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Chrysograyanone, A Novel Chromone Derivative from *Chrysosplenium grayanum* MAXIM.

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Abstract: A novel chromone derivative, chrysograyanon (**1**), has been isolated from fresh whole plant of *Chrysosplenium grayanum* MAXIM. (Saxifragaceae) and its structure was determined to be 3,7-dimethoxy-5-hydroxy-2-(4-methoxy-1β,5α-dihydroxy-2-oxo-5β-methoxycarbonylcyclopent-3-enyl)-chromone (**1**) on the basis of spectroscopic evidences and X-ray analysis.

In the previous papers,[1,2] we reported the isolation of two new flavonols[1] and a cytotoxic principle[2] from the MeOH extract of the fresh whole plant of *Chrysosplenium grayanum* MAXIM. (Saxifragaceae) and their cytotoxic activities and antitumor effects of the principle. In a continuing investigation , we have isolated a novel chromone derivative, named chrysograyanon (**1**). This paper deals with the structure elucidation of **1**.

The 1% MeOH/$CHCl_3$ eluent from the column chromatography of the $CHCl_3$-soluble fraction of the MeOH extract[1,2] was further chromatographed on a silica gel column and elution with EtOAc/*n*-hexane mixture gave compound **1**.

Chrysograyanon (**1**), colorless prisms, mp 231-232° C, $[\alpha]_D^{20}$ +20.0° (*c*, 1.0, pyridine), showed a positive $FeCl_3$ reaction and a positive flavone reaction[3]. The UV spectrum of **1** in MeOH exhibited absorptions at 247 (log ε=4.34), 296 (3.92) and 330 nm (sh, 3.82), and on addition of $AlCl_3$/HCl a significant bathochromic shift was observed,[4),5] though a shift was not observed on addition of NaOAc. The IR spectrum of **1** showed absorption bands at 3460 (OH), 3340 (OH), 1730 (ester CO), 1710 (ketone CO), 1660 (α,β-unsaturated CO), 1620 (benzene ring), 1600 (double bond), and 1230 cm^{-1} (ester). The EI-MS of **1** exhibited the molecular ion (M^+) peak at *m/z* 422 together with strong fragment peaks at *m/z* 363 (M-COOMe) and 167 ($C_8H_7O_4^+$) which may be formed by retro-Diels Alder fragmentation from A-ring. The Molecular formula was determined to be $C_{19}H_{18}O_{11}$ (422.0890, Calcd 422.0848) by high resolution EI-MS analysis. Acetylation of **1** with Ac_2O and pyridine gave a monoacetate (**1a**) , mp 230°C, EI-MS *m/z* 464 (M^+).[6]

The ^{1}H-NMR spectrum of **1** in DMSO-d_6 showed signals due to three hydroxyl protons at δ 12.44 (5-OH), 6.99, and 6.78 ppm, a pair of *meta*-coupled aromatic protons (d, *J*=1.7 Hz) at δ 6.56 and 6.37 ppm, an isolated olefinic proton at δ 5.83 ppm, and four methoxyls at δ 3.91, 3.87, 3.71 and 3.61 ppm. (Table 1)

The ^{13}C-NMR spectrum[7] of **1** exhibited nineteen signals including four methoxyls at δ 52.34 (q, 4'-OMe), 56.04 (q, 7-OMe), 59.23 (q, 3-OMe), and 59.86 ppm (q, 6'-OMe) and three carbonyls at δ 177.85 (s, C-4), 182.57 (s, C-6'), and 195.25 ppm (s, C-2'). The ^{13}C-signals at δ 92.21 (d), 98.88 (d), 105.54 (s), 139.26 (s), 156.40 (s), 156.77 (s), 160.86 (s), and 165.06 ppm (s) were attributed to C-8, C-6, C-10, C-3, C-2, C-9,

Table 1. 2D-NMR Data of Chrysograyanon (1)

Positions	Chemical shifts		Observed correlated carbons	
	^1H	^{13}C	LRCH (J=10 Hz)	LSPD
2		156.40 (s)		
3		139.26 (s)		
4		177.85 (s)		
5		160.86 (s)		
6	6.37 (1H, d)	97.88 (d)	5, 7, 8, 10	5, 8, 10
7		165.06 (s)		
8	6.56 (1H, d)	92.21 (d)	6, 7, 9, 10	6, 9, 10
9		156.77 (s)		
10		105.54 (s)		
1'		84.14 (s)		
2'		196.25 (s)		
3'	5.38 (1H, s)	104.76 (d)	1', 2'*, 5'	1', 5'
4'		169.18 (s)		
5'		84.25 (s)		
6'		182.57 (s)		
5-OH	12.44 (1H, s)		5, 6, 10	5, 6, 10
1'-OH	6.99 (1H, s)		1'	1', 5'
5'-OH	6.78 (1H, s)		4', 5'*, 6'	1', 4', 5', 6'
3-OMe	3.61 (3H, s)	59.23 (q)	3	3
7-OMe	3.87 (3H, s)	56.04 (q)	7	7
4'-OMe	3.71 (3H, s)	52.34 (q)	4'	4'
6'-OMe	3.91 (3H, s)	59.86 (q)	6'	6'

* observed at J=6 Hz.

C-5, and C-7 on the chromone skeleton,[8] respectively, and they were indicative of that 1 has 5-hydroxy-3,7-dimethoxychromone skeleton.[8]

The other ^1H- and ^{13}C-signals were analyzed with the aid of long rang C-H (LRCH) cosy, long rang selective proton decoupling (LSPD), and heteronuclear multiple bond connectivity (HMBC) methods. (Table 1)

In the HMBC spectrum of **1**, the ^1H-signal at δ 6.99 ppm (1'-OH) showed significant long-rang correlations with the ^{13}C-signals at δ 84.14 (C-1'), 156.40 (C-2), and 196.25 ppm (C-2'), while the ^1H-signal at δ 6.78 ppm (5'-OH) showed correlations with the signals at δ 83.25 (C-5'), 169.18 (C-4'), and 182.57 (C-6'), ppm. On the other hand, the ^1H-signal at δ 5.83 ppm (3'-H) showed correlations with the signals at δ 83.25, 84.14, and 196.25 ppm.

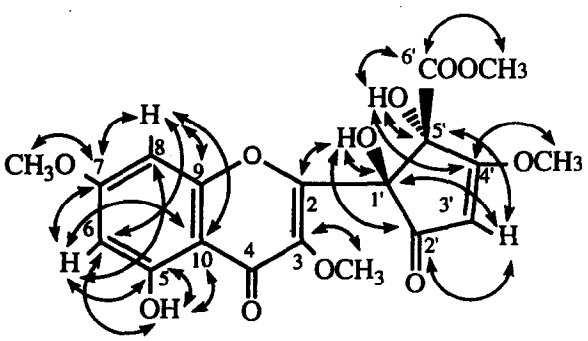

Fig. 1. Significant Multiple-bond connections obserbed in the HMBC Spectrum of **1**

The signal at δ 6.78 ppm also showed significant long-range correlation with the ^{13}C-signal at δ 84.14 ppm in LSPD experiment.The significant multiple-bond correlations obseved in the HMBC spectrum are shown by arrows in Fig. 1, and those observed in LRCH cosy and LSPD spectra are shown in Table 1.

From the foregoing evidence, the planar structure of **1** was established to be 3,7-dimethoxy-5-hydroxy-2-(4-methoxy-1,5-dihyroxy-2-oxo-5-methoxycarbonylcyclopent-3-enyl)-chromone (**1**).

In oder to clarify stereochemistry of 1'- and 5'-positions, we attemped to examine a single crystal X-ray analysis of **1**. The X-ray analysis[9] showed same planar structure for **1** established by the 2D-NMR method, and simultaneously showed the hydroxyl group at the C-1' position to be in β-configuration, and the methoxycarbonyl group at the C-5' position to be in β-configrations.

The crystal structure of **1** is illustrated in Fig. 2, and the fractional atomic corrdinates and the temperature factors for non-hydrogen atoms of **1** is shown in Table 2.

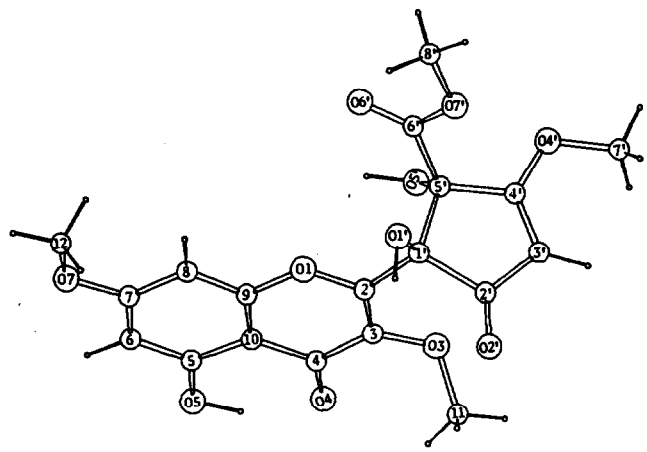

Fig. 2. Crystal structure of chrysograyanon (**1**)

Thus, the structure of chrysograyanon (**1**) was determined to be 3,7-dimethoxy-5-hydroxy-2-(4-methoxy-1β,5α-dihydroxy-2-oxo-5β-methoxycarbonylcyclopent-3-enyl)-chromone (**1**).

Our present result provide the first example of a chromone having a cyclopentenyl group at the C-2 position, which is unique in the structural feature. The cytotoxic activity of **1** is currently under investigation.

References and Notes

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2. Arisawa, M.; Bai, H.; Shimizu, S.; Koshimura, S.; Tanaka, M.;.Sasaki, T.; Morita, N. *Chem. Pharm. Bull.* **1992**, submitted for publication.
3. Colored yellow with Mg+HCl in MeOH solution.
4. Mabry, T. J.; Markham, K. R.; Thomas, M. B. *The Systematic Identification of Flavonoids*; Springer-Verlag, New York, 1970, pp. 33-164.
5. UVλ max (MeOH+AlCl$_3$/HCl) nm 268, 314, 380.
6. EI-MS *m/z* 464 (M^+), 422, 405, 390, 377, 363, 345, 314, 249, 167. ^{1}H-NMR (DMSO-d_6) δ 2.42 (3H, s, OAc), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 3.98 (3H, s,OMe), 5.78 (1H, s, 3'-H), 6.57 (1H, d, *J*=2.3 Hz, 6-H), 6.69 (1H, d, *J*=2.3 Hz, 8-H). ^{13}C-NMR (DMSO-d_6) δ 196.39 (C-2'), 182.43 (C-6'), 171.80 (C-4), 169.36 (C-4'), 168.77 (O$\underline{C}$OCH$_3$), 162.89 (C-7), 157.61 (C-2), 154.19 (C-9), 149.78 (C-5), 140.93 (C-3), 110.54 (C-10), 108.26 (C-6), 104.98 C-

3'), 98.85 (C-8), 84.17 (C-1'), 83.26 (C-5'), 59.28 (OMe-6'), 58.93 (OMe-3), 56.43 (OMe-7), 52.45 (OMe-4'), 20.91 ($OCO\underline{C}H_3$).

7. Multiplicities of ^{13}C-signals were determined by means of DEPT method, and are indicated as s, d, and q.
8. Harborn, J. B.; Marbry, T. J. The Flavonoids: Advances in Research; Chapman and Hall Ltd, London, New York, 1982, pp. 19-134.
9. Crystal data: $C_{19}H_{18}O_{11}$, Mw=422.34, orthorhombic, Pbcn; a=16.485 (4), b=10.589 (2), c=21.11 (1) Å, V=3685 (1) $Å^3$, Z=8, Dcalcd=1.522 g/cm^3. Intensity data were collected within 2θ <120° by using graphaite monochromated Cu Kα radiation (λ=1.54178 Å) at T=285K on a Rigaku AFC5-RU. Absorption correction was not applied [crystal size: 0.3×0.2×0.2 mm, μ(Cu Kα)=10.5 cm^{-1}]. The structure was solved by direct methods and refined by block-diagonal least-squares methods to R=0.052, wR=0.066 for 2253 independent reflections [Fo>3σ(Fo)], using KPPXRAY software in Data Processing Center of Kyoto University.

Table 2. Atomic Coordinates and Equivalent Isotopic Temperature Factors for Non-hydrogen Atoms of Chrysograyanon (1)

atom	x	y	z	Ueq
C-2	0.0431 (1)	0.0116 (3)	0.1530 (1)	0.035 (1)
C-3	0.1054 (2)	-0.0588 (3)	0.1739 (1)	0.037 (1)
C-4	0.0978 (2)	-0.1950 (3)	0.1803 (2)	0.041 (1)
C-5	0.0017 (2)	-0.3763 (3)	0.1675 (2)	0.046 (1)
C-6	0.0751 (2)	-0.4206 (3)	0.1533 (2)	0.049 (1)
C-7	-0.1325 (2)	-0.3358 (3)	0.1353 (2)	0.045 (1)
C-8	-0.1203 (2)	-0.2057 (3)	0.1295 (2)	0.042 (1)
C-9	0.0432 (2)	-0.1654 (3)	0.1446 (1)	0.038 (1)
C-10	0.0190 (2)	-0.2451 (3)	0.1649 (2)	0.089 (1)
C-11	0.2112 (2)	-0.0065 (4)	0.2461 (2)	0.051 (1)
C-12	0.2757 (2)	-0.3062 (4)	0.1147 (2)	0.062 (1)
O-1	0.0307 (1)	-0.0383 (2)	0.1384 (1)	0.039 (1)
O-3	0.1795 (1)	-0.0027 (2)	0.1819 (1)	0.041 (1)
O-4	0.1561 (1)	-0.2629 (2)	0.1965 (1)	0.058 (1)
O-5	0.0599 (2)	-0.4586 (2)	0.1845 (1)	0.062 (1)
O-7	0.2088 (1)	-0.3888 (2)	0.1233 (1)	0.055 (1)
C-1'	0.0455 (2)	0.1515 (3)	0.1390 (1)	0.034 (1)
C-2'	0.1058 (2)	0.2267 (3)	0.1804 (1)	0.037 (1)
C-3'	0.1597 (2)	0.2973 (3)	0.1406 (2)	0.040 (1)
C-4'	0.1415 (2)	0.2754 (3)	0.0802 (1)	0.035 (1)
C-5'	0.0757 (2)	0.1783 (3)	0.0693 (1)	0.033 (1)
C-6'	0.0039 (2)	0.2214 (3)	0.0288 (1)	0.034 (1)
C-7'	0.2406 (2)	0.4119 (4)	0.0383 (2)	0.054 (1)
C-8'	0.0813 (2)	0.3894 (3)	0.0001 (2)	0.051 (1)
O-1'	0.0322 (1)	0.2057 (2)	0.1465 (1)	0.039 (1)
O-2'	0.1007 (1)	0.2311 (2)	0.2379 (1)	0.049 (1)
O-4'	0.1747 (1)	0.2338 (2)	0.0275 (1)	0.044 (1)
O-5'	0.1123 (1)	0.0732 (2)	0.0402 (1)	0.036 (1)
O-6'	-0.0366 (1)	0.1478 (2)	-0.0008 (1)	0.047 (1)
O-7'	-0.0089 (1)	0.3439 (2)	0.0313 (1)	0.042 (1)

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