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A Concise Asymmetric Synthesis of (–)-Hongconin and (–)-1-*epi*-Hongconin

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A concise asymmetric synthesis of (–)-hongconin and (–)-1-*epi*-hongconin is described. The synthesis features an efficient combination of Dötz benzannulation or lactaldehyde arylation and the oxa-Pictet–Spengler reaction as the key steps. The synthesis is completed in 10–11 steps from the chiral pool material (*R*)-methyl lactate.

Introduction

The herbal plant *Eleutherine americana* Merr. et Heyne commonly called Hong-Cong in Chinese, belongs to the Iridaceae family and has been used as folk medicine for remedies of cardiac diseases (angina pectoris). Chen et al.[1] isolated four bioactive natural products (Figure 1), namely, hongconin (**1**), eleutherin (**2**), isoeleutherin (**3**), and eleutherol (**4**), from the rhizomes of *Eleutherine americana*. Pharmacological studies of these compounds indicated that they are able to enhance the blood flow in coronary arteries and that they can also reduce chest pain.[2,3] Eleutherin (**2**) revealed inhibitory activity towards topoisomerase II, a target anticancer agent,[4] whereas isoeleutherin (**3**) showed significant anti-HIV activity.[4]

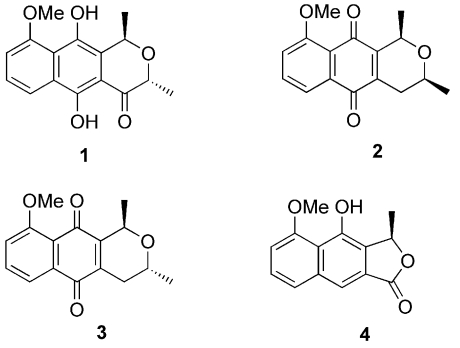
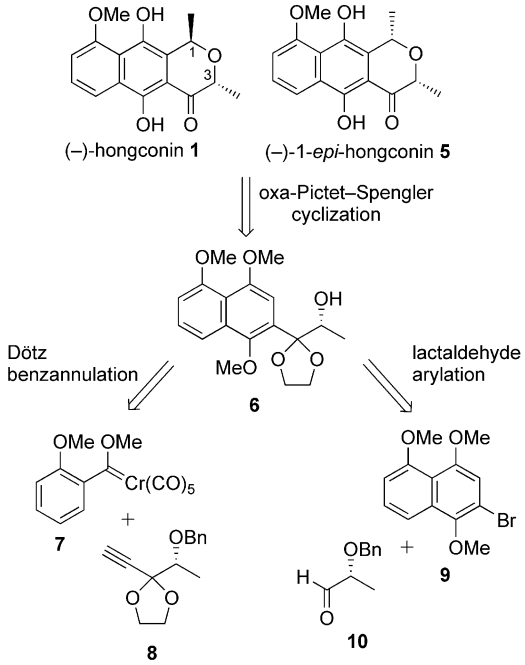


Figure 1. (–)-Hongconin (**1**), (+)-eleutherin (**2**), (–)-isoeleutherin (**3**), and (+)-eleutherol (**4**).

Considering the clinical use and potential pharmacological activities of hongconin towards cardiopathy, it has been an exclusive target for many synthetic chemists. To the best of our knowledge, there are two racemic[5] and two enantioselective[6] syntheses of natural (–)-hongconin, whereas only one enantioselective synthesis of the non-natural enantiomer (+)-hongconin[7] and its C-3 epimer, (+)-3-*epi*-hongconin,[6a] are reported in the literature.

Results and Discussion

In continuation of our efforts towards the enantioselective synthesis of naphthoquinone-centered natural products through Dötz benzannulation and the oxa-Pictet–Spengler reaction,[8] we envisioned a similar strategy for the asymmetric synthesis of (–)-hongconin (**1**) and (–)-1-*epi*-hongconin (**5**), which is an enantiomer of (+)-3-*epi*-hongconin reported earlier.[6a] The retrosynthetic analysis of **1** and **5** is shown in Scheme 1. The oxa-Pictet–Spengler



Scheme 1. Retrosynthetic analysis of (–)-hongconin (**1**) and (–)-1-*epi*-hongconin (**5**).

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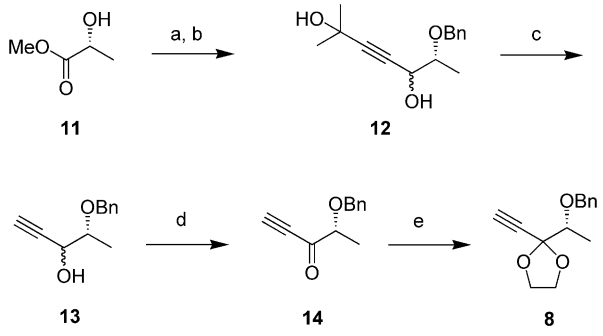
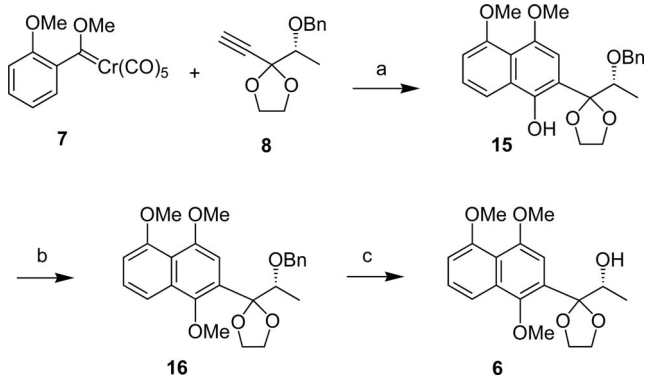
reaction of **6** is expected to give a C-1 diastereomeric mixture (we expected the C-1 diastereomers to be separable from our earlier experience in the synthesis of eleutherin and *iso*-eleutherin),[8a] from which **1** and **5** could be prepared. Compound **6** could be targeted in two ways: (1) by Dötz benzannulation of Fischer carbene **7** with chiral alkyne **8** followed by debenzylation or (2) by arylation of lactaldehyde **10** with **9** followed by usual hydroxy group manipulation.

Synthesis of Compound 6 through Dötz Benzannulation

Chiral alkyne **8** required for Dötz benzannulation was synthesized as shown in Scheme 2. DIBAL-H reduction of benzyl-protected (*R*)-methyl lactate gave aldehyde **10** (90%), which upon alkylation with 2-methylbut-3-yn-2-ol afforded diol **12** in 86% yield. Diol **12**, upon removal of alkyne protection, led to terminal alkyne **13** in 79% yield.[9] The hydroxy group in **13** was oxidized with IBX to give ketone compound **14** in 73% yield. Further protection of



Scheme 2. Synthesis of chiral alkyne **8**. Reagents and conditions: (a) BnBr (1.1 equiv.), NaH (1.2 equiv.), THF, 0 °C to room temp., 6 h, 96%; (b) 1. DIBAL-H (1.01 equiv.), CH_2Cl_2, –78 °C, 1 h, 90%, 2. HC≡C–C(CH$_3$)$_2$OH (1.8 equiv.), HMPA, *n*BuLi (4.0 equiv.), THF, –60 to –20 °C, 2 h, then **10**, –60 °C to room temp., 12 h, 86%; (c) K_2CO_3 (1.05 equiv.), 18-crown-6 (0.3 equiv.), toluene, reflux, 72 h, 79%; (d) IBX (1.2 equiv.), EtOAc, reflux, 12 h, 73%; (e) $(CH_2OH)_2$ (10 equiv.), *p*-TsOH (cat.), benzene, reflux, 30 h, 75%.



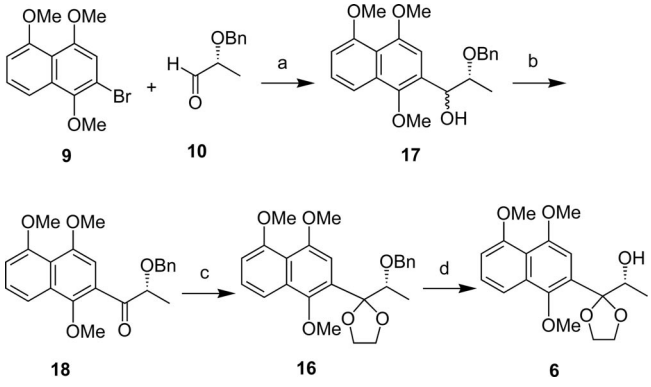
Scheme 3. Synthesis of compound **6** through Dötz benzannulation. Reagents and conditions: (a) THF, 45 °C, 14 h, 52%; (b) NaH (3.0 equiv.), 30 min, MeI (3.5 equiv.), THF, 0 °C to room temp., 6 h, 91%; (c) H_2, 10% Pd/C, MeOH, 1 atm, room temp., 6 h, 72%.

14 with ethylene glycol provided desired chiral alkyne **8** in 75% yield.

Fisher carbene complex **7** was prepared from 2-bromoanisole as reported earlier[8] and then condensed with chiral alkyne **8** in the Dötz benzannulation (Scheme 3)[10] reaction to provide substituted naphthol **15** in an optimized 52% yield. The use of alkynes **13** or **14** in the Dötz benzannulation reaction gave the corresponding benzannulated products in unacceptably low yields. Methylation of the phenolic OH group in **15** afforded **16** in 91% yield. Compound **16** upon hydrogenation with 10% Pd/C afforded desired intermediate compound **6** (72%).

Synthesis of Compound 6 through Lactaldehyde Arylation

Compound **6** was alternatively synthesized as shown in Scheme 4 through lactaldehyde arylation.[11] The nucleophilic addition of the carbanion generated from trimethoxy bromonaphthalene **9**[12] to lactaldehyde **10** gave alcohol **17** in 89% yield. The IBX oxidation of alcohol **17** afforded ketone **18** in 91% yield. Further ketal formation to **16** (88%) and debenzylation afforded compound **6** (72%).

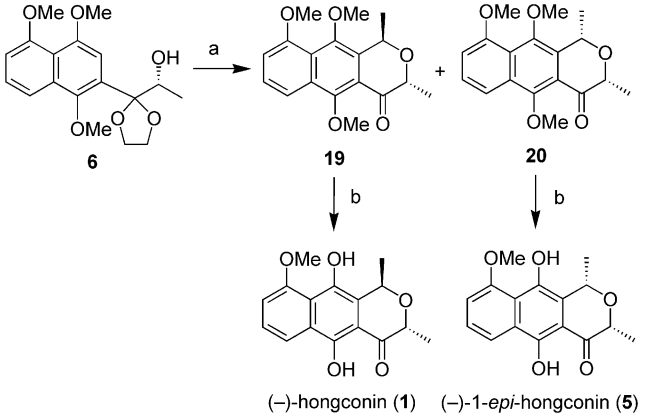


Scheme 4. Synthesis of **6** by lactaldehyde arylation. Reagents and conditions: (a) *n*BuLi (1.2 equiv.), THF, –78 °C, then **10** (1.2 equiv.), –78 °C, 2 h to room temp., 12 h, 89%; (b) IBX (1.2 equiv.), EtOAc, reflux, 12 h, 91%; (c) $(CH_2OH)_2$ (10 equiv.), *p*-TsOH (cat.), benzene, reflux, 30 h, 88%; (d) H_2, 10% Pd/C, MeOH, 1 atm, room temp., 6 h, 72%.

Synthesis of (–)-Hongconin (1) from Compound 6

The synthesis of (–)-hongconin (**1**) and (–)-1-*epi*-hongconin (**5**) was achieved from **6** as shown in Scheme 5. The oxa-Pictet–Spengler reaction[13] of **6** with acetaldehyde dimethylacetal in the presence of $BF_3{\cdot}OEt_2$ gave a mixture of **19**/**20** in a 3:2 ratio.[14] Ketal deprotection also occurred in the same reaction. The mixture of **19**/**20** was easily separated by flash silica gel column chromatography to give **19** (48%) and **20** (31%) from **6**. The cerium ammonium nitrate (CAN) oxidation of **19** to the corresponding quinone followed by reduction with sodium dithionate produced (–)-hongconin (**1**) {$[\alpha]_D^{20}$ = –26.7 (*c* = 0.10, $CHCl_3$); ref.[1] $[\alpha]_D^{20}$ = –26.0 (*c* = 1.94, $CHCl_3$)} in 86% yield. Similarly, CAN oxidation of **20** followed by reduction with sodium dithion-

ate gave non-natural (–)-1-*epi*-hongconin (**5**) {$[a]_D^{20}$ = –204.6 (*c* = 0.13, $CHCl_3$); ref.[6a] *ent*-(**5**), $[a]_D^{20}$ = +207.0 (*c* = 1.94, $CHCl_3$)} in 82% yield. The spectral and analytical data of **1** and **5** were in full agreement with those reported.[6a]



Scheme 5. Synthesis of (–)-**1** and (–)-**5**. Reagents and conditions: (a) $(CH_3O)_2CHCH_3$ (2.0 equiv.), $BF_3{\cdot}OEt_2$ (3.0 equiv.), Et_2O/THF (4:1), room temp., 48 h, **19** (48%), **20** (31%); (b) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv.), MeCN/H_2O (1:1), room temp., 30 min, then $Na_2S_2O_4$ (3.0 equiv.), TBAI (cat.), THF/H_2O (4:3), room temp., 1 h, **1** (86%), **5** (82%).

Conclusions

In summary we have achieved an efficient asymmetric synthesis of (–)-hongconin (**1**) and (–)-1-*epi*-hongconin (**5**). The synthesis features the Dötz benzannulation or lactaldehyde arylation for building the naphthalene unit. The oxa-Pictet–Spengler reaction afforded separable pyran ring diastereomers. Ketal deprotection was also observed under the $BF_3{\cdot}Et_2O$ oxa-Pictet–Spengler cyclization reaction conditions. The synthesis was completed in 10–11 steps from the chiral pool material (*R*)-methyl lactate.

Experimental Section

General Remarks: Flasks were oven or flame dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of argon or nitrogen. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury Plus AS400 spectrometer, and the chemical shifts are based on the TMS peak at δ = 0.00 pm for ^1H NMR and the $CDCl_3$ peak at δ = 77.00 ppm (t) for ^{13}C NMR. IR spectra were obtained with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were measured with a Jasco P-2000 digital polarimeter. HRMS was recorded by using a Micromass Q-Tof micro (YA-105) spectrometer.

(5*R*/*S*,6*R*)-6-Benzyloxy-2-methylhept-3-yne-2,5-diol (12): To a solution of (*R*)-methyl lactate (**11**; 3.0 g, 28.8 mmol) in dry THF (30 mL) at 0 °C was added oil-free NaH (0.83 g, 34.6 mmol, 1.2 equiv.), and the mixture was stirred for 15 min. BnBr (5.42 g, 31.68 mmol, 1.1 equiv.) was added, and the reaction mixture was warmed to room temperature and stirred for 6 h. It was quenched with water, and the solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1) to provide (*R*)-methyl-2-benzyloxypropanoate (5.37 g, 96%) as a colorless oil. Characterization and analytical data are the same as those reported for the enantiomer.[15]

To a solution of (*R*)-methyl-2-benzyloxypropanoate (1.0 g, 5.14 mmol) in dry CH_2Cl_2 (40 mL) at –78 °C under an argon atmosphere was added DIBAL-H (1 M in hexane, 5.2 mL, 5.2 mmol, 1.01 equiv.) dropwise over 10 min. The reaction mixture was stirred for 1 h at –78 °C and then quenched with a saturated solution of Rochelles salt. It was then stirred for 2 h at room temperature and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1) to provide (*R*)-2-benzyloxypropanal (**10**; 0.76 g, 90%) as a colorless oil. Characterization and analytical data are the same as those reported for the enantiomer.[15]

To a solution of 3-methyl-1-butyn-3-ol (1.38 g, 1.6 mL, 16.44 mmol, 1.8 equiv.) and HMPA (1 mL) in dry THF (20 mL) was added *n*BuLi (3 M in hexane, 12.17 mL, 36.52 mmol, 4.0 equiv.) at –60 °C under an atmosphere of nitrogen. The resulting mixture was stirred at –20 °C for 2 h. To the stirred mixture at –60 °C was added a solution of **10** (1.5 g, 9.13 mmol) in dry THF (5 mL). The reaction mixture was warmed to room temperature and stirred for 12 h. It was then quenched with a saturated solution of NH_4Cl (10 mL), and the solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 3:2) to provide **12** (1.95 g, 86%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3396, 3011, 2984, 2934, 2874, 1660, 1455, 1378, 1218, 1168, 1075, 1027, 952, 760, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.28 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.51 (s, 6 H, 2 CH_3), 3.2 (br. s, 2 H, 2,5-OH), 3.62–3.68 (m, 1 H, 6-H), 4.46 (d, *J* = 3.7 Hz, 1 H, 5-H), 4.57 (d, *J* = 12.5 Hz, 1 H, OCH_2Ph), 4.66 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 7.30–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 14.7, 31.1 (2 C), 64.9, 71.1, 77.9, 79.8, 90.7, 90.9, 127.7 (2 C), 127.8, 128.4 (2 C), 137.9 ppm. HRMS (ESI+): calcd. for [$C_{15}H_{20}O_3$ + H] 249.1491; found 249.1496.

(3*R*/*S*,4*R*)-4-Benzyloxypent-1-yn-3-ol (13): To a solution of **12** (1.86 g, 7.49 mmol) in dry toluene (40 mL) at room temperature was added K_2CO_3 (1.06 g, 7.86 mmol, 1.05 equiv.) and 18-crown-6 (0.58 g, 2.24 mmol, 0.3 equiv.), and the solution was heated at reflux for 72 h under an atmosphere of nitrogen. It was then cooled to room temperature and quenched with water (10 mL). The solution was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give **13** (1.125 g, 79%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3419, 3302, 3064, 3031, 2981, 2933, 2874, 2118, 1606, 1455, 1378, 1217, 1138, 1091, 1071, 1028, 993, 754, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.32 (d, *J* = 6.1 Hz, 3 H, CH_3), 2.50 (t, *J* = 1.5 Hz, 1 H, 1-H), 2.81 (br. s, 1 H, 3-OH), 3.65–3.75 (m, 1 H, 4-H), 4.41–4.44 (m, 1 H, 3-H), 4.58 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.69 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 7.28–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 14.6, 64.9, 71.0, 74.0, 76.7, 81.7, 127.7 (2 C), 127.8, 128.4 (2 C), 137.9 ppm. HRMS (ESI+): calcd. for [$C_{12}H_{14}O_2$ + H] 191.1072; found 191.1079.

(4*R*)-4-Benzyloxypent-1-yn-3-one (14): To a solution of **13** (1.12 g, 5.9 mmol) in EtOAc (20 mL) was added IBX (1.97 g, 7.06 mmol, 1.2 equiv.), and the mixture was heated at reflux for 12 h. It was then filtered through a pad of silica gel and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to provide **14** (0.81 g, 73%) as a colorless oil. $[\alpha]_D^{25}$ = +40.6 (*c* = 0.7, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3297, 3020, 2929, 2864, 2098, 1686, 1517, 1455, 1372, 1216, 1074, 1021, 929, 758, 699, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 7.0 Hz, 3 H, CH_3), 3.41 (s, 1 H, 1-H), 4.09 (q, *J* = 7.0 Hz, 1 H, 4-H), 4.49 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.75 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 7.32–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 72.1, 79.6, 80.6, 81.9, 127.9 (2 C), 128.0, 128.5 (2 C), 137.2, 189.0 ppm. HRMS (ESI+): calcd. for [$C_{12}H_{12}O_2$ + Na] 211.0734; found 211.0729.

(2*R*)-2-(1-Benzyloxyethyl)-2-ethynyl-1,3-dioxolane (8): To a solution of **14** (0.8 g, 4.25 mmol) in benzene (20 mL) was added ethylene glycol (2.62 g, 42.25 mmol, 10 equiv.) and *p*-toluenesulfonic acid (100 mg), and the reaction mixture was heated at reflux for 30 h. After cooling to room temperature, the mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL). The solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to provide **8** (0.74 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ = +17.6 (*c* = 1.12, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3280, 3046, 2984, 2894, 2111, 1454, 1374, 1206, 1111, 946, 751, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.59 (s, 1 H, ≡C–H), 3.69 (q, *J* = 6.4 Hz, 1 H, CHOBn), 4.01–4.19 (m, 4 H, –OCH_2CH_2O–), 4.72 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 4.85 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 7.28–7.42 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 65.0, 65.3, 72.7, 73.3, 77.6, 80.1, 104.6, 127.4, 127.7 (2 C), 128.2 (2 C), 138.5 ppm. HRMS (ESI+): calcd. for [$C_{14}H_{16}O_3$ + Na] 255.0996; found 255.0992.

(2*R*)-2-[2-(1-Benzyloxyethyl)-1,3-dioxolan-2-yl]-4,5-dimethoxynaphthalen-1-ol (15): To a solution of freshly prepared chromium carbene complex **7** (0.74 g, 2.16 mmol) in dry and degassed THF (15 mL) was added alkyne **8** (0.60 g, 2.58 mmol, 1.2 equiv.), and the reaction mixture was stirred at 45 °C for 14 h under an atmosphere of nitrogen. It was then cooled to room temperature, exposed to air, and stirred further for 30 min. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 7:3) to give **15** (0.46 g, 52%) as a colorless viscous oil. $[\alpha]_D^{25}$ = +7.9 (*c* = 0.84, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3367, 3063, 2981, 2939, 2893, 1633, 1598, 1582, 1493, 1464, 1388, 1286, 1248, 1216, 1118, 1027, 951, 930, 754, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.1 Hz, 3 H, CH_3), 3.83 (q, *J* = 6.1 Hz, 1 H, CHOBn), 3.90 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 3.99–4.12 (m, 4 H, –OCH_2CH_2O–), 4.67 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.71 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 6.88 (s, 1 H, 3-ArH), 6.92 (d, *J* = 8.2 Hz, 1 H, 6-ArH), 6.98 (t, *J* = 7.3 Hz, 1 H, 7-ArH), 7.15–7.32 (m, 5 H, Ph), 7.68 (d, *J* = 7.3 Hz, 1 H, 8-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 55.2, 58.9, 65.1, 65.2, 72.5, 78.4, 100.5, 108.3, 110.7, 112.5, 119.6, 120.5, 124.4, 126.8, 127.2, 127.7 (2 C), 128.0 (3 C), 139.0, 139.7, 154.9 ppm. HRMS (ESI+): calcd. for [$C_{24}H_{26}O_6$ + H] 411.1808; found 411.1812.

(2*R*)-2-(1-Benzyloxyethyl)-2-(1,4,5-trimethoxynaphthalen-2-yl)-1,3-dioxolane (16): To a solution of **15** (80 mg, 0.19 mmol) in dry THF (5 mL) at 0 °C was added NaH (13.7 mg, 0.57 mmol, 3.0 equiv.), and the reaction mixture was stirred at room temperature for 30 min. It was then cooled to 0 °C and MeI (0.042 mL, 0.67 mmol, 3.5 equiv.) was added. The reaction mixture was stirred for 6 h and then quenched with water (5 mL). The solution was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to provide **16** (75 mg, 91%) as a pale-yellow oil. $[\alpha]_D^{25}$ = –6.6 (*c* = 0.64, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3012, 2937, 2842, 1595, 1508, 1455, 1380, 1339, 1263, 1216, 1127, 1079, 1021, 1002, 954, 756, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.91 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.17–4.21 (m, 4 H, –OCH_2CH_2O–), 4.44 (q, *J* = 6.4 Hz, 1 H, CHOBn), 4.51 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 4.56 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 6.87 (d, *J* = 7.3 Hz, 1 H, 6-ArH), 7.07 (s, 1 H, 3-ArH), 7.12–7.17 (m, 5 H, Ph), 7.40 (t, *J* = 8.3 Hz, 1 H, 7-ArH), 7.65 (dd, *J* = 8.5, 0.6 Hz, 1 H, 8-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 56.5, 56.9, 63.0, 65.3, 65.7, 72.8, 77.5, 105.7, 106.6, 110.8, 115.2, 126.4, 127.2, 127.7 (2 C), 127.9, 128.0 (2 C), 130.3, 132.2, 138.9, 147.3, 152.9, 157.4 ppm. HRMS (ESI+): calcd. for [$C_{25}H_{28}O_6$ + Na] 447.1783; found 447.1788.

(*R*)-1-[2-(1,4,5-Trimethoxynaphthalen-2-yl)-1,3-dioxolan-2-yl]-ethanol (6): To a solution of **16** (0.68 g, 1.6 mmol) in anhydrous MeOH (20 mL) was added 10% Pd/C (0.161 g), and the mixture was stirred for 6 h under an atmosphere of H_2 (1 atm). It was then filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 3:2) to provide **6** (0.39 g, 72%) as a white solid. M.p. 141–142 °C. $[\alpha]_D^{25}$ = –13.9 (*c* = 0.50, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3496, 2956, 2937, 2890, 2841, 1595, 1508, 1462, 1380, 1339, 1264, 1208, 1128, 1079, 1003, 952, 855, 814, 757, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.94 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.03–4.21 (m, 4 H, –OCH_2CH_2O–), 4.48 (q, *J* = 6.1 Hz, 1 H, CH–OH), 6.88 (d, *J* = 7.9 Hz, 1 H, 6-ArH), 6.98 (s, 1 H, 3-ArH), 7.42 (t, *J* = 7.9 Hz, 1 H, 7-ArH), 7.67 (d, *J* = 8.2 Hz, 1 H, 8-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 56.4, 56.8, 63.1, 65.2, 65.4, 70.4, 105.3, 106.7, 111.0, 115.1, 118.7, 126.6, 128.4, 132.1, 147.3, 153.1, 157.3 ppm. HRMS (ESI+): calcd. for [$C_{18}H_{22}O_6$ + H] 335.1494; found 335.1498.

(1*R*/*S*,2*R*)-2-Benzyloxy-1-(1,4,5-trimethoxynaphthalen-2-yl)-propan-1-ol (17): To a solution of **9** (2.8 g, 9.42 mmol) in dry THF (30 mL) at –78 °C under an atmosphere of nitrogen was added *n*BuLi (3 M in hexane, 3.8 mL, 11.3 mmol, 1.2 equiv.) followed by aldehyde **10** (1.85 g, 11.27 mmol, 1.2 equiv.). The reaction mixture was stirred at –78 °C for 2 h and then at room temperature for 12 h. It was then quenched with a saturated solution of NH_4Cl (10 mL), and the solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 7:3) to provide **17** (3.08 g, 89%) as a yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3479, 3065, 3009, 2932, 2848, 1600, 1585, 1463, 1455, 1382, 1348, 1264, 1218, 1126, 1077, 1028, 1006, 810, 757, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.07 (d, *J* = 6.1 Hz, 3 H, CH_3), 3.81 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.59 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 4.65 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 4.67 (q, *J* = 6.2 Hz, 1 H, CHOBn), 5.36 (d, *J* = 3.9 Hz, 1 H, CH–OH), 6.86 (d, *J* = 7.9 Hz, 1 H, 6-ArH), 7.03 (s, 1 H, 3-ArH), 7.27–7.35 (m, 5 H, Ph), 7.40 (t, *J* = 7.9 Hz, 1 H, 7-ArH), 7.61 (d, *J* = 7.6 Hz, 1 H, 8-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 14.0, 56.6, 56.9, 62.0, 70.0, 71.1, 77.7, 104.9, 106.6, 114.8, 126.8, 127.9 (2 C), 128.0, 128.6 (2 C), 128.7, 129.4, 131.1, 138.7, 146.3, 153.7, 157.6 ppm. HRMS (ESI+): calcd. for [$C_{23}H_{26}O_5$ + H] 383.1859; found 383.1854.

(2*R*)-2-Benzyloxy-1-(1,4,5-trimethoxynaphthalen-2-yl)propan-1-one (18): To a solution of **17** (1.04 g, 2.82 mmol) in EtOAc (20 mL) was added IBX (0.95 g, 3.39 mmol, 1.2 equiv.), and the solution was heated at reflux for 12 h. It was then filtered through a pad of silica gel and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give **18** (0.941 g, 91%) as a yellow oil. $[\alpha]_D^{25}$ = +6.9 (*c* = 0.28, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3006, 2937, 2842, 1689, 1594, 1508, 1454, 1378, 1208, 1128, 1080, 1017, 999, 902, 830, 756, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 7.0 Hz, 3 H, CH_3), 3.76 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.60 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.81 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 5.11 (q, *J* = 7.0 Hz, 1 H, CHOBn), 6.95 (s, 1 H, 3-ArH), 6.97 (d, *J* = 7.6 Hz, 1 H, 7-ArH), 7.26–7.40 (m, 5 H, Ph), 7.47 (t, *J* = 8.2 Hz, 1 H, 7-ArH), 7.72 (d, *J* = 8.2 Hz, 1 H, 8-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 56.5, 56.6, 63.7, 71.6, 79.2, 104.1, 108.7, 115.5, 120.3, 126.8, 127.4, 127.6, 127.9 (2 C), 128.3 (2 C), 131.3, 138.0, 149.5, 153.8, 157.4, 203.5 ppm. HRMS (ESI+): calcd. for [$C_{23}H_{24}O_5$ + Na] 403.1521; found 403.1519.

(2*R*)-2-(1-Benzyloxyethyl)-2-(1,4,5-trimethoxynaphthalen-2-yl)-1,3-dioxolane (16) from 18: To a solution of **18** (0.76 g, 2.07 mmol) in benzene (30 mL) was added ethylene glycol (1.28 g, 20.7 mmol, 10 equiv.) and *p*-toluenesulfonic acid (150 mg). The reaction mixture was heated at reflux for 30 h. After cooling to room temperature, it was quenched with a saturated solution of $NaHCO_3$ (15 mL), and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to provide **16** (0.774 g, 88%) as a pale-yellow oil. $[\alpha]_D^{25}$ = –6.8 (*c* = 0.64, $CHCl_3$). Spectral data were the same as those of the product prepared from **15**.

(1*R*,3*R*)-3,4-Dihydro-5,9,10-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (19) and (1*S*,3*R*)-3,4-Dihydro-5,9,10-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one (20): To a solution of **6** (0.12 g, 0.36 mmol) in dry ether/THF (4:1, 5 mL) was added acetaldehyde dimethylacetal (0.08 mL, 0.74 mmol, 2.0 equiv.) and $BF_3{\cdot}Et_2O$ (0.14 mL, 1.09 mmol, 3.0 equiv.) under an atmosphere of nitrogen. The resulting solution was stirred at room temperature for 48 h. It was then quenched with a saturated solution of $NaHCO_3$ (5 mL), and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 9:1 to 7:3) to afford **19** (54 mg, 48%) and **20** (35 mg, 31%) as yellow oils. Data for **19**: $[\alpha]_D^{20}$ = –121.7 (*c* = 0.13, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2977, 2933, 2842, 1694, 1610, 1583, 1569, 1450, 1434, 1364, 1335, 1265, 1178, 1100, 1065, 1008, 975, 846, 769, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.7 Hz, 3 H, 1-Me), 1.67 (d, *J* = 6.7 Hz, 3 H, 3-Me), 3.85 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.59 (q, *J* = 7.0 Hz, 1 H, 1-CH), 5.50 (q, *J* = 7.0 Hz, 1 H, 3-CH), 7.03 (d, *J* = 7.6 Hz, 1 H, 8-ArH), 7.45 (t, *J* = 7.9 Hz, 1 H, 7-ArH), 7.96 (d, *J* = 8.5 Hz, 1 H, 6-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 19.5, 56.2, 62.5, 62.9, 67.6, 71.7, 109.0, 117.0, 117.7, 123.4, 126.6, 131.4, 133.7, 146.2, 154.7, 155.6, 196.8 ppm. HRMS (ESI+): calcd. for [$C_{18}H_{20}O_5$ + H] 317.1389; found 317.1392. Data for **20**: $[\alpha]_D^{25}$ = –55.7 (*c* = 0.58, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2976, 2934, 2842, 1704, 1610, 1575, 1456, 1434, 1383, 1366, 1332, 1264, 1145, 1113, 1083, 1064, 1010, 976, 759, 709, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.4 Hz, 3 H, 1-Me), 1.76 (d, *J* = 6.4 Hz, 3 H, 3-Me), 3.83 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.15 (q, *J* = 6.4 Hz, 1 H, 1-CH), 5.31 (q, *J* = 6.4 Hz, 1 H, 3-CH), 7.03 (d, *J* = 7.6 Hz, 1 H, 8-ArH), 7.46 (t, *J* = 8.2 Hz, 1 H, 7-ArH), 7.97 (d, *J* = 8.5 Hz, 1 H, 6-ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 22.9, 56.3, 61.7, 63.9, 71.8, 75.7, 109.0, 116.9, 119.6, 123.7, 126.7, 131.3, 132.8, 148.2, 154.0, 155.8, 193.2 ppm. HRMS (ESI+): calcd. for [$C_{18}H_{20}O_5$ + H] 317.1389; found 317.1394.

(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)]: To a solution of **19** (46 mg, 0.145 mmol) in acetonitrile/water (1:1, 6 mL) was added CAN (0.16 g, 0.29 mmol, 2 equiv.). The resulting solution was stirred at room temperature for 30 min. It was then quenched with water (5 mL), and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give the crude quinone (50 mg). This was used for the next step without further purification. To a solution of the quinone (50 mg) in THF/water (4:3, 7 mL) was added $Na_2S_2O_4$ (78 mg, 0.45 mmol) followed by a catalytic amount of TBAI (10 mg). The resulting solution was stirred at room temperature for 1 h. It was then quenched with water (5 mL), and the solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1 to 7:3) to provide **1** (36 mg, 86%) as a yellow solid. M.p. 130–132 °C. $[\alpha]_D^{20}$ = –26.7 (*c* = 0.10, $CHCl_3$) {ref.[1] $[\alpha]_D^{20}$ = –26.0 (*c* = 1.94, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3419, 2926, 2854, 1731, 1634, 1584, 1456, 1387, 1287, 1233, 1180, 1116, 1050, 1021, 796, 759, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 6.4 Hz, 3 H, 1-Me), 1.63 (d, *J* = 6.7 Hz, 3 H, 3-Me), 4.07 (s, 3 H, OMe), 4.69 (q, *J* = 6.4 Hz, 1 H, 1-CH), 5.48 (q, *J* = 6.7 Hz, 1 H, 3-CH), 7.01 (d, *J* = 7.9 Hz, 1 H, 8-ArH), 7.38 (t, *J* = 8.2 Hz, 1 H, 7-ArH), 8.04 (d, *J* = 8.5 Hz, 1 H, 6-ArH), 8.98 (s, 1 H, OH), 12.82 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 17.4, 56.4, 67.4, 69.5, 107.8, 109.1, 118.1, 119.6, 120.9, 125.4, 126.0, 139.4, 153.4, 155.7, 202.9 ppm. HRMS (ESI+): calcd. for [$C_{16}H_{16}O_5$ + H] 289.1076; found 289.1081.

(1*S*,3*R*)-3,4-Dihydro-5,10-dihydroxy-9-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-4-one [(–)-1-*epi*-Hongconin (5)]: The title compound was prepared from **20** (31 mg, 0.098 mmol) by following a procedure similar to that described for **1** (obtained from **19**) to give **5** (23 mg, 82%) as a sticky yellow solid. $[\alpha]_D^{20}$ = –204.6 (*c* = 0.13, $CHCl_3$) {ref.[6a] $[\alpha]_D^{20}$ = +207.0 (*c* = 1.94, $CHCl_3$) for the enantiomer}. IR ($CHCl_3$): $\tilde{\nu}$ = 3411, 2927, 2855, 1735, 1650, 1609, 1584, 1458, 1388, 1252, 1234, 1052, 1020, 801, 759, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.7 Hz, 3 H, 1-Me), 1.79 (d, *J* = 6.4 Hz, 3 H, 3-Me), 4.09 (s, 3 H, OMe), 4.28 (q, *J* = 6.4 Hz, 1 H, 1-CH), 5.18 (q, *J* = 6.4 Hz, 1 H, 3-CH), 7.02 (d, *J* = 7.6 Hz, 1 H, 8-ArH), 7.40 (t, *J* = 8.2 Hz, 1 H, 7-ArH), 8.05 (d, *J* = 8.2 Hz, 1 H, 6-ArH), 9.22 (s, 1 H, OH), 12.71 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 21.3, 56.4, 71.8, 74.9, 109.1, 109.4, 118.0, 119.7, 120.3, 125.5, 126.0, 141.0, 153.7, 155.7, 201.7 ppm. HRMS (ESI+): calcd. for [$C_{16}H_{16}O_5$ + H] 289.1076; found 289.1079.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for selected compounds.

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