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Five New Stilbenes from the Stem Bark of *Artocarpus communis*

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Abstract – Five new prenylated stilbenes (**1** - **5**), along with the known compounds cudraflavone C, *trans*-4-isopentenyl-3,5,2',4'-terahydroxystilbene, *trans*-4-(3-methyl-*E*-but-1-enyl)-3,5,2',4'-tetrahydroxystilbene, pannokin G, cycloartobiloxanthone, artonin P, morusin, artocarpin, artonin E, kuwanon C, artobiloxanthone, and artoindonesianin C (**6** - **17**) were isolated from the stem bark of the tropical tree *Artocarpus communis*. The structures were established by NMR spectroscopic analysis, MS studies, and comparison with spectral data reported in the literature.
Keywords – *Artocarpus communis*, *Artocarpus altilis*, Moraceae, stilbene

Introduction

The flowering tropical tree *Artocarpus communis* J. R. Forst. & G. Forst. (Moraceae), synonymous with *Artocarpus altilis*, is native to Indonesia, Papua New Guinea and Pacific and Tropical Asia. It is commonly known as breadfruit, derived from the Greek words "artos" (bread) and "karpos" (fruit), and it is planted for its edible fruit and as an ornamental or shade tree. *A. communis* has been used in traditional medicine in the Pacific Islands for a variety of ailments including liver cirrhosis, hypertension, diabetes, skin ailments, and tapeworm infection.[1] Previous phytochemical investigations of this plant have yielded over 130 compounds, of which, flavonoids, aryl benzofurans, stilbenoids, and lectins are largely responsible for the reported pharmacological effects of the plant.[2] As part of a molecularly targeted screening program at the U.S. National Cancer Institute to discover new bioactive metabolites and potential drug leads from natural products, we investigated the chemistry of a Philippines collection of *A. communis*. The organic solvent extract of the stem bark modulated the activity of the oncogenic transcription factor, hypoxia inducible factor-2 alpha (HIF-2α), in a high-throughput cell-based screen.[3] Hypoxia inducible factors are key regulators of cancer cell adaptation and survival in the low oxygen environments associated with many solid tumors and are thus attractive anticancer therapeutic targets.[4] Details of the HIF-2α screening assay have been previously described.[5] Subsequent chemical investigation of the *A. communis* extract led to the isolation of five new stilbenes (**1** - **5**), together with twelve known compounds (**6** - **17**). The structures of **1** - **5** were elucidated by spectroscopic methods, including 1D and 2D NMR studies, and MS analysis.

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Experimental

General experimental procedures – Optical rotations were measured on a PerkinElmer 241 polarimeter. UV spectra were recorded on a Varian Cary 50 UV/Vis spectrophotometer. NMR spectra were obtained with a Bruker Avance III spectrometer operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C and equipped with a 3 mm cryogenic probe. HRESIMS spectra were acquired on an Agilent Technologies 6530 Accurate-mass Q-TOF LC/MS. HPLC was performed using a Varian PrepStar HPLC using a Phenomenex Luna C_{18} (5 μ, 300 Å, 250 × 10 mm) column.

Plant materials – The stem bark of *A. communis* was collected in the Philippines in July 1992 by D. Doel Soejarto. A voucher specimen (U44Z-7816) is deposited at the Smithsonian Institution, Washington, D. C.

Extraction and isolation – Following the standard NCI extraction protocol, the plant material (353 g) was ground and immersed in CH_2Cl_2-MeOH (1:1) for 15 h in a Soxhlet apparatus.[6] The solvent was removed, and the plant material was immersed for another 15 h in 100% MeOH. The combined extracts were reduced to dryness in vacuo to give 36 g of crude extract.

A portion of the extract (504 mg) was separated by Diol solid-phase extraction eluting with hexane-CH_2Cl_2 (9:1), CH_2Cl_2-EtOAc (20:1), 100% EtOAc, EtOAc-MeOH (5:1) and 100% MeOH. Size exclusion chromatography of the 20:1 CH_2Cl_2-EtOAC fraction (116 mg) on Sephadex LH-20, with hexane-CH_2Cl_2-MeOH (2:5:1) as the eluent, provided eight major fractions (A-H). Fraction E (11.2 mg) was purified by reversed-phase HPLC eluting with a gradient of 60 - 100% acetonitrile over 30 min at a flow rate of 4 mL/min to yield **3** (1.4 mg), **4** (0.5 mg), **5** (0.2 mg), and **9** (1.1 mg). Fractions D (19.1 mg) and G (19.2 mg) were subjected to further Sephadex LH-20 chromatography with 100% MeOH which yielded four sub-fractions each. Sub-fractions C1 (8.1 mg) and D1 (7.0 mg) from fraction D and sub-fraction B1 (10.6 mg) from fraction G were also purified by reversed-phase HPLC eluting with a gradient of 60 - 100% aqueous acetonitrile over 30 min to yield **10** (4.8 mg), **11** (1.4 mg), **12** (3.2 mg), **13** (0.9 mg), and **17** (0.8 mg).

Size exclusion chromatography of the 100% EtOAC fraction (245 mg) on Sephadex LH-20 with hexane-CH_2Cl_2-MeOH (2:5:1) provided seven major sub-fractions (A-H). Sub-fractions D (116 mg) and F (13.0 mg) were purified by reversed-phase HPLC as described above to yield **1** (0.5 mg), **2** (1.2 mg), **6** (0.6 mg), and **14** (12.1 mg). Sub-fraction H (3.1 mg) was purified by reversed-phase HPLC eluting with a gradient of 30 - 100% aqueous acetonitrile over 30 min at a flow rate of 4 mL/min to yield **7** (0.5 mg) and **8** (1.0 mg).

Table 1. ^{1}H NMR Assignments (600 MHz, CD_3OD) for compounds **1** - **5**

	1	**2**	**3**	**4**	**5**
position	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)
1					
2			7.04, s		7.03, d (2.1)
3					
4					
5					
6	7.08, s	7.14, s	7.04, s	7.11, s	7.11, d (2.1)
7	3.41, d (7.0)	6.71, d (9.9)	3.33, m	6.64, d (9.7)	6.38, d (9.70)
8	5.20, br t (7.3)	5.63, d (10.0)	5.34, br t (7.3)	5.68, d (10.0)	5.70, d (9.6)
9					
10	1.80, s	1.39, s	1.75, s	1.45, s	1.41, s
11	1.68, s	1.39, s	1.77, s	1.45, s	1.41, s
12	3.27, d (7.3)	3.20, d (7.3)	3.33, m	6.35, d (8.9)	3.27, d (7.5)
13	5.33, br t (7.3)	5.26, m	5.34, br t (7.3)	5.60, d (9.0)	5.28, tt (1.6, 7.5)
14					
15	1.75, s	1.76, s	1.75, s	1.42, s	1.74, s
16	1.77, s	1.73, s	1.77, s	1.42, s	1.76, s
α	7.32, d (16.2)	7.32, d (16.3)	6.85, d (16.5)	7.24, d (16.2)	6.92, d (16.2)
β	6.71, d (16.2)	6.76, d (16.3)	6.68, d (16.6)	6.87, d (16.4)	6.80, d (16.2)
1′					
2′	6.46, d (2.2)	6.47, d (2.1)	6.46, s	6.45, s	6.45, d (2.3)
3′					
4′	6.14, br t (2.2)	6.15, t (2.1)		6.16, m	6.16, t (2.2)
5′					
6′	6.46, d (2.2)	6.47, d (2.1)	6.46, s	6.45, s	6.45, d (2.3)
4′-CH_3			2.03, s		

An additional 774 mg of the organic crude extract was chromatographed on a Diaion HP-20 resin column eluting with a step gradient from 20% MeOH in H_2O to 100% MeOH to provide five fractions (A-E). Fraction C (219 mg), which eluted with 60% MeOH, was subjected to size exclusion chromatography on Sephadex LH-20, with hexane-CH_2Cl_2-MeOH (2:5:1) as the eluent, providing eight sub-fractions (A-H). Sub-fraction F (56 mg) was separated by Diol solid phase extraction eluting with a step gradient of 1% isopropyl alcohol (IPA) in CH_2Cl_2 to 20% IPA in CH_2Cl_2 to yield five additional sub-fractions (A-E). Sub-fraction B (3.3 mg), eluted with 5% IPA in CH_2Cl_2, provided **15** (0.6 mg) after purification on C_{18} reversed-phase HPLC eluting with a gradient of 70 - 100% aqueous MeOH over 30 min.

Sub-fraction D (303 mg), eluted with 80% MeOH in H_2O from the HP-20 column was chromatographed on LH-20 as above to provide sub-fractions A-E. Sub-fraction D (10.9 mg) was purified by C_{18} reversed-phase HPLC eluting with a gradient of 70 - 100% aqueous MeOH over 30 min. Final purification was achieved on C_{18} HPLC by isocratic elution with 80% MeOH in H_2O containing 0.1% TFA to yield **16** (4.7 mg).

(*E*)-4-(3,5-dihydroxystyryl)-2,6-bis(3-methylbut-2-en-1-yl)benzene-1,3-diol (1) – Colorless gum. UV (MeOH) λ_{max} (log ε) 210 (4.3), 290 (3.8), 328 (3.8) nm; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 381.2062 $[M+H]^+$; (calcd for $C_{24}H_{29}O_4$, 381.2066).

(*E*)-5-(2-(5-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-2*H*-chromen-6-yl)vinyl)benzene-1,3-diol (2) – Colorless gum, UV (MeOH) λ_{max} (log ε) 213 (4.6), 230 (4.5), 290 (4.5) nm; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 379.1899 $[M+H]^+$; (calcd for $C_{24}H_{27}O_4$, 379.1909).

(*E*)-5-(4-hydroxy-3,5-bis(3-methylbut-2-en-1-yl)styryl)-2-methylbenzene-1,3-diol (3) – Colorless gum, UV (MeOH) λ_{max} (log ε) 208 (3.8), 222 (3.7), 317 (3.6) nm; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 379.2258

Table 2. ^{13}C NMR Assignments (150 MHz, CD_3OD) for compounds **1** - **5**

	1	2	3	4	5
position	δ_C, type	δ_C, type	δ_C, type	δ_C, type	δ_C, type
1	119.6, C	119.6, C	130.8, C	119.3, C	131.2, C
2	152.5, C	149.9, C	126.2, CH	152.2, C	123.2, CH
3	118.8, C	112.0, C	130.1, C	111.2, C	122.6, C
4	154.2, C	152.2, C	153.5, C	149.6, C	151.6, C
5	122.5, C	122.9, C	130.1, C	116.0, C	130.4, C
6	124.6, CH	127.2, CH	126.2, CH	124.1, CH	128.8, CH
7	24.0, CH_2	118.6, CH	29.7, CH_2	117.7, CH	123.6, CH
8	124.3*, CH	129.8, CH	123.9, CH	130.3, CH	132.0, CH
9	132.3, C	76.3, C	133.4, C	77.5, C	77.4, C
10	18.0, CH_3	27.9, CH_3	18.0, CH_3	28.2, CH_3	28.2, CH_3
11	26.0, CH_3	27.9, CH_3	26.0, CH_3	28.2, CH_3	28.2, CH_3
12	29.4, CH_2	29.1, CH_2	29.7, CH_2	123.2, CH	29.4, CH_2
13	124.2*, CH	124.8, CH	123.9, CH	129.4, CH	124.1, CH
14	133.2, C	132.0, C	133.4, C	77.9, C	132.7, C
15	17.9, CH_3	18.0, CH_3	18.0, CH_3	28.4, CH_3	18.0, CH_3
16	26.0, CH_3	26.0, CH_3	26.0, CH_3	28.4, CH_3	26.0, CH_3
α	125.0, CH	124.6, CH	128.8, CH	123.5, CH	129.3, CH
β	127.2, CH	127.4, CH	127.0, CH	127.7, CH	127.5, CH
1′	141.9, C	141.9, C	137.4, C	141.7, C	141.2, C
2′	105.8, CH	105.8, CH	105.5, CH	105.7, CH	105.8, CH
3′	159.8, C	159.6, C	157.6, C	159.7, C	159.8, C
4′	102.6, CH	102.5, CH	111.6, C	102.6, CH	102.8, CH
5′	159.8, C	159.6, C	157.6, C	159.7, C	159.8, C
6′	105.8, CH	105.8, CH	105.5, CH	105.7, CH	105.8, CH
4′-CH_3			8.6, CH_3		

*interchangeable

$[M+H]^+$; (calcd for $C_{25}H_{31}O_3$, 379.2273).

4-((*E*)-3,5-dihydroxystyryl)-2,6-bis((*Z*)-3-hydroxy-3-methylbut-1-en-1-yl)benzene-1,3-diol (4) – Colorless gum, UV (MeOH) λ_{max} (log ε) 213 (4.1), 238 (4.2), 289 (4.2), 322 (4.0) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 435.1788 $[M+Na]^+$; (calcd for $C_{24}H_{28}O_6Na$, 435.1784).

5-((*E*)-4-hydroxy-3-((*Z*)-3-hydroxy-3-methylbut-1-en-1-yl)-5-(3-methylbut-2-en-1-yl)styryl)benzene-1,3-diol (5) – Colorless gum, UV (MeOH) λ_{max} (log ε) 213 (4.5), 231 (4.5), 274 (4.4), 322 (4.4) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 403.1877 $[M+Na]^+$; (calcd for $C_{24}H_{28}O_4Na$, 403.1885).

Result and Discussion

The HREIMS of **1** gave a molecular ion of *m/z* 381.2062 $[M+H]^+$, which established a molecular formula of $C_{24}H_{28}O_4$, requiring eleven unsaturation equivalents. ^{13}C NMR resonances at δ 141.9 (C-1'), 105.8 (C-2', 6'), 159.8 (C-3', 5') and 102.6 (C-4') along with ^1H resonances at δ 6.14 (H-4') and 6.46 (H-2', 6') indicated the presence of a symmetrical trisubstituted benzene ring. Two vinyl protons at δ 5.33 (H-13) and 5.20 (H-8), four vinylic methyl groups at δ 1.75 (H-15), 1.77 (H-16), 1.80 (H-10) and 1.68 (H-11), and four allylic protons at δ 3.27 (2H, H-12) and 3.41 (2H, H-7) suggested the presence of two aryl-substituted prenyl moieties. The ^1H NMR showed signals for two *trans* olefinic protons at δ 7.32 (H-α, d, J = 16.2 Hz) and 6.71 (H-β, d, J = 16.2 Hz), and the remaining four unsaturation equivalents were attributed to a penta substituted benzene ring (δ_H 7.08 (1H, s)/δ_C 124.6). This data along with a UV absorbance at λ_{max} 328 suggested the basic structure of a prenylated stilbene.

HMBC correlations from H-α to C-1 (δ 119.6), C-2 (δ 152.5), C-6 (δ 124.6), and C-1' established the connectivity between the two benzene rings. An HMBC correlation from the methylene protons at H-12 to C-4 (δ 154.2), C-5 (δ 122.5) and C-6 allowed placement of one of the prenyl groups on C-5. Similarly, HMBC correlations from the H_2-7 methylene protons to C-2, C-3 (δ 118.8), and C-4 allowed placement of the remaining prenyl group on C-3. The chemical shifts of C-2 (δ 152.5), C-4 (δ 154.2), C-3' (δ 159.8), and C-5' (δ 159.8) indicated the presence of four hydroxy groups, which was consistent with the molecular formula requirements. Comparison of literature values to known prenylated stilbenes showed that the ^1H and ^{13}C NMR signals of **1** were closely related to pannokin G,[7] except for the replacement of a hydroxy group for a methoxy group at C-2.

Compound **2** gave a molecular formula of $C_{24}H_{26}O_4$ with a $[M+H]^+$ pseudomolecular ion peak of *m/z* 1899,

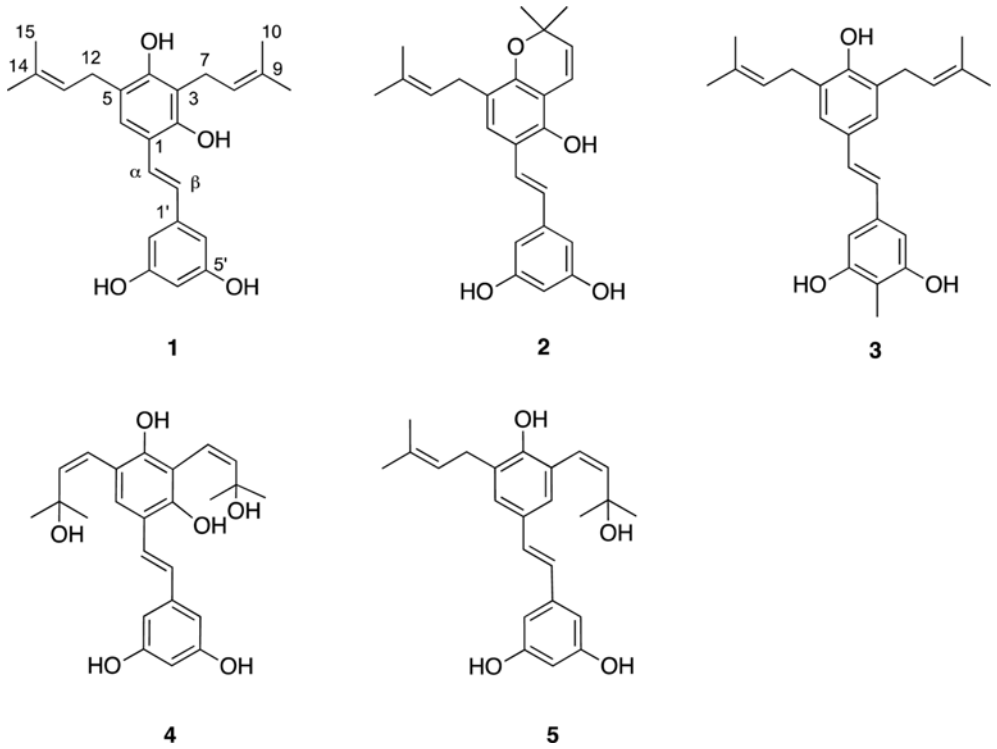

Fig. 1. Structures of compounds **1** - **5** isolated from *Artocarpus communis.*

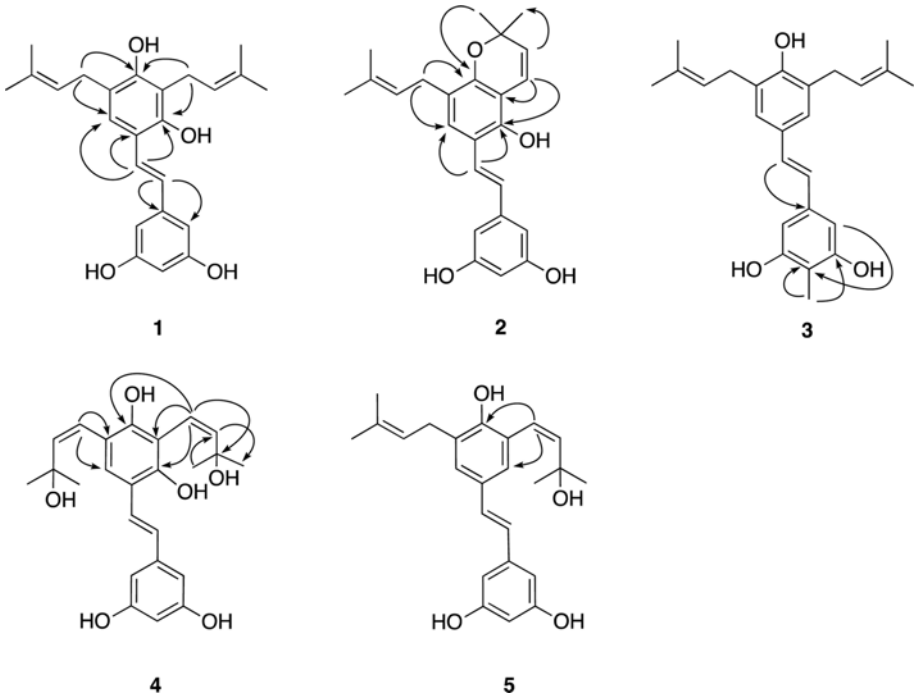

Fig. 2. Key HMBC correlations for compounds **1** - **5**.

requiring twelve unsaturation equivalents. ^{13}C and ^{1}H NMR signals showed the same core stilbene structure except for changes in the prenyl group substituted on C-3 (δ 112.0). Loss of the allylic methylene protons, an additional olefinic proton at δ 6.71 (H-7), and a quaternary carbon at δ 76.3 (C-9) indicated that the prenyl group was cyclized with one of the aryl oxygens to form a benzopyran ring, accounting for the remaining two unsaturation equivalents. HMBC correlations from the olefinic protons at δ 5.63 (H-8) and δ 6.71 (H-7) to C-3 and from H-8 to C-9 and to the methyl carbons at δ 27.9 (C-10, C-11) accounted for the remaining carbon signals and suggested a 2,2-dimethylchromene ring fused at C-3 and C-4 (δ 152.2). An HMBC correlation from H-12 (δ 3.20) to C-4, in addition to a modest 4-bond correlation from H-10/H-11 (δ 1.39) to C-4, confirmed the benzopyran ether link between C-4 and C-9.

The molecular formula of compound **3** was shown to be $C_{25}H_{30}O_3$ with a $[M+H]^+$ molecular ion peak of *m/z* 379.2258, and the ^{1}H and ^{13}C NMR signals closely corresponded with those of **1**. However, only sixteen carbon signals were observed in the ^{13}C spectrum so nine of theses resonances accounted for two carbons each due to symmetry considerations. Another spectral difference was due to an additional aryl methyl signal (δ_C 8.6, δ_H 2.03, 3H, s) and HMBC correlations from the methyl signal to C-3' (δ 157.6), C-5' (δ 157.6), and C-4' (δ 111.6) allowed placement of the methyl group on C-4'. Methylation at the C-4' position has been reported for a number of other stilbene and dihydrostilbenoid derivatives,[8,9] but it is less common than *O*-methylation in this compound class. The loss of a hydroxy group on C-2, as evidenced by a chemical shift change from δ 152.5 in compound **1** to δ 126.2 in compound **3**, and the doubling of a proton signal at δ 7.04 (2H, s, H-2, H-6) pointed to a symmetrically substituted benzene ring. Thus, the structure of **3** was assigned as (*E*)-5-(4-hydroxy-3,5-bis(3-methylbut-2-en-1-yl)styryl)-2-methylbenzene-1,3-diol.

The molecular formula of compound **4** was $C_{24}H_{28}O_6$ with a sodiated $[M+Na]^+$ molecular ion peak at *m/z* 435.1788. The ^{1}H and ^{13}C NMR spectra were similar to compound **1** in the stilbene portion of the molecule but differed in the prenyl groups, with the loss of two allylic protons and the addition of a quaternary carbon bearing oxygen. A disubstituted double bond with a *Z* configuration, as evidenced by the vicinal coupling constant between H-7 (δ 6.64, d, J = 9.7 Hz) and H-8 (δ 5.68, d, J = 10.0 Hz), was substituted on C-3 (δ 111.2) based on HMBC correlations from H-7 to C-2 (δ 152.2), C-3 and C-4 (δ 149.6). Two equivalent methyl groups (δ_C 28.2, δ_H 1.45, 6H) were attached at C-9 (δ 77.5) through HMBC correlations from H-8 to C-10 and C-11. HMBC correlations from H-7, H-8, H-10, and H-11, to a signal at δ 77.5 indicated there was a hydroxy group attached at C-9. The

remaining modified prenyl moiety had the same structural features and was attached on C-5 (δ 116.0) through HMBC correlations from H-12 (δ 6.35) to C-4, C-5, and C-6 (δ 124.1).

Compound **5** had a molecular formula of $C_{24}H_{28}O_4$ with a $[M+Na]^+$ molecular ion peak of *m/z* 403.1877. Comparison of ^{1}H and ^{13}C NMR signals to those of **1** again showed the loss of a hydroxy group on C-2, as evidenced by the change in chemical shift from δ 152.5 in compound **1** to δ 123.2 in **5**, and the addition of an aromatic proton (δ 7.03, 1H, d, J = 2.1 Hz) on C-2 as shown by an HSQC correlation. In addition, there was evidence for one standard prenyl moiety, with one vinyl proton at δ 5.28 (H-13), two vinylic methyl groups at δ 1.74 (H-15) and 1.76 (H-16), and two allylic protons at δ 3.27 (H-12). The remaining aliphatic signals were similar to the modified prenyl moieties in **4**, and this substituent was placed on C-3 (δ 122.6) based on HMBC correlations from H-7 (δ 6.38) to C-4 (δ 151.6) and C-2.

The known compounds were identified as cudraflavone C (**6**),[10] *trans*-4-isopentenyl-3,5,2',4'-tetrahydroxystilbene (**7**),[11] *trans*-4-(3-methyl-*E*-but-1-enyl)-3,5,2',4'-tetrahydroxystilbene (**8**),[12] pannokin G (**9**),[7] cycloartobiloxanthone (**10**),[13] artonin P (**11**),[14] morusin (**12**),[15,16] artocarpin (**13**),[17,18] artonin E (**14**),[19] kuwanon C (**15**),[16,20] artobiloxanthone (**16**),[13] and artoindonesianin C (**17**)[21] by comparing their ^{1}H and ^{13}C NMR, and MS spectral data with literature values. The twelve known compounds have all been previously isolated from members of the genus *Artocarpus*.

Although the stem bark extract of *Artocarpus communis* modulated the activity of HIF-2α in the high-throughput cell-based screening assay, upon isolation and purification of the individual compounds, the activity decreased so none of the compounds had a significant inhibitory effect on the transcriptional activity of HIF-2α at a high-test concentration of 50 μM. Testing of various mixtures of these metabolites failed to recapitulate the activity observed with the crude extract. Further studies of the chemistry and biological properties of the *A. communis* extract will be required to address this discrepancy.

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