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Studies on Triterpenoid Corticomimetics (V)

Oxidation of Presenegenin with Chromium Trioxide-Acetic Acid to Yield 11-Keto and 12-Keto Derivatives

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Abstract □ Oxidation of presenegenin dimethyl ester triacetate with chromium trioxide in acetic acid yielded two compounds, 11-ketone (Ⅳ) and 12-ketone (Ⅵ) derivatives. The latter was a main product. On mild alkaline hydrolysis, Ⅳ afforded 11-keto-presenegenin dimethyl ester (Ⅴ), mp 232~234°, $C_{32}H_{48}O_8$, whereas Ⅵ did 12-keto-presenegenin dimethyl ester-12, 27-hemiketal (Ⅷ), mp 240~242°, $C_{32}H_{50}O_8$.

Keywords □ presenegenin, 11-keto-presenegenin, 12-keto-presenegenin-12, 27-hemiketal.

Derivation of triterpenoids and screening for their corticomimetic activities have been our primary interest. We have prepared 11-oxo derivatives of oleanene and ursene series of pentacyclic triterpenoids such as oleanolic acid,[1,2] hederagenin,[1] β-boswellic acid[3] and pomolic acid.[4]

In order to examine a structure-activity relationship, we chose presenegenin which possesses two carboxyl and three hydroxyl functional groups, being more hydrophilic than the triterpenoids above mentioned. Oxidation of presenegenin dimethyl ester triacetate with chromium trioxide in acetic acid unexpectedly yielded 12-ketone together with 11-ketone; the former was a main product. The present paper describes the elucidation of chemical structures of the two oxygenated compounds.

EXPERIMENTAL METHODS

Preparation of Tenuifolin (I) from Polygalae Radix

Tenuifolin (Ⅰ) was prepared with modifying the method of S.W. Pelletier et. al.,[5] as follows; Polygalae radix (5.2kg, purchased from a market on Chongno Street, Seoul) was extracted four times with hot methanol. Evaporation of solvent gave a residue (1.7kg), which was partitioned into water and ethylacetate. After removing the ethylacetate-soluble materials, the remaining water solution was extracted with butanol to give a crude saponin fraction. Butanol ex. (345g) was hydrolyzed with 10% NaOH in a boiling water bath for 10hrs. After cooling, the hydrolysate was acidified to pH 4 with *d*-HCl. After removing benzene and chloroform soluble materials, the aquous solution was extracted with butanol to give a crude prosapogenin fraction. The fraction was subjected to chromatography on a silica gel column with chloroform/methanol/water (70 : 20 : 1.5) to obtain a main prosapogenin. Crystallization from 50% methanol yielded pure tenuifolin (Ⅰ) (15g). mp : 298°, IR $\nu_{max}^{KBr}cm^{-1}$: 3400(OH), 1715, 1695(COOH), 1630(olefin), PMR δ_{ppm}^{TMS} : (CD_3OD) 0.78, 0.91, 0.96, 1.25, 1.38(5×3H, each s, 5×CH_3), 2.93(1H, m, C_{18}-H), 5.64

(1H, m, C_{12}-H); (pyridine-d_5) 0.88, 1.02, 1.06, 1.53, 1.97(5×3H, each s, 5×CH_3), 3.33(1H, m, C_{18}-H), 4.60(1H, d, C_3-H), 4.69(1H, m, C_2-H), 5.08(1H, d, anomeric H, J=8Hz), 5.72(1H, m, C_{12}-H).

Methylation with diazomethane and acetylation with acetic anhydride-pyridine of I by usual methods gave its dimethyl ester pentaacetate. Recrystallization from hexane/chloroform yielded fine needle crystals. mp : 220°, IR ν_{max}^{KBr} cm^{-1} : 3540(OH), 1760, 1740 (ester), 1635 (olefin), PMR δ_{ppm}^{TMS}($CDCl_3$) : 0.61, 0.79, 0.85, 1.16, 1.25(5×3H, each s, 5×CH_3), 1.93, 1.98, 2.00 (3×3H, each s, 3×$OCOCH_3$), 1.94 (6H, s, 2×$OCOCH_3$), 3.56, 3.62(2×3H, each s, 2×$COOCH_3$), 2.85(1H, dd, C_{18}-H, J=7, 14Hz), 4.45(1H, d, anomeric H, J=8Hz), 5.49(1H, m, C_{12}-H).

Smith's Degradation of Tenuifolin

Tenuifolin (9.9g) was dissolved in methanol (500ml), and sodium periodate (10g) in water (100ml) was added over a period of 30min while the solution was being stirred and cooled in an ice bath. The solution was allowed to stand in the dark at room temp. for two days, and water(2*l*) was added. A precipitate was taken by centrifugation. The precipitate was washed twice with a small volume of water, and suspended with 300ml of water. While the suspension was being stirred, potassium iodide (2g) and arsenic trioxide (5g) were added. An equal volume of 15% potassium hydroxide in ethanol was added. The solution was refluxed in a boiling water bath under nitrogen for 5hrs, cooled, and acidified with *d*-H_2SO_4 to pH 4. Ethanol was removed *in vacuo*, and extraction with ether gave a yellowish residue which was subjected to methylation with diazomethane, and then to acetylation with acetic anhydride-pyridine at root temp. as usual. The reaction mixture was chromatographed on a silica gel column with benzene/ethylacetate (4 : 1) to give presenegenin dimethyl ester diacetate (Ⅱ) (1.2g). mp 208° (amorpous powder), IR $\nu_{max}^{KBr}$$cm^{-1}$: 3520(OH), 1740(ester), 1655(olefin), PMR δ_{ppm}^{TMS} ($CDCl_3$) : 0.69, 0.86, 0.92, 1.27, 1.42(5×3H, each s, 5×CH_3), 2.02, 2.07(2×3H, each s, 2×$OCOCH_3$), 2.90(1H, dd, C_{18}-H, J=7, 14 Hz), 3.63, 3.65(2×3H, each s, 2×$COOCH_3$), 4.09(2H, br. s, $C_{27}H_2$-$OCOCH_3$), 4.18(1H, m, C_2HOH), 5.25(1H, d, C_3H-$OCOCH_3$, J= 4Hz), 5.56(1H, m, $C_{12}H$).

Compound Ⅱ (1g) was further acetylated with acetic anhydride/pyridine (1 : 2) by heating at 100° for 3hr under nitrogen. Evaporation and extraction into ether gave presenegenin dimethyl ester triacetate(Ⅲ). Crystallization from methanol (0.9g), mp : 220°, IR $\nu_{max}^{KBr}$$cm^{-1}$: 1,748, 1,738, 1,727(ester), PMR δ_{ppm}^{TMS}($CDCl_3$) : 0.68, 0.85, 0.91, 1.17, 1.38(5×3H, each s, 5× CH_3), 1.94, 2.01, 2.04(3×3H, each s, 3× $OCOCH_3$), 2.87(1H, dd, $C_{18}H$, J=7, 14Hz), 3.62, 3.65(2×3H, each s, 2×$COOCH_3$), 4.07 (2H, br. s, C_{27}-H_2), 5.31(1H, d, C_3-H, J= 4Hz), 5.40(1H, m, C_2-H), 5.55(1H, m, C_{12} -H).

Oxidation of Presenegenin Dimethyl Ester Triacetate with Chromium Trioxide-Acetic Acid

Compound Ⅲ (2.0g) in acetic acid (100ml) was treated with chromium trioxide (2g) in acetic acid (50ml). The reaction mixture was stirred at room temp. for 3hrs and poured into ice water, and the product was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and freed from solvent. The residue was chromatographed on a silica gel column eluting with benzene/ethylacetate (4 : 1) to yield two products, Ⅳ (amorpous powder, 880mg) and Ⅵ (fine needle crystals

from hexane/chloroform, 980mg).

Ⅳ; mp : 124~126°, UV(λ_{max} in methanol) : 250nm (ε8,700), IR : 1,750, 1,730(ester), 1,665, 1,630(α,β-unsaturated ketone and olefin), PMR δ^{TMS}_{ppm}($CDCl_3$) : 0.86, 0.90, 0.91, 1.34, 1.37(5×3H, each s, 5×CH_3), 1.93, 1.98, 2.05(3×3H, each s, 3×$OCOCH_3$), 2.48 (1H, s, C_9-H), 3.01(1H, dd, C_{18}-H, J=7, 14 Hz), 3.24(1H, dd, C_5-H, J=4, 16Hz), 3.63, 3.65(2×3H, each s, 2×$COOCH_3$), 4.26(2H, br. s, C_{27}-H_2), 5.29(1H, d, C_3-H, J=4Hz), 5.41(1H, m, C_2-H), 5.88(1H, s, C_{12}-H).

Ⅵ (fine needles); mp : 248~250°, UV(methanol) : end absorption only, IR $\nu^{KBr}_{max}cm^{-1}$: 1,750, 1,728(ester), 1,703(6-membered ring ketone), PMR δ^{TMS}_{ppm}($CDCl_3$) : 0.84, 0.94, 0.96, 1.15, 1.38(5×3H, each s, 5×CH_3), 1.94(6H, s, 2×$OCOCH_3$), 2.04(3H, s, 1×$OCOCH_3$), 2.22(2H, m, C_{11}-H_2), 2.56(1H, d, C_{13}-H, J=4Hz), 2.91(1H, m, C_{18}-H), 3.67(6H, s, 2×$COOCH_3$), 4.10(2H, br. s, C_{27}-H_2), 5.28 (1H, d, C_3-H, J=4Hz), 5.41(1H, m, C_2-H).

Alkaline Hydrolysis of IV

A solution of Ⅳ (0.87g) in 0.1M K_2CO_3-85% methanol (21ml) was kept at room temp. for two days, neutralized with *d*-HCl and extracted with chloroform. The extract was dried over sodium sulfate anhydrous and freed from solvent. The residue was chromatographed on a silica gel column eluting with benzene/acetone(3 : 1), giving Ⅴ (0.54g, amorpous powder).

Ⅴ; mp : 232~234°, UV(λ_{max} in methanol) : 250nm(ε8,800), IR $\nu^{KBr}_{max}cm^{-1}$:3,440(OH), 1,730 (ester), 1,660, 1,640(α,β-unsaturated ketone and olefin), PMR δ^{TMS}_{ppm}($CDCl_3$) : 0.86, 0.92, 0.95 (3×3H, each s, 3×CH_3), 1.35(6H, s, 2×CH_3), 2.99(1H, s, C_9-H), 3.05(1H, m, C_{18}-H), 3.33(1H, dd, C_5-H, J=4, 16Hz), 3.63, 3.70(2×3H, each s, 2×$COOCH_3$), 3.93 (1H, d, C_3-H, J=4Hz), 4.08(1H, m, C_2-H), 3.88(2H, dd, C_{27}-H_2, J=12, 38Hz), 5.96(1H, s, C_{12}-H), CMR($CDCl_3$) : Table Ⅰ, MS (m/z) : 560(M^+, $C_{32}H_{48}O_8$, 0.1%), 530(M^+-CH_2=O, 1.9%), 512(M^+-CH_2=O-H_2O, 0.3%), 295 ($C_{16}H_{23}O_5$, 2.8%).

Alkaline Hydrolysis of VI

A solution of Ⅵ (240mg) in 0.2M K_2CO_3-70% methanol was kept at room temp. for 3hrs. An aliquot was taken, neutralized with *d*-HCl and extracted with ether. The extract was dried over sodium sulfate anhydrous and freed from solvent. The residue was chromatographed over silica gel eluting with benzene/acetone(3 : 1), giving Ⅷ.

The remaining reaction mixture was further incubated at 60°C for 10hrs, neutralized with *d*-HCl and extracted with ether. The extract was treated as usual. The residue was chromatographed over silica gel eluting with benzene/acetone (2 : 1) to give Ⅷ.

Compound Ⅷ (0.2g) in 1N NaOH-75% ethanol was incubated at 50°C for 4hrs, neutralized with *d*-HCl and extracted with ether. The extract was treated as usual. The residue was recrystallized from ethylacetate to yield Ⅸ. (150mg) Compound Ⅸ was treated with diazomethane to give Ⅷ.

Ⅶ (amorpous powder); mp : 262~264;°, UV (in methanol) : end absorption only, PMR δ^{TMS}_{ppm} ($CDCl_3$) : 0.81, 0.90, 0.94, 1.17, 1.32(5×3H, each s, 5×CH_3), 1.89(3H, s, $OCOCH_3$), 2.22 (2H, m, C_{11}-H_2), 2.52(1H, d, C_{13}-H, J=4 Hz), 2.85(1H, m, C_{18}-H), 3.65, 3.69(2×3H, each s, 2×$COOCH_3$), 3.89(1H, d, C_3-H, J=4Hz), 3.99(1H, m, C_2-H), 4.09(2H, br. s, C_{27}(OAc)-H_2).

Ⅷ (needle crystals from ether); mp : 240~242°, UV(in methanol) : end absorption only, IR $\nu^{KBr}_{max}cm^{-1}$:3,440(OH), 1,725($COOCH_3$), PMR

δ_{ppm}^{TMS} : ($CDCl_3$) 0.74, 0.92, 0.93, 1.15, 1.33 (5×3H, each s, 5×CH_3), 2.65(1H, m, C_{18}-H), 3.45(2H, ABq, C_{27}-H_2, J=7, 14Hz), 3.69 (6H, s, 2×$COOCH_3$), 3.96(1H, d, C_3-H, J=4Hz), 4.10(1H, m, C_2-H), (DMSO-d_6) 0.65, 1.08, 1.20(3×3H, each s, 3×CH_3), 0.86 (6H, s, 2×CH_3), 3.57, 3.61(2×3H, each s, 2×$COOCH_3$), 4.25~4.50(2H, m, C_2-OH and C_3-OH), 5.85(1H, s, C_{12}-OH), CMR ($CDCl_3$, DMSO-d_6) : Table I, MS(m/z) : 562 (M^+, 0.6%), 531(M^+-CH_2OH, 4.3%), 471 (M^+-CH_2OH-CH_3COOH, 3.2%), 279(a, 42.1 %), 219(b, 39.5%).

Ⅸ (needles); mp>300°, IR $\nu_{max}^{KBr}cm^{-1}$: 3,400 (OH), 3,000-2,500, 1,695(COOH), 1,720 (ester), MS(m/z) : 548(M^+, 3.3%), 517(M^+-CH_2OH, 16.0%), 457(M^+-CH_2OH-CH_3COOH, 15.7%), 279(a, 63.3%), 219(b, 77.7%).

Instrumental Analysis

All melting points were taken on a Mitamura heat block apparatus and uncorrected. IR absorption spectra were obtained in KBr pellets on Perkin-Elmer Model 282B. NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution by a Varian Model FT80A NMR spectrometer with tetramethylsilane as an internal standard. (^1H; 80MHz, ^{13}C; 20MHz) The chemical shifts are recorded in δ. A recording spectrophotometer, Gilford Type 2600 was used for the meaurements of UV-visible absorption spectra. Mass spectra were obtained on a Hewlett Packard GC/MS spectrometer (type 5985B) using an electron impact method.

RESULTS AND DISCUSSION

Tenuifolin (I) (=presenegenin 3-β-D-glucopyranoside) was first obtained by alkaline treatment of saponins fraction of Polygalae radix. Methylation and acetylation of I yielded dimethyl

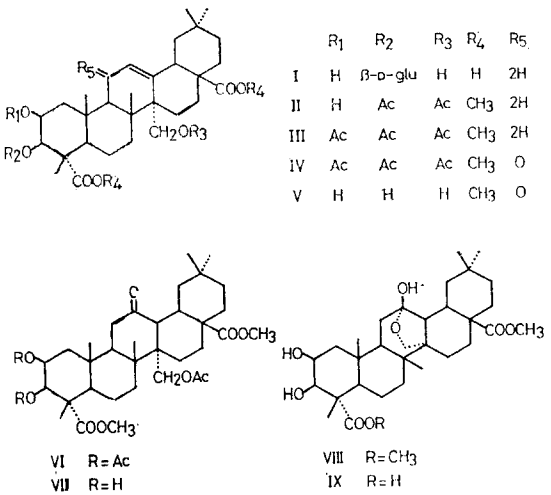


Chart 1

ester pentaacetate. IR and PMR spectra and mp of I and its dimethyl ester pentaacetate were identical with literature references.[5,6]

In order to isolate presenegenin, Smith's degradation of I was carefully undertaken. However, it was very difficult to separate presenegenin from hydrolysate, due to showing many minor by-products and tailing in TLC. Thus, the hydrolysate was methylated with diazomethane and acetylated with acetic anhydride-pyridine at room temp. to yield compound II, mp 208°.

PMR spectrum of II exhibited signals for two acetyl groups at δ 2.02, 2.07 besides five C-methyl at δ0.69, 0.86, 0.92, 1.27, 1.42 and two methyl ester signals at δ3.63, 3.65. Signals at δ4.09 (2H on C_{27}, br. s), 4.18 (1H on C_2, m) and 5.25 (1H on C_3, d, J=4Hz) suggested the presence of 3β, 27-diacetoxy groups in II. Further acetylation of II with acetic anhydride-pyridine at 95° for 3 hrs yielded compound III, mp 220°. PMR spectrum of III showed signals for three acetyl groups at δ 1.94, 2.01, 2.04 and signals at δ4.07 (2H on C_{27}, br. s), 5.31 (1H on C_3, d, J=4Hz)

and 5.40(1H on C_2, m). These results indicated that III is 2β, 3β, 27-triacetyl presengenin dimethyl ester.

Oxidation of III with chromium trioxide in acetic acid gave two oxo compounds, IV(44%) and VI (49%). Compound IV, mp 124~126°, contains α,β-unsaturated ketone as seen from its UV (250nm, ε 8,700) and IR (1665, 1630 cm^{-1}) spectra, which was further confirmed by the signals at δ 5.88(1H on C_{12}, s) and 2.48 (1H on C_9, s) in its PMR spectrum. Thus, IV was assigned to be 2β, 3β, 27-triacetyl-11-oxopresenegenin dimethyl ester.

Hydrolysis of IV under a mild alkaline condition of 0.1M K_2CO_3 in 85% methanol gave V. Compound V (amorpous powder), mp 232~234°, also showed the presence of α,β-unsaturated ketone as judged from its UV (250nm, ε8,800) and IR (1,660, 1,640 cm^{-1}) spectra, which was confirmed by the signals at δ 5.96 (1H on C_{12}, s) and 2.99 (1H on C_9, s) in its PMR spectrum and by the signals at δ 200.9 (C_{11}), 161.4 (C_{13}) and 131.9 (C_{12}) in its CMR spectrum (Table I). Mass spectrum of V showed the molecular ion peak at m/z 560, giving a possible molecular formula, $C_{32}H_{48}O_8$, supporting the one oxygen addition on the molecule of presenegenin dimethyl ester. Reacetylation of V with acetic anhydride-pyridine at 95° for 3 hrs gave IV. Therefore, V must be 11-oxopresenegenin dimethyl ester.

Compound VI (fine needle crystals), mp 248~250°, contains a 6-membered ketone, as seen from its IR spectum (1703 cm^{-1}). PMR spectrum of VI exhibited signals for three acetyl groups (2×3H, 1.94, s; 1×3H, 2.04, s), and for four protons (2H on C_{27}, 4.10, br. s; 1H on C_3, 5.28, d, J=4Hz; 1H on C_2, 5.41, m), suggesting no oxidation of three hydroxyl groups. Multiplicity of one proton on C_{18} at δ 2.91 and the absence of a vinyl proton on C_{12} at δ5 to 6 range were supposed to be associated with introduction of one oxygen function on C_{12} and reduction of the double bond between C_{12} of presenegenin. Thus, VI was assumed to be 12-oxo-presenegenin dimethyl ester triacetate.

Mild alkaline hydrolysis of VI with 0.2M K_2CO_3 in 70% methanol at room temp. for 3

Table I. ^{13}C-NMR chemical shift of 11-keto-presenegenin dimethyl ester(V) and 12-keto-presenegenin-12,27-hemiketal (VIII)

Carbon no.	V	VIII	
	$CDCl_3$	$CDCl_3$	DMSO-d_6
1	43.1	43.8	43.9
2	70.7	71.2	69.7
3	74.7	74.9	74.4
4	53.6	53.2	52.8
5	50.5	52.1	52.0
6	20.3	21.1	20.5
7	33.5	33.9	33.9
8	45.8[a]	41.4	40.5
9	62.6	51.6	51.2
10	36.9	36.0	35.4
11	200.9	70.4	69.2
12	131.9	108.7	107.3
13	161.4	44.0	43.4
14	45.9[a]	46.3	45.4
15	24.4	38.5	37.4
16	22.7	21.9	21.3
17	49.3	49.7	48.7
18	41.2	30.9	30.5
19	44.9	37.1	36.1
20	30.7	30.6	30.0
21	32.6	33.4	32.8
22	31.6	32.4	31.9
23	178.2	178.1	177.2
24	12.1	11.8	11.6
25	18.1	18.2	17.3
26	20.6	17.0	16.4
27	63.1	70.5	78.9
28	177.1	178.1	177.2
29	32.8	33.6	33.3
30	23.6	23.7	23.3
23OOCH$_3$	52.1	52.5[b]	51.6
28OOCH$_3$	51.9	52.3[b]	51.6

a) b): Assignments may be reversed

hr and at 60° for 10 hrs yielded VII and VIII, respectively.

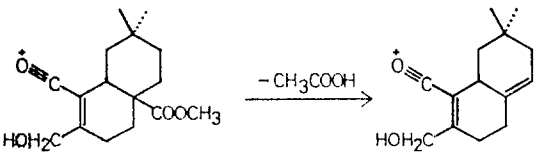
Compound VII (amorpous powder), mp 262~264°, possesses only one acetyl group on C_{27}, because its PMR spectrum showed a signal at δ 1.89 (3H, s) for one acetyl group and a signal at δ 4.09(2H, br. s) for C_{27} $(OCOCH_3)$-$\underline{H}_2$, indicating that VII must be 12-oxopresenegenin dimethyl ester 27-acetate. By mp and PMR data, VII was identical with 12-oxopresenegenin dimethyl ester 27-acetate which was obtained by S.W. Pelletier *et al.*[5]

Compound VIII (needle crystals), mp 240~242°, exhibited the molecular ion peak at m/z 562, giving a possible molecular formular $C_{32}H_{50}O_8$ in its mass spectrum. It does not have any acetyl group, as judged from its IR and PMR spectra. PMR spectrum of VIII in DMSO-d_6 solvent showed a signal of one hydroxyl group at δ 5.85 (1H, s) for a hemiketal besides signals of two hydroxyl group at δ 4.25 to 4.50, suggesting the hemiketal formation between the ketone on C_{12} and the hydroxyl group on C_{27}. This was supported by two signals at δ 70.5 (C_{27}) and 108.7 (C_{12}) in its CMR spectra ($CDCl_3$) (Table I), which did not show signals for ketone at about δ200 and for vinyl group at δ 120 to 140 range. Further, the signal at δ 70.5 for C_{27} in $CDCl_3$ was greatly shifted to δ78.9 in DMSO-d_6, confirming the hemiketal structure of VIII. Reacetylaiton of VIII and VII with acetic anhydride at 95° for 3hrs yielded VI. Therefore, VIII was assigned to be 12-oxopresengenin dimethyl ester-12, 27--hemiketal.

S.W. Pelletier *et al* [5] demonstrated that oxidation of tenuifolin dimethyl ester pentaacetate with *m*-chlorobenzoic acid gave a mixture of two compounds, the corresponding epoxide and a ketone. Treatment of the epoxide with boron trifluoride etherate yielded the ketone. The ketone was proved to be 12-ketotenuifolin dimethyl ester pentaacetate. Its hydrolysis with *d*-HCl yielded a mixture of two compounds, VII and 12-keto-13, 27-cyclopresenegenin dimethyl ester (X). They also demonstrated that acetylation of VII yielded VI, and that VI was converted to X under the condition of 1N NaOH at 50°for 4 hrs.

In the present study, the mild alkaline treatment of VI gave only VIII by way of VII, and the same treatment of VIII under the coniditon of 1N NaOH at 50° for 4 hrs as S.W. Pelletier *et. al*[5] carried out, yielded IX.

Compound IX (needle crystals), mp>300°, exhibited the presence of carboxyl function as seen from its IR spectrum (3000~2500, 1695 cm^{-1}), and did the molecular ion peak at m/z 548, C_{31} $H_{48}O_8$ in its mass spectrum, suggesting that IX was a demethylate of VIII. The fragments of m/z 279 and 219, which were formed by the characteristic McLafferty fragmentation, were shown in IX as well as VIII. Methylation of IX with diazomethane yielded VIII. Thus. IX was assigned to be 12-oxopresenegenin-12, 27-hemiketal-28-monomethyl ester.



a, m/z 279 b, m/z 219

Chart 2

ACKNOWLEDGEMENTS

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