* . The crude product was purified by sgc (H:EA = 6:1) to afford 50 mg (43% yield) of **8**.

**8**: $^1$H NMR ($CDCl_3$) $\delta$ 1.51 (d, $J$ = 6.6 Hz, 3 H), 1.68 (d, $J$ = 6.6 Hz, 3 H), 3.85 (s, 3 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 4.59 (q, $J$ = 6.6 Hz, 1 H), 5.50 (q, $J$ = 6.6 Hz, 1 H), 7.02 (d, $J$ = 7.8 Hz, 1 H), 7.44 (t, $J$ = 8.2 Hz, 1 H), 7.96 (d, $J$ = 8.4 Hz, 1 H); IR ($CDCl_3$) 1689, 1611, 1583, 1263,1100, 900 cm$^{-1}$; MS $m/z$ 91, 115, 136, 155, 171, 185, 199, 229, 257, 272, 301, 316; HRMS $m/z$ for $C_{18}H_{20}O_5$ calcd 316.13107, measured 316.13102; CMR ($CDCl_3$) $\delta$ 17.8, 19.5, 58.2, 62.4, 62.9, 67.6, 71.7, 109.0, 117.0, 117.6, 123.4, 126.5, 131.4, 133.6, 146.2, 154.7, 155.6, 196.7; TLC (H:EA = 2:1) $R_f$ = 0.52.

**Hongconin (1).** To a suspension of **8** (46 mg, 0.146 mmol) and AgO (72 mg, 0.582 mmol) in 3 mL THF at rt was added 0.15 mL of 6 N $HNO_3$. After 1 h, the reaction was quenched by the addition of 3 mL of water. The mixture was extracted with ether (3 × 10 mL) and the organic layer was dried over $Na_2SO_4$ and was concentrated *in vacuo*. The crude product was then dissolved in THF–$H_2O$ (1 mL:0.6 mL) and cooled to 0 °C. This solution was treated with $Na_2S_2O_4$ (26 mg, 0.15 mmol) for 15 min. The mixture was extracted with ether and the organic layer was washed with brine and dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the crude product was purified by sgc to afford 37 mg (88% yield) of **1**.

**1**: $^1$H NMR ($CDCl_3$) $\delta$ 1.53 (d, $J$ = 6.6 Hz, 3 H), 1.64 (d, $J$ = 6.6 Hz, 3 H), 4.07 (s, 3 H), 4.69 (q, $J$ = 6.6 Hz, 1 H), 5.49 (q, $J$ = 6.6 Hz, 1 H), 7.01 (d, $J$ = 7.5 Hz, 1 H), 7.38 (t, $J$ = 8.1 Hz, 1 H), 8.05 (d, $J$ = 8.7 Hz, 1 H), 8.97 (s, 1 H), 12.82 (s, 1 H); IR ($CDCl_3$) 3422, 1646, 1610, 1579, 1458, 1387, 1290, 1253, 1233, 1102, 1053, 924, 979, 760 cm$^{-1}$; CMR ($CDCl_3$) $\delta$ 16.3, 17.4, 58.4, 67.4, 69.4, 107.8, 109.1, 118.0, 119.5, 120.9, 125.4, 125.9, 139.4, 154.3, 155.6, 202.8; MS $m/z$ 91, 173, 227, 245, 273, 288; HRMS $m/z$ for $C_{16}H_{16}O_5$ calcd 288.0998, measured 288.0990; TLC (H:EA = 2:1) $R_f$ = 0.61.

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**Supplementary Material Available:** Copies of proton NMR spectra of **1**, **3**–**8** (7 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.