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Synthesis and antibacterial activity of littorachalcone and related diphenyl ethers

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Abstract—Littorachalcone (**1**) and diacid **10** were synthesized by direct routes. The antibacterial activity of **1**, **10** and synthetic precursors were evaluated. Dialdehyde **3a** showed potent antibacterial activity.

Littorachalcone (**1**), a novel dihydrochalcone dimer, was isolated from the aerial parts of *V. littoralis H. B. K.* along with several flavonoids by Li and coworkers.[1] A related compound verbenachalcone (**2**) was discovered by Li in 2001.[2] Both littorachalcone and verbenachalcone elicited a significant enhancement of nerve growth factor-mediated neurite outgrowth from PC12D cells. Recently, both littorachalcone and analogs of verbenachalcone have been synthesized[3] (see Fig. 1).

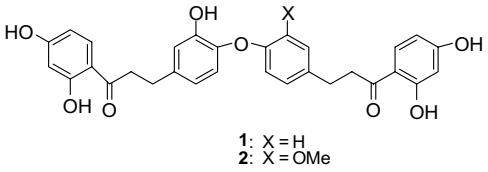

Figure 1. Structures of littorachalcone (**1**) and verbenachalcone (**2**).

Our plan for the synthesis of littorachalcone is shown below. Dialdehyde **3a** will react with two equivalents of the protected 2,4-dihydroxyacetophenone **4** to generate the target compound. The dialdehyde, in turn, would be generated from commercially available para-tolyl ether (**5**) by hydroxylation, protection, and oxidation. Our route is significantly more direct and operationally convenient than that of Nishiyama[3] because we desymmetrize commercially available para-tolyl ether, thus avoiding the protection and deblocking steps necessary in the Nishiyama diaryl ether synthesis (see Fig. 2).

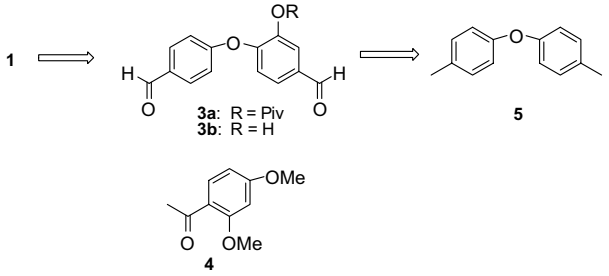

Figure 2. Retrosynthetic analysis for **1**.

Ether **5** was hydroxylated by taking advantage of the selective metalation of diaryl ethers developed initially by Gilman and coworkers.[4] Treatment of **5** with *n*-butyl lithium at 0 °C followed by the addition of trimethyl borate afforded a boronic acid ester. Subsequent hydrogen peroxide-mediated oxidation of the aryl boronic acid ester provided **6** in 82% yield. Protection of the alcohol with pivaloyl chloride and triethylamine afforded ester **7** in 90% yield. We then evaluated two methods to generate dialdehyde **3a** from ester **7**. Radical bromination of **7** using NBS in carbon tetrachloride afforded a dibromide that was unstable to storage. Attempts to convert the dibromide to dialdehyde **3a** using either tetraalkylammonium chromate[5] or *N*-methylmorpholine oxide[6] afforded a mixture of mono aldehyde and dialdehyde

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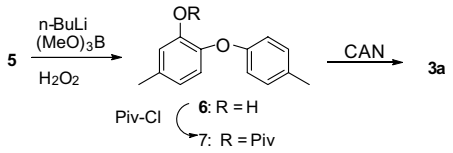

Scheme 1. Synthesis of **3**.

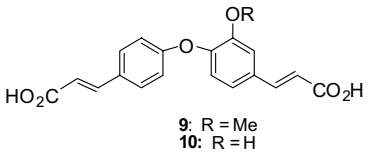

Figure 3. Structures of **9** and **10**.

along with unidentified polar byproducts. Direct oxidation of **7** with ceric ammonium nitrate[7] in aqueous acetic acid at 25 °C produced dialdehyde **3a** in 63% yield (see Scheme 1).

The transformation of **3a** into littorachalcone involves the aldol condensation of two equivalents of a 2,4-dialkoxyacetophenone (**4**) with **3a** followed by the reduction of the double bond and deprotection. Although many simple chalcones have been prepared by the reaction of an acetophenone with an aromatic aldehyde in protic solvents, there are few examples of highly hydroxylated chalcones prepared in this manner.[8] Most syntheses utilized di- or trimethoxy acetophenones. In our hands, the use of 2,4-dimethoxyacetophenone in protic solvents afforded only modest yields of aldol products. The optimal conditions involved the use of the anion of 2,4-dimethoxyacetophenone generated using lithium diisopropylamide (LDA) in THF at −78 °C and aldehyde **3a**. The bis-aldol adduct was produced in 39% yield, with approximately 30% of the mono-aldol product and about 20% of dialdehyde **3a**. The resulting hydroxy ketone was cleanly dehydrated to **8** using *p*-toluenesulfonic acid. The resulting enone was reduced using sodium borohydride and nickel chloride.[9] The pivalate group was cleaved using KOH in water and the methyl ethers were cleaved using boron tribromide[10] (see Scheme 2).

Diacid **9** was isolated from *Curcuma chuanyujin* by Takeda and coworkers as part of a study to identify new plant antioxidants.[11] Compound **10** could be readily synthesized from dialdehyde **3** by a Wittig reaction using carboethoxymethylene triphenylphosphorane followed by hydrolysis of the triester using KOH in methanol (see Fig. 3).

We further tested the antimicrobial properties of compound A by measuring the minimum inhibitory concentration (MIC) using the microdilution method described by Andrews.[12] The MIC value for compound A was ~25 mg/L, while the MIC for ampicillin was ~75 mg/L.

Littorachalcone (**1**) and diacid **10** were synthesized by direct and scalable pathways.[13] The antibacterial activity of **1**, **10**, and their synthetic precursors have been evaluated. Dialdehyde **3a** showed potent antibacterial activity.

Acknowledgment

We thank ISU for partial support of this research.

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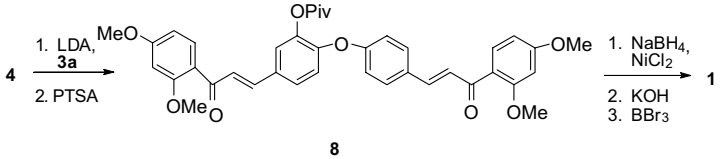
13. Experimental and spectral data for title compounds: *5-Methyl-2-(4-methylphenoxy)-phenol (**6**)*. To the stirred solution of *p*-tolyl ether (1.98 g, 10 mmol) in 20 mL of THF and 20 mL of ether, *n*-BuLi (2.5 M solution in hexane, 4.4 mL, 11 mmol) was added at rt. This solution was boiled for 6 h. Trimethyl borate (1.14 g, 11.0 mmol)



Scheme 2. Synthesis of **1**.

was then added dropwise. The resulting mixture was boiled for an additional 6 h. The reaction was cooled to 0 °C and hydrogen peroxide (30% solution in water, 12 mL) followed by aqueous sodium hydroxide (3 N, 12 mL) solution was added. It was stirred at rt for 1 h and then at 40 °C for 2 h, acidified with 10% HCl and then extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10) to give compound **6** (1.75 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.08, 147.35, 141.59, 134.79, 133.08, 130.48, 130.36, 121.27, 118.85, 117.84, 116.86, 115.56, 21.25, 20.90.

*2,2-Dimethyl-propionic acid 2-(4-methylphenoxy)phenyl ester (**7**).* To a stirred solution of compound **6** (1.8 g, 8.4 mmol) in THF (20 mL), triethyl amine (0.976 g, 9.66 mmol) was added. The mixture cooled to 0 °C and trimethylacetyl chloride (1.08 g, 8.98 mmol) was added at 0 °C. The solution warmed to rt and stirred for 2 h. After this the reaction mixture was filtered through Celite, diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10) to furnish compound **7** (2.25 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8 Hz, 2H), 6.98–6.95 (m, 2H), 6.89 (d, J = 8 Hz, 1H), 6.83 (d, J = 6.8 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, CDCl3) δ 176.78, 155.67, 145.91, 142.48, 134.37, 132.28, 130.36, 130.18, 127.43, 124.30, 120.89, 118.81, 117.44, 39.26, 27.29, 21.02, 20.86.

*2,2-Dimethyl-propionic acid 5-formyl-2-(4-formyl-phenoxy)-phenyl ester (**3**).* The compound **7** (1.10 g, 3.69 mmol) was dissolved in 20 mL of aqueous acetic acid. To this solution was added ceric ammonium nitrate (11 g, 20 mmol) solution in 20 mL of aqueous acetic acid in 10 minutes at rt. The reaction was stirred overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by silica gel chromatography (EtOAc/hexanes, 1:3) to yield compound **3** (0.76 g, 63% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.95 (s, 1H), 7.89 (d, J = 9 Hz, 2H), 7.78 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, CDCl3) δ 190.79, 190.13, 176.25, 161.33, 152.26, 143.39, 133.85, 132.58, 132.30, 132.25, 129.19, 125.21, 121.45, 119.59, 118.26, 39.38, 27.16.

*1-(2,4-dimethoxyphenyl)-3-[4-[4-[3-(2,4-dimethoxyphenyl)-3-oxoprop-2-enyl]-2-pivaloxyphenoxy]phenyl]-2-propene-one (**8**).* To a stirred solution of diisopropyl amine (0.55 g, 5.5 mmol) in THF (10 mL), *n*-BuLi (2.5 M solution in hexane, 2 mL, 5 mmol) at 0 °C was added and the solution was cooled to −78 °C. To this solution was added a solution of 2,4-dimethoxyacetophenone (0.86 g, 4.8 mmol) in THF (5 mL) at −78 °C and stirred for 30 min. A solution of compound **3** (0.52 g, 1.6 mmol) in THF (5 mL) was added to the reaction at the same temperature. The resulting mixture was warmed to 0 °C and the reaction was quenched by adding acetic acid (1 mL in 5 mL of THF). The reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to provide the aldol product (0.42 g, 39% yield).

To a stirred solution of aldol product (0.10 g, 0.15 mmol) in 1,2-dichloroethane, was added catalytic *p*-toluenesulfonic acid. The solution was heated to 50 °C and stirred for 6 h. After this the reaction was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed, and the crude product was purified by silica gel flash chromatography (EtOAc/hexanes, 1:1) to provide compound **8** (0.040 g, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.57–7.53 (m, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.37–7.32 (m, 3H), 7.28 (d, J = 2 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 8 Hz, 2H), 6.40 (s, 2H), 3.81–3.77 (m, 16H), 1.13 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ 190.55, 190.41, 176.52,164.47, 164.39, 160.63, 160.59, 158.54, 148.95, 143.02, 141.37, 140.52, 133.13, 132.83, 131.01, 130.20, 128.56, 127.69, 127.24, 126.48, 123.54, 122.44, 122.32, 121.32, 118.15, 105.41, 98.89, 98.87, 56.05, 56.00, 55.81, 39.36, 27.26.

*1-(2,4-dihydroxyphenyl)-3-[4-[4-[3-(2,4-dihydroxyphenyl)-3-oxopropyl]-2-hydroxyphenoxy]phenyl]-1-propanone (**1**).* Compound **8** (40 mg, 0.06 mmol) was dissolved in 5 mL of methanol and $NiCl_2{\cdot}6H_2O$ (285 mg, 1.2 mmol) followed by 0.5 mL of water was added to this solution with stirring. After 5 min, $NaBH_4$ (18 mg, 0.48 mmol) was added and the reaction was stirred vigorously at rt. After 6 h the reaction mixture was poured into water and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography (EtOAc/hexanes, 1:1) to furnish a diketone (0.03 g, 72% yield).

Diketone (0.10 g, 0.15 mmol) was dissolved in 5 mL of ethanol and KOH (0.080 g, 1.5 mmol) in 5 mL of water was added with stirring to this solution. The resulting mass was boiled for two hours. The reaction mixture was then poured into brine and acidified with 10% HCl solution. The product was extracted with EtOAc, the organic layer was dried over anhydrous $MgSO_4$, the solvent was removed, and the crude product was filtered through silica gel column to provide the hydroxydiketone (0.060 g, 76% yield).

To a stirred solution of the hydroxy diketone (0.040 g, 0.07 mmol) was added boron tribromide (0.17 g, 0.70 mmol) at 0 °C. The solution was stirred for 24 h at rt. The reaction mixture was quenched with water and poured into brine. The mixture was extracted with ethyl acetate. (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed. The crude product was purified by preparative TLC (EtOAc/hexanes, 1:1) to yield **1** (0.010 g, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.83 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 2 Hz, 1H), 6.85–6.79 (m, 4H), 6.44–6.41 (m, 2H), 6.33 (t, J = 2.4 Hz, 2H), 3.34–3.29 (m, 4H), 3.00–2.96 (m, 4H). MS: *m/e*: 514, 363, 352, 313, 286, 264, 185, 163, 149, 108. HRMS: *m/e* calc 514.1628, *m/e* found: 514.1635.

*Diacid **10**.* To a stirred solution of **3a** (0.05 g, 0.15 mmol) in dioxane (5 mL), carboethoxymethylene triphenylphosphorane (0.26 g, 0.6 mmol), potassium bicarbonate (0.12 g, 1.2 mmol) and chloroform (5 ml) were added. The mixture was heated to 110 °C for 18 h. It was cooled to rt, diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was further purified by column chromatography (EtOAc/hexane, 4:6). To the stirred

solution of the above compound (0.05 g, 0.1 mmol) in 10 ml of 50% aqueous ethanol, potassium hydroxide (0.017 g, 0.3 mmol) was added. The mixture was heated to reflux for 3 h. After this the mixture was diluted with ethyl acetate and washed with 10% HCl solution. The organic layer was dried over $MgSO_4$ and was concentrated. The residue was further purified by column chromatography (EtOAc/hexane 7:3) to give compound 10 (0.015 g, 92%).

^{1}H NMR (400 MHz, acetone-d_6) δ 7.70–7.61 (multiplet, 4H), 7.35 (s, 1H), 7.24 (d, J = 8 Hz, 1H) 7.07 (d, J = 8 Hz, 1H) 7.69 (d, J = 8 Hz, 2H), 6.46 (d, J = 4 Hz, 1H), 6.42 (d, J = 4 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6) 172.66, 171.5, 158.62, 146.79, 145.33, 140.79, 138.95, 134.92, 131.92, 129.64, 130.21, 119.64, 119.35, 115.48, 115.32, 114.12.

Methods. Bacterial cultures were prepared by inoculating 5 ml of nutrient broth with single colonies of *Bacillus cereus* and cultured overnight with aeration at 37 °C. The next day, 100 μl of the culture was removed and mixed with 3 ml of nutrient top agar (nutrient broth containing 7% agar) and the mixture plated onto the surface of a nutrient agar plate. After the agar solidified, a 5 mm diameter sterile filter disc was aseptically placed in the center of the plate. 10 μl of each compound in DMSO was pipetted onto the filter disc. After allowing several minutes to dry at room temperature, the plates were incubated overnight at 37 °C.