Monolaterol, the First Configurationally Assigned Phenylphenalenone Derivative with a Stereogenic Center at C-9, from *Monochoria elata*

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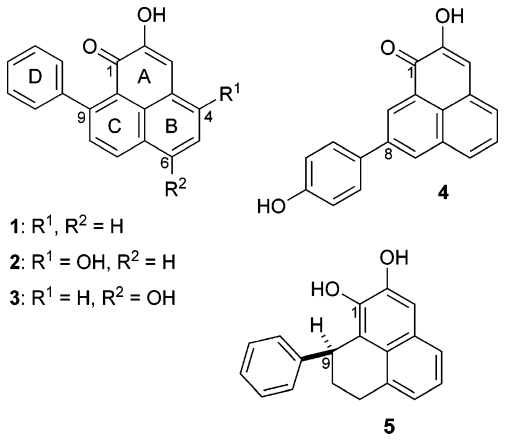
Phytochemical analysis of the roots of *Monochoria elata* resulted in the structure elucidation of monolaterol, the first configurationally assigned phenylphenalenone-type natural product with a stereogenic center at the phenyl-bearing carbon, C-9, and four known phenylphenalenones by MS and NMR methods. The absolute configuration of the new phenyldihydrophenalenediol was assigned by comparing the results of quantum chemical CD calculations and experimental CD spectra, and the crystal structure was determined by X-ray diffraction analysis.

The plant family Pontederiaceae consists of widespread herbs, perennial or annual, aquatic, floating, or rooted in substrate, inhabiting tropical and subtropical regions. *Monochoria* is a small genus of this plant family, and one species, *Monochoria vaginalis*, is considered to be one of the worst weeds next to *Echinochloa colona* in the paddy fields of Southeast Asia.[1] A point mutation in acetolactate synthase of *M. vaginalis* seems to be responsible for the resistance to sulfonylureas, enabling the successful distribution of herbicide resistant *Monochoria* biotypes in rice fields.[2] Thus, effective management strategies should be developed to control this serious weed, and phytochemical investigations could be an excellent basis for understanding ecological survival strategies of members of the genus *Monochoria*. Recently the isolation and structural elucidation of natural compounds from members of the Pontederiaceae revealed sterols, fatty acids, and phenylphenalenones,[3−5] but *Monochoria elata* has so far not been studied phytochemically and the occurrence of phenylphenalenones in the genus *Monochoria* has not yet been reported. Phenylphenalenones and phenylphenalenone-derived natural products like **1**−**4** have been implicated in the complex defense mechanism of plants, and their role as phytoalexins and phytoanticipins is well documented.[6−8] In this paper we report on the isolation, structural elucidation, and determination of the absolute configuration of monolaterol (**5**), a new phenylphenalenone-related compound from *Monochoria elata* Ridley (Pontederiaceae). It represents the first optically active member of this class of secondary metabolites to be analyzed by quantum chemical circular dichroism calculation and X-ray structure analysis. In addition to the new compound, the occurrence of four phenylphenalenones that are known from various Haemodoraceae species is described here for *M. elata*, indicating phytochemical relationships between the two plant families.

Roots of *M. elata* were extracted with EtOH, and the extract was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$-soluble fraction was separated by Sephadex LH-20 column chromatography and semipreparative HPLC and analyzed by TLC, reversed-phase HPLC, and spectrometric methods for the detection of phenylphenalenone-type compounds. Four known phenylphenalenones, 2-hydroxy-9-phenyl-1*H*-phenalen-1-one (**1**, anigorufone), 2,4-dihydroxy-9-phenyl-1*H*-phenalen-1-one (**2**, 4-hydroxyanigorufone), 2,6-dihydroxy-9-phenyl-1*H*-phenalen-1-one (**3**, lachnanthocarpone), and 2-hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**4**), were isolated and identified by comparison of their MS and NMR data with those of authentic references. Lachnanthocarpone (**3**), a known natural product of *Lachnanthes caroliana*[9] (Haemodoraceae) and *Wachendorfia paniculata* (Haemodoraceae),[10] was identified as one of the major components of the $CHCl_3$ fraction. The spectroscopic data matched those of the synthetic compound.[11] Anigorufone (**1**) had previously been isolated from *Anigozanthos rufus*[12] (Haemodoraceae) and 4-hydroxyanigorufone (**2**) from *A. flavidus*.[13] 2-Hydroxy-8-(4-hydroxyphenyl)phenalen-1-one (**4**), bearing the aryl substituent in the unusual 8-position, was first identified from roots and leaves of *Eichhornia crassipes* (Pontederiaceae), and the incorporation of two molecules of L-[1-^{13}C]phenylalanine provided the first experimental evidence of the involvement of an aryl migration in the biosynthesis of 8-phenylphenalenones.[5]



The ^{1}H NMR spectrum of compound **5** measured in acetone-d_6 displayed resonances of a total of nine aromatic protons, resonating between δ 7.50 and 6.97, a signal at δ 4.85 (1H), and two multiplets at δ 2.78 and 2.22 (2H each). Although this ^{1}H signal pattern was rather untypical of a phenylphenalenone structure, the number of 19 carbon atoms of such a skeleton could be deduced from the 17 distinguishable signals of the ^{13}C NMR spectrum, of which two represent pairs of equivalent aromatic methine carbon atoms (δ 128.9, C-3′/5′; δ 128.7, C-2′/6′) of a monosubstituted phenyl ring. 2D NMR methods, especially ^{1}H−^{1}H COSY, HMBC, and HSQC, were used for further structural assignment. The signal of H-2′/6′ (δ 6.97) exhibited HMBC correlations with C-4′ (δ 126.5) and a methine carbon at δ 39.3, which therefore had to be C-9, i.e., the

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carbon bearing the phenyl ring (ring D). The HSQC cross-signal of C-9 indicated one attached proton (δ 4.85, H-9), which gives rise to a key signal in the HMBC spectrum because of its connectivities not only with C-1′ (δ 146.2) and C-2′/6′ of the D-ring but also with three quaternary aromatic (δ 143.4, 127.0, 119.8) and the two methylene carbons, C-7 (δ 25.9) and C-8 (δ 30.9). ^{1}H−^{1}H COSY cross-signals between H-9 and H-8 (δ 2.22) and the latter multiplet with H-7 (δ 2.78) established the aliphatic partial structure of ring C. The HMBC cross-signal of H-7 with C-9 confirmed this structural feature. In addition to H-9, H-7 and three further aromatic methines, namely, H-6 (δ 7.04), H-4 (δ 7.50), and H-3 (δ 7.22), also show long-range ^{1}H−^{13}C-heteronuclear correlations through three bonds with the quaternary carbon resonating at δ 127.0, which therefore must be attributed to C-9b of the phenalene tricycle. A series of ^{1}H−^{1}H COSY cross-peaks {H-6−H-5 (δ 7.17)−H-4} and HMBC correlations, e.g., of H-6 with C-7 (δ 25.9) and C-4 (δ 125.0) and of H-5 with C-6a (δ 135.0) and C-3a (δ 129.9), completed the assignment of ring B. HSQC and mutual HMBC cross-signals between H-3/C-4 and H-4/C-3 confirmed the methine carbon resonating at comparably high field (δ 108.8) to be C-3. Further HMBC cross-signals of the singlet of H-3 with the carbon resonating at δ 143.4 (C-1) and another low-field one at δ 146.0 (C-2) assigned the remaining C atoms of ring A. This assignment is in agreement with the indicated HMBC cross-signals of H-9 with the carbon at δ 143.4 and the quaternary carbon at δ 119.8, which can therefore be allocated to the remaining carbon atom C-9a. On the basis of these data, compound **5** was identified as 8,9-dihydro-9-phenyl-7*H*-phenalene-1,2-diol. This new metabolite was henceforth named monolaterol, after the plant species *Monochoria elata*. A related phenylphenalenone, the dimeric 3,3′-bis(8,9-dihydro-9-phenyl-7*H*-phenalene-1,2,6-triol), has recently been found in extracts of the roots and the rhizomes of *Anigozanthos flavidus*,[13] a member of the Haemodoraceae, another phenylphenalenone-producing plant family.

Monolaterol (**5**) is optically active, with a specific rotation of $[\alpha]_D^{20} = +83.4$. This indicated that the natural product is enantiomerically pure or at least constitutes an enantiomerically enriched mixture, but excluded the presence of a racemate.

Together with the dihydro-9-phenylphenalene-1,2,6-triol dimer of unassigned absolute stereostructure from *A. flavidus*,[13] compound **5** is the first representative of this class of metabolites that bears a stereogenic center at C-9. This precluded an assignment of its absolute configuration by a mere comparison of the circular dichroism (CD) spectrum of **5** with that of any structurally similar, configurationally known substance. For this reason, quantum chemical CD calculations[14−16] appeared to be the method of choice. To check for solvent dependence, the CD of compound **5** was measured in MeOH, EtOH, and MeCN. No significant differences of the experimental CD curves obtained in the three solvents were detected.

The computations were carried out starting arbitrarily with the *S*-enantiomer of **5**. This structure was submitted to a conformational analysis by means of the semiempirical PM3[17] method to find all those minima of the corresponding potential energy surface that should be substantially populated at ambient temperature, thus significantly contributing to the overall CD spectrum. To achieve this objective, reaction coordinates for the flexible molecular parts of **5** were computed, and the minimum structures obtained were further optimized.

In the course of this investigation of the conformational space, a total of 40 minimum geometries were received, of which 12 were found to range below the chosen energetic cutoff of 3 kcal/mol[18] above the global minimum. These 12 structures were further optimized by means of DFT (BLYP/6-31G*),[19−21] thus converging to only four geometries. For each of them a single CD spectrum was calculated using the semiempirical CNDO/S[22] Hamiltonian and a TDDFT approach (B3LYP/TZVP).[20,23,24] For both methods, the

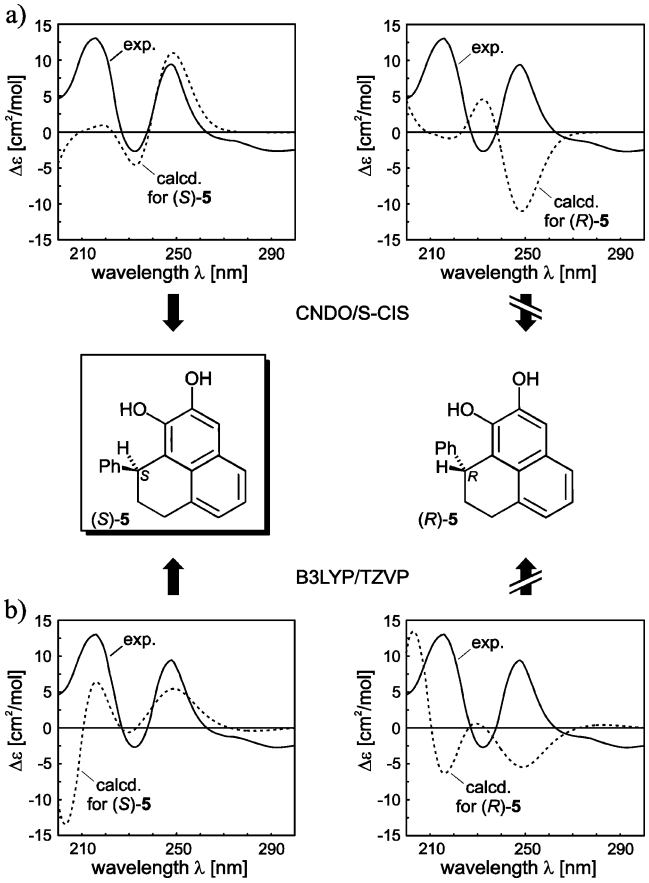

Figure 1. Definition of the absolute configuration of (+)-monolaterol (**5**) by comparison of the experimental CD spectrum with the spectra calculated for (*S*)-**5** and (*R*)-**5** using (a) the CNDO/S Hamiltonian and (b) a TDDFT (B3LYP/TZVP) approach.

resulting four CD curves were summed up weighted according to the Boltzmann statistics, i.e., to the heats of formation of the respective conformers. The overall CD spectra thus obtained were subsequently UV-corrected[25] and compared with the experimental one of **5**. For both theoretical approaches, an excellent agreement between the particular CD curve calculated for (*S*)-**5** (Figure 1, left) was found, while in the case of (*R*)-**5** (Figure 1, right), partially mirror image-like spectra were obtained. Consequently, the absolute configuration of (+)-8,9-dihydro-9-phenyl-7*H*-phenalene-1,2-diol (**5**) was unambiguously assigned as *S*.

The equatorial orientation of H-9 (δ 4.85 in acetone-d_6) was preliminarily deduced from its two small coupling constants (^3J = 4.6 and 2.6 Hz) with the protons at C-8. In acetone-d_6, however, the diastereotopic protons H-7 and H-8 are isochronic, so that the coupling constants could not be extracted from the spectrum and a separate assignment of equatorially and axially oriented diastereotopic protons was impossible from the ^{1}H NMR data obtained. Additional ^{1}H NMR, ^{1}H−^{1}H COSY, and HSQC measurements in benzene-d_6 resulted in well-separated signals of axial and equatorial H-7 (δ 2.89, H-7$_{ax}$; δ 2.60, H-7$_{eq}$) and H-8 (δ 2.05, H-8$_{ax}$; δ 1.98, H-8$_{eq}$). The small coupling constants $^3J_{H-9-H-8ax}$ = 5.0 Hz and $^3J_{H-9-H-8eq}$ = 4.0 Hz confirmed the equatorial orientation of H-9 (δ 4.57 in benzene-d_6). For an axial H-9, a large coupling with H-8$_{ax}$ was anticipated, which, however, was not observed in the spectrum. This finding is not unexpected, because an equatorially oriented phenyl ring at C-9 seems to be energetically disfavored because of an 1,3-allylic strain with the OH group at C-1, possibly even leading to a restricted rotation about the C-9−C-1′ bond. An axial phenyl group, by contrast, should not be sterically hindered. These considerations were confirmed by DFT calculations (B3LYP/cc-pVTZ),[20,23,26] favoring the conformer with an axially arranged

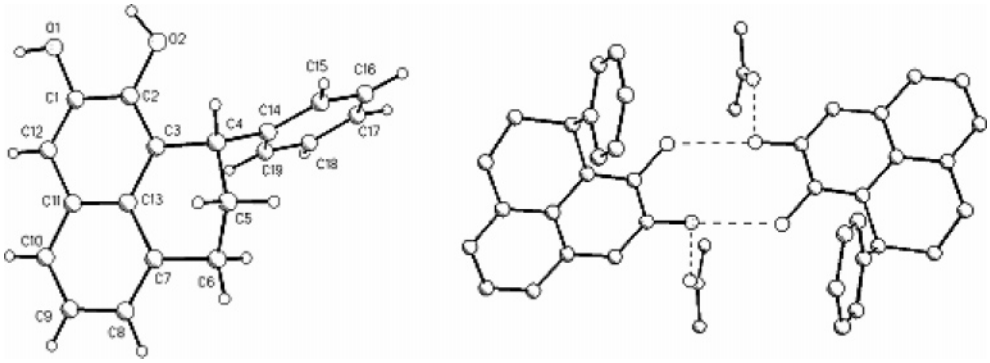

Figure 2. Molecular structure (left, numbering of the X-ray diffraction study) and hydrogen-bonded dimers (right) of (+)-(*S*)-8,9-dihydro-9-phenyl-7*H*-phenalene-1,2-diol (**5**) in crystals obtained from acetone.

phenyl substituent at the stereogenic center over the one with the phenyl ring in an equatorial position, by 1.6 kJ mol^{-1}.

The conformational analysis in solution was supplemented by X-ray diffraction measurements in order to determine the orientation of the proton and the phenyl ring at C-9, in the solid state. Figure 2 shows that, in the crystal, the phenyl ring D is oriented nearly perpendicular (torsion angle C-5−C-4−C-14−C-19 = 96.4°, numbering of the X-ray diffraction study, Figure 2) to the planar aromatic naphthalene system (rings A and B) and ring C is fixed in a five-point coplanar conformation. Thus, the crystal structure confirmed the axial orientation of the phenyl substituent and hence is very similar to the geometry in solution as determined by NMR. The crystal structure also revealed that compound **5** occurs in a 1:1 ratio with a molecule of the solvent acetone in the solid state. Furthermore, each two molecules of **5** are associated to one another via two hydrogen bonds between their hydroxy groups at C-1 and C-2. Additional hydrogen bonds were observed between the 2-hydroxy group of each molecule of **5** and the adjacent acetone unit.

Dihydrophenalenones have been reported as constituents of the chemical profile of Pontederiaceae,[4] Musaceae,[27] and Haemodoraceae.[13] More biosynthetic investigations are required for understanding the role of these compounds classified as precursors or transformation products of phenylphenalenones. The partially hydrogenated substructure of ring C of **5** is in striking contrast to the majority of other members of the phenylphenalenone family, which display nearly planar tricyclic phenalenone ring systems with only the pendent aryl slightly deviating from the plane. This unusual natural product **5** extends the structural diversity of phenylphenalenone-type compounds significantly and may give rise to modified bioactivities of such compounds. Moreover, the knowledge of the absolute configuration of chiral dihydrophenalenones such as compound **5** is relevant for the interaction with potential target proteins. Investigations into the ecological properties of isolated phenylphenalenones and their related compounds have been initiated.

Experimental Section

General Experimental Procedures. Solvents and chemicals used were of analytical or HPLC grade. The melting point of compound **5** was determined using a Büchi melting point B-540 (Büchi, Flawil, Switzerland). The optical rotation was determined on a Jasco J-815 CD spectrometer (Jasco, Gross-Umstadt, Germany). UV spectra were recorded on a Perkin-Elmer Lambda-16 UV/vis spectrometer. Experimental CD spectra were measured at room temperature in a cuvette (pathlength 1 mm) at a concentration of 0.3 mmol L^{-1} in MeOH, EtOH, and MeCN as solvents using a Jasco J-710 spectropolarimeter (Jasco). IR data were recorded on a Nicolet Avatar 370 DTGS (Thermo Electron, Madison, WI). NMR spectra were measured on a Bruker AV 500 NMR spectrometer (Bruker Biospin, Rheinstetten, Germany) equipped with a CryoPlatform. ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H−^{1}H COSY, HMBC, and HSQC spectra were recorded using a 5 mm TXI CryoProbe. The operating frequencies were 500.13 MHz for acquisition of ^{1}H NMR and 125.75 MHz for ^{13}C NMR spectra. Samples were measured at 300 K in acetone-d_6 or benzene-d_6 with TMS as the internal standard. EI and HREI mass spectra were recorded on a MasSpec sector field mass spectrometer (Micromass Ltd., Manchester, UK) with a direct insertion probe.

TLC was performed on silica gel 60 F_{254} using precoated plates (layer thickness 0.25 mm). Compounds on TLC plates were detected at UV 254 and 365 nm and from their visible absorbance. Sephadex LH-20 column chromatography was conducted using an open column (350 × 15 mm). Semipreparative HPLC was performed on a Merck Hitachi LiChrograph chromatography system (L-6200A gradient pump, L-4250 UV−vis detector) using a Nucleosil 100 RP-18 column (10 μm; 250 × 10 mm). Analytical HPLC was carried out on an Agilent 1100 chromatography system (binary pump G1312A, autosampler G1313A) using a LiChrospher 100 RP-18 column (5 μm; 250 × 4 mm). Peaks were detected at 200−600 nm using an Agilent DAD G1315B.

Plant Material. Plants of *M. elata* were raised at the Botanical Garden of the University of Halle (Germany) and in the greenhouses of the Max Planck Institute for Chemical Ecology in Jena (Germany). The plants were grown in soil (Klasmann Erden: clay and sand 1:3) under greenhouse conditions (day 24−26 °C, night 18−21 °C; humidity: 60−70%; light: 6 a.m. to 10 p.m.; the natural photoperiod was supplemented with 8 h illumination from Phillips Sun-T Agro 400 Na lights). Voucher specimens are lodged in the greenhouses of the Max Planck Institute for Chemical Ecology in Jena.

Isolation and Purification. Roots (125 g fresh wt) of *M. elata* were rinsed with H_2O, frozen with liquid N_2, ground, and exhaustively extracted with ethanol at room temperature. The EtOH extract was evaporated (<40 °C) and partitioned between $CHCl_3$−H_2O. The $CHCl_3$ fraction was subjected to gel permeation chromatography on a Sephadex LH-20 column using a step gradient of *n*-hexane−acetone (90:10 → 0:100 in 10% steps). Further purification was achieved by means of semipreparative reversed-phase HPLC using MeCN−H_2O (0.1% TFA) from 10 to 85% MeCN as a gradient in 50 min at a flow rate of 3.5 mL/min. Analytical reversed-phase HPLC runs for purity check were conducted using a linear gradient of MeCN−0.1% aqueous TFA (15:85 → 95:5) in 60 min at a flow rate of 0.8 mL/min. Amounts of compounds isolated from *M. elata* were as follows: 2-hydroxy-9-phenyl-1*H*-phenalen-1-one (**1**), 1.1 mg; 2,4-dihydroxy-9-phenyl-1*H*-phenalen-1-one (**2**), 2.7 mg; 2,6-dihydroxy-9-phenyl-1*H*-phenalen-1-one (**3**), 3.2 mg; 2-hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**4**), 4.1 mg; monolaterol (**5**), 12.3 mg.

Computational Methods. The conformational analysis was performed on a Linux AMD MP 2800+ workstation by means of the semiempirical PM3[17] method and a DFT (BLYP/6-31G*)[19−21] approach, as both implemented in the program package GAUSSIAN 98,[28] starting from preoptimized geometries generated by the TRIPOS force field as part of the molecular modeling package SYBYL 7.0.[29] The wave functions required for the computation of the oscillator and rotatory strengths of the electronic transitions from the ground state to excited states were obtained by CNDO/S[22] calculations followed by CIS computations including 784 singly occupied configurations and the ground state determinant, by means of the BDZDO/MCDSPD[30] program package. Furthermore, UV and CD computations were undertaken using TDDFT with the B3LYP[20,23] hybrid functional and a

TZVP[24] basis set, as included in the TURBOMOLE[31] suite of programs, considering the first 100 excited states. The corresponding oscillator and rotatory strengths thus obtained were in both approaches summed energetically weighted, following the Boltzmann statistics. Finally, the overall UV and CD spectra were simulated as sums of Gaussian functions centered at the wavelengths of the respective electronic transitions and multiplied by the corresponding oscillator or rotatory strengths, transformed into absorption and $\Delta\epsilon$ values, respectively.

X-ray Diffraction. The intensity data for compound **5** were collected on a Nomius KappaCCD diffractometer, using graphite-monochromated Mo Kα radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[32] The COLLECT data collection software, Nonius B.V., Netherlands, 1998, was used. The structure was solved by direct methods (SHELXS)[33] and refined by full-matrix least-squares techniques against F_0^2 (SHELXL-97).[34] The hydrogen atoms were located by difference Fourier synthesis and refined isotropically. The non-hydrogen atoms were refined anisotropically.[34] XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations.

(+)-(*S*)-8,9-Dihydro-9-phenyl-7*H*-phenalene-1,2-diol (5): pale yellow crystals (acetone); mp 99−102 °C; t_R 37.9 min; $[\alpha]_{D(589\ nm)}^{20}$ +83.4, $[\alpha]_{546\ nm}^{20}$ +89.4, $[\alpha]_{495\ nm}^{20}$ +60.1, $[\alpha]_{400\ nm}^{20}$ +24.1, $[\alpha]_{300\ nm}^{20}$ +37.3 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (2.7), 245 (2.0) nm; IR (KBr) ν_{max} 1617, 1274, 621 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.50 (1H, d, J = 8.3 Hz, H-4), 7.22 (1H, s, H-3), 7.19 (2H, dd, J = 8.1, 7.2 Hz, H-3′/H-5′), 7.17 (1H, dd, J = 8.3, 6.9 Hz, H-5), 7.12 (1H, dt, J = 7.2, 2.1 Hz, H-4′), 7.04 (1H, ddd, J = 6.9, 2.4, 1.2 Hz, H-6), 6.97 (2H, dd, J = 8.2, 2.1 Hz, H-2′/H-6′), 4.85 (1H, dd, 4.6, 2.6 Hz, H-9), 2.78 (2H, m, H-7), 2.22 (2H, m, H-8); ^{1}H NMR (benzene-d_6, 500 MHz) δ 7.52 (1H, d, J = 8.1 Hz, H-4), 6.93 (1H, s, H-3), 7.24 (1H, dd, J = 8.1, 7.0 Hz, H-5), 7.03 (1H, brd, J = 7.0 Hz, H-6), 7.00−6.91 (5H, m, H-2′−H-6′), 4.57 (1H, dd, 5.0, 4.0 Hz, H-9), 2.89 (1H, ddd, J = 16.0, 12.9, 4.5, H-7a), 2.60 (1H, ddd, J = 16.0, 4.0, 3.0 Hz, H-7e), 2.05 (1H, dddd, J = 12.9, 12.9, 5.0, 4.0, H-8a), 1.98 (1H, m, H-8e); ^{13}C NMR (acetone-d_6, 125 MHz) δ 146.2 (C, C-1′), 146.0 (C, C-2), 143.4 (C, C-1), 135.0 (C, C-6a), 129.9 (C, C-3a), 128.9 (CH, C-2′/C-6′), 128.7 (CH, C-3′/C-5′), 127.0 (C, C-9b), 126.5 (CH, C-4′), 125.0 (CH, C-4), 123.8 (CH, C-5), 122.7 (CH, C-6), 119.8 (C, C-9a), 108.8 (CH, C-3), 39.3 (CH, C-9), 30.9 (CH_2, C-8), 25.9 (CH_2, C-7); EIMS *m*/*z* 276 $[M]^+$ (100); HREIMS *m*/*z* 276.11590 (calcd for $C_{19}H_{16}O_2$, 276.11503). Crystal data[35] for $C_{19}H_{16}O_2 \cdot C_3H_6O$, M = 334.40 g mol^{-1}, colorless prism, size 0.03 × 0.03 × 0.03 mm^3, monoclinic, space group *C*2, a = 24.2636(9) Å, b = 8.0884(5) Å, c = 9.3582(6) Å, β = 104.802(4)°, V = 1775.63(17) Å^3, T = −90 °C, Z = 4, ρ_{calcd} = 1.251 g cm^{-3}, μ(Mo Kα) = 0.82 cm^{-1}, F(000) = 712, 6377 reflections in h(−31/31), k(−10/10), l(−12/10), measured in the range 1.74° ≤ θ ≤ 27.48°, completeness θ_{max} = 99.8%, 3929 independent reflections, R_{int} = 0.034, 2966 reflections with $F_o > 4\sigma(F_o)$, 290 parameters, 1 restraint, $R1_{obs}$ = 0.049, $wR2_{obs}$ = 0.100, $R1_{all}$ = 0.0765, $wR2_{all}$ = 0.1136, GOOF = 1.011, Flack parameter −0.2(12), largest difference peak and hole 0.172/−0.180 e Å^{-3}.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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