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Synthesis of (+) 8-O- Cinnamyl- *p*-chlorogoniotriol and its Analogues

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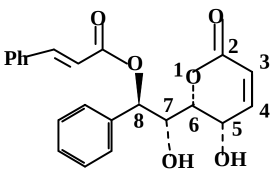
Abstract: (+) 8-O-Cinnamyl-*p*-chlorogoniotriol (*p*-chlorohowiinol A) and its analogues have been synthesized in nine steps from α-D-glucoheptonic-γ-lactone. Pharmacological tests showed that most of the compounds possessed antitumor activities toward tumor cell *in vitro.*

Keywords: Stereoselective synthesis, (+) 8-O-cinnamyl-*p*-chlorogoniotriol (*p*-chlorohowiinol A), antitumor activity, analogues .

Howiinol A **1**[1], a novel lactone isolated from the ethanolic extracts of the root and stem bark of *Goniothamus howii* Merr. (Annoaceae) in our laboratory, has been shown to possess significant antitumor activities toward human tumor *in vitro* and *in vivo* and low toxicity. Recently, we have synthesized **1** and its derivatives with different ester groups



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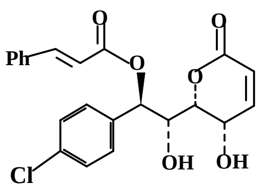
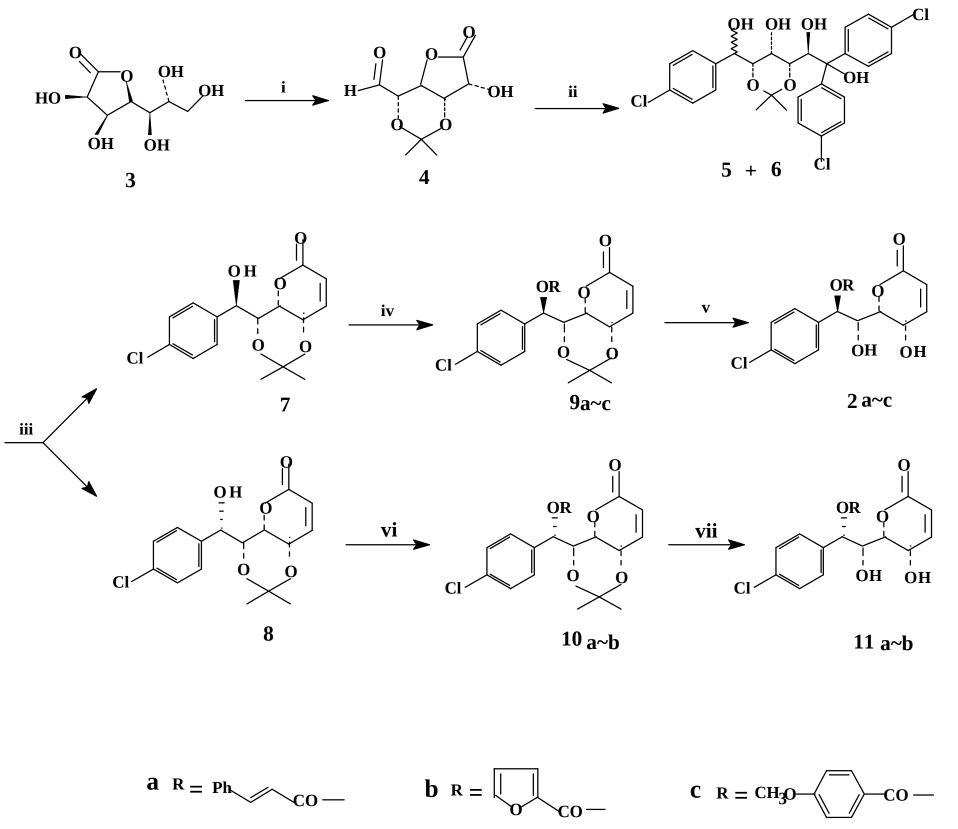


2a

starting from commercially available α-D-glucoheptonic -γ-lactone. In order to find their relationship of structure and activity and to search for drugs with more potent antitumor activity, we have synthesized (+) 8-O-cinnamyl-*p*-chlorogoniotriol (*p*-Chloro-howiinol A) and its analogues. The route is depicted in the **scheme**. In our previous work lactone **3** was transformed into **4** in a yield of 71.3%, by 3 steps[2]. The carbonyl compound **4** reacted immediately with p-Cl-C_6H_4MgBr (Grignard reaction was initiated with I_2 under N_2 , refluxed in THF for 5 h to obtain *p*-Cl-C_6H_4MgBr), giving **5** and **6** (6α-isomer of **5**) in an overall of yield 32.4% (**5**, 18.5%)[3]. Both isomers were difficult to separate. The mixture without further separation was oxidized by sodium periodate followed immediately by Wittig alkenation furnishing the stereoselective products, which were induced to lactonize by catalytic amount of 1.8-diazabicydo-[5.4.0] undec-7-ene-(DBU) in THF at 70~80℃providing the pyrone **7** in 63.8% yield (calculated from **5)**, m.p.

203~4℃, $[\alpha]_D^{28}$ 121.9 (0.11 AcOEt) and **8** (8α-isomer of **7**) in 51.3% yield (calculated

Scheme



Reagents and conditions:
i. 3 steps: Me_2CO, H_2SO_4; 65% AcOH; $NaIO_4$.
ii. *P*-Cl-PhMgX, pure N_2, I_2, reflux.
iii. 3 steps: $NaIO_4$, MeOH-H_2O, room temp., 18 h; ph_3p=$CHCO_2Et$, -15℃, 3 h; cat. DBU; THF, 70~80℃, 24 h.
iv and vi. acid chloride, DMAP, Et_3N, CH_2Cl_2, room temp..
v and vii. 75% aq. AcOH, 80-90℃, 3 h.

from **6**), mp. 197~198℃, $[\alpha]_D^{28}$ -59.1 (C 0.11 AcOEt). Both compounds were easily separated by silica gel chromatography (Rf:**7** 0.23, **8** 0.32, ethyl acetate: petroleum ether, 1:1). The esterification of **7** with cinnamyl chloride gave the ester $\mathbf{9_a}$ in 86.9% yield, m.p. 224~226℃, $[\alpha]_D^{28}$ 111.6 (C 0.10 AcOEt). Acid hydrolysis of the

Table. IR, MS, ^{1}HNMR data of compounds

Comd	IR (KBr, cm^{-1})	EI-MS (m/z, %)	^{1}HNMR (δ ppm, $CDCl_3$)
7	3446, 1708	311 (M^++2－Me, 1), 309 (M^+－Me, 3), 97 (100)	1.32 (3H, s, CH_3), 1.33 (3H, s, CH_3), 3.95 (1H, dd, *J*=1.8, 8.7Hz, 7-H), 4,34 (1H, dd, *J*=1.8, 6.3Hz, 5-H), 4.50 (1H, t, *J*=1.8Hz, 6-H), 5.11 (1H, d, *J*=8.7Hz, 8-H), 6.23 (1H, d, *J*=9.6Hz, 3-H), 6.90 (1H, dd, *J*=6.3, 9.6Hz, 4-H), 7.24~7.49 (4H, m, ph)
8	3496, 1714	311 (M^++2－Me, 1), 309 (M^+－Me, 3), 97 (100)	1.52 (3H, s, CH_3), 1.56 (3H, s, CH_3), 3.62 (1H, t, *J*=1.8Hz, 6-H), 3.85 (1H, dd, *J*=1.8, 8.7Hz, 7-H), 4.19 (1H, dd, *J*=2.1, 6.0Hz, 5-H), 5.14 (1H, d, *J*=9.0Hz, 8-H), 6.18 (1H, d, *J*=9.6Hz, 3-H), 6.80 (1H. dd, *J*=5.7, 9.6Hz, 4-H), 7.35 (2H, dd, *J*=1.5, 6.0Hz, ph), 7.46 (2H, dd, *J*=1.5, 6.0Hz, ph)
9_a	1730, 1737	441(M^++2－Me, 0.2), 439 (M^+－Me, 0.6), 131 (100)	1.33 (3H, s, CH_3), 1.36 (3H, s, CH_3), 4.29 (1H, dd, *J*=1.5. 9.3Hz, 7-H) 4.42 (2H, m, 5-H, 6-H), 6.11 (1H, d, J=9.3Hz, 8-H), 6.26 (1H, d, *J*=9.6Hz, 3-H), 6.65 (1H, d, *J*=15.9Hz, 2'-H), 6.89 (1H, dd, *J*=6.0, 9.6Hz, 4-H), 7.26~7.60 (9H, m, ph), 7.69 (1H, d, *J*=15.9Hz, 3'-H)
9_b	1730, 1716	405 (M^++2－Me, 0.2), 403 (M^+－Me, 0.6), 95 (100)	1.32 (3H, s, CH_3), 1.36 (3H, s, CH_3), 4.35～4.40 (3H, m, 5-H, 6-H, 7-H), 6.18 (1H, d, *J*=9.3Hz, 8-H), 6.24 (1H, J=9.6Hz, 3-H), 6.50 (1H, dd, J=1.8, 3.3Hz, 4'-H), 6.88 (1H, dd, J=5.4, 9.9Hz, 4-H), 7.21 (1H, d, J=3.3Hz, 3'-H), 7.33 (2H, d, J=7Hz, ph), 7.41 (2H, d, J=7.0Hz, ph), 7.54 (1H, d, 7.0Hz, 5'-H)
9_c	1730, 1710	445 (M^++2－Me, 3), 443 (M^+－Me, 9), 135 (100)	1.33 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 4.33～4.41 (3H, m, 5-H, 6-H, 7-H), 6.20 (1H, d, *J*=9.0Hz, 8-H), 6.32 (1H, d, *J*=9.0Hz, 3-H), 6.85～6.92 (3H, m, 4-H, ph), 7.28～7.41 (4H, m, ph), 7.98 (2H, dd, *J*=2.1, 6.9Hz, ph),
10_a	1732, 1710	441 (M^++2－Me, 0.2), 439 (M^+－Me, 0.6), 131(100)	1.48 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.52 (1H, t, J=2.1Hz, 6-H), 4.23 (1H, dd, *J*=1.8, 6.0Hz, 5-H), 4.27 (1H, dd, *J*=1.5, 9.0Hz, 7-H), 6.16 (1H, d, *J*=9.6Hz, 3-H), 6.25 (1H, d, *J*=9.3Hz, 8-H), 6.46 (1H, d, *J*=15.9Hz, 2'-H), 6.82 (1H,dd, *J*=1.6, 9.3Hz, 3-H), 7.33～7.65 (9H, m, ph), 7.73 (1H, d, *J*=15.9Hz, 3'-H)
10_b	1732, 1716	405 (M^++2－Me, 0.2), 403 (M^+－Me, 0.6), 95 (100)	1.45 (3H, s, CH_3), 1.57 (3H, s, CH_3), 3.55 (1H, t, *J*=1.8Hz, 6-H), 4.24 (1H, dd, *J*=1.5, 6.0Hz, 5-H), 4.32 (1H, dd, *J*=1.8, 9.0Hz, 7-H), 6.16 (1H, d, *J*=9.0Hz, 8-H), 6.34 (1H, d, *J*=9.9Hz, 3-H), 6.50 (1H, dd, *J*=1.8, 3.3Hz, 4'-H), 6.78 (1H, dd, *J*=6.0, 9.3Hz, 4-H), 7.19 (1H, d, *J*=3Hz, 3'-H), 7.25～7.57 (5H, m, ph, 5'-H)
11_a	1730, 1715	396 (M^+－H_2O, 1), 131 (100)	4.06 (1H, t, *J*=2.7, 6-H), 4.32 (1H, dd, *J*=1.5, 6.0Hz, 5-H), 4.46 (1H, dd, *J*=3.6, 6.9Hz, 7-H), 6.06 (1H, d, *J*=9.6Hz, 3-H), 6.27 (1H, d, *J*=6.6Hz, 8-H), 6.55 (1H, d, *J*=15.9Hz, 3'-H), 6.94 (1H, dd, *J*=6.0, 9.6Hz, 4-H), 7.32～7.51 (9H, m. ph), 7.65 (1H, d, *J*=15.9Hz, 3'H)
11_b	3440,1712	378 (M^+, 1), 361 (M^+＋1－H_2O, 6), 95 (100)	4.10 (1H, t, *J*=1.8Hz, 6-H), 4.34 (1H, dd, *J*=1.8, 6.0Hz, 5-H), 4.52 (1H, brs, 7-H), 6.08 (1H, d, *J*=9.3Hz, 3-H), 6.34 (1H, d, *J*=6.9Hz, 8-H), 6.53 (1H, brs, 4'-H), 6.89 (1H, dd, *J*=6.0, 9.3Hz, 4-H), 7.32～7.59 (6H, m, ph, 3'-H, 5'-H)

2_a	3386, 1730, 1667	396 (M^+－H_2O, 1), 131 (100)	4.40 (1H, dd, *J*=2.4, 6.0Hz, 5-H), 4.47 (1H, t, *J*=2.7Hz, 6-H), 4.50 (1H, dd, *J*=3.6, 7.5Hz, 7-H), 6.03 (1H, d, *J*=7.5Hz, 8-H), 6.12 (1H, d, *J*=9.6Hz, 3-H), 6.44 (1H, d, *J*=15.9Hz 2'-H), 7.00 (1H, dd, *J*=4.2, 9.6Hz, 4-H), 7.31～7.54 (9H, m, ph), 7.72 (1H, d, *J*=15.9Hz, 3'-H)
2_b	3338,1716	378 (M^+, 1), 361 (M^+＋1－H_2O, 6), 95 (100)	4.42 (1H, dd, *J*=2.7, 6.0Hz, 5-H), 4.46 (1H, t, *J*=2.7Hz, 6-H), 4.57 (1H, dd, *J*=3.6, 7.5Hz, 7-H), 6.06 (1H, d, *J*=7.5Hz, 8-H), 6.10 (1H, d, *J*=9.6Hz, 3-H), 6.51 (1H, dd, *J*=1.8, 3.3Hz 4'-H), 7.99 (1H, dd, *J*=6.0, 9.6Hz, 4-H), 7.36 (2H, d, *J*=6.6Hz, ph), 7.40 (1H, m, ph, 3'-H)
2c	3319,1697	401 (M^+ ＋ 1 － H_2O, 0.1), 225 (65), 135 (100)	3.84 (3H, s, CH_3O), 4.39 (1H, dd, *J*=2.4, 5.7Hz, 5-H), 4.49 (H, t, *J*=2.7Hz, m, 6-H), 4.56 (1H, dd, *J*=2.7, 6.6Hz, 7-H), 6..12 (1H, d, *J*=9.9Hz, 3-H), 6.20 (1H, d, *J*=6.6Hz, 8-H), 6.85～6.94 (3H, m, 4-H, ph), 7.29～7.46 (4H, m, ph), 7.95～8.02 (2H, dd, *J*=2.3 , 6.9Hz, ph)

acetone protecting group in compound **9_a** gave the target compound **2_a** , in 71.5% yield, 168~169℃, $[\alpha]_D^{28}$ 71.2 (C 0.13 AcOEt). Compounds **$2_{b\sim c}$** and **$11_{a\sim b}$** were

Synthesized by the same method. The IR, MS, ^{1}HNMR data of (+)-8-O-cinnamyl-*p*-chloro-goniotriol (*p*-Chloro-howiinol A) and its analogues are given in the **Table**. Antitumor activities of ten compounds **$2_{a\sim b}$**, **7**, **8**, **$9_{a\sim b}$**, **$10_{a\sim b}$** and **$11_{a\sim b}$** were screened *in vitro* by MTT methods. The compounds **$2_{a\sim b}$**, **7**, **8** and **$9_{a\sim b}$** were similar to Howiinol A in the inhibition against A2783, HCF8, Bel 7402, KB (IC_{50} 2.22×10^{-6}mol/L~9.23×10^{-6}mol/L), but antitumor activities of **$11_{a\sim b}$** were very low. Compounds **$10_{a\sim b}$** showed to possess significant antitumor activities toward human tumor cell (IC_{50} 0.74×10^{-6}mol/L~1.76×10^{-6}mol/L). The antitumor activities of **$10_{a\sim b}$** were slightly better than that of Howiinol A..

Acknowledgments

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References and Notes

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4. selective physical data (mp ℃, $[\alpha]_D^{28}$):
   2_b 175～176, 98.2(c 0.07); **2_c** 221～222, 75.0(c 0.1); **9_b** 228～229, 81.6(c 0.09); **9_c** 153～154,91.4(c 0.11); **10_a** 205～206, -54.1(c 0.09); **10_b** 213～214, -19.7(c 0.09); **11_a** 155～156, -52.8(c 0.08); **11_b** 159～160, -13.4(c 0.08).

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