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First total synthesis of Three Anti-tyrosinase Activity Prenylated Flavanones from *Dalea boliviana*

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ABSTRACT

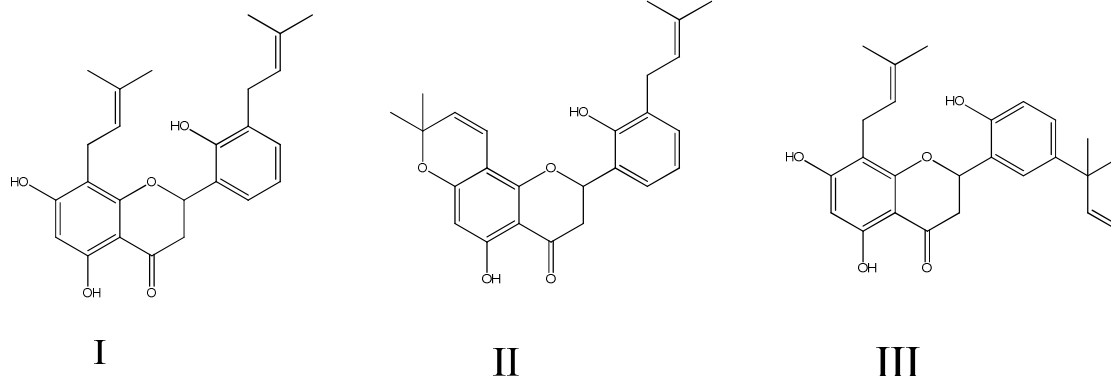
The total synthesis of three new prenylated flavanones, (2*S*)-5,7,2'-trihydroxy-8,3'-diprenylflavanone (**I**), (2*S*)-5,2'-dihydroxy-6'',6''-dimethylchromeno-(7,8:2,3'')-3'-prenylflavanone (**II**) and (2*S*)-5,7,2'-trihydroxy-5'-(1''',1'''-dimethylallyl)-8-prenyl flavanone (**III**) was first achieved through C-prenylation, protection of phenolic hydroxyl group, aldolcondensation, cyclization and deprotection starting from substituted benzaldehyde, 2,4,6-trihydroxy aceto phenenone and *o*-hydroxybenzaldehyde, with total yield of 42%. All structures of new compounds were confirmed by IR, ¹H NMR and LCMS.

Keywords: *Dalea boliviana*: Anti-tyrosinase activity; Flavanone; Isoprenylflavanoids.

Abbreviations: DDQ - 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MOMCl - chloromethyl methyl ether

INTRODUCTION

Natural isophenylflavanoids exist widely in the plant kingdom and exhibit many important biological and pharmacological activities [1-4]. **I**, **II** and **III** (Fig.1), three new prenylated isolated from the n-hexane extract of *Dalea boliviana* roots. [5]. The above-mentioned compounds were evaluated in vitro in relation to their inhibitory effect on the tyrosinase activity. *Dalea boliviana* is an exclusively American genus with more than 250 species distributed in arid regions of the southwestern United States to the central regions of Argentina and Chile. The synthesis of **I**, **II** and **III** has not been reported so far. Here we would like to report the total synthesis of Anti-tyrosinase Activity Prenylated Flavanones i.e. **I**, **II** and **III** for the first time.



EXPERIMENTAL SECTION

Melting points were recorded on a V Scientific melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer BX1 FTIR spectrophotometer, ^1H NMR (400 MHz) & ^{13}C NMR (100 MHz) spectra on a Bruker 400 MHz NMR spectrometer and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on Agilent 1100 Series LC/MS and elemental analysis was carried out on a Vario El Elementar instrument. Column chromatography was carried out using ACME silica gel (100-200 mesh/finer than 200 mesh).

RESULTS AND DISCUSSION

3.1. General Procedure

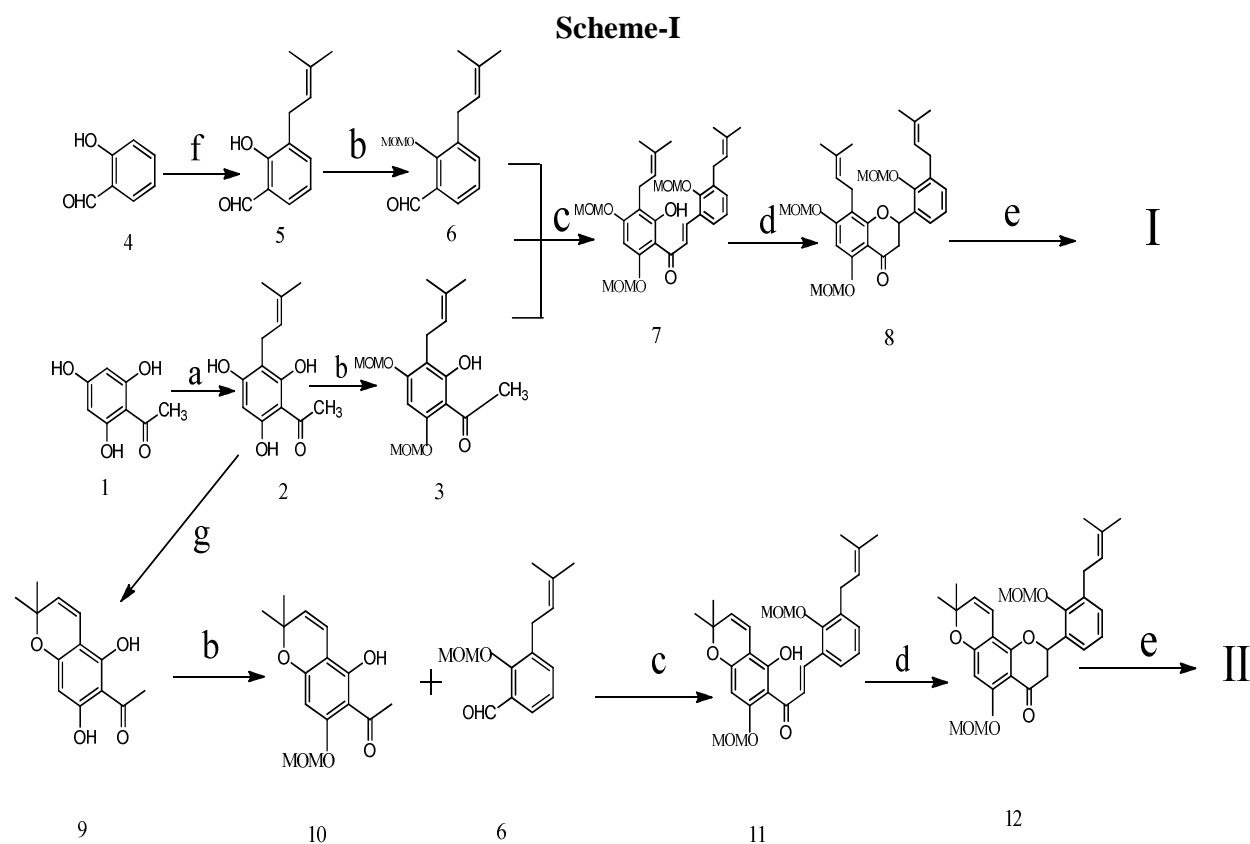
The desired isoprenylated flavanones were synthesized as shown in **Scheme-I** and **Scheme-II** starting from 2,4,6-trihydroxyacetophenone **1**, which was prenylated with isoprenylbromide to furnish (1-(2,4,6-trihydroxy-3-(3-methylbut-2-en-1-yl)phenyl)ethanone) **2**, according to reported method [6]. Selective methoxymethylation of **2** with chloromethyl methyl ether (MOMCl) and anhydrous K_2CO_3 in dry acetone gave compound (1-(2-hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)ethanone) **3** [7]. Treatment of (2-hydroxybenzaldehyde) **4** and isoprenylbromide with KOH in water yielded major product 2-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde **5** [8]. Compound **5** was regioselectively protected with MOMCl to give compound (2-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde) **6** [9].

Compound **3** was condensed with Compound **6** in hydrous ethanolic solution by the action of KOH- H_2O -EtOH under Nitrogen to give compound (E-1-(2-hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-3-(2-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)prop-2-en-1-one) **7** in 56 % yield [10]. Compound **7** was refluxed in solution of NaOAc in ethanol for 24 hours to form (5,7-bis(methoxymethoxy)-2-(2-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-8-(3-methylbut-2-en-1-yl)-chroman-4-one) **8** in 72 % yield, followed by hydrolysis with 3N HCl in MeOH to afford (**I**) in 87% yield (**Scheme-I**).

Compound (1-(5,7-dihydroxy-2,2-dimethyl-2H-chromen-6-yl)ethanone) **9** was obtained from compound **2** by the action of DDQ refluxed in benzene [11]. Compound (1-(5-hydroxy-7-

(methoxymethoxy)-2,2-dimethyl-2*H*-chromen-6-yl)ethanone)**10** prepared from compound **9** by standard methoxy methylation in 85% yielded.

Compound **10** was condensed with compound **6** in hydrous ethanolic solution by the action of KOH-H₂O in EtOH, under Nitrogen to give compound ((*E*)-1-(5-hydroxy-7-(methoxymethoxy)-2,2-dimethyl-2*H*-chromen-6-yl)-3-(2-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)prop-2-en-1-one)**11** in 52 % yielded. Compound **11** refluxed in a solution of NaOAc in EtOH for 24 hours to form compound (5-(methoxy-methoxy)-2-(2-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-8,8-dimethyl-2,3-di-hydropyrano-[2,3-*f*]chromen-4(8*H*)-one) **12** in 73% yielded, followed by hydrolysis with 3*N* HCl in MeOH to afford (**II**) in 78% yielded (**Scheme-I**).

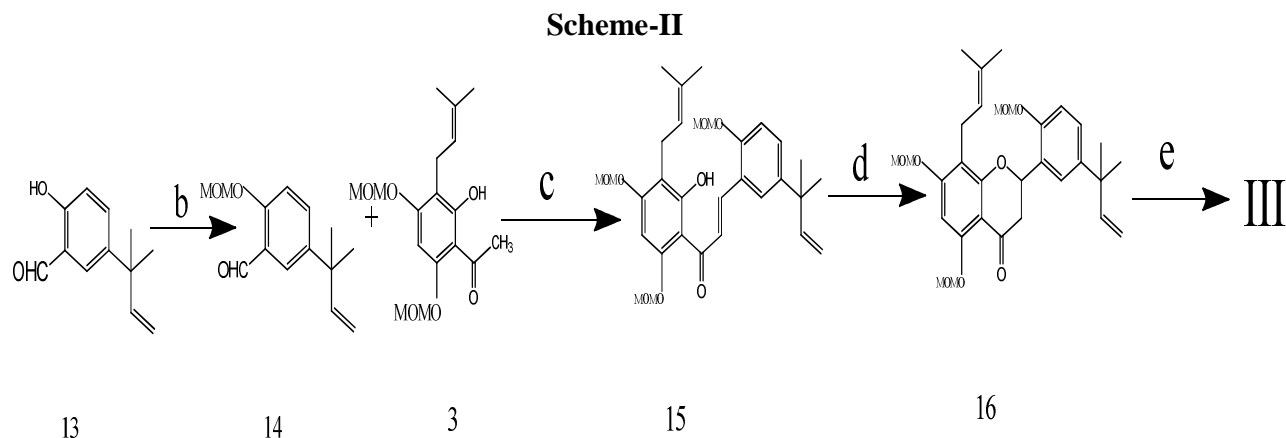


Reagents and conditions:

- (a) Isoprenylbromide, THF, rt, 24h, 55%
- (b) MOMCl, K₂CO₃, Acetone, reflux, 84%,
- (c) KOH-H₂O-EtOH, N₂, 76%
- (d) NaOAc, EtOH-H₂O, reflux, 24h,
- (e) MeOH, HCl, reflux 87%,
- (f) Isoprenylbromide, KOH-H₂O
- (g) DDQ, benzene, reflux 85%.

Compound (2-hydroxy-5-(2-methylbut-3-en-2-yl)benzaldehyde) **13** was regioselectively protected with chloromethyl methyl ether to give compound (2-(methoxymethoxy)-5-(2-methylbut-3-en-2-yl)benzaldehyde) **14** in 86% yielded. Compound **14** was condensed with

compound **3** in hydrous ethanolic solution by the action of KOH–H₂O, EtOH under Nitrogen to give compound (Chalcone)**15** in 52% yielded. Compound **15** was refluxed in a solution of NaOAc in EtOH for 24 hours to form compound **16** in 68 % yielded followed by hydrolysis with 3N HCl in MeOH to afford (**III**). (Scheme-II).



Reagents and conditions:

(b) MOMCl, K₂CO₃, Acetone, reflux, 86%

(c) KOH-H₂O-EtOH, N₂, 52%

(d) NaOAc, EtOH-H₂O, reflux, 24h

(e) MeOH, HCl, reflux 68.%

3.2.1 Synthesis of Chalcones (7):

To a cold solution of the substituted acetophenone **3** (0.3 mmol) and benzaldehyde **6** (0.33 mmol) in EtOH solution of KOH in (2.0g) in H₂O-EtOH (2.0ml) solution was added with stirring. The resulting mixture was stirred under nitrogen at room temperature for 36h. The total reaction mixture was pour into ice cold water acidified with dilute HCl, and extracted with CHCl₃. The combined organic layer was washed with NaHCO₃ and water dried over Na₂SO₄ and concentrated in vaccum. The residue was chromatographed over Silica gel by elution with Hexane-EtOAc (4:1) to give chalcone (Yellow coloured solid) **7**. Yield: 76%, mp: 62-64 °C; IR (CHCl₃) ν_{max} cm⁻¹: 3109, 2989, 1630, 1575, 1160, ¹H NMR δ_{H} (400MHz, CDCl₃): 1.75, 1.80 (3H, s, CH₃), 1.63, 1.74 (3H, s, CH₃), 3.49 (3H, s, OCH₃), 3.52 (6H, s, OCH₃X2), 6.21 (1H, d, J =7Hz), 7.12 (1H, d, J =7Hz), 7.65 (1H, d, J =7Hz), 7.98 (1H, d, J =16Hz), 14.36 (1H, br-s, OH); LCMS (POSITIVE MODE): 540 [M+H]⁺.

3.2.2 Synthesis of Flavanone (8):

A solution of **7** (0.2 mmol) and NaOAc (200mg) in EtOH (4.0mL) with 3 drops of water was refluxed for 24 h. The reaction mixture was diluted with cold water (20 mL) and extracted with CHCl₃. The combined organic layer was washed with NaHCO₃ and water dried over Na₂SO₄ and concentrated in vaccum. The residue was chromatographed over Silica gel by elution with Hexane-EtOAc (4:1) to give Flavanone **8**. (Pale yellow coloured solid)

Yield :72%, mp: 82-84°C ; IR (CHCl₃) ν_{max} cm⁻¹: 2950, 1690, 1610, 1155: ¹H NMR: δ_{H} (400MHz, CDCl₃): 1.69 (6H, br, s), 1.60-1.69 (3H, s, CH₃), 2.94 (2H, d, J=7Hz), 3.32 (2H, d,

J=7Hz), 5.65 (1H, t, J=7Hz), 5.68 (1H, t, J=7Hz), 5.6 (6H, s, OCH₂O), 3.89 (9H, s, OCH₃), 6.05 (1H, s), 6.94 (t, J=7.5Hz), 7.16 (1H, dd, J=7.5Hz), 7.25 (1H, d, J=7.5Hz): LCMS (POSITIVE MODE): 540 [M+H]⁺.

3.2.3 Demethoxymethylation of OH-Protected Flavanones (I, II and III):

To a solution of precursor to flavanone (0.1 mmol) in MeOH was added 10% HCl. The resulting mixture was refluxed, then poured into ice cold water and extracted with CHCl₃. The combined organic layer was washed with water, saturated NaHCO₃ solution and then dried over Na₂SO₄. After removal of solvent the residue was chromatographed over silicagel. Elution with Hexane-EtOAc (4:1) gave the desire molecules.

3.2.4 (2S)-5,7,2'-trihydroxy-8, 3'-diprenylflavanone (I):

Yeild : 87%, mp: 56-58 °C; IR (CHCl₃) ν_{\max} cm⁻¹: 3445, 1634, 1542, 1448; ¹H NMR δ_{H} (400 MHz, CDCl₃): 1.72 (3H, s, H-4''), 1.72 (3H, s, H-5''), 1.76 (3H, s, H-4'''), 1.76 (3H, s, H-5'''), 2.90 (2H, dd, J=3.0 & 17.3 Hz, H-3a), 3.19 (2H, dd, J=3.0 & 17.3 Hz, H-3b), 3.31 (2H, d, J=7.3Hz, H-1'') 3.36 (2H, d, J=7.3Hz, H-1'''), 5.19 (1H, t, J=7.3Hz, H-2''), 5.32 (1H, t, J=7.3Hz, H-2'''), 5.67 (1H, dd, J=3.0 & 13.0Hz, H-2), 5.89 (OH, br, s, OH-2'), 6.03 (1H, s, H-6), 6.91 (1H, t, J=7.5Hz, H-5'), 7.11 (1H, dd, J=1.3 & 7.5Hz, H-4'), 7.23 (1H, dd, J=1.3 & 7.5Hz, H-6'), 12.03 (OH, s, OH-5'); ¹³C NMR (100MHz, CDCl₃): δ 196.7 (C-4), 163.4 (C-5), 162.3 (C-7), 159.5 (C-9), 152.0 (C-2'), 135.4 (C-3'''), 135.0 (C-3''), 130.1 (C-4'), 127.7 (C-3'), 124.9 (C-1'), 124.7 (C-6'), 121.5 (C-2''), 121.4 (C-2'''), 120.6 (C-5'), 106.3 (C-8), 103.2 (C-10), 97.1 (C-6), 76.6 (C-2), 41.9 (C-3a), 29.8 (C-1'''), 25.8 (C-4'''), 25.7 (C-4''), 21.7 (C-1''), 17.8 (C-5''), 17.8 (C-5'''): LCMS (POSITIVE MODE): 409 [M+H]⁺.

3.2.5(2S)-5,2'-dihydroxy-6'',6''-dimethylchromeno-(7,8:2,3')-3'-prenylflavanone(II):

Yeild : 78%, mp: 52-54 °C; IR (CHCl₃) ν_{\max} cm⁻¹: 3445, 1640, 1544, 1437, ; ¹H NMR δ_{H} (400 MHz, CDCl₃): 1.42 (3H, s, H-6''), 1.44 (3H, s, H-6''), 1.78 (3H, s, H-4'''), 1.79 (3H, s, H-5'''), 2.90 (2H, dd, J=3.8 & 17.3Hz, H-3a), 3.05 (2H, dd, J=12.2 & 17.3Hz, H-3b), 3.39 (2H, d, J=7.0Hz, H-1''), 5.32 (1H, m, H-2'''), 5.47 (1H, d, J=10.0 Hz, H-5''), 5.70 (1H, dd, J=3.8 & 12.2 Hz, H-2), 5.92 (OH, br, s, OH-2'), 6.02 (1H, s, H-6), 6.54 (1H, d, J=10.0Hz, H-4''), 6.92 (1H, t, J=7.6Hz, H-5'), 7.14 (1H, dd, J=1.8 & 7.4Hz, H-4'), 12.10 (OH, s, OH-5) ; ¹³C NMR (100MHz, CDCl₃): δ 196.0 (C-4), 163.7 (C-5), 162.0 (C-7), 156.4 (C-9), 150.0 (C-2'), 135.6 (C-3'''), 131.0 (C-4'), 127.4 (C-3'), 126.4 (C-5''), 125.0 (C-1'), 124.7 (C-6'), 120.9 (C-2'''), 120.2 (C-5'), 115.2 (C-4''), 102.7 (C-10), 102.0 (C-8), 97.6 (C-6), 78.0 (C-5''), 76.2 (C-2), 42.0 (C-3a), 29.7 (C-1'''), 28.5 (C-6''), 28.3 (C-6''), 25.5 (C-4'''), 17.7 (C-5'''): LCMS (POSITIVE MODE): 407 [M+H]⁺.

3.2.5 (2S)-5,7,2'-trihydroxy-5'-(1''',1'''-dimethylallyl)-8-prenylflavanone (III):

Yeild : 68%, mp: 49-51 °C; IR(KBr) ν_{\max} cm⁻¹: 3385, 2960, 2918, 1632, 1600, 1504, 1265: ¹H NMR δ_{H} (400 MHz, CD₃COCD₃): 1.63 (3H, s, H-4'), 1.65 (3H, s, H-5''), 1.78 (3H, s, H-4'''), 1.78 (3H, s, H-5'''), 2.90 (2H, dd, J=3.0 & 17.0Hz, H-3a), 3.04 (2H, dd, J=12.5 & 17.0Hz, H-3b), 3.28 (2H, d, J=7.5, H-1'') 5.00 (2H, *trans*, d, J=10.5Hz, H-3'''), 5.03 (2H, *cis*, d, J=17.3Hz, H-3'''), 5.28 (1H, t, J=7.5Hz, H-2''), 5.76 (1H, dd, J=3.2 & 12.5Hz, H-2), 5.91 (OH, br, s, OH-2'), 6.02 (1H, dd, J=10.5 & 17.0Hz, H-2'''), 6.05 (1H, s, H-6), 6.87 (2H, d, J=8.3Hz, H-3'), 7.20 (1H, dd, J=2.5 & 8.2Hz, H-4'), 7.62 (1H, d, J=2.5Hz, H-6'), 12.0 (OH, br, s, OH-5); ¹³C NMR

(100MHz, CD₃COCD₃): 196.8 (C-4), 164.2 (C-5), 162.0 (C-7), 160.2 (C-9), 151.5 (C-2'), 148.2 (C-2''), 139.5 (C-5'), 130.2 (C-3''), 126.6 (C-6'), 125.0(C-1'), 124.0 (C-4'), 122.7 (C-2''), 115.0 (C-3'), 110.0 (C-3'''), 107.5 (C-8), 102.4 (C-10), 95.6 (C-6), 74.8 (C-2), 41.8 (C-3a), 40.2 (C-1'''), 28.0 (C-4'''), 28.0 (C-5'''), 25.0 (C-4'''), 21.6 (C-1''), 17.2 (C-5'') : LCMS (POSITIVE MODE): 409 [M+H]⁺.

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