New *p*-Terphenyl and Polyketide Metabolites from the Sclerotia of *Penicillium raistrickii*

Gilbert N. Belofsky,[†] Katherine B. Gloer,[†] James B. Gloer,*[,†] Donald T. Wicklow,[‡] and Patrick F. Dowd[‡]

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, and Agricultural Research Service, National Center for Agricultural Utilization Research, USDA, Peoria, Illinois 61604

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Three new *p*-terphenyls (**1**−**3**), a new xanthone derivative (**4**), and two known fungal metabolites (**5** and **6**) have been isolated from the sclerotia of *Penicillium raistrickii* (NRRL 2039). The structures for 3,3″-dihydroxy-6′-desmethylterphenyllin (**1**); 3′-demethoxy-6′-desmethyl-5′-methoxycandidusin B (**2**); 6′-desmethylcandidusin B (**3**); and 1,3,5,6-tetrahydroxy-8-methylxanthone (**4**) were determined on the basis of HRMS and NMR data. Although compounds **1** and **4** exhibited mild antiinsectan and antibacterial activity, griseofulvin (**5**) was responsible for most of the activity of the sclerotial extract in dietary assays against the corn earworm *Helicoverpa zea*.

Sclerotia are propagational structures produced by certain fungal species to survive harsh environmental conditions and to serve as sources of fungal inoculum upon germination. An extensive chemical survey of *Aspergillus* spp. sclerotia led to the discovery of a variety of new natural products with antiinsectan and other biological activities.[1] The specific allocation of effective concentrations of antiinsectan compounds to fungal sclerotia suggests that these metabolites may play a role in defending sclerotia from consumption by insects.

During similar investigations of sclerotia and sclerotioid ascostromata produced by *Penicillium* and *Eupenicillium* spp.,[1,2] extracts of *Penicillium raistrickii* Smith (Trichocomaceae) (NRRL 2039) displayed potent antiinsectan activity in dietary assays against the corn earworm (*Helicoverpa zea*). Fractionation of these extracts afforded three new *p*-terphenyls (**1**−**3**), a new xanthone derivative (**4**), the well-known fungal metabolite griseofulvin (**5**), and its 6-desmethyl analogue (**6**).[3−6] The structures of 3,3″-dihydroxy-6′-desmethylterphenyllin (**1**); 3′-demethoxy-6′-desmethyl-5′-methoxycandidusin B (**2**); 6′-desmethylcandidusin B (**3**); and 1,3,5,6-tetrahydroxy-8-methylxanthone (**4**) were assigned on the basis of HRMS and NMR data, and compounds **5** and **6** were identified by comparison of their spectral data with literature values for **5**.[4,5] Details of the isolation, structure elucidation, and biological activities of these metabolites are reported here.

Results and Discussion

Bioassay-guided fractionation of organic extracts of *P. raistrickii* (NRRL 2039) sclerotia by Si gel VLC, solvent partitioning, and Sephadex LH-20 column chromatography afforded metabolites **1**−**6**. The HRFABMS, ^{13}C NMR (Table 1), and DEPT data for the most abundant metabolite from the CH_2Cl_2−MeOH extract (compound **1**) indicated a molecular formula of $C_{19}H_{16}O_7$ (12 unsaturations). Signals for a methoxy group, seven aromatic protons (one isolated), and 18 sp^2 carbons were present in the NMR spectra (Table 1). DEPT data accounted for all but six exchangeable protons, suggesting the presence of six phenolic OH groups in the molecule. Two 1,2,4-trisubstituted aromatic rings were identified based on ^{1}H−^{1}H coupling constants and COSY results, and the corresponding ^{13}C NMR shifts (assigned based on HMQC and HMBC data) required that they each be 1,2-dioxygenated. The remaining six sp^2 carbon signals must represent a third, pentasubstituted and trioxygenated aromatic ring to account for the molecular formula, the final protonated sp^2 carbon, and the last four degrees of unsaturation.

The data for **1** were consistent with a terphenyl-type structure bearing a methoxy substituent and six OH groups. An HMBC correlation of the methoxy signal with C-3′ placed this group on the central, pentasubstituted aromatic ring. The substitution pattern for this ring was assigned based on observations of NOESY correlations of the signals for H-2″ and H-6″ with those for H-5′ and H_3CO-3′. Compound **1** was identified as 3,3″-dihydroxy-6′-desmethylterphenyllin based on these results and on comparison of the NMR assignments with literature values for similar compounds, such as terphenyllin.[7−9]

The NMR data (Table 1) and HMBC results for two closely related metabolites (**2** and **3**) were suggestive of a pair of structural isomers containing a terphenyl core structure similar to that of **1**, although the molecular formula for these metabolites ($C_{19}H_{14}O_7$) required an additional degree of unsaturation. The ^{1}H NMR spectra for both compounds contained signals for a methoxy group; a 1,2,4-trisubstituted benzene ring; and three isolated aromatic protons. The remaining five protons indicated by the molecular formula must belong to phenolic OH groups. The observed changes in the NMR spectra for **2** and **3** relative to those of **1**, as well as the remaining oxygen atom and degree of unsaturation, were consistent with the presence of an ether bridge connecting two of the aromatic rings in **1** to form a dibenzofuran unit.

* To whom correspondence should be addressed: Tel.: (319) 335-1361. Fax: (319) 335-1270. E-mail: james-gloer@uiowa.edu.
[†] University of Iowa.
[‡] USDA.

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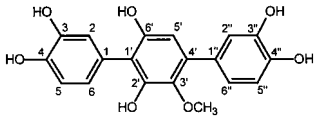
Table 1. NMR Data for Compounds **1**−**3** in CD_3OD

	1		**2**		**3**	
position	δ_C[a]	δ_H[b] (mult.; J_{HH})	δ_C[a]	δ_H[b] (mult.; J_{HH})	δ_C[a]	δ_H[b] (mult.; J_{HH})
1	126.8		116.6		116.5	
2	119.3	6.89 (d, 1.9)	152.0		151.6	
3	145.7		98.9	6.92 (s)	98.9	6.99 (s)
4	145.2		146.1		146.5	
5	116.2	6.82 (d; 8.1)	142.9		143.2	
6	123.7	6.76 (dd; 8.1, 1.9)	108.6	7.46 (s)	108.6	7.45 (s)
1′	117.1		113.8		115.2	
2′	149.0		154.9		150.8	
3′	139.5		103.7	6.84 (s)	136.6	
3′-OCH_3	60.8	3.38 (s)			61.3	3.77 (s)
4′	134.5		133.9		132.9	
5′	108.2	6.34 (s)	141.2		110.5	6.58 (s)
5′-OCH_3			61.0	3.42 (s)		
6′	151.8		146.5		148.9	
1″	131.5		131.9		131.7	
2″	117.1	7.08 (d; 2.0)	117.4	7.11 (d; 2.0)	117.8	7.04 (d; 2.0)
3″	145.9[c]		145.9		145.9	
4″	145.7[c]		145.7		145.6	
5″	116.0	6.81 (d; 8.1)	116.2	6.82 (d; 8.1)	116.1	6.81 (d; 8.2)
6″	121.4	6.92 (dd; 8.1, 2.0)	121.8	6.96 (dd; 8.1, 2.0)	122.0	6.88 (dd; 8.2, 2.0)

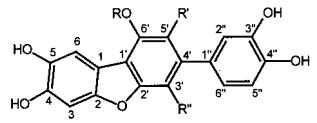
[a] 75 MHz. [b] 600 MHz. [c] Assignments may be interchanged.

The structure for **2** was assigned as 3′-demethoxy-6′-desmethyl-5′-methoxycandidusin B based on HRFABMS data, 1D NMR (Table 1) and HMBC results, and chemical shift considerations. The ^1H NMR assignments for **2** were comparable to those reported for candidusin B (**7**), a cytotoxic fungal metabolite previously isolated from *Aspergillus candidus* Link.[10] The numbering of the tetrasubstituted ring in **2** reflects the change in priority as a result of additional oxygen substitution and is consistent with the numbering system for candidusin B. Several key HMBC correlations were useful in establishing the connectivity of the aromatic rings in **2**, and support the proposed structural assignment. An HMBC correlation of H-6 with C-1′ permitted connection of the tetrasubstituted and pentasubstituted aromatic rings. Additional correlations of H-2″ and H-6″ with C-4′, and of H-3′ with C-1″, linked the central pentasubstituted ring with the trisubstituted aromatic ring. NOESY correlations provided additional information about the substitution pattern of the central aromatic ring in **2**. Strong NOESY correlations of H-2″ with H-3′ and the C-5′ methoxy signal indicated that the trisubstituted ring must be linked to the central ring between these two positions. The only remaining regiochemical assignment concerned the attachment of C-2 through an ether bridge to the central ring at positions C-2′ or C-6′. Comparison of the calculated ^{13}C NMR chemical shifts for the two possible regioisomers[11] with those for **2**, and with data for the other related metabolite **3**, led to the assignment of the structure for **2** as shown.

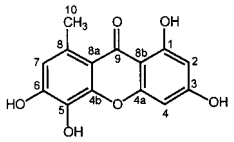
Based on chemical shift analysis, HMBC data, and comparison of NMR data with those for **2** and candidusin B (**7**),[10] compound **3** was determined to be a structural isomer of **2**. It was clear from the NMR data that the two isomers must differ in the substitution pattern of the central ring. In order for compound **3** to be consistent with the arrangement found in candidusin B, yet be different from compound **2**, the methoxy group must be located at the 3′ position and the proton at the 5′ position. This arrangement is also the only pattern for which the observed ^{13}C NMR shifts are fully consistent with calculated values.[11] The structure for compound **3** was therefore assigned as 6′-desmethylcandidusin B. Given the close structural relationship of compounds **2** and **3** with the terphenyllin analogue **1**, these two new candidusin analogues can be viewed as arising from oxidative cyclization of either the 2′- or the 6′-hydroxy group with C-6 in **1**.



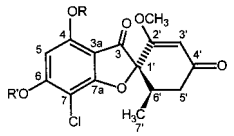
1



2 R = R″ = H; R′ = OCH_3
3 R = R′ = H; R″ = OCH_3
7 R = CH_3; R′ = H; R″ = OCH_3



4



5 R = R′ = CH_3
6 R = CH_3; R′ = H

Members of the *p*-terphenyl structural class have been previously reported as fungal metabolites, primarily from liquid culture extracts of *A. candidus*.[7−10] In addition, we recently reported three new prenylated members of this class as constituents of the sclerotia of *Aspergillus arenarius*.[12] The biosynthesis of *p*-terphenyl metabolites has been linked to the shikimic acid pathway through studies demonstrating incorporation of ^{14}C-labeled phenylalanine.[13] To our knowledge, this is the

first report of *p*-terphenyl metabolites from any member of the genus *Penicillium*.

Several additional metabolites were isolated from *P. raistrickii* sclerotial extracts. Another new compound (**4**) had a molecular formula of $C_{14}H_{10}O_6$ (10 unsaturations) based on HRFABMS and ^{13}C NMR results. The ^1H NMR data revealed the presence of three aromatic protons, an aryl methyl group, and a hydrogen-bonded phenolic OH proton. The ^{13}C NMR spectrum contained a single carbonyl resonance at δ 181.9 and was characteristic of a xanthone. An IR absorption observed at 1650 cm^{-1} is also consistent with this type of structure.

Placement of the substituents on the xanthone ring system was accomplished by analysis of 1D and 2D NMR experiments. Based on its downfield shift, the phenolic proton signal at δ 13.4 (OH-1) must be hydrogen-bonded with the carbonyl oxygen. Meta coupling (J_{CH} = 2.1 Hz) between H-2 and H-4 and the lack of any ortho couplings required placement of a substituent at C-3. HMBC correlations observed for OH-1, for the isolated aromatic proton (H-7), and for the methyl group were useful in the assignment of most of the remaining NMR shifts for **4**. These assignments are consistent with NMR data reported for known xanthones.[14−16]

The known compounds griseofulvin (**5**) and 6-desmethylgriseofulvin (**6**) were identified by analysis of NMR and MS data and by comparison of the data for **5** with literature values[4,5] and with NMR data for an authentic standard. Griseofulvin (**5**) has been previously isolated from liquid culture extracts of *P. raistrickii*, among many other sources.[5] Although other properties for **6** have been previously reported,[6] to our knowledge, no NMR data have been published. Complete NMR assignments and HMBC data for **6** are provided in the Experimental Section.

Xanthone metabolites and the griseofulvins are known to be of polyketide origin.[17] The known compound most closely related to xanthone **4** is norlichexanthone, which lacks the hydroxy group at C-5. Norlichexanthone was isolated as an antibacterial constituent of *Penicillium patulum*, which also produces griseofulvin.[18]

Although the isolated yields of compounds **1**−**6** were limited by the complexity of the sclerotial extracts, these yields indicated that the three major components (compounds **1**, **3**, and **5**) were present in the sclerotia at a minimum of 80, 300, and 400 ppm, respectively. Compounds **1**−**6** were evaluated for antiinsectan activity in dietary assays against the corn earworm *H. zea* and the fungivorous beetle *Carpophilus hemipterus*. Griseofulvin (**5**) was found to be responsible for a significant portion of the antiinsectan activity of the extracts. An evaluation of the antiinsectan activity of griseofulvin has been previously reported.[19] When tested against *H. zea* larvae at levels approximating its minimum sclerotial concentration (ca. 400−500 ppm), griseofulvin produced a 70% reduction in growth rate relative to controls. At these concentrations, griseofulvin also caused a 30% reduction in feeding rate in *C. hemipterus* larvae. When tested at 500 ppm, the terphenyllin analogue (**1**) induced a 28% reduction in growth rate in *H. zea* larvae. Compound **1** also exhibited moderate antibacterial activity against *Staphylococcus aureus* (ATCC 29213), producing a 13-mm zone of inhibition in a standard disk assay at 200 μg/disk. Xanthone **4** produced 11-mm and 12-mm zones of inhibition when tested against *S. aureus* and *Bacillus subtilis* (ATCC 6051), respectively, at the same concentration. Compounds **1**, **3**, and **4** showed no activity against *Candida albicans* (ATCC 14053) when tested at 200 μg/disk.

Although liquid cultures of *Penicillium* spp. have been extensively surveyed for novel metabolites, there have been no reports to our knowledge of biologically active natural products isolated specifically from the sclerotia of *Penicillium* spp. The occurrence of these metabolites in *P. raistrickii* sclerotia may be analogous to the presence of unique antiinsectan compounds in the sclerotia of *Aspergillus* spp.[1]

Experimental Section

General Experimental Procedures. Details of insect bioassays have been described elsewhere.[20] Column chromatography employed Fisher 60−200 mesh Si gel, unless otherwise indicated. NMR spectra were referenced to residual protiated solvent signals. Multiplicities of carbon signals were verified through DEPT experiments. HMQC and HMBC data were optimized for $^1J_{CH}$ = 150.2 Hz and $^nJ_{CH}$ = 8.3 Hz, respectively. Descriptions of other NMR parameters, as well as NMR, MS, UV, and IR instrumentation, have been provided elsewhere.[21]

Fungal Material. The culture of *P. raistrickii* (NRRL 2039) was obtained from the Agricultural Research Service (ARS) collection of the USDA National Center for Agricultural Utilization Research in Peoria, IL. The NRRL 2039 strain was originally isolated from moldy cotton yarn in Great Yarmouth, Great Britain, in 1929.[22] *P. raistrickii* grows rapidly and produces abundant pale brown sclerotia. It is not known to produce a teleomorphic state. Sclerotia were produced by solid substrate fermentation on autoclaved corn kernels using general procedures described previously.[23] The harvested sclerotia were then ground to a powder and stored at 4 °C until extraction.

Extraction and Isolation. A sample of ground sclerotia (379 g) was extracted for 24 h with 3 L of 2:1 CH_2Cl_2−MeOH to provide, after evaporation, 37.4 g of crude extract. This material was preadsorbed onto ca. 5 g of Si gel in a solution of 2:1 CH_2Cl_2−MeOH. The solvent was removed under vacuum, and the resulting powder was subjected to vacuum liquid chromatography (VLC) over a prepacked column bed [7 cm (i.d.) × 5 cm (h)] of TLC-grade Si gel (65 g; Fluka Kieselgel GF_{254}) equilibrated with 500 mL of hexane. The column was eluted using a stepwise gradient beginning with hexane (500 mL), continuing with 500 mL aliquots of EtOAc in hexane (25%, 50%, 75%, 100%), followed by 100% CH_2Cl_2, then MeOH in CH_2Cl_2 (1%, 2%, 3%, 5%, 10%, 30%). The three fractions that eluted with 75% EtOAc, 100% EtOAc, and 100% CH_2Cl_2 were combined on the basis of TLC analysis, and the solvents were evaporated. The residue (2.6 g) was taken up in 100 mL of 10% H_2O in MeOH and extracted with hexane (3 × 33 mL) to remove fatty acids. H_2O (20 mL) was added to the aqueous MeOH layer, which was then extracted with $CHCl_3$ (3 × 33 mL), followed by EtOAc (3 × 33 mL). The EtOAc extract (168 mg) was further fractionated by Sephadex LH-20 column chromatography (1.8 cm × 44 cm) eluting with ca. 500 mL of 3:1:1 hexane−

toluene−MeOH, followed by ca. 500 mL of 100% MeOH, and collecting 4-mL fractions. Fractions of similar composition as determined by TLC were pooled. This procedure afforded compounds **1** (fractions 189−213; 60 mg) and **3** (fractions 225−229; 13 mg), and a mixture of **2** and **3** (fractions 220−224; 12 mg). Si gel column chromatography of another subfraction (fractions 159−165; 17 mg) employed a gradient consisting of 100% CH_2Cl_2 (30 mL) followed by MeOH in CH_2Cl_2 (15 mL each of 1%, 2%, 5%, 10%, and 20%). This fractionation produced seven fractions, yielding compound **4** (10 mg) in fractions 3−6.

A separate, ground sclerotial sample (161 g) was extracted successively with 800 mL each of pentane, CH_2Cl_2, EtOAc, and 10% H_2O in MeOH. The CH_2Cl_2 extract (937 mg) was subjected to VLC on Si gel (Baker 40 μm; 3.5 cm × 4.0 cm; 200 mL CH_2Cl_2) beginning with 100% CH_2Cl_2, followed by increasing percentages of MeOH in CH_2Cl_2 (100 mL each of 1%, 2%, 3%, 4%, 5%, 10%, 30%, 50%). This procedure yielded 9 fractions. Fractions 1−4 (eluted up to 3% MeOH in CH_2Cl_2) were combined, and the resulting material (540 mg) was subjected to chromatography on Sephadex LH-20 (2.5 cm × 30 cm; 3:1:1 hexane−toluene−MeOH; 0.5 mL/min) to yield compounds **5** (fractions 26−34; 68 mg) and **6** (fractions 50−62; 34 mg). Similar fractionation of the EtOAc extract (1.02 g) by VLC and Sephadex LH-20 column chromatography failed to resolve a mixture of compounds **2** and **3**. This mixture (43 mg) was combined with the 12-mg sample of coeluted **2** and **3** obtained from the previously described sclerotial extract. Chromatography of this material on a Si gel column (2.5 cm × 18 cm) using a linear gradient of MeOH (3−10%) in CH_2Cl_2 at a flow rate of ca. 20 mL/min afforded compound **2** (3 mg) in the fraction eluting at ca. 5% MeOH.

3,3″-Dihydroxy-6′-desmethylterphenyllin (1): off-white solid; mp 248−250°(dec); UV (MeOH) λ_{max} 236 (ϵ 6000), 264 (5900), 297 (6300); ^{1}H and ^{13}C NMR data, see Table 1; HMBC correlations (CD_3OD) H-2 → C-4, 6, 1′; H-5 → C-1, 3, 4; H-6 → C-2, 4, 1′; OCH_3-3′ → C-3′; H-5′ → C-1′, 3′, 6′, 1″; H-2″ → C-4′, 4″, 6″; H-5″ → C-1″, 3″; H-6″ → C-4′, 2″, 4″; FABMS (thioglycerol) *m*/*z* 357 [(M + H)$^+$, rel int 22], 342 (2), 325 (4), 307 (3), 274 (10), 257 (16), 232 (14), 197 (11); HRFABMS (3-NBA), found *m*/*z* 356.0908 (M$^+$), calcd for $C_{19}H_{16}O_7$, 356.0896.

3′-Demethoxy-6′-desmethyl-5′-methoxycandidusin B (2): off-white gum; UV (MeOH) λ_{max} 239 nm (ϵ 13 000), 274 (11 000), 303 (14 000), 323 (14 000); ^{1}H and ^{13}C NMR data, see Table 1; HMBC correlations (CD_3OD) H-3 → C-1, 2, 4, 5; H-6 → C-2, 4, 5, 1′; H-3′ → C-1′, 2′, 5′, 1″; OCH_3-5′ → C-5′; H-2″ → C-4′, 4″, 6″; H-5″ → C-1″, 3″, 4″; H-6″ → C-4′, 2″, 4″; FABMS (thioglycerol) *m*/*z* 354 (M$^+$, rel int 11), 338 (14), 313 (5), 279 (7), 257 (4), 237 (6), 197 (13); HRFABMS (3-NBA), found *m*/*z* 354.0742 (M$^+$), calcd for $C_{19}H_{14}O_7$, 354.0740.

6′-Desmethylcandidusin B (3): pale yellow oil; UV (MeOH) λ_{max} 240 nm (ϵ 6700), 281 (sh; 5200), 299 (5700), 331 (6400); ^{1}H and ^{13}C NMR data, see Table 1; HMBC correlations (CD_3OD) H-3 → C-1, 2, 4, 5; H-6 → C-2, 4, 5, 1′; H-5′ → C-1′, 3′, 6′, 1″; OCH_3-3′ → C-3′; H-2″ → C-4′, 4″, 6″; H-5″ → C-1″, 3″; H-6″ → C-4′, 2″, 4″; FABMS (thioglycerol) *m*/*z* 354 (M$^+$, rel int 14), 323 (2), 306 (2), 279 (19), 274 (23), 257 (20), 232 (21), 197 (15); HRFABMS (3-NBA), found *m*/*z* 354.0759 (M$^+$), calcd for $C_{19}H_{14}O_7$, 354.0740.

1,3,5,6-Tetrahydroxy-8-methylxanthone (4): pale yellow oil; UV (MeOH) λ_{max} 250 nm (ϵ 12 000), 277 (5000), 322 (9700); IR ν_{max} (film on AgCl) 3197 (br, OH), 2926, 1650, 1612, 1585, 1519, 1455, 1322, 1282, 1166 cm^{-1}; ^{1}H NMR (DMSO-d_6) 13.4 (s, OH-1), 6.64 (s, H-7), 6.33 (d, J = 2.1 Hz, H-4), 6.10 (d, J = 2.1 Hz, H-2), 2.63 (s, H_3-9); ^{13}C NMR (DMSO- d_6) 181.9 (C-9), 164.6 (C-3), 163.1 (C-1), 156.6 (C-4a), 150.7 (C-6), 147.1 (C-4b), 131.0 (C-8), 130.5 (C-5), 115.3 (C-7), 111.0 (C-8a), 101.9 (C-8b), 97.6 (C-2), 93.2 (C-4), 22.3 (C-10); HMBC correlations (DMSO- d_6) OH-1 → C-2, 8b; H-2 → C-1, 3, 4, 8b; H-4 → C-2, 3, 4a, 8b; H-7 → C-5, 6, 8a, 10; H_3-10 → C-7, 8, 8a; FABMS (thioglycerol) *m*/*z* 275 (M + H)$^+$ (rel int 100); HRFABMS (3-NBA), found *m*/*z* 275.0541 (M + H)$^+$, calcd for $C_{14}H_{11}O_6$, 275.0556.

Griseofulvin (5): yellow solid; properties of **5** have been previously reported.[4,5]

6-Desmethylgriseofulvin (6): yellow solid; ^{1}H NMR ($CDCl_3$) 6.24 (s, H-5), 5.54 (s, H-3′), 3.88 (s, 4-OCH_3), 3.61 (s, 2′-OCH_3), 3.02 (dd, J = 17, 14 Hz, H-5′a), 2.82 (m, H-6′), 2.43 (dd, J = 17, 4.8 Hz, H-5′b), 0.95 (d, J = 6.9 Hz, H_3-7′); ^{13}C NMR ($CDCl_3$) 197.5 (C-4′) 192.1 (C-3), 171.1 (C-2′), 169.9 (C-7a), 162.2 (C-6), 157.9 (C-4), 104.8 (C-3a), 104.8 (C-3′), 95.3 (C-7), 93.7 (C-5), 91.0 (C-1′), 56.7* (4-OCH_3), 56.4* (2′-OCH_3), 40.0 (C-5′), 36.4 (C-6′), 14.2 (C-7′) (* indicates that assignments for these carbon atoms may be interchanged); HMBC correlations ($CDCl_3$) H-5 → C-3 (4-bond), 3a, 4, 6, 7; 4-OCH_3 → C-4; 2′-OCH_3 → C-2′; H-3′ → C-1′, 2′, 4′, 5′; H_2-5′ → C-1′, 3′, 4′, 6′, 7′; H-6′ → C-3, 1′, 5′, 7′; H_3-7′ → C-1′, 5′, 6′; mp and UV data,[6] and EIMS data[24] for **6** have been previously reported.

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