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An Efficient and Rapid Synthetic Route to Biologically Interesting Pyranochalcone Natural Products

Yong Rok Lee*, Xue Wang and Likai Xia

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea

* Author to whom correspondence should be addressed; Tel: +82-53-8102529; Fax: +82-53-8104631; E-mail: yrlee@yu.ac.kr

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Abstract: An efficient and concise total synthesis of naturally occurring pyranochalcones was achieved from readily available 2,4-dihydroxyacetophenone and 2,4-dihydroxy-6-methoxyacetophenone. The key steps in the synthetic strategy were ethylenediamine diacetate-catalyzed benzopyran formation and aldol reactions.

Keywords: Ethylenediamine diacetate, Pyranyl ring formation, Pyranochalcone natural products, Aldol reaction

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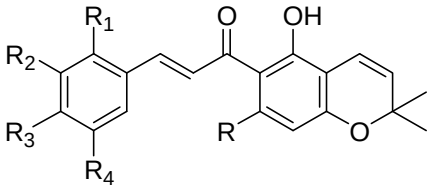
Introduction

Pyranochalcones are an abundant subclass of the flavonoids and are widely distributed in nature [1]. They were primarily isolated from *Lonchocarpus utilus* or *subglaucescens* and *Pongamia glabra* [2]. Members of the pyranochalcones have been associated with a wide variety of biological activities such as antimutagenic, antimicrobial, anti-ulcer and antitumor activities and some plants are used in in China and Europe as traditional medicines [3]. This wide range of biological properties has stimulated interest in the synthesis of naturally occurring pyranochalcones (Figure 1). Among these, compound **1** was recently isolated from *Artocarpus communis* which is known as an edible fruit in the Pacific islands [4]. Some of the molecules isolated from this plant have shown antinephritus activity [5] and as 5-lipoxygenase inhibitors [6]. Pyranochalcone **1** has also been shown to possess potent inhibitory activity on nitric oxide production in RAW 264.7 mouse macrophage cells [4]. Glabrachromene II (**2**) and glabrachalcone (**3**) were both isolated from *Pongamia glabra* [7] and *Millettia pachycarpa* [8].

Pongachalcone I (**4**) was isolated from *Tephrosia deflexa,* and it has been shown to have antibacterial activity [9]. Interestingly, the structure of obovatachalcone isolated from *Tephrosia tunicate* was consistent with that of pongachalcone I [10]. Glaychalcones A (**5**) and B (**6**) were isolated from *Glycosmis citrifolia*, which is used in folk medicine for the treatment of skin itch, scarbies, and ulcers [11]. Although several synthetic approaches to pyranochalcones have been developed [12], there are only a few synthetic routes to grabrachalcone (**4**), pongachalcone I (**5**) and glychalcone A (**6**) [13]. However, these synthetic approaches have been limited due to their many reaction steps, harsh reaction conditions and low yields due to side reactions [13]. In particular, no synthetic approaches to natural products **1**-**2** and **6** have been reported.

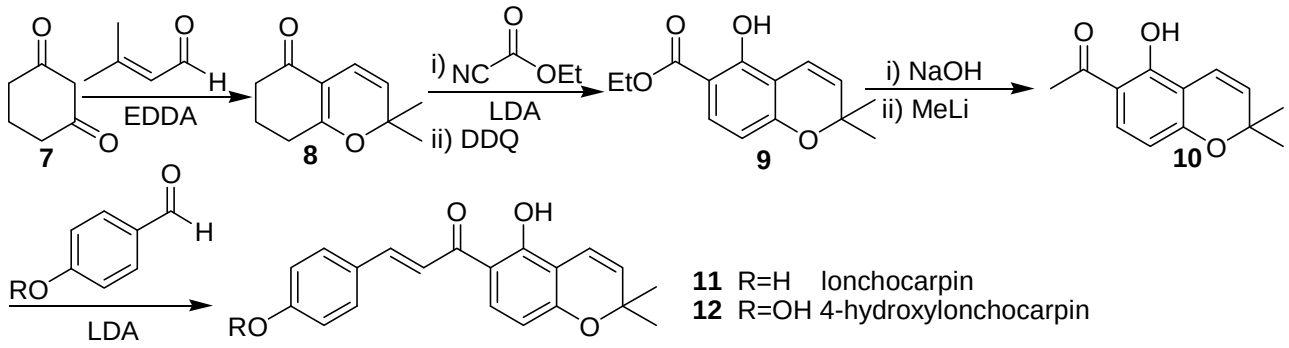
Figure 1.



1 R=R_2=R_4=H, R_1=R_3=OH
2 R=R_1=R_4=H, R_2=R_3=OCH_2CH_2O Glabrachromene II
3 R=R_2=H, R_1= R_3=R_4=OCH_3, Glabrachalcone
4 R=OCH_3, R_1=R_2=R_3=R_4=H Pongachalcone I = Obovatachalcone
5 R=OCH_3, R_1=R_2=R_4=H, R_3=OCH_3 Glychalcone A
6 R=OCH_3, R_1=R_4=H, R_3=R_4=OCH_3 Glychalcone B

We have reported convergent synthetic routes to naturally occurring pyranochalcones, lonchocarpin (**11**) and 4-hydroxylonchocarpin (**12**) via a key intermediate **10**, as shown in Scheme 1 [14]. Although the overall yield from **7** to benzopyran **10** is satisfactory (5-steps, 45%), more simple and more concise synthetic routes are still needed. Accordingly, there has been considerable research on improved synthetic approaches of pyranochalcone derivatives.

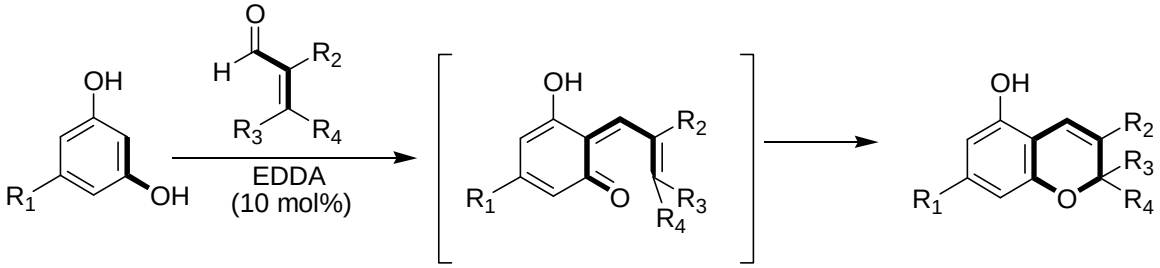
Scheme 1.



Recently, we developed an efficient and simple methodology for preparing benzopyrans by ethylenediamine diacetate-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes [15]. These reactions involve a formal [3+3]-cycloaddition via a 6π-electrocyclization (Scheme 2). To develop an efficient and rapid synthetic routes to biologically interesting pyranochalcone natural products as

shown in Figure 1, we investigated the ethylenediamine diacetate-catalyzed reactions of 2,4-dihydroxy-acetophenone and 2,4-dihydroxy-6-methoxyacetopheneone with 3-methyl-2-butenal to give benzo-pyrans as a one-pot procedure. By using synthesized bezopyrans as a key intermediate, we report herein total synthesis of pyranochalcone natural products **1**-**6**.

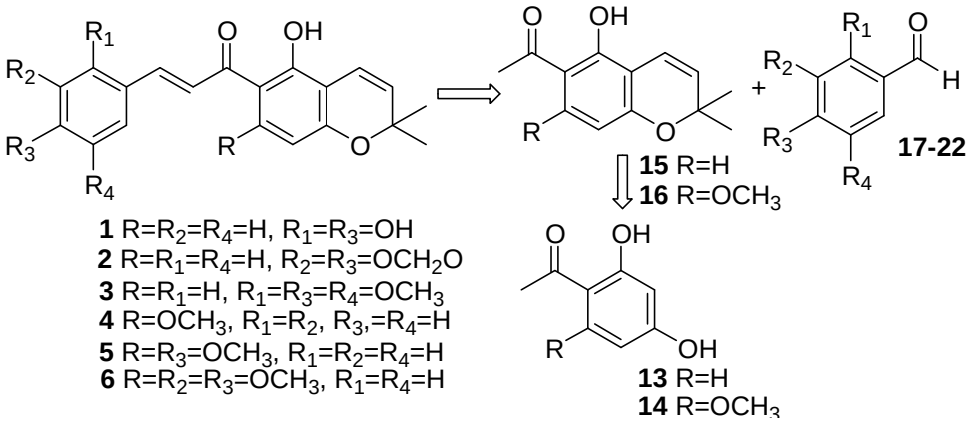
Scheme 2.



Results and Discussion

The retrosynthetic strategy for the synthesis of pyranochalcone natural products **1**-**6** is shown in Scheme 3. Natural products **1**-**6** could be prepared from base-catalyzed aldol reactions of benzopyrans **15** and **16** with the corresponding benzaldehydes **17**-**22.** The crucial intermediates **15** and **16** could be generated from the readily available materials **13** and **14** using ethylenediamine diacetate-catalyzed benzopyran formation reactions.

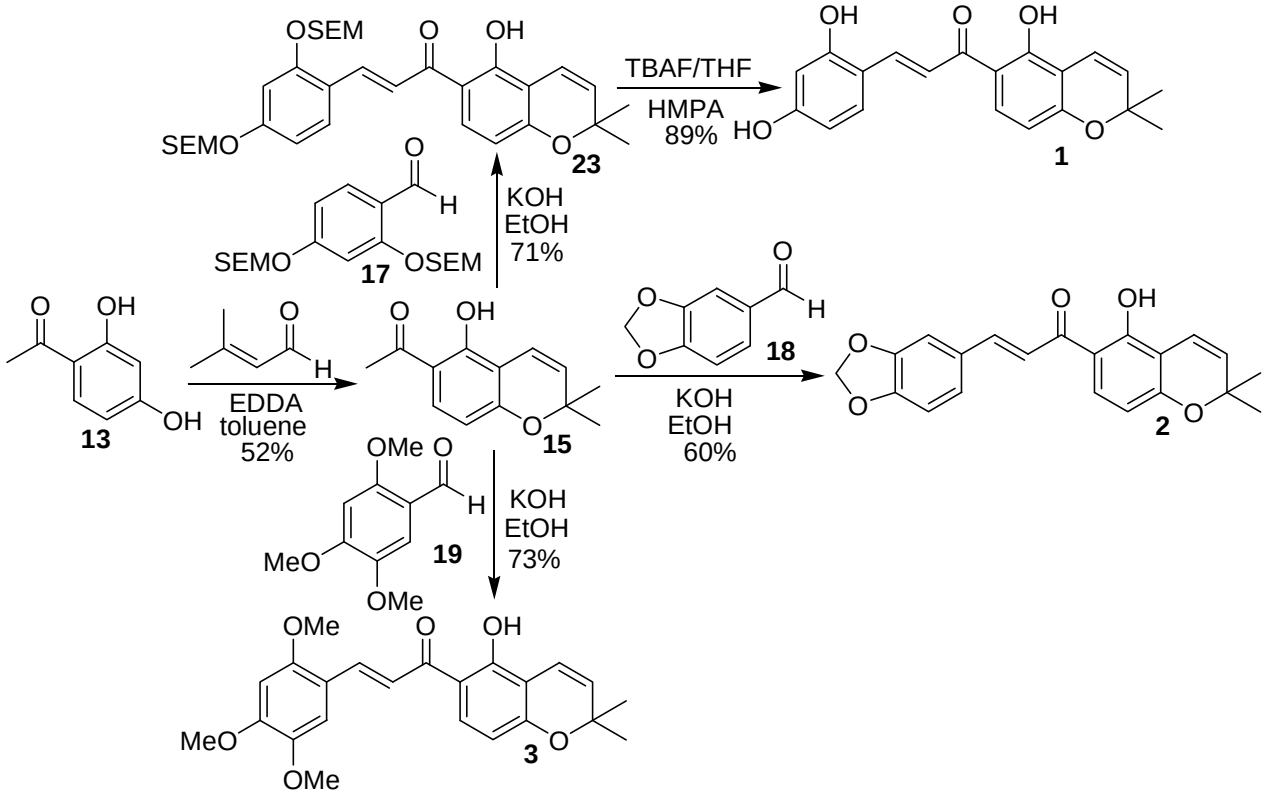
Scheme 3. Retrosynthetic analysis of pyranochalcone natural products **1**-**6**.



The benzopyran **15** was first prepared starting from 2,4-dihydroxyacetophenone (**13**) as shown in Scheme 4. A reaction of **13** with 3-methyl-2-butenal in the presence of 10 mol % of ethylenediamine diacetate in refluxing toluene for 12 h gave desmethyl isoencecalin (**15**) in 52% yield, which was isolated from *Blepharispermum subseeile* [16]. It has also shown to have strong antifungal, antibacterial, and anti-implantation activities [17]. To complete the synthesis of natural products, aldol reactions were next tried. Attempts to condense compound **15** to 2,4-dihydroxybezaldehyde using KOH in ethanol were unsuccessful. After examining many procedures, a reaction of compound **15** with protected benzopyran **17** using KOH in ethanol at room temperature for 48 h provided compound **23** in 71% yield, which was deprotected with TBAF/HMPA in refluxing THF for 5 h to give

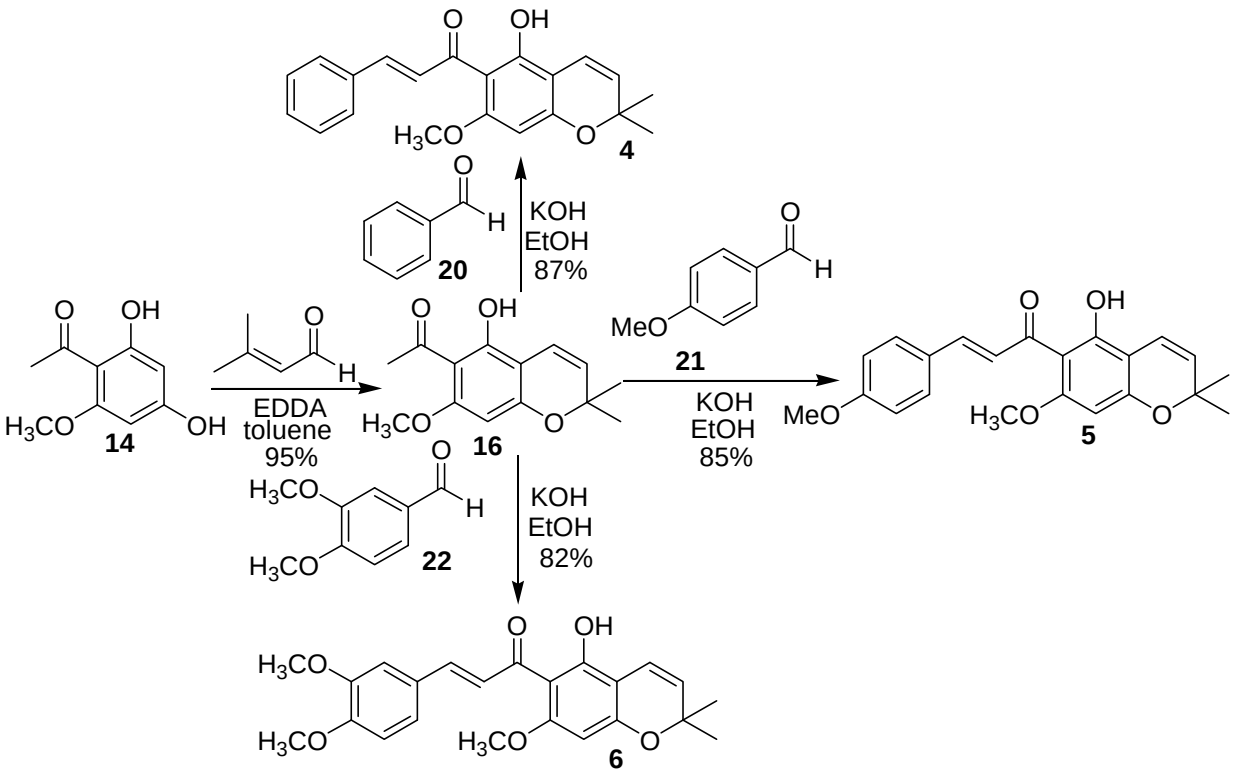
compound **1** (89%). The spectral data of compound **1** was in good agreement with that of the natural product reported in the literature [4]. Reaction of **15** with piperonal **18** using KOH in ethanol at room temperature for 48 h gave glabrachromene II (**2)** in 60% yield, whereas treatment with 2,4,5-trimethoxybenzaldehyde **19** gave glabrachalcone (**3**) in 73% yield. The spectral data of compounds **2** and **3** was in agreement with that of the natural products reported in the literature [7, 8a].

Scheme 4.



The total synthesis of pongachalcone I (**4**), and glychalcones A (**5**) and B (**6**) was investigated starting from 2,4-dihydroxy-6-methoxyacetopheneone (**14**) as shown in Scheme 5. Treatment of **14** with 3-methyl-2-butenal in the presence of 10 mol % of ethylenediamine diacetate in refluxing toluene for 12 h gave isoevodionol **16** in a yield of 95%, which was isolated from *Mariscus pedunculatus* and *Evodia lepta* [18]. Reaction of compound **16** with benzaldehyde **20** using KOH in ethanol at room temperature for 48 h afforded pongachalcone I (**4**) in yield of 87%. The spectral data of our synthetic material **4** is the same as values reported in the literature [12a]. Treatment of **16** with 4-methoxy-benzaldehyde **21** using KOH in ethanol gave glychalcone A (**5**) in 85% yield, whereas reaction with 3,4-dimethoxybenzaldehyde **22** afforded glychalcone B (**6**) in 82% yield. The spectral data of compounds **5** and **6** was in good agreement with that of the natural products reported in the literature [11]. Interestingly, in the ^{1}H-NMR spectrum of compound **5**, no doublets were observed for the H-α and H-β protons of chalcone moiety. These protons gave rise to a singlet at δ 7.76, integrating for 2 protons due to the same chemical shifts of H-α and H-β [19].

Scheme 5.



Conclusions

An efficient and concise total synthesis of biologically interesting pyranochalcone natural products **1**-**6** was accomplished from readily available 2,4-dihydroxyacetophenone and 2,4-dihydroxy-6-methoxyacetophenone. The key strategy in the synthetic procedures involves the ethylenediamine diacetate-catalyzed benzopyran formation and the aldol reactions.

Experimental

General

All the experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker Model ARX spectrometer (operating at 300 and 75 MHz, respectively) using δ = 77.0 ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS and MS spectra were carried out at the Korea Basic Science Institute.

Desmethylisoencecalin (**15**) [16]

To a solution of 2,4-dihydroxyacetophenone (**13**) (456 mg, 3.0 mmol) and 3-methyl-2-butenal (378 mg g, 4.5 mmol) in toluene (20 mL) was added ethylenediamine diacetate (54 mg, 0.3 mmol) at room

temperature. The reaction mixture was refluxed for 12 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **15** (340 mg, 52%) as a solid: mp 101-103 ^{o}C; ^{1}H-NMR δ 12.95 (1H. s), 7.49 (1H, d, J= 8.8 Hz), 6.69 (1H, d, J= 10.0 Hz), 6.31 (1H, d, J= 8.8 Hz), 5.56 (1H, d, J= 10.0 Hz), 2.51 (3H, S), 1.43 (6H, s); ^{13}C-NMR δ 203.1, 160.1, 160.0, 132.0, 128.6, 116.2, 114.2, 109.6, 108.7, 78.1, 28.7, 26.6; IR (neat) 2976, 2930, 1630, 1618, 1487, 1426, 1366, 1329, 1273, 1211, 1165, 1125, 1071, 896 cm^{-1}.

3-[2,4-Bis-(2-trimethylsilanylethoxy)phenyl]-1-(5-hydroxy-2,2,dimethyl-2H-chromen-6-yl)propenone (**23**)

To a solution of **15** (109 mg, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and aldehyde **17** (299 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **23** (213 mg, 71%) as an oil: ^{1}H-NMR δ 13.8 (1H, s), 8.15 (1H, d, J= 15.5 Hz), 7.69 (1H, d, J= 8.9 Hz), 7.57 (1H, d, J= 8.7 Hz), 7.77 (1H, d, J= 15.5 Hz), 6.87 (1H, d, J= 2.3 Hz), 6.74 (1H, d, J= 10.0 Hz), 6.71 (1H, dd, J= 8.7, 2.2 Hz), 6.34 (1H, d, J= 8.9 Hz), 5.57 (1H, d, J= 10.0 Hz), 5.30 (2H, s), 5.24 (2H, s), 3.80-3.69 (4H, m), 1.44 (6H, s), 0.98-0.90 (4H, m), -0.02 (18H, s); ^{13}C-NMR δ 192.9, 161.3, 161.2, 158.6, 140.1, 131.0, 130.3, 128.5, 118.9, 118.7, 116.4, 114.6, 109.7, 108.5, 103.8, 93.6, 93.1, 78.1, 77.9, 77.8, 77.6, 67.0, 28.7, 18.5, -0.9; IR (neat) 2955, 1634, 1605, 1485, 1294, 1252, 1117, 1005, 937, 837 cm^{-1}; HRMS *m/z* (M^{+}) calcd for $C_{32}H_{46}O_7Si_2$: 598.2782. Found: 598.2784.

3",3"-Dimethylpyrano[3',4']-2,4,2'-trihydroxychalcone (**1**) [4]

To a solution of **23** (120 mg, 0.2 mmol) in THF (10 mL) and HMPA (1 mL) was added TBAF (0.3 mL of 1.0 M in THF, 0.3 mmol) and the mixture was refluxed for 5 h. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **1** (68 mg, 89%) as a solid: : mp 145-146 ^{o}C; ^{1}H-NMR δ 8.05 (1H, d, J= 15.5 Hz), 7.69 (1H, d, J= 8.9 Hz), 7.60 (1H, d, J= 15.5 Hz), 7.45 (1H, d, J= 8.5 Hz), 6.73 (1H, d, J= 10.0 Hz), 6.44 (1H, dd, J= 8.5, 2.2 Hz), 6.36 (1H, d, J= 2.2 Hz), 6.33 (1H, d, J= 8.9 Hz), 5.57 (1H, d, J= 10.0 Hz), 1.44 (6H, s); IR (KBr) 3441, 2965, 1632, 1614, 1571, 1454, 1376, 1261, 1116, 803, 763 cm^{-1}; HRMS *m/z* (M^{+}) calcd for $C_{20}H_{18}O_5$: 338.1154. Found: 338.1153.

Glabrachromene II (**2**) [7]

To a solution of **15** (109 mg, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and aldehyde **18** (113 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **2** (105 mg, 60%) as a solid:

mp 119-120 ^{o}C;^{1}H-NMR δ 7.72 (1H, d, J= 15.6 Hz), 7.68 (1H, d, J= 9.0 Hz), 7.37 (1H, d, J= 15.6 Hz), 7.14 (1H, s), 7.11 (1H, d, J= 7.9 Hz), 6.82 (1H, d, J= 7.8 Hz), 6.74 (1H, d, J= 10.0 Hz), 6.35 (1H, d, J= 9.0 Hz), 6.01 (2H, s), 5.57 (1H, d, J= 10.0 Hz), 1.45 (6H, s); ^{13}C-NMR δ 191.8, 160.9, 159.7, 150.0, 148.4, 144.1, 130.5, 129.2, 128.1, 125.4, 118.2, 115.9, 114.0, 109.4, 108.7, 108.2, 106.6, 101.7, 77.8, 28.3; IR (KBr)2978, 1634, 1582, 1487, 1449, 1379, 1211, 1113, 1042, 976, 930, 843, 789, 735, 720 cm^{-1}.

Glabrachalcone (**3**) [8]

To a solution of **15** (109 mg, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and aldehyde **19** (147 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **3** (145 mg, 73%) as a solid: mp 130-131 ^{o}C; ^{1}H-NMR δ 8.14 (1H, d, J= 15.5 Hz), 7.70 (1H, d, J= 8.9 Hz), 7.49 (1H, d, J= 15.5 Hz), 7.08 (1H, s), 6.73 (1H, d, J= 10.0 Hz), 6.49 (1H, s), 6.34 (1H, d, J= 8.9 Hz), 5.56 (1H, d, J= 10.0 Hz), 3.92 (3H, s), 3.89 (6H, s), 1.43 (6H, s); ^{13}C-NMR δ 192.4, 160.9, 159.4, 154.8, 152.6, 143.2, 139.7, 130.5, 128.0, 118.0, 116.0, 115.3, 114.2, 111.5, 109.4, 108.0, 96.6, 77.7, 56.5, 56.3, 56.1, 28.3; IR (KBr) 2977, 1611, 1505, 1468, 1433, 1339, 1279, 1206, 1107, 1026, 923, 847, 805, 728 cm^{-1}.

Isoevodionol (**16**) [18]

To a solution of 2,4-dihydroxy-6-methoxyacetophenone (**14**) (364 mg, 2.0 mmol) and 3-methyl-2-butenal (252 mg g, 3.0 mmol) in toluene (20 mL) was added ethylenediamine diacetate (36 mg, 0.2 mmol) at room temperature. The reaction mixture was refluxed for 12 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **16** (472 mg, 95%) as a solid: mp 128-129 ^{o}C; ^{1}H-NMR 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 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) 2924, 2855, 1620, 1464, 1362, 1269, 1206, 1159, 1125, 891, 831, 731cm^{-1}.

Pongachalcone I (**4**) [9]

To a solution of **16** (124 mg, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and benzaldehyde **20** (80 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **4** (146 mg, 87%) as a solid: mp 105-106 ^{o}C;^{1}H-NMR δ 14.70 (1H, s), 7.87 (1H, d, J= 15.6 Hz), 7.76 (1H, d, J= 15.6 Hz), 7.60-7.57 (2H, m), 7.42-7.34 (4H, m), 6.68 (1H, d, J= 10.0 Hz), 5.91 (1H, s), 5.45 (1H, d, J= 10.0 Hz), 3.89 (3H, s), 1.45 (6H, s); ^{13}C-NMR δ 192.5, 162.5, 162.4, 160.3, 142.0, 135.5, 129.9, 128.8, 127.5, 125.2, 122.2, 115.9,

105.9, 102.8, 91.4, 78.2, 55.7, 28.3; IR (KBr) 2926, 2855, 1618, 1580, 1451, 1424, 1339, 1287, 1235, 1200, 1148, 1125, 978, 872, 810, 766, 727, 700 cm^{-1}.

Glychalcone A (**5**) [11]

To a solution of **16** (124 mg, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and benzaldehyde **21** (102 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **5** (156 mg, 85%) as a solid: mp 90-91 ^oC; ^1H-NMR δ 14.71 (1H, s), 7.76 (2H, s), 7.55 (2H, d, J= 8.9 Hz), 6.91 (2H, d, J= 8.9 Hz), 6.67 (1H, d, J= 10.0 Hz), 5.91 (1H, s), 5.44 (1H, d, J= 10.0 Hz), 3.89 (3H, s), 3.83 (3H, s), 1.43 (6H, s); ^{13}C-NMR δ 193.0, 167.7, 161.6, 161.3, 155.9, 142.6, 130.2, 128.7, 125.4, 124.8, 117.0, 114.7, 106.6, 103.3, 92.9, 78.0, 55.9, 28.2; IR (KBr) 2975, 1621, 1576, 1512, 1451, 1424, 1260, 1235, 1198, 1173, 1148, 1123, 1063, 1026, 829, 710 cm^{-1}; EIMS m/z 366 (M^+, 45), 351 (33), 232 (10), 218 (12), 217 (100).

Glychalcone B (**6**) [11]

To a solution of **16** (124 mg, 0.5 mmol) in ethanol (10 mL) and water (2 mL) was added potassim hydroxide (140 mg, 2.5 mmol) and benzaldehyde **22** (125 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 x 50 mL), washing with 2N-HCl solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **5** (163 mg, 82%) as a solid: mp 126-127 ^oC;^1H-NMR δ 14.78 (1H, s), 7.72 (1H, d, J= 15.6 Hz), 7.66 (1H, d, J= 15.6 Hz), 7.14 (1H, dd, J= 8.4, 2.2 Hz), 7.05 (1H, d, J= 2.2 Hz), 6.82 (1H, d, J= 8.4 Hz), 6.61 (1H, d, J= 10.0 Hz), 5.85 (1H, s), 5.40 (1H, d, J= 10.0 Hz), 3.89 (3H, s), 3.86 (3H, s), 3.84 (3H, s), 1.39 (6H, s); ^{13}C-NMR δ 192.5, 162.5, 160.2, 148.3, 142.3, 130.0, 125.6, 125.3, 125.0, 121.0, 116.1, 109.1, 108.6, 106.7, 101.5, 100.7, 91.5, 79.2, 64.3, 55.9, 28.3; IR (KBr) 2975, 1621, 1576, 1512, 1451, 1424, 1260, 1235, 1198, 1173, 1148, 1123, 1063, 1026, 829, 710 cm^{-1}.

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