A Concise, Enantioselective Synthesis of (−)- and (+)-Hongconin

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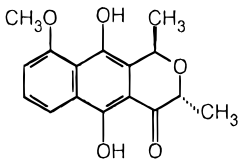
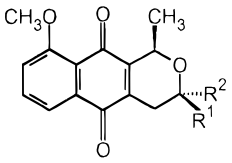
Optically pure enone **9c**, available in three steps from known 6-deoxy D-galactal derivative **7b**, reacts with cyanophthalide **6** to directly afford the natural product (−)-hongconin (**1**), a compound from traditional Chinese medicine recently shown to exhibit antianginal activity. The enantiomer of **1** and its (+)-*cis*-diastereomer were also synthesized in a parallel fashion from the L-sugar counterpart. The use of *C*-glycoside Michael acceptors, as opposed to their *O*-glycoside counterparts, represents a potentially useful simplification of phthalide annulation methodology in synthesizing numerous other such optically pure isochromanquinoids, since it obviates the inconvenience of additional steps late in the synthetic scheme associated with reductive manipulation of a remaining acetal moiety into the desired pyran ring substituent.

Introduction

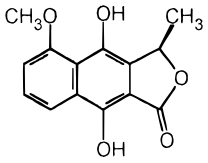
The rhizome of the South Chinese herbal plant *Eleutherine americana* Merr. et Heyne (Iridaceae), known as "Hong-Cong" in Chinese, has long been used as a folk remedy for coronary disorders.[1] A formulation of four naphthalene derivatives isolated from the extracts by Chen and co-workers[2] [namely, a novel component, hongconin (**1**), as well as the previously known compounds **2**−**4**[3]], was subsequently demonstrated to increase coronary blood flow in isolated guinea pig heart and to exhibit human antianginal efficacy approximately equal to that of dipyridamole.[2a,4] To the best of our knowledge, the individual abilities of the four agents to confer cardioprotection have yet to be discerned, and additional studies are thus needed to clarify this phenomenon and perhaps identify one superior component of the four. Furthermore, the obvious structural similarity of these agents to well-known isochromanquinones such as kalafungin and the nanaomycins has suggested other potential medicinal applications for the eleutherines.[5]



(-)-Hongconin (**1**)



(+)-Eleutherine (**2**): $R^1 = CH_3$, $R^2 = H$
(-)-Isoeleutherine (**3**): $R^1 = H$, $R^2 = CH_3$



(+)-Eleutherol (**4**)

It comes as no surprise, then, that hongconin has attracted the interest of synthetic chemists, since an investigation of its medicinal potential will likely require amounts of material in excess of its low natural occurrence. Kraus and co-workers recently reported a nine-step racemic synthesis from 2,5-dimethoxybenzaldehyde.[6] Interestingly, Swenton and co-workers had previously disclosed that their well-known and versatile cyanophthalide donor **6**[7] could react with levoglucosenone to provide chiral intermediates *en route* to naphtho[2,3-*c*]-pyran-5,10-quinone antibiotics, and they have just elaborated one of these into (−)-hongconin.[8] By similar methodology, Tatsuta and co-workers used an L-rhamnose-derived Michael acceptor to ultimately afford optically pure kalafungin and nanaomycins A and D.[9] In these latter two programs, however, a number of peripheral operations were required after the coupling step to install and/or adjust the stereochemistry of the pyran ring substituents in the target compounds. We foresaw that subsequent advances in *C*-glycoside synthesis could allow conversion of the appropriate glycal (see retrosynthetic analysis in Scheme 1) into a more fully constructed Michael acceptor already possessing hongconin's dimethylpyran skeleton in its proper stereochemistry, such that its reaction with **6** might provide hongconin directly. The reduction of this strategy to practice in the synthesis of (+)-*ent*-hongconin (**1a**) and the resulting elucidation of hongconin's previously undetermined absolute config-

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(1) Hainan-Renmin Hospital Guanxinbin-Keyan-Xiaozu, *Hainan-Weisheng* **1977**, *2*, 43.

(2) (a) Chen, Z.; Huang, H.; Wang, Y.; Li, Y.; Ding, J. *Zhongcaoyao* **1981**, *12*, 484; *Chem. Abstr.* **1982**, *97*, 20699. (b) Chen, Z.; Huang, H.; Wang, C.; Li, Y.; Ding, J.; Sankawa, U.; Noguchi, H.; Iitaka,Y. *Heterocycles* **1984**, *22*, 691. (c) Chen, Z.; Huang, H.; Wang, C.; Li, Y.; Ding, J.; Sankawa, U.; Noguchi, H.; Iitaka, Y. *Chem. Pharm. Bull.* **1986**, *14*, 2743.

(3) (a) Schmid, H.; Meijer, T. M.; Eböthner, A. *Helv. Chim. Acta* **1950**, *33*, 595. (b) Schmid, H.; Eböthner, A.; Burger, M. *Ibid.* **1950**, *33*, 609. (c) Schmid, H.; Eböthner, A.; Meijer, T. M. *Ibid.* **1950**, *33*, 1751. (d) Schmid, H.; Eböthner, A. *Ibid.* **1951**, *34*, 1041. (e) Schmid, H.; Eisenhuth, W. *Ibid.* **1958**, *41*, 2021.

(4) Ding, J.; Huang, H. *Zhongcaoyao* **1982**, *13*, 499; *Chem. Abstr.* **1983**, *98*, 113584.

(5) (a) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572. (b) Moore, H. W. *Science* **1977**, *197*, 527.

(6) (a) Kraus, G. A.; Li, J.; Gordon, M.; Jensen, J. H. *J. Org. Chem.* **1994**, *59*, 2219. (b) Kraus, G. A.; Li, J. *Synlett* **1993**, 525.

(7) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.

(8) (a) Swenton, J. S.; Freskos, J. N. *J. Chem. Soc., Chem. Commun.* **1985**, 658. (b) Kraus and co-workers had previously developed the use of **6** in phthalide annulation chemistry to synthesize racemic kalafungin, pachybasin, and chrysophanol: Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439. (c) For Swenton and co-workers' synthesis of hongconin, see: Swenton, J. S.; Frekos, J. N.; Dalidowicz, P.; Kerns, M. L. *J. Org. Chem.* **1996**, *61*, 459−464.

(9) Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.

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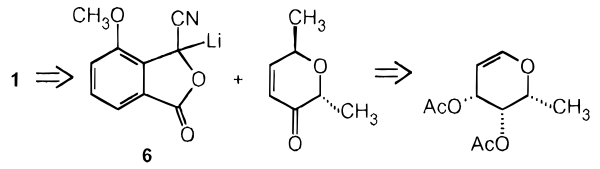
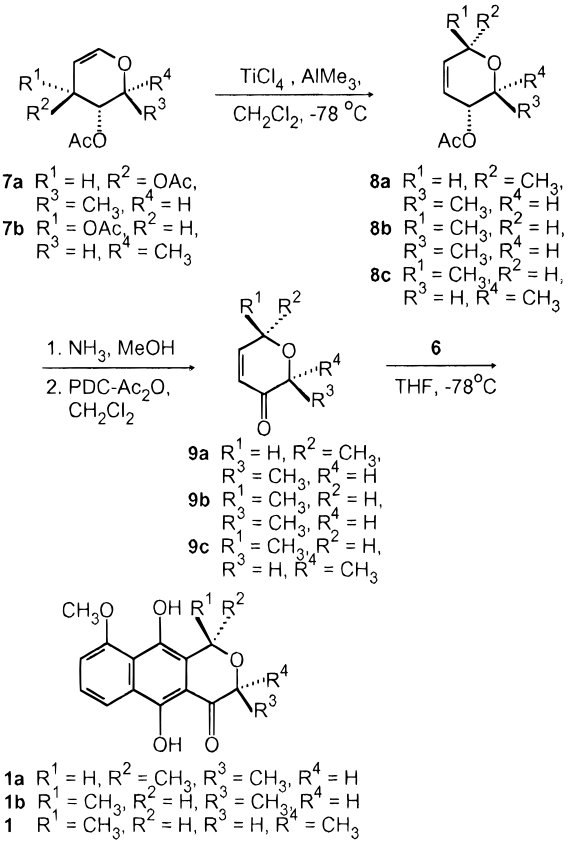
0022-3263/96/1961-0455$12.00/0

Scheme 1



Scheme 2

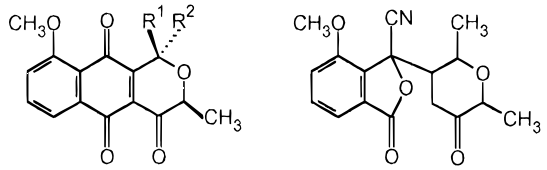


uration were the subjects of our recent communication.[10] Herein we report the experimental details of that work, along with its extension to the first enantioselective synthesis of naturally occurring (−)-hongconin,[11] as well as a related diastereomer, 3-*epi*-hongconin (**1b**).

Results and Discussion

At the outset of our enterprise, it was reasonable to extrapolate from the known absolute configurations of the pyran ring substituents in **2**−**4**[3b,e] and assign hongconin's (**1**'s) absolute configuration on a provisional basis, since the four compounds are presumed to be biosynthetically related.[2c] (Note that only the relative stereochemistry of **1** was defined by the X-ray crystallographic studies.[2c]) Such considerations argue for a methyl group "up" at the 1-position, since that feature is common to **2**−**4**.[12] The "correct" (*i.e.*, either the D or the L) carbohydrate synthon corresponding to the natural product would thus more likely be **9c**, rather than **9a**. We noted, however, that a synthesis of the "wrong" enantiomer would nevertheless be worthwhile, since in the case of some related pyranonaphthoquinone systems both enantiomers have been isolated and found to be biologically active.[13] Thus, for the initial exploration into the viability of our synthetic approach, we resorted to considerations of economy and expedience and chose to begin with commercially available 3,4-di-*O*-acetyl-L-quinoval (3,4-di-*O*-acetyl-6-deoxy-L-glucal, **7a**).

Lewis acid-catalyzed C-1 alkylation[14] of **7a** led to a 4:5 mixture of epimers **8a** and **8b** that were easily separated by chromatography. The stereochemistry at C-1 of these two species was tentatively assigned and later confirmed through NOE studies on their respective end products and by correlation to published physical data for the natural product. As shown in Scheme 2, **8a** and **8b** were elaborated in parallel via routine *O*-deacetylation (ammonia−methanol) and oxidation (pyridinium dichromate−acetic anhydride)[20] into enones **9a** and **9b**, respectively. In general, the reaction between **6** and enones **9**, along with ensuing chromatography, occurred most smoothly when **9** was used in slight excess (1.1 equiv). Extended reaction times and/or warming to room temperature produced minor amounts of the corresponding quinone (*i.e.*, **10a** or **10b**[15]), presumably as a result of air



oxidation *in situ* of the hydroquinone. On the other hand, when the reaction was quenched prematurely (directly after complete consumption of **6**, but prior to complete product formation), high yields of an intermediate (**11**) could be isolated (by chromatography, followed by recrystallization) and subsequently converted to **1** in near quantitative yield by re-exposure to reaction conditions.[16] All physical data of synthetic **1a** were identical to those

(11) This achievement is shared with J. S. Swenton and co-workers, whose work is described in the accompanying paper.

(12) Such a rationale was most probably responsible for the uniform adoption in the literature of structure **1** to represent hongconin, even though its absolute configuration had not been experimentally established.

(13) For example, nanaomycin D and kalafungin are enantiomers, and the antibiotics granaticin and medermycin have been found in either enantiomeric form. See ref 9.

(14) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925.

(15) Quinones **10** proved difficult to purify and were therefore not fully characterized. Evidence for the assigned structures consist of the following data. **10a**: R_f = 0.1 (solvent B); ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H, J = 6.29 Hz), 1.71 (d, 3H, J = 6.76 Hz), 3.79 (q, 1H, J = 6.26 Hz), 3.95 (s, 3H), 4.74 (q, 1H, J = 6.69 Hz), 7.38 (dd, 1H, J = 2.37 Hz, J = 7.15 Hz), 7.68−7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.67, 17.19, 56.61, 66.10, 68.49, 116.50, 117.98, 119.60, 120.05 (2C), 132.57, 135.79 (2C), 186.00, 192.92. **10b**: R_f = 0.1 (solvent B); ^{1}H NMR ($CDCl_3$) δ 1.39 (d, 3H, J = 6.80 Hz), 1.62 (d, 3H, J = 6.60 Hz), 3.95 (s, 3H), 4.23 (q, 1H, J = 6.85 Hz), 4.94 (q, 1H, J = 6.64 Hz), 7.54 (dd, 1H, J = 0.88 Hz, J = 7.67 Hz), 7.68−7.76 (m, 2H); MS (m/z) 285, 203. Some epimerization was noted, presumably at C-1, as had previously been reported for the structurally similar **2** and **3** (ref 3e). C-1 epimerizations in such systems have been exploited by Tatsuta and co-workers as a means of obtaining the desired stereochemistry at that position during a synthesis of kalafungin (ref 9).

(16) Although **11** was converted to **1** upon treatment with *t*-BuOK alone, yields increased when $Na_2S_2O_4$ was included as an antioxidant (see Experimental Section). Structures of the type **11** are possible intermediates in reactions between cyanophthalides and Michael acceptors (see ref 8b, as well as a report by Biehl and co-workers: Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 5685). Compound **11**'s occurrence here was first suspected when the odor of HCN was detected during workup of its conversion to **1**. Its proposed structure was corroborated by its ^{1}H NMR spectrum and decoupling experiments, as well as by ^{13}C NMR, IR, and mass spectral data (see Experimental Section).

of naturally occurring hongconin, except, unfortunately, for the sign of optical rotation: $[\alpha]^{20}_D$ +25.8° (*c* 1.94, $CHCl_3$) {lit., natural product:[2c] $[\alpha]^{20}_D$ −26.0° (*c* 1.94, $CHCl_3$)}. The absolute configuration of (−)-hongconin is thus depicted by **1**, as previously suspected.

Since compound **1b** differs from (−)-hongconin only in the stereochemical disposition of the 3-methyl group, the prospect of epimerizing C-3 appeared to be a viable route to **1**, even if present as a mixture with remaining **1b**, since we had identified a solvent system capable of separating **1a** and **1b**.[17] Toward this end, a di-*O*-benzyl-protected derivative of **1b** was prepared; all attempts to epimerize this species resulted only in decomposition (no experimental details provided). Our subsequent recourse to employing the D-isomer of **7a** to obtain **1**, however, was preempted by our finding that C-1 alkylation of di-*O*-acetyl-D-fucal (3,4-di-*O*-acetyl-6-deoxy-D-galactal, **7b**)[18] by the action of the same reagents as above led exclusively to *trans*-dimethyl adduct **8c** in moderate yield. We believe that the hindered face of a Lewis acid-chelated intermediate causes nucleophilic addition of Me^- to occur via the opposite face of the pyranose ring, thus resulting in the observed trans selectivity. Processing of **8c** as above led to enone **9c** and finally to synthetic (−)-hongconin, **1**: $[\alpha]^{20}_D$ −25.0° (*c* 1.94, $CHCl_3$).

In summary, both enantiomers of hongconin have been prepared in optically pure form in four steps from L-quinoval and D-fucal diacetates using cyanophthalide annulation chemistry.

Experimental Section

General Methods. All reactions were monitored by thin-layer chromatography (TLC). Adsorption chromatography was carried out using E. Merck silica gel products: (a) TLC on 0.2 mm aluminum-backed plates, (b) column chromatography using 230−400 mesh silica gel. Visualization of the TLC plates was by 254 nm UV light and by spray−heat development using a *p*-anisaldehyde−sulfuric acid reagent.[19] The solvent systems for adsorption chromatography were A, 8:1 hexanes−ethyl acetate; B, 4:1 hexanes−ethyl acetate; C, dichloromethane; and D, 1:1:1 hexanes−ethyl acetate−dichloromethane. Anhydrous solvents were prepared as follows: dichloromethane was distilled from calcium hydride; THF was refluxed with sodium−benzophenone ketyl and distilled. Reagent *tert*-butyl alcohol was distilled from sodium. All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were evaporated at aspirator vacuum at about 25 °C unless otherwise indicated. Elemental analyses were furnished by Atlantic Microlab, Inc., Atlanta, GA. ^1H and ^{13}C NMR spectra were recorded at 250 and 90 MHz, respectively. The mass spectral analyses were obtained in the electron-impact mode on a VG-ZAB instrument at the University of Tennessee.

General Procedure for the Synthesis of Compounds 8. To a solution of the appropriate glycal **7** (1.0 g, 4.66 mmol) in dichloromethane at −78 °C was added dropwise $TiCl_4$ (1.0 M in toluene, 5.13 mL, 1.1 equiv) to afford a cloudy yellow-orange mixture which was allowed to stir for 15 min. $AlMe_3$ (2.0 M in hexane, 3.5 mL, 1.5 equiv) was then added dropwise, whereupon the reaction mixture immediately turned black. The reaction mixture was allowed to stir at −78 °C for 6 h, at the end of which time the reaction was quenched by the addition of saturated $NaHCO_3$ (10 mL) and the solution was allowed to warm to room temperature. The gelatinous mixture was filtered through Celite, washed with brine, dried ($MgSO_4$), concentrated, and submitted to flash chromatography (solvent A or C). Careful evaporation of the fractions at 20 °C afforded the appropriate *C*-glycoside [**7a** (1.00 g, 4.67 mmol) → **8a** + **8b** (704 mg, 89% overall); **7b** (1.69 g, 7.90 mmol) → **8c** (830 mg, 72% based on 237 mg of recovered starting material)] as detailed in the following paragraphs.

5-*O*-Acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-L-*arabino*-hept-3-enitol (8a). Beginning with glycal **7a**, **8a** was obtained as a volatile oil containing a small amount of hexanes (as shown by ^1H NMR spectroscopy): $[\alpha]^{20}_D$ −133.0° (*c* 1.0, $CHCl_3$); R_f = 0.35 (solvent B); ^1H NMR ($CDCl_3$) δ 1.17 (d, 3H, *J* = 6.54 Hz), 1.22 (d, 3H, *J* = 6.8 Hz), 2.02 (s, 3H), 3.85 (dq, 1H, *J* = 4.76 Hz, *J* = 6.49 Hz), 4.25 (m, 1H), 4.81 (bm, 1H), 5.67 (dm, 1H, *J* = 10.27 Hz), 5.82 (dm, 1H, *J* = 10.28 Hz); ^{13}C NMR ($CDCl_3$) δ 16.82, 19.52, 21.07, 66.12, 68.31, 69.46, 122.17, 135.12, 170.54. Anal. Calcd for $C_9H_{14}O_3 \cdot 0.08C_6H_{14}$: C, 64.24; H, 8.96. Found: C, 64.28; H, 8.95.

3-*O*-Acetyl-2,6-anhydro-1,4,5,7-tetradeoxy-D-*ribo*-hept-4-enitol (8b). Beginning with glycal **7a**, **8b** was obtained as a volatile oil: $[\alpha]^{20}_D$ −175.0° (*c* 1.0, $CHCl_3$); R_f = 0.45 (solvent B); ^1H NMR ($CDCl_3$) δ 1.11 (d, 3H, *J* = 6.81 Hz), 1.14 (d, 3H, *J* = 5.92 Hz), 1.99 (s, 3H), 3.45 (m, 1H), 4.37 (m, 1H), 4.97 (bd, 1H, *J* = 8.69 Hz), 5.57 (bd, 1H, *J* = 10.23 Hz), 5.69 (bd, 1H, *J* = 10.20 Hz); ^{13}C NMR ($CDCl_3$) δ 18.36, 20.94, 21.06, 70.67, 71.01, 72.26, 124.69, 134.06, 170.28. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.28. Found: C, 63.60; H, 8.33.

3-*O*-Acetyl-2,6-anhydro-1,4,5,7-tetradeoxy-D-*arabino*-hept-4-enitol (8c). Beginning with glycal **7b** and conducting the addition of $AlMe_3$ and subsequent stirring at −50 °C instead of −78 °C, **8c** was obtained as a volatile oil containing a small amount of water and dichloromethane, as shown by ^1H NMR spectroscopy): $[\alpha]^{20}_D$ −406.0° (*c* 1.6, $CHCl_3$); R_f = 0.35 (solvent B); ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, *J* = 6.44 Hz), 1.25 (d, 3H, *J* = 6.86 Hz), 2.10 (s, 3H), 4.03 (dm, 1H, *J* = 2.76 Hz, *J* = 6.5 Hz), 4.43 (q, 1H, *J* = 2.32 Hz, *J* = 6.85 Hz), 4.98 (dd, 1H, *J* = 2.80 Hz, *J* = 4.82 Hz), 5.86 (ddd, 1H, *J* = 1.9 Hz, *J* = 4.96 Hz, *J* = 7.12 Hz), 5.98 (dd, 1H, *J* = 2.95 Hz, *J* = 10.21 Hz); ^{13}C NMR ($CDCl_3$) δ 16.10, 18.23, 21.00, 65.48, 66.29, 68.54, 121.84, 136.25, 170.89. Anal. Calcd for $C_9H_{14}O_3 \cdot 0.035CH_2Cl_2 \cdot 0.15H_2O$: C, 61.61; H, 8.22; Cl, 1.6. Found: C, 61.50; H, 8.22, Cl, 1.6.

General Procedure for the Synthesis of Compounds 9. The appropriate acetate **8** (0.400 g, 2.35 mmol) was treated with a saturated ammonia−methanol solution (50 mL) for 24 h at room temperature. After evaporation of solvent, the resulting crude alcohol was redissolved in dichloromethane (50 mL) and treated with pyridinium dichromate (PDC, 1.00 g, 1.1 equiv). After 15 min of stirring, acetic anhydride (0.18 mL, 0.8 equiv)[20] was added, and the reaction mixture was allowed to stir overnight at room temperature, after which time it was diluted with ether (50 mL) and filtered through Celite. The filtrate was concentrated and submitted to flash chromatography (solvent C). Careful evaporation of the fractions at 20 °C provided the appropriate enone (75−90%, two steps) described in the following paragraphs.

2,6-Anhydro-1,4,5,7-tetradeoxy-L-*threo*-hept-4-en-3-ulose (9a). Beginning with **8a** (400 mg, 2.37 mmol), **9a** (269 mg, 90%) was obtained as a volatile oil: $[\alpha]^{20}_{578}$ +2° (*c* 1.0, $CHCl_3$); R_f = 0.45 (solvent B); ^1H NMR ($CDCl_3$) δ 1.38 (d, 1H, *J* = 7.0 Hz), 1.40 (d, 1H, *J* = 7.0 Hz), 4.33 (q, 1H, *J* = 6.95 Hz), 4.61 (m, 1H, *J* = 6.96 Hz), 6.01 (dd, 1H, *J* = 1.93 Hz, *J* = 10.37 Hz), 6.93 (dd, 1H, *J* = 2.47 Hz, *J* = 10.43 Hz); ^{13}C NMR ($CDCl_3$) δ 15.15, 18.70, 65.79, 73.25, 124.53, 151.80, 197.01; HRMS calcd for $C_7H_{10}O_2$ 126.068, found 126.068.

2,6-Anhydro-1,4,5,7-tetradeoxy-D-*erythro*-hept-4-en-3-ulose (9b). Beginning with **8b** (1.00 g, 5.91 mmol), **9b** (569 mg, 76%) was obtained as a volatile oil: $[\alpha]^{20}_{365}$ −606° (*c* 1.0, $CHCl_3$); R_f = 0.7 (solvent C); ^1H NMR ($CDCl_3$) δ 1.37 (d, 3H, *J* = 1.47 Hz), 1.40 (d, 3H, *J* = 2.09 Hz), 4.07 (dq, 1H, *J* = 1.8 Hz, *J* = 6.61 Hz), 4.50 (m, 1H), 6.06 (dd, 1H, *J* = 2.46 Hz, *J* = 10.22 Hz), 6.87 (dd, 1H, *J* = 1.41 Hz, *J* = 10.17 Hz); ^{13}C NMR

(17) TLC: silica gel, 115:1 toluene−MeOH (**1a**, R_f = 0.38; **1b**, R_f = 0.45).

(18) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4158. 3,4-Di-*O*-acetyl-D-fucal was prepared from D-fucose using a standard literature preparation for 6-deoxy glycals: Pigman, W.; Roth, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405.

(19) Schaumberg, J. P.; Hokanson, G. C.; French, J. C.; Smal, E.; Baker, D. C. *J. Org. Chem.* **1985**, *50*, 1651, footnote 33 therein.

(20) Garegg, P. J.; Samuelsson B. *Carbohydr. Res.* **1978**, *67*, 267.

($CDCl_3$) δ 15.30, 20.58, 70.22, 76.68, 126.10, 152.13, 196.80; HRMS calcd for $C_7H_{10}O_2$ 126.068, found 126.068.

2,6-Anhydro-1,4,5,7-tetradeoxy-D-*threo*-hept-4-en-3-ulose (9c). Beginning with **8c** (403 mg, 2.38 mmol), **9c** (224 mg, 75%) was obtained as a volatile oil: $[\alpha]^{20}_D$ −53.4° (*c* 2.6, $CDCl_3$); ^{1}H NMR, ^{13}C NMR, TLC data identical to that of **9a**; HRMS calcd for $C_7H_{10}O_2$ 126.068, found 126.067.

General Procedure for the Synthesis of Compounds 1, 1a, and 1b. To a solution of *t*-BuOH (0.21 mL, 1.1 equiv), LiCl (0.060 g, cat.), and THF (20 mL) at −78 °C was added dropwise BuLi (2.5 M in hexane, 0.87 mL, 1.1 equiv). To this solution was added dropwise a solution of **6** (0.375 g, 1.98 mmol) in THF (10 mL). The resulting yellow solution was allowed to stir for 10 min, whereupon a solution of **9** (0.30 g, 1.1 equiv) in dichloromethane (5 mL) was added dropwise. The reaction was allowed to continue at −78 °C for 4−6 h. Saturated NH_4Cl (25 mL) and ether (25 mL) were then added, and the mixture was allowed to warm to room temperature. After extractions with ether (4 × 20 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and submitted to flash chromatography (solvent A) to provide the appropriate isochroman hydroquinones (56−75%) described in the following paragraphs.

(1*S*,3*S*)-(+)-3,4-Dihydro-5,10-dihydroxy-9-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (*ent*-Hongconin, 1a). Beginning with **9a** (150 mg, 0.793 mmol), **1a** (128 mg, 56%) was obtained as a bright yellow powder: $[\alpha]^{20}_D$ +25.8° (*c* 1.94, $CHCl_3$); R_f = 0.5 (solvent B); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, *J* = 6.61 Hz), 1.63 (d, 3H, *J* = 6.70 Hz), 4.04 (s, 3H), 4.68 (q, 1H, *J* = 6.58 Hz), 5.47 (q, 1H, *J* = 6.73 Hz), 6.98 (d, 1H, *J* = 7.77 Hz), 7.35 (t, 1H, *J* = 8.05 Hz), 8.01 (d, 1H, *J* = 8.42 Hz), 8.94 (s, 1H), 12.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.25, 17.36, 56.34, 67.35, 69.44, 107.80, 109.12, 118.05, 119.59, 120.96, 125.36, 125.93, 139.43, 154.35, 155.68, 202.87.

(1*R*,3*S*)-(+)-3,4-Dihydro-5,10-dihydroxy-9-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (3-*epi*-Hongconin, 1b). Beginning with **9b** (33 mg, 0.174 mmol), **1b** (32 mg, 64%) was obtained as a bright yellow powder: $[\alpha]^{20}_D$ +207.0° (*c* 1.94, $CHCl_3$); R_f = 0.85 (solvent C); ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, *J* = 6.58 Hz), 1.77 (d, 3H, *J* = 6.30 Hz), 4.06 (s, 3H), 4.26 (q, 1H, *J* = 6.61 Hz), 5.15 (q, 1H, *J* = 6.28 Hz), 6.99 (d, 1H, *J* = 7.76 Hz), 7.37 (t, 1H, *J* = 8.07 Hz), 8.02 (d, 1H, *J* = 8.37 Hz), 9.19 (s, 1H), 12.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.49, 21.30, 56.42, 71.83, 74.89, 109.06, 109.40, 118.02, 119.74, 120.26, 125.49, 125.98, 141.00, 153.68, 155.68, 159.29, 201.68; HRMS calcd for $C_{16}H_{16}O_5$: 288.100, found 288.101.

(1*R*,3*R*)-(−)-3,4-Dihydro-5,10-dihydroxy-9-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (Hongconin, 1) and 1-(2,6-dimethyl-5-oxo-tetrahydropyran-3-yl)-7-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (11). Beginning with **9c** (375 mg, 1.98 mmol), **1** (63 mg, 11%) was directly obtained as a bright yellow powder: $[\alpha]^{20}_D$ −25.0° (*c* 1.94, $CHCl_3$), lit.[2c] $[\alpha]_D$ −26.0° (*c*, 1.94 $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and TLC data identical to those of **1a**. Along with **1** was obtained **11** as colorless crystals after recrystallization from ether−hexanes (400 mg, 70%): ^{1}H NMR ($CDCl_3$): δ 1.08 (d, 3H, *J* = 6.65 Hz), 1.30 (d, 3H, *J* = 6.80 Hz), 2.91−3.15 (m, 3H), 3.50−3.54 (m, 1H), 4.03−4.16 (q, 1H, *J* = 6.77 Hz), 4.03 (s, 3H), 7.28 (d, 1H, *J* = 7.99 Hz), 7.57 (d, 1H, *J* = 7.27 Hz), 7.69 (t, 1H, *J* = 7.87 Hz); ^{13}C NMR ($CDCl_3$) δ 15.52, 18.96, 36.43, 45.43, 56.38, 66.14, 73.12, 79.12, 114.65, 116.81, 118.31, 127.10, 130.64, 133.95, 154.33, 166.40, 208.94; IR (cm^{-1}, KBr) 1790, 1720; HRMS calcd for $C_{17}H_{17}O_5N$ 315.111, found 315.110.

Conversion of 11 to 1. To a solution of compound **11** (50 mg, 0.17 mmol) in THF (8 mL) at −78 °C were added $Na_2S_2O_4$ (10 mg, 0.35 equiv) and *t*-BuOK (10 mg, 0.5 equiv), whereupon the clear solution gradually became bright yellow. After continued stirring at −78 °C, TLC (solvent D) showed the complete conversion of **11** (R_f = 0.4) to **1** (R_f = 0.5). Following workup as described above, compound **1** was obtained (43 mg, 96%).

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Supporting Information Available: ^{1}H NMR spectra of **1a**, **1b**, **8a**, **8b**, **8c**, **9a**, and **9b**; ^{1}H and ^{13}C NMR spectra of **11** (9 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.

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