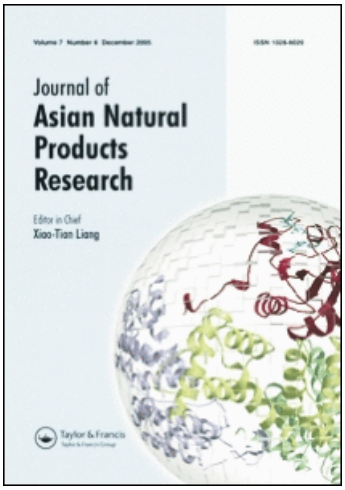

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Synthesis and enantiomeric resolution of (±)-pinocembrin

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A convenient method for the synthesis and enantiomeric resolution of (±)-pinocembrin has been developed. This route involves the hydrogenation of 5,7-dihydroxyflavone, the derivatization of racemic pinocembrin with chiral amine, and the separation of the diastereoisomers due to their different physical properties.

Keywords: pinocembrin; synthesis; enantiomeric resolution; chiral amine

1. Introduction

Pinocembrin (Figure 1), a flavanone, has a chiral center at C-2. (*S*)-Pinocembrin, $[\alpha]_D^{15}$ −45.3 (*c*. 0.9, acetone), has been isolated from propolis, *Pinus cembra*, *Eucalyptus sieberi*, *Alnus sieboldiana*, etc., which has been reported to have many pharmacological actions including therapeutical effect for cardio/cerebrovascular diseases, anti-inflammatory, antibacterium, antioxidant, and testosterone 5α-reductase inhibitory activities [1–3]. Its promising pharmacological profiles coupled with its low natural content have attracted much attention from us. Herein, we would like to describe a method for the synthesis and resolution of the racemic pinocembrin.

2. Results and discussion

(±)-Pinocembrin (**1**) has been synthesized via 5,7-dihydroxyflavone as the starting material in one step (Scheme 1). Hydrogenation of **2** with 10% Pd–C and H_2 affords **1** in 84% yield.

As shown in Figure 1, the asymmetry C-2 is the chiral center of pinocembrin. To resolve the enantiomers by derivatization, we focus on the carbonyl group. The protection of the 7-hydroxyl of pinocembrin (**1**) with benzyl chloride affords compound **3** in 93% yield. The treatment of **3** with (L)-(-)-α-methylbenzylamine using $TiCl_4$ as a catalyst and separation of the product via column chromatography give **4a** and **4b** in 55% yield. The hydrolysis of **4a** and **4b**, respectively, furnishes **3a** and **3b** in 92 and 91% yield. Finally, (*S*)-pinocembrin and (*R*)-pinocembrin are obtained, respectively, by the hydrogenolysis of the benzyl groups of compounds **3a** and **3b** in 91 and 93% yield.

3. Experimental

3.1 General experimental procedures

Melting points were obtained on a YRT-3 Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 2401 MC Autopol polarimeter. The ^{1}H NMR spectra were recorded on a Varian Mercury-400 NMR spectrometer, and MS on a ZAB-2F Mass spectrometer. TLC was carried out on silica gel layers (Qingdao Haiyang Chemical Co., Ltd Qingdao, China).

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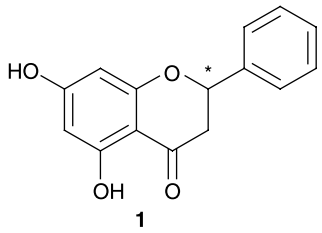


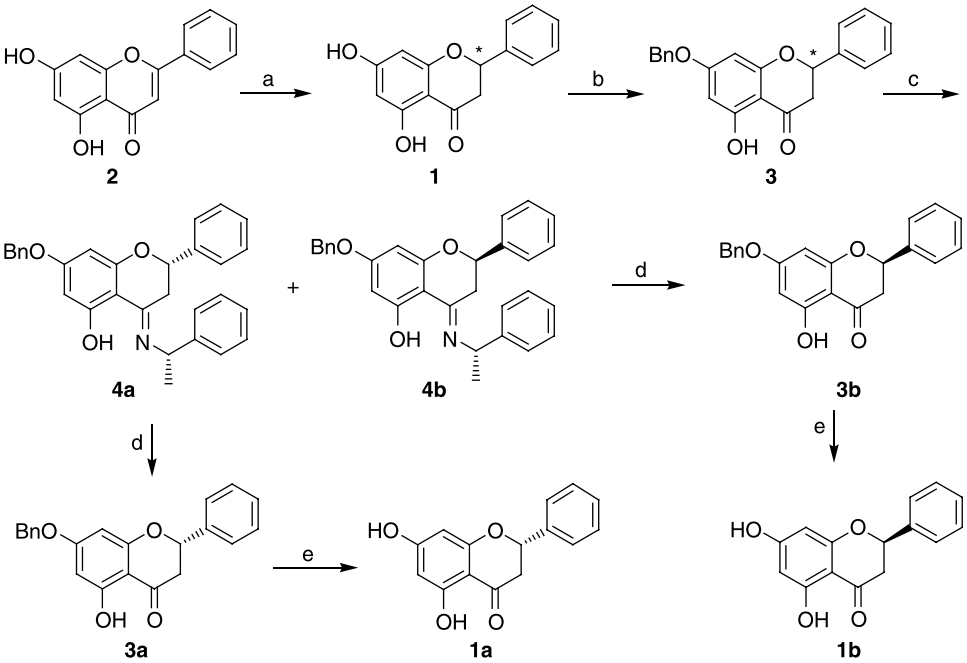
Figure 1. Structure of (±)-pinocembrin.

3.2 (±)-Pinocembrin (1)

Compound **2** (5 g, 19.7 mmol) and 10% Pd–C (1 g) were added in EtOH (650 ml). The mixture was then hydrogenized at 60°C and 3 atm for 2 h. After filtration, the solvent was evaporated under reduced pressure, and the resultant residue was chromatographed [SiO_2, petroleum ether (b.p. 60–90°C)–ethyl acetate–methanol 100:10:2] to afford compound **1** (3.9 g, 77%); m.p. 200–201°C (Ref. [4] 199–200°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.03 (s, 1H, C_5-OH), 7.46–7.37 (m, 5H, Ar-H), 6.00 (s, 2H, C_8-H, C_6-H), 5.43 (dd, 1H, C_2-H, $J = 3.2$, 12.7 Hz), 3.09 (dd, 1H, C_3-H, $J = 17.1$, 12.7 Hz), 2.83 (dd, 1H, C_3-H, $J = 17.1$, 3.2 Hz); EIMS *m/z* (%): 256 [M^+, 75], 124 [$M^+ - C_8H_8 - CO$, 100].

3.3 7-Benzyloxy-5-hydroxyflavanone (3)

A mixture of 5,7-dihydroxyflavanone (**1**) (12.76 g, 50 mmol), benzyl chloride (7.5 ml, 65 mmol), potassium iodide (0.46 g, 2.75 mmol), and anhydrous potassium carbonate (7.60 g, 55 mmol) in acetone (200 ml) was heated under reflux for 2 h. Then, the mixture was filtered under reduced pressure to give the crude product. Compound **3** was purified from light petroleum, forming clusters of almost colorless (16.21 g, 93%); m.p. 80–82°C (Ref. [5] 67–69°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.93 (s, 1H, C_5-OH), 7.39–7.27(m, 10H, Ar-H), 6.08 (s, 1H, C_8-H), 6.07 (s, 1H, C_6-H), 5.35 (dd, 1H, C_2-H, $J = 2.8$,



Scheme 1. Synthesis and resolution of pinocembrin. Reagents and conditions: (a) Pd–C (10%), EtOH, 60°C, 2 h; (b) BnCl, K_2CO_3, KI, acetone, reflux, 2 h; (c) (L)-(-)-α-methylbenzylamine, Et_3N, $TiCl_4$, benzene, N_2, 48 h; (d) HCl (1 N), EtOH, EtOAc, reflux, 1.5 h; (e) Pd–C (10%), DMF, HCl (1 N), 4 h.

12.8 Hz), 5.00 (s, 2H, C_6H_6-CH_2), 3.02 (dd, 1H, C_3-H, $J = 17.2$, 12.8 Hz), 2.75 (dd, 1H, C_3-H, $J = 17.2$, 2.8 Hz); ESIMS *m/z* (%): 347.1 [M + H^+, 100], 369.1 [M + Na^+, 5].

3.4 (2S)-7-Benzyloxy-2-phenyl-4-((S)-1-phenylethylimino)chroman-5-ol (4a) and (2R)-7-benzyloxy-2-phenyl-4-((S)-1-phenylethylimino)chroman-5-ol (4b)

A dried three-necked round-bottomed flask equipped with a dropping funnel and thermometer was charged with 7-benzyloxy-5-hydroxyflavanone (**3**) (14.98 g, 43.3 mmol) and dry benzene (100 ml). The solution was then cooled to 0°C with ice under a N_2 atmosphere, and to it was added a solution of (L)-(-)-α-methylbenzylamine (Aldrich, 98%; 5.57 ml, 43.3 mmol) and triethylamine (12 ml, 86.6 mmol) in dry benzene (20 ml). While the temperature was kept below 10°C, a solution of $TiCl_4$ (2.39 ml, 22 mmol) in dry benzene (10 ml) was added dropwise over 15 min. The red–brown suspension was allowed to warm to room temperature and stirred for 24–48 h. The suspension was filtered through a funnel charged with Celite. The filtrate was concentrated *in vacuo* to give a red–brown oil that was chromatographed (SiO_2, petroleum ether (b.p. 60–90°C)–ethyl acetate 10:1) to afford compounds **4a** (5.93 g) and **4b** (4.26 g) as yellow oil (total yield 55%). Compound **4a**: $[\alpha]_D^{20}$ + 149.8 (*c*. 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.93 (s, 1H, C_5-OH), 7.36–7.15 (m, 15H, Ar-H), 6.04 (d, 1H, C_8-H, $J = 4.0$ Hz), 5.86 (d, 1H, C_6-H, $J = 4.0$ Hz), 5.06 (d, 1H, C_2-H, $J = 12.0$ Hz), 4.95 (s, 2H, C_6H_6-CH_2), 4.74 (s, 1H, N-CH), 3.00 (d, 1H, C_3-H, $J = 16.0$ Hz), 2.48 (dd, 1H, C_3-H, $J = 12.0$, 16.0 Hz), 1.58 (d, 3H, CH_3, $J = 8.0$ Hz); ESIMS *m/z* (%): 450.3 [M + H^+, 100], 899.4 [2M + H^+, 72]; compound **4b**: $[\alpha]_D^{20}$ + 62.0 (*c*. 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.07 (s, 1H, C_5-OH), 7.46–7.29 (m, 15H, Ar-H), 6.17 (d, 1H, C_8-H, $J = 4.0$ Hz), 6.00 (d, 1H, C_6-H, $J = 4.0$ Hz), 5.06 (s, 2H, C_6H_6-CH_2), 5.01 (dd, 1H, C_2-H, $J = 4.0$, 12.0 Hz), 4.81 (q, 1H, N-CH, $J = 8.0$ Hz), 2.99 (dd, 1H, C_3-H, $J = 4.0$, 16.0 Hz), 2.89 (dd, 1H, C_3-H, $J = 12.0$, 16.0 Hz), 1.59 (d, 3H, CH_3, $J = 8.0$ Hz); ESIMS *m/z* (%): 450.3 [M + H^+, 100], 899.4 [2M + H^+, 89].

3.5 (S)-7-Benzyloxy-5-hydroxyflavanone (3a)

A mixture of compound **4a** (5.93 g, 13.2 mmol), ethyl acetate (50 ml), ethanol (30 ml), and hydrochloric acid (1 mol/L, 30 ml) was heated under reflux for 1.5 h. The reaction mixture was cooled to room temperature and neutralized with aqueous sodium hydroxide (10%, w/v) to pH 6. The reaction mixture was cooled to room temperature and compound **3a** came out as clusters of almost colorless (4.19 g, 92%); m.p. 91.8–92.5°C; $[\alpha]_D^{20}$ −30.78 (*c*. 0.5, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.06 (s, 1H, C_5-OH), 7.52–7.33 (m, 10H, Ar-H), 6.21 (s, 1H, C_8-H), 6.17 (s, 1H, C_6-H), 5.62 (dd, 1H, C_2-H, $J = 3.2$, 12.0 Hz), 5.17 (s, 2H, C_6H_5-CH_2), 3.31 (dd, 1H, C_3-H, $J = 12.4$, 17.7 Hz), 2.81 (dd, 1H, C_3-H, $J = 3.2$, 17.7 Hz); ESIMS *m/z* (%): 347.1 [M + H^+, 100].

3.6 (R)-7-Benzyloxy-5-hydroxyflavanone (3b)

Compound **3b** was prepared by the same procedure for **3a** using **4b** as the starting material (4.26 g, 9.5 mmol). The title compound **3b**: clusters of almost colorless (2.98 g, 91%); m.p. 97.9–98.4°C; $[\alpha]_D^{20}$ + 30.88 (*c*. 0.5, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.06 (s, 1H, C_5-OH), 7.52–7.33 (m, 10H, Ar-H), 6.21 (s, 1H, C_8-H), 6.17 (s, 1H, C_6-H), 5.63 (dd, 1H, C_2-H, $J = 2.8$, 12.4 Hz), 5.17 (s, 2H, C_6H_5-CH_2), 3.31 (dd, 1H, C_3-H, $J = 12.4$, 16.4 Hz), 2.81 (dd, 1H, C_3-H, $J = 2.8$, 16.4 Hz); ESIMS *m/z* (%): 347.1 [M + H^+, 100].

3.7 (S)-5,7-Dihydroxyflavanone (1a)

Compound **3a** (4.19 g, 12.1 mmol), 10% Pd–C (3.35 g), and dilute hydrochloric acid (20 ml) were added in DMF (70 ml). The mixture was then hydrogenized at room temperature for 4 h. The catalyst was removed by filtration, and the

solvent was evaporated under reduced pressure. The resultant residue was purified by column chromatography (SiO_2, petroleum ether (b.p. 60–90°C)–ethyl acetate 5:1) to afford pure **1a** as a white powder (2.82 g, 91%); m.p. 192–193°C; $[\alpha]_D^{20}$ −45.63 (*c*. 0.5, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.11 (s, 1H, C_5-OH), 10.81 (s, 1H, C_7-OH), 7.51–7.37 (m, 5H, Ar-H), 5.91 (s, 1H, C_8-H), 5.88 (s, 1H, C_6-H), 5.57 (dd, 1H, C_2-H, $J = 3.2$, 12.6 Hz), 3.24 (dd, 1H, C_3-H, $J = 12.6$, 17.0 Hz), 2.77 (dd, 1H, C_3-H, $J = 3.2$, 17.0 Hz); HRESIMS *m/z* 257.0818 (calcd for $C_{15}H_{13}O_4$, 257.0813) (Ref. [6] 194–195°C; $[\alpha]_D^{32}$ −52 (*c*. 0.19, methanol)).

3.8 (R)-5,7-Dihydroxyflavanone (1b)

Compound **1b** was prepared by the same procedure for **1a** using **3b** as the starting material (2.98 g, 8.61 mmol). The title compound **1b**: white powder (2.05 g, 93%); m.p. 191.3–192.4°C; $[\alpha]_D^{20}$ + 45.83 (*c*. 0.5, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.11 (s, 1H, C_5-OH), 10.81 (s, 1H, C_7-OH), 7.51–7.37 (m, 5H, Ar-H), 5.91 (s, 1H, C_8-H), 5.88 (s, 1H, C_6-H), 5.57 (dd, 1H, C_2-H, $J = 3.2$, 12.6 Hz), 3.24 (dd, 1H, C_3-H, $J = 12.6$, 17.0 Hz), 2.77 (dd, 1H, C_3-H, $J = 3.2$, 17.0 Hz); HRESIMS *m/z* 257.0817 (calcd for $C_{15}H_{13}O_4$, 257.0813).

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