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The Total Synthesis of Retrojusticidin B, Justicidin E, and Helioxanthin

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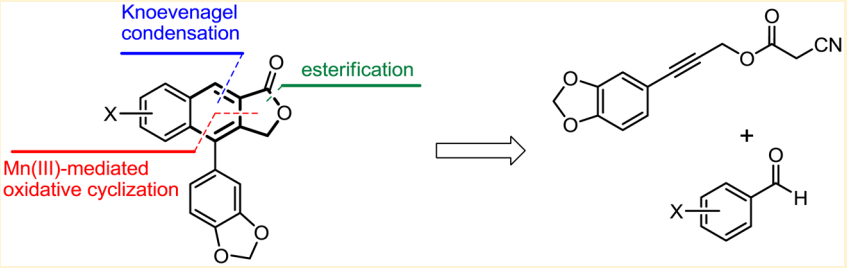
Supporting Information



ABSTRACT: Making use of a tandem free radical cyclization process mediated by $Mn(OAc)_3$ as a key operation, the total synthesis of retrojusticidin B, justicidin E, and helioxanthin has been concisely achieved in four or five steps in an overall yield of 45, 33 and 44%, respectively, from a common starting material **5**.

INTRODUCTION

Structurally, lignans are a large family of dimeric propyl phenols and could be broadly divided into eight classes in nature.[1] Among them, lignans containing an arylnaphthalene lactone core, as typified by retrojusticidin B, retrochinensin, justicidin E, and helioxanthin (Figure 1), were isolated from a variety of plant species from different parts,[2] including bark, root, leaf, fruit, and seed, and belong to a group noted for various biological activities, such as antitumor,[3] antiviral,[4] antibacterial,[5] cytotoxic,[6] HIV-1 reverse transcriptase,[7] and phosphodiesterase inhibitory activities.[8] Very recently, helioxanthin was evaluated in vitro to inhibit various steps involved in brain tumor metastasis and retarded the migration of both melanoma and brain endothelial cells, indicating that natural products might play a critical role in modern medicine as the horizon of biological knowledge expands.[9]

Thus, developing various synthetic methods to synthesize naturally occurring compounds in a more efficient manner becomes more and more important, particularly considering that the extinction of terrestrial and marine species is so rapid. As documented, arylnaphthalene lignans had been known to be synthesized by many different approaches, by which the desired arylnaphthalene lactone cores were mainly constructed via Diels–Alder reaction,[10] Au-catalyzed annulation,[11] Pd- or Ag-catalyzed [2 + 2 + 2] cocyclization,[12] dehydro-Diels–Alder reaction,[13] and benzannulation.[4b,14] In continuation of our studies on the synthesis of natural and unnatural lignans for new drug screening, we have developed several efficient cyclization processes to have facile access to linear [6,6,5] or [5,6,5] tricyclic systems (Scheme 1).[15−17]

These protocols are currently extended to the synthesis of various natural products containing either cyclopenta[*b*]-naphthalene or benzo[*b*]fluorene skeletons, such as stealthins and kinamycins.[18] In addition, it was discovered that, instead of using α-cyano ketones as substrates, the corresponding α-cyano esters, as typified by compound **2** in the model study in Scheme 2, could also undergo the same free radical cyclization cascade to afford synthetically useful arylnaphthalene lactone skeletons (e.g., **3** in Scheme 2).[15−17,19] In general, the α-cyano ketone system (Scheme 1) is more reactive than α-cyano esters for the cyclization process. Herein, we wish to report that making use of this newly developed methodology as a key operation, the synthesis of retrojusticidin B, justicidin E, and helioxanthin, respectively, has been experimentally realized. Compared to the above conventional methods in synthesizing the arylnaphthalene natural products,[10−14,4b] the advantage of the present free radical cascade method exhibits higher yields, shorter synthetic routes, and more economy. Results are presented as follows.

RESULTS AND DISCUSSION

According to Scheme 2, the project began with synthesizing phenylnaphthalene lactone **4** as a model study. Esterification of 3-phenyl-2-propyn-1-ol and cyanoacetic acid in the presence of EDCI and DMAP gave rise to α-cyano ester **1** in almost quantitative yield (97%). Compound **1** was subjected to a modified Knoevenagel condensation, by which Hantzsch ester was added in one pot to reduce the aldol condensation product formed *in situ*, to afford intermediate **2** in 81% yield. α-Cyano

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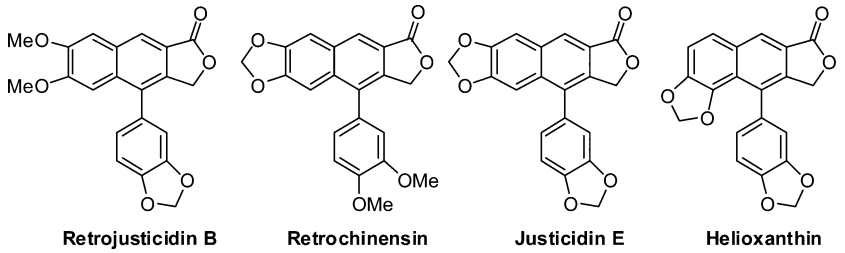
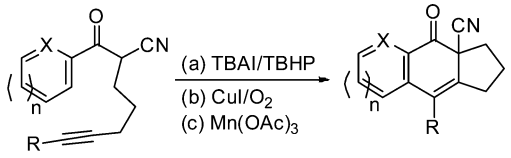


Figure 1. Natural arylnaphthalene lignans.

Scheme 1. Tandem Cyclization via a Free Radical Catalytic Process under Conditions (a), (b), or (c)



ester **2** was transformed into α-cyano lactone **3** in 75% yield under a tandem radical annulation process mediated by manganese(III) acetate.[17] Finally, compound **3** was reduced with SmI_2, followed by DDQ oxidation, to furnish the desired product **4** in 84% yield over two steps.[20] Alternatively, reductive decyanation could be fulfilled via lithium naphthalenide (LN),[21] but yields were much lower.

Encouraged by the success of the model study, the synthesis of retrojusticidin B was then attempted following the similar approach starting from alkynol **5**, commercially available or readily prepared according to the procedure reported in the literature.[11] As illustrated in Scheme 3, compound **5** was subjected to esterification to furnish cyano ester **6** in almost quantitative yield (98%), which, in turn, underwent Knoevenagel condensation in the presence of Hantzsch ester to afford the key intermediate **7** in 85% yield. Compound **7** was converted to a pair of separable regioisomers **8** (67%) and **9** (22%) with $Mn(OAc)_3$ in a sealed pressure vessel at 90 °C for 16 h. The desired retrojusticidin B was unexpectedly achieved in 80% yield when decyanation of isomer **8** was carried out with SmI_2 in the presence of triethylamine under air.[22] The mechanistic insight of the rapid aromatization under these reaction conditions is not fully understood, and worth further studies. By this synthetic strategy, retrojusticidin B was accomplished in four steps in an overall yield of 45%.

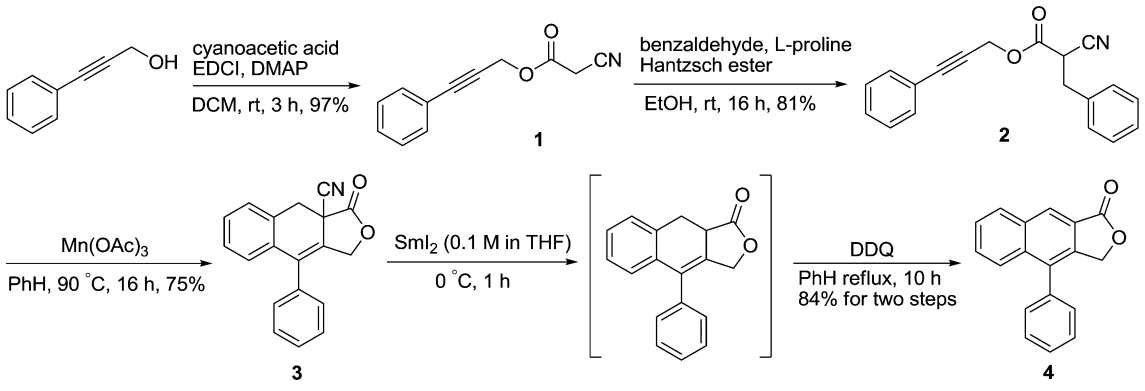
A similar approach was further extended to synthesize justicidin E and helioxanthin starting from the common intermediate α-cyano ester **6**. As depicted in Scheme 4, compound **6** was first coupled with piperonal to afford the key intermediate **10** in moderate yield (78%), which, in turn, underwent Mn(III)-mediated oxidative cyclization to give a pair of inseparable regioisomers **11** and **12** in a ratio of 3:1 in 71% yield. The mixture of compounds **11** and **12** was then reduced with SmI_2 and triethylamine under air to afford justicidin E and helioxanthin, respectively, in 59% and 20%, which were readily purified by HPLC. By this approach, justicidin E was achieved in four steps in an overall yield of 33% starting from compound **5**. Indeed, helioxanthin could be obtained exclusively via a more efficient synthetic design, as illustrated in Scheme 5.

Instead of piperonal, 6-bromopiperonal was employed to couple with compound **6** to furnish compound **13** (83%), which could undergo cyclization regioselectively. Bromo lactone **14** (68%) thus obtained was further reduced with SmI_2 (85%), followed by hydrogenolysis (92%), to achieve helioxanthin in five steps in an overall yield of 44% starting from compound **5**. The spectroscopic data of synthetic retrojusticidin B, justicidin E, and helioxanthin were found to be in good agreement with those reported in the literature.[10−14]

CONCLUSION

In conclusion, it is envisioned that the newly developed approach mediated by Mn(III) oxidative cyclization of α-cyano ester systems can be extended to the synthesis of many structurally diverse arylnaphthalene lactones concisely, which could be used to synthesize natural or unnatural lignans for new drug screening by appropriate structural modifications of the starting material. It is believed that the above tandem cyclization protocol is a valuable and significant addition to synthetic organic chemistry.

Scheme 2. Synthesis of Phenylnaphthalene Lactone 4



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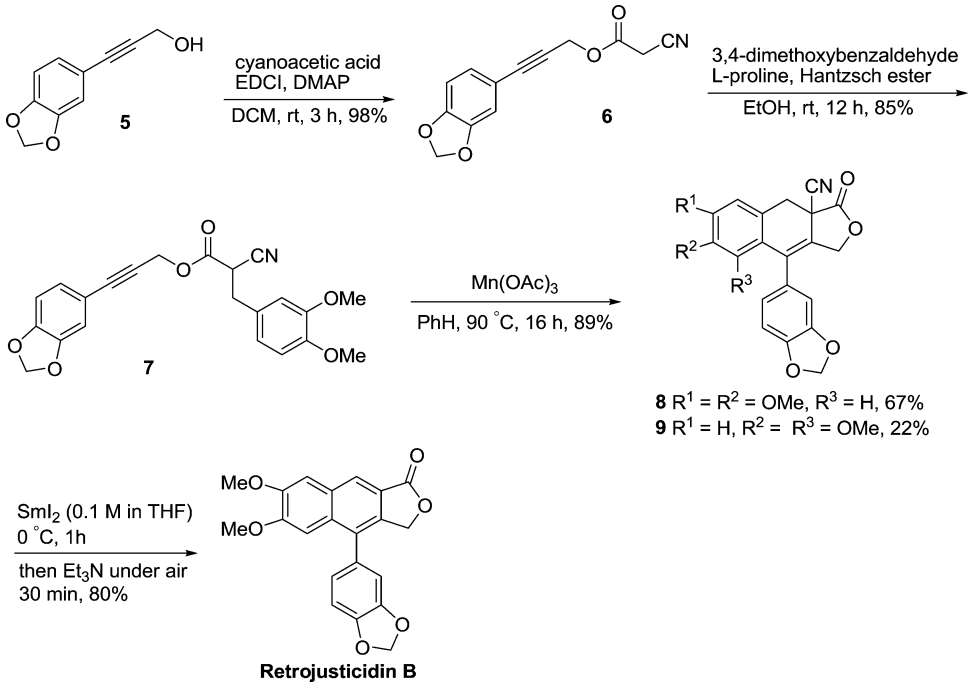
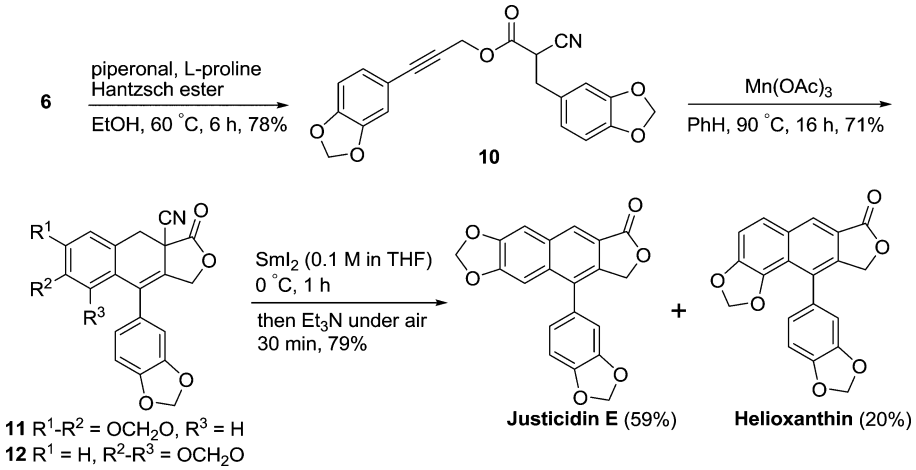
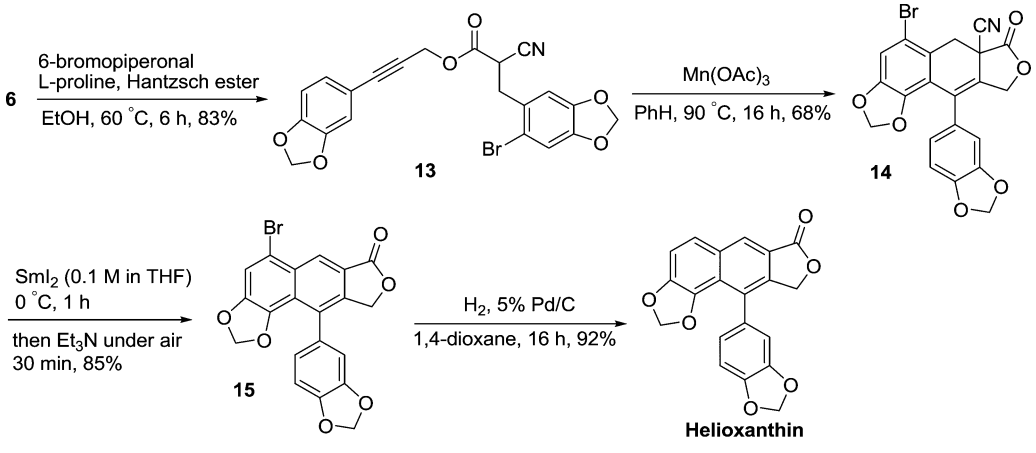
Scheme 3. Synthesis of Retrojusticidin B



Scheme 4. Synthesis of Justicidin E and Helioxanthin



Scheme 5. Synthesis of Helioxanthin



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EXPERIMENTAL SECTION

General Experimental Procedure. All reactions were performed under air unless otherwise stated. All solvents and reagents were employed as received without further purification. Analytical thin-layer chromatography was performed on SiO_2 60 F-254 plates, and flash column chromatography was carried out using SiO_2 60 (particle size 0.040−0.055 mm, 230−400 mesh). Visualization was performed under UV irradiation at 254 nm, followed by staining with aqueous potassium permanganate [$KMnO_4$ (3 g) and K_2CO_3 (20 g) in 300 mL of H_2O containing 5 mL of an aqueous solution of NaOH (5%, w/v)] and charring by heat gun. Infrared spectra (IR) were recorded on an FT-IR spectrometer and expressed in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. Chloroform-*d* was used as the solvent and TMS (δ = 0.00 ppm) as an internal standard. Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), q (quartet), dd (doublet of doublets), m (multiplet), br (broad). Coupling constants (J) are expressed in Hz. HRMS was obtained on a triple quadrupole mass analysis using an electrospray ionization (ESI) source, and spectral data were recorded as m/z values. Melting points were measured using an electrothermal instrument.

3-Phenylprop-2-ynyl 2-Cyanoacetate (1). A mixture of 3-phenyl-2-propyn-1-ol (6.0 g, 45.4 mmol), cyanoacetic acid (7.6 g, 90.8 mmol), EDCI (13.0 g, 68.0 mmol), and DMAP (831.4 mg, 6.8 mmol) in CH_2Cl_2 (80.0 mL) was stirred at room temperature for 3 h. After reaction was complete, the mixture was washed with water, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). Organic layers were combined and dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:6) to afford compound **1** (8.7 g, 97%) as a yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.77 (d, J = 1.6 Hz, 2H), 7.42−7.28 (m, 3H), 5.01 (s, 2H), 3.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.4, 131.9, 129.1, 128.3, 121.5, 112.6, 87.7, 81.2, 54.9, 24.6; IR (CH_2Cl_2 cast): 2929, 2360, 2245, 1755, 1490, 1173 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{12}H_9NO_2$: 199.0623 $[M]^+$, found: 199.0633.

3-Phenylprop-2-ynyl 2-Cyano-3-phenylpropanoate (2). To a solution of compound **1** (4.0 g, 20.0 mmol) in ethanol (200.0 mL) at room temperature was sequentially added benzaldehyde (2.5 g, 24.1 mmol), L-proline (460.0 mg, 4.0 mmol), and Hantzsch ester (5.0 g, 20.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 16 h and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:10) to afford compound **2** (4.6 g, 81%) as a yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.45−7.46 (m, 2H), 7.37−7.28 (m, 8H), 5.07 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 3.81 (dd, J = 8.8, 6.0 Hz, 1H), 3.32 (dd, J = 14.0, 6.0 Hz, 1H), 3.24 (dd, J = 14.0, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.9, 134.9, 131.9, 129.1, 129.0, 128.9, 128.4, 127.9, 121.6, 115.7, 87.7, 81.4, 54.9, 39.6, 35.7; IR (CH_2Cl_2 cast): 3490, 3032, 2936, 2251, 1751, 1490, 1190 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{15}NO_2$: 289.1103 $[M]^+$, found: 289.1102.

3-Oxo-9-phenyl-1,3,3α,4-tetrahydronaphtho[2,3-*c*]furan-3α-carbonitrile (3). A mixture of compound **2** (1.0 g, 3.4 mmol) and $Mn(OAc)_3$ (1.8 g, 6.8 mmol) in benzene (34.0 mL) was stirred in a sealed pressure vessel at 90 °C for 16 h. After reaction was complete, the mixture was filtered through a pad of Celite, followed by washing with CH_2Cl_2 (3 × 30 mL). The filtrate was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:8) to afford compound **3** (744.8 mg, 75%) as a white solid. mp 138−139 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.47−7.43 (m, 3H), 7.38−7.36 (m, 2H), 7.34−7.21 (m, 3H), 7.05 (d, J = 7.2 Hz, 1H), 5.33 (d, J = 13.6 Hz, 1H), 4.80 (d, J = 13.6 Hz, 1H), 3.48 (d, J = 15.6 Hz, 1H), 3.23 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 138.1, 134.4, 133.1, 130.1, 129.5, 129.4, 128.9, 128.8, 128.6, 128.3, 127.8, 124.2, 115.0, 70.0, 40.4, 34.4; IR (CH_2Cl_2 cast): 3062, 2360, 2235, 1786, 1444, 1155 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{13}NO_2$: 287.0946 $[M]^+$, found: 287.0945.

4-Phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (4). Compound **3** (160.0 mg, 0.5 mmol) was dissolved in a solution of SmI_2 (0.1 M) in THF (33.4 mL, 3.3 mmol) at 0 °C under argon. After stirring for 1 h at 0 °C, reaction was allowed to warm up to room temperature and quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the residue, which without purification was dissolved in benzene (5.0 mL) and treated with DDQ (249.7 mg, 1.0 mmol). The reaction mixture was heated up to reflux for 10 h, and then cooled down and filtered through a pad of Celite, followed by washing with CH_2Cl_2 (3 × 30 mL). The organic layer was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:8) to afford compound **4** (120.1 mg, 84%) as a white solid. mp 161−162 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.53 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.63−7.49 (m, 5H), 7.39 (d, J = 7.2 Hz, 2H), 5.28 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.2, 138.4, 135.7, 134.8, 134.1, 133.6, 130.1, 129.3, 129.1, 129.0, 128.4, 126.7, 126.4, 125.8, 122.9, 69.5; IR (CH_2Cl_2 cast): 3061, 2924, 1763, 1632, 1024 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{18}H_{12}O_2$: 260.0837 $[M]^+$, found: 260.0837.

3-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-ynyl 2-Cyanoacetate (6). A mixture of 3-(benzo[*d*][1,3]dioxol-5-yl)prop-2-yn-1-ol **5** (5.0 g, 28.4 mmol), cyanoacetic acid (5.0 g, 58.7 mmol), EDCI (10.0 g, 52.1 mmol), and DMAP (500.0 mg, 4.1 mmol) in CH_2Cl_2 (60.0 mL) was stirred at room temperature for 3 h. After reaction was complete, the mixture was washed with water, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). Organic layers were combined and dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:6) to afford compound **6** (6.7 g, 98%) as a yellow solid. mp 109−110 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 6.88 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H), 5.00 (s, 2H), 3.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.4, 148.5, 147.4, 126.8, 114.6, 112.6, 111.7, 108.4, 101.4, 87.6, 79.7, 55.0, 24.6; IR (CH_2Cl_2 cast): 2929, 2360, 2232, 1753, 1489, 1215 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{13}H_9NO_4$: 243.0532 $[M]^+$, found: 243.0533.

3-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-ynyl 2-Cyano-3-(3,4-dimethoxyphenyl)propanoate (7). To a solution of compound **6** (1.5 g, 6.1 mmol) in ethanol (50.0 mL) at room temperature was sequentially added 3,4-dimethoxybenzaldehyde (1.2 g, 7.3 mmol), L-proline (140.0 mg, 1.2 mmol), and Hantzsch ester (1.5 g, 6.1 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 h and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:3) to afford compound **7** (2.0 g, 85%) as a white solid. mp 100−101 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 6.85−6.75 (m, 4H), 5.99 (s, 2H), 4.99 (d, J = 15.6 Hz, 1H), 4.95 (d, J = 15.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.78 (dd, J = 8.4, 5.6 Hz, 1H), 3.26 (dd, J = 14.0, 5.6 Hz, 1H), 3.18 (dd, J = 14.0, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.0, 149.0, 148.6, 148.5, 147.4, 127.3, 126.8, 121.3, 115.8, 114.7, 112.0, 111.8, 111.3, 108.4, 101.4, 87.6, 79.8, 55.8, 55.7, 54.9, 39.8, 35.4; IR (CH_2Cl_2 cast): 2937, 2360, 2232, 1750, 1517, 1034 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{22}H_{19}NO_6$: 393.1212 $[M]^+$, found: 393.1213.

9-(Benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxy-3-oxo-1,3,3α,4-tetrahydronaphtho[2,3-*c*]furan-3α-carbonitrile (8). A mixture of compound **7** (1.4 g, 3.5 mmol) and $Mn(OAc)_3$ (2.8 g, 10.6 mmol) in benzene (40.0 mL) was stirred in a sealed pressure vessel was stirred at 90 °C for 16 h. After reaction was complete, the mixture was filtered through a pad of Celite, followed by washing with CH_2Cl_2 (3 × 30 mL). The filtrate was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford compound **8** (921.5 mg, 67%) as a white solid. mp 130−131 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.91−6.88 (m, 2H), 6.75−6.65 (m, 2H), 6.61 (s, 1H), 6.06−6.03 (m, 2H), 5.31 (d, J = 13.6 Hz, 1H), 4.82 (d, J = 13.6 Hz, 1H), 3.95 (s, 3H), 3.73 (s, 3H), 3.35 (d, J = 15.2 Hz,

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1H), 3.17 (d, J = 15.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.0, 149.5, 148.3, 148.0, 137.4, 128.1, 125.6, 123.3, 123.1, 122.8, 121.4, 115.3, 111.9, 111.2, 109.7, 108.5, 101.4, 70.1, 56.0 (2C), 40.7, 34.1; IR (CH_2Cl_2 cast): 2937, 2234, 1791, 1514, 1257 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{22}H_{17}NO_6$: 391.1056 $[M]^+$, found: 391.1056.

9-(Benzo[*d*][1,3]dioxol-5-yl)-7,8-dimethoxy-3-oxo-1,3,3*α*,4-tetrahydronaphtho[2,3-*c*]furan-3*α*-carbonitrile (9). Yield: 22%; pale yellow solid. mp 237−238 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.69−6.51 (m, 2H), 6.00−5.98 (m, 2H), 5.26 (d, J = 14.0 Hz, 1H), 4.82 (d, J = 14.0 Hz, 1H), 3.84 (s, 3H), 3.35 (d, J = 14.8 Hz, 1H), 3.31 (s, 3H), 3.07 (d, J = 14.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 153.6, 147.6, 136.1, 130.7, 126.4, 124.0, 123.2, 120.7, 114.9, 112.6, 107.8, 101.3, 70.1, 61.0, 55.8, 40.8, 35.5; IR (CH_2Cl_2 cast): 2922, 2356, 2238, 1792, 1479, 1257 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{22}H_{17}NO_6$: 391.1056 $[M]^+$, found: 391.1054.

Retrojusticidin B. The compound **8** (120.0 mg, 0.3 mmol) was dissolved in a solution of SmI_2 (0.1 M) in THF (18.0 mL, 1.8 mmol) at 0 °C under argon. After stirring for 1 h at 0 °C, Et_3N (0.08 mL, 0.6 mmol) was added at the same temperature by syringe under air. The reaction mixture was stirred for another 30 min at 0 °C, and then saturated aqueous NH_4Cl solution (3 mL) was added and the mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford retrojusticidin B (87.4 mg, 80%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.28 (s, 1H), 7.28 (s, 1H), 7.08 (s, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 1.2 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.10 (d, J = 1.2 Hz, 1H), 6.06 (d, J = 1.2 Hz, 1H), 5.20 (s, 2H), 4.04 (s, 3H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.6, 152.0, 150.1, 148.3, 147.6, 137.9, 131.9, 131.6, 129.8, 129.7, 124.1, 122.7, 121.3, 109.5, 109.0, 107.6, 104.0, 101.4, 69.5, 56.0, 55.9.

3-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-ynyl 3-(Benzo[*d*][1,3]-dioxol-5-yl)-2-cyanopropanoate (10). To a solution of compound **6** (7.2 g, 29.6 mmol) in ethanol (200.0 mL) at room temperature was sequentially added piperonal (5.3 g, 35.5 mmol), L-proline (680.0 mg, 5.9 mmol), and Hantzsch ester (7.4 g, 29.6 mmol) in one portion. The reaction mixture was stirred at 60 °C for 6 h and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:4) to afford compound **10** (8.7 g, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 6.89 (d, J = 1.6 Hz, 1H), 6.77−6.73 (m, 4H), 5.98 (s, 2H), 5.93 (s, 2H), 4.99 (d, J = 15.6 Hz, 1H), 4.95 (d, J = 15.6 Hz, 1H), 3.75 (dd, J = 8.0, 5.6 Hz, 1H), 3.22 (dd, J = 14.0, 5.6 Hz, 1H), 3.15 (dd, J = 14.0, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.9, 148.5, 147.9, 147.4, 147.2, 128.5, 126.9, 122.4, 115.7, 114.8, 111.8, 109.3, 108.6, 108.4, 101.4, 101.1, 87.6, 79.8, 54.9, 39.8, 35.5; IR (CH_2Cl_2 cast): 2901, 2232, 1750, 1490, 1038 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{21}H_{15}NO_6$: 377.0899 $[M]^+$, found: 377.0898.

9-(1,3-Benzodioxol-5-yl)-6-oxo-5,8-dihydrofuro[3′,4′:6,7]-naphtho[2,3-*d*][1,3]dioxole-5*α*(6*H*)-carbonitrile (11) and 10-(1,3-Benzodioxol-5-yl)-7-oxo-6,9-dihydrofuro[3′,4′:6,7]-naphtho[1,2-*d*][1,3]dioxole-6*α*(7*H*)-carbonitrile (12). A mixture of compound **10** (300.0 mg, 0.8 mmol) and $Mn(OAc)_3$ (639.0 mg, 2.3 mmol) in benzene (10.0 mL) was stirred in a sealed pressure vessel at 90 °C for 16 h. After reaction was complete, the mixture was filtered through a pad of Celite, followed by washing with CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford compound **11**:**12** = 3/1 (213.0 mg, 71%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.89−6.83 (m, 4H), 6.78−6.57 (m, 6H), 6.03−5.97 (m, 7H), 5.80−5.76 (m, 1H), 5.33−5.26 (m, 2H), 4.85 (d, J = 13.6 Hz, 1H), 4.79 (d, J = 13.6 Hz, 1H), 3.87 (d, J = 14.6 Hz, 1H), 3.30 (d, J = 15.6 Hz, 1H), 3.12 (d, J = 15.6 Hz, 1H), 3.06 (d, J = 14.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 168.7, 148.5, 147.9, 147.4, 145.2, 137.4, 134.2, 128.0, 127.1, 125.1, 124.5, 123.4, 123.2, 122.7, 121.9, 121.8, 115.1, 114.8, 109.4, 108.6, 108.5, 108.3, 101.6, 101.5, 101.4, 101.2, 77.2, 69.9, 40.9, 40.6, 34.8, 34.5; IR (CH_2Cl_2 cast): 2905, 2360, 2238, 1790, 1761, 1488, 1234 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{21}H_{13}NO_6$: 375.0743 $[M]^+$, found: 375.0742.

Justicidin E and Helioxanthin. The mixture of compounds **11** and **12** (120.0 mg, 0.3 mmol) was dissolved in a solution of SmI_2 (0.1 M) in THF (19.2 mL, 1.9 mmol) at 0 °C under argon. After stirring for 1 h at 0 °C, Et_3N (0.08 mL, 0.6 mmol) was added at the same temperature by syringe under air. The reaction mixture was stirred for another 30 min at 0 °C, and then saturated aqueous NH_4Cl (3 mL) was added and the mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The organic layer was concentrated under reduced pressure to give the crude residue, which was subjected to purification by HPLC with 250 × 10 mm Hypersil GOLD 5 μ semi-prep column (H_2O/MeOH, 1:9); flow rate = 0.5 mL min^{-1} to afford justicidin E (61.8 mg, 59%) as a white solid and helioxanthin (20.6 mg, 20%) as a white solid.

Justicidin E. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.27 (s, 1H), 7.31 (s, 1H), 7.10 (s, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.80−6.78 (m, 2H), 6.10−6.08 (m, 4H), 5.23 (d, J = 14.8 Hz, 1H), 5.18 (d, J = 14.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.5, 150.5, 148.4, 148.2, 147.7, 138.4, 133.4, 132.6, 131.3, 129.6, 124.7, 122.7, 121.6, 109.6, 109.0, 105.3, 102.1, 101.9, 101.4, 69.4.

3-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-ynyl 3-(6-Bromobenzo-[*d*][1,3]dioxol-5-yl)-2-cyanopropanoate (13). To a solution of compound **6** (4.6 g, 18.9 mmol) in ethanol (200.0 mL) at room temperature was sequentially added 6-bromopiperonal (5.0 g, 21.8 mmol), L-proline (435.0 mg, 3.7 mmol), and Hantzsch ester (4.8 g, 18.9 mmol) in one portion. The reaction mixture was stirred at 60 °C for 6 h and concentrated under reduced pressure to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:10) to afford compound **13** (7.1 g, 83%) as a white solid. mp 130−131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.02 (s, 1H), 6.99 (dd, J = 8.0, 1.6 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.84 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 5.97 (d, J = 1.2 Hz, 1H), 5.96 (d, J = 1.2 Hz, 1H), 5.01 (s, 2H), 3.95 (dd, J = 9.2, 6.4 Hz, 1H), 3.44 (dd, J = 14.0, 6.4 Hz, 1H), 3.15 (dd, J = 14.0, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.7, 148.5, 148.3, 147.6, 147.4, 127.3, 126.9, 115.4, 114.8, 114.7, 113.0, 111.9, 111.2, 108.4, 102.0, 101.4, 87.7, 79.8, 55.1, 37.4, 36.1; IR (CH_2Cl_2 cast): 2231, 1749, 1480, 1037 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{21}H_{14}BrNO_6$: 455.0004 $[M]^+$, found: 455.0005.

10-(1,3-Benzodioxol-5-yl)-5-bromo-7-oxo-6,9-dihydrofuro-[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxole-6*α*(7*H*)-carbonitrile (14). A mixture of compound **13** (300.0 mg, 0.6 mmol) and $Mn(OAc)_3$ (530.0 mg, 1.9 mmol) in benzene (10.0 mL) was stirred in a sealed pressure vessel at 90 °C for 16 h. After reaction was complete, the mixture was filtered through a pad of Celite, followed by washing with CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford compound **14** (185.5 mg, 68%) as a yellow solid. mp 217−218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.04 (s, 1H), 6.86−6.84 (br, 1H), 6.64−6.62 (m, 2H), 6.05−6.02 (m, 2H), 5.83−5.80 (m, 2H), 5.32 (d, J = 13.8 Hz, 1H), 4.85 (d, J = 13.8 Hz, 1H), 3.95 (d, J = 15.8 Hz, 1H), 2.83 (d, J = 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3, 148.9, 148.5, 145.2, 134.1, 127.9, 122.7, 122.0, 116.6, 115.4, 114.5, 113.2, 108.2, 101.9, 101.5, 69.7, 40.7, 34.6; IR (CH_2Cl_2 cast): 2234, 1793, 1447, 1020 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{21}H_{12}BrNO_6$: 452.9848 $[M]^+$, found: 452.9845.

10-(1,3-Benzodioxol-5-yl)-5-bromofuro[3′,4′:6,7]naphtho-[1,2-*d*][1,3]dioxol-7(9*H*)-one (15). The compound **14** (100.0 mg, 0.2 mmol) was dissolved in a solution of SmI_2 (0.1 M) in THF (13.0 mL, 1.3 mmol) at 0 °C under argon. After stirring for 1 h at 0 °C, Et_3N (0.08 mL, 0.6 mmol) was added at the same temperature by syringe under air. The reaction mixture was stirred for another 30 min at 0 °C, and then saturated aqueous NH_4Cl (3 mL) was added and the mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The organic layer was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash

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chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford compound **15** (72.4 mg, 85%) as a yellow solid. mp 261−262 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.88 (s, 1H), 7.64 (s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.78−6.75 (m, 2H), 6.06 (d, J = 11.2 Hz, 2H), 5.95 (d, J = 9.8 Hz, 2H), 5.24 (d, J = 15.4 Hz, 1H), 5.17 (d, J = 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8, 147.6, 147.4, 146.6, 141.8, 140.5, 129.9, 129.8, 128.9, 127.2, 122.3, 122.2, 117.3, 116.2, 109.5, 108.1, 102.0, 101.3, 69.4; IR (CH_2Cl_2 cast): 1767, 1487, 1239, 1037 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{20}H_{11}BrO_6$: 425.9739 $[M]^+$, found: 425.9739.

Helioxanthin. To a solution of compound **15** (72.4 mg, 0.17 mmol) in 1,4-dioxane (10.0 mL) was added 5% Pd/C (20 mg) at room temperature, and the mixture was stirred for 16 h under an atmosphere of H_2 (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford helioxanthin (54.4 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.43 (s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.82−6.79 (m, 2H), 6.06 (dd, J = 11.6, 1.2 Hz, 2H), 5.96 (dd, J = 9.2, 1.2 Hz, 2H), 5.23 (q, J = 15.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1, 147.4, 146.9, 141.7, 139.7, 130.7, 130.4, 129.1, 127.4, 125.4, 122.3, 121.5, 121.1, 111.8, 109.6, 107.9, 101.5, 101.2, 69.5.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of novel compounds and synthetic natural products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00866.

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Notes

The authors declare no competing financial interest.

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