# Total Syntheses of Pyranoquinoline Alkaloids: Simulenoline, Huajiaosimuline, and (±)-7-Demethoxyzanthodioline

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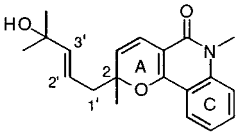
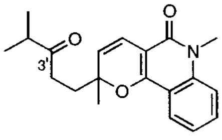
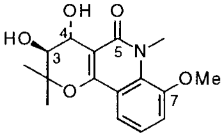
Pyranoquinoline alkaloids simulenoline **1**[1,2] and huajiaosimuline **2**[3] were isolated from root barks of *Zanthoxylum simulans*, a shrub found in Taiwan and mainland China. While simulenoline **1** was the most recently isolated of the two alkaloids, a third pyranoquinoline alkaloid zanthodioline **3** from the same species was just recently disclosed in the literature.[1] These novel monoterpenoid pyranoquinolines are potent inhibitors of platelet aggregation. For example, at a concentration of 100 $\mu$g/mL, simulenoline **1** demonstrates a nearly complete suppression of platelet aggregation induced in vitro by collagen, arachidonic acid, and PAF in general.[1] While simulenoline **1** and zanthodioline **3** are not cytotoxic, huajiaosimuline **2** is toxic toward several human cultured cell lines, especially the estrogen receptor-positive breast cancer cells, ZR-75-1.[3] Structurally, these alkaloids contain three fused six-membered rings with a unique terpenoid side chain at C-2. The BC-ring is essentially the quinolone nucleus, and the A-ring is a 2*H*-pyran.



**1**: simulenoline



**2**: huajiaosimuline



**3**: zanthodioline

These natural products became attractive to us because we have been developing a formal [3 + 3] cycloaddition reaction[4−6] for constructing complex heterocycles from $\alpha,\beta$-unsaturated iminiums and 1,3-dicarbonyl equivalents.[7−10] Although quite a few synthetic approaches to pyranoquinoline alkaloids have been reported,[10d,g,11,12] *there appear to be no general methods for preparations of those pyranoquinoline alkaloids with substitutions on the pyranyl ring.* Our methodology offers a solution to this limitation and provides a direct and convenient access to the 2*H*-pyranyl A-ring. We report here the first total syntheses of simulenoline, huajiaosimuline, and (±)-7-demethoxyzanthodioline, thereby demonstrating the first synthetic applications of this formal [3 + 3] cycloaddition methodology in natural product synthesis.

As shown in Figure 1, we envisioned that the 2*H*-pyranyl A-ring in these alkaloids (a general structure is shown as **4**) may be obtained efficiently via the key formal [3 + 3] cycloaddition reaction using the $\alpha,\beta$-unsaturated iminium **5** and 4-hydroxy-2-quinolone **6** as the 1,3-dicarbonyl equivalent. This reaction proceeds through a tandem process[13] consisting of a Knoevenagel condensation followed by a 6$\pi$-electron electrocyclic ring-closure of the 1-oxatriene intermediate[14] leading to the 2*H*-pyranyl A-ring. Our work in this area specifically using $\alpha,\beta$-unsaturated iminiums[7] has provided a practical

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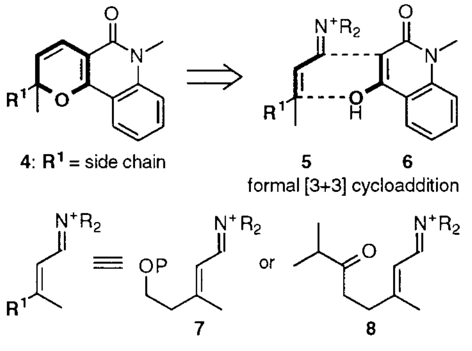
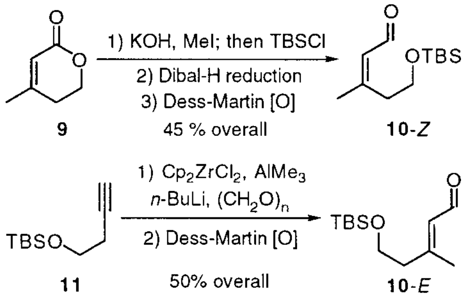


**Figure 1.**

**Scheme 1**

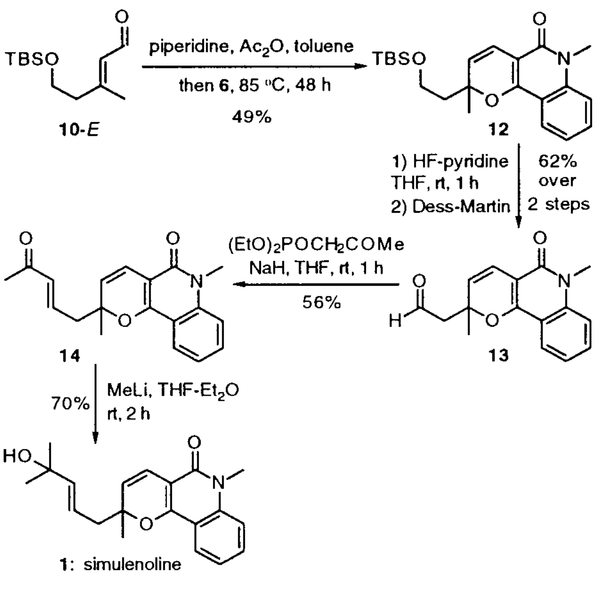


solution to the regiochemical problems suffered in previous studies.[10]

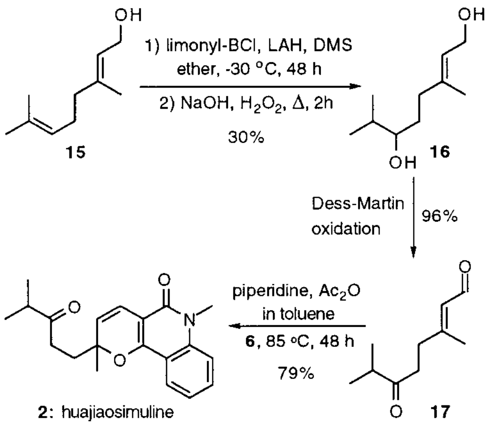
We would like to demonstrate three features through this synthetic study. First, for synthesis of simulenoline **1**, the [3 + 3] cycloaddition will be carried out using the $\alpha,\beta$-unsaturated iminium **7** leading to the 2*H*-pyranyl A-ring. The appropriate terpenoid side chain may be assembled subsequently using various synthetic methods, thereby demonstrating the tolerance of the pyranyl formal cycloadduct under various reaction conditions. Second, for synthesis of huajiaosimuline **2**, the $\alpha,\beta$-unsaturated iminium **8**, which already contains the suitable terpenoid side chain, will be prepared and used in the key cycloaddition reaction, thereby leading to the most convergent approach. Finally, we intend to prepare (±)-7-demethoxyzanthodioline to feature the ability to functionalize the endocyclic olefin in the 2*H*-pyranyl A-ring and to unambiguously confirm the structural assignment of **3** with regard to the relative configuration at C3 and C4.[1–3]

The corresponding $\alpha,\beta$-unsaturated aldehyde **10**[15] required for preparing the iminium **7** may be prepared in two different ways. While **10**-*Z* was synthesized from the lactone **9**[16] in three steps with an overall yield of 45%, **10**-*E* was prepared from the homopropargyl ether **11** in two steps in 50% overall yield (Scheme 1). Although the preparation of **10**-*E* was the more efficient one, both **10**-*E* and **10**-*Z* would be useful for studying the effect of the geometric configurations of $\alpha,\beta$-unsaturated iminiums (*E* versus *Z*) on the rate of formal [3 + 3] cycloadditions. However, the isomerization of the *Z*-iminium to the *E*-iminium occurred readily under the current reaction conditions employed for the formal [3 + 3] cycloaddition reaction.

**Scheme 2**



**Scheme 3**



With the aldehyde **10**-*E* in hand, the appropriate iminium was generated using piperidine and $Ac_2O$, and a subsequent formal [3 + 3] cycloaddition reaction with 4-hydroxy-2-quinolone **6** provided the desired pyran **12** in 49% yield (Scheme 2). A number of other [3 + 3] cycloaddition reactions using aldehyde **10**-*E* or **10**-*Z* also seem to consistently provide the maximum yield at about 50% yield. Removal of the TBS group could only be accomplished by using HF-pyridine in THF,[17] and Dess–Martin oxidation of the intermediate alcohol gave the aldehyde **13** in 62% overall yield. Modified Wittig olefination using $(EtO)_2POCH_2COMe$ and NaH afforded the enone **14** in 56% yield with a trans/cis ratio ≥95:5, and the addition of excess MeLi[18] to the enone **14** provided simulenoline **1** in 70% yield.[19]

For total synthesis of huajiaosimuline **2**, the ketoenal **17** was first prepared for the key [3 + 3] formal cycloaddition reaction. As shown in Scheme 3, a facile entry to **17** would involve a regio- and chemoselective hydroboration of geraniol **15** using limonyl-BH-$SMe_2$.[20,21] By

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[15] All new compounds are characterized by $^{1}$H NMR, $^{13}$C NMR, FTIR, and mass spectroscopy.

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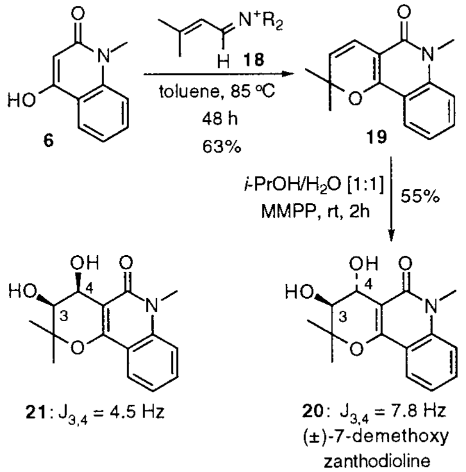
[17] Addition of TBAF or using other basic conditions led to only decomposition of the starting material **12**.

[18] A 1.0 equivalent sample of MeLi led to low conversions presumably due to enolization of the enone **14**. Thus, excess (2.5 equiv) of MeLi was used to drive the reaction to completion.

[19] We were not able to obtain any authentic samples of these natural products, but the synthetic samples matched completely in $^{1}$H NMR and/or $^{13}$C NMR with those reported in refs 1 and 3.

**Scheme 4**



modifying the literature procedure for preparation as well as utilization of limonyl-BH-SMe$_2$,[22] we were able to obtain the desired diol **16** in 30% yield from geraniol **15**. Our yield is slightly lower than the best yield reported in the literature.[21] In addition to recovered starting material (20−30%), undesired diol and triol resulting from hydroboration at the wrong olefin or both olefins were also isolated in ≤10% yield. A subsequent Dess−Martin oxidation of **16** led to the ketoenal **17** in 96% yield. Under the standard conditions, [3 + 3] cycloaddition reaction of **17** with **6** afforded huajiaosimuline **2** in 79% yield,[19] and the keto group survives the reaction condition. Although this sequence suffers from the low yielding hydroboration step, it is overall an extremely short and concise synthetic pathway to a natural product that possesses significant medicinal properties.

Finally, the total synthesis of (±)-7-demethoxyzanthodioline could be carried out via the formal cycloaddition using the 2-quinolone **6** and α,β-unsaturated iminium **18**. The formal [3 + 3] cycloaddition led to the tricycle **19** in 63% yield under the standard conditions. Compound **19** is itself a natural product, *N*-methylflindersine, that was isolated from the same root bark.[2,11,12] Dihydroxylation of the endocyclic olefin in the pyranyl ring of **19** using MMPP (magnesium monoperoxyphthalate) in *i*-PrOH/H$_2$O (1:1) at room temperature led to the formation (±)-7-demethoxyzanthodioline **20** in 55% yield with a trans/cis isomeric ratio 9:1, and the *J* value for H3−H4 vicinal coupling in the trans isomer is 7.8 Hz while it is 4.5 Hz for the cis isomer **21** (Scheme 4). The cis isomer **21** was unambiguously assigned by a direct preparation in 59% yield from **19** using OsO$_4$, K$_3$Fe[CN]$_6$, and K$_2$CO$_3$ in *t*-BuOH/H$_2$O (1:1) at room temperature [24 h]. By comparing with the reported *J* value (7.8 Hz), this synthesis confirms the tentatively assigned trans configuration at C3 and C4 for zanthodioline **3**.[1]

We have described here the first total syntheses of novel pyranoquinoline alkaloids simulenoline, huajiaosimuline, and (±)-7-demethoxyzanthodioline. The key feature of these concise total syntheses is the formal [3 + 3] cycloadditon reaction using α,β-unsaturated iminiums and 4-hydroxy-2-quinolones. These applications demonstrate various degrees of convergency and versatility of this formal cycloaddition strategy in natural product synthesis and offer a direct and convenient access to pyranoquinoline alkaloids with various substitutions on the pyranyl ring.

## Experimental Section

All reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. The thin-layer chromatography (TLC) analysis was done using EM Science silica gel-60 plates (0.25 mm in thickness) with F254 as the fluorescence indicator. The eluted plates were developed under UV detector and/or stained with either an aqueous solution of potassium permanganate (KMnO$_4$) or an alcoholic solution of phosphomolybdic acid (PMA). Chromatographic purifications were performed on EM Science silica gel (230−400 mesh) by the flash technique.[23]All reactions were carried out under either argon or nitrogen in oven-dried (150 °C) or flame-dried glassware.

**Pyran 12.** In a flame-dried 25 mL round-bottom flask was dissolved 546.0 mg (2.39 mmol) of aldehyde **10**-*E* (see the Supporting Information for the preparation) in 10 mL of toluene. The solution was cooled to 0 °C, and 204.0 mg (0.24 mL, 2.39 mmol) of piperidine was added. After the solution was stirred for 5 min, 204.0 mL (2.39 mmol) of acetic anhydride was added, and the resulting reaction mixture was stirred at 85 °C for 1 h.

To the iminium solution prepared above was added 279.0 mg (1.59 mmol) of 4-hydroxy-1-methyl-2-(1*H*)-quinolone. The flask was sealed with a rubber septum and Parafilm, and a hose clamp was used to secure the septum. After the reaction mixture was heated at 85 °C for 48 h, the flask was cooled to room temperature and the solvent removed under reduced pressure. Purification via silica gel column chromatography (gradient eluent: 0−20% ethyl acetate in hexane) yielded 280.0 mg (49% yield) of the pyran **12** as an orange oil: $R_f = 0.47$ (silica gel, 50% ethyl acetate/hexane); $^1$H NMR (300 MHz, CDCl$_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.51 (m, 3H), 2.08 (m, 2H), 3.71 (s, 3H), 3.83 (t, 2H, $J = 6.9$ Hz), 5.54 (d, 1H, $J = 10.2$ Hz), 6.79 (d, 1H, $J = 10.2$ Hz), 7.25 (t, 1H, $J = 7.5$ Hz), 7.33(d, 1H, $J = 7.8$ Hz), 7.57 (td, 1H, $J = 1.5, 7.5$ Hz), 7.97 (dd, 1H, $J = 1.5, 7.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ −5.7, 18.0, 25.8, 27.1, 29.2, 43.8, 58.7, 80.1, 105.2, 113.9, 115.5, 118.0, 121.6, 122.9, 125.3, 130.8, 139.0, 154.5, 160.8; IR (neat) cm$^{-1}$ 2953s, 2928s, 2856m, 1654s, 1609s, 1588m, 1570m; mass spectrum (EI) *m*/*e* (relative intensity) 328 (56) (M$^+$ − 29), 260 (28), 226 (100), 187 (34), 185 (25).

**Aldehyde 13 (The Intermediate Alcohol (Not Shown in the Text)).** To a solution of 95.0 mg (0.266 mmol) of pyranoquinolone **12** in 2 mL of THF was added ~0.5 mL of HF−pyridine. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with 1 mL of saturated NaHCO$_3$ solution, and an excess of solvent and reagents were removed under reduced pressure. The residue was dissolved in 25 mL of ethyl acetate and washed with an equal volume of saturated aqueous NaCl. The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel column (gradient eluent: 0−100% ethyl acetate in hexane) to provide 63.2 mg (88% yield) of the desired alcohol as a light yellow solid: mp 126−128 °C; $R_f$= 0.07 (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, CDCl$_3$) δ 1.52 (s, 3H), 2.13 (m, 2H), 3.69 (s, 3H), 3.90 (t, 2H, $J = 6.6$ Hz), 5.56 (d, 1H, $J = 9.9$ Hz), 6.82 (d, 1H, $J = 9.9$ Hz), 7.23 (t, 1H, $J = 7.5$), 7.33 (d, 1H, $J = 7.8$ Hz), 7.56 (td, 1H, $J = 1.5, 7.5$ Hz), 7.93 (dd, 1H, $J = 1.5, 7.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 27.1, 29.3, 43.7, 58.6, 105.6, 80.7, 114.1, 115.8, 118.5, 121.9, 122.9, 125.3, 131.0, 139.3, 155.0, 160.9; IR (KBr) cm$^{-1}$ 3418brs, 2974m, 2940m, 1650s, 1616s, 1582m, 1506m; mass spectrum (MALDI) *m*/*e* (relative intensity) 271 (15) M$^+$, 256 (11), 226 (100); *m*/*e* calcd for C$_{16}$H$_{17}$NO$_3$ 271.1208, found 271.1202.

To a solution of 53.8 mg (0.198 mmol) of the alcohol prepared above in 3 mL of CH$_2$Cl$_2$ was added 101.0 mg (0.238 mmol) of Dess−Martin periodinane reagent. After the solution was stirred

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(20) Jadhav, P. K.; Kulkarni, S. U. *Heterocycles* **1982**, *18*, 169.

(21) Julia, M.; Roy, P. *Tetrahedron* **1986**, *42*, 5003.

(22) We experienced difficulties in isolating and purifying limonyl-BCl-SMe$_2$ from the reaction of limonene with BH$_2$Cl-SMe$_2$,[20] and thus, limonyl-BH-SMe$_2$ was directly prepared from the crude limonyl-BCl-SMe$_2$ via LiAlH$_4$ reduction and used in situ. The ratio of limonyl-BH-SMe$_2$ to compound **15** was 1:1 instead 2:1 used in the literature.[21]

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

at room temperature for 30 min, 1 mL of 2-propanol was added and the reaction mixture was stirred for an additional 5 min before it was concentrated under reduced pressure. The crude residue was vacuum-filtered through silica gel on a medium porosity Buchner funnel, eluting with ethyl acetate. After removal of the solvent under reduced pressure, the crude residue was purified by silica gel column (gradient eluent: 0−25% ethyl acetate in hexane) to afford 37.3 mg (70% yield) of the aldehyde **13** as a red oil: $R_f = 0.19$ (50% ethyl acetate/hexane); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.65 (s, 3H), 2.86 (d, 2H, $J = 2.5$ H), 3.71 (s, 3H), 5.61 (d, 1H, $J = 10.0$), 6.87 (d, 1 H, $J = 10.0$ Hz), 7.24 (td, 1H, $J = 8.0$ Hz), 7.33 (d, 1H, $J = 8.0$ Hz), 7.56 (td, 1H, $J = 1.5$, 8.0 Hz), 7.90 (dd, 1H, $J = 1.5$, 8.5 Hz), 9.92 (t, 1H, $J = 2.5$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 27.1, 29.4, 53.8, 78.9, 105.8, 114.2, 115.4, 119.6, 122.0, 123.0, 123.9, 131.4, 139.5, 154.8, 160.7, 199.5; IR (neat) cm$^{-1}$ 2974m, 1719s, 1684m, 1648s, 1570m, 1540m; mass spectrum (MALDI) *m/e* (relative intensity) 269 (19) M$^+$, 248 (14), 227 (17), 226 (100); *m/e* calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1053.

**Enone 14.** To a suspension of 5.0 mg (0.127 mmol, 60% dispersion) of NaH in 2 mL of THF was added slowly via syringe a solution of 24.7 mg (0.0245 mL, 0.127 mmol) of diethyl-(2-oxopropyl)phosphonate in 1 mL of THF. After the mixture was stirred for 10 min, a solution of 34.3 mg (0.127 mmol) of aldehyde **13** in 1 mL of THF was added via cannula. The flask was stirred at room temperature for 1 h before it was concentrated under reduced pressure. The resulting residue was dissolved in 25 mL of ethyl acetate and washed with an equal volume of water. The aqueous layer was extracted two times with 25 mL portions of ether. The combined organics were washed with an equal volume of saturated aqueous NaCl and dried over $Na_2SO_4$. The solvent was evaporated, and the crude residue was purified by silica gel column (gradient eluent of 0−30% ethyl acetate in hexane) to give 21.9 mg (56% yield) of the enone **14** as a colorless oil: $R_f = 0.11$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.55 (s, 3H), 2.17 (s, 3H), 2.68 (ddd, 2H, $J = 1.2$, 1.5, 9.0 Hz), 3.70 (s, 3H), 5.51 (d, 1H, $J = 9.9$ Hz), 6.09 (dt, 1H, $J = 1.2$, 15.9 Hz), 6.83 (dt, 1H, $J = 1.2$, 15.9 Hz), 6.85 (d, 1H, $J = 9.9$ Hz), 7.23 (td, 1H, $J = 1.5$, 7.8 Hz), 7.32 (d, 1H, $J = 8.4$ Hz), 7.55 (td, 1H, $J = 1.5$, 7.5 Hz), 7.90 (dd, 1H, $J = 1.5$, 7.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.7, 27.1, 29.3, 44.0, 80.1, 105.9, 114.2, 115.6, 119.4, 121.9, 123.0, 124.4, 131.2, 134.5, 139.5, 141.0, 155.0, 160.8, 198.0; IR (neat) cm$^{-1}$ 2974w, 1697m, 1671s, 1648s, 1587m, 1569m, 1558m; mass spectrum (MALDI) *m/e* (relative intensity) 309 (1) M$^+$, 226 (100), 149 (35); *m/e* calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1360.

**Simulenoline 1.** To a solution of 27.0 mg (0.088 mmol) of the enone **14** in 2 mL of 50% THF/$Et_2O$ solution at −78 °C was added dropwise via syringe 0.060 mL of 1.4 M MeLi. After being warmed to room temperature, the reaction mixture was stirred for another 2 h before it was quenched with 0.01 mL of methanol. The reaction mixture was again cooled to −78 °C, and another 0.09 mL of 1.4 M MeLi were added. The reaction mixture was again stirred for 2 h at room temperature and quenched with 1 mL of methanol. The reaction mixture was diluted to 25 mL with ether and washed with 25 mL of saturated aqueous NaCl. The organic phase was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Purification via silica gel (gradient eluent: 0−40% ethyl acetate in hexane) yielded 20.0 mg (70% yield) of simulenoline **1** as a yellow oil. All spectra matched the reported values for the natural product: $R_f = 0.29$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (s, 3H), 1.19 (s, 3H), 1.52 (s, 3H), 2.47 (dd, $J = 1.2$, 5.1 Hz), 3.69 (m, 3H), 5.49 (d, 1H, $J = 10.2$ Hz), 5.71 (m, 2H), 6.80 (d, 1H, $J = 10.2$ Hz), 7.23 (td, 1H, $J = 1.2$, 8.1 Hz), 7.32 (d, 1H, $J = 8.4$ Hz), 7.55 (td, 1H, $J = 1.5$, 8.1 Hz), 7.95 (dd, 1H, $J = 1.5$, 8.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.7, 29.5, 29.6, 44.1, 70.6, 80.7, 105.9, 114.1, 115.8, 118.7, 120.3, 121.8, 123.1, 125.1, 131.0, 131.3, 139.3, 142.5, 155.0, 160.9; IR (neat) cm$^{-1}$ 3416m, 2970m, 2928m, 1646s, 1619s, 1584m; mass spectrum (MALDI) *m/e* (relative intensity) 326 (6) M$^+$, 272 (36), 226 (100), 188 (44); *m/e* calcd for $C_{20}H_{24}NO_3$ 326.1756, found 326.1768.

**Huajiaosimuline 2.** To a solution of 180.0 mg (1.07 mmol) of the ketoenal **17** (see the Supporting Information for the preparation) in 4 mL of toluene at 0 °C was added 91.0 mg (0.11 mL, 1.07 mmol) of piperidine. After the mixture was stirred at 0 °C for 5 min, 109.0 mg (0.10 mL, 1.07 mmol) of acetic anhydride was added. The reaction mixture was stirred at 85 °C for 1 h.

To this iminium solution was then added 125.0 mg (0.713 mmol) of 4-hydroxy-1-methyl-2-(1*H*)-quinolone. The flask was sealed with a rubber septum and Parafilm, and a hose clamp was used to secure the septum. The reaction mixture was heated at 85 °C for 48 h before it was cooled to room temperature. The excess solvent and reagents were removed under reduced pressure, and the crude residue was purified by silica gel column (gradient eluent: 0−20% ethyl acetate in hexane) to give 183.0 mg (79% yield) of huajiaosimuline **2** as a yellow oil: $R_f = 0.33$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.02 (d, 3H, $J = 6.9$ Hz), 1.05 (d, 3H, $J = 6.9$ Hz), 1.49 (s, 3H), 2.04 (m, 1H), 2.20 (m, 1H), 2.54 (m, 1H), 2.64 (m, 2H), 3.71 (s, 3H), 5.44 (d, 1H, $J = 9.9$ Hz), 6.83 (d, 1H, $J = 9.9$ Hz), 7.25 (t, 1H, $J = 7.5$ Hz), 7.34 (d, 1H, $J = 8.4$ Hz), 7.58 (td, 1H, $J = 1.5$, 7.5 Hz), 7.93 (dd, 1H, $J = 1.5$, 8.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.2, 18.3, 27.5, 29.3, 35.2, 35.3, 41.0, 81.1, 105.3, 114.1, 115.7, 119.2, 121.8, 123.1, 124.6, 131.0, 139.4, 155.2, 160.9, 214.0; IR (neat) cm$^{-1}$ 2969m, 2930m, 1711s, 1651s, 1587m, 1570m; mass spectrum (MALDI) *m/e* (relative intensity) 325 (9) M$^+$, 310 (7), 226 (100); *m/e* calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1679.

***N*-Methylflindersine 19.** To a solution of 126.0 mg (1.50 mmol) of 3-methyl-3-butenal in 4 mL of toluene at 0 °C was added 91.0 mg (0.148 mL, 1.50 mmol) of piperidine. After the mixture was stirred at 0 °C for 5 min, 128.0 mg (0.142 mL, 1.50 mmol) of acetic anhydride was added. The reaction mixturewas stirred at 85 °C for 1 h.

To this iminium solution was added 175.0 mg (1.00 mmol) of 4-hydroxy-1-methyl-2-(1*H*)-quinolone. The flask was sealed with a rubber septum and Parafilm, and a hose clamp was used to secure the septum. The reaction mixture was heated at 85 °C for 48 h before it was cooled to room temperature. The excess solvent and reagents were removed under reduced pressure, and the crude residue was purified by silica gel column (gradient eluent: 0−20% ethyl acetate in hexane) to afford 153.0 mg (63% yield) of *N*-methylflindersine **19** as an orange crystalline solid: mp 81−82 °C; $R_f = 0.38$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.46 (s, 6H), 3.63 (s, 3H), 5.48 (d, 1H, $J = 9.9$ Hz), 6.71 (d, 1H, $J = 9.9$ Hz), 7.15 (t, 1H, $J = 7.8$ Hz), 7.23 (d, 1H, $J = 8.7$ Hz), 7.47 (td, 1H, $J = 1.5$, 8.1 Hz), 7.89 (d, 1H, $J = 8.1$ Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.2, 29.2, 78.7, 105.8, 114.0, 116.0, 117.9, 121.7, 123.0, 126.3, 130.8, 139.2, 155.2, 160.9; IR (KBr) cm$^{-1}$ 2974m, 2927m, 1648s, 1586m; mass spectrum (MALDI) *m/e* (relative intensity) 241 (21) M$^+$, 227 (18), 226 (100); *m/e* calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1106.

**(±)-7-Demethoxyzanthodioline 20.** To a solution of 86.0 mg (0.356 mmol) of *N*-methylflindersine **19** in 2-propanol and water (2:1) was added 40.0 mg (0.8 mmol) of magnesium monoperoxyphthalate. After being stirred at room temperature for 2 h, the solution was diluted with 20 mL with ethyl acetate and washed once with saturated aqueous $NaHCO_3$. The aqueous phase was extracted two times with an equal volume of ethyl acetate. The combined organics were washed with saturated aqueous NaCl and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel column (gradient eluent: 0−20% ethyl acetate in hexane) to give 54.0 mg (55% yield) of **20** as a white solid. $^1$H NMR indicated a 9:1 trans/cis ratio for the diols: mp 193−194 °C; $R_f = 0.10$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.30 (s, 3H), 1.62 (s, 3H), 3.61 (s, 3H), 3.83 (brs, 1H, for −O*H*), 3.88 (d, 1H, $J = 7.5$ Hz), 4.76 (d, 1H, $J = 7.5$ Hz), 5.74 (brs, 1H, for −O*H*), 7.23 (td, 1H, $J = 0.9$, 7.8 Hz), 7.34 (d, 1H, $J = 8.4$ Hz), 7.58 (td, 1H, $J = 1.5$, 7.5 Hz), 7.99 (dd, 1H, $J = 1.5$, 7.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 19.2, 26.1, 26.1, 29.0, 29.0, 67.8, 74.9, 81.1, 105.9, 114.1, 115.9, 122.2, 123.9, 131.3, 139.1, 155.0, 163.6; IR (KBr) cm$^{-1}$ 2395brs, 2977m, 2937m, 1634s, 1614s, 1578s; mass spectrum (MALDI) *m/e* (relative intensity) 275 (1) M$^+$, 257 (4), 242 (3), 226 (9), 204 (100); *m/e* calcd for $C_{15}H_{17}NO_4$ 275.1158, found 275.1155.

***cis*-(±)-7-Demethoxyzanthodioline 21.** In a 50 mL round-bottom flask, 21.0 mg (0.085 mmol) of *N*-methylflindersine **19**, 84.0 mg (0.255 mmol) of $K_3Fe(CN)_6$, and 35.0 mg (0.255 mmol) of $K_2CO_3$ were dissolved in a 50% solution of *tert*-butyl alcohol and water. A catalytic amount of $OsO_4$ was added, and the reaction mixture was stirred for 24 h at room temperature. The reaction was terminated by diluting with 20 mL with ethyl acetate and washing once with saturated aqueous $NaHCO_3$. The aqueous phase was extracted two more times with an equal volume of ethyl acetate. The combined organics were washed with saturated aqueous NaCl and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel column (gradient eluent: 0−20% ethyl acetate in hexane) to provide 14.0 mg (59% yield) of *cis*-(±)-7-demethoxyzanthodioline **21** as a white solid. $^1$H NMR indicated exclusive *cis*-diol formation: mp 163−164 °C; $R_f = 0.22$ (50% ethyl acetate/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.65 (s, 3H), 3.25 (s, 1H, for −O*H*), 3.70 (s, 3H), 3.89 (d, 1H, $J = 4.5$ Hz), 5.02 (d, 1H, $J = 4.5$ Hz), 6.20 (s, 1H, for −O*H*), 7.27 (t, 1H, $J = 8.1$ Hz), 7.36 (d, 1H, $J = 8.1$ Hz), 7.60 (td, 1H, $J = 1.5, 8.1$ Hz), 8.05 (dd, 1H, $J = 1.5, 8.1$ Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 23.3, 24.3, 29.0, 63.4, 69.7, 80.1, 103.7, 114.1, 116.0, 122.2, 124.1, 131.3, 138.9, 155.6, 164.4; IR (KBr) cm$^{-1}$ 3485brm, 2978w, 2938w, 1634s, 1613s, 1579s, 1504m; mass spectrum (MALDI) *m*/*e* (relative intensity) 275 (1) M$^+$, 226 (2), 205 (15), 204 (100); *m*/*e* calcd for $C_{15}H_{17}NO_4$ 275.1158, found 275.1160.

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**Supporting Information Available:** $^1$H NMR spectra of all new compounds as well as supplemental procedures for preparations of compounds **10**-*E*/*Z* and **16**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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