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Concise Synthetic Approaches to Naturally Occurring β-Hydroxypyranochalcones: First Total Synthesis of Purpurenone, Its Derivative, and Praecansone B

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The total synthesis of biologically interesting β-hydroxypyranochalcones, purpurenone (**1**), its derivative **2**, praecansone B (**3**), and pongapinone A (**4**) has been accomplished starting from commercially available 2,4-dihydroxyacetophenone or 6-methoxy-2,4-dihydroxyacetophenone in 3 steps by a convergent strategy through benzopyran formations, *O*-methylations, and coupling reactions.

Key Words : β-Hydroxypyranochalcone, Purpurenone, Praecansone B, Pongapinone A, Benzopyran formation

Introduction

Pyranochalcones and β-hydroxypyranochalcones are abundant subclasses of flavonoid and are widely distributed in nature.[1] They have been associated with a wide variety of biological activities such as antimutagenic, antimicrobial, anti-ulcer, anti-leishmania, antimalarial, and antitumor activities, and some plants containing these compounds are used in traditional medicines in China and Europe.[2] Among these, purpurenone (**1**) and its derivative **2** with β-hydroxypyranochalcone moiety were isolated from *Lonchocarpus subglaucescens*, which is found in southeast Brazil (Figure 1).[3] Purpurenone (**1**) was also isolated from *L. montanus*, which is an ornamental tree popularly known as "cabelouro" or "carrancudo" in Brazil.[4] Praecansone B (**3**) was isolated from *Tephrosia aequilata*, which is well distributed in the tropical regions of the world.[5] The roots of this plant are used to treat venereal diseases and the leaves to relieve abdominal pains.[6] This compound showed activity against *Trypanosoma brucei rhodensiense* (strain STIB 900, stage trypomastigotes) with IC_{50} 5.9 μg/mL and *Trypanosoma cruzi* (strain Tulahuen C4, stage trypomastigotes) with IC_{50} 7.6 μg/mL.[5] Pongapinone A (**4**) was isolated from the bark of *Pongamia pinnata*, an Indonesian medical plant as known "Warrt".[7] Pongapinone A (**4**) exhibited an inhibitory activity against interleukin-1 production with IC_{50} 2.5 μg/mL.[7]

This wide range of biological properties has stimulated interest in the synthesis of naturally occurring β-hydroxypyranochalcones. No synthetic approaches to naturally occurring compounds **1-3** have been reported so far. Although one convergent synthetic approach to pongapinone A (**4**) starting from 3,5-dimethoxyphenol has been reported in 7 steps (7.6%, overall yield),[8] there is still a demand for a more efficient and concise synthetic method that can efficiently provide β-hydroxypyranochalcones.

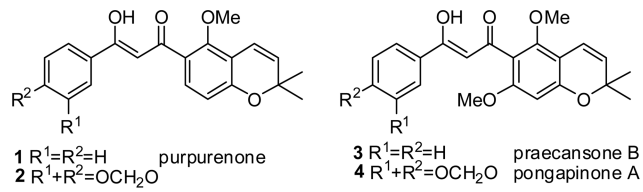
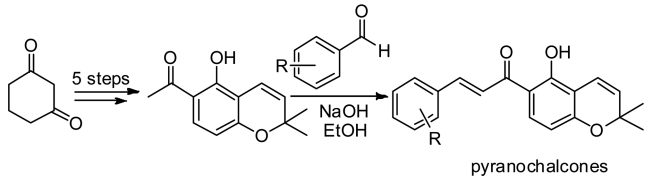


Figure 1. Naturally occurring purpurenone (**1**), its derivative **2**, praecansone B (**3**), and pongapinone A (**4**) with β-hydroxypyranochalcone moiety.

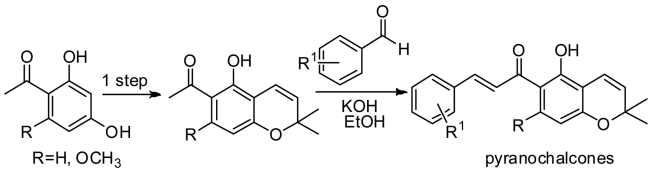
We have reported convergent routes for the synthesis of biologically interesting pyranochalcones starting from cyclohexane-1,3-dione through reactions of 2*H*-pyran formation, aromatization, and aldol condensation in 6 steps (Scheme 1).[9] Although the overall yield (41-44%) from cyclohexane-1,3-dione to pyranochalcones was satisfactory, simpler and more concise synthetic routes were needed.

In order to overcome limitations of this process having many reaction steps, we have developed other new synthetic approaches for pyranochalcones starting from readily available resorcinol derivatives through reactions of benzopyran formation and aldol condensation in 2 steps (Scheme 2).[10]

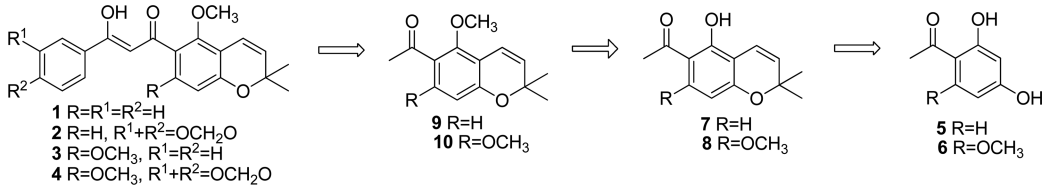
The developed approaches provided synthetic routes for the synthesis of pyranochalcones without bearing β-hydroxy group on the chalcone skeleton. As an expansion and ongoing study of our previous work, we report herein concise and



Scheme 1



Scheme 2



Scheme 3

efficient synthetic approaches for β-hydroxypyranochalcones. We report herein the first total synthesis of purpurenone (**1**), its derivative **2**, and praecansone B (**3**) starting from readily available 2,4-dihydroxyacetophenone or 6-methoxy-2,4-dihydroxyacetophenone. We also report herein concise total synthesis of naturally occurring pongapinone A (**4**) starting from 6-methoxy-2,4-dihydroxyacetophenone.

Results and Discussion

The retrosynthetic approaches for synthesizing purpurenone (**1**), its derivative **2**, praecansone B (**3**), and pongapinone A (**4**) were analyzed as shown in Scheme 3. Naturally occurring compounds **1-4** could be prepared by $MgBr_2{\cdot}OEt_2$-promoted coupling reactions of **9-10** with the corresponding acid chlorides. The bezopyrans **9-10** could be generated from **7** and **8** through *O*-methylation reactions. The intermediates **7-8** could be derived from commercially available 2,4-dihydroxyacetophenone (**5**) and 6-methoxy-2,4-dihydroxyacetophenone (**6**) by benzopyran formation reactions.

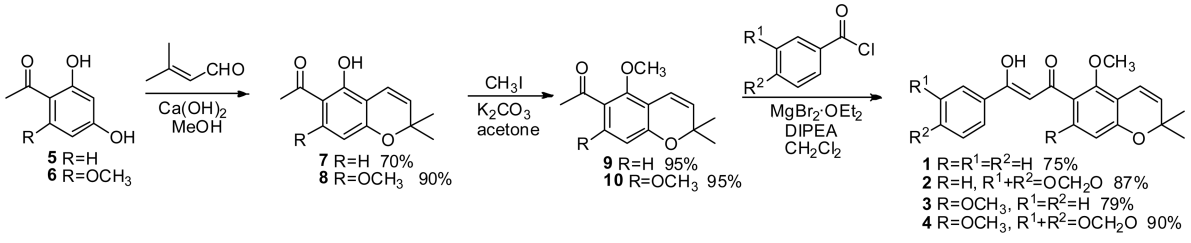
The total synthesis of natural compounds **1-4** was next attempted starting from 2,4-dihydroxyacetophenone (**5**) and 6-methoxy-2,4-dihydroxyacetophenone (**6**) as shown in Scheme 4. Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate-catalyzed or $Ca(OH)_2$-mediated reactions of resorcinols[11] or 1,3-dihydroxyxanthen-9-one[12] to α,β-unsaturated aldehydes. This methodology provided a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl ring in moderate yield.[11,12] Utilizing this methodology, reactions of **5** and **6** with 3-methyl-2-butenal in the presence of 1.0 equivalent of $Ca(OH)_2$ in refluxing methanol for 12 h or 18 h gave the desired benzopyrans **7** and **8** in 70 and 90% yield, respectively. Treatment of **7** and **8** with methyl iodide in the presence of K_2CO_3 in acetone at room temperature or refluxing acetone for 12 h afforded **9** (95%) and **10** (95%).

To give β-hydroxypyranochalcones, condensations of **9** and **10** with benzoyl chloride were next carried out under several bases. Treatment of **9** and **10** with benzoyl chloride in the presence of 2 equivalents of sodium hydride in refluxing THF gave no any desired products. Reaction of **9** with benzoyl chloride in the presence of 1.1 equivalent of lithium diisopropylamide in THF at −78 °C for 2 h followed by addition of benzoyl chloride gave purpurenone (**1**) in 60% yield, whereas that of **10** with benzoyl chloride provided praecansone B (**3**) in 35% yield, together with *O*-acylation product (20%). In order to efficiently synthesize these compounds without any formation of *O*-acylation product with high yields, we used $MgBr_2{\cdot}OEt_2$-promoted coupling reaction described by Coltart.[13] Reactions of **9** with benzoyl chloride or piperonyloxy chloride in the presence of $MgBr_2{\cdot}OEt_2$ (2.0 equiv.) and *N*,*N*-diisopropylethylamine (3.0 equiv) in methylene chloride at room temperature for 1 h afforded purpurenone (**1**) and its derivative **2** in 75 and 87% yield, respectively. Similarly, treatment of **10** with benzoyl chloride or piperonyloxy chloride at room temperature for 1 h afforded praecansone B (**3**) and pongapinone A (**4**) in 79 and 90% yield, respectively. The spectral data of synthetic materials **1-4** were in agreement with those of the natural products reported in the literature.[3,5,7,8]

In conclusion, concise total syntheses of naturally occurring β-hydroxypyranochalcones, purpurenone (**1**), its derivative **2**, praecansone B (**3**), and pongapinone A (**4**) were carried out starting from 2,4-dihydroxyacetophenone (**6**) or 6-methoxy-2,4-dihydroxyacetophenone through benzopyran formation reactions followed by *O*-methylations and subsequent coupling reactions.

Experimental

$MgBr_2{\cdot}OEt_2$-promoted coupling reactions were conducted in an atmosphere. Other reactions were carried out in a nitrogen atmosphere. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed



Scheme 4

using silica gel 9385 (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model DPX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent. IR spectra were recorded on a Varian FTS-4000 FTIR spectrophotometer.

1-(5-Hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (7). $Ca(OH)_2$ (0.74 g, 10.0 mmol) was added to a solution of 2,4-dihydroxyacetophenone (1.52 g, 10.0 mmol) and 3-methyl-2-butenal (1.0 g, 12.0 mmol) in methanol (15 mL). The suspension was stirred at refluxing condition for 12 h. The reaction mixture was evaporated under reduced pressure. 1 N HCl (5 mL) and water (30 mL) were added, and the mixture was extracted with ethyl acetate (30 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (20:1) gave product **7** (1.53 g, 70%) as a yellow solid: mp 101-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.96 (1H, s), 7.49 (1H, d, *J* = 8.7 Hz), 6.69 (1H, d, *J* = 10.0 Hz), 6.31 (1H, d, *J* = 8.7 Hz), 5.57 (1H, d, *J* = 10.0 Hz), 2.52 (3H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 160.1, 132.0, 128.6, 116.2, 114.2, 109.6, 108.7, 78.1, 28.7, 26.6; IR (KBr) 3464, 2974, 2929, 1636, 1615, 1483, 1425, 1368, 1329, 1273, 1210, 1163, 1114, 1070, 892, 830, 807, 727 cm^{-1}.

1-(5-Hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (8). $Ca(OH)_2$ (0.74 g, 10.0 mmol) was added to a solution of 2,4-dihydroxy-6-methoxyacetotophenone (1.82 g, 10.0 mmol) and 3-methyl-2-butenal (1.0 g, 12.0 mmol) in methanol (15 mL). The suspension was stirred at refluxing condition for 18 h. The reaction mixture was evaporated under reduced pressure. 1 N HCl (5 mL) and water (30 mL) were added, and the mixture was extracted with ethyl acetate (30 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (20:1) gave product **8** (2.23 g, 90%) as a yellow solid: mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.01 (1H, s), 6.62 (1H, d, *J* = 10.0 Hz), 5.85 (1H, s), 5.38 (1H, d, *J* = 10.0 Hz), 3.81 (3H, s), 2.56 (3H, s), 1.46 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 162.8, 161.7, 160.0, 125.2, 115.9, 105.5, 102.5, 90.5, 78.0, 55.4, 32.9, 28.2; IR (KBr) 3464, 2924, 2855, 1620, 1464, 1362, 1269, 1206, 1159, 1125, 891, 831, 731 cm^{-1}.

1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (9). To a solution of **7** (1.30 g, 6.0 mmol) and K_2CO_3 (2.07 g, 15.0 mmol) in acetone (30 mL) was added methyl iodide (1.02 g, 7.2 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. 1 N HCl (5 mL) and water (30 mL) were added, and the mixture was extracted with ethyl acetate (30 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate (20:1) to give **9** (1.32 g, 95%) as a solid: mp 102-103°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 8.7 Hz), 6.57 (2H, m), 5.65 (1H, d, *J* = 10.0 Hz), 3.77 (3H, s), 2.57 (3H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 158.2, 157.1, 131.3, 130.7, 125.2, 116.8, 115.0, 112.9, 77.1, 63.3, 30.4, 28.2; IR (KBr) 3469, 2973, 1663, 1589, 1567, 1457, 1271, 1214, 1110, 1066, 989, 832, 742 cm^{-1}.

1-(5,7-Dimethoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (10). To a solution of **8** (2.10 g, 8.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) in acetone (30 mL) was added methyl iodide (1.36 g, 9.6 mmol). The reaction mixture was refluxing for 12 h. The solvent was evaporated under reduced pressure. 1 N HCl (5 mL) and water (30 mL) were added, and the mixture was extracted with ethyl acetate (30 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate (10:1) to give **10** (2.0 g, 95%) as a solid: mp 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (1H, d, *J* = 10.0 Hz), 6.17 (1H, s), 5.50 (1H, d, *J* = 10.0 Hz), 3.75 (3H, s), 3.73 (3H, s), 2.46 (3H, s), 1.40 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 157.6, 155.9, 154.2, 131.3, 118.3, 116.4, 108.0, 96.1, 76.8, 63.6, 55.8, 32.5, 27.8; IR (KBr) 2975, 1697, 1608, 1570, 1467, 1364, 1200, 1115, 1104, 937, 839, 746 cm^{-1}.

Purpurenone (1). $MgBr_2{\cdot}OEt_2$ (517 mg, 2.0 mmol) was added to a stirred solution of **9** (232 mg, 1.0 mmol) and benzoyl chloride (211 mg, 1.5 mmol) in CH_2Cl_2 (5 mL), followed by the addition of DIPEA (324 mg, 2.5 mmol). Stirring was continued for 30 min and then EtOAc (2.5 mL) and 1 N HCl (4 mL) were added. Stirring was continued for further 20 min and water (30 mL) was added. The mixture was extracted with EtOAc (20 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate (20:1) to give **1** (252 mg, 75 %) as a solid: mp 52-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.19 (1H, s), 7.97-7.94 (2H, m), 7.73 (1H, d, *J* = 8.7 Hz), 7.52-7.43 (3H, m), 7.16 (1H, s), 6.67 (1H, d, *J* = 8.4 Hz), 6.65 (1H, d, *J* = 10.0 Hz), 5.68 (1H, d, *J* = 10.0 Hz), 3.79 (3H, s), 1.45 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 184.4, 157.6, 156.1, 135.6, 132.1, 130.7, 128.6, 127.0, 121.7, 116.4, 115.1, 113.0, 96.6, 76.9, 62.6, 28.1; IR (KBr) 3489, 2970, 2930, 1588, 1459, 1368, 1276, 1219, 1110, 1075, 887, 808, 776 cm^{-1}.

(*Z*)-3-Hydroxy-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-phenylprop-2-en-1-one (2). $MgBr_2{\cdot}OEt_2$ (517 mg, 2.0 mmol) was added to a stirred solution of **9** (232 mg, 1.0 mmol) and piperonyloyl chloride (277 mg, 1.5 mmol) in CH_2Cl_2 (5 mL), followed by the addition of DIPEA (324 mg, 2.5 mmol). Stirring was continued for further 20 min and water (30 mL) was added. The mixture was extracted with EtOAc (20 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel *n*-hexane/ethyl acetate (15:1) to give **2** (331 mg, 87%) as a solid: mp 89-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 8.7 Hz), 7.55 (1H, dd, *J* = 8.1, 1.8 Hz), 7.42 (1H, d, *J* = 1.8 Hz), 7.03 (1H, s), 6.85 (1H, d, *J* = 8.1 Hz), 6.65 (1H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* =

10.0 Hz), 6.03 (2H, s), 5.68 (1H, d, J = 10.0 Hz), 3.77 (3H, s), 1.44 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 183.0, 157.4, 156.0, 151.1, 148.1, 130.7, 130.5, 130.3, 122.7, 121.4, 116.4, 115.1, 113.0, 108.2, 107.2, 101.8, 96.0, 76.9, 62.5, 28.1; IR (KBr) 3450, 2968, 2894, 1587, 1454, 1249, 1215, 1111, 1066, 1033, 982, 789 cm^{-1}.

Praecansone B (3). $MgBr_2$·OEt_2 (517 mg, 2.0 mmol) was added to a stirred solution of **10** (262 mg, 1.0 mmol) and benzoyl chloride (211 mg, 1.5 mmol) in CH_2Cl_2 (5 mL), followed by the addition of DIPEA (324 mg, 2.5 mmol). Stirring was continued for further 20 min and water (30 mL) was added. The mixture was extracted with EtOAc (20 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate (15:1) to give **3** (265 mg, 79%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.31 (1H, s), 7.91-7.89 (2H, m), 7.49-7.41 (3H, m), 6.50 (1H, d, J = 10.0 Hz), 6.48 (1H, s), 6.23 (1H, s), 5.52 (1H, d, J = 10.0 Hz), 3.77 (3H, s), 3.76 (3H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 182.0, 158.3, 156.4, 155.1, 135.0, 132.1, 128.5, 127.7, 127.0, 116.5, 114.2, 108.0, 100.5, 96.1, 76.9, 63.1, 60.0, 27.9; IR (neat) 3513, 2971, 1602, 1469, 1368, 1294, 1200, 1141, 1108, 1008, 943, 696 cm^{-1}.

Pongapinone A (4). $MgBr_2$·OEt_2 (517 mg, 2.0 mmol) was added to a stirred solution of **10** (262 mg, 1.0 mmol) and piperonyloyl chloride (277 mg, 1.5 mmol) in CH_2Cl_2 (5 mL), followed by the addition of DIPEA (324 mg, 2.5 mmol). Stirring was continued for further 20 min and water (30 mL) was added. The mixture was extracted with EtOAc (20 mL × 3) and washed with water (30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate (15:1) to give **4** (369 mg, 90%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.40 (1H, s), 7.50 (1H, m), 7.38 (1H, d, J = 1.8 Hz), 6.83 (1H, d, J = 8.4 Hz), 6.50 (1H, d, J = 10.0 Hz), 6.35 (1H, s), 6.22 (1H, s), 6.02 (2H, s), 5.52 (1H, d, J = 10.0 Hz), 3.77 (3H, s), 3.76 (3H, s), 1.41 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 183.0, 158.3, 156.2, 155.1, 151.1, 148.0, 129.6, 127.8, 127.7, 122.8, 116.5, 113.8, 108.1, 107.1, 101.8, 99.8, 96.0, 76.9, 63.1, 56.0, 27.9; IR (neat) 3452, 2971, 1601, 1469, 1358, 1252, 1110, 1036, 931, 812, 739 cm^{-1}.

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