

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/5796415>

# Structure Elucidation of a Dihydropyranone from *Tapinanthus dodoneifolius*

ARTICLE in JOURNAL OF NATURAL PRODUCTS · JANUARY 2008

Impact Factor: 3.8 · DOI: 10.1021/np070355x · Source: PubMed

CITATIONS

23

READS

98

12 AUTHORS, INCLUDING:



Maurice Ouedraogo

University of Ouagadougou

18 PUBLICATIONS 51 CITATIONS

SEE PROFILE



Clarisse Vandebrouck

Université de Poitiers

46 PUBLICATIONS 1,045 CITATIONS

SEE PROFILE



Christian Cognard

Signalisation et Transports ioniques Memb...

83 PUBLICATIONS 1,535 CITATIONS

SEE PROFILE



Frédéric Becq

Université de Poitiers- CNRS

162 PUBLICATIONS 2,842 CITATIONS

SEE PROFILE

## Structure Elucidation of a Dihydropyranone from *Tapinanthus dodoneifolius*

Maurice Ouedraogo,<sup>†</sup> Hélène Carreyre,<sup>‡</sup> Clarisse Vandebrouck,<sup>†</sup> Jocelyn Bescond,<sup>†</sup> Guy Raymond,<sup>†</sup> Innocent-Pierre Guissou,<sup>§</sup> Christian Cognard,<sup>†</sup> Frédéric Becq,<sup>†</sup> Daniel Potreau,<sup>†</sup> Alain Cousson,<sup>⊥</sup> Jérôme Marrot,<sup>○</sup> and Jean-Marie Coustard<sup>\*,‡</sup>

*Institut de Physiologie et Biologie Cellulaires, Université de Poitiers, CNRS/UMR 6187, 40 Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France, Laboratoire de Synthèse et Réactivité des Substances Naturelles, Université de Poitiers, UMR CNRS 6514, 40 Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France, Institut de Recherche en Sciences de la Santé (IRSS/CNRST), BP 7192, Ouagadougou, Burkina Faso, Laboratoire Léon Brillouin, CEA Saclay, Bâtiment 563, F-91191 Gif sur Yvette Cedex, France, and Institut Lavoisier, UMR CNRS 8180, Université de Versailles, St Quentin en Yvelines, 45 Avenue des Etats-Unis, F-78035 Versailles Cedex, France*

Received July 21, 2007

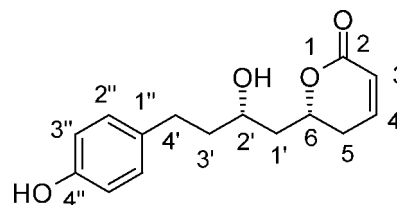
A new dihydropyranone, (*R*)-6-[(*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (**1**), was isolated from *Tapinanthus dodoneifolius*. The structure was determined from spectroscopic and X-ray crystallographic analysis. Compound **1** (named dodoneine) showed a relaxing effect on precontracted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

*Tapinanthus dodoneifolius* (DC) Dancer (Lorenthaceae), known as African mistletoe, is a hemiparasite 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.<sup>1–4</sup>

The sample of *T. dodoneifolius* DC Dancer 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), [α]<sub>D</sub><sup>25</sup> +40.2 (c 0.4, CHCl<sub>3</sub>, >99% ee). FT-IR analysis revealed the presence of conjugated carbonyl (1698 cm<sup>-1</sup>) and OH (3351 cm<sup>-1</sup>) groups. UV absorption at λ<sub>max</sub> 275 nm indicated the presence of an α,β-unsaturated δ-lactone moiety. The molecular weight was estimated from an ESIMS experiment (M + Na<sup>+</sup> 285 and M<sub>2</sub> + Na<sup>+</sup> 547), and the molecular formula C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>, with seven degrees of unsaturation, was deduced from HRESIMS of the pseudomolecular ion (M + Na)<sup>+</sup>. <sup>1</sup>H NMR analysis in CDCl<sub>3</sub> 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* ≈ 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 <sup>13</sup>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<sub>2</sub> and six CH groups (2 × two aromatic, two vinylic, and two >CH–O–). <sup>1</sup>H–<sup>1</sup>H COSY, HMBC, and HMQC experiments indicated that the *para*-substituted

phenolic ring is bearing a –CH<sub>2</sub>–CH<sub>2</sub>– group, a methylene group is between two >CH–O–, and the α,β-unsaturated lactone ring is substituted at the 6 position. The <sup>1</sup>H and <sup>13</sup>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.<sup>5–7</sup> 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 isopropylidene derivative **3**. In the <sup>13</sup>C NMR spectrum, the isopropylidene methyl groups resonated as separate signals at δ<sub>C</sub> 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.<sup>8</sup>

In the biphasic system water/CH<sub>2</sub>Cl<sub>2</sub> containing K<sub>2</sub>CO<sub>3</sub>, **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**.<sup>9</sup> The spectroscopic properties of **4** agreed with values reported elsewhere for related systems.<sup>9,10</sup> 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).<sup>11–13</sup> 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<sub>2</sub> 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

\* To whom correspondence should be directed. Tel: +33 (0)54 945 4100. Fax: +33 (0)54 945 3501. E-mail: jean.marie.coustard@univ-poitiers.fr.

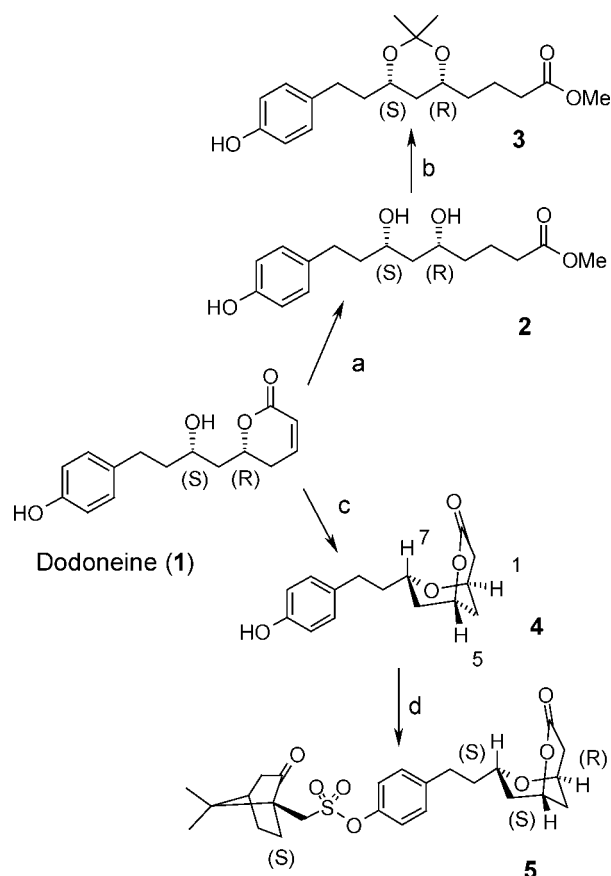
<sup>†</sup> Institut de Physiologie et Biologie Cellulaires, Université de Poitiers.

<sup>‡</sup> Laboratoire de Synthèse et Réactivité des Substances Naturelles, Université de Poitiers.

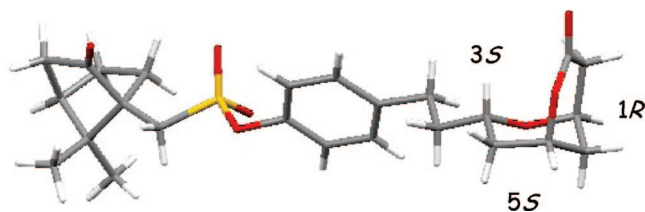
<sup>§</sup> Institut de Recherche en Sciences de la Santé, Ouagadougou.

<sup>⊥</sup> Laboratoire Léon Brillouin, Saclay.

<sup>○</sup> Institut Lavoisier, Versailles.

Scheme 1. Dodoneine (1) Chemical Transformations<sup>a</sup>

<sup>a</sup> (a)  $\text{H}_2$ -Pd/C(10%) in methanol, (b) 2,2-dimethoxypropane in anhydrous acetone, *para*-toluenesulfonic acid as catalyst,  $\Delta$ , (c)  $\text{K}_2\text{CO}_3$  as catalyst, in the biphasic system water/ $\text{CH}_2\text{Cl}_2$ , (d) (1*S*)-(+)-10-camphorsulfonyl chloride in pyridine, DMAP as catalyst.



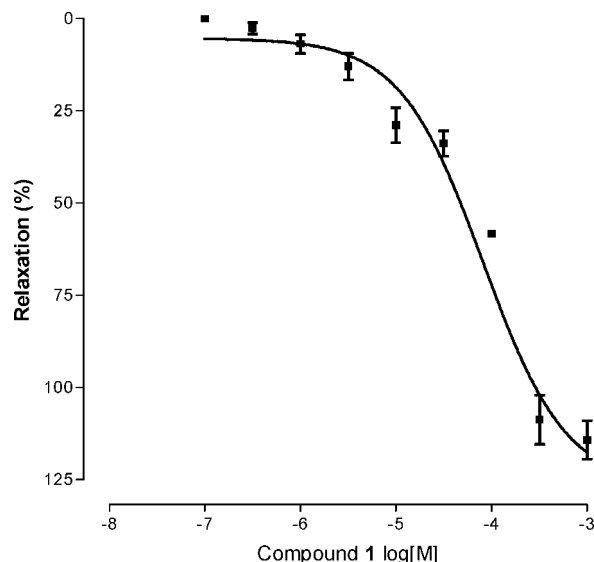
**Figure 1.** X-ray crystal structure of camphorsulfonate **5** showing the stereogenic centers.

activity.<sup>14,15</sup> Dodoneine (**1**) relaxed precontracted aortic rings with half-maximal relaxation  $\text{IC}_{50}$  value of  $81.4 \pm 0.9 \mu\text{M}$  ( $n = 4$ ) (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 Polartonic 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 ( $^1\text{H}$  at 300 MHz and  $^{13}\text{C}$  at 75 MHz) or a Bruker Advance DPX500 spectrometer ( $^1\text{H}$  at 500 MHz and  $^{13}\text{C}$  at 125 MHz), in  $\text{CDCl}_3$  solution at 25 °C, and the solvent signal was used as a secondary reference for  $^{13}\text{C}$  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 (Sapota-



**Figure 2.** Vasorelaxant effect of dodoneine (**1**) on rat aorta. Concentration-dependent curve is displayed, showing the vasorelaxation effect on the aortic rings precontracted with  $1 \mu\text{M}$  norepinephrine.

ceae)) near the town of Loubila, 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.

**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 ( $3 \times 100 \text{ mL}$ ), then with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 100 \text{ mL}$ ), methanol ( $3 \times 100 \text{ mL}$ ), 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  $\text{CH}_2\text{Cl}_2/\text{EtOH}$  (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-dihydroyran-2-one (1):** colorless crystals  $\text{C}_{15}\text{H}_{18}\text{O}_4 \cdot \text{H}_2\text{O}$  (petroleum ether/toluene); mp 57–58 °C;  $[\alpha]_D^{25} +40.2$  (c 0.40  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 227 (2.59), 275 (1.86) nm; IR (KBr)  $\nu_{\text{max}}$  3351, 2920, 1698, 1514  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$  6.98 (d,  $J = 8.5 \text{ Hz}$ , 2H, H-2'), 6.88 (dt,  $J = 9.7, 4.3 \text{ Hz}$ , 1H, H-4), 6.69 (dt,  $J = 8.5, 2.5 \text{ Hz}$ , 2H, H-3''), 6.02 (dt,  $J = 10.4, 1.5 \text{ Hz}$ , 1H, H-3), 4.64 (dddd,  $J = 7.7, 7.7, 5.4 \text{ Hz}$ , 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,  $J = 14.7, 8.2 \text{ Hz}$ , 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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta_{\text{C}}$  164.7 (qC, C-2), 154.6 (qC, C-4'), 145.9 (CH, C-4), 133.9 (qC, C-1'), 129.8 (2  $\times$  CH, C-2''), 121.6 (CH, C-3), 115.7 (2  $\times$  CH, C-3''), 77.5 (CH, C-6), 69.0 (CH, C-2'), 42.4 (CH<sub>2</sub>, C-1'), 39.7 (CH<sub>2</sub>, C-3'), 31.2 (CH<sub>2</sub>, C-4'), 29.9 (CH<sub>2</sub>, C-5); ESIMS  $m/z$  285 ( $\text{M} + \text{Na}^+$ ); HRESIMS  $m/z$  285.1094 (calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$ , 285.1103).

The enantiomeric excess was determined by chiral stationary-phase HPLC analysis (Daicel Chiralcel OD-H (4.5 mm  $\times$  25 cm) column with eluent *i*-PrOH/hexane 40/60, flow rate  $0.8 \text{ mL} \cdot \text{min}^{-1}$ ,  $t_{\text{R}}$  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  $\text{H}_2$  for 2 h. After filtration through sintered glass and washing of the filter with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 2 \text{ mL}$ ), the organic phases were reassembled, then evaporated under vacuum. A short column chromatography (Polar phase cyanopropylsilane bonded to silica gel  $40 \mu\text{m}$ ,  $60 \text{ \AA}/\text{CH}_2\text{Cl}_2$ ) afforded **2** (56 mg, 95%) as a colorless oil:  $[\alpha]_D^{25} -10.8$  (c 0.88,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta_{\text{H}}$  7.30 (br s, 1H, OH phenol), 6.98 (d,  $J = 8.5 \text{ Hz}$ , 2H ar), 6.74 (d,  $J = 8.5 \text{ Hz}$ , 2H, arH), 4.11 (br s, 2  $\times$  OH alcohol), 3.84 (br s, 2  $\times$   $>\text{CH-O}$ ), 3.65 (s, 3H,  $\text{OCH}_3$  ester), 2.54 (m, 2H, benzylic  $\text{CH}_2$ ), 2.32 (t,  $J = 7.3 \text{ Hz}$ , 2H,  $\text{CH}_2$ ), 1.68 (m, 4H), 1.56 (m,

2H), 1.47 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta_{\text{C}}$  174.7 (C=O ester), 154.2 (*ipso* C-OH), 133.3 (*ipso* C-alkyl), 129.5 ( $2 \times \text{arC}$ ), 115.3 ( $2 \times \text{arC}$ ), 72.31 (>CH-O), 72.23 (>CH-O), 51.7 (OCH<sub>3</sub> ester), 42.5 (CH<sub>2</sub>, C-6), 39.7 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 35.7 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 20.5 (CH<sub>2</sub>, C-3); ESIMS  $m/z$  319 ( $\text{M} + \text{Na}^+$ ); HRESIMS  $m/z$  319.1514 (calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_5\text{Na}^+$ , 319.1521).

**4-[(4S,6R)-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)<sub>2</sub>CMe<sub>2</sub> (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  $\text{CH}_2\text{Cl}_2$  (3 mL), neutralized with 2 drops of  $\text{Na}_2\text{CO}_3$  saturated solution, then dried with anhydrous  $\text{MgSO}_4$ . The organic phase was removed and the solid residue further extracted with  $\text{CH}_2\text{Cl}_2$  (3 mL). The organic phases were reassembled, then concentrated under vacuum. A short column chromatography (Polar phase cyano-propylsilane bonded to silica gel 40  $\mu\text{m}$ , 60 Å/hexane/ $\text{CH}_2\text{Cl}_2$ , 3:1) afforded **3** (26 mg, 83%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} -10.5$  ( $c$  0.80,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta_{\text{H}}$  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,  $2 \times >\text{CH-O}$ ), 3.66 (s, 3H, OCH<sub>3</sub> ester), 2.60 (m, 2H, CH<sub>2</sub>), 2.31 (t,  $J = 7.6$  Hz, CH<sub>2</sub>), 1.6–2.8 (m, 4H), 1.4–1.6 (m, 2H), 1.401 (s, 3H, isopropylidene CH<sub>3</sub>), 1.396 (s, 3H, isopropylidene CH<sub>3</sub>), 1.25 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta_{\text{C}}$  174.2 (C=O ester), 153.7 (*ipso* C-phenol), 134.0 (*ipso* C-alkyl), 129.6 ( $2 \times \text{CH meta-phenol}$ ), 115.1 ( $2 \times \text{CH ortho-phenol}$ ), 98.6 (isopropylidene qC), 68.6 (>CH-O), 67.8 (>CH-O), 51.5 (ester OMe), 38.1 CH<sub>2</sub> ( $\beta$ -ar CH<sub>2</sub>), 36.9 (dioxane CH<sub>2</sub>), 35.7 ( $\gamma$ -ester CH<sub>2</sub>), 33.8 ( $\alpha$ -ester CH<sub>2</sub>), 30.2 (CH<sub>3</sub> isopropylidene), 30.2 (benzylic CH<sub>2</sub>), 20.6 ( $\beta$ -ester CH<sub>2</sub>), 19.9 (CH<sub>3</sub> isopropylidene); ESIMS  $m/z$  359 ( $\text{M} + \text{Na}^+$ ); HRESIMS  $m/z$  359.1840 (calcd for  $\text{C}_{19}\text{H}_{28}\text{O}_5\text{Na}^+$ , 359.1834).

**(1R,5S,7S)-[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  $\text{CH}_2\text{Cl}_2$  (3.5 mL) were added  $\text{K}_2\text{CO}_3$  (15 mg) and water (0.5 mL), and the mixture was stirred under  $\text{N}_2$  for 6 h. The organic phase was separated and washed with brine ( $2 \times 1$  mL), dried over  $\text{MgSO}_4$ , and evaporated under vacuum to afford a white product, which was further crystallized from acetonitrile (47 mg, 87%): mp 170–171 °C;  $[\alpha]_{\text{D}}^{25} -37.5$  ( $c$  0.44,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (MeOH/ $\text{CDCl}_3$  300 MHz)  $\delta_{\text{H}}$  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);  $^{13}\text{C}$  NMR (MeOH/ $\text{CDCl}_3$ , 75 MHz)  $\delta_{\text{C}}$  172.4 (C=O lactone), 155.9 (*ipso* C-OH), 133.3 (*ipso* C-alkyl), 130.0 ( $2 \times \text{CH meta-phenol}$ ), 115.9 ( $2 \times \text{CH ortho-phenol}$ ), 74.7 (>CH-O), 66.8 (>CH-O), 65.5 (>CH-O), 38.6 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 31.1 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>); ESIMS  $m/z$  285 ( $\text{M} + \text{Na}^+$ ); HRESIMS  $m/z$  285.1093 (calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}^+$ , 285.11028).

**(5S)-7,7-Dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonic acid 4-[(2-((1R,3S,5S)-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 (1S)-(+)-10-camphorsulfonyl chloride (205 mg, 0.8 mmol) and DMAP (5 mg) at RT. After 1 h reaction time,  $\text{CH}_2\text{Cl}_2$  (6 mL) was added, and the resulting solution was washed with a 10% solution of  $\text{NaHCO}_3$  ( $3 \times 5$  mL). The organic phase was dried with  $\text{MgSO}_4$  and evaporated under vacuum to afford a viscous oil. Preparative thin-layer chromatography over silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 98:2) afforded camphorsulfonate **5** (50 mg, 68%), which was crystallized from acetonitrile: mp 143–144 °C,  $[\alpha]_{\text{D}}^{25} +12.7$  ( $c$  0.44,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta_{\text{H}}$  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<sub>3</sub>), 0.91 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta_{\text{C}}$  214.1 (C=O ketone), 169.7 (C=O lactone), 147.4 (*ipso* C-OH), 140.8 (*ipso* C-alkyl), 129.7 ( $2 \times \text{CH meta-phenol}$ ), 122.0 ( $2 \times \text{CH ortho-phenol}$ ), 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<sub>2</sub>), 37.5 (CH<sub>2</sub>), 36.9 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 31.0 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 19.9 (CH<sub>3</sub>), 19.7 (CH<sub>3</sub>).

**X-ray Crystallographic Analysis of Compound 5.**<sup>13</sup> Suitable single crystals for X-ray analyses were grown from a solution of acetonitrile. A colorless crystal of dimensions  $0.28 \times 0.22 \times 0.04$  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 K $\alpha$  radiation ( $\lambda = 0.71073$  Å). Six sets of narrow data frames (60 s per frame) were collected at different values of  $\theta$  for one and five initial values of  $\varphi$  and  $\omega$  using  $0.5^\circ$  increments of  $\varphi$  or  $\omega$ , respectively. Data reductions were accomplished using SAINT V7.03.<sup>11</sup> The substantial redundancy (3.84) in data allowed a semiempirical absorption correction (SADABS V2.10)<sup>11</sup> 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.<sup>12</sup>

Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms. Crystal data:  $\text{C}_{25}\text{H}_{32}\text{O}_7\text{S}$ ,  $M_w = 476.57$ , monoclinic, space group  $P2_1$ ; dimensions:  $a = 8.700(4)$  Å,  $b = 10.245(5)$  Å,  $c = 13.949(7)$  Å,  $\beta = 100.21(2)^\circ$ ,  $V = 1223.5(10)$  Å<sup>3</sup>;  $Z = 2$ ;  $D_c = 1.294$  g cm<sup>-3</sup>;  $\mu = 0.174$  mm<sup>-1</sup>; total reflections collected: 12 246; independent reflections: 4296 ( $2613F_o > 4\sigma(F_o)$ ); data were collected up to a  $2\theta_{\text{max}}$  value of  $50^\circ$  (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<sup>-3</sup>.

**Contraction Measurement on Isolated Aortic Rings.** All experiments were performed on male Wistar rats (250–300 g).<sup>14,15</sup> 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  $\text{CaCl}_2$ , 1.2 mM  $\text{MgCl}_2$ , 15 mM  $\text{NaHCO}_3$ , 1.2 mM  $\text{KH}_2\text{PO}_4$ , 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<sub>2</sub> and 5% CO<sub>2</sub>. 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<sub>50</sub> is the drug concentration inducing a half-maximal vasorelaxation effect (or inhibition of contraction). Data are presented as mean  $\pm$  SE of four experiments.

**Acknowledgment.** Thanks to CNRS-France and to the University of Poitiers-France (“Programme d’Actions Incitatives”) for financial support. Thanks also to “Agence Universitaire de la Francophonie” for a research grant to one of us (M.O.). Special thanks to D. Lesur (University of Picardie, France) and to L. Lemée (UMR 6514, University of Poitiers, France).

## References and Notes

- Cepleanu, F.; Hamburger, M. O.; Sordat, B.; Msonthi, J. D.; Gupta, M. P.; Saadoun, M.; Hostettman, K. *Int. J. Pharmacol.* **1994**, *323*, 294–307.
- Deeni, Y. Y.; Sadiq, N. M. *J. Ethnopharmacol.* **2002**, *83*, 235–240.
- Ouedraogo, S.; Traoré, A.; Somé, N.; Lompo, M.; Guissou, P. I.; Schott, C.; Bucher, B.; Andriantsitohaina, R. *Afr. J. Trad. Comp. Alt. Med.* **2005**, *2* (1), 25–30.
- Ouedraogo, M.; Ouedraogo, S.; Ouedraogo, L.; Traoré, A.; Belem-tougri, G. R.; Sawadogo, L. L.; Guissou, I. P. *Afr. J. Trad. CAM* **2005**, *2*, 166–176.
- Sabitha, G.; Bashkar, V.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8179–8181.
- Tosaki, S.-Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495–498.
- Sabitha, G.; Fatima, N.; Swapna, R.; Yadav, J. S. *Synthesis* **2006**, *17*, 2879–2884.
- Rychnovsky, S. D.; Skaltitz, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
- Hayakawa, H.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 707–711.
- Graas, S. D.; Hunter, T. J.; O’Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685.
- APEX2 version 2.0–2; Bruker AXS: Madison, WI, 2003.
- SHELXTL version 6.14; Bruker AXS: Madison, WI, 2001.

- (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)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk), or <http://www.ccdc.cam.ac.uk>.
- (14) Robert, R.; Thoreau, V.; Norez, C.; Cantereau, A.; Kitzis, A.; Mettey, Y.; Rogier, C.; Becq, F. *J. Biol. Chem.* **2004**, 279, 21160–21168.
- (15) Vandebrouck, C.; Melin, P.; Norez, C.; Robert, R.; Guibert, C.; Mettey, Y.; Becq, F. *Respir. Res.* **2006**, 7, 113–123.

NP070355X