DOI: 10.1002/ejoc.201000318

General Approach to 2,3-Dibenzyl-γ-butyrolactone Lignans: Application to the Total Synthesis of (±)-5′-Methoxyyatein, (±)-5′-Methoxyclusin, and (±)-4′-Hydroxycubebinone

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Keywords: Lignans / Natural products / Lactones / Total synthesis / Synthetic methods

The total synthesis of natural lignans 5′-methoxyyatein (**1**), 5′-methoxyclusin (**2**), and 4′-hydroxycubebinone (**3**), in racemic form, has been achieved by a newly developed strategy, wherein lithium naphthalenide induced decyanation was employed as a key operation to establish the essential *trans* configuration of the butyrolactone ring.

Introduction

To date, several hundred lignans have been discovered in many plant species from various parts, including the bark, root, leaf, flower, fruit, and seed. Lignans are also assumed to function as phytoalexins, providing protection for the plants against diseases and pests such as wood rot fungi.[1] Structurally, lignans are dimeric propyl phenols; the natural products are broadly divided into eight classes.[2] Among them, dibenzylbutyrolactone lignans are an important family, and they are noted for a wide variety of biological activities, including cytotoxic and antiviral, as well as cancer protective properties.[3–5]

Koga and co-workers reported the first total synthesis of dibenzylbutyrolactone lignans deoxypodorhizon and hinokinin in optically pure form by the use of a chiral intermediate derived from L-glutamic acid.[6] Subsequently, many compounds of the series such as cordigerine, isoyatein, and cubebinone have also been synthesized.[7–9] Dibenzylbutyrolactone lignan (+)-5′-methoxyyatein (**1**) was first identified in 2003 from the whole plant of *Peperomia duclouxii*, traditionally used to treat various types of cancer in the southwest provinces of China.[10] Two years later, its congeners (–)-5′-methoxyclusin (**2**) and (–)-4′-hydroxycubebinone (**3**) were isolated[11] from the fruits of *Piper cubeba*, a popular medicinal plant extensively used in Indonesia for the treatment of asthma, diarrhea, and abdominal pain.[12] To acquire an adequate amount of these lignans to validate their claimed anticancer and/or antiviral activities, herein, we wish to report that natural lignans **1**, **2**, and **3** (Figure 1), in racemic form, have been synthesized in an effective synthetic sequence, making use of lithium naphthalenide[13] (LN)-induced decyanation as a key step to establish the essential *trans* relation of the substituents on the butyrolactone ring.

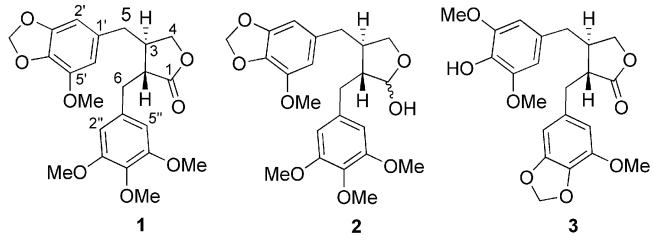

Figure 1. Natural dibenzylbutyrolactone lignans.

Results and Discussion

Using dibenzylbutyrolactone (**8**) as an initial model, our retrosynthetic strategy is outlined in Scheme 1. It is anticipated that target **8** should be obtained through LN-induced reductive decyanation of compound **7**, as indicated by many successful historical cases.[14] The formation of desired intermediate **7** could probably be effected through a two-step synthetic sequence involving intramolecular Knoevenagel condensation–hydrogenation[15] followed by benzylation from cyano ester **5**, which could be readily provided by treating keto alcohol **4** with cyanoacetic acid.

Along the axis of the retrosynthetic analysis, **8** was prepared according to a synthetic sequence shown in Scheme 2. Cyano ester **5** was obtained in 90% yield by coupling keto alcohol **4**, readily prepared through a documented two-step procedure,[16] with cyanoacetic acid in the presence of Me_2NPOCl_2 and pyridine.[17] Other coupling reagents such as *N,N′*-dicyclohexylcarbodiimide (DCC) and 1-

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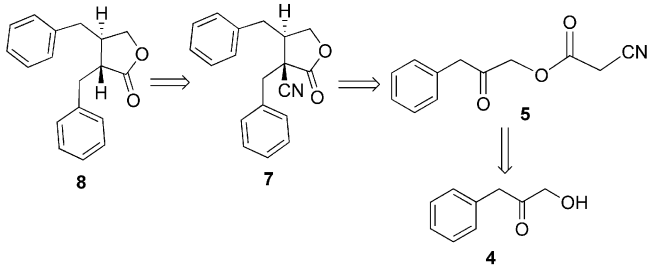
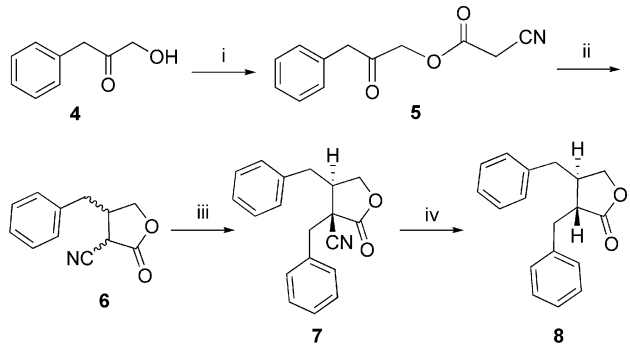


Scheme 1. Retrosynthetic analysis of dibenzylbutyrolactone (**8**).

ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) gave rise to desired product **5** under similar conditions albeit in moderate yields (60–70%).

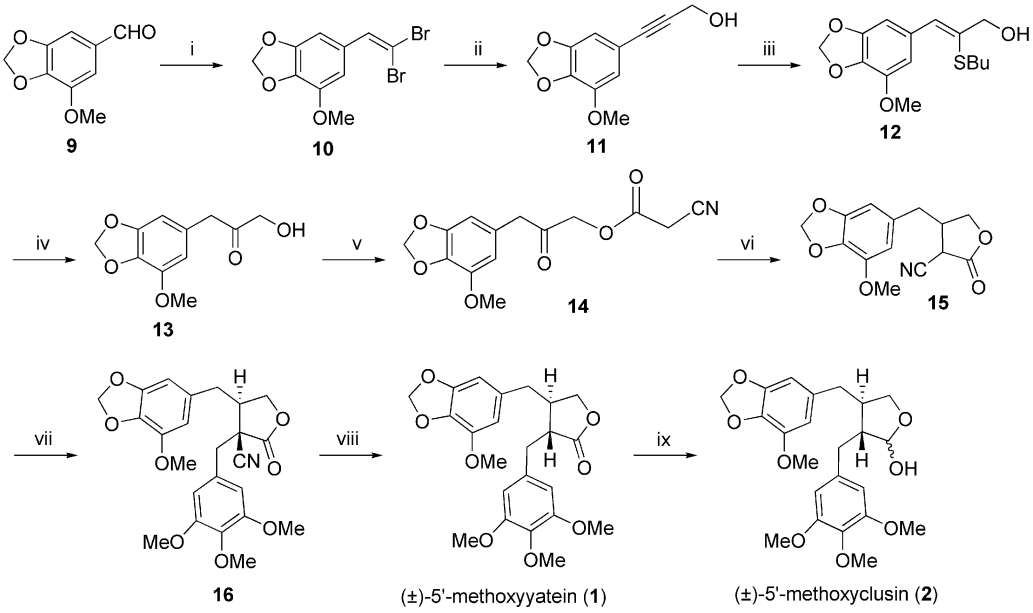


Scheme 2. Reagents and conditions: (i) $(CH_3)_2NPOCl_2$, pyridine, $CNCH_2COOH$, CH_2Cl_2, 0 °C to room temp., 24 h, 90%; (ii) L-proline, Hantzsch ester, ethanol, room temp., 24 h, 92%; (iii) benzyl bromide, K_2CO_3, THF, room temp., 24 h, 82%; (iv) LN (3.5 equiv.), THF, –45 °C, 30 min then NH_4Cl (aq.), –45 °C to room temp., 78%.

Cyano ester **5** thus obtained was subjected to tandem Knoevenagel condensation and hydrogenation in one pot with L-proline and Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate)[15a,15b] to afford butyrolactone **6** as a pair of inseparable diastereomers (1:2.5) in 92% yield. As reported,[15c] Knoevenagel condensation catalyzed with L-proline can also be effected with pyrrolidine and other pyrrolidine-based catalysts, and mechanistically, subsequent Hantzsch ester reduction on the Knoevenagel product might result in racemic diastereomers. Compound **6** was subsequently treated with benzyl bromide under basic conditions. The benzylation was assumed to take place preferentially from the sterically less hindered side to give dibenzylcyanobutyrolactone **7** (82%) as the only diastereomer. Finally, removal of the cyano group in **7** was achieved by LN-induced reductive decyanation to give desired *trans*-dibenzylbutyrolactone **8**, the spectroscopic data (^1H and ^{13}C NMR) of which are in high agreement with those reported in the literature.[8,9]

Encouraged by the synthesis of **8**, we embarked on the total synthesis of lignans **1** and **2** by using 5-methoxypiperonal, commercially available, as the starting material (Scheme 3). Aldehyde **9** was subjected to Corey–Fuchs olefination[18] to furnish vinyl dibromide **10** (80%). Elimination and lithium–halogen exchange of **10** followed by trapping the ensuing lithium alkynylide with paraformaldehyde gave alkynol **11** in 92% yield. Compound **11** thus obtained was smoothly converted into keto alcohol **13** in 59% yield via intermediate **12** over two steps, involving butanethiol addition and acidic hydrolysis.[16]

With keto alcohol **13** in hand, its esterification with cyanoacetic acid was carried out efficiently by using $(CH_3)_2$-



Scheme 3. Reagents and conditions: (i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 80%; (ii) *n*BuLi, THF, –78 °C, $(CH_2O)_n$, room temp., 3 h, 92%; (iii) BuSH, NaOH, CH_3CN, 75 °C, 2 h, 82%; (iv) C_2H_5OH/1 N H_2SO_4 (4:1), 50 °C, 24 h, 72%; (v) $(CH_3)_2NPOCl_2$, pyridine, $CNCH_2COOH$, CH_2Cl_2, 0 °C to room temp., 24 h, 92%; (vi) L-proline, Hantzsch ester, ethanol, room temp., 24 h, 82%; (vii) 3,4,5-trimethoxybenzyl bromide, K_2CO_3, THF, room temp., 24 h, 80%; (viii) LN (3.5 equiv.), THF, –45 °C, 30 min then NH_4Cl (aq.), –45 °C to room temp., 95%; (ix) DIBAL, toluene, –78 °C, 2 h, 72%.

$NPOCl_2$/pyridine[17] to yield key intermediate **14** (92%), which in turn underwent intramolecular Knoevenagel condensation–hydrogenation[15] in one pot to afford butyrolactone **15** as a pair of inseparable diastereomers (1:2.1) in 82% yield. This diastereomeric mixture was further alkylated with 3,4,5-trimethoxybenzyl bromide to give *trans*-dibenzylbutyrolactone **16** (80%), the structure of which was unambiguously confirmed by an X-ray crystallographic analysis (Figure 2).[19] The identification of **16** also lends support to the structural assignment of previous cyanobutyrolactone **7**. Finally, the cyano group was reductively removed with LN to afford 95% of the racemic form of desired lignan **1**, the spectroscopic data (^{1}H and ^{13}C NMR) of which were highly consistent with those reported in the literature.[10] Further reduction of product **1** with DIBAL produced lignan **2** as a pair of inseparable epimers (1:1.4) in 72% yield. The spectroscopic data (^{1}H and ^{13}C NMR) for the major epimer were found to be in good agreement with those reported in the literature.[11]

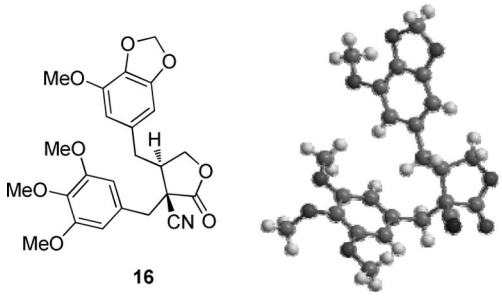
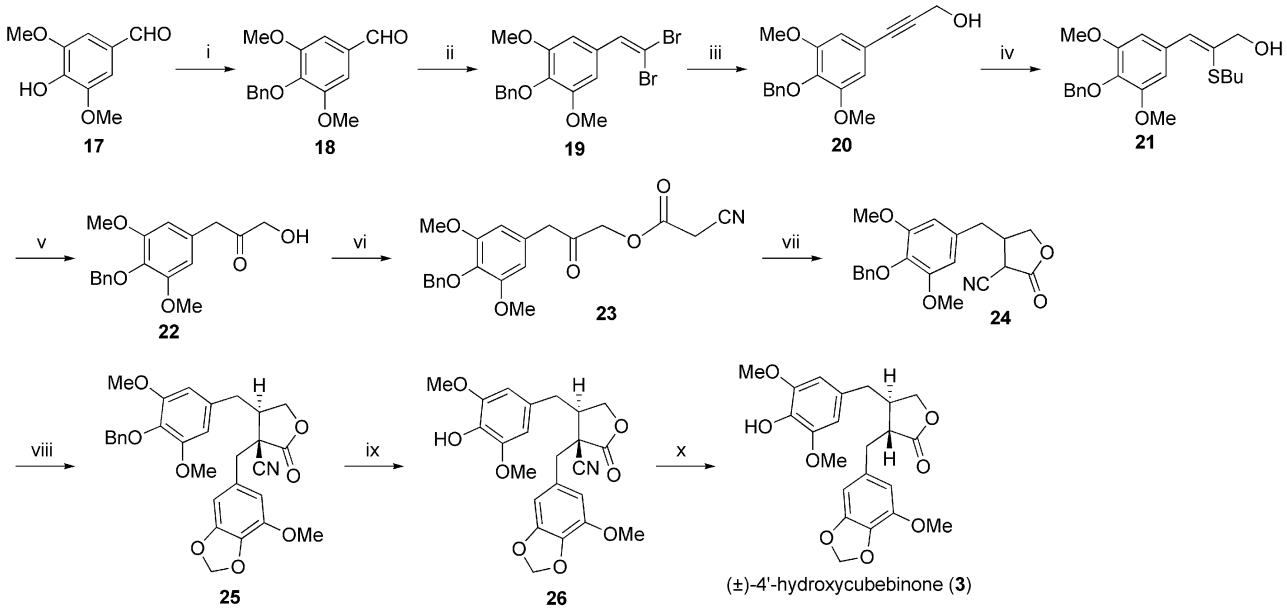


Figure 2. The X-ray picture of butyrolactone **16** (thermal ellipsoids are shown at 50% probability).

Similarly, aldehyde **18**, readily obtained from **17** by benzylation, was subjected to Corey–Fuchs olefination, lithium–halogen exchange and elimination, butanethiol addition–hydrolysis, esterification, and intramolecular Knoevenagel condensation–hydrogenation to furnish butyrolactone **24** as a pair of inseparable diastereomers (1:1.5) in 28% yield over six steps. This diastereomeric mixture was further alkylated with 5-methoxypiperonyl bromide to give butyrolactone **25** as a single product (82%), which was again assumed to be the *trans* isomer as suggested by analogue **16**. Deprotection of the benzyl group in **25** was efficiently completed under standard conditions (H_2, 10% Pd/C) in 10 min, giving rise to the corresponding cyano lactone **26** (98%; Scheme 4), which in turn underwent typical LN-induced decyanation to afford target **3** in 95% yield. The spectroscopic data (^{1}H and ^{13}C NMR) of synthetic lignan **3** are in full agreement with those reported in the literature.[11] As such, the total synthesis of natural lignans 5′-methoxyyatein (**1**), 5′-methoxyclusin (**2**), and 4′-hydroxycubebinone (**3**), in racemic form, was accomplished in an overall yield of 25, 18, and 19% in 8, 9, and 10 steps, respectively, starting from the appropriate phenolic aldehydes.

Conclusions

In conclusion, we have developed a new and general strategy to access 2,3-dibenzyl-γ-butyrolactone lignans with ease. It is highly conceivable that this synthetic approach might find potential utility to generate a library of structurally diverse 2,3-disubstituted butyrolactones, including natural as well as non-natural lignans, for the purpose of new drug discovery. Currently, its enantioselective version is un-



Scheme 4. Reagents and conditions: (i) benzyl bromide, K_2CO_3, THF, reflux, 12 h, 92%; (ii) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 82%; (iii) *n*BuLi, THF, –78 °C, $(CH_2O)_n$, room temp., 3 h, 85%; (iv) BuSH, NaOH, CH_3CN, 75 °C, 2 h, 80%; (v) ethanol/1 N H_2SO_4 (4:1), 50 °C, 24 h, 70%; (vi) $(CH_3)_2NPOCl_2$, pyridine, $CNCH_2COOH$, CH_2Cl_2, 0 °C to room temp., 24 h, 88%; (vii) L-proline, Hantzsch ester, ethanol, room temp., 24 h, 80%; (viii) 5-methoxypiperonyl bromide, K_2CO_3, THF, room temp., 24 h, 82%; (ix) H_2, Pd/C (10% w/w), methanol, room temp., 10 min, 98%; (x) LN (3.5 equiv.), THF, –45 °C, 30 min then NH_4Cl (aq.), –45 °C to room temp., 95%.

der active investigation with particular emphasis on synthesizing advanced intermediates (i.e., **7**, **16**, and **25**) in enantiomerically pure form through the process of asymmetric catalytic hydrogenation.[20]

Experimental Section

General: All reactions were performed under an argon or nitrogen atmosphere unless otherwise stated. All solvents were dried prior to use, and reagents were employed as received. Analytical thin-layer chromatography was performed on SiO_2 60 F-254 plates, and flash column chromatography was carried out by using SiO_2 60 (particle size 0.040–0.055 mm, 230–400 mesh), both of which are available from Merck. Visualization was performed under UV irradiation at 254 nm followed by staining with vanillin (60 g of vanillin in 1 L of 95% ethanol containing 10 mL of conc. H_2SO_4) and charring with a heat gun. Fourier transform infrared spectra (IR) were recorded with a Bomen MR-100 instrument. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance EX 400 FT NMR or Bruker DMX-600. [D]Chloroform 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), t (triplet), q (quartet), quint. (quintet), sext. (sextet), sept. (septet), dd (doublet of doublets), dt (doublet of triplets), br. (broadened), m (multiplet). HRMS were taken with a JEOL JMS-HX110 spectrometer.

2-Oxo-3-phenylpropyl Cyanoacetate (5): To a solution of cyanoacetic acid (0.50 g, 5.88 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (80 mL) at 0 °C was added sequentially pyridine (1.43 mL, 17.63 mmol, 3.0 equiv.), *N*,*N*-dimethyl phosphoramidodichloridate (1.40 mL, 11.76 mmol, 2.0 equiv.), and compound **4** (0.88 g, 5.88 mmol, 1.0 equiv.). The resulting solution was stirred at room temperature under an argon atmosphere for 24 h. The solution was poured into ice-cold 1 N hydrochloric acid (100 mL) and extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford compound **5** (1.15 g, 90% yield) as a white solid. M.p. 95–97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5 H), 4.79 (s, 2 H), 3.72 (s, 2 H), 3.52 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4 (CO), 162.4 (CO), 132.2 (C), 129.3 (2 CH), 128.9 (2 CH), 127.5 (CH), 112.7 (CN), 68.8 (CH_2), 46.1 (CH_2), 24.2 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2954, 2259, 1757, 1725, 1419, 1184 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}NO_3$ 217.0739; found 217.0742.

4-Benzyl-2-oxotetrahydrofuran-3-carbonitrile (6): To a solution of compound **5** (1.00 g, 4.60 mmol, 1.0 equiv.) in ethanol (200 mL) was added L-proline (0.12 g, 0.92 mmol, 0.2 equiv.) and the Hantzsch ester (1.17 g, 4.60 mmol, 1.0 equiv.), and the resulting reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was concentrated under reduced pressure and directly loaded onto a silica gel column with or without aqueous workup and purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 0.5:9.5) to afford compound **6** (0.86 g, 92% yield) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$, major isomer): δ = 7.36–7.14 (m, 5 H), 4.41 (dd, *J* = 9.2, 7.6 Hz, 1 H), 4.03 (t, *J* = 9.4 Hz, 1 H), 3.42 (dd, *J* = 11.0, 0.8 Hz, 1 H), 3.22–3.18 (m, 1 H), 3.05 (dd, *J* = 14.0, 6.0, Hz, 1 H), 2.87 (dd, *J* = 14.0, 8.3 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, major isomer): δ = 167.8 (CO), 125.4 (C), 129.2 (2 CH), 129.0 (2 CH), 128.8 (CH), 114.2 (CN), 71.3 (CH_2), 43.0 (CH), 37.0 (CH), 36.5 (CH_2) ppm. ^1H NMR (600 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 4.28 (dd, *J* = 9.7, 6.1 Hz, 1 H), 4.19 (dd, *J* = 9.6, 5.1 Hz, 1 H), 3.80 (dd, *J* = 7.8, 1.0 Hz, 1 H), 3.18–3.13 (m, 1 H), 3.07–3.06 (m, 1 H), 2.76 (dd, *J* = 10.2, 10.1, Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 167.8 (CO), 136.3 (C), 128.7 (2 CH), 127.6 (2 CH), 127.3 (CH), 112.8 (CN), 70.8 (CH_2), 40.0 (CH), 37.2 (CH), 34.8 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3063, 3029, 2912, 2254, 1783, 1165, 1014 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}NO_2$ 201.0790; found 201.0789.

(3*R,4*R**)-3,4-Dibenzyl-2-oxotetrahydrofuran-3-carbonitrile (7):** To a solution of compound **6** (0.50 g, 2.48 mmol) in THF (10 mL) at room temperature under an argon atmosphere was added K_2CO_3 (0.41 g, 2.98 mmol). After stirring the mixture for 30 min, benzyl bromide (0.35 mL, 2.98 mmol) was added dropwise. The reaction mixture was stirred for 24 h at room temperature and then 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. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford compound **7** (0.59 g, 82% yield) as a white solid. M.p. 100–102 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.06 (m, 10 H), 4.09–4.0 (m, 2 H), 3.36 (dd, *J* = 25.8, 14.0 Hz, 2 H), 2.78–2.64 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (CO), 136.4 (C), 132.8 (C), 130.1 (2 CH), 129.0 (2 CH), 128.9 (2 CH), 128.5 (2 CH), 128.3 (CH), 127.3 (CH), 115.2 (CN), 70.3 (CH_2), 48.2 (C), 43.4 (CH), 39.3 (CH_2), 35.1 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2954, 2923, 2259, 1757, 1419, 1184 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{17}NO_2$ 291.1259; found 291.1257.

(3*R,4*R**)-3,4-Dibenzyldihydrofuran-2(3*H*)-one (8):** To a solution of compound **7** (0.20 g, 0.69 mmol) in THF (10 mL) at –45 °C under an argon atmosphere was added a solution of lithium naphthalenide (LN, 3.5 equiv.) in THF by syringe. After stirring the mixture for 30 min at –45 °C, saturated aqueous ammonium chloride solution (2–3 mL) was added at the same temperature by syringe. The reaction mixture was stirred for another 30 min at room temperature and then diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford target **8** (0.14 g, 78% yield) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 8 H), 6.99–6.97 (m, 2 H), 4.07 (dd, *J* = 9.0, 7.7 Hz, 1 H), 3.84 (dd, *J* = 9.0, 8.0 Hz, 1 H), 3.09 (dd, *J* = 14.0, 5.1 Hz, 1 H), 2.96 (dd, *J* = 14.0, 7.1 Hz, 1 H), 2.65–2.59 (m, 2 H), 2.52–2.49 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.5 (CO), 137.9 (C), 137.6 (C), 129.2 (2 CH), 128.7 (2 CH), 128.7 (2 CH), 128.5 (2 CH), 126.9 (CH), 126.7 (CH), 71.1 (CH_2), 46.4 (CH), 41.2 (CH), 38.4 (CH_2), 35.0 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3027, 2921, 1772, 1496, 1455, 1148, 1016 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{18}O_2$ 266. 1307; found 266.1304.

6-(2,2-Dibromoethenyl)-4-methoxy-1,3-benzodioxole (10): To a solution of carbon tetrabromide (9.20 g, 27.75 mmol, 1.0 equiv.) in CH_2Cl_2 (75 mL) was added triphenylphosphane (14.56 g, 55.51 mmol, 2.0 equiv.) portion wise over 5 min at 0 °C, and the resulting dark-red solution was stirred for 30 min at the same temperature. A solution of 5-methoxypiperonal (**9**; 5.00 g, 27.75 mmol, 1.0 equiv.) in CH_2Cl_2 (75 mL) was added, and the reaction mixture was stirred for 1 h at 0 °C and then warmed up to room temperature. Stirring was continued for another 2 h. A 1:1 mixture of H_2O/brine solution was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 × 25 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford

compound **10** (7.46 g, 80% yield) as a white solid. M.p. 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 6.79 (s, 1 H), 6.68 (s, 1 H), 5.95 (s, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C), 143.2 (C), 136.2 (2 CH), 135.5 (C), 129.4 (C), 102.4 (CH), 101.7 (CH_2), 88.1 (C), 56.5 (CH_3) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2894, 1628, 1506, 1429, 1135, 1045, 930 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_8Br_2O_3$ 335.8820; found 335.8825.

3-(7-Methoxy-1,3-benzodioxol-5-yl)prop-2-yn-1-ol (11): To a solution of compound **10** (14.00 g, 41.66 mmol, 1.0 equiv.) in THF (150 mL) was added *n*BuLi (2.5 M in hexanes, 41.67 mL, 2.5 equiv.) slowly by syringe at –78 °C, and the solution was stirred at –78 °C for 45 min and paraformaldehyde (1.89 g, 62.50 mmol, 1.5 equiv.) was added slowly with a powder funnel. The resulting reaction mixture was stirred at room temperature for 3 h. Saturated aqueous ammonium chloride solution was added, and the layers were separated. The aqueous layer was extracted with EtOAc (6 × 25 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford compound **11** (7.91 g, 92% yield) as a white solid. M.p. 60–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 6.54 (s, 1 H), 5.91 (s, 2 H), 4.40 (s, 2 H), 3.80 (s, 3 H), 2.73 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3 (C), 143.1 (C), 136.0 (C), 115.8 (C), 111.5 (CH), 105.7 (CH), 101.6 (CH_2), 85.6 (C), 85.2 (C), 56.3 (CH_3), 51.2 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3352, 2920, 2226, 1623, 1510, 1434, 1010, 1156, 972 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{10}O_4$ 206.0579; found 206.0581.

(2*Z*)-2-(Butylsulfanyl)-3-(7-methoxy-1,3-benzodioxol-5-yl)prop-2-en-1-ol (12): To a suspension of compound **11** (2.00 g, 9.70 mmol, 1.0 equiv.) and powdered NaOH (0.46 g, 11.64 mmol, 1.2 equiv.) in CH_3CN (20 mL) was added butanethiol (1.56 mL, 14.55 mmol, 1.5 equiv.) by syringe, and the slurry was heated to 75 °C for 2 h. The crude reaction mixture was concentrated to a dark orange oil, and the residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford compound **12** (2.35 g, 82% yield) as a red colored oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (s, 1 H), 6.85 (s, 1 H), 6.68 (s, 1 H), 5.96 (s, 2 H), 4.78 (s, 2 H), 3.88 (s, 3 H), 2.75 (q, *J* = 7.4 Hz, 2 H), 1.55–1.50 (m, 2 H), 1.41–1.34 (m, 2 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (C), 148.4 (C), 143.0 (C), 134.7 (C), 132.5 (CH), 130.3 (C), 109.6 (CH), 103.6 (CH), 101.5 (CH_2), 68.0 (CH_2), 56.4 (CH_3), 31.8 (CH_2), 31.4 (CH_2), 21.8 (CH_2), 13.5 (CH_3) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3426, 2958, 1627, 1506, 1428, 1221, 1021 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{20}O_4S$ 296.1082; found 296.1081.

1-Hydroxy-3-(7-methoxy-1,3-benzodioxol-5-yl)propan-2-one (13): Compound **12** (2.00 g, 6.75 mmol, 1.0 equiv.) was diluted with a stock solution of ethanol/1 N H_2SO_4 (4:1, 50 mL). The biphasic mixture was heated to 50 °C to form a homogeneous solution, which was stirred for 24 h at 50 °C. The solution was warmed to room temperature and brine (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford compound **13** (1.08 g, 72% yield) as a white solid. M.p. 60–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 1 H), 6.33 (s, 1 H), 5.94 (s, 2 H), 4.26 (s, 2 H), 3.86 (s, 3 H), 3.59 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3 (CO), 149.0 (C), 143.5 (C), 134.4 (C), 126.8 (C), 108.7 (CH), 103.3 (CH), 101.3 (CH_2), 67.3 (CH_2), 56.4 (CH_3), 45.4 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3449, 2901, 1721, 1635, 1509, 1434, 1198, 1133, 1143, 1093, 927 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{12}O_5$ 224.0685; found 224.0691.

3-(7-Methoxy-1,3-benzodioxol-5-yl)-2-oxopropyl Cyanoacetate (14): To a solution of cyanoacetic acid (0.60 g, 7.05 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (80 mL) at 0 °C was added sequentially pyridine (1.71 mL, 21.16 mmol, 3.0 equiv.), *N*,*N*-dimethyl phosphoramidodichloridate (1.68 mL, 14.11 mmol, 2.0 equiv.), and compound **13** (1.58 g, 7.05 mmol, 1.0 equiv.). The resulting solution was stirred at room temperature under an argon atmosphere for 24 h. The solution was poured into ice-cold 1 N hydrochloric acid (100 mL) and extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 5:5) to afford compound **14** (1.9 g, 92% yield) as brown crystals. M.p. 118–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (s, 1 H), 6.34 (s, 1 H), 5.94 (s, 2 H), 4.80 (s, 2 H), 3.87 (s, 3 H), 3.62 (s, 2 H), 3.56 (s, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.3 (CO), 162.4 (CO), 149.3 (C), 143.8 (C), 134.8 (C), 126.2 (C), 112.5 (CN), 108.7 (CH), 103.4 (CH), 101.6 (CH_2), 68.7 (CH_2), 56.6 (CH_3), 46.2 (CH_2), 24.3 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2968, 2941, 2253, 1751, 1732, 1094, 928 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{13}NO_6$ 291.0743; found 291.0748.

4-[(7-Methoxy-1,3-benzodioxol-5-yl)methyl]-2-oxotetrahydrofuran-3-carbonitrile (15): To a solution of compound **14** (1.00 g, 3.43 mmol, 1.0 equiv.) in ethanol (200 mL) was added L-proline (0.08 g, 0.69 mmol, 0.2 equiv.) and the Hantzsch ester (0.87 g, 3.43 mmol, 1.0 equiv.), and the resulting reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was concentrated under reduced pressure and directly loaded onto a silica gel column without aqueous workup and purified by flash column chromatography (EtOAc/*n*-hexane, 2:8) to give compound **15** (1.03 g, 82% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$, major isomer): δ = 6.36 (s, 1 H), 6.29 (s, 1 H), 5.96 (s, 2 H), 4.44 (dd, *J* = 9.4, 7.4 Hz, 1 H), 4.02 (t, *J* = 9.4 Hz, 1 H), 3.89 (s, 3 H), 3.43 (d, *J* = 10.5 Hz, 1 H), 3.16–3.12 (m, 1 H), 2.95 (dd, *J* = 14.1, 5.9 Hz, 1 H), 2.76 (dd, *J* = 14.1, 8.4 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, major isomer): δ = 166.9 (CO), 150.9 (C), 139.4 (C), 134.5 (C), 133.3 (C), 115.5 (CN), 108.5 (CH), 102.7 (CH), 101.7 (CH_2), 71.2 (CH_2), 56.9 (CH_3), 43.2 (CH), 37.1 (CH), 37.0 (CH_2), 29.7 (CH_2) ppm. ^{1}H NMR (600 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 6.31 (s, 1 H), 6.30 (s, 1 H), 4.30 (dd, *J* = 9.7, 6.2 Hz, 1 H), 4.21 (dd, *J* = 9.7, 5.4 Hz, 1 H), 3.88 (s, 3 H), 3.74 (d, *J* = 7.8 Hz, 1 H), 3.08 (dd, *J* = 13.9, 6.2 Hz, 1 H), 3.02–2.98 (m, 1 H), 2.68 (dd, *J* = 13.9, 9.6 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 101.6 (CH_2), 71.1 (CH_2), 56.9 (CH_3), 40.4 (CH), 36.7 (CH_2), 35.0 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2921, 2846, 2253, 1784, 1634, 1091, 931 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{13}NO_5$ 275.0794; found 275.0793.

(3*R,4*R**)-4-{(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)methyl}-2-oxo-3-(3,4,5-trimethoxybenzyl)tetrahydrofuran-3-carbonitrile (16):** To a solution of compound **15** (0.50 g, 1.82 mmol) in THF (10 mL) at room temperature under an argon atmosphere was added K_2CO_3 (0.30 g, 2.18 mmol) in one portion. After stirring for 30 min, a solution of 3,4,5-trimethoxybenzyl bromide (0.57 g, 2.18 mmol) in THF (5 mL) was added by syringe. The resulting reaction mixture was stirred for 24 h at the same temperature. 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. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford compound **16** (0.66 g, 80% yield) as a white crystalline solid. M.p. 150–153 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.37 (s, 2 H), 6.23 (s, 2 H), 5.88 (s, 2 H), 4.15 (dd, *J* = 9.4, 7.1 Hz, 1 H), 3.99 (t, *J* = 9.4 Hz,

1 H), 3.82 (s, 3 H), 3.78 (s, 6 H), 3.77 (s, 3 H), 3.23 (d, J = 14.0 Hz, 1 H), 3.09 (d, J = 14.0 Hz, 1 H), 2.69–2.58 (m, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3 (CO), 153.3 (C), 149.1 (C), 143.6 (C), 137.8 (C), 134.2 (C), 130.6 (C), 128.3 (C), 115.3 (CN), 108.3 (CH), 107.1 (CH), 102.2 (CH), 101.4 (CH_2), 70.3 (CH_2), 60.7 (CH_3), 56.5 (CH_3), 56.0 (CH_3), 48.0 (C), 43.0 (CH), 39.4 (CH_2), 35.1 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2941, 2238, 1786, 1636, 1592, 1509, 1459, 1130, 928 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{25}NO_8$ 455.1580; found 455.1581.

(±)-5′-Methoxyyatein (1): To a solution of compound **16** (0.20 g, 0.44 mmol) in THF (10 mL) at –45 °C under an argon atmosphere was added a solution of lithium naphthalenide (3.5 equiv.) in THF. After stirring the mixture for 30 min at –45 °C, saturated aqueous ammonium chloride solution (2–3 mL) was added at the same temperature by syringe. The reaction mixture was stirred for another 30 min at room temperature and was diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 2:8) to afford lignan **1** (0.18 g, 95% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.34 (s, 1 H), 6.15 (br. s, 1 H), 6.13 (br. s, 1 H), 5.91 (m, 2 H), 4.17 (dd, J = 9.1, 7.3 Hz, 1 H), 3.88 (dd, J = 9.1, 7.3 Hz, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.93 (dd, J = 14.0, 5.3 Hz, 1 H), 2.88 (dd, J = 14.0, 6.7 Hz, 1 H), 2.59 (dd, J = 13.3, 6.3 Hz, 1 H), 2.54–2.50 (m, 1 H), 2.51 (dd, J = 13.3, 8.1 Hz, 1 H), 2.46–2.45 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.5 (CO), 153.2 (C), 153.2 (C), 149.1 (C), 143.5 (C), 136.8 (C), 133.9 (C), 133.3 (C), 132.3 (C), 108.2 (CH), 106.1 (CH), 106.1 (CH), 102.4 (CH), 101.4 (CH_2), 71.1 (CH_2), 60.8 (CH_3), 56.7 (CH_3), 56.1 (CH_3), 56.1 (CH_3), 46.4 (CH), 41.0 (CH), 38.6 (CH_2), 35.2 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2938, 1766, 1508, 1452, 1126, 927 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{26}O_8$ 430.1628; found 430.1630.

(±)-5′-Methoxyclusin (2): To a solution of lignan **1** (0.10 g, 0.23 mmol) in anhydrous toluene (5 mL) was added a solution of diisobutylaluminum hydride (1.0 M in hexane, 0.70 mL, 0.70 mmol) over a period of 5 min (the solution turned yellow) at –78 °C. After 2 h at –78 °C, the reaction mixture was warmed to room temperature and treated with a saturated aqueous ammonium chloride solution (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford a pair of inseparable epimers (1:1.4) of lignan **2** (0.072 g, 72% yield) as a pale-yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$, selected peaks of the major isomer): δ = 6.30 (s, 1 H), 6.30 (s, 1 H), 6.19 (s, 1 H), 6.18 (s, 1 H), 5.89 (s, 2 H), 5.22 (br. s, 1 H), 4.0 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.78 (s, 3 H), 3.76 (m, 1 H), 2.76 (m, 1 H), 2.58 (m, 1 H), 2.43 (m, 1 H), 2.18 (m, 1 H), 2.15 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, selected peaks of the major isomer): δ = 153.0 (C), 153.0 (C), 148.8 (C), 143.4 (C), 136.3 (C), 134.9 (C), 134.5 (C), 133.4 (C), 107.9 (CH), 105.7 (CH), 105.6 (CH), 103.3 (CH), 102.4 (CH), 101.2 (CH_2), 72.1 (CH_2), 60.8 (CH_3), 56.5 (CH_3), 56.0 (CH_3), 56.0 (CH_3), 52.8 (CH), 46.0 (CH), 39.1 (CH_2), 34.1 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3416, 2935, 1509, 1452, 1240, 1128, 928 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{28}O_8$ 432.1784; found 432.1786.

4-(Benzyloxy)-3,5-dimethoxybenzaldehyde (18): To a suspension of aldehyde **17** (5.00 g, 27.45 mmol, 1.0 equiv.) and potassium carbonate (7.97 g, 57.64 mmol, 2.1 equiv.) in THF (100 mL) was added benzyl bromide (3.92 mL, 32.93 mmol, 1.2 equiv.). The resulting reaction mixture was heated at reflux for 12 h, then cooled and poured into water and extracted with EtOAc (4 × 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 3:7) to afford compound **18** (6.87 g, 92% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.46–7.28 (m, 5 H), 7.09 (s, 2 H), 5.11 (s, 2 H), 3.88 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0 (CHO), 153.8 (C), 142.2 (C), 137.0 (C), 131.7 (C), 128.4 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 106.5 (CH), 74.9 (CH_2), 56.1 (CH_3) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2940, 2842, 1692, 1587, 1327, 1126 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{16}O_4$ 272.1049; found 272.1049.

2-(Benzyloxy)-5-(2,2-dibromoethenyl)-1,3-dimethoxybenzene (19): This compound was prepared from **18** by following a synthetic procedure similar to that described for **10**. Treatment of **18** (5.00 g, 18.36 mmol, 1.0 equiv.) with carbon tetrabromide (6.09 g, 18.36 mmol, 1.0 equiv.) and triphenylphosphane (9.63 g, 36.72 mmol, 2.0 equiv.) gave compound **19** (6.45 g, 82% yield) as a white solid. M.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.0 Hz, 2 H), 7.39 (s, 1 H), 7.34–7.27 (m, 3 H), 6.77 (s, 2 H), 5.01 (s, 2 H), 3.81 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (C), 137.5 (C), 137.1 (C), 136.5 (CH), 130.5 (C), 128.3 (CH), 128.0 (CH), 127.8 (CH), 105.7 (CH), 88.5 (C), 74.8 (CH_2), 56.0 (CH_3) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2998, 2958, 1579, 1453, 1418, 1245, 1130 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{16}Br_2O_3$ 427.9446; found 427.9435.

3-[4-(Benzyloxy)-3,5-dimethoxyphenyl]prop-2-yn-1-ol (20): This compound was prepared from **19** by following a synthetic procedure similar to that described for **11**. Treatment of **19** (5.00 g, 11.68 mmol, 1.0 equiv.) with *n*BuLi (2.5 M in hexanes, 11.68 mL, 2.5 equiv.) and paraformaldehyde (0.53 g, 17.52 mmol, 1.5 equiv.) gave compound **20** (2.96 g, 85% yield) as a white solid. M.p. 60–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 1.6 Hz, 2 H), 7.43–7.28 (m, 3 H), 6.64 (s, 2 H), 5.0 (s, 2 H), 4.46 (s, 2 H), 3.78 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2 (C), 137.5 (C), 137.3 (C), 128.4 (CH), 128.0 (CH), 127.8 (CH), 117.6 (C), 108.8 (CH), 86.4 (C), 85.4 (C), 74.9 (CH_2), 56.0 (CH_3), 51.3 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3419, 2938, 2221, 1578, 1502, 1236, 1127 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{18}O_4$ 298.1205; found 298.1199.

(*Z*)-3-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2-(butylthio)prop-2-en-1-ol (21): This compound was prepared from **20** by following a synthetic procedure similar to that described for **12**. Treatment of **20** (2.00 g, 6.70 mmol, 1.0 equiv.) with powdered NaOH (0.32 g, 8.04 mmol, 1.2 equiv.) in CH_3CN (20 mL) and butanethiol (1.08 mL, 10.06 mmol, 1.5 equiv.) gave compound **21** (2.08 g, 80% yield) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.2 Hz, 2 H), 7.33–7.26 (m, 3 H), 6.93 (s, 2 H), 6.72 (s, 1 H), 5.0 (s, 2 H), 4.80 (s, 2 H), 3.81 (s, 6 H), 2.76 (q, J = 7.4 Hz, 2 H), 1.56–1.51 (m, 2 H), 1.40–1.34 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (C), 152.7 (C), 137.5 (C), 136.2 (C), 132.4 (CH), 131.1 (C), 128.1 (CH), 127.8 (CH), 127.5 (CH), 106.7 (CH), 74.7 (CH_2), 67.7 (CH_2), 55.8 (CH_3), 31.6 (CH_2), 31.2 (CH_2), 21.6 (CH_2), 13.3 (CH_3) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3412, 2957, 1221, 1578, 1332, 1128 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{28}O_4S$ 388.1708; found 388.1708.

1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-3-hydroxypropan-2-one (22): This compound was prepared from **21** by following a synthetic procedure similar to that described for **13**. Treatment of **21** (2.00 g, 5.15 mmol, 1.0 equiv.) with ethanol/1 N H_2SO_4 (4:1) gave compound **22** (1.14 g, 70% yield) as a white solid. M.p. 58–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.2 Hz, 2 H), 7.34–7.26

(m, 3 H), 6.38 (s, 2 H), 4.96 (s, 2 H), 4.26 (s, 2 H), 3.78 (s, 6 H), 3.62 (s, 2 H), 2.80 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3 (CO), 153.6 (C), 137.6 (C), 136.1 (C), 128.3 (CH), 128.0 (CH), 127.7 (CH), 106.2 (CH), 74.9 (CH_2), 67.4 (CH_2), 56.0 (CH_3), 45.9 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3479, 2939, 2841, 1722, 1591, 1505, 1242, 1126 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{20}O_5$ 316.1311; found 316.1312.

3-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2-oxopropyl Cyanoacetate (23): This compound was synthesized from **22** by following a synthetic procedure similar to that described for **14**. Treatment of **22** (2.23 g, 7.05 mmol, 1.0 equiv.) with cyanoacetic acid (0.60 g, 7.05 mmol, 1.0 equiv.), pyridine (1.71 mL, 21.16 mmol, 3.0 equiv.), and *N*,*N*-dimethyl phosphoramidodichloridate (1.68 mL, 14.11 mmol, 2.0 equiv.) gave compound **23** (2.38 g, 88% yield) as a brown crystalline solid. M.p. 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 7.6 Hz, 2 H), 7.34–7.24 (m, 3 H), 6.38 (s, 2 H), 4.97 (s, 2 H), 4.80 (s, 2 H), 3.79 (s, 6 H), 3.65 (s, 2 H), 3.55 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4 (CO), 162.4 (CO), 153.6 (C), 137.5 (C), 136.0 (C), 128.3 (CH), 128.0 (CH), 127.7 (CH), 112.7 (CN), 106.2 (CH), 74.8 (CH_2), 68.6 (CH_2), 56.0 (CH_3), 46.3 (CH_2), 24.1 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2939, 2842, 2261, 1762, 1736, 1592, 1423, 1244, 1126 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{21}NO_6$ 383.1369; found 383.1362.

4-[4-(Benzyloxy)-3,5-dimethoxybenzyl]-2-oxotetrahydrofuran-3-carbonitrile (24): This compound was synthesized from **23** by following a synthetic procedure similar to that described for **15**. Treatment of **23** (1.00 g, 2.61 mmol, 1.0 equiv.) with L-proline (0.06 g, 0.52 mmol, 0.2 equiv.) and the Hantzsch ester (0.67 g, 2.61 mmol, 1.0 equiv.) gave compound **24** (0.77 g, 80% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$, major isomer): δ = 7.46–7.44 (m, 2 H), 7.33–7.31 (m, 2 H), 7.29–7.26 (m, 1 H), 6.31 (s, 2 H), 4.96 (s, 2 H), 4.39–4.36 (m, 1 H), 3.99–3.96 (m, 1 H), 3.79 (s, 6 H), 3.78 (d, J = 8.9 Hz, 1 H), 3.16–3.12 (m, 1 H), 2.95 (ab, d, J = 14.0, 5.8 Hz, 1 H), 2.74 (ab, d, J = 14.0, 8.5 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, major isomer): δ = 167.8 (CO), 153.9 (C), 137.5 (C), 136.2 (C), 131.3 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 114.3 (CN), 105.8 (CH), 75.0 (CH_2), 71.3 (CH_2), 56.2 (CH_3), 42.9 (CH), 37.0 (CH), 36.9 (CH_2) ppm. ^{1}H NMR (600 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 6.38 (s, 2 H), 4.25–4.23 (m, 1 H), 4.18–4.16 (m, 1 H), 3.79 (s, 6 H), 3.41 (d, J = 8.9 Hz, 1 H), 3.07–3.04 (m, 1 H), 3.03–2.98 (m, 1 H), 2.66–2.63 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, selected peaks of minor isomer): δ = 167.9 (CO), 153.8 (C), 137.6 (C), 136.0 (C), 132.2 (C), 128.4 (CH), 112.9 (CN), 105.7 (CH), 70.7 (CH_2), 56.1 (CH_3), 40.1 (CH), 37.1 (CH), 35.2 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2940, 2248, 1787, 1591, 1459, 1127 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{21}NO_5$ 367.1420; found 367.1416.

(3*R,4*R**)-4-[4-(Benzyloxy)-3,5-dimethoxybenzyl]-3-{[7-methoxybenzo[*d*][1,3]dioxol-5-yl]methyl}-2-oxotetrahydrofuran-3-carbonitrile (25):** This compound was synthesized from **24** by following a synthetic procedure similar to that described for **16**. Treatment of **24** (0.50 g, 1.36 mmol) with K_2CO_3 (0.23 g, 1.63 mmol) and 5-methoxypiperonyl bromide (0.4 g, 1.63 mmol) gave compound **25** (0.59 g, 82% yield) as a white solid. M.p. 122–125 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.8 Hz, 2 H), 7.30–7.25 (m, 3 H), 6.35 (s, 1 H), 6.31 (s, 2 H), 6.25 (s, 1 H), 5.91 (dd, J = 3.3, 1.4 Hz, 2 H), 4.97 (s, 2 H), 4.16 (dd, J = 9.4, 7.1 Hz, 1 H), 4.02 (t, J = 9.4 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 6 H), 3.25 (d, J = 14.1 Hz, 1 H), 3.01 (d, J = 14.1 Hz, 1 H), 2.76 (dd, J = 12.5, 4.8 Hz, 1 H), 2.68–2.66 (m, 1 H), 2.65 (dd, J = 12.5, 9.1 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2 (CO), 153.7 (C), 149.0 (C), 143.6 (C), 137.4 (C), 135.7 (C), 135.0 (C), 132.1 (C), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.8 (C), 115.3 (CN), 109.9 (CH), 105.4 (CH), 104.1 (CH), 101.5 (CH_2), 74.8 (CH_2), 70.3 (CH_2), 56.6 (CH_3), 55.9 (CH_3), 48.0 (C), 43.0 (CH), 39.0 (CH_2), 35.4 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 2940, 2842, 2238, 1784, 1592, 1508, 1455, 1129, 926 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{29}NO_8$ 531.1893; found 531.1888.

(3*R,4*R**)-4-(4-Hydroxy-3,5-dimethoxybenzyl)-3-{(7-methoxybenzo-[*d*][1,3]dioxol-5-yl)methyl}-2-oxotetrahydrofuran-3-carbonitrile (26):** A mixture of compound **25** (0.50 g, 0.94 mmol) and Pd/C (10%, 0.05 g) in MeOH (25 mL) was stirred under a H_2 atmosphere for 10 min at room temperature. The crude reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:1) to afford compound **26** (0.41 g, 98% yield) as a white solid. M.p. 107–110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.33 (s, 1 H), 6.32 (s, 1 H), 6.26 (s, 1 H), 5.96 (dd, J = 4.0, 1.0 Hz, 2 H), 5.48 (br. s, 1 H), 4.15 (dd, J = 9.4, 7.0 Hz, 1 H), 4.02 (t, J = 9.4 Hz, 1 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 3.28 (d, J = 14.1 Hz, 1 H), 3.05 (d, J = 14.1 Hz, 1 H), 2.79–2.77 (m, 1 H), 2.68–2.62 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3 (CO), 149.1 (C), 147.3 (C), 143.8 (C), 135.2 (C), 133.9 (C), 127.4 (C), 126.9 (C), 115.3 (CN), 110.0 (CH), 105.2 (CH), 104.2 (CH), 101.6 (CH_2), 70.4 (CH_2), 56.7 (CH_3), 56.2 (CH_3), 48.1 (C), 43.3 (CH), 39.2 (CH_2), 35.3 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3480, 2939, 2847, 2239, 1783, 1635, 1516, 1456, 1216, 1115, 925 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{23}NO_8$ 441.1424; found 441.1422.

(±)-4′-Hydroxycubebinone (3): This compound was synthesized from **26** by following a synthetic procedure similar to that described for lignan **1**. Treatment of cyanobutyrolactone **26** (0.20 g, 0.45 mmol) with lithium naphthalenide (3.5 equiv.) followed by quenching with saturated aqueous ammonium chloride solution gave lignan **3** (0.18 g, 95% yield) as a pale-yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 6.27 (s, 1 H), 6.26 (s, 1 H), 6.26 (s, 1 H), 5.91 (s, 2 H), 5.44 (s, 1 H), 4.17 (dd, J = 9.0, 7.2 Hz, 1 H), 3.88 (dd, J = 9.1, 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 2.92 (dd, J = 14.0, 5.2 Hz, 1 H), 2.83 (dd, J = 14.0, 7.1 Hz, 1 H), 2.58–2.57 (m, 2 H), 2.57–2.49 (m, 1 H), 2.48–2.45 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.5 (CO), 148.9 (C), 147.1 (C), 147.1 (C), 143.5 (C), 134.0 (C), 133.5 (C), 132.1 (C), 128.9 (C), 108.6 (CH), 105.4 (CH), 105.1 (CH), 103.2 (CH), 101.4 (CH_2), 71.2 (CH_2), 56.6 (CH_3), 56.3 (CH_3), 56.2 (CH_3), 46.4 (CH), 41.2 (CH), 38.8 (CH_2), 35.0 (CH_2) ppm. IR (CH_2Cl_2, cast): $\tilde{\nu}$ = 3504, 2938, 1763, 1626, 1613, 1513, 1454, 1325, 1124, 1106, 922 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{24}O_8$ 416.1471; found 416.1459.

Acknowledgments

We are grateful to the National Science Council and the National Health Research Institutes of the Republic of China for financial support.

[1] B. Raffaelli, A. Hoikkala, E. Leppala, K. Wahala, *J. Chromatogr. B* **2002**, *777*, 29–43.

[2] a) D. C. Ayres, J. D. Loike, *Lignans: Chemical, Biological and Clinical Properties*, Cambridge University Press, Cambridge, **1990**; b) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75–96 and references cited therein.

[3] a) S. E. Rickard, L. U. Thompson, *ACS Symp., Ser.* **1997**, *662*, 273–293; b) D. M. Tham, C. D. Gardner, W. L. Haskell, *J. Clin. Endocrinol. Metab.* **1998**, *83*, 2223–2235; c) C. D. N. Humfrey, *Nat. Toxins* **1998**, *6*, 51–59; d) J. M. Cline, C. L. Hughes Jr., *Cancer Treat. Res.* **1998**, *94*, 107–134; e) W. Mazur, H. Ad-

lercreutz, *Pure Appl. Chem.* **1998**, *70*, 1759–1776; f) S. Bingham, *Pure Appl. Chem.* **1998**, *70*, 1777–1783.
[4] a) J. L. Charlton, *J. Nat. Prod.* **1998**, *61*, 1447–1451; b) A. J. Vlietinck, T. De Bruyne, S. Apers, L. A. Pieters, *Planta Med.* **1998**, *64*, 97–109.
[5] a) S. R. Stitch, J. K. Toumba, M. B. Groen, C. W. Funke, J. Leemhuis, J. Vink, G. F. Woods, *Nature* **1980**, *287*, 738–740; b) K. D. R. Setchell, A. M. Lawson, F. L. Mitchell, H. Adlercreutz, D. N. Kirk, M. Axelson, *Nature* **1980**, *287*, 740–742; c) M. Axelson, J. Sjovall, B. E. Gustafsson, K. D. R. Setchell, *Nature* **1982**, *298*, 659–660; d) L. U. Thompson, P. Robb, M. Serraino, F. Cheung, *Nutr. Cancer* **1991**, *16*, 43–52.
[6] K. Tomioka, K. Koga, *Tetrahedron Lett.* **1979**, *20*, 3315–3318.
[7] a) K. Lalami, R. Dhal, E. Brown, *Heterocycles* **1988**, *27*, 1131–1134; b) J. L. Belletire, N. O. Mahmoodi, *Synth. Commun.* **1989**, *19*, 3371–3378; c) M. Bella, G. Piancatelli, M. C. Pigro, *Tetrahedron* **1999**, *55*, 12387–12398; d) S. Kamlage, M. Sefkow, B. L. Pool-Zobel, M. G. Peter, *Chem. Commun.* **2001**, 331–332; e) S. Kamlage, M. Sefkow, N. Zimmermann, M. G. Peter, *Synlett* **2002**, 77–80; f) D. J. Bennett, P. L. Pickering, N. S. Simpkins, *Chem. Commun.* **2004**, 1392–1393; g) R. Singh, G. C. Sing, S. K. Ghosh, *Tetrahedron Lett.* **2005**, *46*, 4719–4722.
[8] M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* **2007**, *9*, 1821–1824.
[9] T. Momose, G. Tanabe, H. Tsujimori, O. Muraoka, *Chem. Pharm. Bull.* **1992**, *40*, 2525–2530.
[10] N. Li, J. L. Wu, J. I. Sakai, M. Ando, *J. Nat. Prod.* **2003**, *66*, 1421–1426.
[11] T. Usia, T. Watabe, S. Kadota, Y. Tezuka, *J. Nat. Prod.* **2005**, *68*, 64–68.
[12] a) Y. Ogata, T. Iwasako (Eds.), *Medicinal Herb Index in Indonesia*, 2nd ed., PT Eisai Indonesia Jakarta, **1995**, p. 21; b) S. Sastroamidjojo, *In Obat Asli Indonesia* (Eds.: A. Tjokronegoro), Dian Rakyat, Indonesia, **1997**, p 171.
[13] For the preparation of a stock solution of LN in THF, see: a) H. J. Liu, J. Yip, K. S. Shia, *Tetrahedron Lett.* **1997**, *38*, 2253–2256; b) H. J. Liu, X. Shang, *Tetrahedron Lett.* **1998**, *39*, 367–370.
[14] a) P. K. Amancha, Y. C. Lai, I. C. Chen, H. J. Liu, J. L. Zhu, *Tetrahedron* **2010**, *66*, 871–877; b) W. S. Chang, K. S. Shia, H. J. Liu, T. W. Ly, *Org. Biomol. Chem.* **2006**, *4*, 3751–3753; c) H. J. Liu, T. W. Ly, C. L. Tai, J. D. Wu, J. K. Liang, J. C. Guo, N. W. Tseng, K. S. Shia, *Tetrahedron* **2003**, *59*, 1209–1226; d) J. D. Wu, K. S. Shia, H. J. Liu, *Tetrahedron Lett.* **2001**, *42*, 4207–4209; e) H. J. Liu, Y. L. Ho, J. D. Wu, K. S. Shia, *Synlett* **2001**, 1805–1807; f) C. L. Tai, T. W. Ly, J. D. Wu, K. S. Shia, H. J. Liu, *Synlett* **2001**, 214–217; g) H. J. Liu, J. Yip, *Synlett* **2000**, 1119–1122; h) J. L. Zhu, K. S. Shia, H. J. Liu, *Chem. Commun.* **2000**, 1599–1600; i) K. S. Shia, N. Y. Chang, J. Yip, H. J. Liu, *Tetrahedron Lett.* **1997**, *38*, 7713–7716.
[15] a) D. B. Ramachary, M. Kishor, G. Babul Reddy, *Org. Biomol. Chem.* **2006**, *4*, 1641–1646; b) D. B. Ramachary, M. Kishor, K. Ramakumar, *Tetrahedron Lett.* **2006**, *47*, 651–656; c) C. Mukhopadhyay, P. K. Tapaswi, R. J. Butcher, *Tetrahedron Lett.* **2010**, *51*, 1797–1802; d) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2003**, *42*, 4233–4237; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[16] M. S. Waters, J. A. Cowen, C. J. C. Mc Williums, P. E. Maligres, D. Askin, *Tetrahedron Lett.* **2000**, *41*, 141–144.
[17] H. J. Liu, W. H. Chan, S. P. Lee, *Tetrahedron Lett.* **1978**, *19*, 4461–4464.
[18] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
[19] CCDC-723466 (for **16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Single crystals of **16** were recrystallized from EtOAc/*n*-hexane and mounted in the 150 K, N_2 stream of Siemens Smart CCD diffractometer equipped with a Mo-K_α radiation source (λ = 0.71073 Å). Crystal data: $C_{24}H_{25}NO_8$, M = 455.45, monoclinic, a = 11.0132(5) Å, b = 10.0380(5) Å, c = 20.8248(10) Å, V = 2298.43(19) Å^3, space group $P2_1/n$, Z = 4, a total of 17219 reflections were collected in the range $1.96 < 2\theta < 26.40$. Of these, 4707 were independent; for the observed data, wR_2 = 0.1432, R = 0.0844.
[20] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.

Received: March 8, 2010
Published Online: May 11, 2010

