A SIMPLE SYNTHESIS OF SELINONE, AN ANTIFUNGAL COMPONENT OF *MONOTES ENGLERI*

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Abstract: A new synthesis of racemic 5,7-dihydroxy-2-[4-(3-methyl-but-2-enyloxy)-phenyl]chroman-4-one (*selinone*) (rac-**1a**) isolated from *Monotes engleri* GILG. was accomplished by two routes starting from MOM-protected phloracetophenone (**2**).

Introduction

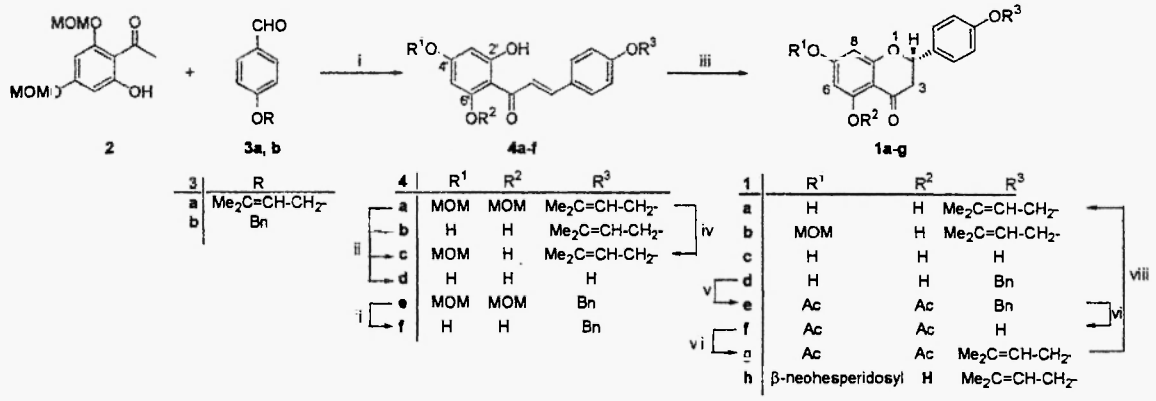
Recently one of us has described the isolation and structure elucidation of (±)-5,7-dihydroxy-2-[4-(3-methyl-but-2-enyloxy)-phenyl]chroman-4-one (*rac*-**1a**) from *Monotes engleri* GILG. Which shows remarkable antifungal activity against *Candida* albicans.[1] Its levoratatory enantiomer, (–)-selinone (**1a**) has also been isolated from *Selinum vaginatum*.[2] In continuation of our investigation on biologically active natural products,[3-6] we report now a new synthesis of racemic selinone (*rac*-**1a**) starting from MOM-protected phloracetophenone (**2**).

Results and discussion

Our synthetic approach to *rac*-**1** was based on the well-documented transformation of 2',4',6'-trihydroxychalcones into 5,7-dihydroxyflavanones under mild basic conditions.[7,8]

Therefore 1-(2-hydroxy-4,6-dimethoxymethoxyphenyl)ethanone (**2**)[9] and 4-(3-methyl-but-2-enyloxy)benzaldehyde (**3**)[10] were converted into the corresponding 2'-hydroxychalcone (**4a**) in the presence of potassium hydroxide in ethanol with 46% yield. The deprotection (**4a** → **4b**) under mild acidic condition (10% HCl / MeOH) and cyclization (**4b** → *rac*-**1a**) on treatment with sodium acetate afforded racemic selinone (*rac*-**1a**) in low yield (13%) beside its 7-methoxymethyl-ether (*rac*-**1b**) (23%) and racemic naringenin (*rac*-**1c**) (37%). TLC-monitoring of the first step of this transformation (**4a** → **4b**) has clearly shown that the cleavage of the C-6' methoxymethyl group of **4a** took place very rapidly to result in **4c**. However, it was followed not only by the cleavage of its methoxymethyl group, but surprisingly by its prenyl one as well. By the treatment of **4a** with 5% HCl in methanol at room temperature followed on treatment with sodium acetate *rac*-**1b** could be obtained in good yield (60%). All of our attempts to transform *rac*-**1b** to *rac*-**1a** were unsuccessful under different conditions ($SnCl_4$ or BF_3 in dichloromethane at -10°C or Amberlyst-15 in benzene at 50°C).

Scheme 1.



Reaction conditions: i) KOH/EtOH, rt.; ii) 10% HCl/MeOH, reflux; iii) NaOAc/MeOH; iv) 5% HCl/MeOH, rt.; v) Ac_2O/dry pyridine, rt.; vi) H_2-Pd/MeOH, rt; vii) 3-methyl-2-buten-1-ol, Ph_3P, diisopropyl azodicarboxylate, dry THF; viii) NaOMe/dry MeOH

In order to achieve a practical route to racemic selinone (*rac*-**1a**), 5,7-diacethyl-naringenin (*rac*-**1f**) was prepared in racemic form by a simple five-step sequence starting from **2** and **3b**[11] (**2** and **3b** → **4e** → **4f** → *rac*-**1d** → *rac*-**1e** → *rac*-**1f**). Subsequently, *rac*-**1f** was prenylated by 3-methyl-2-buten-1-ol under Mitsunobu condition[12] to afford racemic selinone peracetate (*rac*-**1g**) whose saponification with 1 N sodium methoxide in methanol gave *rac*-**1a** in good yield (95%). All spectra of *rac*-**1a** are identical with those of the natural and synthetic product prepared by Wagner *et al.* from **1h**.[13]

Experimental

General experimental procedures: Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The analytical and preparative TLC were performed on plates Kieselgel 60 F_{254} (Fa. Merck). The ^{1}H-NMR spectra were recorded on Bruker WP-200 spectrometer with TMS as internal standard in $CDCl_3$ and in DMSO (marked by an asterisk*). The chemical shifts are given in δ (ppm) and the spin-spin coupling constants (*J*) in Hz. HRMS were recorded in EI mode at 70 eV on a VG 7035 MS spectrometer. For workup the solutions were dried ($MgSO_4$) and concetrated in *vacuo*.

1-(2-hydroxy-4,6-dimethoxymethoxyphenyl)-3-[4-(3-methyl-but-2-enyloxy)phenyl]-prop-2-en-1-one (4a)

A solution of KOH (20 g) in water (20 mL) was added to the stirred solution of **2** (4.23 g, 16 mmol) and **3a** (3.14 g; 16 mmol) in ethanol (40 ml). The reaction mixture was stirred for 8 hours and then solvent was evaporated. The residue was diluted with water (100 mL), acidified with 10% HCl (pH = 2), and then the product was extracted with ethyl acetate (3x30 mL). Organic layer was washed with water (2x10 mL), dried and evaporated to give red solid residue whose crystallization from methanol resulted in **4a** as orange crystals (3.18 g; 46%; m.p.: 72-75 °C). ^{1}H-NMR: 1.76 (3H, s; CH_3),, 1.81 (3H, s; CH_3), 3.48 (3H, s; OCH_3), 3.54 (3H, s; OCH_3), 4.55 (2H, d; *J* = 6.7, CH_2), 5.19 (2H, s; OCH_2O), 5.29 (2H, s; OCH_2O), 5.52 (1H, m; CH), 6.25 (1H, d; *J* = 2.34, 3'-H), 6.31 (1H, d; *J* = 2.34, 5'-H), 6.93 (2H, d; *J* = 8.74, 3"-H, 5"-H), 7.55 (2H, d; *J* = 8.74, 2"-H, 6"-H), 7.81 (2H, s; 2-H, 3-H), 13.95 (1H, s; 2'-OH). HRMS *m/z*: 428.1837 (calcd for $C_{24}H_{28}O_7$, 428.1835).

(±)-5,7-dihydroxy-2-[4-(3-methyl-but-2-enyloxy)phenyl]chroman-4-one (*rac*-1a) (*rac-selinone*) and (±)-5-Hydroxy-7-methoxymetoxy-2-[4-(3-methyl-but-2-enyloxy)phenyl]chroman-4-one (*rac*-1b) and (±)-5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one (*rac*-1c) (*rac-naringenin)

To the stirred solution of **4a** (0.23 g; 0.54 mmol) in methanol (10 ml) 1 ml 10% HCl was added and the reaction mixture was refluxed for 2–3 hours. Subsequently 0.51 g NaOAc was added and the stirring was continued for 3 hours. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and dried. Evaporation of the solvent gave an oil (160 mg) which was purified by column chromatography (hexane-ethyl acetate = 3:1) to furnished *rac*-**1a**, **-1b**, and **-1c**. *rac*-**1a** (24 mg, 13%) m.p. 143-145°C. ^{1}H-NMR*: 1.71 (3H, s; CH_3), 1.74 (3H, s; CH_3), 2.71 (1H, dd; *J* = 3.04, 17.01; 3-H_{eq}), 3.09 (1H, dd; *J* = 12.6, 17.01;

3-H_{ax}), 4.54 (2H, d; J = 6.64; CH_2), 5.23 (1H, dd; J = 3.04, 12.6; 2-H), 5.43 (1H, m; CH), 5.88 (2H, s; 8-H, 6-H), 6.96 (1H, d; J = 8.7, 2'-H, 6'-H), 7.42 (1H, d; J = 8.7, 3'-H, 5'-H), 10.83 (1H, s; 7-OH), 12.15 (1H, s; 5-OH). HRMS *m/z* 340.1309 (calcd for $C_{20}H_{20}O_5$, 340.1311). It was also obtained from *rac*-**1g** in 95% yield by treatment with 1N sodium methoxyde in methanol at room temperature.

rac-**1b**: 50 mg (23%, m.p.: 91-93 °C), ^{1}H-NMR : 1.75 (3H, s; CH_3), 1.80 (3H, s; CH_3), 2.78 (1H, dd; J = 3.16, 17.18; 3-H_{eq}), 3.11 (1H, dd; J = 12.96, 17.18; 3-H_{ax}), 3.46 (3H, s; OCH_3), 4.53 (2H, d; J = 6.7; CH_2), 5.16 (2H, s; OCH_2O), 5.36 (1H, dd; J =3.16, 12.96; 2-H), 5.48 (1H, m; CH), 6.17 (1H, d; J = 2.26; 6-H), 6.20 (1H, d; J = 2.26; 8-H), 6.98 (2H, d; J = 8.8; 2'-H, 6'-H), 7.39 (2H, d; J = 8.8, 3"-H, 5"-H), 11.96 (1H, s; 5-OH). HRMS *m/z* 384.1574 (calcd for $C_{22}H_{24}O_6$, 384.1573).

rac-**1c**: (55 mg, 37%) m.p.: 244-246°C. ^{1}H-NMR*: 2.66 (1H, dd; J = 2.56, 17.14, 3-H_{eq}), 3.26 (1H, dd; J = 12.84, 17.14, 3-H_{ax}), 5.43 (1H, dd; J = 2.56, 12.84, 2-H), 5.87 (2H, s; 6-H, 8-H), 6.81 (2H, d; J = 8.48, 2'-H, 6'-H), 7.33 (2H, d; J = 8.48, 3'-H, 5'-H), 9.60 (1H, s; 4'-OH), 10.8 (1H, s; 7-OH), 12.15 (1H, s; 5-OH). HRMS *m/z* 272.0689 (calcd for $C_{15}H_{12}O_5$, 272.0685).

(±)-5-Hydroxy-7-methoxymetoxy-2-[4-(3-methyl-but-2-enyloxy)phenyl]chroman-4-one (*rac*-1b)

To the stirred solution of **4a** (0.23 g; 0.54 mmol) in methanol (50 ml) 2 ml 5% HCl was added and the reaction mixture was stirred at room temperature for 8 hours. Subsequently 0.51 g NaOAc was added and the stirring was continued at 50°C for 3 hours. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and dried. Evaporation of the solvent gave an oil (200 mg) which was purified by column chromatography (hexane-ethyl acetate = 3:1) to furnished *rac*-**1b** as white crystalline solid (115 mg, 60%, m.p.: 91.5-93°C).

1-(2-hydroxy-4,6-dimethoxymethoxyphenyl)-3-(4-benzyloxyphenyl)-prop-2-en-1-one (4e)

A solution of KOH (5 g) in water (50 mL) was added to the stirred solution of **2** (1.82 g; 7.1 mmol) and **3b** (1.5 g; 7.1 mmol) in ethanol (100 ml). The reaction mixture was stirred for 5 days at 40°C. The solvent was evaporated and the residue was diluted with water (100 mL), acidified with 10% HCl (pH = 2), and the product was extracted with ethyl acetate (3x30 mL). Organic layer was washed with water (2x10 mL), dried. Evaporation of the solvent gave an an oil (3.16g), which was purified by column chromatography to furnished **4e** as yellow crystals (1.74 g, 54%; m.p.: 115-117

°C. ^{1}H-NMR: 3.48 (3H, s; OCH_3), 3.53 (3H, s; OCH_3), 5.11 (2H, s; OCH_2O), 5.19 (2H, s; OCH_2O), 5.29 (2H, s; CH_2Ph), 6.24 (1H, d; J = 2.28, 3'-H), 6.31 (1H, d, J = 2.28, 5'-H) 7.0 (2H, d; J = 8.72, 2"-H, 6"-H), 7.39 (5H, m; Ph), 7.56 (2H, d; J = 8.74, 3"-H, 5"-H), 7.75 (1H, d; J = 16.85, 3-H), 7.85 (1H, d, J – 16.85, 2-H) 13.92 (1H, s; 2'-OH). HRMS *m/z* 450.1676 (calcd for $C_{26}H_{26}O_7$, 450.1679).

(±)-5,7-Dihydroxy-2-(4-benzyloxyphenyl)chroman-4-one (*rac*-1d)

A solution of **4e** (1.7 g; 3.7 mmol) and 10% HCl (5.7 ml) in methanol (300 ml) was stirred over night at room temperature. Subsequently 3.69 g NaOAc was added, and stirring was continued for 5 hours at 70°C. After evaporation of the solvent the residue was diluted with water, and the product was extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated to give an oil whose purification by column chromatography (hexane-ethyl acetate = 3:1) resulted in *rac*-**1d** (0.60 g; 43.9%) as a yellow crystals. mp: 219-222 °C (MeOH). ^{1}H NMR*: 2.71 (1H, dd, J = 3. 17, 3-H_{eq}), 3.25 (1H, dd, J = 4.5, 12.42, 3-H_{ax}), 5.17 (2H, s, OCH_2), 5.5 (1H, dd, J = 2.6, 12.36, 2-H), 7.03 (1H, s, 6-H), 7.08 (1H, s, 8-H) 7.28-7.46 (9H, m, Ar-H), 10.84 (1H, s, 7-OH), 12.14 (1H, s, 5-OH). HRMS *m/z* 362.1158 (calcd for $C_{22}H_{18}O_5$, 362.1154).

(±)-5,7-Diacethoxy-2-(4-benzyloxyphenyl)chroman-4-one (*rac*-1e)

A solution of **1d** (600 mg; 1.66 mmol) and acetic anhydride (5 mL) in dry pyridine (20 ml) was stirred for 2 days at room temperature. After the usual workup the precipitated product was filtered off, washed with water and dried, then crystallized from methanol gave *rac*-**1e** as yellow crystals (300 mg; 50%) mp.: 97-101°C (MeOH). ^{1}H-NMR: 2.28 (3H, s, OAc), 2.38 (3H, s, OAc), 2.73 (1H, dd, J = 2.8, 16.64, 3-H_{eq}), 3.06 (1H, dd, J = 13.45, 16.68, 3-H_{ax}), 5.08 (2H, s, OCH_2), 5.42 (1H, dd, J = 2.72, 13.4, 2-H), 6.52 (1H, d, J = 2.05, 6-H), 6.76 (1H, d, J = 1.6, 8-H), 7.02 (2H, d, J = 11.3, Ar-H), 7.39 (7H, m, Ar-H). HRMS *m/z* 446.1368 (calcd for $C_{26}H_{22}O_7$, 446.1366).

(±)-5,7-Diacethoxy-2-(4-hydroxyphenyl)chroman-4-one (*rac*-1f)

A solution of **1e** (250 mg, 0.56 mmol) in dry methanol (100 mL) was hydrogenated in the presence of Pd/C (120 mg) at r.t.. The usual workup gave *rac*-**1f** (152 mg, 76%) as a yellow solid of m.p.: 118-121°C. ^{1}H-NMR: 2.28 (3H, s, OAc), 2.37 (3H, s, OAc), 2.67 (1H, dd, J = 2.56, 16.45, 3-H_{eq}), 3.02 (1H, dd, J = 13.52, 16.45, 3-H_{ax}), 5.31 (1H, dd, J = 2.56, 13.52, 2-H), 6.53 (1H, d, J = 2.19, 6-H), 6.74 (1H, d, J = 2.19, 8-H), 6.82 (2H, d, J = 8.4, 2'-H, 6'-H), 7.23 (2H, d, J = 8.4, 3'-H, 5'-H). HRMS *m/z* 356.0891 (calcd for $C_{19}H_{16}O_7$, 356.0896).

(±)-5,7-Diacethoxy-2-[4-(3-methyl-but-2-enyloxy)phenyl]chroman-4-one (*rac*-1g)

To a solution of diacetate **1f** (120 mg, 0.34 mmol), triphenylphosphine (107 mg, 0.41 mmol) and 3-methyl-2-buten-1-ol (50 μL, 50 mmol) in dry THF (10 mL) cooled to 0°C was added dropwise over 30 min under argon a solution of diisoprophyl azodicarboxylate (85 μL, 55 mmol) in dry THF (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After removal of the solvent in *vacuo*, the residue was purified by column chromatography (hexane–ethyl acetate = 2:1) to give rac-**1g** as white crystals of m.p.: 71.5-72°C (86 mg, 60%). 1H-NMR: δ: 1.76 (3H, s; CH_3), 1.81 (3H, s; CH_3), 2.30 (3H, s, OAc), 2.39 (3H, s, OAc), 2.74 (1H, dd; J = 2.56, 16.45; 3-H_{eq}), 3.09 (1H, dd; J = 13.16, 16.45; 3-H_{ax}), 4.54 (2H, d; J = 6.58; CH_2), 5.44 (1H, dd; J = 2.56, 13.16; 2-H), 5.50 (1H, m; CH), 6.53 (1H, d, J = 2.19; 5-H), 6.77 (1H, d, J = 2.19, 6-H), 6.97 (2H, d, J = 11.33, 2"-H, 6"-H), 7.37 (2H, d, J = 11.33, 3'-H, 5'-H). HRMS *m/z* 424.1524 (calcd for $C_{24}H_{24}O_7$, 424.1522).

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