First synthesis of antitubercular natural product 2-hydroxy-5-(4-hydroxy-benzyl) benzaldehyde (Forkienin)

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The synthesis of 2-hydroxy-5-(4-hydroxybenzyl)benzaldehyde an antitubercular compound, from the readily available starting compound *p*-hydroxybenzoic acid in 4 steps is described.

Keywords: antitubercular, microwave, solvent less, natural product

Tuberculosis (TB) is one of the most devastating diseases and presents a global health threat of escalating proportions.[1] TB is the second leading infectious cause of mortality today behind only HIV/AIDS. The impetus for developing new structural classes of anti-tuberculosis drugs comes from the emergence of multi-drug resistant (MDR) strains that are resistant to commonly used drugs. Substantially longer treatment is needed as a result of resistance, and there is a resurgence of disease in immuno-compromised patients. Recently many new structural classes of anti-TB agents, exhibiting promising activity against drug-sensitive and drug-resistant strains of the causative organism *Mycobacterium tuberculosis* have appeared.

Microtropis fokienensis Dunn (Celastraceae) is a small shrub that grows in the high-altitude forests throughout southern China and Taiwan.[2] Various triterpenes,[3,4] sesquiterpenes alkaloids,[5] dihydroagarofuranoid sesquiterpenes[6,7] are widely distributed in plants of the family Celastraceae. Many of these compounds exhibit antitumour,[3,4] anti-inflammatory,[7] insecticidal,[6] and anti-AIDS[3] activities. A new hydroxybenzylsalicylaldehyde (Forkienin) has been isolated and identified from the root of *M. fokienesis*.[8] Its antitubercular activities against *M. tuberculosis* has been evaluated in *vitro*.

Some reactions without solvent[9] are more efficient and selective as compared to reactions carried out in solvents. Organic transformations under microwave irradiation generally proceed with greater selectivity,[10-13] under simpler reaction conditions than the analogues homogeneous reactions.

We report here the novel synthesis of the title compound through the use of microwave irradiation as the key step. *p*-Hydroxybenzoic acid **2** was transformed into corresponding acid chloride **3** with thionyl chloride.[14] Solvent free Friedal craft acylation[15] of phenol with *p*-hydroxybenzoyl chloride **3** under microwave irradiation in presence of TiO_2, which is non toxic, inexpensive and commercially available, gave bis-(4-hydroxy-phenyl)-methanone **4** in 70% yield. Compound **4** was then converted into bis-(4-hydroxy-phenyl)-methane **5** via

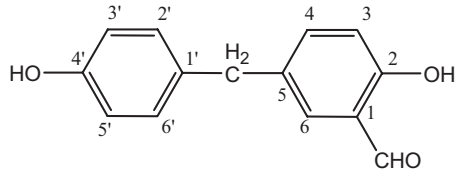


Fig.1

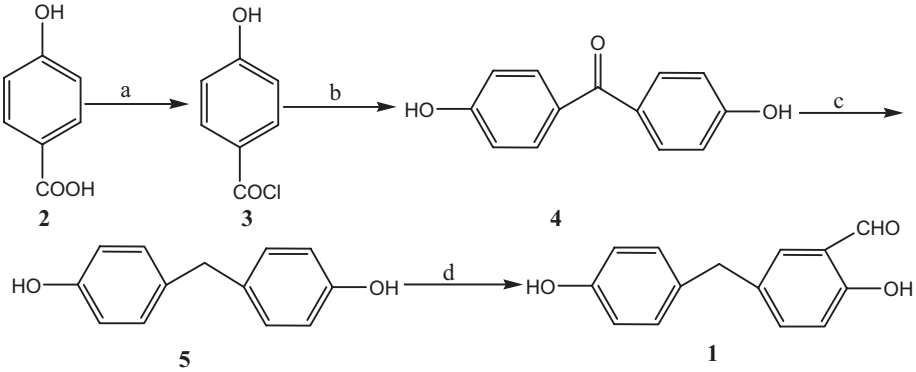
microwave assisted Wolf-Kishner reduction.[16] Formylation of **5** by a Reimer–Tiemann reaction[17] gave the natural product forkienin **1,** the spectral data of which was in good agreement with that reported in literature.[8]

Experimental

Melting points were determined with a Sunbim melting point apparatus. IR spectra were determined on a Perkin Elmer model 1430 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Joel 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. Microwave induced reactions were carried out in a domestic microwave (MG-396 W A, 2450 MHz, 800W).

4-Hydroxybenzoylchloride **(3):** A 100 ml two-necked flask fitted with a dropping funnel and a gas absorption trap connected at the top to reflux condenser was charged with 4-hydroxybenzoic acid **(2)** (2.0 g, 14.49 mmol). Redistilled thionyl chloride 2.05 g (17.38 mmol), was added drop wise through dropping funnel. The flask was heated gently on a water bath for 30–40 minutes. The product was distilled to give the pure acid chloride (**3)** (1.69 g, 75%). b.p. 268–272°C at atmospheric pressure (278.9 ± 23.0°C[18]), IR($CHCl_3$)/ν_{max} cm^{-1}: 3390, 1810, 872. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.27 (bs, 1H, –O*H*, D_2O exchangeable), 7.40 (d, *J* = 7.8 Hz, 2H), 8.29 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 166.1, 156.0, 133.2, 126.5, 122.3.

Bis-(4-hydroxy-phenyl)-methanone **(4):** A mixture of phenol (0.96 g, 10.25 mmol) and TiO_2 (0.40 g, 5.06 mmol) with 4-hydroxybenzoylchloride **(3)** (1.60 g, 10.25 mmol) was irradiated in a microwave oven (320 W) for 25 s. The workup followed by chromatographic purification afforded pure bis-(4-hydroxy-phenyl)-methanone (**4)** (1.53 g, 70%). m.p. 214–217°C (215–219°C[19]),



Scheme 1 (a) $SOCl_2$, heat (b) Phenol, TiO_2, MWI (c) NH_2NH_2, KOH, triethyleneglycol, MWI (d) $CHCl_3$, NaOH.

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IR($CHCl_3$)/ν_{max} cm^{-1}: 3255, 2923, 1724, 1592, 1473, 1375, 1164. ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.80 (bs, 1H, –O*H*, D_2O exchangeable), 6.68 (d, *J* = 8.4 Hz, 4H), 7.74 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR ($CDCl_3$, 300 MHz): 170.1, 156.2, 132.1,129.2, 115.6

Bis-(4-hydroxy-phenyl)-methane **(5):** A solution of bis-(4-hydroxy-phenyl)-methanone **(4)** (1.50 g, 7.0 mmol) and 55% hydrazine hydrate (1.07 g, 1.7 mmol) in a conical flask was treated with ethylene glycol (1 ml) and the contents of the flask were irradiated in the microwave oven at 320 W for 30 s. The mixture was cooled in an ice bath for 5 min. The compound was collected in a suction flask, washed with cold ethanol and air dried to get bis-(4-hydroxy-phenyl)-methanehydrazone (1.31 g, 82%). Ethylene glycol (1.0 ml) and potassium hydroxide (1.40 g, 25 mmol) were irradiated in the microwave oven for 10 s to dissolve the base. Bis-(4-hydroxy-phenyl)-methanehydrazone (1.30 g, 5.74 mmol) was then added to the conical flask containing the mixture of ethylene glycol and potassium hydroxide and irradiated in the microwave oven (320 W) for 10 s. The brown solution was then diluted with 1 ml of deionised water, acidified with 6M HCl until pH = 2, and extracted with diethyl ether (3 × 10 ml). The ether solution was dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo* to give bis-(4-hydroxy-phenyl)-methane **(5) (**0.45 g, 40%). m.p. 159–162°C (literature value 159–162°C[2o]), IR($CHCl_3$)/ν_{max} cm^{-1}: 3347, 2937, 1499, 887, 753. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.6 (s, 2H), 5.30 (bs, 1H, –O*H*, D_2O exchangeable), 6.92 (d, *J* = 8.4 Hz, 4H), 7.21 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 156.6, 130.0, 129.6, 115.6, 45.3.

2-Hydroxy-5-(4-hydroxybenzyl)benzaldehyde **(1):** A stirred warm solution of sodium hydroxide 2.5 g in water (2.5 ml) in the flask was treated with a solution of bis-(4-hydroxy-phenyl)-methane **(5)** (0.45 g, 2.27 mmol) in water (2.0 ml). Chloroform (0.50 g, 4.26 mmol) was added in three portions at intervals of 15 min. The mixture was heated on a boiling water bath for 1 h to complete the reaction and the excess chloroform was removed by evaporation under vacuum. The solution was cooled and acidified cautiously with dilute sulfuric acid and steam distilled. Extracted the distillate at once with ether and removed most of the ether from the extract. Added about twice the volume of saturated sodium metabisulfite solution to the crude 2-hydroxy-5-(4-hydroxybenzyl)benzaldehyde **(1),** stirred vigorously for at least half an hour and allowed to stand for 1 h. The paste of the bisulfite compound was washed with alcohol 4 ml, and with ether 4 ml. The bisulfite compound was decomposed by warming in round bottomed flask on a water bath with dilute sulfuric acid, allowed to cool and the aldehyde was extracted with ether. The work-up yielded 2-hydroxy-5-(4-hydroxybenzyl)benzaldehyde (**1**) (0.21 g, 42%). Amorphous powder[5] IR($CHCl_3$)/ν_{max} cm^{-1}: 3470, 1670, 1215. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.90 (s, 2H, –C*H*$_2$–), 4.80 (bs, 1H, –O*H*, D_2O exchangeable), 6.80 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.2, 2.3 Hz, 1H), 9.81 (s, 1H, C*H*O–), 10.72 (bs, 1H, –O*H*, D_2O exchangeable). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 190, 163.5, 156.9, 136.5, 135.5, 133.2, 131.8, 129.7, 128.7, 119.2, 115.7, 39.8.

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