Communications to the Editor

[Chem. Pharm. Bull. 32(3)1244—1247(1984)]

A NEW GLYCOSYL ESTER OF A 3,4-SECO-TRITERPENE FROM KOREAN MEDICINAL PLANT, ACANTHOPANAX CHIISANENSIS (ARALIACEAE)

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From leaves and stem-bark of Korean medicinal plant, Acanthopanax chiisanensis, a new glycoside was isolated and its structure was established as the α-L-rhamnopyranosyl(1→4)-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl ester of 1(R)-hydroxy-3,4-seco-lup-4(23),20(30)-dien-3,11α-olactone. This is the first example of a naturally occurring glycoside of 3,4-seco-triterpene.

KEYWORDS—— Acanthopanax chiisanensis; Araliaceae; Korean folk medicine; chiisanoside; chiisanogenin; 3,4-seco-triterpene ^{13}C NMR; oligo-glycosyl ester

A folk medicine, leaves and stem-bark of Acanthopanax chiisanensis Nakai (智異山五加 ; Araliaceae) is used as an anti-rheumatic, an anti-inflamatic and a tonic in Korea. An ether-insoluble and 1-butanol(saturated with water)-soluble fraction of a methanolic extract of the leaves was chromatographed on silica gel to give a new glycoside named chiisanoside (1), colorless needles, mp 228°C (from 1-BuOH), $[\alpha]_D^{14}$ +7.7° (c=1.69, MeOH), $C_{48}H_{74}O_{19}\cdot 3H_2O$, yield: 0.2%, which was also isolated from the stem-bark in a lower yield than from the leaves.

On hydrolysis with crude hesperidinase,[1] 1 afforded an acid-unstable aglycone named chiisanogenin (2), colorless needles, mp 232-234°C (from Et_2O), $[\alpha]_D^{22}$ +86.4° (c=0.66, MeOH), $C_{30}H_{44}O_5\cdot H_2O$, MS: m/z 484($M^+$) and 466($M^+-H_2O$). As shown in Tables I and II, the ^1H and ^{13}C NMR spectra showed that the following groups occur in 2: two isopropenyls (MS of 2: m/z 41 $CH_3-\overset{|}{C}=CH_2$), one carboxyl, one secondary hydroxyl and one lactone associated with a secondary hydroxyl group together with three methyls on quarternary carbons, eight methylenes, five methines and four quarternary carbons. On treatment with diazomethane in ether, 2 afforded a monomethyl ester (3) which on catalytic hydrogenation over PtO_2 gave a tetrahydromonomethyl ester (4). These results coupled with the biogenetic considerations suggested that 2 would be represented by a derivative of 3,4-seco-betulinic acid (5) having one secondary hydroxyl group and one lactone group ($-COO-\overset{|}{C}H-$). This was supported by a proton signal of 2 at δ 2.97 (1H, dd J=11 and 11Hz) which was proved in the present study, to be characteristic of H-19 of lupane-type triterpenes having a carboxyl group at C-17 and a 20(30)-double bond such as betulinic acid (6), being absent in the spectra of betulin (7) and 4. Further, comparison of the ^{13}C NMR spectrum of 2 with that of 6 [2] revealed that the signals due to D and E ring-carbons of 6, except for C-13, as well as those of C-20, -28, -29 and -30 of 6 appeared at almost the same positions as that of 2. This also indicated that no additional functional group is located at the D and E rings of 2.

The lactone group was found to be relatively stable and a dicarboxylic acid could not be obtained from 2 even by careful neutralization of its alkaline solution. Inspection of the molecular model demonstrated that the location of a secondary hydroxyl group capable of forming the lactone with the 3-carboxylic acid of 5 must be limited to its 11 position (either α- or β-configuration). On reductive opening of the lactone group with $NaBH_4$-$AlCl_3$,[3] 2 yielded a trihydroxy-compound (8) and the coupling pattern of the proton signal of this compound at δ 3.97 (1H, ddd J=11, 11 and 6Hz) was consistent with that of the 11α-hydroxyl group of the steroid series.[4] The unexpected coupling pattern of the lactonyloxy proton of 2 (δ 4.53 (1H, ddd J=8, 8 and 8Hz)) may be explained in terms of the deformation of its C ring due to the lactone ring formation.

The location of a secondary hydroxyl group of 2 was elucidated to be at C-1 by the following evidence. The proton signals of 2 at δ 2.93(1H, d J=15Hz) and 2.72(1H, dd J=15 and 8Hz) were assigned to methylene protons vicinal to the lactone-carbonyl group; the irradiation of the former resulted in the transformation of the latter into a doublet (J=8Hz) and the irradiation of the latter led to the transformation of a carbinyl proton signal at δ 3.57(1H, d J=8Hz) into a singlet. The absence of the coupling between the carbinyl proton and the proton at δ 2.93 must be due to the nearly 90° of their dihedral angle. On acid hydrolysis, 1 yielded glucose, rhamnose and a modified aglycone (9) together with several other minor products formed from its genuine aglycone (2). The ^1H and ^{13}C NMR spectra of 9 (Tables I and II) indicated the disappearance of one of two isopropenyl groups of 2 and formation of geminal methyls on a carbon attached to an ether linkage, formulating 9 as shown in Chart 2. The formation of 9 from 2 as well as the decoupling experiment between proton signals on C-2 (δ 2.34(1H, dd J=11 and 14Hz) and 3.09(1H, dd J=3 and 14Hz)) and a signal at δ 4.31(1H, dd J=3 and 11Hz) of 9 further substantiated the location of the secondary hydroxyl group of 2 at C-1. It is notable that in the spectrum of 9, the coupling of H-1 with both the protons on C-2 was observed in contrast to the case of 2. The chirality of C-1 was established to be R by means of the modified Horeau method,[5] leading to the formulation of 2 as shown in Chart 1.

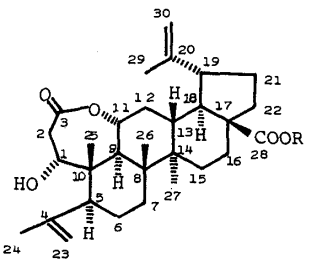
Finally, the structure of 2 was confirmed by comparison of the ^{13}C NMR spectrum of 8 with that of 3,4-seco-lup-4(23),20(30)-diene-3,28-diol (10) prepared from betulin (7) through 11-13, 5 and 14

Table I. ^1H-Chemical Shifts (δ) in $CDCl_3$

	2[a]	3[c]	4[c]	8[a]	9[b]
25-Me	0.91(s)[d]	0.90(s)[d]	0.84(s)[d]	1.01(s)[d]	0.96(s)[d]
26-Me	1.02(s)[d]	1.01(s)[d]	0.98(s)[d]	1.03(s)[d]	1.02(s)[d]
27-Me	1.08(s)[d]	1.06(s)[d]	1.02(s)[d]	1.31(s)[d]	1.11(s)[d]
30-Me	——	——	e	——	——
23-Me	——	——	e	——	1.18(s)[d]
24-Me	1.73(s)	1.74(s)	e	1.84(s)	1.25(s)[d]
29-Me	1.69(s)	1.69(s)	e	1.70(s)	1.69(s)
2-H2	2.72 (dd J=15,8)	e	e	e	3.09 (dd J=14,3)
	2.93 (d J=15)	e	e	e	2.34 (dd J=11,14)
19-H	2.97 (ddd J=11,11,4)	e	e	3.00 (ddd J=11,11,4)	3.00 (ddd J=11,11,4)
1-H	3.57 (d J=8)	3.58 (d J=8)	3.95 (d J=7)	e	4.31 (dd J=11,3)
11-H	4.53 (ddd J=8,8,8)	e	4.58 (ddd J=8,8,8)	3.97 (ddd J=11,11,6)	3.94 (ddd J=11,11,5)
23-H2	4.83(br s)	4.85(br s)	——	4.76(br s)	——
	4.86(br s)	4.85(br s)	——	4.88(br s)	——
30-H2	4.64(br s)	4.63(br s)	——	4.63(br s)	4.64(br s)
	4.76(br s)	4.76(br s)	——	4.76(br s)	4.76(br s)
-COOMe	——	3.67(s)	3.65(s)	——	——

a:measured at 270MHz; b:measured at 400MHz; c:measured at 90MHz; d:unassigned; e:obscure.

Chart 1



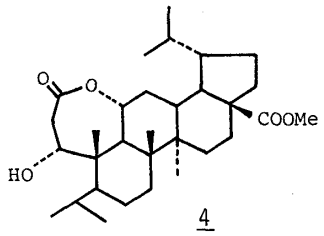
1:R=β-Glc(6→1)β-Glc(4→1)α-Rha
2:R=H
3:R=Me

Table II. ^{13}C-Chemical Shifts (δ) in $CDCl_3$

C	1[a]	2[a]	6[2)]	7[2)]	8	9	10	15	C	1[a]	2[a]	6[2)]	7[2)]	8	9	10	15
1	75.0	75.3	39.0	38.8	79.1	86.4[d]	32.6	32.7	16	32.5	32.7	32.6	29.2	32.1	32.2	29.0	29.6
2	38.6	38.7	27.6	27.4	36.9	37.9[d]	26.0	22.2	17	56.7	56.4	56.3	47.9	56.2	56.3	47.6	46.3
3	173.1	172.9	78.2	79.1	62.1	173.3	63.3	65.0	18	47.5	47.9	47.1	47.9	46.9	46.8	47.6	47.7
4	147.6	147.7	39.0	38.8	154.4	79.7	147.9	147.7	19	49.5	49.6	49.4	48.8	48.7	48.8	48.6	48.7
5	49.5	49.6	55.5	55.3	46.6	55.6[e]	50.2	50.3	20	150.7	150.5	150.9	150.5	149.7	149.9	150.2	150.9
6	25.1	25.2	18.4	18.3	25.8	36.1[d]	24.9	25.1	21	29.5	29.7	29.9	29.8	29.7	29.9	29.6	29.6
7	33.4	33.6	34.5	34.3	34.6	*	35.1	35.3	22	36.8	37.3	37.3	34.0	37.6	37.4[c]	33.8	34.6
8	41.6	41.6	40.8	41.0	42.3	*	40.4	40.6	23	113.9	113.9	28.2	28.1	113.9	24.4[c]	112.9	113.1
9	44.0	44.2	50.7	50.5	51.4	48.1[e]	40.4	40.6	24	23.5[b]	23.6[b]	15.4	15.4	21.4[b]	32.3[c]	23.1	23.1
10	44.0	44.2	37.3	37.3	46.7	46.5	38.9	39.1	25	18.9[b]	19.0[b]	16.1	16.1	17.1[b]	18.5[b]	20.3	20.3
11	70.2	70.6	21.0	20.9	69.8	68.3	21.2	21.4	26	17.9[b]	17.9[b]	16.1	16.1	15.3[b]	17.6[b]	16.1	15.9
12	32.2	32.5	25.6	25.2	33.5	35.2[d]	24.5	24.6	27	13.8	13.8	14.8	14.8	14.6	15.0	14.6	14.8
13	35.2	35.3	38.2	37.2	36.8	37.0	37.2	37.2	28	175.0	178.6	178.9	60.2	180.5	179.6	60.1	62.6
14	42.1	42.2	42.5	42.8	42.8	42.5	40.3	43.1	29	18.9	19.0	19.4	19.1	19.3	18.9	19.0	19.3
15	30.7	31.1	30.8	27.1	30.5	30.5	27.0	27.1	30	110.6	110.6	109.4	109.7	110.4	110.2	109.6	109.9

a: measured in C_5D_5N; b-e: may be interchanged; *: obscure (overlapped by other signal).

Chart 2



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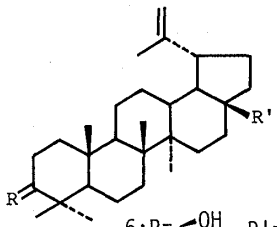
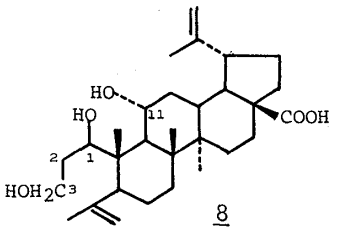


6: R= R'=-COOH

7: R=  R'=-CH_2OH

11: R= =O R'=-COOH

12: R= =NOH R'=-COOH



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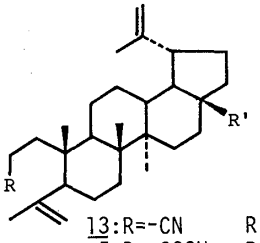

13: R=-CN R'=-COOH

5: R=-COOH R'=-COOH

14: R=-COOMe R'=-COOMe

10: R=-CH_2OH R'=-CH_2OH

15: R=-CH_2OAc R'=-CH_2OAc

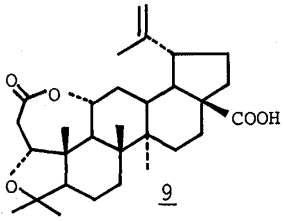

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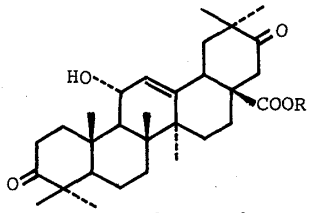
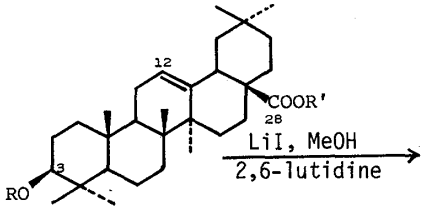
Table III. ^{13}C-Chemical Shifts (δ) of Sugar Moiety in C_5D_5N

Carbon	1	16[9)]
Glc-1	95.2	96.1
-2	73.8	73.8
-3	78.4	78.4
-4	70.5	70.7
-5	76.3	76.4
-6	69.2	69.3
Glc-1'	104.7	104.8
-2'	75.2	75.2
-3'	76.9	76.4
-4'	78.4	78.0
-5'	77.8	77.1
-6'	61.3	61.2
Rha-1	102.5	102.7
-2	72.5[a]	72.6
-3	72.3[a]	72.6
-4	73.8	73.8
-5	70.2	70.2
-6	18.3	18.4

a: may be reversed.

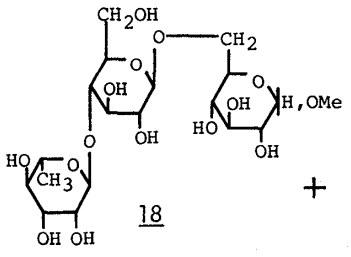


16: R=β-Glc^{6}—β-Glc^{4}—α-Rha



17: R=α-Ara^{2}—α-Rha^{3}—β-Rib

R'=β-Glc^{6}—β-Glc^{4}—α-Rha



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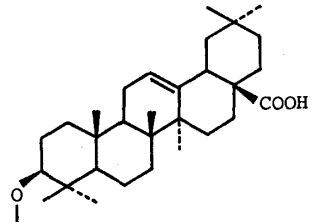

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by the abnormal Beckmann rearrangement.[6] Assignment of the carbon signals of 10 was established by comparison with the spectrum of its diacetate (15) in consideration of the acetylation shift.[7] It was substantiated that all of the carbon signals due to the D and E rings of 5 appeared in the spectrum of 8 and the signals due to carbons on the A, B and C rings of 8 could be reasonably assigned considering the hydroxylation shifts[8] at C-1 and -11α positions of 10 (Table II).

The MS of a peracetate of 1 exhibited fragment ions at m/z 849 [(Glc-Glc-Rha)Ac_9], 561[(Glc-Rha)Ac_6] and 273(terminal Rha-Ac_3). On going from 2 to 1, the signal due to the carboxyl carbon (δ 178.6) was displaced to δ 175.0 while other carbon signals remained almost unshifted, indicating that a glycosyl linkage of 1 must be located at its 28-carboxyl group. On searching the carbon signal assignments of rhamnosyl-glucosyl-glucosyl ester units in the literature, the carbon signals of the sugar moiety of 1 were found to be identical with those of papyrioside L-IIc(16), an oligo-glycosyl ester from Tetrapanax papiriferum (Araliaceae)[9] as shown in Table III. Recently, we have found that on refluxing with anhydrous LiI and 2,6-lutidine in anhydrous methanol, a glycosyl ester linkage at the 28-carboxylic acid of triterpenes can be selectively cleaved without any cleavage of 3-O-glycoside bonding to give quantitatively a corresponding methyl glycoside (an anomeric mixture) together with its sapogenin or prosapogenin.[10] For instance, the treatment of huzhangoside B (17) recently isolated from Anemone rivularis (Ranunculaceae) under this condition afforded methyl oligo-glycoside (18) and its prosapogenin (19) almost quantitatively as shown in Chart 2.[11] Treatment of 1 under the same condition yielded a methyl oligo-glycoside which was identical with 18. It follows that 1 can be formulated as α-L-rhamnopyranosyl(1⟶4)-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl ester of 2. This is the first example of the glycosides of 3,4-seco-triterpenes in nature.

ACKNOWLEDGEMENT The authors are grateful to Professor T. Nakajima and Miss N. Yoshida, Tokyo Medical and Dental University for the measurement of ^1H NMR at 270MHz and to JEOL Co. Ltd. for the measurement of ^1H NMR at 400MHz. Thanks are also due to Professor T.Suga, Faculty of Science, Hiroshima University for his advice on 3,4-seco-triterpenes.

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(Received January 5, 1984)