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STRUCTURES OF MOMORDICOSIDES F_1, F_2, G, I, K AND L, NOVEL CUCURBITACINS IN THE FRUITS OF MOMORDICA CHARANTIA L.

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Abstract: Two bitter cucurbitacins, momordicosides K and L, and four non-bitter cucurbitacins, momordicosides F_1, F_2, G and I, were isolated from the immature fruits of Momordica charantia L. (Cucurbitaceae) and their structures were elucidated.

Cucurbitacins comprise a group of triterpenes, most of which are bitter principles commonly distributed in the cucurbitaceous plants. The fruits of Momordica charantia L. (Cucurbitaceae) taste bitter, and had been expected to contain cucurbitacins.

The triterpenoid constituents in this plant have been extensively investigated in this laboratory, and we reported the isolation and structures of five non-bitter cucurbitacins designated as momordicosides A~E isolated from the seeds.[1] They are the second example of the rare cucurbitacins which have no oxygen function at C_{11}.[2]

In this paper, we wish to report the structures of two bitter glycosides, momordicosides K and L, and four non-bitter glycosides, momordicosides F_1, F_2, G and I, isolated from the immature fruits, which are the novel cucurbitacins differ from ones hitherto reported.

The MeOH extractive of the fresh fruits was washed with water, and from the water-insoluble material, momordicosides were isolated in crystalline form by column chromatography.

F_1:	$C_{37}H_{60}O_8 \cdot 2.5H_2O$	mp 198-203°	$[\alpha]_D$ -111.0°	$[\theta]_{200}$ -82800°(MeOH)	yield 0.003%
F_2:	$C_{36}H_{58}O_8 \cdot H_2O$	155-158°	$[\alpha]_D$ -96.5°		0.0003
G:	$C_{37}H_{60}O_8 \cdot 2H_2O$	183-187°	$[\alpha]_D$ -107.3°		0.0009
I:	$C_{36}H_{58}O_8 \cdot H_2O$	210-216°	$[\alpha]_D$ -110.2°		0.0006
K:	$C_{37}H_{60}O_9 \cdot 1/2H_2O$	236-237°	$[\alpha]_D$ +63.3°	$[\theta]_{208}$ +58500°(MeOH)	0.0018
L:	$C_{36}H_{58}O_9 \cdot 2H_2O$	227-232°	$[\alpha]_D$ +57.3°		0.0002

Enzymatic hydrolysis of F_1 using the crude hesperidinase provided F_1-aglycone ($C_{31}H_{50}O_3$, mp 139-140°, $[\alpha]_D$ -90.6°, $[\theta]_{199}$ -43500° (MeOH)) and D-glucose. ^{1}H NMR data[3] [δ 1.31(6H, s), 3.22 (3H, s, OCH_3), 3.60 (H,m), 3.55, 3.67(1H each, d, J=9 Hz), 5.60 (2H, br.s), 5.61 (H, dd, J=10, 4 Hz), 6.14 (H, dd, J=10, 2 Hz)] and ^{13}C NMR data[3] (Table) of F_1-aglycone and ^{13}C NMR data of F_1 suggested that F_1 is a mono-β-D-glucopyranoside of a tetracarbocyclic five-ring triterpene having partial structures presented below.

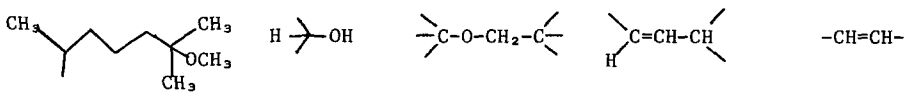
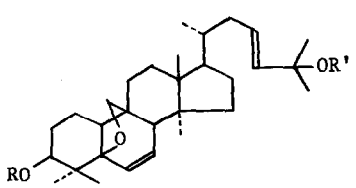


Table ^{13}C NMR Chemical Shifts of Momordicosides and Their Aglycones

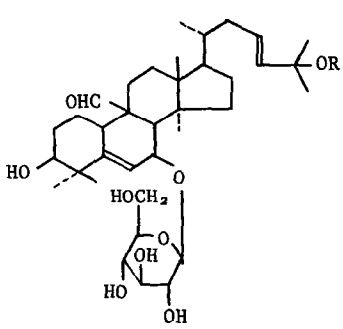
[(a): aglycone moiety, (s): sugar moiety]

momordicosides	quat. C	oxygen-bearing C	olefinic C
F_1	39.0, 45.2 45.4, 48.8	(a) 52.2q, 74.8s, 80.0t, 85.4d, 85.8s (s) 63.0t, 71.7d, 75.7d, 78.3d(x2) 106.8d	128.3d, 129.9d 134.1d, 137.6d
G	38.9, 45.1 45.3, 48.7	(a) 52.1q, 74.7s, 79.9t, 84.9d, 85.7s (s) 63.1t, 69.0d, 72.3d, 72.8d, 75.8d 103.6d	128.0d, 129.6d 133.8d, 137.3d
F_1-aglycone	37.5, 45.4 45.6, 48.7	52.1q, 74.7s, 76.2d, 79.8t, 87.5s	128.3d, 131.2d 132.4d, 137.6d
F_2	39.0, 45.2 45.4, 48.8	(a) 69.7s, 80.1t, 85.1d, 85.9s (s) 63.3t, 69.2d, 72.4d, 73.0d, 76.1d 103.8d	124.1d, 129.9d 134.1d, 141.7d
I	39.0, 45.2 45.3, 48.8	(a) 69.7s, 80.0t, 85.4d, 85.8s (s) 63.0t, 71.8d, 75.7d, 78.3d(x2) 106.8d	124.1d, 129.9d 134.1d, 141.6d
I-aglycone	37.6, 45.4 45.6, 48.8	69.7s, 76.2d, 79.8t, 87.6s	124.1d, 131.3d 132.4d, 141.7d
K*	41.8 45.6, 47.9	(a) 50.0q, 71.5d, 74.7s, 74.7d, 207.0d (s) 62.7t, 71.7d, 75.4d, 78.3d, 78.5d 101.5d	121.9d, 128.0d 137.3d, 147.1s
L*	41.8 45.5, 47.9	(a) 69.6s, 71.5d, 74.7d, 206.9d (s) 62.8t, 71.5d, 75.4d, 78.5d(x2) 101.4d	122.0d, 123.8d 141.3d, 147.2s
F_1H-1ag	38.6, 46.1 48.5, 49.9	76.8d, 78.5t, 89.9s	
F_1H-2ag	39.6, 41.7 46.4, 49.4	65.5t, 76.0d	120.4d, 142.9s

* The 4th quaternary carbon signal may overlap probably on the signal at δ 41.8.

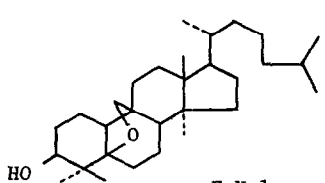


F_1: R= β-D-glucopyranosyl, R'=CH_3
F_2: R= β-D-allopyranosyl, R'=H
G : R= β-D-allopyranosyl, R'=CH_3
I : R= β-D-glucopyranosyl, R'=H

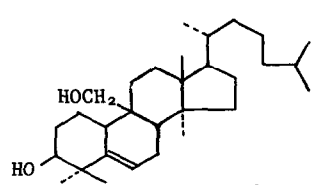


K: R= CH_3

L: R= H



F_1H-1ag



F_1H-2ag

When F_1-acetate was hydrogenated over PdO in EtOH, two products (F_1H-1 and F_1H-2) having no methoxyl group were obtained.[4] They were separately saponified and methanolyzed to give respective aglycones, F_1H-1ag ($C_{30}H_{52}O_2$, mp 133-134°, $[\alpha]_D$ +31.4°) and F_1H-2ag ($C_{30}H_{52}O_2 \cdot H_2O$, mp 169-170°, $[\alpha]_D$ +40.5°). The ^1H NMR and ^{13}C NMR spectra indicated that F_1H-1ag is a saturated alcohol in which the ether linkage is retained. F_1H-2ag is a diol which has a primary hydroxyl group and a trisubstituted double bond which were derived by reductive cleavage of the ether ring and migration of the double bond. The chemical shift of the olefinic proton (δ5.76, br.d, J=6 Hz) and its signal pattern are similar to those (δ5.61, br.d, J=5.5 Hz) of cucurbit-5-ene-3β,22(S),23(R),24(R),25-pentaol (A-aglycone)[1] and the ^{13}C NMR chemical shift of olefinic and quaternary carbons are almost the same with those of A-aglycone[1] (olefinic C: 119.1d and 143.0s. quaternary C: 34.8, 41.6, 46.8 and 49.2) except for the chemical shift of the quaternary carbon to which the hydroxymethyl group is linked.

The keto-aldehyde ($C_{30}H_{46}O_2$, EI-MS:m/z 440 (M^+), mp 123-125°, IR(KBr): 1718, 1725(sh.) cm^{-1}) obtained by oxidation of F_1H-2ag with pyridinium chlorochromate in CH_2Cl_2 showed a negative CD spectrum ($[\theta]_{280}$ -3400°(dioxane))[5]. These data indicate that F_1H-2ag is cucurbit-5-ene-3β,19-diol, and hence, F_1 is a 3-O-β-D-glucopyranoside of 5,19-epoxy-25-methoxy-5β-cucurbita-6,23-dien-3β-ol, and this formulation is well supported by CD curves of F_1 and F_1-aglycone which showed $[\theta]_{200}$-82800° and $[\theta]_{199}$-43500°, respectively.[6]

G exhibited almost the same ^1H NMR and ^{13}C NMR spectra with those of F_1 except for signals of the sugar moiety. When G-permethylate was hydrogenated and methanolyzed, F_1H-1ag and a methylated sugar were provided. The latter was identified as methyl 2,3,4,6-tetra-O-methyl β-D-allopyranoside by its specific rotation (-14.7°)[7] and by examination of the ^1H NMR spectrum [δ 4.60(H_1, d, J=8 Hz), 2.99(H_2,dd, J=8, 3 Hz), 4.00 (H_3, t, J=3, 2 Hz), 3.22 (H_4, dd, J=2, 12 Hz), 3.80 (H_5,m)]. The J-value (8 Hz) of the anomeric proton of the sugar moiety of G-permethylate indicates that D-allopyranose is in β-configuration.

Thus, G is the 3-O-β-D-allopyranoside of F_1-aglycone.

F_2 and I are considered to be the C_{25}-OH derivatives corresponding to G and F_1, respectively, because they showed similar ^1H NMR spectra to those of G and F_1, except that they exhibited a deshielded signal (δ1.53) due to two methyl groups on C_{25} and no methoxyl signal, and also because the ^{13}C NMR signal of C_{25} was shifted up-field ca 5 ppm from those of G and F_1.

Their relationship to G and F_1 were established by converting them into permethylates of G and F_1, respectively. Therefore, F_2 is the 3-O-β-D-allopyranoside of 5,19-epoxy-5β-cucurbita-6,23-diene-3β,25-diol, and I is its 3-O-β-D-glucopyranoside.

K is suggested by ^1H NMR and ^{13}C NMR data to be a mono-β-D-glucopyranoside of a tetracyclic triterpene having a tertiary formyl group (δ10.43, s), a disubstituted and a trisubstituted double bonds, two secondary hydroxyl groups, and a tertiary methoxyl group at the terminal of the side chain, and L to be the corresponding C_{25}-OH derivative. The same permethylate was obtained when K and L were separately methylated.

The aglycone (Lag)($C_{30}H_{48}O_4$, mp 190-193°) of L showed ^1H NMR signals of one carbinyl proton (H, δ 4.36, br.d, J=5 Hz) coupled with an olefinic proton (H, δ 6.25, br.d, J=5 Hz), one carbinyl proton (H, δ 3.81, br.s) and two olefinic protons (2H, δ 5.91, br.s). The ^1H NMR spectrum of L also depicted the signal of a carbinyl proton at δ 3.81 and this signal was

shifted down-field (ca δ 5.0) by acetylation. This fact indicates that the glucose is linked not to the isolated hydroxyl group, but to the one allylic to the trisubstituted double bond.

$NaBH_4$ reduction of K provided a primary alcohol Kred (mp 195-197°, $[\alpha]_D$ +60.1°, $[\theta]_{205}$ +87900° (MeOH)), which gave F_1-aglycone on treatment with 50% AcOH in MeOH at 38°.

When Kred was hydrogenated over PdO, the glucopyranosyl group was eliminated and two compounds identical with F_1H-lag and F_1H-2ag were yielded. F_1-aglycone is not the genuine aglycone of Kred, and it is considered to be derived from the glycoside by bond fission between the aglycone-C and the glucose-O giving an intermediate C_7 carbonium cation, subsequent migration of the double bond and then formation of the linkage between C_5 carbonium cation and the oxygen of the primary hydroxyl group. Formation of F_1H-lag by hydrogenation is also supposed to be initiated by cleavage of C_7-O bond, followed by migration of the double bond and formation of the ether ring, reductive opening of which leads to F_1H-2ag.

The orientation of C_7-hydroxyl group was determined as β from the positive CD curve of Kred[6] and from the J-values(5 Hz) of C_6-H and C_7-H of Lag.[8]

These data and consideration have led us to the conclusion that Kred is a 7-O-β-D-glucopyranoside of 25-methoxy-cucurbita-5,23-diene-3β,7β,19-triol, and K and L are 7-O-β-D-glucopyranosides of 19-oxo-25-methoxy-cucurbita-5,23-diene-3β,7β-diol and its C_{25}-OH derivative, respectively.

Momordicosides F_1, F_2, G and I are the first cucurbitacins having 5β-cucurbitane skeleton occurred in nature, and K and L are noted as the new cucurbitacins having C_9-formyl and 7-O-β-D-glucopyranosyl groups. Among momordicosides, G and F_2 are the first members of cucurbitacins having D-allose as a component sugar.

References and Notes

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2) The first cucurbitacin having no oxygen function at C_{11} is litsomentol (5α-cucurbit-24-ene-3β,5α-diol) isolated from the bark of Litsea tomentosa Heyne (Lauraceae): T.R. Govindachari, N. Viswanathan and P. A. Mohamed, Tetrahedron, 27, 4991 (1971).

3) ^1H NMR and ^{13}C NMR spectra were taken in pyridine-d_5 using tetramethylsilane as an internal standard(s: singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet, br: broad).

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5) R. Tschesche, G. Biernoth and G. Snatzke, Ann., 674, 196 (1964)

6) A. I. Scott and A. D. Wrixon, Tetrahedron , 27, 4787 (1971)

7) β-anomer: -19.0° , α-anomer: +148.5°(unpublished data reported by K. Mihashi et al. of this university at the 101st Annual Meeting of The Pharmaceutical Society of Japan, Kumamoto, April, 1981)

8) The signal of C_6-H of 3β,7α,11β-triacetoxy-cucurbit-5-ene is reported as a broad singlet ($W_{1/2}$ 4 Hz) and that of C_7-H as a broad doublet (J=7 Hz).

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