JOURNAL OF NATURAL PRODUCTS

Article

Cite This: J. Nat. Prod. XXXX, XXX, XXX−XXX

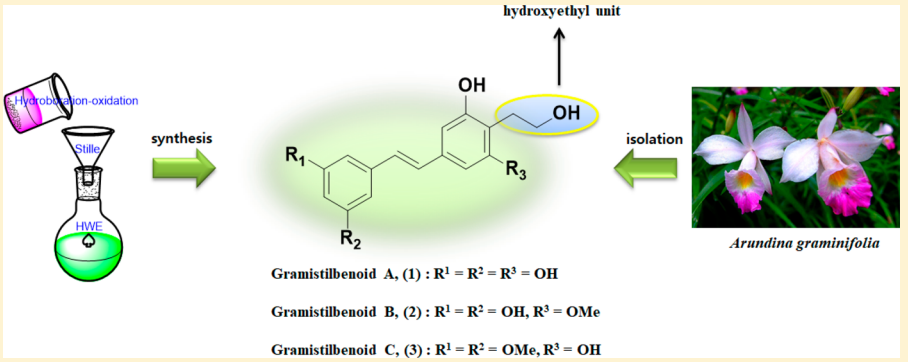
pubs.acs.org/jnp

# Total Synthesis of Gramistilbenoids A, B, and C

Dipesh S. Harmalkar, Qili Lu, and Kyeong Lee*

College of Pharmacy, Dongguk University-Seoul, Goyang, 10326, Republic of Korea

Supporting Information




**ABSTRACT:** Stilbenes are biologically active metabolites of plants that have the potential to attenuate a broad range of human diseases. Gramistilbenoids are a class of natural products with a stilbene skeleton, isolated from the bamboo orchid (*Arundina graminifolia*), and with significant cytotoxicity against cancer cell lines (NB4, A549, SHSY5Y, PC3, and MCF7). These are the first identified naturally occurring diphenylethylenes to possess a hydroxyethyl unit. However, some of these compounds are not abundant in nature, and thus, their synthesis is advantageous. This paper reports the first synthesis of gramistilbenoids A (**1**), B (**2**), and C (**3**), with overall yields of 10, 2, and 8% respectively. These natural products were synthesized using key reactions, such as Horner−Wadsworth−Emmons olefination, Stille coupling, and hydroboration−oxidation.

Natural products have always been an important source of pharmacological compounds. Plant-derived natural extracts are a powerful source of drugs for treating human diseases and are the main source of medicines for the treatment of several illnesses. Consequently, natural products continue to attract the attention of medicinal chemists because of their fascinating structural diversity and complexity.

Natural stilbenes are phenolic compounds characterized by the presence of a 1,2-diphenylethylene backbone. Because of their broad spectrum of biological functions, particularly their cancer chemoprevention activity, these compounds have received considerable attention and have been extensively reviewed.[1a] Stilbenes occur in many plant species including peanut (*Arachis hypogaea*), wine grape (*Vitis vinifera*), sorghum (*Sorghum bicolor*), and many tree species (*Pinus* and *Picea*).[1b] Numerous stilbene analogues show considerable structural diversity and may occur as diphenylethylenes, bibenzyls, phenanthrenes, 9,10-dihydrophenanthrene derivatives, and some phenolic compounds.[2] Such analogues are known to display a wide range of fascinating biological activities such as antioxidant,[3a] antiviral,[3b] antimicrobial,[3c] anti-inflammatory,[4a] anti-HIV,[4b] and anticarcinogenic.[4c,d]

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a potent member of the stilbene family and is the most studied natural polyphenolic compound (Figure 1). Resveratrol exhibits anticancer activity, indicated by its ability to suppress the proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers, cancers of the breast, prostate, stomach, colon, pancreas, and ovarian and cervical carcinomas. The molecule also provides some antiaging health benefits, including improved metabolism and cardioprotection.[5−11] Glycosylated stilbenes from the Chinese herb, *Polygonum multiflorum*, show diverse biological activities, including antitumor, antioxidant, hair growth promotion, antiaggregation, antiatherosclerosis, and anti-inflammatory effects.[12a−f]

Piceatannol (3,4′,3′,5-*trans*-trihydroxystilbene), the lesser-known congener of resveratrol, also exhibits potential anticancer properties. It has the ability to hinder the growth of various tumors and possesses antiparasitic, antibacterial, and antiproliferative properties.[13a] Piceatannol and the natural analogues of *trans*-resveratrol have been shown to be potent inhibitors of cytochrome-P4501A2 (CYP1A2) (7-ethoxyresorufin-*O*-dealkylation assay).[13b] Pinosylvin (3,5-dihydroxy-*trans*-stilbene, Figure 1) a natural stilbenoid, is a resveratrol analogue extracted from *Pinus* species that exerts cancer chemopreventive effects, and inhibits oxidative stress and inflammation.[14a] It also exhibits antimicrobial activity, showing a relatively high activity range against *Saccharomyces cerevisiae* and *Candida albicans*.[14b] Pawhuskin A, a geranylated stilbene displays in vitro opioid receptor affinity. Its beneficial properties have inspired the search for new and more effective analogues.[15]

Received: October 16, 2017

ACS Publications © XXXX American Chemical Society and American Society of Pharmacognosy



DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

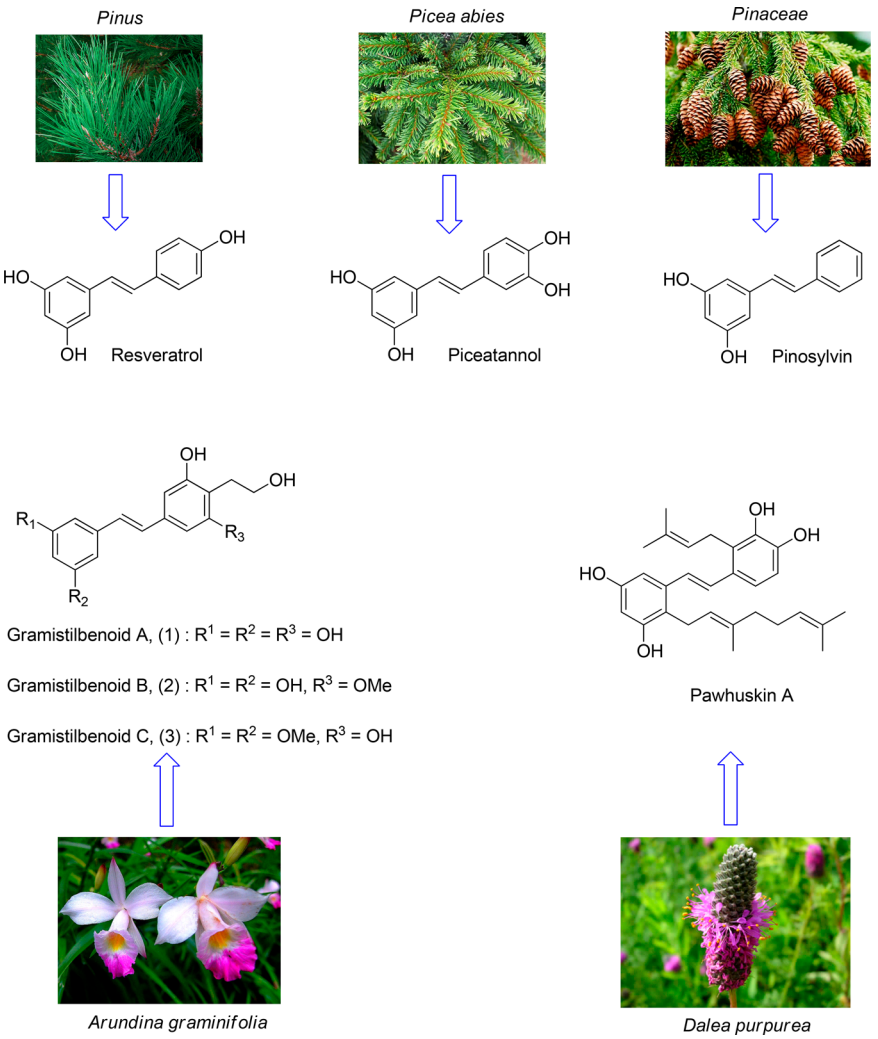
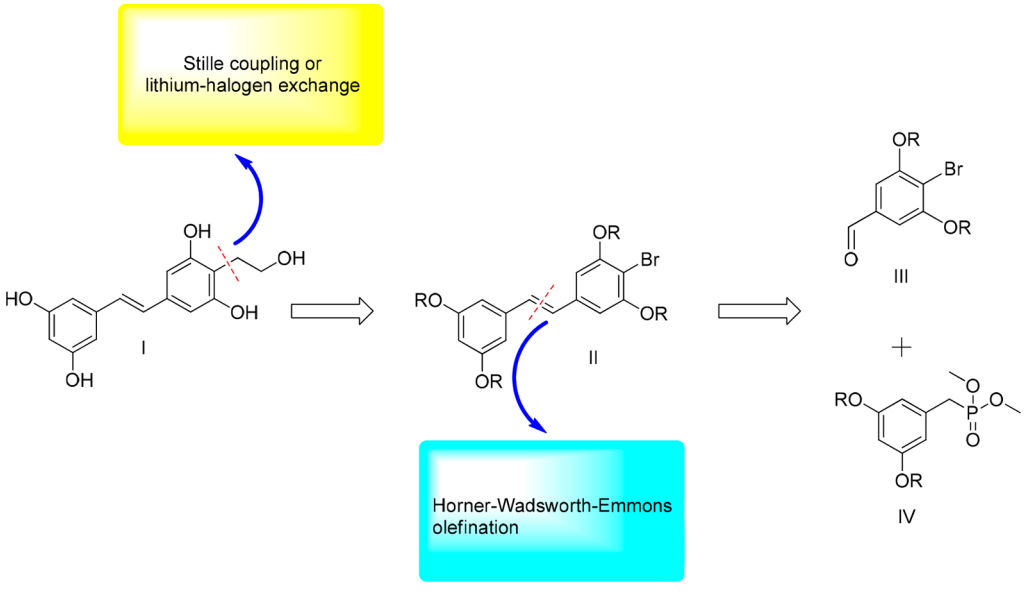



**Figure 1.** Biologically active naturally occurring stilbene analogues.

**Scheme 1. Retrosynthetic Approach to Gramistilbenoids**

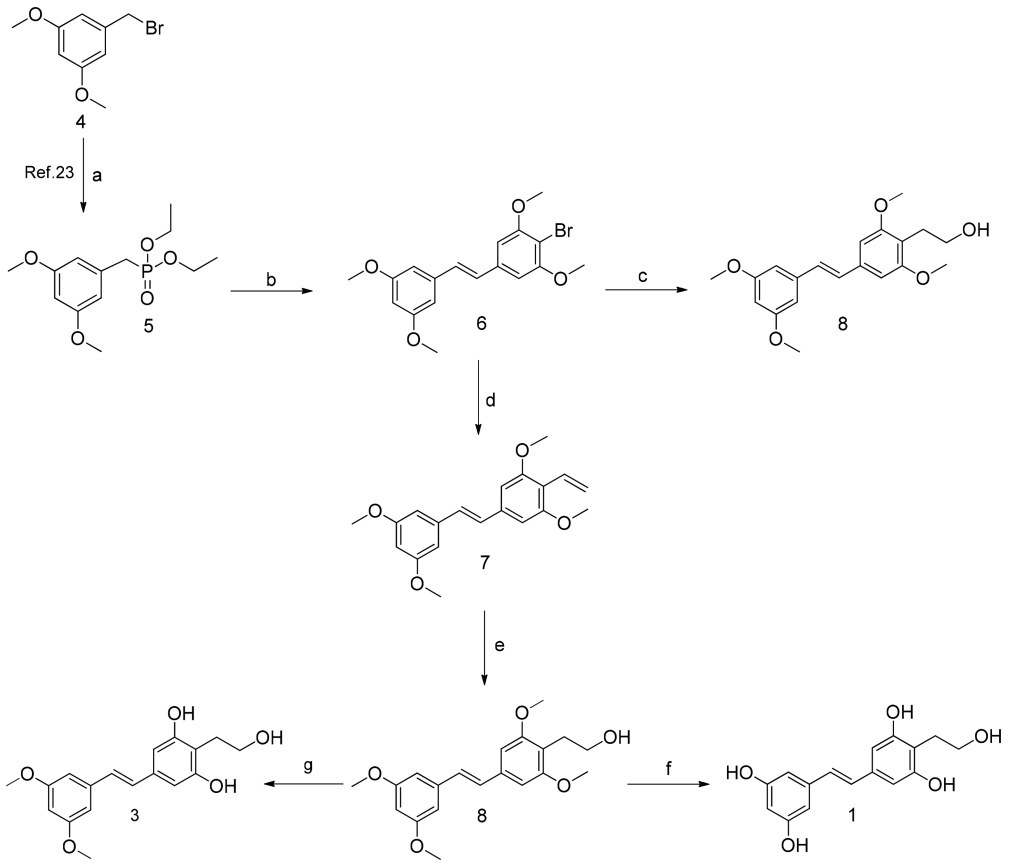



*Arundina graminifolia* (Orchidaceae), known as the bamboo orchid, is a terrestrial multi perennial orchid. It is widely distributed in Southeast Asia, from the Himalayas to western Indonesia. The presence of stilbenoids, bibenzyls, phenan-



DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

**Scheme 2. Synthesis of Gramistilbenoid A (1)**[a]




[a]Reagents and conditions: (a) $P(OEt)_3$, TBAI, 130 °C, 6 h; 90%; (b) 4-Bromo-3,5-dimethoxy- benzaldehyde, NaH, THF, 12 h, 66%; (c) 2.5 M *n*-BuLi in hexanes, 2.5 M ethylene epoxide in THF, THF, −78 °C, 33%; (d) Tributyl(vinyl)tin, CsF, Pd(*t*-$Bu_3P)_2$, toluene, 110 °C, 12 h, 88%; (e) 0.5 M 9-BBN in THF, $H_2O_2$, 2.0 M NaOH, THF, 24 h, 72%; (f) $BBr_3$, $CH_2Cl_2$, −40 °C to rt, 12 h, 64%; (g) 2.0 equiv $BBr_3$, $CH_2Cl_2$, −40 °C to rt, 2 h, 58%.

threnes, and other phenolic compounds has been reported in *A. graminifolia*.[16−21] The entire plant is used in traditional Dai medicine for the treatment of food poisoning and blood stasis and as a liver detoxifying agent. The phenolic compounds gramistilbenoids A, B, and C were first isolated from *A. graminifolia* and showed cytotoxicity against several cancer cell lines (NB4, A549, SHSY5Y, PC3, and MCF7) with $IC_{50}$ values ranging from 1.8 to 8.7 μM.[22] Structurally, they differ in the degree of *O*-methylation. To date, the simple structure and important bioactivity of stilbenes have generated significant interest in the total synthesis of such compounds. Herein, we report the first total synthesis of gramistilbenoids A (**1**), B (**2**), and C (**3**).

## RESULTS AND DISCUSSION

**Retrosynthetic Analysis.** The retrosynthetic analysis for gramistilbenoids A, B, and C is shown in Scheme 1. The synthetic process can be divided into two parts (i.e., Stille coupling and the Horner−Wadsworth−Emmons (HWE) olefination reaction). It relies on an initial disconnection of the hydroxyethyl group of **I** to give **II**. The addition of a hydroxyethyl group was envisioned via treatment of **II** with *n*-butyllithium (*n*-BuLi) and ethylene epoxide or by Stille coupling and a subsequent hydroboration−oxidation reaction. The selective preparation of the (*E*)-stilbene **II**, could be done from **III** and **IV**, via the HWE olefination reaction. In the case of gramistilbenoids B and C, the methoxymethyl (MOM) group was selected as the hydroxy protecting group in the initial step.

*Synthesis of Gramistilbenoid A (**1**).* Based on the retrosynthetic analysis, the synthesis commenced from the readily available 3,5-dimethoxybenzyl bromide (**4**), which underwent Arbuzov reaction when heated with triethyl phosphite and tetrabutylammonium iodide (TBAI), to give the phosphonate **5** (Scheme 2). The resulting phosphonate was susceptible to the HWE olefination reaction with 4-bromo-3,5 dimethoxybenzaldehyde in the presence of sodium hydride (NaH) to afford the (*E*)-stilbene **6**.[23] When treated with *n*-BuLi and subsequently with ethylene epoxide, compound **6** afforded **8** possessing the appropriate hydroxyethyl moiety.[24] However, this reaction was not reproducible and resulted in trace amounts of the expected compound. Thus, a vinyl group was introduced by carbon−carbon bond formation via Stille coupling using tributyl(vinyl)tin, a Pd catalyst, and CsF to give compound **7**.[25a−c] Hydroboration−oxidation of compound **7** using 1.0 M $BH_3$ or 0.5 M 9-BBN in THF gave compound **8** with improved overall yield.[26a] Deprotection of the *O*-methyl groups of **8** with $BBr_3$ smoothly furnished the natural product, gramistilbenoid A (**1**) (Scheme 2).[26b] In an effort to improve the yield of the Stille coupling, different reaction conditions were screened with Pd catalysts such as Pd(*t*-$Bu_3P)_2$ or $Pd(PPh_3)_4$, with CsF as the fluoride source, and THF or toluene as solvents (Table 1). The best results, providing


DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

maximum yield, were achieved using toluene as a solvent with $Pd(t\text{-}Bu_3P)_2$ and CsF.

**Table 1. Reaction Conditions Screened for Stille Coupling**


| entry | solvent | catalyst | additive | yield | temp °C |
|---|---|---|---|---|---|
| 1 | THF | $Pd(PPh_3)_4$ | — | 25% | 66 |
| 2 | THF | $Pd(t\text{-}Bu_3P)_2$ | CsF | 69% | 66 |
| 3 | toluene | $Pd(t\text{-}Bu_3P)_2$ | CsF | 88% | 110 |

Gramistilbenoid C (**3**) possessing two phenolic groups was obtained by demethylation of **8** using $BBr_3$ (Scheme 2). The selective deprotection of the methoxy groups on the ring bearing a hydroxyethyl unit was confirmed by the heteronuclear multiple bond correlation (HMBC) spectra (Figure S-32, Supporting Information).

*Synthesis of MOM-Protected Aldehydes (**14** and **17**).* For the synthesis of gramistilbenoids B and C, MOM-protected aldehydes **14** and **17** were prepared as shown in Scheme 3. The commercially available 4-bromo-3,5-dihydroxybenzoic acid (**9**) was esterified using thionyl chloride and MeOH, to give methyl 4-bromo-3,5-dihydroxybenzoate (**10**).[27] Protection of the phenolic groups using MOMCl in the presence of *N,N*-diisopropylethylamine (DIPEA), gave mono- and diprotected esters **11** and **15**, respectively, with compound **15** more abundant than **11**.[28]

Reduction of di-MOM-protected ester **15** with lithium aluminum hydride (LAH) afforded the benzyl alcohol **16**,[28] which was oxidized to give aldehyde **17** using pyridinium chlorochromate (PCC) (overall yield 65%).[29] Additionally, methylation of compound **11** with MeI and $K_2CO_3$ gave compound **12**,[27] which was subsequently converted to aldehyde **14** over two steps as depicted in Scheme 3 (overall yield 15%).

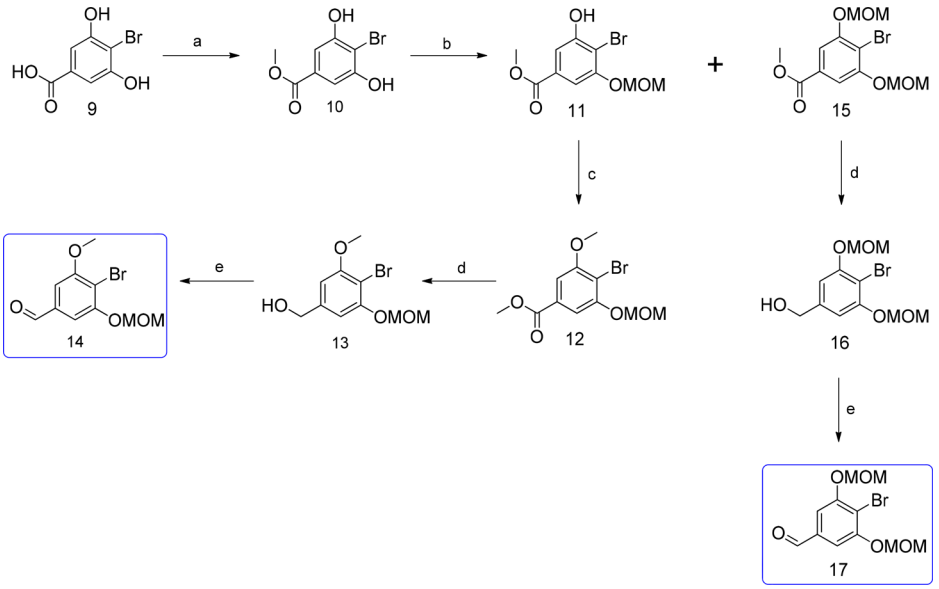
*Synthesis of Gramistilbenoid C (**3**).* Gramistilbenoid C was synthesized via an alternative route (Scheme 4). The synthesis of gramistilbenoid C was attempted via aldehyde **17** because it was more convenient to synthesize than **14**. Accordingly, HWE olefination using aldehyde **17** and phosphonate ester **5** selectively afforded (*E*)-stilbene **18**, which on Stille coupling gave the target **19**.

Furthermore, **19** was subjected to hydroboration−oxidation using 0.5 M 9-BBN in THF. However, there was no conversion even with prolonged stirring (48 h at rt, followed by 12 h at 55 °C), mainly because of the bulkiness of 9-BBN and steric hindrance from the MOM groups. Thus, 1.0 M $BH_3$ in THF was employed, and the reaction mixture was stirred at 55 °C. Under these conditions, the reaction was completed after 12 h. The isolation and subsequent purification of the product were quite difficult; however, column chromatography separation using 0−2% MeOH in $CH_2Cl_2$ afforded **20** as a thick colorless oil. After confirming the formation of **20** by $^1H$ NMR spectroscopy, deprotection of the MOM-groups under acidic conditions afforded gramistilbenoid C (**3**).[30] The NMR spectra of gramistilbenoid C from Schemes 2 and 4 were identical.

*Synthesis of Gramistilbenoid B (**2**).* With aldehyde **14** available, the required phosphonate ester **23** was synthesized from the commercially available 3,5-dimethoxybenzyl bromide (**4**) in three steps (Scheme 5). Demethylation of **4** using 1.0 M $BBr_3$ in $CH_2Cl_2$ generated the phenolic compound **21**, which was protected with the MOM group to give compound **22**. An Arbuzov reaction on **22** afforded the required phosphonate ester **23** (overall yield 34%).

With aldehyde **14** and MOM-protected phosphonate ester **23** in hand, gramistilbenoid B was synthesized similar to gramistilbenoid C. An HWE olefination reaction between **14** and **23**, afforded (*E*)-stilbene **24**. The Stille coupling gave vinyl stilbene **25** that was subjected to hydroboration−oxidation to yield compound **26**. MOM deprotection of **26** with 4.0 M HCl

**Scheme 3. Synthesis of MOM-Protected Aldehydes (14 and 17)**[a]

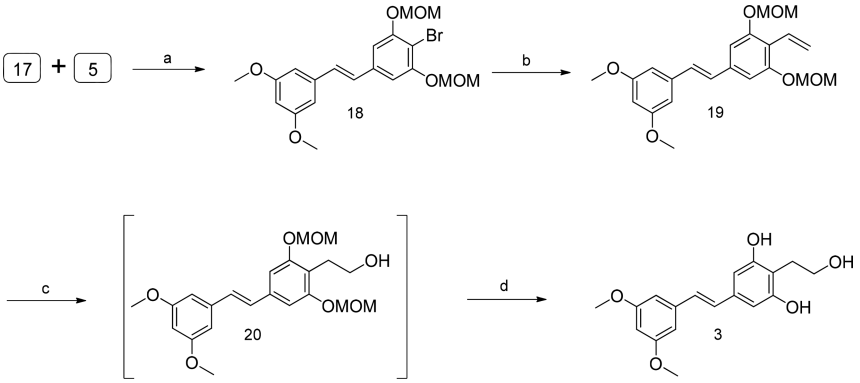



[a]Reagents and conditions: (a) $SOCl_2$, MeOH, 4 h, reflux, 95%; (b) MOMCl, DIPEA, $CH_2Cl_2$, 0 °C to rt, 36% for **11**, 86% for **15**; (c) MeI, $K_2CO_3$, DMF, 12 h, 95%; (d) 2.0 M LAH in THF, THF, −10 °C, 5 min, 63% for **13**, 93% for **16**; (e) PCC, Celite, $CH_2Cl_2$, 12 h, 69% for **14** and 83% for **17**.



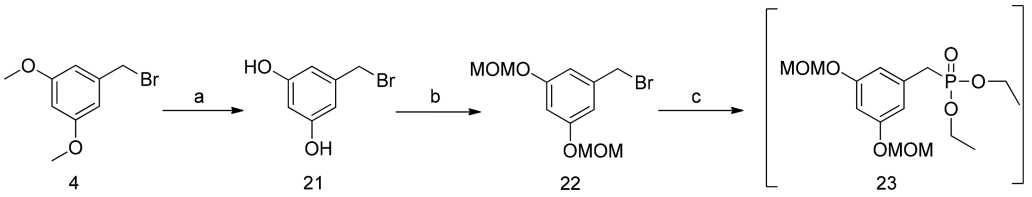
DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

**Scheme 4. Synthesis of Gramistilbenoid C (3)**[a]



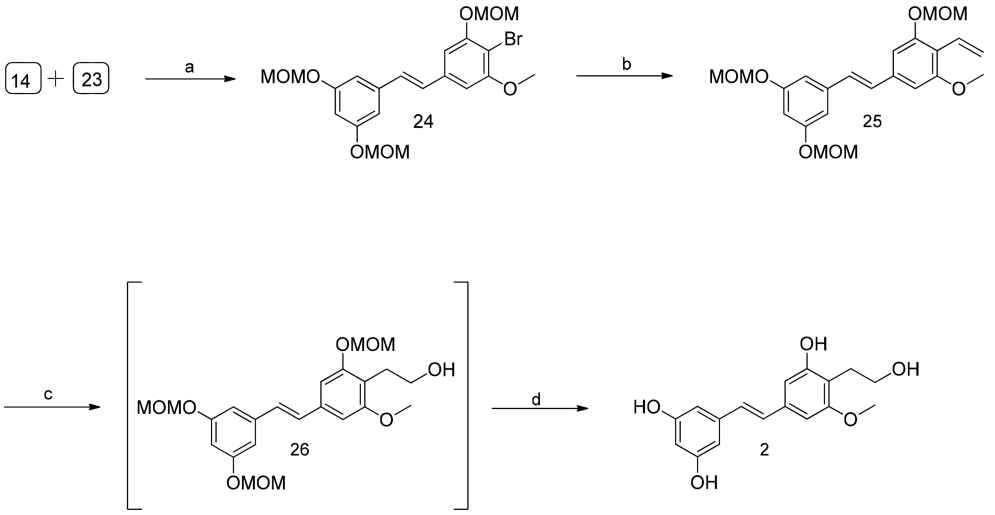

[a]Reagents and conditions: (a) NaH, THF, 12 h, 54%; (b) Tributyl(vinyl)tin, CsF, Pd(*t*-$Bu_3P)_2$, toluene, 110 °C, 12 h, 82%; (c) 1.0 M $BH_3$ in THF, $H_2O_2$, 2.0 M NaOH, THF, 55 °C, 12 h, 73%; (d) 4.0 M HCl in dioxane, MeOH, 2 h, 60 °C, 38%.

**Scheme 5. Synthesis of MOM-Protected Phosphonate Ester (23)**[a]




[a]Reagents and Conditions: (a) 1.0 M $BBr_3$, $CH_2Cl_2$, 0 °C to rt, 6 h, 70%; (b) MOMCl, DIPEA, $CH_2Cl_2$, 0 °C to rt, 12 h, 49%; (c) $P(OEt)_3$ TBAI, 130 °C, 6 h 88%.

**Scheme 6. Synthesis of Gramistilbenoid B (2)**[a]




[a]Reagents and conditions: (a) NaH, THF, 12 h, 53%; (b) Tributyl(vinyl)tin, CsF, Pd(*t*-$Bu_3P)_2$, toluene, 110 °C, 12 h, 89%; (c) 1.0 M $BH_3$ in THF, $H_2O_2$, 2.0 M NaOH, THF, 12 h, 55 °C, 75%; (d) 4.0 M HCl in dioxane, MeOH, 3 h, 60 °C, 38%.

in dioxane afforded the natural product gramistilbenoid B (**2**) (Scheme 6).[30]

In conclusion, the first total synthesis of the natural products, gramistilbenoids A, B, and C were completed. The envisioned synthetic route was achieved using commercially available starting materials by applying HWE olefination, Stille coupling, and hydroboration−oxidation reactions as the key steps. Gramistilbenoids displayed cytotoxicity against several cancer cell lines. Furthermore, the synthetic methodology is well suited to the development of new structural analogues.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** All the commercial chemicals were of reagent grade and were used without further purification. Reactions were conducted under an atmosphere of dried argon in flame-dried glassware. Melting points were measured on Thermo Scientific-9200 apparatus. Infrared (IR) spectra were recorded on an FT-IR Nicolet iS5 spectrometer (ThermoFisher Scientific, Madison, WI, U.S.A.). $^1$H NMR spectra were determined on a Varian (400 or 600 MHz) spectrometer (Varian Medical Systems, Inc., Palo Alto, CA, U.S.A.). The $^1$H NMR data are reported as peak multiplicities: s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, br for broad singlet, and m for multiplet.$^{13}$C NMR spectra



DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

were recorded on a Varian (100 MHz) spectrometer. The values of the chemical shifts are expressed in $\delta$ values (ppm), and the coupling constants ($J$) are reported in Hertz (Hz). Mass spectra were recorded using high-resolution mass spectrometry (HRMS, ESI-MS), obtained on a G2 QTOF mass spectrometer (Waters Corp, Milford, U.S.A.). Products were purified by column or flash chromatography (Biotage, Sweden) using silica gel 60 (230−400 mesh Kieselgel 60). TLC on 0.25 mm silica plates (E. Merck; silica gel 60 F254) was used to monitor the reactions. Spots were detected by viewing under UV light and colorized with charring after dipping in anisaldehyde or basic $KMnO_4$ solution.

*(E)-2-Bromo-5-(3,5-dimethoxystyryl)-1,3-dimethoxybenzene (**6**).* Triethyl phosphite (5.76 g, 34.0 mmol) was added to 3,5-dimethoxybenzyl bromide (**4**) (5.00 g, 21.0 mmol) containing a catalytic amount of tetrabutylammonium iodide (0.79 g, 2.10 mmol), and the reaction mixture was heated at 130 °C for 6 h. Excess triethyl phosphite was removed by heating at 80 °C under vacuum. Diethyl 3,5-dimethoxybenzylphosphonate (**5**) was obtained as a colorless oil (5.60 g, 90%). Compound **5** was used for the next step without further purification.

Diethyl 3,5-dimethoxybenzylphosphonate (**5**) (5.00 g, 17.0 mmol) was dissolved in THF (20.0 mL), and the mixture was stirred at 0 °C under Ar. NaH (60% dispersion in mineral oil, 3.40 g, 86.0 mmol) was slowly added. After 30 min, a solution of 4-bromo-3,5-dimethoxybenzaldehyde (3.82 g, 15.0 mmol) in THF (8.0 mL) was added dropwise. The reaction mixture was stirred for 12 h at rt and monitored by TLC. After completion of the reaction, the mixture was cooled to 0 °C, and excess NaH was destroyed with water. The reaction mixture was poured on ice, followed by the addition of 2.0 N HCl until pH 6, and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 0−5% EtOAc in hexanes), producing **6** as a white solid (3.90 g, 66% yield): mp 161−162 °C; IR (neat) $\nu_{max}$ 1587.62, 1572.65, 1455.67, 1426.66, 1245.10, 1150.58, 1119.69, 1056.99, 964.34, 829.58 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.05 (d, $J$ = 16.4 Hz, 1H), 7.00 (d, $J$ = 16.0 Hz, 1H), 6.71 (s, 2H), 6.68 (d, $J$ = 2.4 Hz, 2H), 6.42 (t, $J$ = 2.4 Hz, 1H), 3.95 (s, 6H), 3.83 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 161.1, 157.2, 138.8, 137.6, 129.5, 128.7, 104.7, 102.9, 100.5, 100.4, 56.5, 55.4; HRMS $m/z$ 379.0606 (calcd for $C_{18}H_{20}BrO_4$ $[M + H]^+$, 379.0545).

*(E)-5-(3,5-Dimethoxystyryl)-1,3-dimethoxy-2-vinylbenzene (**7**).* Tributyl(vinyl)tin (0.53 mL, 1.80 mmol), CsF (0.36 g, 2.40 mmol), and Pd($t$-$Bu_3P$)$_2$ (6.00 mg, 0.01 mmol) were added to a solution of stilbene **6** (0.46 g, 1.20 mmol) in toluene (8.0 mL). The solution was refluxed for 12 h and monitored by TLC. After completion of the reaction, the solution was cooled and filtered through a silica pad to remove a fine tan powder, which was thoroughly washed with $Et_2O$. The filtrate was concentrated in vacuo to give a crude product, which was purified by flash chromatography (silica gel, 0−4% EtOAc in hexanes), to give **7** as a light green solid (0.35 g, 88% yield): mp 120−121 °C; IR (neat) $\nu_{max}$ 1585.16, 1557.82, 1453.17, 1422.05, 1401.31, 1359.83, 1198.61, 1144.87, 1115.64, 1054.36, 998.73, 941.22, 819.60 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.02 (s, 2H), 6.97 (dd, $J$ = 17.8, 12.2 Hz, 1H), 6.69 (s, 2H), 6.67 (d, $J$ = 2.0 Hz, 2H), 6.40 (s, 1H), 6.10 (dd, $J$ = 18.0, 2.8 Hz, 1H), 5.44 (dd, $J$ = 12.2, 2.6 Hz, 1H), 3.90 (s, 6H), 3.83 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 161.0, 158.7, 139.1, 137.2, 129.3, 128.8, 127.2, 118.5, 114.8, 104.6, 102.3, 100.2, 55.7, 55.4; HRMS $m/z$ 327.1681 (calcd for $C_{20}H_{23}O_4$ $[M + H]^+$, 327.1596).

*(E)-2-[4-(3,5-Dimethoxystyryl)-2,6-dimethoxyphenyl]ethanol (**8**).*
*a. Lithium−Halogen Exchange.* To a stirred solution of bromostilbene **6** (0.10 g, 0.26 mmol) in THF (8.0 mL) at −78 °C, 2.5 M $n$-BuLi in hexanes (0.21 mL, 0.54 mmol) was added dropwise. After stirring for 30 min, ethylene epoxide (0.73 mL, 1.82 mmol) was added dropwise and stirred for 1 h at 0 °C. The reaction mixture was carefully quenched with $NH_4Cl$ (sat. aq., 10 mL), followed by extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 0−50% EtOAc in hexanes) yielded alcohol **8** (0.03 g, 33% yield) as a white solid.

*b. Hydroboration−Oxidation.* A solution of compound **7** (0.44 g, 1.34 mmol) in dry THF (10.0 mL) was cooled to 0 °C, and 0.5 M 9-BBN in THF (13.0 mL, 6.70 mmol) was added. The reaction mixture was kept in an ice bath for 30 min, and left at rt for 20 h. The reaction progress was monitored by TLC. After the reaction was complete, the solution was cooled to 0 °C, and MeOH (2.0 mL) was added dropwise. When gas evolution had ceased, $H_2O$ (2.0 mL) was added, followed by a mixture of 2.0 M NaOH (2.0 mL, 3.20 mmol) and $H_2O_2$ (30% (w/w) in $H_2O$, 1.06 mL, 9.30 mmol). The ice bath was removed, and the mixture was stirred vigorously at rt for 4 h. The mixture was filtered to remove the precipitate and the filtrate was diluted with EtOAc (20.0 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (silica gel, 0−50% EtOAc in hexanes), furnishing **8** as a white solid (0.33 g, 72% yield): mp 153−154 °C; IR (neat) $\nu_{max}$ 3324.59, 1585.15, 1445.19, 1416.31, 1154.18, 1125.30, 956.46, 814.28 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.05 (d, $J$ = 16.4 Hz, 1H), 6.99 (d, $J$ = 16.0 Hz, 1H), 6.71 (s, 2H), 6.68 (d, $J$ = 2.4 Hz, 2H), 6.40 (s, 1H), 3.88 (s, 6H), 3.84 (s, 6H), 3.77 (t, $J$ = 6.0 Hz, 2H), 2.98 (t, $J$ = 6.6 Hz, 2H), 1.83 (br, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 161.0, 158.6, 139.2, 136.8, 129.5, 128.5, 115.3, 104.5, 102.2, 100.1, 62.8, 55.8, 55.4, 26.6; HRMS $m/z$ 345.1787 (calcd for $C_{20}H_{25}O_5$ $[M + H]^+$, 345.1702).

*(E)-5-(3,5-Dihydroxystyryl)-2-(2-hydroxyethyl)benzene-1,3-diol [Gramistilbenoid A, (**1**)].* To a stirred solution of **8** (0.23 g, 0.67 mmol) in $CH_2Cl_2$ (5.0 mL), at −40 °C under Ar, $BBr_3$ (0.33 mL, 3.40 mmol) was added. The temperature was gradually increased to rt over a period of 1 h and stirring was continued until completion of the reaction. The unreacted $BBr_3$ was destroyed by adding ice at 0 °C. The mixture was warmed to rt, stirred for 40 min, and concentrated in vacuo. The residue was diluted with EtOAc (20 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, 0−50% EtOAc in hexanes) afforded **1** as a brown semisolid (0.12 g, 64% yield): IR (neat) $\nu_{max}$ 3186.61, 2916.30, 1585.57, 1429.62, 1354.25, 1291.87, 1141.12, 1021.56, 974.78, 816.24, 759.06 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 9.42 (s, 2H), 9.22 (s, 2H), 6.81 (d, $J$ = 16.0 Hz, 1H), 6.72 (d, $J$ = 16.0 Hz, 1H), 6.48 (s, 2H), 6.39 (d, $J$ = 1.6 Hz, 2H), 6.14 (s, 1H), 3.77 (br, 1H), 3.47 (t, $J$ = 8.2 Hz, 2H), 3.05 (t, $J$ = 8.0 Hz, 2H); $^{13}C$ NMR (methanol-$d_4$, 100 MHz) $\delta$ 159.6, 157.8, 140.6, 138.3, 129.5, 129.2, 113.4, 105.6, 105.4, 103.0, 31.4, 28.8; HRMS $m/z$ 289.1101 (calcd for $C_{16}H_{17}O_5$ $[M + H]^+$, 289.1076).

*(E)-5-(3,5-Dimethoxystyryl)-2-(2-hydroxyethyl)benzene-1,3-diol [Gramistilbenoid C, (**3**)].* The experimental procedure for the synthesis of **3** was the same as for **1**. The crude product was purified by silica gel column chromatography (0−50% EtOAc in hexanes) to yield **3** as a brown semisolid (80.0 mg, 58% yield): IR (neat) $\nu_{max}$ 3449.26, 3380.20, 1586.62, 1425.49, 1262.60, 1197.09, 1154.60, 1128.04, 1071.38, 1035.97, 958.06, 821.73 $cm^{-1}$; $^1H$ NMR (methanol-$d_4$, 400 MHz,) $\delta$ 6.94 (d, $J$ = 16.4 Hz, 1H), 6.90 (d, $J$ = 16.4 Hz, 1H), 6.65 (d, $J$ = 2.4 Hz, 2H), 6.49 (s, 2H), 6.38 (t, $J$ = 2.2 Hz, 1H), 3.79 (s, 6H), 3.46 (t, $J$ = 8.4 Hz, 2H), 3.14 (t, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR (methanol-$d_4$, 100 MHz) $\delta$ 162.5, 157.8, 140.8, 138.3, 130.3, 129.1, 113.6, 105.8, 105.4, 100.7, 55.8, 31.4, 28.9; HRMS $m/z$ 317.1408 (calcd for $C_{18}H_{21}O_5$ $[M + H]^+$, 317.1389).

*(E)-2-Bromo-5-(3,5-dimethoxystyryl)-1,3-bis(methoxymethoxy)-benzene (**18**).* The experimental procedure for the synthesis of **18** was the same as for **6**. The crude product was purified by flash chromatography (silica gel, 0−10% EtOAc in hexanes), yielding **18** as a white solid (0.26 g, 54% yield): mp 77−78 °C; IR (neat) $\nu_{max}$ 1583.93, 1452.59, 1398.16, 1332.49, 1240.49, 1140.67, 1108.7, 1072.41, 1012.79, 918.61 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.03 (d, $J$ = 16.0 Hz, 1H), 6.99 (s, 2H), 6.98 (d, $J$ = 16.4 Hz, 1H), 6.66 (d, $J$ = 2.4 Hz, 2H), 6.41 (t, $J$ = 2.2 Hz, 1H), 5.30 (s, 4H), 3.82 (s, 6H), 3.55 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 160.9, 155.1, 138.8, 137.6, 129.7, 128.3, 170.5, 104.5, 102.9, 100.5, 95.1, 56.4, 55.3; HRMS $m/z$ 439.3065 (calcd for $C_{20}H_{24}BrO_6$ $[M + H]^+$, 439.0756).


DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

*(E)-5-(3,5-Dimethoxystyryl)-1,3-bis(methoxymethoxy)-2-vinylbenzene (**19**).* The experimental procedure for the synthesis of **19** was the same as for **7**. The crude product was purified by flash chromatography (silica gel, 0−10% EtOAc in hexanes) to yield **19** as a white solid (0.06 g, 82% yield): mp 74−75 °C; IR (neat) $\nu_{max}$ 1591.74, 1459.15, 1424.39, 1390.44, 1345.16, 1318.48, 1269.98, 1193.98, 1148.71, 1105.05, 1084.84, 1055.74, 1029.87, 957.11, 914.26 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.01 (s, 2H), 6.97 (s, 2H), 6.96 (d, $J$ = 18.0 Hz, 1H), 6.67 (d, $J$ = 2.4 Hz, 2H), 6.40 (t, $J$ = 2.4 Hz, 1H), 6.11 (dd, $J$ = 18.0, 2.8 Hz, 1H), 5.47 (dd, $J$ = 12.0, 2.8 Hz, 1H), 5.27 (s, 4H), 3.83 (s, 6H), 3.52 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 160.9, 156.3, 139.1, 137.4, 129.1, 128.9, 127.3, 118.9, 116.5, 106.7, 104.5, 100.4, 94.7, 56.2, 55.4; HRMS $m/z$ 387.1815 (calcd for $C_{22}H_{27}O_6$ $[M + H]^+$ 387.1808).

*(E)-5-(3,5-Dimethoxystyryl)-2-(2-hydroxyethyl)benzene-1,3-diol [Gramistilbenoid C, (**3**)].* A solution of compound **19** (0.05 g, 0.12 mmol) in dry THF (5.0 mL) was cooled to 0 °C and 1.0 M $BH_3$ in THF (0.13 mL, 0.13 mmol) was added. The reaction mixture was left in an ice bath for 30 min, and then heated to 55 °C for 12 h, after which it was cooled to 0 °C and MeOH (0.5 mL) was added dropwise. When gas evolution had ceased, $H_2O$ (0.5 mL) was added, followed by a mixture of 2.0 M NaOH (0.07 mL, 0.15 mmol) and $H_2O_2$ (30% (w/w) in $H_2O$, 0.09 mL, 0.86 mmol). The ice bath was removed, and the mixture was stirred vigorously at rt for 5 h. The mixture was filtered to remove the precipitate, and the filtrate was diluted with EtOAc (15.0 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (0−2% MeOH in $CH_2Cl_2$) to give **20** as a colorless oil (37.0 mg, 73%). The oil was used for the final step without further purification.

HCl (4.0 M in dioxane, 0.09 mL, 0.36 mmol) was added to a stirred solution of the intermediate **20** (37.0 mg, 0.11 mmol) in MeOH (6.0 mL). Stirring was continued at 60 °C for 2 h. After completion of the reaction, the solution was cooled, saturated $NaHCO_3$ solution (5.0 mL) was added, and the MeOH was evaporated. After extracting the reaction mixture with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (0−50% EtOAc in hexanes), affording gramistilbenoid C (**3**) as a brown semisolid (11.0 mg, 38% yield).

*(E)-5-[3,5-Bis(methoxymethoxy)styryl]-2-bromo-1-methoxy-3-(methoxymethoxy)benzene (**24**).* Triethyl phosphite (0.54 g, 3.29 mmol) was added to compound **22** (0.60 g, 2.06 mmol) with a catalytic amount of tetrabutylammonium iodide (76.0 mg, 0.20 mmol), and the reaction mixture was heated at 130 °C for 6 h. Excess triethyl phosphite was removed by heating at 80 °C under vacuum, giving **23** as a colorless oil (0.63 g, 88%). Compound **23** was used for the next step without further purification.

The experimental procedure for the synthesis of **24** was the same as for **6**. The crude product was purified by flash chromatography (silica gel, 0−10% EtOAc in hexanes) to give **24** as a white semisolid (0.15 g, 53% yield): IR (neat) $\nu_{max}$ 1583.93, 1452.59, 1398.16, 1332.49, 1240.04, 1140.67, 1108.70, 1072.41, 1012.79, 918.61 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.04 (d, $J$ = 16.0 Hz, 1H), 6.99 (d, $J$ = 16.4 Hz, 1H), 6.95 (d, $J$ = 1.6 Hz, 1H), 6.88 (d, $J$ = 2.0 Hz, 2H), 6.75 (d, $J$ = 1.6 Hz, 1H), 6.66 (t, $J$ = 2.0 Hz, 1H), 5.30 (s, 2H), 5.19 (s, 4H), 3.95 (s, 3H), 3.55 (s, 3H), 3.50 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 158.5, 157.1, 155.1, 139.0, 137.5, 129.3, 128.7, 107.8, 106.8, 104.8, 103.6, 101.7, 95.1, 94.4, 56.4, 56.1; HRMS $m/z$ 469.3107 (calcd for $C_{21}H_{26}BrO_7$ $[M + H]^+$, 469.0862).

*(E)-5-[3,5-Bis(methoxymethoxy)styryl]-1-methoxy-3-(methoxymethoxy)-2-vinylbenzene (**25**).* The experimental procedure for the synthesis of **25** was the same as for **7**. The crude product was purified by flash chromatography (silica gel, 0−10% EtOAc in hexanes) to yield **25** as a white semisolid (0.10 g, 89% yield): IR (neat) $\nu_{max}$ 1583.93, 1452.59, 1398.16, 1332.49, 1240.04, 1140.67, 1108.70, 1072.41, 1012.79, 918.61 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.01 (s, 2H), 6.95 (dd, $J$ = 18.0, 5.6 Hz, 1H), 6.91 (s, 1H), 6.88 (d, $J$ = 2.0 Hz, 2H), 6.75 (s, 1H), 6.65 (t, $J$ = 2.2 Hz, 1H), 6.10 (dd, $J$ = 18.0, 2.8 Hz, 1H), 5.46 (dd, $J$ = 12.0, 2.8 Hz, 1H), 5.26 (s, 2 H), 5.19 (s, 4H), 3.91 (s, 3H), 3.52 (s, 3H), 3.50 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 158.7, 158.5, 156.2, 139.3, 137.2, 129.2, 128.6, 127.2, 118.7, 115.6, 107.7, 106.0, 104.6, 102.9, 94.7, 94.4, 56.2, 56.1, 55.7; HRMS $m/z$ 417.4232 (calcd for $C_{23}H_{29}O_7$ $[M + H]^+$, 417.1913).

*(E)-5-[3-Hydroxy-4-(2-hydroxyethyl)-5-methoxystyryl]benzene-1,3-diol [Gramistilbenoid B, (**2**)].* A solution of compound **25** (0.08 g, 1.34 mmol) in dry THF (10.0 mL) was cooled to 0 °C and 1.0 M $BH_3$ in THF (13.0 mL, 6.70 mmol) was added. The reaction mixture was left in an ice bath for 30 min and then heated at 55 °C for 12 h, after which it was cooled to 0 °C and MeOH (2.0 mL) was added dropwise. When gas evolution had ceased, $H_2O$ (2.0 mL) was added, followed by a mixture of 2.0 M NaOH (2.0 mL, 3.20 mmol) and $H_2O_2$ (30% (w/w) in $H_2O$, 1.06 mL, 9.30 mmol). The ice bath was removed and the mixture was stirred vigorously at rt for another 5 h. The mixture was filtered to remove the precipitate, and the filtrate was diluted with EtOAc (20.0 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0−2% MeOH in $CH_2Cl_2$), which yielded **26** as a colorless oil (63.0 mg, 75%). The oil obtained was used for the final step without further purification.

HCl (4.0 M in dioxane, 0.16 mL, 0.65 mmol) was added to a stirred solution of the intermediate **26** (47.0 mg, 0.11 mmol) in MeOH (6.0 mL). Stirring was continued at 60 °C for 3 h. After completion of the reaction, the solution was cooled, saturated $NaHCO_3$ solution (5.0 mL) was added, and the MeOH was evaporated. After extracting the reaction mixture with EtOAc (3 × 5 mL) the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (0−1% MeOH in $CH_2Cl_2$) to obtain **2** as a brown semisolid (7.00 mg, 38%): IR (neat) $\nu_{max}$ 3287.39, 2914.07, 1585.06, 1450.66, 1146.41, 1090.41, 1000.81, 954.15, 830.95 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 600 MHz) $\delta$ 9.32 (s, 1H), 9.24 (s, 2H), 6.91 (d, $J$ = 16.2 Hz, 1H), 6.88 (d, $J$ = 16.2 Hz, 1H), 6.68 (s, 1H), 6.59 (s, 1H), 6.41 (d, $J$ = 1.8 Hz, 2H), 6.15 (t, $J$ = 2.1 Hz, 1H), 4.67 (t, $J$ = 5.1 Hz, 1H), 3.78 (s, 3H), 3.41−3.37 (m, 2H), 2.72 (t, $J$ = 7.8 Hz, 2H); $^{13}C$ NMR (methanol-$d_4$, 100 MHz) $\delta$ 160.4, 159.8, 157.7, 140.8, 138.1, 129.8, 129.3, 142.3, 107.5, 106.0, 103.1, 101.7, 62.5, 56.1, 27.7; HRMS $m/z$ 303.1234 (calcd for $C_{17}H_{19}O_5$ $[M + H]^+$, 303.1232).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00865.

Experimental procedures for compounds **10**−**17**, **21**, and **22**, and $^1H$ and $^{13}C$ NMR spectra for the new compounds and new intermediates, including HMBC spectra for synthetic gramistilbenoid C (**3**) (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*Phone: +82-31-961-5214. E-mail: kaylee@dongguk.edu.

### ORCID

Dipesh S. Harmalkar: 0000-0002-0201-2916

Kyeong Lee: 0000-0002-5455-9956


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (Nos. 2012M3A9C1053532 and 2015M3A6A4065734).



DOI: 10.1021/acs.jnatprod.7b00865
J. Nat. Prod. XXXX, XXX, XXX−XXX

## REFERENCES


(1) (a) Fulda, S. *Drug Discovery Today* **2010**, *15*, 757−765. (b) Parage, C.; Tavares, R.; Réty, S.; Baltenweck-Guyot, R.; Poutaraud, A.; Renault, L.; Heintz, D.; Lugan, R.; Marais, G. A. B.; Aubourg, S.; Hugueney, P. *Plant Physiol.* **2012**, *160*, 1407−1419.

(2) Shen, T.; Wang, X. N.; Lou, H. X. *Nat. Prod. Rep.* **2009**, *26*, 916−935.

(3) (a) Jung, J. C.; Lim, E.; Lee, Y.; Kang, J. M.; Kim, H.; Jang, S.; Oh, S.; Jung, M. *Eur. J. Med. Chem.* **2009**, *44*, 3166−3174. (b) Evers, D. L.; Wang, X.; Huong, S. M.; Huang, D. Y.; Huang, E. S. *Antiviral Res.* **2004**, *63*, 85−95. (c) Albert, S.; Horbach, R.; Deising, H. B.; Siewert, B.; Csuk, R. *Bioorg. Med. Chem.* **2011**, *19*, 5155−5166.

(4) (a) Lee, M.; Kim, S.; Kwon, O. K.; Oh, S. R.; Lee, H. K.; Ahn, K. *Int. Immunopharmacol.* **2009**, *9*, 418−424. (b) Bedoya, L. M.; del Olmo, E.; Sancho, R.; Barboza, B.; Beltrán, M.; García-Cadenas, A. E.; Sánchez-Palomino, S.; López-Pérez, J. L.; Muñoz, E.; San Feliciano, A.; Alcamí, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4075−4079. (c) Mikstacka, R.; Stefański, T.; Różański, J. *Cell. Mol. Biol. Lett.* **2013**, *18*, 368−397. (d) Sirerol, J. A.; Rodríguez, M. L.; Mena, S.; Asensi, M. A.; Estrela, J. M.; Ortega, A. L. *Oxid. Med. Cell. Longevity* **2016**, *2016*, 3128951.

(5) Markus, M. A.; Morris, B. J. *Clin. Interv. Aging* **2008**, *3*, 331−339.

(6) Aggarwal, B. B.; Bhardwaj, A.; Aggarwal, R. S.; Seeram, N. P.; Shishodia, S.; Takada, Y. *Anticancer Res.* **2004**, *24*, 2783−2840.

(7) Goswami, S. K.; Das, D. K. *Cancer Lett.* **2009**, *284*, 1−6.

(8) Athar, M.; Back, J. H.; Kopelovich, L.; Bickers, D. R.; Kim, A. L. *Arch. Biochem. Biophys.* **2009**, *486*, 95−102.

(9) Pervaiz, S.; Holme, A. L. *Antioxid. Redox Signaling* **2009**, *11*, 2851−2897.

(10) Camins, A.; Junyent, F.; Verdaguer, E.; Beas-Zarate, C.; Rojas-Mayorquín, A. E.; Ortuño-Sahagún, D.; Pallàs, M. *Pharmaceuticals* **2009**, *2*, 194−205.

(11) Nalli, M.; Ortar, G.; Moriello, A. S.; Morera, E.; Di Marzo, V.; De Petrocellis, L. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 899−902.

(12) (a) Li-Shuang, L. V.; Gu, X.; Ho, C. T.; Tang, J. *J. Food Lipids* **2006**, *13*, 131−144. (b) Kimura, Y.; Okuda, H. *J. Pharm. Pharmacol.* **2000**, *52*, 1287−1295. (c) Sun, Y. N.; Cui, L.; Li, W.; Yan, X. T.; Yang, S. Y.; Kang, J. I.; Kang, H. K.; Kim, Y. H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4801−4805. (d) Xiang, K.; Liu, G.; Zhou, Y. J.; Hao, H. Z.; Yin, Z.; He, A. D.; Da, X. W.; Xiang, J. Z.; Wang, J. L.; Ming, Z. Y. *Thromb. Res.* **2014**, *133*, 211−217. (e) Yao, W.; Fan, W.; Huang, C.; Zhong, H.; Chen, X.; Zhang, W. *Biomed. Pharmacother.* **2013**, *67*, 140−145. (f) Zeng, C.; Xiao, J. H.; Chang, M. J.; Wang, J. L. *Molecules* **2011**, *16*, 8552−8568.

(13) (a) Piotrowska, H.; Kucinska, M.; Murias, M. *Mutat. Res., Rev. Mutat. Res.* **2012**, *750*, 60−82. (b) Mikstacka, R.; Rimando, A. M.; Szalaty, K.; Stasik, K.; Baer-Dubowska, W. *Xenobiotica* **2006**, *36*, 269−285.

(14) (a) Jančinová, V.; Perečko, T.; Nosál, R.; Harmatha, J.; Šmidrkal, J.; Drábiková, K. *Acta Pharmacol. Sin.* **2012**, *33*, 1285−1292. (b) Lee, S. K.; Lee, H. J.; Min, H. Y.; Park, E. J.; Lee, K. M.; Ahn, Y. H.; Cho, Y. J.; Pyee, J. H. *Fitoterapia* **2005**, *76*, 258−260.

(15) Belofsky, G.; French, A. N.; Wallace, D. R.; Dodson, S. L. *J. Nat. Prod.* **2004**, *67*, 26−30.

(16) Liu, M. F.; Han, Y.; Xing, D. M.; Shi, Y.; Xu, L. Z.; Du, L. J.; Ding, Y. *J. Asian Nat. Prod. Res.* **2004**, *6*, 229−232.

(17) Liu, M. F.; Han, Y.; Xing, D. M.; Wang, W.; Xu, L. Z.; Du, L. J.; Ding, Y. *J. Asian Nat. Prod. Res.* **2005**, *7*, 767−770.

(18) Li, L.; Xu, W. X.; Liu, C. B.; Zhang, C. M.; Zhao, W.; Shang, S. Z.; Deng, L.; Guo, Y. D. *Asian J. Chem.* **2015**, *27*, 3525−3526.

(19) Gao, X.; Yang, L.; Shen, Y.; Shu, L.; Li, X.; Hu, Q. F. *Bull. Korean Chem. Soc.* **2012**, *33*, 2447−2449.

(20) Li, Y. K.; Zhou, B.; Ye, Y. Q.; Du, G.; Niu, D. Y.; Meng, C. Y.; Gao, X. M.; Hu, Q. F. *Bull. Korean Chem. Soc.* **2013**, *34*, 3257−3260.

(21) Hu, Q. F.; Zhou, B.; Huang, J. M.; Gao, X. M.; Shu, L. D.; Yang, G. Y.; Che, C. T. *J. Nat. Prod.* **2013**, *76*, 292−296.

(22) Hu, Q. F.; Zhou, B.; Ye, Y. Q.; Jiang, Z. Y.; Huang, X. Z.; Li, Y. K.; Du, G.; Yang, G. Y.; Gao, X. M. *J. Nat. Prod.* **2013**, *76*, 1854−1859.

(23) Li, Y. Q.; Li, Z. L.; Zhao, W. J.; Wen, R. X.; Meng, Q. W.; Zeng, Y. *Eur. J. Med. Chem.* **2006**, *41*, 1084−1089.

(24) Nicolaou, K. C.; Sun, Y. P.; Korman, H.; Sarlah, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5875−5878.

(25) (a) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144−13145. (b) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem. - Eur. J.* **2005**, *11*, 3294−3308. (c) Gajare, A. S.; Jensen, R. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Synlett* **2005**, No. 1, 144−148.

(26) (a) Kachare, D.; Song, X. P.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2720−2723. (b) Shadakshari, U.; Rele, S.; Nayak, S. K.; Chattopadhyay, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43B*, 1934−1938.

(27) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem. - Eur. J.* **2002**, *8*, 1856−1871.

(28) Chakrapani, L.; Jung, E. M.; Lee, Y. R. *Helv. Chim. Acta* **2010**, *93*, 829−836.

(29) Mao, F.; Yan, J.; Li, J.; Jia, X.; Miao, H.; Sun, Y.; Huang, L.; Li, X. *Org. Biomol. Chem.* **2014**, *12*, 5936−5944.

(30) Gester, S.; Pietzsch, J.; Wuest, F. R. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 105−113.




DOI: 10.1021/acs.jnatprod.7b00865
*J. Nat. Prod.* XXXX, XXX, XXX−XXX