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Note

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Unusual Isomeric Corniculatolides from Mangrove, *Aegiceras corniculatum*

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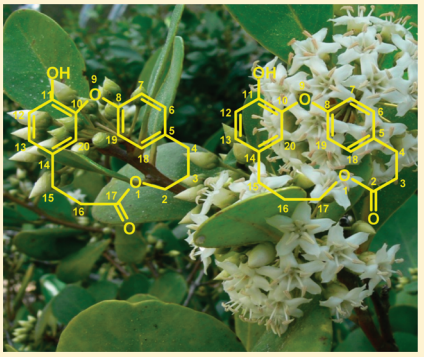
Supporting Information

ABSTRACT: Four new isomeric macrolides of combretastatin D-2 congeners named isocorniculatolide A (**1**), 11-*O*-methylisocorniculatolide A (**2**), 11-*O*-methylcorniculatolide A (**3**), and 12-hydroxy-11-*O*-methylcorniculatolide A (**4**), and the known corniculatolide A (**5**), arjunolic acid, and maslinic acid were isolated from the $CHCl_3$ extract of the bark of *Aegiceras corniculatum*. The structures of the new compounds (**1**–**4**) were elucidated by a combination of spectroscopic analysis (**1**–**5**), chemical modifications, and single-crystal X-ray analysis (**1**).



Aegeceras corniculatum (syn. *A. majus;* family Aegeceratacae) is a small tree or shrub that grows in the mangrove swamps of Asia and Australia. It has been used traditionally to treat asthma, diabetes, inflammation, and rheumatism.[1] The earlier pharmacological studies revealed cytotoxicity, itchytoxicity,[2] anti-inflammatory, antioxidant,[1] and tyrosine phosphatase 1B inhibitory[3] activities of this plant. A number of saponins, triterpenes, sterols, and hydroquinones[1,3,4] have been previously reported from this plant. The metabolites that were isolated from mangroves often possess unique structural features and incorporate new or unusual assemblages of functional groups.[5−8] In the course of our search for bioactive metabolites from Indian mangrove plants, the $CHCl_3$ extract of the bark of *A. corniculatum* afforded four new isomeric macrolides of combretastatin D-2 congeners, named isocorniculatolide A (**1**), 11-*O*-methylisocorniculatolide A (**2**), 11-*O*-methyl corniculatolide A (**3**), and 12-hydroxy-11-*O*-methylcorniculatolide A (**4**), and the known corniculatolide A[9,10] (**5**), arjunolic acid,[11] and maslinic acid.[12] The D-series of combretastatins are reported only from *Combretum caffrum*[13,14] and *Getonia fluoribunda*[9] (Combretaceae). Herein the isolation and structure elucidation of the isolated metabolites **1**–**5** (Figure 1) from the bark of *A. corniculatum* are reported. This is the first isolation of combretastatin D-2 congeners from *A. corniculatum*.

Preliminary ^1H NMR analyses of compounds **1**–**5** revealed structural similarity and indicated the presence of a rare caffrane[13] skeleton. Compound **1** was obtained as colorless crystals, mp 200–202 °C. The HR-ESIMS of compound **1** displayed a protonated molecular ion $[M + H]^+$ at m/z 299.1283 (calcd 299.1278) to deduce a molecular formula of

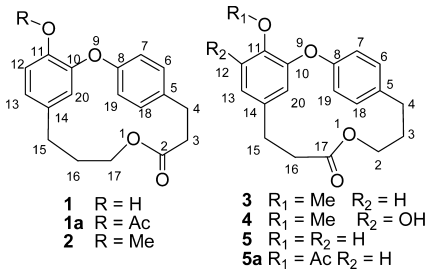


Figure 1. Compounds isolated from *Aegiceras corniculatum*.

$C_{18}H_{18}O_4$, suggesting 10 degrees of unsaturation. Its molecular formula suggested the compound to be isomeric to corniculatolide A (**5**).[9,10] The IR spectrum exhibited absorption bands for hydroxy (3390 cm^{-1}) and carbonyl (1714 cm^{-1}) functionalities. It gave a monoacetate (**1a**) on acetylation with acetic anhydride in pyridine, indicative of only one acylable hydroxy group in the molecule.

Compound **1** showed similar ^1H and ^{13}C NMR spectra (Tables 1 and 2) to those of compound **5** (see Supporting Information) with respect to chemical shifts and coupling constants, while the overall spin systems for the macrolactone and aromatic rings remain unchanged according to ^1H–^1H COSY and HMBC experiments (Figure 2). Minor differences in the chemical shifts of the corresponding protons in compound **1** and corniculatolide A show their close relationship. The characteristic difference between these two could,

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Table 1. ^{1}H NMR Chemical Shifts of Compounds 1, 1a, 2, 3, 4, 5, and 5a (600 MHz, in $CDCl_3$)

	1	1a	2	3	4	5	5a
position	δ_H (J, Hz)	δ_H (J, Hz)	δ_H (J, Hz)	δ_H (J, Hz)	δ_H (J, Hz)	δ_H (J, Hz)	δ_H (J, Hz)
2				4.06, m	4.05, m	4.05, m	4.06, m
3	2.52, t (6.8)	2.52, t (6.7)	2.53, t (6.7)	2.10, m	2.09, m	2.09, m	2.08, m
4	3.03, t (6.8)	3.02, t (6.7)	3.03, t (6.7)	2.81, t (6.5)	2.80, m	2.81, m	2.79, t (6.6)
6	7.25, d (8.3)	7.22 d (8.3)	7.23, d (8.5)	7.29 d (8.3)	7.29, d (8.3)	7.30, d (8.4)	7.25, d (8.4)
7	7.02, d (8.3)	7.03 d (8.3)	7.05, d (8.5)	7.01 d (8.3)	7.01, d (8.3)	7.01, d (8.4)	7.01, d (8.4)
12	6.85, d (8.3)	6.94 d (8.1)	6.83, d (8.1)	6.81 d (8.1)		6.83, d (8.1)	6.93, d (8.1)
13	6.60, dd (8.3, 2.3)	6.69 dd (8.1, 1.8)	6.65, dd (8.1, 1.7)	6.66, dd (8.1, 1.8)	6.35, s	6.60, dd (8.1, 2.1)	6.65, dd (8.1, 2.1)
15	2.48, t (6.7)	2.51 t (6.9)	2.49, t (6.8)	2.85, m	2.80, m	2.84, m	2.88, t (5.2)
16	1.73, m	1.76, m	1.73, m	2.26, m	2.24, m	2.25, m	2.27, m
17	3.58, t (6.7)	3.58, t (6.9)	3.63, t (6.8)				
18	7.25, d (8.3)	7.22, d (8.3)	7.23, d (8.5)	7.29, d (8.3)	7.29, d (8.3)	7.30, d (8.4)	7.25, d (8.4)
19	7.02, d (8.3)	7.03, d (8.3)	7.05, d (8.5)	7.05, d (8.3)	7.01, d (8.3)	7.01, d (8.4)	7.01, d (8.4)
20	5.38, d (2.3)	5.53, d (1.8)	5.38, d (1.7)	5.30, d (1.8)	4.85, s	5.29, d (2.1)	5.42, d (1.8)
OH	5.57, br s				5.76, br s	5.53, br s	
OMe			3.95, s	3.95, s	4.06, s		
OAc		2.39, s					2.39, s

Table 2. ^{13}C NMR Chemical Shifts of Compounds 1, 1a, 2, 3, 4, 5, and 5a (150 MHz,in $CDCl_3$)

	1	1a	2	3	4	5	5a
position	δ_C	δ_C	δ_C	δ_C	δ_C	δ_C	δ_C
2	173.1	173.1	173.1	63.9	63.9	63.9	63.9
3	38.6	38.5	38.6	28.6	28.6	28.6	28.6
4	32.3	32.4	32.4	33.9	33.9	33.9	33.9
5	137.9	137.7	137.5	137.4	137.6	137.9	137.7
6	130.6	130.5	130.5	131.0	130.9	131.1	131.0
7	123.7	123.7	123.9	123.6	123.4	123.5	123.4
8	155.9	155.9	156.2	154.5	154.5	154.2	154.4
10	149.2	153.1	151.7	151.1	153.9	149.0	153.1
11	142.7	139.4	146.4	146.1	133.1	142.5	139.2
12	115.3	117.0	112.1	113.2	149.0	114.9	114.2
13	122.1	122.7	121.4	120.8	107.7	121.5	121.2
14	131.5	137.0	132.2	133.1	136.3	132.6	136.6
15	28.2	28.4	28.2	26.9	27.3	27.0	27.3
16	26.3	26.8	26.7	32.7	32.3	32.7	32.3
17	62.2	61.9	62.1	173.9	173.3	173.9	173.5
18	130.6	130.5	130.5	131.0	130.9	131.1	131.0
19	123.7	123.7	123.9	123.6	123.4	123.5	123.4
20	115.4	122.7	116.2	111.6	105.7	112.6	122.4
OMe			56.2	56.1	61.3		
$OCOCH_3$		169.2					169.3
$OCOCH_3$		20.8					20.8

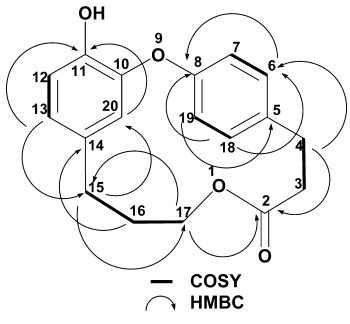

Figure 2. Key COSY and HMBC correlations of compound 1.

however, be seen within the macrolactone structure due to the possibility of lactone formation between C-2 and C-17 or vice versa analogous to 5. The connectivities from C-15 to C-17 were evident from the ^{1}H−^{1}H COSY cross-peaks, viz., H-15/H-16 and H-16/H-17. All the proton and carbon resonances have been assigned on the basis of 2D-NMR interpretation (Table 3). Its HMBC spectrum exhibited a strong correlation between the carbonyl carbon (C-2) and the 17-methylene, which was crucial in assembling the macrolide portion of 1.

The ^{1}H−^{1}H NOESY spectrum revealed the spatial correlations between H-20 and H-16/H-17/H-19 (Figure 3). From the ^{1}H and ^{13}C NMR, ^{1}H−^{1}H COSY, and ^{1}H−^{1}H NOESY spectra, a computer-generated 3D structure was obtained by using the molecular modeling program CS CHEM 3D version 11 with MMFF force field calculations for energy minimization in the Discovery Studio Module. The calculated distances between H-20/H-19 (3.659 Å), H-20/H-16 (2.191 Å), H-20/H-17 (2.653 Å), H-13/H-15 (2.579 Å),

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Table 3. Key HMBC, ^{1}H−^{1}H COSY, and ^{1}H−^{1}H NOESY Correlations of Compound 1

position	HMBC	COSY	NOESY
3	C2, C4, C5	4	18
4	C2, C3, C5, C6, C18	3	6
6	C4, C7, C8, C18	7	4
7	C5, C6, C8, C19	6	
12	C10, C11, C14	13	
13	C11, C15, C20	12	15
15	C13, C14, C16, C17, C20	16	13
16	C14, C15, C17	15, 17	20
17	C2, C15, C16	16	20
18	C4, C6, C8, C19	19	3
19	C5, C6, C8, C18	18	20
20	C10, C11, C13, C14, C15		15, 16, 17

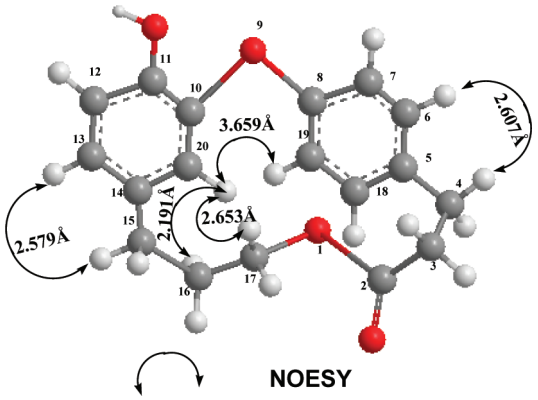

Figure 3. Key NOESY correlations of compound **1**.

and H-4/H-6 (2.607 Å) are less than 4.00 Å; this is consistent with the well-defined NOESY observed for each of these pairs.

Finally, the position of the lactone moiety between C-2 and C-17 was supported by X-ray crystal structure determination (Figure 4 and Table S1) to establish the structure of compound **1** as isocorniculatolide A.

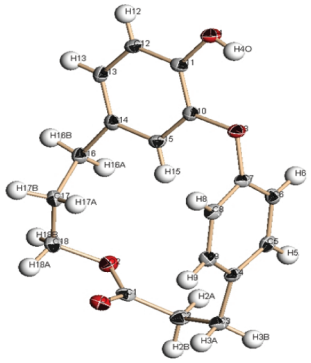

Figure 4. ORTEP drawing of compound **1**.

Biosynthetically, the isomers **1** and **5** are most probably derived from phenylalanine. Partial reduction of the carboxylic acid moiety seems to be the key step prior to the lactonization in the proposed biosynthetic pathway (Scheme S1).

Compound **2** was obtained as colorless crystals. Its HR-ESIMS showed an $[M + H]^+$ ion at m/z 313.1445 (calcd 313.1434). When considered in conjunction with ^{1}H and ^{13}C NMR data, this indicated a molecular formula of $C_{19}H_{20}O_4$ with 10 sites of unsaturation. The ^{1}H NMR spectrum of **2** resembles that of **1**, except for the presence of an *O*-methyl group at δ_H 3.95 (s, 3H) (Table 1). The ^{13}C NMR values of all the carbons of **2** agreed closely with those of **1** except for the differences in the chemical shifts of C-10, C-11, and C-12, which were consistent with the presence of an *O*-methyl group.[15] 2D-NMR analysis (Table S2 and Figure S1) showed that **2** was the 11-*O*-methyl derivative of **1**.

The HR-ESIMS of compound **3** showed a sodiated molecular ion peak at m/z 335.1251 ($[M + Na]^+$, calcd 335.1259). Its spectroscopic properties closely resemble those of **5**. It showed an *O*-methyl absorption at 2852 cm^{-1} in its IR spectrum, suggesting that it might be a methyl ether of **5**. This was supported by the presence of an *O*-methyl group at δ 3.95 (s, 3H) in its ^{1}H NMR spectrum (Table 1). The coupling patterns of aromatic protons in the ^{1}H NMR spectrum suggested that the methoxy group was situated at C-11. NOESY spectrum of **3** revealed the correlation between the methoxy protons and H-12. The 2D-NMR spectra (Table S2 and Figure S2) supported its structure as 11-*O*-methylcorniculatolide A.

Compound **4** was analyzed as $C_{19}H_{20}O_5$ (329.1373 m/z $[M + H]^+$ by HR-ESIMS. Its ^{1}H NMR spectrum closely resembles that of **3**, except for the presence of an additional hydroxy group at C-12 (Table 1). Diagnostic ^{1}H−^{1}H COSY, HSQC, and HMBC correlations revealed that **4** was the hydroxylated analogue of 11-*O*-methylcorniculatolide A. The structural assignments of compound **4** were supported by comparison of the spectroscopic data of **4** with those of **3**. The ^{1}H and ^{13}C NMR chemical shift values of **4** were fully consistent with those of **3** except in the region from C-10 to C-14. This is in accordance with the introduction of a hydroxy group at C-12, which was further confirmed by 2D-NMR interpretation (see Table S2 and Figure S2) to derive the structure of **4** as 12-hydoxy-11-*O*-methylcorniculatolide A.

Interestingly, the H-20 signal in compounds **1**−**5** was strongly shielded, because this proton is located above the plane of the other aromatic ring. Dreiding models of **1** and **5** showed that the two aromatic rings are perpendicular to each other, analogous to the D-series of combretastatins. The X-ray crystal structure of **1** also further supported this observation.

Active fraction AEG-7 afforded arjunolic acid and maslinic acid. These triterpenoids are responsible for the traditional use of mangrove in the treatment of inflammatory diseases. Another active fraction, AEG-3, afforded stigmasterol, corniculatolide A, an unidentified minor constituent (^{1}H NMR in SI as a mixture as well as pure form after separation), and new compounds **1**−**4**. The activity of this fraction may be attributed to the presence of minor constituents that could not be identified. Compounds **1**−**5** were found to be inactive in an agar diffusion assay against the bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Klebsiella pneumoniae*, and the fungi *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus flavus*.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on a Fischer-John micro melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet-740 FT-IR spectrophotometer. The NMR spectra were recorded with Bruker Avance (300 MHz), Varian Inova (400 MHz), and Bruker Avance II (600 MHz) for ^{1}H and 75/100/150 MHz for ^{13}C NMR spectra in $CDCl_3$ with TMS as internal standard. Coupling constants are given in

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Hz. The ESIMS data were recorded on an Agilent 1100 MSD with an ESI SL trap. The HR-ESIMS data were acquired on an Agilent 6510 Q-TOF and ESI probe. The UV−vis spectra were obtained using a JASCO V-550 spectrophotometer. The X-ray diffraction measurements were carried out at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and Mo Kα fine-focus sealed tube (λ = 0.71073 Å).

The bark of *A. corniculatum* was collected in March 2009 from the Nizampatnam (latitude: 15°53′ N, longitude: 80°38′ E) coast of India and identified by Prof. B. Kondala Rao, Department of Marine Living Sources, Andhra University, Visakhapatnam. A voucher specimen (# IIC-MG-107) has been deposited at the Herbarium of Natural Product Chemistry, IICT.

The air-dried bark (5.0 kg) of *A. corniculatum* was ground to a fine powder and was extracted with $CHCl_3$ (10 L) in a Soxhlet apparatus for 18 h to give the crude extract (32.0 g). The $CHCl_3$ extract (31.0 g) was subjected to VLC on silica gel (230−400 mesh) and eluted with mixtures of *n*-hexane and acetone−MeOH of increasing polarity to give 30 fractions of 800 mL each. The identical fractions were pooled based on the TLC profile. A total of nine main fractions (AEG-1−8) were obtained and were tested for antimicrobial activity in an agar diffusion assay. Fractions displaying significant activity were further fractionated, using the methods described below. TLC profiles were used to examine the pattern of significant components present in the active fractions.

Fraction AEG-3 (60 mg), a complex mixture of crude macrolides, was obtained by gradient elution with *n*-hexane and acetone (8:2). Repeated silica gel CC of this fraction gave four fractions (F_1−F_4) and revealed the presence of isomeric macrolide mixtures of **1** and **5** (20 mg); **2** and a minor constituent (2 mg); **3** and stigmasterol (10 mg); and **4** and a minor constituent (4 mg).

Fractions F_1−F_3 on subsequent silica gel CC afforded the metabolites **2** (1 mg), **3** (2 mg), and **4** (1 mg), minor constituents (<0.004 mg), and stigmasterol (7 mg). Our initial attempt to isolate compound **1** was complicated by the presence of isomer **5**, which coeluted during chromatography. Fraction F_4 was further chromatographed on silica gel, eluting with (*n*-hexane−acetone, 88:12 step gradient) to give fractions F_4-1, F_4-2, F_4-3, F_4-4, and F_4-5. Compound **1**, however, remained impure even after subsequent attempts to isolate it using repeated silica gel CC of combined fractions F_4-1 and F_4-2. Surprisingly, an enriched solution of **1** in a mixture of *n*-hexane and acetone was crystallized to obtain pure compound **1** (4 mg). Fraction F_4-5 was crystallized from a mixture of *n*-hexane and acetone to afford compound **5** (10 mg) as colorless crystals. The triterpenoids arjunolic acid (30 mg) and maslinic acid (10 mg) were also isolated from another active fraction (AEG-7) obtained by VLC.

*Acetylation of compounds **1** and **5**.* Compound **1** or **5** (each 2 mg) was dissolved in a mixture of C_5H_5N (0.2 mL) and Ac_2O (0.2 mL), and the solution was left overnight at ambient temperature. After usual workup, the product was purified by recrystallization from *n*-hexane to afford **1a** (2 mg) and **5a** (2 mg), respectively.

*Isocorniculatolide A (**1**):* $C_{18}H_{18}O_4$; colorless needles from a mixture of *n*-hexane and acetone (7:3); R_f 0.5 (*n*-hexane−acetone, 7.5:2.5); mp 202−203 °C; UV (CH_3OH) λ_{max} 279 nm (ε 2739); IR (KBr) ν_{max} 3390, 2963, 1714, 1594, 1518, 1427, 1271, 1218 cm^{-1}; ^1H, ^{13}C, and 2D-NMR data (see Tables 1−3 and Figures 2, 3); HR-ESIMS *m*/*z* 299.1283 $[M + H]^+$ (calcd for $C_{18}H_{19}O_4$, 299.1278).

*11-Acetoxyisocorniculatolide A (**1a**):* $C_{20}H_{20}O_5$; IR (KBr) ν_{max} 1760, 1730, 1594, 1504, 1435, 1255, 1190 cm^{-1}; ^1H, and ^{13}C NMR data (see Tables 1, 2); HR-ESIMS *m*/*z* 341.1371 $[M + H]^+$ (calcd for $C_{20}H_{21}O_5$, 341.1384).

*11-O-Methylisocorniculatolide A (**2**):* $C_{19}H_{20}O_4$; colorless needles from acetone; R_f 0.5 (*n*-hexane−acetone, 8:2); mp 134−136 °C; UV (CH_3OH) λ_{max} 278 nm (ε 1856); IR (KBr) ν_{max} 2928, 1729, 1516, 1438, 1416, 1259, 1208 cm^{-1}; ^1H, ^{13}C, and 2D-NMR data (see Tables 1, 2 and S2); HR-ESIMS *m*/*z* 313.1445 $[M + H]^+$ (calcd for $C_{19}H_{21}O_4$,313.1434).

*11-O-Methylcorniculatolide A (**3**):* $C_{19}H_{20}O_4$; colorless needles from acetone; R_f 0.45 (*n*-hexane−acetone, 8:2); mp 142−145 °C; UV (CH_3OH) λ_{max} 278 nm (ε 2482); IR (KBr) ν_{max} 2963, 1714, 1594, 1518, 1444, 1428, 1218, 1201 cm^{-1}; ^1H, ^{13}C, and 2D-NMR data (see Tables 1, 2 and S2); HR-ESIMS *m*/*z* 335.1251 $[M + Na]^+$ (calcd for $C_{19}H_{20}O_4$ Na, 335.1259).

*12-Hydroxy-11-O-methylcorniculatolide A (**4**):* $C_{19}H_{20}O_5$; colorless needles from a mixture of *n*-hexane and acetone (7:3); R_f 0.5 (hexane−acetone, 7:3); mp 244−245 °C; UV (CH_3OH) λ_{max} 275 nm (ε 1795); IR (KBr) ν_{max} 3445, 2924, 1728, 1595, 1505, 1436, 1214 cm^{-1}; ^1H, ^{13}C, and 2D-NMR data (see Tables 1, 2 and S2); HR-ESIMS *m*/*z* 329.1373 $[M + H]^+$ (calcd for $C_{19}H_{21}O_5$ Na,329.1388).

*Corniculatolide A (**5**):* $C_{18}H_{18}O_4$; colorless needles from *n*-hexane and acetone (8:2); R_f 0.45 (*n*-hexane−acetone, 7.5:2.5); mp 175−177 °C; UV (CH_3OH) λ_{max} 278 nm; IR (KBr) ν_{max} 3441, 2964, 1706, 1595, 1514, 1441, 1246, 1212 cm^{-1}; ^1H and ^{13}C NMR data (see Tables 1, 2); HR-ESIMS *m*/*z* 299.1299 $[M + H]^+$ (calcd for $C_{18}H_{19}O_4$, 299.1283).

*11-Acetoxycorniculatolide A (**5a**):* $C_{20}H_{20}O_5$; IR (KBr) ν_{max} 1765, 1730, 1594, 1505, 1433, 1258, 1216 cm^{-1}; ^1H, and ^{13}C NMR data (see Tables 1, 2); HR-ESIMS *m*/*z* 341.1370 $[M + H]^+$ (calcd for $C_{20}H_{21}O_5$, 341.1384).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental Section: collection, extraction, and isolation; spectral data of compounds **1**−**5**; $^1H/^{13}C$ NMR, DEPT, and all 2D-NMR spectra for **1** to **4**; $^1H/^{13}C$ NMR and DEPT spectra of **5**; ^1H NMR of unidentified minor constituent and acetylated compounds of **1** and **5**; ^1H NMR spectra of a mixture of subfractions; X-ray data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor S. R. Anjaneyulu Ammanamanchi for his pioneering research in the area of natural products.

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