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First Synthesis of (±)-Monotesone B and New Syntheses of (±)-Lonchocarpol A and (±)-Bavachin

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The first synthesis of (±)-monotesone B and new syntheses of (±)-lonchocarpol A and (±)-bavachin have been achieved starting from the corresponding MOM-protected *C*-prenylated acetophenone derivatives. Their antifungal activity was tested against *Candida albicans*.

Keywords: *C*-prenylated flavanones, monotesone B, lonchocarpol A, bavachin, synthesis, antifungal activity.

In recent years, the synthesis and pharmacology of prenylated flavanones have been intensively investigated due to their wide range of biological activities [1-6]. (±)-Monotesone B (**1a**) and (±)-lonchocarpol A (**1c**) have been isolated from *Monotes engleri* by one of us [7], besides *O*-prenylated flavanones such as (±)-selinone (**1h**) and (-)-*2S*-monotesone A [(-)-**1i**]; their structures were elucidated by online LC/UV/NMR analysis. The laevorotatory enantiomer of **1c** was previously isolated from *Lonchocarpus miniflorus* [8] and prepared by nuclear prenylation of naringenin (**1j→1c**), in rather poor yield (3.6 %) [9]. (-)-Bavachin (**1f**) has been isolated from *Psoralea coryfolia* [10] and its synthesis has been carried out in racemic form by a three-step sequence starting from β-resacetophenone with 0.5 % overall yield [11]. In continuation of our studies on the synthesis of prenylated flavanones with potential antifungal activity [12], herein we report efficient three-step syntheses of (±)-monotesone B (**1a**), (±)-lonchocarpol A (**1c**) and (±)-bavachin (**1f**).

For the synthesis of (±)-monotesone B (**1a**) and (±)-lonchocarpol A (**1c**), 1-[2-hydroxy-4,6-bis(methoxymethoxy)-3,5-bis(3-methyl-but-2- enyl) phenyl]ethanone (**2a**) [3] served as a suitable starting material. Thus its condensation with 3,5-bis(methoxymethoxy)benzaldehyde (**3a**) [13] and 4-(methoxymethoxy)benzaldehyde (**3b**) [2] in the presence of potassium hydroxide in ethanol resulted in the corresponding 2'-hydroxychalcones **4a** and **4b** of *E* geometry in 44 % and 46 % yield, respectively. In the following step of their synthesis, the ring closure of these MOM-protected 2'-hydroxychalcones (**4a**, **b**) took place very smoothly under mild alkaline conditions (NaOAc/ethanol/water/Δ) to result in flavanone derivatives *rac*-**1b** and -**1d** in 79% and 68% yield, respectively. The cleavage of methoxymethyl protecting groups of *rac*-**1d** surprisingly did not result in (±)-lonchocarpol A (**1c**) under mild acidic conditions (10% HCl/MeOH/Δ), but only the methoxymethyl group at C-5 was removed (*rac*-**1d** → *rac*-**1e**). From a previous observation [14], deprotection of *rac*-**1e,** resulting in (±)-lonchocarpol A (**1c**), could be achieved by BF_3•OEt_2 in the presence of a good nucleophile, such as dimethylsulfide in dichloromethane at room temperature. Under the same conditions, the deprotection of *rac*-**1b** and -**1d** could also be performed to give (±)-monotesone B (**1a**) and (±)-lonchocarpol A (**1c**) in moderate yield (21%, 52%), respectively. All physical and spectroscopic data of *rac*-**1a** and -**1c** have been found to be identical with those of the natural products. Starting from 1-[2-hydroxy-4-(methoxymethoxy)-5-(3-methyl-but-2-enyl)phenyl]ethanone (**2b**) [15], the synthesis of (±)-bavachin (**1f**) has now been accomplished in similar manner (**2b** + **3b** → **4c**→ **1g**→ **1f**), resulting

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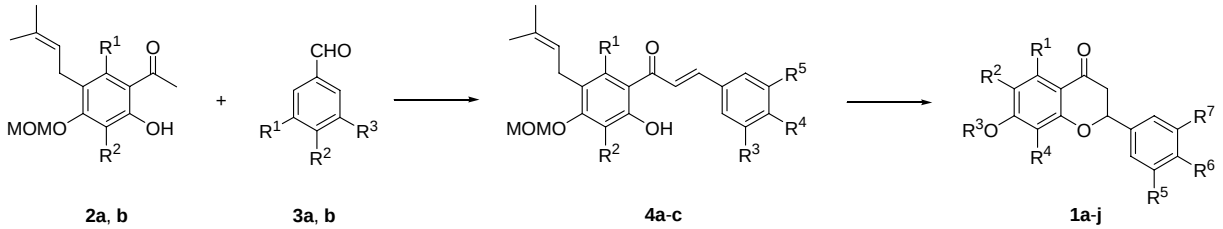

2a, **b** **3a**, **b** **4a-c** **1a-j**

2	R^1	R^2	**3**	R^1	R^2	R^3	**4**	R^1	R^2	R^3	R^4	R^5
a	OMOM	Pr	**a**	OMOM	H	OMOM	**a**	OMOM	Pr	OMOM	H	OMOM
b	H	H	**b**	H	OMOM	H	**b**	OMOM	Pr	H	OMOM	H
							c	H	H	H	OMOM	H

1	R^1	R^2	R^3	R^4	R^5	R^6	R^7
a	OH	Pr	H	Pr	OH	H	OH
b	OMOM	Pr	MOM	Pr	OMOM	H	OMOM
c	OH	Pr	H	Pr	H	OH	H
d	OMOM	Pr	MOM	Pr	H	OMOM	H
e	OH	Pr	MOM	Pr	H	OMOM	H
f	H	Pr	H	H	H	OH	H
g	H	Pr	MOM	H	H	OMOM	H
h	OH	H	H	H	H	OPr	H
i	OH	H	H	H	H	OPr	OH
j	OH	H	H	H	H	OH	H

Pr : 

Scheme 1

in the mp and spectral data being identical to those of the natural product.

The antifungal activity of *rac*-**1a**, **-1c** and **-1f** was examined on *Candida albicans* (ATCC10231) grass poured onto SDA culture medium (3 x 10^{-6} cell/ml) by the agar diffusion method, using nystatin as control and 70% EtOH containing 1.5 % DMSO as solvent. None of the test solutions showed activity at the concentrations used (10, 25, 50, 100 μM). Since (±)-selinone (**1h**) and (-)-*2S*-monotesone A [(-)-**1i**] have been found [7] to be active, with MIC values of 10 μg/ml and 20 μg/ml, respectively, it is presumed that the structural prerequisite of antifungal activity of prenylated flavanones is the presence of an *O*-prenylaryl moiety in the molecule. Further study of structure-activity relationship is in progress.

Experimental

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. For column chromatography, 0.063-0.200 mesh silica gel (Merck) was used. Analytical and preparative TLC was performed on Merck Kieselgel 60 F_{254} pre-coated aluminium and glass plates, respectively. ^{1}H NMR spectra were obtained on Bruker WP-200 and Bruker DRX 500 spectrometers, in $CDCl_3$ with TMS as internal standard; coupling constants are expressed in Hz and chemical shifts are given in ppm. IR spectra were obtained using a Perkin Elmer 16 PC FT-IR instrument. High resolution (R = 15000) MS spectra were obtained in a VG-7035 spectrometer (70 eV, emission current 200 μA, 150 °C, accelerating voltage 4 kV) using perfluorokerosene (PFK) as a reference compound by a peak matching technique. Elemental analyses were obtained using a Carlo Erba 1106 EA instrument. The preparation of the following compounds was described earlier: **2a** [3], **2b** [15], **3a** [13], **3b** [2].

General procedure for preparation of MOM-protected 2'-hydroxychalcone derivatives (**2a-c**)***:*** A cooled aqueous solution of KOH (40 mM dissolved in a mixture of 2.5 mL of water and 2.5 mL of ethanol) was added to the stirred solution of the corresponding MOM-protected acetophenone (**2a**, **b**) (1mM) and benzaldehyde (**3a-c**) (1.5 mM) derivatives in ethanol (5 mL) at 0 °C under Ar atmosphere. After completion of the reaction, the

mixture was diluted with water, acidified with 10% HCl (pH = 2) and then the product was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with water, dried over $MgSO_4$ and evaporated in vacuum to give a red solid residue. Purification by column chromatography (*n*-hexane-ethyl acetate, 6:1) afforded **4a**, **4b** and **4c**, respectively.

3-[3,5-Bis(methoxymethoxy)phenyl]-1-[2-hydroxy-4,6-bis(methoxymethoxy)-3,5-bis(3-methyl-but-2-enyl)phenyl]propenone (**4a**)

Yield (6 h): 44%, Dark yellow oil.
IR (KBr): 3628, 1634, 1594 cm^{-1}.
^1H NMR (500 MHz) δ: 1.71 (6H, s, 2 x CH_3), 1.77 (6H, s, 2 x CH_3), 3.35 (2H, d, *J* = 9.9, CH_2), 3.41 (2H, d, *J* = 10.4, CH_2,), 3.44 (3H, s, OCH_3), 3.49 (6H, s, OCH_3), 3.58 (3H, s, OCH_3), 4.84 (2H, s, OCH_2O), 4.99 (2H, s, OCH_2O), 5.19 (4H, s, 2 x OCH_2O), 5.23 (2H, m, Pr-CH), 6.80 (1H, s, $H_{4'}$), 6.98 (2H, d, *J* = 2.0, Ar-H), 7.71 (1H, d, *J* = 15.7, CH), 7.75 (1H, d, *J* = 15.7, CH), 12.52 (1H, s, 2-OH).
HRMS: m/z [M^+] calcd for $C_{33}H_{44}O_{10}$: 600.6947; found: 600.6944.

1-[2-Hydroxy-4,6-bis(methoxymethoxy)-3,5-bis(3-methyl-but-2-enyl)phenyl]-3-[4-(methoxymethoxy)phenyl]propenone (**4b**)

Yield (20 h): 46%, Red oil.
IR (KBr): 3430, 1628, 1602 cm^{-1}.
^1H NMR (200 MHz) δ: 1.75 (6H, s, CH_3), 1.77 (6H, s, CH_3), 3,39 (2H, d, *J* = 6.6, CH_2), 3,41 (2H, d, *J* = 6.2, CH_2), 3.43 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 4.84 (2H, s, OCH_2O), 4.98 (2H, s, OCH_2O), 5.21 (2H, s, OCH_2O), 5.22 (2H, m, Pr-CH), 7.06 (2H, d, *J* = 3.8, Ar-H), 7.59 (2H, d, *J* = 4.4, Ar-H), 7.66 (1H, d, *J* = 7.8, CH), 7.83 (1H, d, *J* = 8.2, CH), 12.58 (1H, s, 2-OH).
HRMS: m/z [M^+] calcd for $C_{31}H_{40}O_8$: 540.6429; found: 540.6431

1-[2-Hydroxy-4-(methoxymethoxy)-5-(3-methyl-but-2-enyl)phenyl]-3-[4-(methoxymethoxy)phenyl]propenone (**4c**)

Yield (40 h): 50%, Yellow crystals.
MP: 56 – 60 °C.
IR (KBr): 3446, 1636, 1570 cm^{-1}.
^1H NMR (200 MHz) δ: 1.71 (3H, s, CH_3), 1.77 (3H, s, CH_3), 3.3 (2H, d, *J* = 7.1, CH_2), 3.46 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 5.23 (2H, s, OCH_2O), 5.25 (2H, s, OCH_2O), 5.29 (1H, m, Pr-CH), 6.65 (1H, s, Ar-H_3), 7.11 (2H, d, *J* = 8.7, Ar-$H_{2',6'}$), 7.45 (2H, d, *J* = 2.1, Ar-$H_{3',5'}$), 7.54 (1H, d, *J* = 11, CH), 7.86 (1H, d, *J* = 8.4, CH), 13.31 (1H, s, 2-OH).
Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89, H, 6.84. Found C, 69.85; H = 6.81.

General procedure for preparation of MOM-protected flavanones (**1b**, **d**, **g**)

To a stirred solution of the corresponding MOM-protected 2'-hydroxychalcones (**4a-c**) (1 mM) in ethanol (15 mL), NaOAc (10 mM) and a few drops of water were added and the reaction mixture was refluxed for the indicated time. The reaction mixture was diluted with cooled water and the product was extracted with EtOAc (3 x 10 mL). The organic layer was washed with water, dried over $MgSO_4$ and evaporated in vacuum to give a red residue which was purified by column chromatography (*n*-hexane-ethyl acetate, 6:1) affording **1b**, **d** and **g**, respectively.

2-[3,5-Bis(methoxymethoxy)phenyl]-5,7-bis(methoxymethoxy)-6,8-bis(3-methyl-but-2-enyl)chroman-4-one (**1b**)

Yield (3 h): 79%, Light yellow oil.
IR (KBr): 1684, 1582 cm^{-1}.
^1H NMR (500 MHz) δ: 1.63 (3H, s, CH_3), 1.67 (6H, s, 2 x CH_3), 1.75 (3H, s, CH_3), 2.8 (1H, dd, J_1 = 2.9, J_2 = 16.7, 3-H_1), 2.96 (1H, dd, J_1 = 3.5, J_2 = 13.1, 3-H_2), 3.38 (4H, d, *J* = 6.4, *J* = 7.0, 2 x CH_2), 3.48 (6H, s, 2 x OCH_3), 3.58 (6H, s, 2 x OCH_3), 4.97 (2H, s, OCH_2O), 5.01 (2H, s, OCH_2O), 5.16 (4H, s, 2 x OCH_2O), 5.25 (2H, m, Pr-CH) 5.34 (1H, dd, J_1 = 2.6, J_2 = 13.0, 2-H), 6.73 (1H, s, Ar-H), 6.79 (2H, s, Ar-H).
HRMS: m/z [M^+] calcd for $C_{33}H_{44}O_{10}$: 600.6947; found: 600.6942.

5,7-Bis(methoxymethoxy)-2-[4-(methoxymethoxy)phenyl]-6,8-bis(3-methyl-but-2-enyl)chroman-4-one (**1d**)

Yield (5 h): 68.7 %, Yellow oil.
IR (KBr): 1684, 1602 cm^{-1}.
^1H NMR (200 MHz) δ: 1.71 (6H, s, 2 x CH_3), 1.77 (6H, s, 2 x CH_3), 2.96 (1H, dd, J_1 = 1.8, J_2 = 6.6, 3-H_1), 3.01 (1H, dd, J_1 = 1.6, J_2 = 6.6, 3-H_2), 3.37 (2H, d, *J* = 4.8, CH_2), 3.4 (2H, d, *J* = 5.8, CH_2), 3.49 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 4.97 (2H, s, OCH_2O), 5.03 (2H, s, OCH_2O), 5.2 (2H, s, OCH_2O), 5.25 (2H, m, Pr-CH), 5.36 (1H, dd, J_1 =

2.5, J_2 = 5.6, 2-H), 7.07 (2H, d, J = 4.6, Ar-$H_{2', 6'}$), 7.36 (2H, d, J = 4.4, Ar-$H_{3', 5'}$).
HRMS: m/z [M^+] calcd for $C_{31}H_{40}O_8$: 540.6429; found: 540.6426.

7-(Methoxymethoxy)-2-[4-(methoxymethoxy)phenyl]-6-(3-methyl-but-2-enyl)chroman-4-one (**1g**)

Yield (5h): 46%, Orange crystals.
MP: 53-59 °C.
IR (KBr): 1684, 1612 cm^{-1}.
^{1}H NMR (200 MHz) δ: 1.72 (3H, s, CH_3), 1.74 (3H, s, CH_3), 2.78 (1H, dd, J_1 = 1.2, J_2 = 6.7, 3-H_1), 3.02 (1H, dd, J_1 = 1.4, J_2 = 6.8, 3-H_2), 3.28 (2H, d, J = 3.0, CH_2), 3.47 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 5.2 (2H, s, OCH_2O), 5.25 (2H, s, OCH_2O), 5.28 (1H, m, Pr-CH), 5.39 (1H, dd, J_1 = 1.0, J_2 = 5.4, 2-H), 6.7 (1H, s, Ar-H_6), 7.09 (2H, d, J = 3.4, Ar-$H_{2', 6'}$), 7.4 (2H, d, J = 3.4, Ar-$H_{3', 5'}$), 7.71 (1H, s, Ar-H_8).
Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found C, 69.88; H = 6.89.

Preparation of 1a: To a stirred solution of *rac*-**1b** (0.11 g, 0.2 mM) and Me_2S (0.1 mL) in dry dichloromethane (1.5 mL), BF_3•Et_2O (0.1 mL) was added at room temperature. After 20 minutes the reaction mixture was diluted with dichloromethane (5 mL) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuum. The residue was purified by preparative TLC (*n*-hexane-ethyl acetate, 2:1) to give **1a** (16 mg, 21%).

IR (KBr): 3378, 1628, 1604 cm^{-1}.
^{1}H NMR (200 MHz) δ: 1.74 (9H, s, 3 x CH_3), 1.81 (3H, s, CH_3), 2.83 (1H, dd, J = 4.0, 3-H_1), 2.98 (1H, dd, J = 4.7, 3-H_2), 3.03 (1H, s, OH), 3.35 (4H, d, 2 x CH_2), 3.48 (1H, s, OH), 5.25 (2H, m, Pr-CH), 5.29 (1H, dd, 2-H), 5.32 (1H, s, OH), 6.41 (1H, s, Ar-H), 6.56 (2H, d, Ar-H), 12.67 (1H, s, OH).
HRMS: m/z [M^+] calcd for $C_{25}H_{28}O_6$: 424.4851; found: 424.4853.

Preparation of 1c: *Rac*-**1d** (0.15 g, 0.3 mM) was dissolved in methanol (20 mL) and refluxed with 10 % HCl (2 mL) for 1 hour. After the usual workup and purification *rac*-**1e** was obtained as a colourless oil (0.124 g, 89.8%).

^{1}H NMR (500 MHz) δ: 1.58 (3H, s, CH_3), 1.71 (6H, s, 2 x CH_3), 1.77 (3H, s, CH_3), 2.81 (1H, dd, J_1 = 3.0, J_2 = 17.1, 3-H_1), 3.03 (1H, dd, J_1 = 4.1, J_2 = 17.0, 3-H_2), 3.32 (4H, d, J = 6.2, CH_2), 3.5 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 4.99 (2H, m, Pr-CH), 5.17 (4H, s, 2 x OCH_2O), 5.35 (1H, dd, J_1 = 2.8, J_2 = 12.9, 2-H), 7.07 (2H, d, J = 8.6, Ar-$H_{2', 6'}$), 7.36 (2H, d, J = 8.5, Ar-$H_{3', 5'}$), 12.05 (1H, s, 5-OH).
HRMS: m/z [M^+] calcd for $C_{29}H_{36}O_7$: 496.5905; found: 496.5907.

Demethoxymethylation of *rac*-**1e** (0.14 g, 0.28 mM) in dry dichloromethane (2.5 mL) in the presence of Me_2S (0.14 mL) and BF_3•Et_2O (0.14 mL) at room temperature resulted, after one and a half hours, in *rac*-**1c** (0.06 g, 52%, a viscous, yellow oil) in pure form.

IR (KBr): 3384, 1630, 1518 cm^{-1}.
^{1}H NMR (500 MHz) δ: 1.74 (6H, s, 2 x CH_3), 1.79 (6H, s, 2 x CH_3), 2.77 (1H, dd, J_1 = 2.9, J_2 = 17.0, 3-H_1), 3.02 (1H, dd, J_1 = 4.2, J_2 = 12.8, 3-H_2), 3.29 (2H, d, J = 7.0, CH_2), 3.34 (2H, d, J = 6.7, CH_2), 4.92 (1H, s, OH), 5.18 (2H, m, Pr-CH), 5.33 (1H, dd, J_1 = 2.8, J_2 = 12.8, 2-H), 6.35 (1H, s, 7-OH), 6.87 (2H, d, J = 8.5, Ar-$H_{2', 6'}$), 7.32 (2H, d, J = 8.3, Ar-$H_{3', 5'}$), 12.32 (1H, s, 5-OH)
HRMS: m/z [M^+] calcd for $C_{25}H_{28}O_5$: 408.4857; found: 408.4860.

Preparation of 1f: To a solution of *rac*-**1g** (0.28 g, 0.7 mM) in methanol (6 mL), 10 drops of 10 % HCl were added and the mixture was refluxed for 2.5 hours. After the usual workup and purification *rac*-**1f** was obtained in pure form (0.043 g, 18.7%).

Yellow crystals.
MP: 181-185 °C (lit [11]: 183-184 °C, lit [10]: 189 °C].
IR (KBr): 3374, 1654, 1600 cm^{-1}.
^{1}H NMR (200 MHz) δ: 1.73 (3H, s, CH_3), 1.77 (3H, s, CH_3), 2.8 (1H, dd, J_1 = 3.1, J_2 = 16.9, 3-H_1), 3.02 (1H, dd, J_1 = 3.8, J_2 = 16.9, 3-H_2), 3.33 (2H, d, J = 7.2, CH_2), 5.07 (1H, s, OH), 5.29 (1H, m, Pr-CH), 5.38 (1H, dd, J_1 = 3.1, J_2 = 13.0, 2-H), 5.94 (1H, s, OH), 6.43 (1H, s, Ar-H), 6.84 (2H, d, J =6.5, Ar-H), 7.34 (2H, d, J = 8.5, Ar-H), 7.69 (1H, s, Ar-H)
Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.04; H, 6.23. Found C, 74.10; H = 6.25.

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