First Total Synthesis of Justicidone, a *p*-Quinone-Lignan Derivative from *Justicia hyssopifolia*[1)]

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The first synthesis of justicidone (4-(1′,3′-Benzodioxol-5′-yl)-6-methoxynaphtho[2,3-*c*]furan-1,5,8(3*H*)-trione) was carried out from piperonal, as a starting compound, through a lineal process using well known reactions.

Key words justicidone; synthesis; lignan

Justicidone (**1**), is a C-5, C-8 dioxo-lignan derivative isolated from *Justicia hyssopifolia*[2)] (Acanthaceae), whose structure may be considered as having either *para*-naphthoquinone or lignan-derivative features. The interesting biological activity of lignans,[3—5)] and *orto*- and *para*-quinones[6—8)] could be perhaps improved if both types of compounds were included in one common structure. Due to the potential biological activity of justicidone and, on the other hand, that *Justicia hyssopifolia* could only render this compound in a few milligrams, then we became interested in the synthesis of this compound, that we report herein.

Results and Discussion

The proposed synthetic strategy, shown in Chart 1, involves the compound **9**, which by oxidation, may lead to the synthetic objective **1**. There is a variety of methods to synthesize lignans of the 1-arylnaphthalene skeleton.[9—16)] Nevertheless, it has been described, up to now, no natural lignan derivative of the 1-arylnaphthalene type which presents the 2,4,5-substitution pattern in the A ring. In reality, this type of substitution is not common in lignans, being magnoshinin, a dihydro-1-arylnaphthalene lignan derivative, the only compound of this type with such a substitution pattern described in the literature as a natural compound isolated from *Magnolia salicifolia*.[17)] This compound was efficiently synthesized by Yoshida *et al.*[18)] and by Yvon *et al.*[19)]

We initiated the synthesis of justicidone (**1**) by preparing **2** from Piperonal (Chart 2). Treatment of **2** with *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF) for an hour, followed by the addition of 2(5*H*)-furanone, gave rise to **3**. The enolate derived from **3** by the reaction of this compound with lithium diisopropylamide (LDA) in THF was captured by 2,4,5-trimethoxybenzaldehyde which led to a diastereomeric mixture of compounds **4**, which was separated, as it is described in the experimental part, into the diastereomers **4a** and **4b**. The protection of the mixture of **4** was removed by the reaction with HgO in Et_2O–BF_3, to give, as it was expected, a diastereomeric mixture of **5**, which was also separated into **5a** and **5b**. Both compounds **5** and **6** in Chart 2 could lead directly to **9** by acidic treatment after protonation of the carbonyl oxygen and electrophilic substitution on the carbocation. Nevertheless, all attempts for the diastereomeric mixture **5** to be transformed into **9**, failed and instead of **9** gave **6**, which unexpectedly also resisted to give **9** in a more intense acidic treatment. It would be expected that a more reactive (less stable) carbocation could give the aromatic electrophilic substitution and cause closure of the ring, but not its aromatization, in an easier way. So, reduction of **6** with $NaBH_4$ gave **7**, which by treatment with trifluoroacetic acid (TFA) in benzene gave **8**. This last compound was aromatized by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give **9**. Oxidation of **9** with ceric ammonium nitrate (CAN) gave justicidone (**1**). On the other hand, oxidation of **8** with CAN gave also compound **1**, whose structure was determined by ^{1}H-NMR spectroscopy and HR-MS. These data have already been reported.[2)]

Experimental

General Reactions were carried out under dry nitrogen used directly from the cylinder. THF was dried by distillation from sodium/Ph_2CO. Titration of the *n*-BuLi solutions was carried out with *N*-benzylbenzamide to a blue endpoint.[20)] The NMR spectra were recorded on a Brucker Avance 300 MHz and Brucker Avance 400 MHz spectrometers in $CDCl_3$, unless otherwise noted. Chemical shifts are given in ppm with TMS as the internal standard. IR spectra were obtained on a Brucker IFS 28/55 (FTIR) spectrometer and UV spectra on a JASCO V-560. Low resolution mass spectra were run on a VG Micromass ZAB-2F and high-resolution mass spectra on a VG Micromass ZAB-2F at 70 eV. HPLC were performed on a JASCO PU-

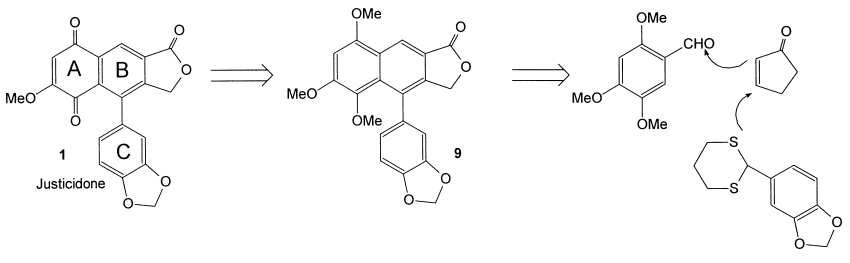

Chart 1. Synthetic Strategy

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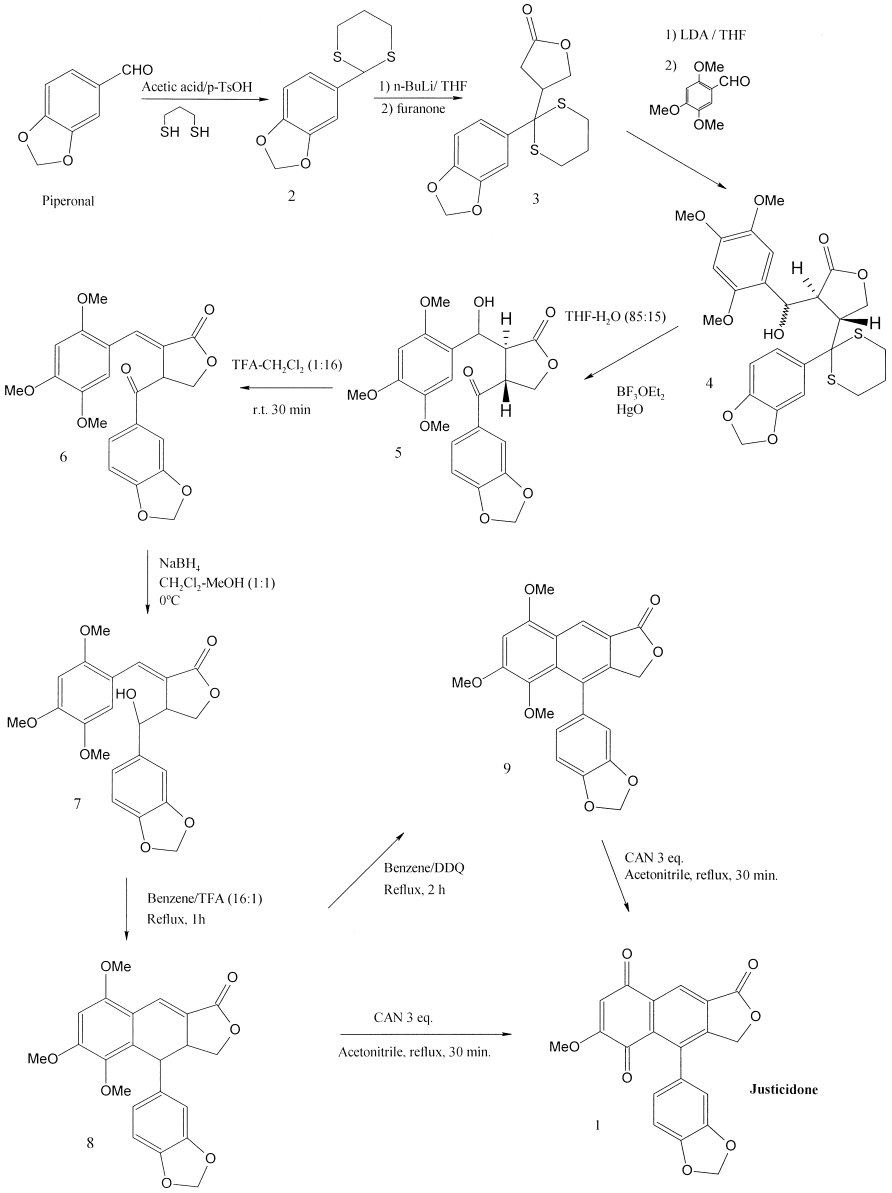

Chart 2. Total Synthesis of Justicidone

1580 apparatus equipped with a JASCO UV-575 UV detector, using a Kromasil Si (250×10 i.d., 5 μm) column. Merck silica gel (0.063—0.200) was used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out on precoated Polygram Sil G/UV plates.

5-(1′,3′-Dithian-2′-yl)-1,3-benzodioxole (2) To a solution of piperonal (1 g=6.66 mmol) in 100 ml of acetic acid, 0.67 ml (6.67 mmol) of propanedithiol and 40 mg (0.21 mmol) of monohydrated *p*-toluensulfonic acid were added. The mixture was stirred for one hour and the crude extracted with ethyl acetate. The product was purified by column chromatography, with *n*-hexane : ethyl acetate, 80 : 20 as eluent, yielding 100% (1.5 g) of a colourless solid compound. mp: 84.5—85.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.17—1.82 (2H, complex), 3.08—2.85 (4H, complex), 5.08 (1H, s), 5.94 (2H, s), 6.74 (1H, d, J=6.8 Hz), 6.93 (1H, d, J=6.8 Hz), 6.98 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 25.0 (t), 32.1 (d), 51.1 (s), 101.2 (t), 108.3 (d), 108.4 (d), 121.3 (d), 132.9 (s), 147.6 (s), 147.7 (s). IR ν_{max} (NaCl) cm^{-1}: 761, 811, 932, 1040, 1174, 1245, 1362, 1440, 1480, 1502, 2891, 2937. UV λ_{max} (EtOH) nm (log ε): 204 (4.54), 243 (3.62), 290 (3.48). HR-MS *m/z*: 240.025318 (Calcd for $C_{11}H_{12}O_2S_2$: 240.027873). MS *m/z*: 240 (M^+) (81), 167 (12), 166 (100), 135 (11).

4-[2′-(1″,3″-Benzodioxol-5″-yl)-1′,3′-dithian-2′-yl]dihydro-2(3*H*)-furanone (3) In a 250 ml three neck round bottomed flask, previously dried by keeping it at 100 °C in the stove for 24 h, was solved 1 g (4.16 mmol) of compound **2** in 50 ml of dried THF. The solution was kept under nitrogen with stirring at −78 °C and one equivalent of *n*-BuLi (2.6 ml of *n*-BuLi 1.6 M in *n*-hexane) was then added, keeping the reaction in the same conditions for 1 h. Then one equivalent (295 μl) of 2(5*H*)-furanone, dissolved in 12 ml of dried THF, was added and the reaction was kept in the same conditions for two more hours. After the addition of 3 ml of concentrated acetic acid, the mixture was allowed to reach the room temperature. The crude of the reaction was extracted in the habitual way with ethyl acetate and the organic phase was dried over anhydrous sodium sulphate. The product, after being purified by column chromatography, using as eluent *n*-hexane : ethyl acetate 80 : 20, was obtained as an oil in 89% yield (1.21 g). ^{1}H-NMR ($CDCl_3$) δ: 1.81—2.01 (2H, complex), 2.43 (1H, dd, J_1=J_2=8.0 Hz), 2.73—2.68 (4H, complex), 2.84 (1H, dd, J_1=J_2=8.0 Hz), 3.01 (1H, q, J=8.0 Hz), 4.19 (1H, dd, J_1=J_2=8.0 Hz), 4.41 (1H, dd, J_1=J_2=8.0 Hz), 6.01 (2H, s), 6.88 (1H, d, J=8.8 Hz), 7.46 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.7 (t), 27.1 (t), 27.1 (t), 30.1 (t), 48.1 (d), 60.6 (s), 68.5 (t), 101.5 (t), 108.3 (d), 123.1 (d), 127.9 (d), 132.9 (s), 147.1 (s), 148.6 (s), 175.7 (s). IR ν_{max} (NaCl) cm^{-1}: 2907, 1777, 1662, 1602, 1482, 1238, 1175, 1037, 930, 800, 755. UV λ_{max} (EtOH) nm (log ε): 207 (4.23), 248 (3.51), 290 (3.46). HR-MS *m/z*: 324.050575 (Calcd for $C_{15}H_{16}O_4S_2$: 324.049003). MS *m/z*: 324 (M^+) (8), 250 (4), 239 (100), 208 (5), 165 (23), 159 (4).

(*S,*S**)-4-[2′-(1″,3″-Benzodioxol-5″-yl)-1′,3′-dithian-2′-yl]-3-[hydroxy(2,4,5-trimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone (4)** Diisopropylamine (0.25 ml, 1.78 mmol) and 4.5 ml of dried THF were placed

in a 25 ml two neck round bottomed flask, previously dried at 100 °C over night, under nitrogen and with stirring. The mixture was kept at −78 °C, and then 1 ml of *n*-BuLi 1.6 M in hexane was added. After 30 min, a solution of 500 mg (1.54 mmol) of **3** in 12 ml of THF was added to the initial mixture and allowed the reaction work for one more hour. At this point, a solution of 330 mg of 2,4,5-trimethoxy benzaldehyde in 5 ml of dried THF was added, followed, after 1 h, of 0.4 ml of acetic acid and allowed the mixture to rise to the room temperature. The mixture of the reaction was extracted with ethyl acetate and the product was purified by silica column chromatography, with *n*-hexane/ethyl acetate 70 : 30 and 60 : 40 as eluent mixtures. 0.76 g of an oily isomeric mixture were obtained in a 95% yield. An aliquot of this mixture was separated by HPLC with *n*-hexane/ethyl acetate 50 : 50 as eluent. **4a**. ^{1}H-NMR ($CDCl_3$) δ: 1.90—180 (2H, complex), 2.67—2.44 (4H, complex), 2.83 (1H, d, J=7.9 Hz), 3.11 (1H, s), 3.72 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 4.31 (1H, t, J=9.5 Hz), 4.87 (1H, d, J=9.5 Hz), 5.34 (1H, br s), 5.95 (1H, d, J=6.8 Hz), 6.27 (1H, s), 6.55 (1H, d, J=8.2 Hz), 6.84 (1H, s), 7.10 (1H, s), 7.17 (1H, d, J=8.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 24.5 (t), 26.6 (t), 27.1 (t), 47.3 (d), 48.2 (d), 55.4 (q), 56.1 (q), 56.9 (q), 63.0 (s), 69.8 (d), 70.0 (t), 96.7 (d), 101.4 (t), 107.3 (d), 109.3 (d), 111.0 (d), 119.6 (d), 123.1(d), 132.8 (s), 142.9 (s), 146.5 (s), 147.8 (s), 149.1 (s), 149.7 (s), 178.5 (s). IR ν_{max} (NaCl) cm^{-1}: 2937, 1753, 1612, 1514, 1466, 1402, 1207, 1124, 1035, 907, 828, 757. UV λ_{max} (EtOH) nm (log ε): 237 (4.33), 289 (4.24). HR-MS *m/z*: 520.118881 (Calcd for $C_{25}H_{28}O_8S_2$: 520.122562). MS *m/z*: 520 (M^+) (6), 324 (8), 239 (100), 197 (44), 181 (13), 165 (31), 125 (7). **4b**. ^{1}H-NMR ($CDCl_3$) δ: 1.86—1.82 (2H, complex), 2.69—2.52 (5H, complex), 2.86 (1H, d, J=5.4 Hz), 3.74 (3H, s), 3.79 (3H, s), 3.89 (3H, s), 4.30 (1H, t, J=7.1 Hz), 4.87 (1H, d, J=7.1 Hz), 5.05 (1H, d, J=6.0 Hz), 6.00 (2H, d, J=27 Hz), 6.61 (1H, s), 6.44 (1H, s), 6.68 (1H, d, J=6.0 Hz), 6.94 (1H, s), 7.31 (1H, d, J=6.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 24.4 (t), 26.8 (t), 27.1 (t), 49.2 (d), 50.6 (d), 55.9 (q), 55.9 (q), 56.3 (q), 62.5 (s), 68.1 (d), 69.0 (t), 96.7 (d), 101.8 (t), 107.1 (d), 108.8 (d), 109.9 (d), 119.2 (s), 123.4 (d), 132.4 (s), 143.4 (s), 147.0 (s), 148.5 (s), 149.2 (s), 150.3 (s), 177.6 (s). IR ν_{max} (NaCl) cm^{-1}: 2937, 1753, 1612, 1514, 1466, 1402, 1207, 1124, 1035, 907, 828, 757. UV λ_{max} (EtOH) nm (log ε): 237 (4.33), 289 (4.24). HR-MS *m/z*: 520.126022 (Calcd for $C_{25}H_{28}O_8S_2$: 520.122562). MS *m/z*: 520 (M^+) (4), 324 (7), 239 (100), 197 (37), 181 (13), 165 (30), 125 (6).

(*S,*S**)-4-(1′,3′-Benzodioxol-5′-ylcarbonyl)-3-[hydroxy(2‴,4‴,5‴-trimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone (5)** Boron trifluoride diethyl etherate (0.6 ml) and HgO (1.0 g) were added to a solution of 0.76 g (1.46 mmol) of the isomeric mixture **4a** and **4b** in 32 ml of THF–H_2O (85 : 15). The reaction was kept for 2 h and a half, at room temperature. Then it was stopped by the addition of 76 ml of CH_2Cl_2 and the suspension was filtered through celite and washed with CH_2Cl_2. The organic phase was washed twice with $NaHCO_3$ (saturated solution) and twice with brine, and dried on anhydrous Na_2SO_4. After elimination of solvent at vacuum, 0.53 g of an oil (1.23 mmol) were obtained (yield=84%). An aliquot of this mixture was separated by HPLC with *n*-hexane/ethyl acetate 60 : 40 as an eluent. **5a**. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (3H, s), 3.75 (3H, s), 3.80 (3H, s), 3.92 (1H, dd, J_1=8.7 Hz, J_2=3.0 Hz), 4.12 (1H, t, J=8.0 Hz), 4.40 (1H, q, J=8.5 Hz), 4.51 (1H, t, J=8.5 Hz), 5.56 (1H, br s), 6.03 (2H, s), 6.34 (1H, s), 6.75 (1H, d, J=8.2 Hz), 7.04 (1H, s), 6.90 (1H, s), 7.20 (1H, d, J=8.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 42.4 (d), 49.6 (d), 55.8 (q), 56.0 (q), 56.2 (q), 66.4 (d), 68.9 (t), 96.8 (d), 102.0 (t), 107.7 (d), 107.7 (d), 110.0 (d), 119.7 (s), 124.4 (d), 130.4 (s), 142.8 (s), 148.3 (s), 149.0 (s), 149.7 (s), 152.3 (s), 176.8 (s), 194.8 (s). IR ν_{max} (NaCl) cm^{-1}: 1767, 1672, 1605, 1506, 1443, 1253, 1205, 1032, 929, 869, 752. UV λ_{max} (EtOH) nm (log ε): 239 (4.19), 294 (4.07). HR-MS *m/z*: 430.124199 (Calcd for $C_{22}H_{22}O_9$: 430.126383). MS *m/z*: 430 (M^+) (20), 412 (14), 263 (50), 197 (100), 149 (99), 121 (16), 65 (14). **5b**. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (1H, t, J=8.8 Hz), 3.71 (3H, s), 3.75 (3H, s), 3.81 (3H, s), 4.25—4.10 (2H, complex), 4.48 (1H, t, J=7.5 Hz), 5.32 (1H, d, J=8.7 Hz), 6.03 (2H, s), 6.07 (1H, s), 6.75 (1H, d, J=8.2 Hz), 6.86 (1H, s), 7.05 (1H, s), 7.16 (1H, d, J=8.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 44.7 (d), 50.9 (d), 55.9 (q), 56.2 (q), 56.4 (q), 67.4 (d), 69.0 (t), 96.8 (d), 102.0 (t), 107.6 (d), 107.8 (d), 111.2 (d), 118.8 (s), 124.4 (d), 130.5 (s), 143.7 (s), 150.2 (s), 167.9 (s), 170.7 (s), 172.1 (s), 178.0 (s), 194.0 (s). IR ν_{max} (NaCl) cm^{-1}: 1767, 1672, 1605, 1506, 1443, 1253, 1205, 1032, 929, 869, 752. UV λ_{max} (EtOH) nm (log ε): 239 (4.19), 294 (4.07). HR-MS *m/z*: 430.123238 (Calcd for $C_{22}H_{22}O_9$: 430.126383). MS *m/z*: 430 (M^+) (9), 412 (25), 263 (52), 197 (52), 149 (100), 121 (15), 65 (11).

4-(1′,3′-Benzodioxol-5′-ylcarbonyl)-3-(2″,4″,5″-trimethoxybenzylidene)dihydro-2(3*H*)-furanone (6) TFA (2.5 ml) was added drop by drop to a solution of 530 mg (1.23 mmol) of the isomeric mixture **5a** and **5b** in 40 ml of CH_2Cl_2. The reaction was kept 30 min at room temperature with stirring. The mixture of the reaction was extracted in the usual way with ethyl acetate, then washed three times with saturated $NaHCO_3$. After removing the solvent at vacuum, we obtained 510 mg of a yellowish oil, which presented blue fluorescence to the ultraviolet light (yield=98%). ^{1}H-NMR ($CDCl_3$) δ: 3.42 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 4.32 (1H, dd, J_1=9.2 Hz, J_2=4.1 Hz), 4.68 (1H, t, J=9.4 Hz), 5.10—5.05 (1H, m), 6.07 (1H, s), 6.43 (1H, s), 6.62 (1H, s), 6.88 (1H, d, J=8.2 Hz), 7.38 (1H, d, J=1.5 Hz), 7.49 (1H, dd, J_1=8.2 Hz, J_2=1.5 Hz), 8.10 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 47.4 (d), 55.8 (q), 56.0 (q), 56.3 (q), 67.5 (t), 96.8 (d), 102.2 (t), 108.2 (d), 108.2 (d), 111.9 (d), 114.4 (s), 119.7 (s), 124.7 (d), 129.8 (s), 135.2 (d), 142.9 (s), 148.8 (s), 152.1 (s), 152.6 (s), 154.1 (s), 171.9 (s), 193.7 (s). IR ν_{max} (NaCl) cm^{-1}: 1747, 1674, 1606, 1510, 1442, 1284, 1248, 1035, 755. UV λ_{max} (EtOH) nm (log ε): 236 (7.81), 301 (7.75). HR-MS *m/z*: 412.118057 (Calcd for $C_{22}H_{20}O_8$: 412.115818). MS *m/z*: 412 (M^+) (37), 363 (7), 263 (47), 197 (12), 181 (13), 168 (8), 149 (100).

4-[1′,3′-Benzodioxol-5′-yl(hydroxy)methyl]-3-(2″,4″,5″-trimethoxybenzylidene)dihydro-2(3*H*)-furanone (7) Three equivalents (0.12 g) of $NaBH_4$ were added to a solution of 450 mg (1.09 mmol) of **6** in 14 ml of a mixture CH_2Cl_2/MeOH 50 : 50 at 0 °C. After 30 min, distilled water was slowly added, keeping the temperature at 0 °C. The mixture of the reaction was extracted with CH_2Cl_2, drying the organic phase with anhydrous sodium sulphate. After removing the solvent, 452 mg (yield 100%) of a yellow paste were obtained. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (1H, m), 3.91 (3H, s), 3.93 (3H, s), 3.96 (3H, s), 4.20 (1H, t, J=8.1 Hz), 4.36 (1H, d, J=9.5 Hz), 4.88 (1H, d, J=6.2 Hz), 5.93 (2H, s), 6.52 (1H, s), 6.71 (2H, s), 6.76 (1H, s), 7.44 (1H, s), 8.05 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 45.6 (d), 56.0 (q), 56.4 (q), 56.7 (q), 66.8 (t), 74.0 (d), 96.8 (d), 101.1 (t), 106.7 (d), 108.1 (d), 112.2 (d), 114.5 (s), 116.4 (s), 120.0 (d), 122.1 (s), 134.0 (d), 143.0 (s), 147.6 (s), 147.9 (s), 152.2 (s), 154.4 (s), 172.6 (s). IR ν_{max} (NaCl) cm^{-1}: 3012, 2909, 1741, 1608, 1507, 1407, 1209, 1035, 930, 753. UV λ_{max} (EtOH) nm (log ε): 229 (5.40), 237 (5.39), 291 (5.38). HR-MS *m/z*: 414.133110 (Calcd for $C_{22}H_{22}O_8$: 414.131468). MS *m/z*: 414 (M^+) (99), 396 (17), 383 (56), 355 (12), 264 (65), 236 (32), 205 (21), 189 (31), 168 (43), 151 (47), 149 (100), 135 (20), 93 (26).

4-(1′,3′-Benzodioxol-5′-yl)-5″,6″,8″-trimethoxy-3a,4-dihydro-3-naphtho[2,3-*c*]furan-1(3*H*)-one (8) 600 mg (1.45 mmol) of the compound **7**, dissolved in 25 ml of benzene, were treated, drop by drop, with 1.60 ml of TFA. The mixture of the reaction was kept under reflux for 1 h, and then was extracted with ethyl acetate, washed three times with saturated $NaHCO_3$, and the organic layer dried over Na_2SO_4. 0.534 g (1.35 mmol 93% yield) of an amorphous solid were obtained. ^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 3.96—3.63 (3H, complex), 4.31 (1H, t, J=8.8 Hz), 5.92 (2H, br s), 6.50 (1H, s), 6.71 (3H, s), 7.81 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 43.2 (d), 49.0 (d), 55.8 (q), 56.2 (q), 59.8 (q), 72.2 (t), 95.6 (d), 100.9 (t), 107.5 (d), 108.0 (d), 115.8 (s), 119.9 (d), 121.7 (s), 127.7 (d), 132.2 (s), 137.8 (s), 141.8 (s), 146.1 (s), 147.9 (s), 155.0 (s), 156.9 (s), 170.2 (s). IR ν_{max} (NaCl) cm^{-1}: 2938, 1749, 1588, 1486, 1465, 1206, 1179, 1037, 753. UV λ_{max} (EtOH) nm (log ε): 293 (3.81), 358 (3.87). HR-MS *m/z*: 396.120209 (Calcd for $C_{22}H_{20}O_7$: 396.120903). MS *m/z*: 396 (M^+) (100), 365 (25), 335 (9), 289 (6).

4-(1′,3′-Benzodioxol-5′-yl)-5,6,8-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (9) A mixture of **8** (10 mg) and DDQ (25 mg) in dry benzene (10 ml) was refluxed for 2 h. After cooling, the solvent was removed and residue was dissolved in ethyl acetate. The crude was extracted in the usual way with ethyl acetate, and dried on anhydrous Na_2SO_4. After purification by HPLC, the compound **9** was isolated as an oil in 44% yield along with traces of justicidone. ^{1}H-NMR ($CDCl_3$) δ: 3.22 (3H, s), 4.04 (3H, s), 4.06 (3H, s), 5.09 (2H, q, J=15.2 Hz), 6.02 (2H, br s), 6.77—6.74 (3H, complex), 6.87 (1H, d, J=7.5 Hz), 8.91 (1H, s). HR-MS *m/z*: 394.098274 (Calcd for $C_{22}H_{18}O_7$: 394.105253). MS *m/z*: 394 (M^+) (92), 379 (24), 367 (60), 349 (68), 333 (8), 321 (18), 158 (30), 102 (100).

4-(1′,3′-Benzodioxol-5′-yl)-6-methoxynaphtho[2,3-*c*]furan-1,5,8(3*H*)-trione (1) 200 mg of **8** dissolved in 150 ml of acetonitril were heated at 80 °C and a solution of 0.91 g (3 equivalents) of CAN dissolved in 2 ml of water was added. The mixture of the reaction was kept in reflux for 30 min. Then, after cooling, the mixture of the reaction was poured over ethyl acetate/H_2O. The organic layer was washed five times with distilled water to eliminate all CAN, then concentrated, dried over Na_2SO_4 and taken to dryness by eliminating the solvent at vacuum. After purification by silica column chromatography, eluted with *n*-hexane : ethyl acetate 60 : 40, 100 mg (54%) of justicidone (**1**) were obtained. mp: 114—115 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 5.06 (1H, d, J=16.4 Hz), 5.17 (1H, d, J=16.4 Hz), 6.05 (2H, d, J=10.8 Hz), 6.26 (1H, s), 6.62 (1H, dd, J_1=1.6 Hz, J_2=8.4 Hz), 6.63 (1H, s), 6.90 (1H, d, J=8.4 Hz), 8.72 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 56.7 (q), 69.7 (t), 101.4 (t), 107.9 (d), 109.0 (d), 109.2 (d), 120.3 (d), 123.9

(d), 129.1 (s), 129.7 (s), 131.7 (s), 135.0 (s), 138.6 (s), 147.9 (s), 148.3 (s), 151.4 (s), 161.0 (s), 169.1 (s), 179.3 (s), 182.9 (s). IR ν_{max} (NaCl) cm^{-1}: 2924, 2852, 1772, 1688, 1651, 1619, 1504, 1455, 1223, 1064, 1012. λ_{max} (EtOH) nm ($\log \varepsilon$): 252 (4.92), 276 (4.69), 322 (4.29). HR-MS *m*/*z*: 364.0557 (Calcd for $C_{20}H_{12}O_7$: 364.0583). MS *m*/*z*: 364 (M^+) (100), 334 (41), 306 (31), 278 (12), 250 (12), 207 (8), 163 (10), 91 (21), 69 (26), 57 (55).

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References and Notes

1) In memory of Professor Antonio González González.
2) Pérez J. A., Boluda C., López H., Trujillo J. M., *Chem. Pharm. Bull.*, **52**, 130—131 (2004).
3) Ayres D. C., "Lignans. Chemical, Biological and Clinical Properties," Cambridge University Press, Cambridge, 1990, pp. 85—111.
4) MacRae W. D., Towers H. N., *Phytochemistry*, **23**, 1207—1220 (1984).
5) Lewis N. G., Davin L. B., "Comprehensive Natural Products Chemistry," Vol. 1, ed. by Meth-Cohn, Elsevier, New York, 1999, pp. 639—712.
6) Perry N. B., Blunt J. W., Munro M. H. G., *J. Nat. Prod.*, **54**, 978—985 (1991).
7) Papageorgiou V. P., Assimopoulou A. M., Couladouros E. A., Hepworth D., Nicolaou K. C., *Angew. Chem. Int. Ed.*, **38**, 271—300 (1999).
8) Khan R. M., Mlungwana S. M., *Phytochemistry*, **50**, 439—442 (1999).
9) Gonzaláz A. G., Pérez J. P., Trujillo J. M., *Tetrahedron*, **34**, 1011—1013 (1978).
10) Pelter A., Ward R. S., Pritchard M. C., Kay I. T., *J. Chem. Soc. Perkin Trans. I*, **1988**, 1603—1613 (1988).
11) Ogiku T., Seki M., Takahashi M., Ohmizu H., Iwasaki T., *Tetrahedron Lett.*, **31**, 5487—5490 (1990).
12) Harrowven D. C., *Tetrahedron Lett.*, **32**, 3735—3738 (1991).
13) Harrowven D. C., Dennison S. T., *Tetrahedron Lett.*, **34**, 3323—3326 (1993).
14) Kamal A., Daneshtalab M., *Tetrahedron Lett.*, **35**, 3879—3882 (1994).
15) Cow C., Leung C., Charlton J. L., *Can. J. Chem.*, **78**, 553—561 (2000).
16) Mizufune H., Nakamura M., Mitsudera H., *Tetrahedron Lett.*, **42**, 437—439 (2001).
17) Kikuchi T., Kadota S., Yanada K., Tanaka K., Watanabe K., Yoshizaki M., Yokoi T., Shingu T., *Chem. Pharm. Bull.*, **31**, 1112—1114 (1983).
18) Yoshida S.-I., Ogiku T., Ohmizu H., Iwasaki T., *Synlett.*, **1994**, 895—898 (1994).
19) Yvon B. L., Datta P. K., Le T. N., Charlton J. L., *Synthesis*, **2001**, 1556—1560 (2001).
20) Burchat A. F., Chong J. M., Nielsen N., *J. Organometallic Chemistry*, **542**, 281—283 (1997).