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Synthesis of Yangjinhualine A

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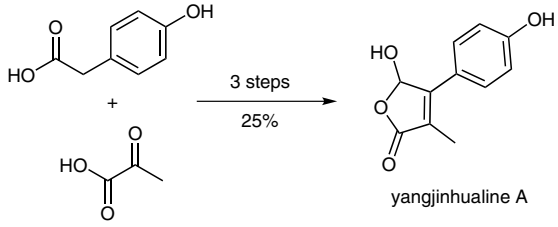

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Abstract Selective reduction of 3-(4-hydroxyphenyl)-2-methylmaleic anhydride provides access the corresponding γ-hydroxybutenolide natural product yangjinhualine A.

Key words anhydrides, regioselectivity, reduction, lactones, natural products

Maleic anhydride, γ-hydroxybutenolide, and butenolide are common structural motifs present in many natural products that display a broad range of biological properties.[1,2] Five representative examples of lactol-bearing bioactive natural products are shown in Figure 1.[3] Compounds of this type exhibit ring–chain tautomerism, so that even in nature they exist in racemic form at the γ-position. Few methods are known for the synthesis of γ-hydroxybutenolides of this type. Most of the existing methods are based on the condensation of glyoxylic acid with aldehydes or esters bearing active α-hydrogen atoms,[2b,4] oxyfunctionalization of 2-(silyloxy)furans,[5] oxidation of furans,[6] or γ-hydroxylation reactions.[7]

Datura metel is one of the 50 basic herbs used in traditional Chinese medicine, in which it is called *yangjinhua*.[8] Recently, *yangjinhua* has been used clinically in China for treatment of psoriasis.[9] However, ingestion of *D. metel* in any form is dangerous and requires extreme caution.[10] The principal toxic elements are tropane alkaloids that can lead to severe side effects.[11] In 2008, Feng and co-workers reported the isolation of very small amounts (0.000027% by dry weight) of yangjinhualine A (**1a**) from the dried flowers of *D. metel*.[3a] Recently, Ding and co-workers also isolated this natural product from *Streptomyces* species YIM66017.[12]

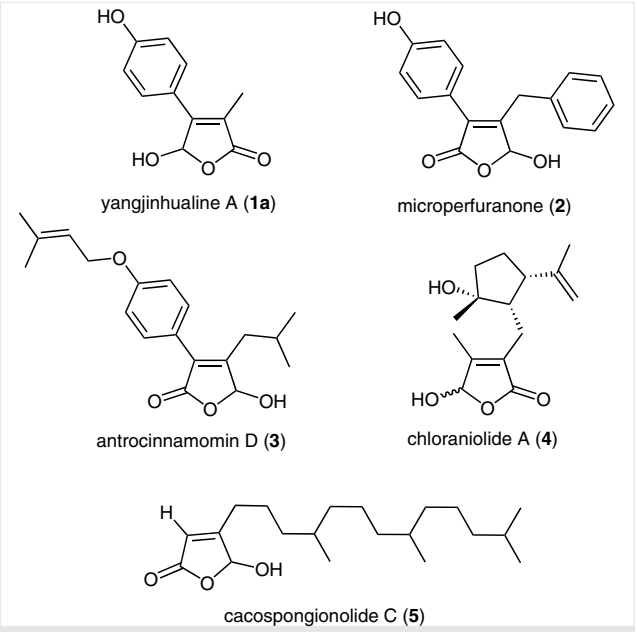
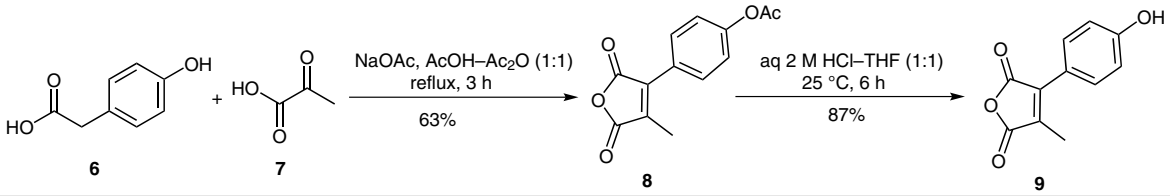


Figure 1 Naturally occurring bioactive lactols

A 2,2-diphenyl-1-picrylhydrazyl radical-scavenging assay for yangjinhualine A showed activity with an IC_{50} value of 57.12 μg/mL. Only one synthesis of this natural product has been reported in the literature.[5b] This was accomplished by a strategy involving a Suzuki–Miyaura cross-coupling and 2-(silyloxy)furan oxyfunctionalization. Regioselective controlled reduction of the corresponding nonsymmetrical maleic anhydrides or the controlled oxidation of the corresponding butenolides is a challenging task in the synthesis of naturally occurring lactols. In this context, we report a simple approach to yangjinhualine A.

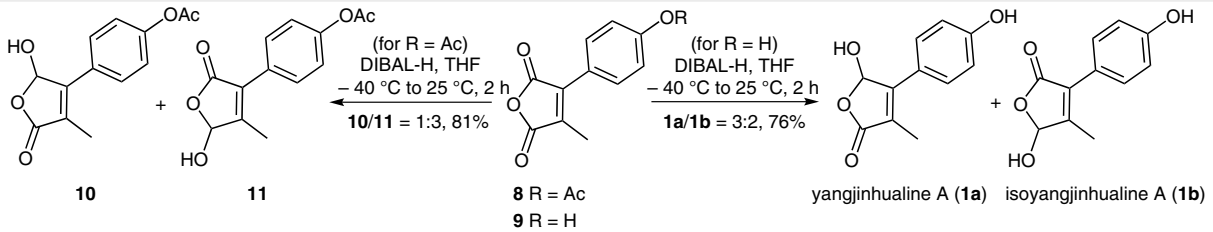


Scheme 1 Preparation of essential aryl(methyl)maleic anhydrides

In a continuation of our studies on the synthesis of anhydride- and butenolide-based bioactive natural products,[13] we surmised that 3-(4-hydroxyphenyl)-4-methylfuran-2,5-dione (**9**) might be a potential precursor to yangjinhualine A. As shown in Scheme 1, the sodium acetate–acetic anhydride-mediated dehydrative intermolecular condensation of (4-hydroxyphenyl)acetic acid (**6**) with pyruvic acid (**7**), followed by concomitant intramolecular cyclization, gave 4-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)phenyl acetate (**8**) in 63% yield.[14] Deacylation of anhydride **8** with 2 M hydrochloric acid in tetrahydrofuran gave the desired 3-(4-hydroxyphenyl)-4-methylfuran-2,5-dione (**9**) in 87% yield.

Regioselective reduction of anhydrides **8** and **9** by four different reducing agents was examined.[15,16] Reductions of anhydrides **8** and **9** by sodium triacetoxyborohydride, lithium tri-*tert*-butoxyaluminum hydride, or sodium tri(*sec*-butyl)borohydride showed poor selectivity and gave mixtures of the corresponding products **10** and **11** or **1a** and **1b**, respectively (Scheme 2); these products could be separated by column chromatography. However, comparatively good results were obtained by using diisobutylaluminum hydride (DIBAL-H) as the reducing agent at –40 to 25 °C. Treatment of the acetoxy anhydride **8** with DIBAL-H gave a mixture of products **10** and **11** (Scheme 2). Separation of this mixture by column chromatography on silica gel gave **10** and **11** in a ~1:3 ratio and 81% total yield. For steric and electronic reasons, reduction by DIBAL-H occurs mainly at the unhindered anhydride carbonyl group, which is more reactive as a result of the electron-withdrawing inductive effect of the acetate group, giving lactol **11** in 61% yield. Further acetate deprotection in compounds **10** and **11** by using 2 M hydrochloric acid gave the desired product yangjinhualine A (**1a**) and isoyangjinhualine A (**1b**) in 92% and 85% yield, respectively. The structures of regioisomers **1a** and **1b** were assigned by means of ^{1}H NMR spectroscopy. As a result of conjugation with the 4-hydroxyphenyl group, the lactol carbon in product **1b** was expected to be relatively more electron rich than that in **1a**. As expected, the methine proton in the natural product **1a** (δ = 6.39) was more deshielded than that in the nonnatural product **1b** (δ = 5.95).

Finally, this structural assignment was confirmed by comparison with the reported data for the natural product **1a**. The hydroxy anhydride **9**, on treatment with DIBAL-H, gave a mixture of the desired natural product yangjinhualine A (**1a**) and isoyangjinhualine A (**1b**) directly. Column chromatographic separation of the resulting mixture on silica gel gave products **1a** and **1b** in a ~3:2 ratio and 76% total yield. For electronic reasons, DIBAL-H preferentially forms a complex with the unhindered carbonyl group, which is more electron rich as a result of the electron-donating mesomeric effect of the hydroxyl group. As a result, reduction occurs preferentially at this carbonyl group through intramolecular delivery of the hydride to give the lactol **1a** in 46% yield. However, lowering the reaction temperature to –78 °C did not improve the regioselectivity or yield from either substrate. The analytical and spectral data for the synthesized natural product yangjinhualine A (**1a**) were in complete agreement with the reported data.[3a,5b,12] Starting from (4-hydroxyphenyl)acetic acid, natural yangjinhualine A (**1a**) and nonnatural isoyangjinhualine A (**1b**) were obtained in three steps and 25% and 33% overall yields, respectively (an average of a 65% yield each step for **1a** and a 70% yield for each step for **1b**). Oxidation of **11** and **1b** to the corresponding anhydrides should provide an effective strategy for recycling the undesired regioisomer.[17]



Scheme 2 Regioselective reduction of anhydrides: synthesis of yangjinhualine A (**1a**) and isoyangjinhualine A (**1b**)

In summary, we have demonstrated a new route to bioactive natural product yangjinhualine A by using regioselective reduction of the corresponding aryl(methyl)maleic anhydride as a key step. The demonstrated balance between the steric and electronic factors in the reported regioselective reduction reactions of aryl(methyl)maleic anhydrides is noteworthy from the point of view of basic chemistry. We foresee that the present approach might be useful in obtaining several complex bioactive natural and non-natural products for structure–activity relationship studies.

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AV 200 MHz NMR spectrometer and a Bruker AV 400 MHz NMR spectrometer with TMS as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker AV 200 MHz NMR spectrometer (50 MHz) and a Bruker AV 400 MHz NMR spectrometer (100 MHz). Mass spectra were recorded on a Thermo Finnigan TOF mass spectrometer. High-resolution mass spectra (ESI) were recorded on a Thermo Scientific Q Exactive hybrid quadrupole Orbitrap spectrometer with a TOF mass analyzer. IR spectra were recorded on a Bruker ALPHA FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 or 200–400 mesh). Commercially available pyruvic acid, 4-$HOC_6H_4CH_2CO_2H$, $NaBH(OAc)_3$, Li(*t*-BuO)$_3$AlH, NaB[*s*-Bu]$_3$H, and DIBAL-H were used.

4-(4-Methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)phenyl Acetate (8)

NaOAc (123 mg, 1.50 mmol) was added to a stirred solution of 4-$HOC_6H_4CH_2CO_2H$ (**6**, 152 mg, 1.00 mmol) and pyruvic acid (**7**, 0.083 mL, 1.20 mmol) in a mixture of AcOH (1.50 mL) and Ac_2O (1.50 mL) at r.t. The mixture was then refluxed for 3 h under argon. A mixture of AcOH and Ac_2O was distilled off under vacuum, H_2O (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel; PE–EtOAc (4:1)] to give a white solid; yield: 155 mg (63%); mp 102–105 °C.

IR (neat): 1751, 1655, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.35 (s, 3 H), 7.28 (d, *J* = 10 Hz, 2 H), 7.72 (d, *J* = 10 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 21.1, 122.4, 125.0, 130.9, 138.6, 139.0, 152.6, 164.8, 166.1, 168.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}O_5$: 247.0601; found: 247.0601.

3-(4-Hydroxyphenyl)-4-methylfuran-2,5-dione (9)

A solution of anhydride **8** (123 mg, 0.50 mmol) in THF (2 mL) and 2 M aq HCl (2 mL) was stirred at 25 °C for 6 h. The solution was then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, PE–EtOAc (2:1)] to give a white solid; yield: 89 mg (87%); mp 166–168 °C.

IR (neat): 3364, 1820, 1748, 1635, 1604 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 5.38 (s, 1 H), 6.97 (d, *J* = 8 Hz, 2 H), 7.65 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 10.8, 116.7, 120.5, 132.6, 136.7, 140.3, 161.3, 167.0, 168.2.

MS (ESI): *m*/*z* = 205 [M + H]$^+$.

Lactols 1a, 1b, 10, and 11; General Procedure

A 1 M solution of DIBAL-H in toluene (0.18 mL, 0.18 mmol) was added dropwise over 10 min to a stirred solution of anhydride **8** or **9** (74/60 mg, 0.15 mmol) in anhydrous THF (5 mL) at −40 °C. The mixture was stirred at −40 °C for 1 h and then at 25 °C for 1 h. The reaction was quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give mixture of products **10** and **11** or **1a** and **1b**, respectively. This residue was purified by column chromatography [silica gel, PE–EtOAc (3:1 or 3:2, respectively)] to give pure products **10** and **11** in a 1:3 ratio or products **1a** and **1b** in a 3:2 ratio, respectively.

4-(2-Hydroxy-4-methyl-5-oxo-2,5-dihydrofuran-3-yl)phenyl Acetate (10)

White solid; yield: 15 mg (20%); mp 133–135 °C.

IR (neat): 3328, 1738 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ = 2.08 (d, *J* = 2 Hz, 3 H), 2.30 (s, 3 H), 6.44 (s, 1 H), 7.25 (d, *J* = 8 Hz, 2 H), 7.69 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 10.3, 20.9, 99.2, 123.3, 126.1, 130.1, 131.0, 153.3, 155.9, 170.8, 174.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}O_5$: 249.0757; found: 249.0760.

4-(5-Hydroxy-4-methyl-2-oxo-2,5-dihydrofuran-3-yl)phenyl Acetate (11)

White solid; yield: 45 mg (61%); mp 84–86 °C.

IR (neat): 3225, 1749, 1700, 1644, 1602 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 2.32 (s, 3 H), 4.60 (br s, 1 H), 5.98 (s, 1 H), 7.16 (d, *J* = 8 Hz, 2 H), 7.50 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.5, 21.1, 98.2, 121.7, 126.9, 127.6, 130.1, 150.7, 157.6, 169.7, 171.4.

MS (ESI): *m*/*z* = 271 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{12}NaO_5$: 271.0577; found: 271.0571.

5-Hydroxy-4-(4-hydroxyphenyl)-3-methylfuran-2(5*H*)-one (1a; Yangjinhualine A)

White solid; yield: 28 mg (46%); mp 209–211 °C (Lit.[5b] 210–212 °C).

IR (neat): 3274, 1680, 1632, 1604 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ = 2.07 (d, *J* = 2 Hz, 3 H), 6.39 (s, 1 H), 6.89 (d, *J* = 8 Hz, 2 H), 7.54 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 10.5, 99.1, 116.6, 122.6, 123.7, 131.6, 156.8, 160.6, 175.4.

MS (ESI): *m*/*z* = 207 [M + H]$^+$.

Compound **1a** was also obtained in 92% yield (38 mg) from **10** (50 mg, 0.20 mmol) by using the same procedure as described for the preparation of **9**.

5-Hydroxy-3-(4-hydroxyphenyl)-4-methylfuran-2(5*H*)-one (1b; Isoyangjinhualine A)

White solid; yield: 18 mg (30%); mp 127–129 °C.

IR (neat): 3253, 1734, 1667, 1605 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.13 (s, 3 H), 5.95 (s, 1 H), 6.84 (d, *J* = 8 Hz, 2 H), 7.34 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.6, 99.8, 116.2, 122.0, 128.9, 131.5, 157.6, 159.1, 173.4.

HRMS (ESI): *m*/*z* (%) $[M + H]^+$ calcd for $C_{11}H_{11}O_4$: 207.0652; found: 207.0650.

Compound **1b** was also obtained in 85% yield (35 mg) from **11** (50 mg, 0.20 mmol) by using the same procedure as described for the preparation of **9**.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379582.

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