Two New 7-Geranyloxycoumarins from the Bark of Aegle Marmelos, an Indonesian Medicinal Plant

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Two new 7-geranyloxycoumarins, chloromarmin and aeglin, were isolated from the bark of *Aegle marmelos*, and their structures were assigned to be 7-(7-chloro-6*R*-hydroxy-3,7-dimethyl-2-octenyloxy)coumarin (**1**) and 7-[6*R*-(β-D-glucopyranosyloxy)-4*R*,7-dihydroxy-3,7-dimethyl-2-octenyloxy]coumarin (**2**), respectively.

In the course of studies on the constituents of the bark of *Aegle marmelos* CORREA, an Indonesian folk medicine (Indonesian name "Maja", Rutaceae), we have isolated four 7-geranyloxycoumarins, epoxyaurapten,[1] marmin,[2] and two new coumarins named chloromarmin and aeglin, respectively. Here we report the structural elucidation of chloromarmin (**1**) and aeglin (**2**) along with the synthesis of aeglin.

The methanol extract of the air-dried bark (2.2 kg, collected at Lalantuka, Flores Island) was partitioned between AcOEt and water. The water soluble portion was further extracted with n-BuOH. The AcOEt soluble portion was subjected to column chromatography on silica gel (hexane-AcOEt) repeatedly to afford chloromarmin (**1**, 0.033% from the dried bark) together with epoxyaurapten (**3**, 0.049%) and marmin (**4**, 0.099%). Repetition of column chromatography [silica gel($CHCl_3$-MeOH-H_2O)] of the n-BuOH soluble portion followed by HPLC (LiChrosorb RP-18, H_2O-MeOH) furnished aeglin (**2**, 0.021%) (Figure 1).

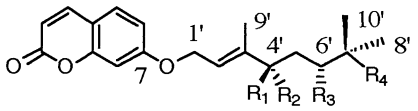

Figure 1. Structures of Geranyloxycoumarins
1: R_1=R_2=H, R_3=OH, R_4=Cl
2: R_1=R_4=OH, R_2=H, R_3=O-β-D-glucopyranosyl
3: R_1=R_2=H, R_3= -O- =R_4
4: R_1=R_2=H, R_3=R_4=OH
5: R_2=H, R_1=R_3=R_4=OH
6: R_1=H, R_2=R_3=R_4=OH

Chloromarmin (**1**), colorless oil, $[\alpha]^{24}_D$ +27.3 ° (c 0.85, EtOH), $C_{19}H_{23}O_4Cl$, showed absorption bands due to hydroxy group(3560 cm^{-1}), lactone carbonyl (1730 cm^{-1}), and benzene ring (1620 cm^{-1}) in the IR spectrum. The ^{1}H-NMR(300MHz, $CDCl_3$) spectra of **1** showed signals ascribed to five coumarin protons [δ 6.25 (d, J=9.5 Hz, 3-H), 6.80 (d, J=2.4 Hz, 8-H), 6.85 (dd, J= 2.4, 8.4 Hz, 6-H), 7.37 (d, J= 8.4 Hz, 5-H), 7.65 (d, J= 9.5 Hz, 4-H)], one methylene group [δ 4.61 (d, J= 6.6 Hz, 1'-H_2)] adjacent to oxygen function, two methylene groups [δ 2.17 (ddd, J= 6.6, 9.2, 15.3 Hz, 4'-H_a), 2.40 (ddd, J= 4.8, 9.6, 15.3 Hz, 4'-H_b), 1.54 (m, 5'-H_a), 1.77 (m, 5'-H_b)], one proton of trisubstituted olefin [δ 5.33 (br.t, J= 6.6 Hz, 2'-H)]. one hydroxymethylene proton [δ 3.49 (d, J= 10.2 Hz, 6'-H)], and three methyl groups [δ 1.55, 1.59 (both s, 8'-Me, 10'-Me), 1.78 (br.s, 9'-Me)] and the ^{13}C NMR (75 MHz, Table 1) of **1** showed carbon signals due to a 7-hydroxycoumarin and a dihydrogeranyl moiety, which were completely analyzed by ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY. Furthermore, Chloromarmin (**1**) showed characteristic fragment ions at m/z 315 [M^+-HCl], 273[M^+-C_3H_6Cl], 189 [M^+-$C_9H_5O_3$ (umbelliferone)], and 162 [M^+-$C_{10}H_{17}OCl$]. Treatment of **1** with pyridine-DMAP afforded epoxyaurapten (**3**) (77%), which furnished marmin (**4**) (81%) on treatment with 5% aq. H_2SO_4-THF. Consequently, the absolute configuration of 6'-hydroxyl function can be assigned to be *R*, the same as those in epoxyaurapten (**3**) and marmin (**4**), and the absolute structure of **1** was determined to be depicted in Figure 1.

Table 1. C-13 Chemical shifts (δ in ppm) of chloroarmin (**1**), aeglin (**2**), and the triols **5** and **6**

C	1	6	5	2	
-2	161.3	163.4	163.4	160.9	106.2(C-1")
-3	113.0	114.4	114.5	113.2	78.5(C-2")
-4	143.3	145.6	145.4	143.9	75.4(C-3")
-5	128.7	130.4	130.4	129.5	71.5(C-4")
-6	113.2	114.0	114.0	113.2	78.4(C-5")
-7	162.0	163.7	163.8	162.5	62.4(C-6")
-8	101.6	102.5	102.5	101.8	
-9	155.8	157.1	157.1	156.3	
-10	112.5	113.3	113.3	112.8	
-1'	65.4	66.3	66.5	65.8	
-2'	119.0	122.3	119.8	118.3	
-3'	141.9	145.8	145.8	145.9	
-4'	36.3	73.4	73.6	71.4	
-5'	29.1	36.8	38.1	38.6	
-6'	78.3	77.0	74.0	87.7	
-7'	76.0	77.8	75.8	71.9	
-8'	29.3	25.8	25.6	26.8	
-9'	16.8	11.7	13.1	13.3	
-10'	27.2	24.7	25.1	25.1	

1 in deuteriochloroform; **2** in deuteriopyridine; **5** and **6** in tetradeuteriomethanol.

Aeglin (**2**), mp 218-219℃ (crystallized from $CHCl_3$-MeOH-H_2O), $[\alpha]^{24}_D$ +25.9° (c 0.63, EtOH),$C_{25}H_{34}O_{11}$, showed absorption bands due to hydroxyl group (3600-3100cm^{-1}), lactone carbonyl (1730cm^{-1}), and benzene ring (1615 cm^{-1}) in the IR spectrum. The ^{1}H NMR (300 MHz, C_5D_5N) spectra of **2** showed signals ascribed to five coumarin protons [δ 6.30 (d, J= 9.5 Hz, 3-H), 6.92 (d, J= 8.8 Hz, 6-H), 6.94 (s, 8-H), 7.37 (d, J= 8.8 Hz, 5-H), 7.66 (d, J= 9.5 Hz, 4-H)], one methylene group [δ 4.73 (d, J= 6.4 Hz, 1'-H_2)] adjacent to oxygen function, one methylene group [δ 2.04 (m, 5'-H_2)], one proton of trisubstituted olefin [δ 5.27 (br.t, J= 6.0 Hz, 2'-H)], one hydroxymethylene proton [δ 4.46 (br.d, J= 1.8 Hz, 6'-H)], three methyl groups [δ 1.35, 1.43 (both s, 8'-H_3, 10'-H_3), 1.85 (br.s, 9'-H_3)], and one anomeric proton [δ 5.16 (d, J= 7.2Hz)], and the ^{13}C NMR (75MHz, Table

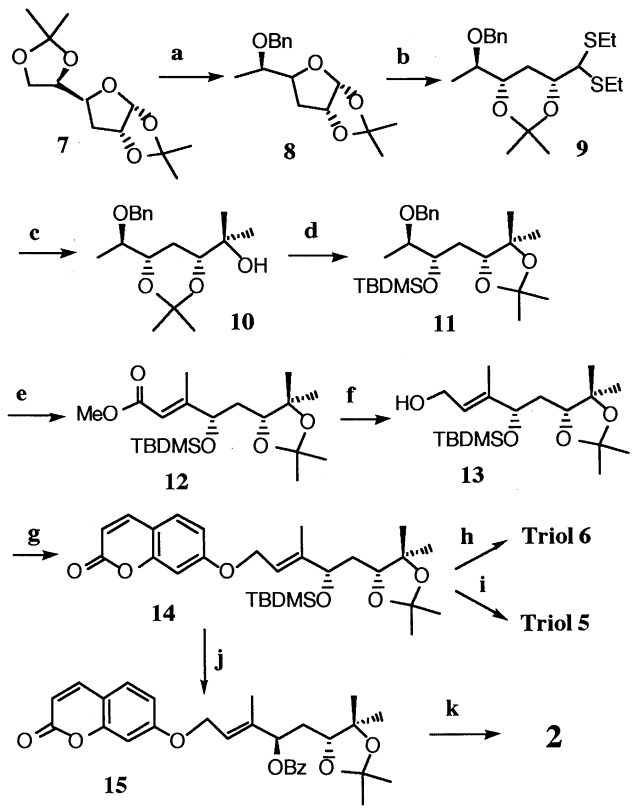

Figure 2. Synthesis of Aeglin (**2**) and Triols **5** and **6**.
a) 1) 80%AcOH; 2)TsCl, Py, 94% ; 3)$LiAlH_4$,THF, 90%; 4)NaH, BnBr, Bu_4NI, THF, r.t, 82%. **b)** 1) 2M HCl aq; EtSH, THF, r.t., quant.; 3) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2, 0°, 94%. **c)** 1) MeI, $NaHCO_3$,(1:1)-H_2O-THF, 98%; 2) MeLi, THF, -78°, 78%; 3) Swern oxidn., 94%; 4) MeLi, THF, -78°, 99%. **d)** TsOH, acetone, r.t.; TBDMSCl, imidazole, DMF, 0°, 74%. **e)** 1) H_2, Pd-C, $NaHCO_3$, EtOH, r.t., 83%; 2) Swern oxidn.; 3) $MeOCOCH_2PO(OMe)_2$, BuLi, THF. **f)** DIBAL-H, toluene, 80% from **11**. **g)** 1) Ph_3P, CBr_4, CH_2Cl_2, 98%; 2) 7-Hydroxycoumarin, NaH, DMF, 49%. **h)** 2M HCl aq, 73%. **i)** 1) Bu_4NF, AcOH, THF, r.t., 93%; 2) Ph_3P, AcOH, DEAD, THF, r.t., 99%; 3) 4M NaOH aq-MeOH; conc HCl-MeOH, 63%. **j)** 1) Bu_4NF, AcOH, THF, r.t., 93%; 2) Ph_3P, BzOH, DEAD, THF, r.t., 99%. **k)** 1) 2M HCl aq, THF, 85%; 2) **16**, $BF_3 \cdot Et_2O$, 36%; 3) 10%KOH-MeOH; Dowex-50W H^+, 66%.

I) of **2** showed carbon signals due to 7-hydroxycoumarin, a dihydro-geranyl moiety, and a hexose moiety, which were completely analyzed by ^1H-^1H COSY and ^1H-^{13}C COSY. Methanolysis of **2** with 9% HCl-MeOH provided the triol **5** and methyl D-glucopyranoside. Treatment of **2** with a cellulase also gave **5** and D-glucose. The location at 6'-position of the glycosidic linkage in **2** was confirmed by the glycosidation shifts observed in the ^{13}C NMR spectra of **2** as compared with **5** for signals assignable to C-6'(+13.7ppm) and C-5'(+0.5ppm), and by the COLOC experiment of **2** which exhibited the presence of a characteristic cross-peak between the anomeric proton (1"-H) and the hydroxymethylene proton (6'-H). The coupling constant observed for the anomeric proton (1"-H, J= 7.2Hz) in ^1H NMR spectrum of **2** also indicated the β-glycoside linkage for the D-glucose moiety. Based on these evidences, the structure of **2** was determined except the absolute configuration of the dihydrogeranyl moiety. By analogy with the absolute configuration of **1**, **3**, and **4**, the carbon atom in the 6'-positin in **5** (hence, in **2**) was expected to have *R*-configuration. Accordingly, the synthesis of the triols **5** and **6** via the *t*-butyldimethylsilyl ether **14** was attempted utilizing the absolute configuration of carbons in 2- and 4-positions of D-glucose.

3-Deoxy-1,2:5,6-di-O-isopropylidene-D-glucofuranose[3] (**7**) was converted into the triols **5** and **6** as shown in Figure 2. One-step dimethylation of a methyl ester derived by oxidation of the aldehyde by MeLi afforded **10** with less satisfactory results, therefore, stepwise dimethylation of aldehyde into **10** via ketone was adopted. The *E* geometry of the methoxycarbonyl function of **12** was ascertained by consideration of the mechanism of Horner-Emmons reaction and furthermore by ^{13}C NMR analysis. The inversion of the configuration at 4'-position in the *t*-butyldimethylsilyl ether **14** by Mitsunobu reaction followed by hydrolyses afforded the 4'*R*,6'*R*-triol **5**, which showed ^{13}C NMR spectrum (Table 1) and specific rotation value[$[\alpha]^{24}_D$+16.0° (c 1.62, MeOH)] identical with those of the triol **5** [$[\alpha]^{24}_D$ +16.0° (c 0.35, MeOH)] derived from **2**, whereas the 4'*S*,6'*R*-triol **6** prepared from **14** showed ^{13}C NMR spectrum (Table 1) and specific rotation value[$[\alpha]^{24}_D$ +22.1° (c 1.80, MeOH)] different from those for the triol **5** derived from natural aeglin (**2**). Thus, the absolute structure of **2** was confirmed as shown in Figure 1. Therefore, **14** was converted into the 4'*R*-benzoate **15**, which gave aeglin **2** by treatment with 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetimidoyl-D-glucopyranose (**16**) and boron trifluoride etherate followed by alkaline hydrolysis. Synthetic **2** thus obtained was indistinguishable by $[\alpha]_D$, ^1H NMR, ^{13}C NMR, IR, EI-MS from natural **2**.

References and Notes

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