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Total synthesis and antihypertensive activity of (±)7,8-dihydroxy-3-methyl-isochromanone-4

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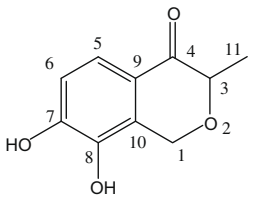
ABSTRACT

This letter describes the total synthesis, preliminary biological evaluation and mechanism studies of a novel and structurally unique isochromanone, (±)7,8-dihydroxy-3-methyl-isochromanone-4 (**1**), a nature product contained in banana (*Musa sapientum* L.) peel. The bioassay showed that compound **1** displays potent antihypertensive activity in renal hypertensive rats and further mechanism studies revealed that it is an ACE inhibitor.

Hypertension is a leading cause of the human angiocardiopathy death, approximately 1 billion individuals worldwide are estimated to have blood pressure (BP) levels that warrant treatment, and the prevalence of chronic heart disease and end-stage renal disease has increased in recent years. Therapeutic intervention is the most common method used to control hypertension and reduce hypertension-related organ damage. During the last few decades, great progress has been made in finding new antihypertensive drugs and currently there are three main categories of antihypertensive drugs available: (1) diuretics, adrenergic receptor blockers; (2) calcium channel blockers and (3) inhibitors targeting the renin–angiotensin system (RAS), namely angiotensin-converting enzyme (ACE) inhibitors and angiotensin type 1 (AT_1) receptor antagonists. Despite the development of antihypertensive drugs, effective BP control remains a major medical challenge and there has been a consistent demand for novel and more effective therapies. Antihypertensive product from plants is an important resource to find new lead for further structure modification.[1]

The peel of banana has a great resource in China, which has been widely used as a folk medicine for antihypertension, antiulceration, antibacterial and so on.[2] Recently, we first reported a novel and structurally unique isochromanone, (±)7,8-dihydroxy-3-methyl-isochromanone-4 (**1**), isolated from banana (*Musa sapientum* L.) peel extract.[3] The structure of compound **1** has been identified by extensive spectra. A preliminary bioassay proved that compound **1** displays potent antihypertensive activity in a renal hypertensive rats (RHRs). However, the low abundance of this compound impeded the further biological tests both in vitro and in vivo. As our long-term interest, we initialized the project towards the study of total synthesis of compound **1** and its derivatives. In this letter, we wish to report the total syntheses of compound **1** as well as its biological evaluations.



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In our recent study, a more efficient synthesis of compound **1** was found. The synthetic route is shown in Scheme 1. Metal-halogen exchange provided favourable conditions leading *o*-bromophenylalkanoic acid to self-condensation.[4] Treatment of *o*-brom-

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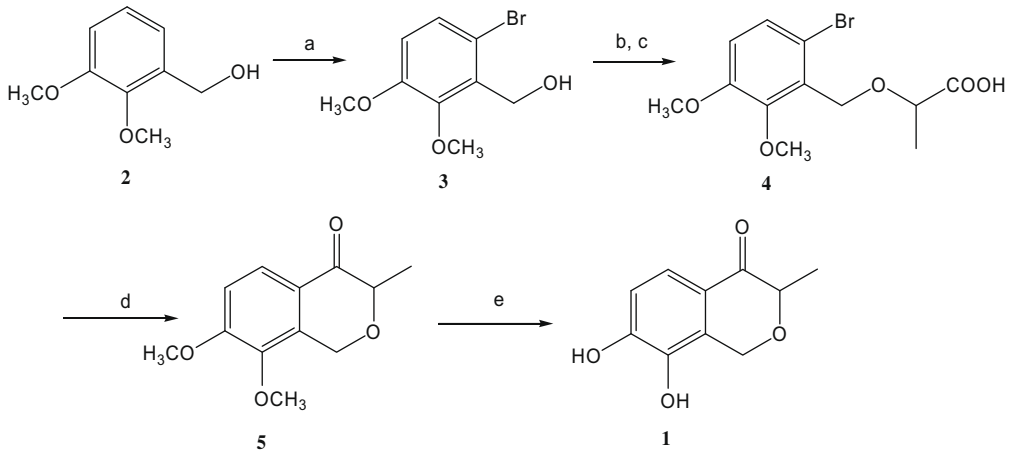

Scheme 1. Reagents and conditions: (a) NBS, THF, rt, 93%; (b) $CH_3BrCHCOOC_2H_5$, anhydrous DMF, NaH, rt, 82%; (c) MeOH, 10% NaOH, rt, then 10% HCl, 92%; (d) *n*-BuLi, anhydrous THF, −78 °C to room temperature, 60%; (e) $AlCl_3$, $CHCl_3$, reflux, 50%.

ophenylalkanoic acid with *n*-BuLi in THF at temperatures ranging from −110 to 0 °C afforded the expected benzocycloalkenone in good yield.[5] As shown in Scheme 1, compound **3** was achieved through a regioselective bromination with NBS in quite high yield. Subsequent alkylation of **3** with ethyl 2-bromopropionate in presence of NaH, followed by saponification of the ethyl ester gave compound **4.**[6] Intermediate **4** was treated with *n*-BuLi in THF at −78 °C, and then the temperature was allowed to rise to room temperature to give compound **5**, in 60% yield. After deprotection of phenolic methyl ether **5** by $AlCl_3$ in $CHCl_3$, target compound (±)7,8-dihydroxy-3-methyl-isochromanone-4 (**1**) was obtained. The spectral data of synthetic compound **1** was identical with those of natural sample **1.**[7]

The compound **1** showed potent antihypertensive activity on the two-kidney–one-clip renal hypertensive rats[8,9] and the antihypertensive activity of synthetic compound **1** was identical with that of natural sample **1**. In acute antihypertensive tests, captopril was used as a positive control, the maximum antihypertensive effect on systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) of compound **1** at the dose of 100.0 mg/kg/day was approximately equivalent to that of captopril at the dose of 25.0 mg/kg/day. The therapeutic effects of compound **1** occurred evidently 2 h after treatment and lasted for 6–8 h (Figs. 1 and 2).

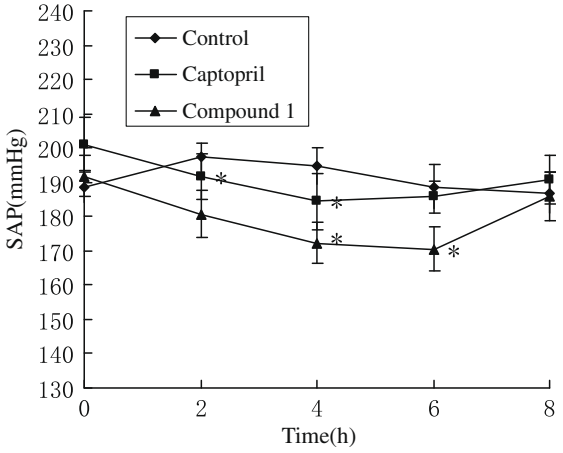

Figure 1. The acute antihypertensive activity of compound **1** in RHRs (SAP, systolic arterial pressure). Data are presented as mean ± SEM, $n = 8$. Significance indicated by: $^{*}P < 0.05$; $^{**}P < 0.01$, versus control.

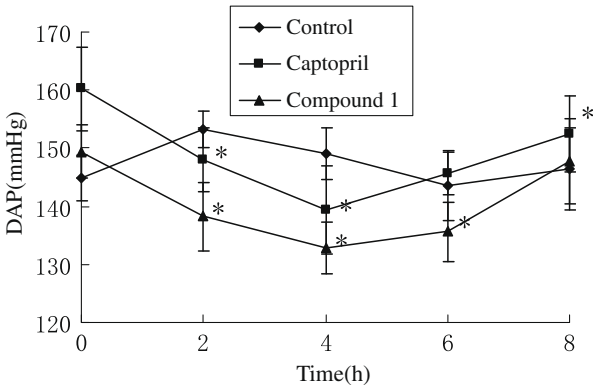

Figure 2. The acute antihypertensive activity of compound **1** in RHRs (DAP, diastolic arterial pressure). Data are presented as mean ± SEM, $n = 8$. Significance indicated by: $^{*}P < 0.05$; $^{**}P < 0.01$, versus control.

In therapeutic antihypertensive tests, the maximum antihypertensive effect on SAP and DAP of compound **1** (100.0 mg/kg/day) and captopril (25.0 mg/kg/day) were also approximately equivalent. RHRs were given compound **1** and captopril by gastic perfusion for 12 days. Both SAP and DAP in compound **1**-treated group were decreased significantly on the second day after treatment, and then were maintained at constant level. Stopped administra-

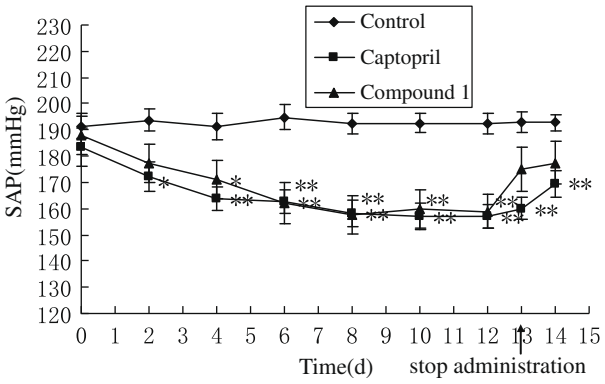

Figure 3. The therapeutic antihypertensive activity of compound **1** in RHRs (SAP, systolic arterial pressure). Data are presented as mean ± SEM, $n = 8$. Significance indicated by: $^{*}P < 0.05$; $^{**}P < 0.01$, versus control.

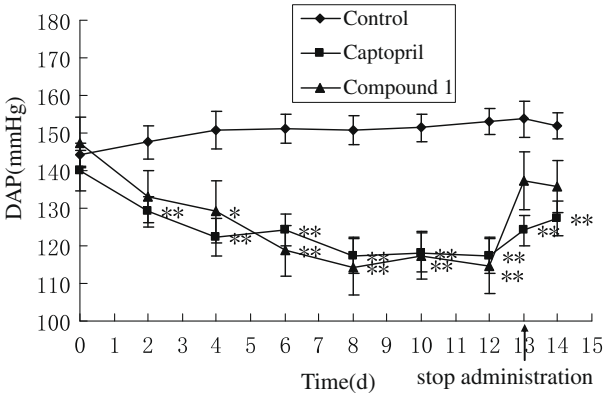

Figure 4. The therapeutic antihypertensive activity of compound **1** in RHRs (DAP, diastolic arterial pressure). Data are presented as mean ± SEM, $n = 8$. Significance indicated by: $^{*}P < 0.05$; $^{**}P < 0.01$, versus control.

Table 1
ACE inhibitory activity of compound **1** in vitro

Level (mol/L)	Restrain rate of captopril (%)	Restrain rate of compound **1** (%)	Restrain rate of DMSO
10^{-4}	94 ± 0.2*	77 ± 12*	
10^{-5}	94 ± 0.3*	61 ± 16*	
10^{-6}	95 ± 0.1*	61 ± 12*	
10^{-7}	97 ± 0.2*	74 ± 11*	
10^{-8}	96 ± 5*	87 ± 9*	
10^{-10}	48 ± 0.1*	44 ± 13*	
10^{-11}	47 ± 0.6*	41 ± 24*	
10^{-12}	42 ± 0.6*	34 ± 15*	
			18 ± 34

($\bar{x} \pm s$, $n = 6$), $^{*}P < 0.05$ versus control.

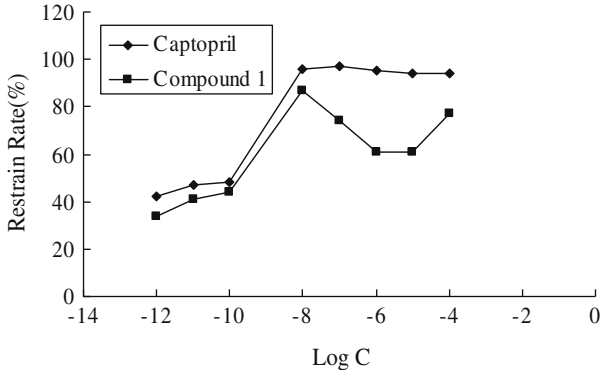

Figure 5. ACE inhibitory activity test of compound **1**.

tion for three days, the blood pressure went up but still in the lower level comparing with the placebo (Figs. 3 and 4).

The preliminary test showed that compound **1** has moderate ACE inhibitory activity in vitro (Table 1 and Fig. 5). In the test, ACE was obtained from pig lung extract.[10] The results showed that, compared with the negative control, the inhibition of ACE by compound **1** increases markedly with the increased concentration of compound **1** from 10^{-12} to 10^{-8} mol/L, which is approximately equivalent to that of captopril. Conversely, the inhibition of ACE by compound **1** decreases with the increased concentration of compound **1** from 10^{-8} to 10^{-5} mol/L, but the inhibitory activity against ACE by captopril has no change under the same concentration. While compared with the negative control, the compound **1**-induced inhibition of ACE increases with the increased concentration between 10^{-5} and 10^{-4} mol/L. This result is interesting and further studies on the mechanism of compound **1** are currently in progress and will be reported in due course.

In summary, the present contribution describes the total syntheses of (±)7,8-dihydroxy-3-methyl-isochromanone-4. The current method presents a very promising synthetic process for compound **1** and its derivatives. The preliminary bioassay showed that compound **1** displays potent antihypertensive activity in renal hypertensive rats. The mechanism studies found that compound **1** has moderate ACE inhibitory activity and beneficial effects in reducing blood pressure, which indicates that ACE is its potential target, or at least one of its acting targets. In view of these properties, (±)7,8-dihydroxy-3-methyl-isochromanone-4 is likely to have an interesting therapeutic potential for the development of more efficient antihypertensive natural drugs, in order to improve the pharmacological treatment of hypertension.

Acknowledgment

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7. *Analytical data for synthetic compound **1**:* Mp 174–176 °C (dec.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.44 (d, 1H, $J = 8.5$ Hz, Ar–H); 6.92 (d, 1H, $J = 8.5$ Hz, Ar–H), 5.05 (d, 1H, $J = 15.5$ Hz, $-CH_2-$), 4.75 (d, 1H, $J = 15.5$ Hz, $-CH_2-$), 4.18 (q, 1H, $J = 6.5$ Hz, –CH–), 1.38 (d, 3H, $J = 6.5$ Hz, $-CH_3$). IR (KBr, cm^{-1}): 3432, 3428, 2987, 1664, 1613, 1558, 1480, 1450, 1394, 1363, 1306, 1256, 1216, 1120, 1074, 951, 908, 825, 788. ESI-MS: 193 $[M-H]^-$. Anal. Calcd for $C_{10}H_{10}O_4\,1/2H_2O$: C, 59.11; H, 5.42; O, 35.47. Found: C, 58.75; H, 5.72; O, 35.53. Analytical data for natural sample **1**: m.p. 174–176 °C (dec.), $[\alpha]_D^{20}$ −7.75 (*c* 0.34, acetone). ^{1}H NMR (CD_3COCD_3, 300 MHz): δ (ppm) 7.43 (d, 1H, $J = 8.5$ Hz, Ar–H); 6.91 (d, 1H, $J = 8.5$ Hz, Ar–H), 5.03 (d, 1H, $J = 15.5$ Hz, $-CH_2-$), 4.75 (d, 1H, $J = 15.5$ Hz, $-CH_2-$), 4.22 (q, 1H, $J = 6.1$ Hz, –CH–), 1.38 (d, 3H, $J = 6.1$ Hz, $-CH_3$). ^{13}C NMR (CD_3COCD_3): δ (ppm) 195.17 (C-4), 170.02 (C-7), 150.58 (C-8), 140.50 (C-10), 130.79 (C-5), 123.34 (C-6), 115.01 (C-9), 78.01 (C-3), 63.30 (C-1), 15.95 (C-11). ESI-MS: 193 $[M-H]^-$. IR (KBr, cm^{-1}): 3432, 3428, 2987, 2844, 1664, 1613, 1480, 1394, 1306, 1220.
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