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Synthesis of *Gingerenone* C and 5-Hydroxy-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4″-hydroxyphenyl)-3-heptanone

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Abstract: The two diarylheptanoids (E)-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4″-hydroxyphenyl) hept-4-en-3-one **1** (*Gingerenone* C) and (±)-5-hydroxy-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4″-hydroxyphenyl)-3-heptanone **2** were synthesized from vanillin **3** and 4-hydroxybenzaldehyde **9**.

Keywords: Diarylheptanoids, (E)-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4″-hydroxyphenyl)hept-4-en-3-one, *Gingerenone* C, (±)-5-hydroxy-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4′-hydroxyphenyl)-3-heptanone, synthesis.

Diarylheptanoids constitute a distinct group of metabolites of natural plant characterized by two aromatic rings linked by a linear seven aliphatic chain. There have been few reports on the biological activities of diarylheptanoids, most of which appearing in the areas of anti-inflammatory, anti-oxidative, superoxide scavenging and anti-hepatotoxic effects[1, 2]. Some of them are used as traditional medicine in Asia[3]. Compound **1** and **2** were firstly isolated from the rhizomes of *Zingiber offical* respectively[4, 5]. So far the synthesis of these two compounds have not been reported yet. Herein, we report the synthesis of these two diarylheptanoids (E)-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4″-hydroxyphenyl)hept-4-en-3-one **1** (*Gingerenone* C) and (±)-5-hydroxy-1-(4′-hydroxy-3′-methoxyphenyl)-7-(4′-hydroxyphenyl)-3-heptanone **2**. The synthetic route is outlined in **Scheme**.

Vanillin **3** was protected with MOMCl following by condensation with acetone to give α, β-unsaturated ketone **5**. Hydrogenation of compound **5** with 5% Pd/C afford compound **6** and **7** in a total yield of 98%. The ratio of **6** to **7** is 1:3. The mixture **6** and **7** without separation was oxidized by PCC under mild conditions to afford unique **7**. MOM protected compound **9** gave compound **10** which was converted to compound **11** by Wittigg reaction using Ph_3P=CHCOOMe. Compound **11** was then reduced by $LiAlH_4$ and hydrogenation with 5% Pd/C to afford compound **13**.

The protection group of MOM is unstable, so before condensation reaction, which should be converted to benzyl group.

The condensation of compound **8** with **15** proceeded successfully in a high yield. In the condensation, LDA was employed which reacted with **8** first, and both C-1 and

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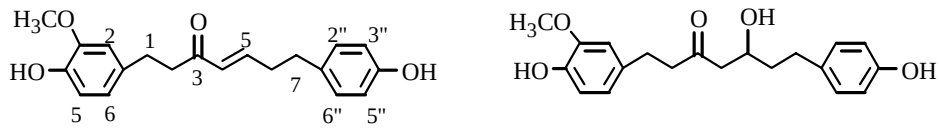
C-3 could be attacked to produce kinetically and thermodynamically controlled products respectively. The kinetically controlled product was the major product, if the reaction proceeded at low temperature.

Debenzylation with 5% Pd/C in the mixture of MeOH and $CHCl_3$(1:1) gave the products **1** and **2** in ratio 2:1. Dehydration of **2** with P-TsOH gave **1**.

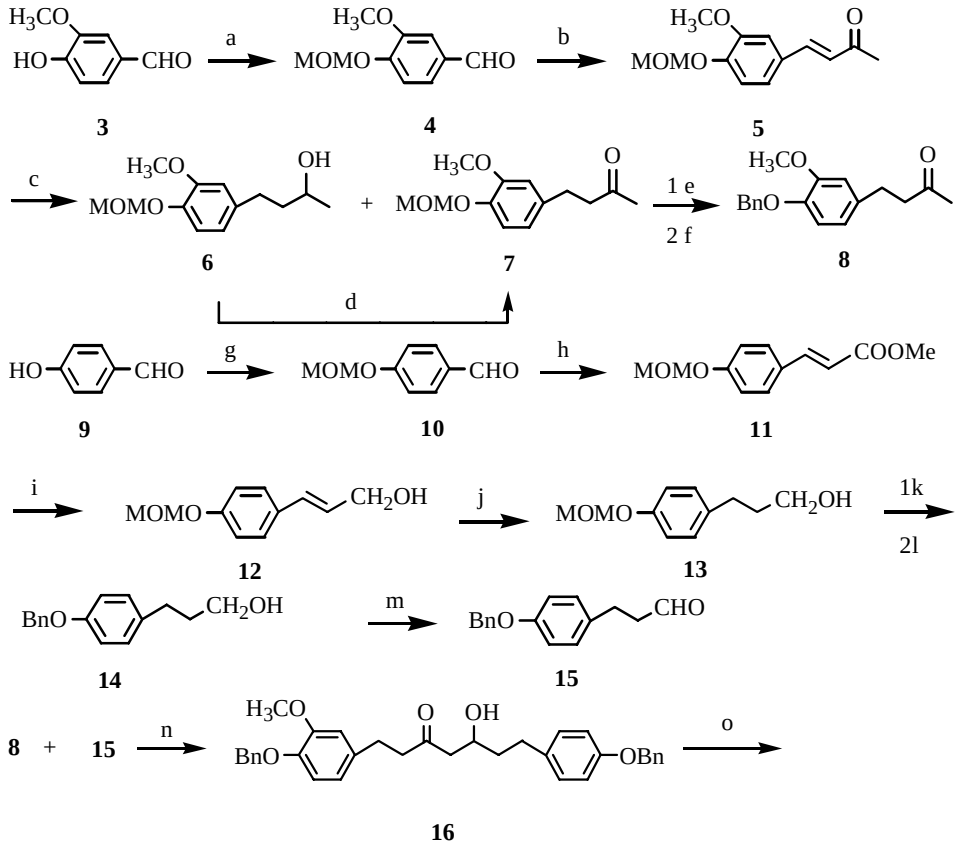
Synthetic compound **2** is racemic, and the absolute structure at C-5 in natural **2** had not been determined[5]. The structure of both synthetic **1** and natural **1**[4] is entgegen(J_{trans}= 15.8 Hz). The spectral data of synthetic compounds **1** and **2** were in accordance with those of literature[4,5,6].

The structures of compound **1** and **2**



1 **2**

Scheme Synthesis route of diarylheptanoids



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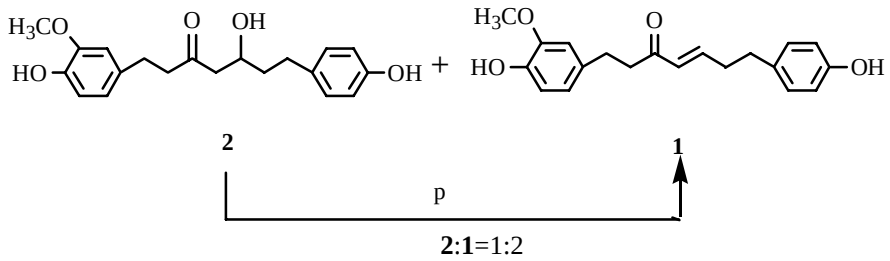

Reagents and conditions: a) MOMCl, K_2CO_3, acetone, 40°C, 3 h, 95%; b) Acetone, 1% NaOH, rt., 1 h, 95%; c) 5% Pd/C, H_2, rt., 24 h, 98%; d) PCC, rt., 5 h, 85%; e) 6mol/L HCl, MeOH, 40°C, 15 min, 95%; f) benzyl bromide, K_2CO_3, 50°C, 10 h, 95%; g) MOMCl, K_2CO_3, acetone, 40°C, 2.5 h, 97%; h) Ph_3P=CHCOOMe, C_6H_6, reflux, 10 h, 98%; i) $LiAlH_4$, ether, rt., 30 min., 90%; j) 5% Pd/C, H_2, rt., 24 h, 98%; k) 6mol/L HCl, MeOH, 40°C, 15 min, 96%; l) benzyl bromide, K_2CO_3, 50°C, 10 h, 97%; m) PCC, rt., 5 h, 87%; n)LDA, THF, -78℃, 15 min, 90%; o) MeOH:$CHCl_3$(1:1), 5% Pd/C, H_2, rt., 24 h, 90%; p) anhydrous CH_3CN:$CHCl_3$(1:1), P-TsOH, 60°C, 30 min., 90%.

References and Notes

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6. **2**: colorless oil. IR(KBr, cm^{-1}) 3390, 1699, 1608,1515. MS (FAB)*m/z* 344(M^+). ESI Positive MS 345.1698$[M+H]^+$, (cacld.345.1697). Natural **2**($[\alpha]_D^{25}=0^o$, C=0.2, EtOH).

^{1}HNMR data of compound **2** ($CDCl_3$, δ ppm, J Hz)

Synthetic **2**(200 MHz)	Natural **2**(400 MHz)
1.59-1.79(m, 2H, H-6)	1.45(m, 1H, 6a)
2.54(d, 2H, J 5.9, H-4)	1.75(m, 1H, 6a)
2.57-2.87(m, 6H, H-1,2,7)	2.50(dd, 1H, J 17.7,7.3, 4a)
3.18(bs, 1H, -OH)	2.57(dd, 1H, J 17.7,3.1, 4b)
3.83 (s, 3H, -OCH_3)	2.60(m, 1H, 7a)
4.03(m, 1H, H-5)	2.71(t, 2H, H-2)
5.47(bs, 1H, -OH)	2.72(m, 1H, 7b)
5.58(bs, 1H, -OH)	2.82(t, 2H, H-1)
6.63(dd, 1H, J 7.8,2.0, H-6′)	3.86(s, 3H, -OCH_3)
6.66(s, 1H, H-2′)	4.02(m, 1H, H-5)
6.73(dd, 2H, J 8.4, 2.0, H-3″, 5″)	6.66(br d, 1H, J 7.9, H-6′)
6.80(d, 1H, J 7.8, H-5′)	6.67(br s, 1H, H-2′)
7.03(dd, 2H, J 8.4, 2.0, H-2″, 6″).	6.75(d, 2H, J 8.5, H-3″,5″)
	6.83(d, 1H, J 7.9, H-5′)
	7.05(d, 2H, J 8.5, H-2″,6″).

1: pale yellow oil. IR(KBr, cm^{-1}) 3396, 1651, 1611, 1513. EIMS 326(100), 205(27), 137(31), 124(26), 107(63). ESI Positive MS 327.1593$[M+H]^+$, (cacld.327.1591).

^{1}HNMR data of compound **1** ($CDCl_3$, δ ppm, J Hz)

Synthetic **1**(200 MHz)	Natural **1**(100 MHz)
2.59-2.73(m, 6H, H-1,6,7)	2.20-2.83(m, 8H, H-1,2,6,7)
2.83(m, 2H, H-2)	3.86(s, 3H, -OCH_3)
3.82(s, 3H, -OCH_3)	6.10(d, 1H, J 16.0, H-4)
5.04(br s, 1H, -OH)	6.50-7.10(m, 8H,H-2′,2″,3″,5,5′,5″,6′, 6″)
5.47(br s, 1H, -OH)	
6.08(d, 1H, J 15.8, H-4)	
6.52(dd, 1H, J 8.8,1.8, H-6′)	
6.66-6.84(m, 5H, H-2′,5′,3″,5″,5)	
7.00(d, 2H, J 8.0, H-2″,6″)	

Due to the difference of solvent $CDCl_3$ the spectrum of –OH of natural compound **1** and **2** hadn't been observed.

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