Structure Elucidation of a Dihydropyranone from *Tapinanthus dodoneifolius*

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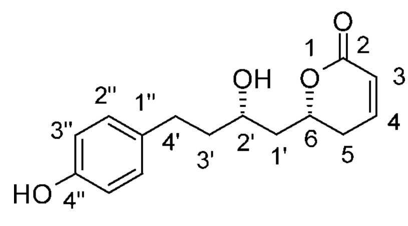
A new dihydropyranone, (*R*)-6-[(*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (**1**), was isolated from *Tapinanthus dodoneifolius.* The structure was determined from spectroscopic and X-ray crystallographic analysis. Compound **1** (named dodoneine) showed a relaxing effect on preconstricted rat aortic rings (IC_{50} of 81.4 ± 0.9 μM).

Tapinanthus dodoneifolius (DC) Dancer (Lorenthaceae), known as African mistletoe, is a hemiplant parasite widely spread in the Sahelian region. *T. dodoneifolius* is used as a remedy to treat wounds, stomachache, diarrhea, cholera, nervous confusion, and cardiovascular and respiratory diseases. Chemical screening indicated the presence of tannins, anthracenosides, anthraquinones, alkaloids, saponins, sterols, and triterpenes in the plant.[1–4]

The sample of *T. dodoneifolius* DC Danser used in this study was collected in June 2005 on a sheanut tree (*Vitellaria paradoxa* CF Gaertn (Sapotaceae)), in Loumbila, 20 km northeast from Ouagadougou, Burkina Faso (West Africa).

The dried and ground whole plant was extracted using an accelerated solvent extractor apparatus (ASE, Dionex) operating at 60 °C and under pressure. The physiological activity of the methanolic extract was close to the effects observed from the conventional extract of the whole plant. A TLC analysis of its methanolic extract indicated the presence of the main compound **1**, a viscous oil that slowly crystallized with one molecule of water to afford colorless prisms that were further purified by crystallization from petroleum ether/toluene: melting point 57–58 °C (uncorrected), $[\alpha]^{25}_{D}$ +40.2 (*c* 0.4, $CHCl_3$, >99% ee). FT-IR analysis revealed the presence of conjugated carbonyl (1698 cm^{-1}) and OH (3351 cm^{-1}) groups. UV absorption at λ_{max} 275 nm indicated the presence of an α,β-unsaturated δ-lactone moiety. The molecular weight was estimated from an ESIMS experiment (M + Na^+ 285 and M_2 + Na^+ 547), and the molecular formula $C_{15}H_{18}O_4$, with seven degrees of unsaturation, was deduced from HRESIMS of the pseudomolecular ion $(M + Na)^+$. ^1H NMR analysis in $CDCl_3$ revealed the presence of a *para*-substituted phenyl ring, with signals at δ 6.98 and 6.69, two coupled vinylic protons at δ 6.82 and 5.95 (α,β-conjugated lactone) on a *cis*-double-bond ($J \approx 9.6$ Hz), two exchangeable protons at δ 1.59 and 2.17 (broad signals, OH), and seven aliphatic protons appearing as multiplets ranging from δ 4.57 to 1.72. The ^{13}C NMR data showed 13 signals including a carbonyl resonance at δ 164.7, six aromatic or vinylic signals from δ 154.6 to 115.8, and six aliphatic carbon signals ranging from δ 77.5 to 29.9. A DEPT 135 experiment revealed the presence of four CH_2 and six CH groups (2 × two aromatic, two vinylic, and two >CH−O−). $^1H-^1H$ COSY, HMBC, and HMQC experiments indicated that the *para*-substituted phenolic ring is bearing a $-CH_2-CH_2-$ group, a methylene group is between two >CH−O−, and the α,β-unsaturated lactone ring is substituted at the 6 position. The ^1H and ^{13}C NMR data of this 6-alkyl-substituted-5,6-dihydro-2*H*-pyran-2-one moiety were very similar to values reported elsewhere for compounds having comparable structural features.[5–7] Compound **1** exists as a sole dextrorotatory enantiomer, as indicated by polarimetric analysis and chiral liquid chromatography.



Dodoneine (**1**).

The relative configuration of both asymmetric carbons was established as follows: reduction of **1** in methanol, with hydrogen over Pd/C, led to the 1,3-diol methyl ester **2** (Scheme 1). This compound reacted with 2,2-dimethoxypropane, under acidic catalysis, to afford the isopropylydene derivative **3**. In the ^{13}C NMR spectrum, the isopropylydene methyl groups resonated as separate signals at δ_C 19.87 and 30.25, consistent with a *syn*-1,3-diol configuration in the starting compound **2** (Scheme 1). Otherwise, an *anti*-1,3-diol configuration should have given two signals close to 25 ppm.[8]

In the biphasic system water/CH_2Cl_2 containing K_2CO_3, **1** underwent an easy intramolecular cyclization by conjugate addition of the hydroxyl group to the double bond, to afford the thermodynamically stable bicyclic lactone **4**.[9] The spectroscopic properties of **4** agreed with values reported elsewhere for related systems.[9,10] Treatment of **4** with (1*S*)-(+)-10-camphorsulfonyl chloride afforded the corresponding optically active camphorsulfonate **5**. X-ray crystallographic analysis, because of the known configuration of the camphorsulfonate moieties, allowed the absolute configuration determination of every asymmetric carbon in **5** (Scheme 1).[11–13] The configurations of the C-1 and C-7 carbons in the bicyclic compound **4** are identical to the corresponding carbons in **1** (Scheme 1). These observations are in agreement with the structure of the *syn*-1,3-diol methyl ester **2** and also imply that no inversion of configuration had occurred during the reduction of **1** with H_2 over Pd/C (Figure 1). Thus, it was concluded that **1** is (*R*)-6-[(*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one, named dodoneine.

Experiments using dodoneine (**1**) were performed on rat aortic rings mounted in an organ bath apparatus to study the vasodilator

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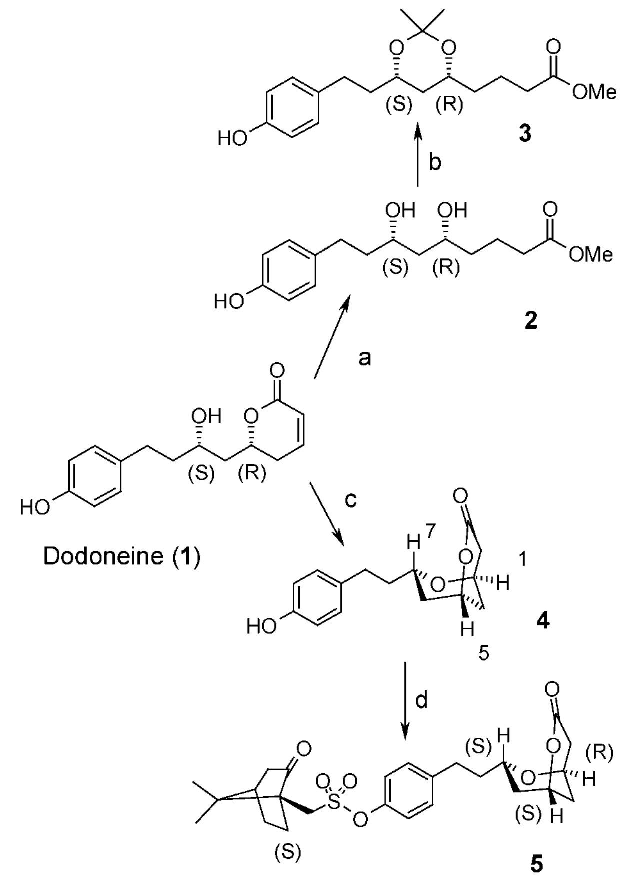
Scheme 1. Dodoneine (**1**) Chemical Transformations[a]



[a] (a) H_2-Pd/C(10%) in methanol, (b) 2,2-dimethoxypropane in anhydrous acetone, *para*-toluenesulfonic acid as catalyst, Δ, (c) K_2CO_3 as catalyst, in the biphasic system water/CH_2Cl_2, (d) (1*S*)-(+)-10-camphorsulfonyl chloride in pyridine, DMAP as catalyst.

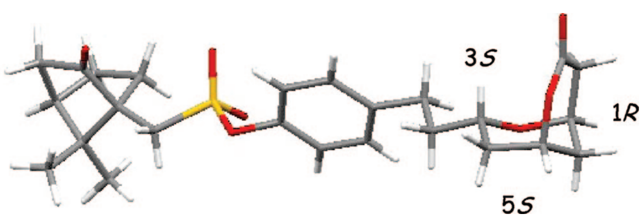


Figure 1. X-ray crystal structure of camphorsulfonate **5** showing the stereogenic centers.

activity.[14,15] Dodoneine (**1**) relaxed preconstricted aortic rings with half-maximal relaxation IC_{50} value of 81.4 ± 0.9 μM (n = 4) (Figure 2).

Experimental Section

General Experimental Procedures. Melting points were determined on a Büchi melting point B-545 apparatus and are uncorrected. Optical rotations were measured at room temperature on a Schmidt Polatronic HH8 polarimeter. UV spectra were recorded on a Genesys Thermo Spectronic 10UV spectrophotometer. IR spectra were recorded on a Nicolet Magna 750 FTIR as a KBr pellet. NMR spectra were recorded on a Bruker Advance DPX300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz) or a Bruker Advance DPX500 spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz), in $CDCl_3$ solution at 25 °C, and the solvent signal was used as a secondary reference for ^{13}C NMR analysis. Analytical HPLC was performed on a Waters 2487 chromatograph equipped with a UV dual detector (measured at 227 and 275 nm). Preparative extraction was realized on an ASE 100 Dionex apparatus.

Plant Material. *Tapinanthus dodoneifolius* (DC.) Danser was collected on a sheanut tree (*Vitellaria paradoxa* CF Gaertn (Sapotaceae)) near the town of Loumbila, 20 km northeast of Ouagadougou, Burkina Faso (West Africa), in June 2005. A voucher specimen was deposited in the Herbarium of the Department of Vegetal Biology, University of Ouagadougou, Burkina Faso, with the reference no. 002.

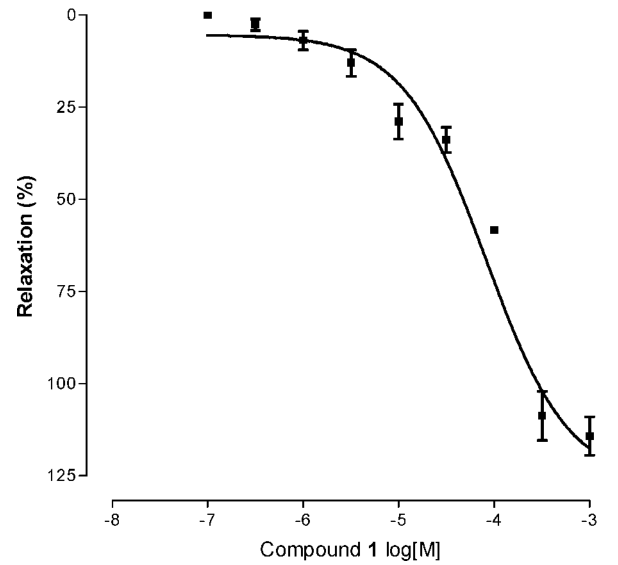


Figure 2. Vasorelaxant effect of dodoneine (**1**) on rat aorta. Concentration-dependent curve is displayed, showing the vasorelaxation effect on the aortic rings preconstricted with 1 μM norepinephrine.

Extraction and Isolation. The air-dried and ground whole plant of *T. dodoneifolius* (49.7 g) was packed in the column of the accelerated solvent extractor apparatus (ASE, Dionex). The extraction temperature was set to 60 °C with a flow rate of 10 mL/min. The column was first percolated with petroleum ether (3 × 100 mL), then with CH_2Cl_2 (3 × 100 mL), methanol (3 × 100 mL), and finally water (100 mL). The solvents were eliminated under reduced pressure, to afford 1.6, 1.2, 10.1, and 3.3 g of extracted material as viscous, colored oils or solid (water), respectively.

The methanolic extract (3.00 g) was chromatographed on silica gel, using CH_2Cl_2/EtOH (0 to 5% EtOH) to afford compound **1** (0.90 g, 3.0%) as a colorless, very viscous oil that slowly crystallized.

(*R*)-6-[(*S*)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (1): colorless crystals $C_{15}H_{18}O_4 \cdot H_2O$ (petroleum ether/toluene); mp 57–58 °C; $[\alpha]^{25}_D$ +40.2 (c 0.40 $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (2.59), 275 (1.86) nm; IR (KBr) ν_{max} 3351, 2920, 1698, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.98 (d, J = 8.5 Hz, 2H, H-2′), 6.88 (dt, J = 9.7, 4.3 Hz, 1H, H-4), 6.69 (dt, J = 8.5, 2.5 Hz, 2H, H-3″), 6.02 (dt, J = 10.4, 1.5 Hz, 1H, H-3), 4.64 (dddd, J = 7.7, 7.7, 7.7, 5.4 Hz, 1H, H-6), 3.80 (br multiplet, 1H, H-2′), 2.60 (m, 2H, H-4′), 2.38 (m, 2H, H-5), 2.00 (dt, J = 14.7, 8.2 Hz, 1H, H-1′), 2.15 (br s, 1H, OH), 1.78 (m, 1H, H-1′), 1.72 (m, 2H, H-3′), 1.5 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.7 (qC, C-2), 154.6 (qC, C-4″), 145.9 (CH, C-4), 133.9 (qC, C-1″), 129.8 (2 × CH, C-2″), 121.6 (CH, C-3), 115.7 (2 × CH, C-3″), 77.5 (CH, C6), 69.0 (CH, C-2′), 42.4 (CH_2, C-1′), 39.7 (CH_2, C-3′), 31.2 (CH2, C-4′), 29.9 (CH_2, C-5); ESIMS m/z 285 (M + Na)$^+$; HRESIMS m/z 285.1094 (calcd for $C_{15}H_{18}O_4Na$, 285.1103).

The enantiomeric excess was determined by chiral stationary-phase HPLC analysis (Daicel Chiralcel OD-H (4.5 mm × 25 cm) column with eluent *i*-PrOH/hexane 40/60, flow rate 0.8 mL·min^{-1}, t_R 8.41 min).

(5*R*,7*S*)-5,7-Dihydroxy-9-(4-methoxyphenyl)nonanoic acid methyl ester (2). Compound **1** (52 mg, 0.20 mmol) in MeOH (4 mL) under stirring was treated with Pd/C 10% (25 mg) under H_2 for 2 h. After filtration through sintered glass and washing of the filter with CH_2Cl_2 (2 × 2 mL), the organic phases were reassembled, then evaporated under vacuum. A short column chromatography (Polar phase cyanopropylsilane bonded to silica gel 40 μm, 60 Å/CH_2Cl_2) afforded **2** (56 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −10.8 (c 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.30 (br s, 1H, OH phenol). 6.98 (d, J = 8.5 Hz, 2H ar), 6.74 (d, J = 8.5 Hz, 2H, arH), 4.11 (br s, 2 × OH alcohol), 3.84 (br s, 2 × >CH-O), 3.65 (s, 3H, OCH_3 ester), 2.54 (m, 2H, benzylic CH_2), 2.32 (t, J = 7.3 Hz, 2H, CH_2), 1.68 (m, 4H), 1.56 (m, 2H), 1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 174.7 (C=O ester), 154.2 (*ipso* C-OH), 133.3 (*ipso* C-alkyl), 129.5 (2 × arC), 115.3 (2 × arC), 72.31 (>CH-O), 72.23 (>CH-O), 51.7 (OCH_3 ester), 42.5 (CH_2, C-6), 39.7 (CH_2), 37.2 (CH_2), 35.7 (CH_2), 33.8 (CH_2), 30.7 (CH_2), 20.5 (CH_2, C-3); ESIMS *m/z* 319 (M + Na)$^+$; HRESIMS *m/z* 319.1514 (calcd for $C_{16}H_{24}O_5Na^+$, 319.1521).

4-{(4*S*,6*R*)-6-[2-(4-Hydroxyphenyl)ethyl]-2,2-dimethyl-[1,3]dioxin-4-yl}butyric acid methyl ester (3). To a stirred solution of **2** (27.5 mg, 0.093 mmol) in anhydrous acetone (4 mL) were added $(MeO)_2CMe_2$ (21 mg, 0.202 mmol) and *p*-TsOH (4 mg). After refluxing under nitrogen for 3 h, the solvent was eliminated under vacuum. The residue was dissolved in CH_2Cl_2 (3 mL), neutralized with 2 drops of Na_2CO_3 saturated solution, then dried with anhydrous $MgSO_4$. The organic phase was removed and the solid residue further extracted with CH_2Cl_2 (3 mL). The organic phases were reassembled, then concentrated under vacuum. A short column chromatography (Polar phase cyanopropylsilane bonded to silica gel 40 μm, 60 Å/hexane/CH_2Cl_2, 3:1) afforded **3** (26 mg, 83%) as a colorless oil: $[\alpha]^{25}_D$ −10.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.03 (dt, *J* = 8.2, 2.3 Hz, 2H, *meta*-phenol), 6.75 (dt, *J* = 8.2, 2.3 Hz, 2H, *ortho*-phenol), 5.29 (br s, 1H, −-OH), 3.76 (m, 2H, 2 × >CH-O), 3.66 (s, 3H, OCH_3 ester), 2.60 (m, 2H, CH_2), 2.31 (t, *J* = 7.6 Hz, CH_2), 1.6–2.8 (m, 4H), 1.4–1.6 (m, 2H), 1.401 (s, 3H, isopropylydene CH_3), 1.396 (s, 3H, isopropylydene CH_3), 1.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 174.2 (C=O ester), 153.7 (*ipso* C-phenol), 134.0 (*ipso* C-alkyl), 129.6 (2 × CH *meta*-phenol), 115.1 (2 × CH *ortho*-phenol), 98.6 (isopropylydene qC), 68.6 (>CH-O), 67.8 (>CH-O), 51.5 (ester OMe), 38.1 CH_2 (β-ar CH_2), 36.9 (dioxane CH_2), 35.7 (γ-ester CH_2), 33.8 (α-ester CH_2), 30.2 (CH_3 isopropylydene), 30.2 (benzylic CH_2), 20.6 (β-ester CH_2), 19.9 (CH_3 isopropylydene); ESIMS *m/z* 359 (M + Na)$^+$; HRESIMS *m/z* 359.1840 (calcd for $C_{19}H_{28}O_5Na^+$, 359.1834).

(1*R*,5*S*,7*S*)-[2-(4-Hydroxyphenyl)ethyl]-2,6-dioxabicyclo[3.3.1]-nonan-3-one (4). To a stirred solution of dodoneine **1** (57 mg, 0.2 mmol) in CH_2Cl_2 (3.5 mL) were added K_2CO_3 (15 mg) and water (0.5 mL), and the mixture was stirred under N_2 for 6 h. The organic phase was separated and washed with brine (2 × 1 mL), dried over $MgSO_4$, and evaporated under vacuum to afford a white product, which was further crystallized from acetonitrile (47 mg, 87%): mp 170–171 °C; $[\alpha]^{25}_D$ −37.5 (*c* 0.44, $CHCl_3$); ^{1}H NMR (MeOH/$CDCl_3$ 300 MHz) δ_H 6.99 (dt, *J* = 8.5, 2.4 Hz, 2H, *meta*-phenol), 6.71 (dt, *J* = 8.5, 2.5 Hz, 2H, *ortho*-phenol), 4.87 (m, 1H, >CH-O), 4.34 (br s, 1H, >CH-O), 3.65 (m, 1H, >CH-O), 2.6 (cm, 4H), 1.98 (m, 3H), 1.92 (m, 1H), 1.7 (cm, 3H); ^{13}C NMR (MeOH/$CDCl_3$, 75 MHz) δ_C 172.4 (C=O lactone), 155.9 (*ipso* C-OH), 133.3 (*ipso* C-alkyl), 130.0 (2 × CH, *meta*-phenol), 115.9 (2 × CH, *ortho*-phenol), 74.7 (>CH-O), 66.8 (>CH-O), 65.5 (>CH-O), 38.6 (CH_2), 37.6 (CH_2), 36.8 (CH_2), 31.1 (CH_2), 30.1 (CH_2); ESIMS *m/z* 285 (M + Na)$^+$; HRESIMS *m/z* 285.1093 (calcd for $C_{15}H_{18}O_4Na^+$, 285.11028).

((*S*)-7,7-Dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)methanesulfonic acid 4-[2-((1*R*,3*S*,5*S*)-7-oxo-2,6-dioxabicyclo[3.3.1]non-3-yl)ethyl)phenyl ester (5). To a solution of bicyclic lactone **4** (44 mg, 0.09 mmol) in pyridine (1.5 mL) were added (1*S*)-(+)-10-camphorsulfonyl chloride (205 mg, 0.8 mmol) and DMAP (5 mg) at RT. After 1 h reaction time, CH_2Cl_2 (6 mL) was added, and the resulting solution was washed with a 10% solution of $NaHCO_3$ (3 × 5 mL). The organic phase was dried with $MgSO_4$ and evaporated under vacuum to afford a viscous oil. Preparative thin-layer chromatography over silica gel (CH_2Cl_2/MeOH, 98:2) afforded camphorsulfonate **5** (50 mg, 68%), which was crystallized from acetonitrile: mp 143–144 °C, $[\alpha]^{25}_D$ +12.7 (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.21 (s, 4H, arH), 4.90 (br s, 1H, >CH-O), 4.40 (br s, 1H, >CH-O), 3.77 (br s, 1H, >CH-O), 3.80 (d, *J* = 15.0 Hz, 1H), 3.19 (d, *J* = 15.0 Hz, 1H), 2.80 (m, 3H), 2.5 (m, 3H), 2.0 (cm, 6H), 1.6 (cm, 5H), 1.15 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 214.1 (C=O ketone), 169.7 (C=O lactone), 147.4 (*ipso* C-OH), 140.8 (*ipso* C-alkyl), 129.7 (2 × CH, *meta*-phenol), 122.0 (2 × CH *ortho*-phenol), 73.0 (>CH-O), 65.9 (>CH-O), 65.0 (>CH-O), 58.1 (qC), 47.9 (qC), 47.4, 42.8 (CH), 42.4 (CH_2), 37.5 (CH_2), 36.9 (CH_2), 36.4 (CH_2), 31.0 (CH_2), 29.7 (CH_2), 26.8 (CH_2), 25.1 (CH_2), 19.9 (CH_3), 19.7 (CH_3).

X-ray Crystallographic Analysis of Compound 5.[13] Suitable single crystals for X-ray analyses were grown from a solution of acetonitrile. A colorless crystal of dimensions 0.28 × 0.22 × 0.04 mm was mounted with Araldite on a glass fiber. X-ray intensity data were collected at room temperature, *T* = 293(2) K, on a Bruker-Nonius X8-APEX2 CCD area-detector diffractometer using Mo Kα radiation (λ = 0.71073 Å). Six sets of narrow data frames (60 s per frame) were collected at different values of θ for one and five initial values of φ and ω using 0.5° increments of φ or ω, respectively. Data reductions were accomplished using SAINT V7.03.[11] The substantial redundancy (3.84) in data allowed a semiempirical absorption correction (SADABS V2.10)[11] to be applied, on the basis of multiple measurements of equivalent reflections. The structures were solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELXTL V6.14.[12]

Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms. Crystal data: $C_{25}H_{32}O_7S$, M_w = 476.57, monoclinic, space group $P2_1$; dimensions: a = 8.700(4) Å, b = 10.245(5) Å, c = 13.949(7) Å, β = 100.21(2)°, V = 1223.5(10) Å^3; Z = 2; D_c = 1.294 g cm^{-3}; μ = 0.174 mm^{-1}; total reflections collected: 12 246; independent reflections: 4296 ($2613F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 50° (99.9% coverage), $F(000)$ = 508, number of variables: 300; R_1 = 0.0732, wR_2 = 0.2069, GOF = 0.984; max./min., absolute structure parameter −0.04(14), residual electron density 0.434 /−0.230 e Å^{-3}.

Contraction Measurement on Isolated Aortic Rings. All experiments were performed on male Wistar rats (250−300 g).[14,15] The thoracic aorta of animals killed by cervical dislocation was removed and placed into Krebs solution containing 120 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgCl_2$, 15 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 11 mM D-glucose, and 10 mM Hepes, pH 7.4. After separation of connective tissues, the thoracic segment of aorta was cut into rings of 3 mm in length. The preparation was then transferred into a 5 mL organ bath containing Krebs solution bubbled with a mixture of 95% O_2 and 5% CO_2. Each aortic ring was suspended between two stainless steel hooks. One of the hooks was mounted at the bottom of the bath, whereas the other was connected to a IT1-25 force displacement transducer (Emka Technologies). All experiments were performed at 37 °C. A basal tension of 2 g was applied in all experiments. During 1 h, tissues were rinsed three times in Krebs solution, and the basal tone was always monitored and adjusted to 2 g. Norepinephrine (10^{-6} M) was used to evoke the sustained contractile response. Once the sustained tension was established, the tissues were allowed to equilibrate further for 30 min before cumulative addition of **1** to the bath. Cumulative concentration–response relationship for the relaxant effect of dodoneine was determined in aortic rings following stable contraction. The relaxant effect was expressed as percentage contraction of the norepinephrine-constricted arterial rings. IC_{50} is the drug concentration inducing a half-maximal vasorelaxation effect (or inhibition of contraction). Data are presented as mean ± SE of four experiments.

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(13) Crystallographic data for compound **5** have been deposited with the Cambridge Crystallographic Data Centre (deposit number CCDC 653149). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336 033 or e-mail: deposit@ccdc.cam.ac.uk), or http//www.ccdc.cam.ac.uk.

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