

# SYNTHESIS OF THE GINSENG GLYCOSIDES AND THEIR ANALOGS

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## ABSTRACT

In an attempt toward the synthesis of the difficultly accessible ginseng saponins the four dammarane glycosides identical to the natural ginsenosides -Rh<sub>2</sub>, -F<sub>2</sub>, compound K and chikusetsusaponin -LT<sub>8</sub> have been prepared from betulafolienetriol (= dammar - 24 - ene - 3 $\alpha$ , 12 $\beta$  20(S) - triol). 3 - O -  $\beta$  - D - Glucopyranoside of 20(S) - protopanaxadiol (= ginsenoside -Rh<sub>2</sub>) have been obtained by the regio- and stereoselective glycosylation of the 12 - O - acetyldammar - 24 - ene - 3 $\beta$ , 12 $\beta$ , 20(S) - triol. The 12 - ketoderivative of 20(S) - protopanaxadiol has been used as aglycon in synthesis of chikusetsusaponin -LT<sub>8</sub>. Attempted regio- and stereoselective glycosylation of the less reactive tertiary C - 20 - hydroxyl group in order to synthesize the 20 - O -  $\beta$  - D - glucopyranoside of 20(S) - protopanaxadiol (= compound K) using 3, 12 - di - O - acetyldammar - 24 - ene - 3 $\beta$ , 12 $\beta$ , 20(S) - triol as aglycon was unsuccessful. Glycosylation of 3, 12 - diketone of betulafolienetriol followed by NaBH<sub>4</sub> reduction yielded the 20 - O -  $\beta$  - D - glucopyranoside of dammar - 24 - ene - 3 $\beta$ , 12 $\alpha$ , 20(S) - triol, the 12 $\alpha$  - epimer of 20(S) - protopanaxadiol. Moreover, a number of semisynthetic ocotillo - type glucosides, analogs of natural pseudoginsenosides, have been prepared.

## INTRODUCTION

Ginseng, the famous plant drug has been used as an expensive traditional medicine in oriental countries for more than 5000 years. Since the beginning of this century, a number of Japanese, European, Korean chemists have concerned themselves with isolation and structure elucidation of ginseng saponins. However, even the basic skeleton of the major sapogenin was not characterized until 1960. After many twists and turns it was determined that the major saponins of ginseng were not oleanane oligoglycosides, which are very common in nature, but that the genuine sapogenins were represented by triterpenes of the dammarane type (Ref. 1, 2). This was the first example of the occurrence of dammarane saponins in nature.

Sapogenins named panaxadiol and panaxatriol were isolated from the crude ginseng saponin mixture by hydrolysis with dilute mineral acid in boiling aqueous ethanol. The skeletons of panaxadiol and panaxatriol (6 $\alpha$  - hydroxypanaxadiol) were found to be a tetracyclic triterpenes with a trimethyl pyran ring at the 17 - position (Fig. 1). Meanwhile by the intensive chemical studies on hydrolysis of ginseng saponins it

was concluded that the panaxadiol and panaxatriol must be artifacts formed during acid hydrolysis. The genuine saponins seemed to be substances which were named 20(S) - protopanaxadiol and 20(S) - protopanaxatriol (Fig. 2).

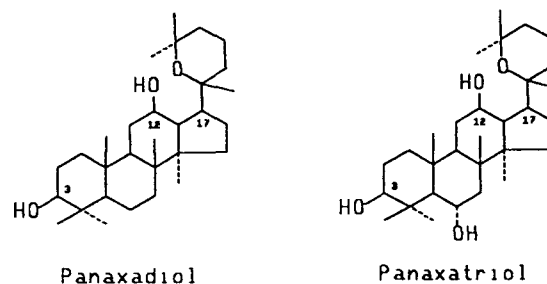


Fig. 1

The complications encountered in the isolation and structure determination were mainly due to an unexpected acid catalyzed epimerization of the tertiary hydroxyl group at C - 20(S) to C - 20(R) which was followed by cyclization of side chain. The presence of a  $\beta$  - hydroxyl group on C - 12 was shown to be essential for this acid catalyzed reaction, since compounds without such a group underwent dehydration of the tertiary hydroxyl on C - 20 in preference to epimerization and cyclization of the side chain. This undesirable reaction accompanied acid hydrolysis of the saponins to the sapogenins. Up to now the isolation and

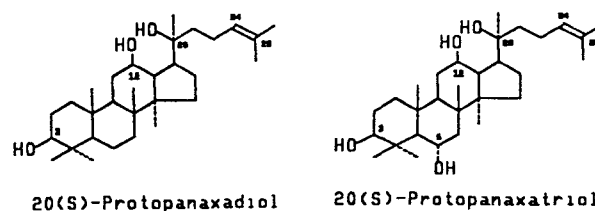


Fig. 2

structural elucidation of most of the ginseng saponins, ginsenosides have been performed [Ref. 3]. The common sapogenin of ginsenosides -Rb<sub>1</sub>, -Rb<sub>2</sub>, -Rc and -Rd is represented by 20(S) - protopanaxadiol (dammar - 24 - ene - 3 $\beta$ , 12 $\beta$ , 20(S) - triol) (1) and that of ginsenosides -Re, -Rf, -Rg<sub>1</sub> and -Rg<sub>2</sub> is formulated as 20(S) - protopanaxatriol (dammar - 24 - ene - 3 $\beta$ , 6 $\alpha$ , 12 $\beta$ , 20(S) - tetraol). The sugar moieties of the gi-

nosenosides whose sapogenin is 20(S)-protopanaxadiol are attached to C-3-OH and C-20-OH, while those of 20(S)-protopanaxatriol are attached to C-6-OH and C-20-OH, or to C-6-OH only (Fig. 3).

The scarcity of the natural ginsenosides has prompted a search for the routes of synthesis from the relatively accessible substances.

The triterpene of the dammarane series, betula-foliene-triol (dammar-24-ene-3 $\alpha$ ,12 $\beta$ , 20(S)-triol) (2) first isolated from the common birch *Betula Alba* [Ref. 4] and later identified in the leaves of Far-East species of the genus *Betula*, differs from the genuine sapogenin of the *ginseng* saponins, 20(S)-protopanaxadiol, in the configuration at C-3 only.

To this reason triol 2 may be used both as a model compound in glycosylation reactions and as a starting material to prepare 20(S)-protopanaxadiol via 3-keto-derivative 3 followed by NaBH<sub>4</sub> reduction (Fig. 4)

### SEMISYNTHETIC GLUCOSIDES OF BETULAFOLIENETRIOL AND 20(S)-PROTOPANAXADIOL

Choosing a method for the synthesis of glycosides of rare polycyclic alcohols, it is desirable to promote stereospecificity and impede reactions that regenerate the initial alcohols. We have shown that the orthoester and Helferich methods for glycosylating steroid and triterpene alcohols are most highly stereospecific [Ref. 5, 6].

Condensation of betulafoliene-triol 2 with 3, 4, 6-tri-O-acetyl-D-glucose 1, 2-(tert-Butyl orthoacetate) in chlorobenzene in the presence of 2, 4, 6-tri-methylpyridinium perchlorate (2, 4, 6-collidinium perchlorate) under azeotropic distillation results in dehydration of the side chain to give the 20-dehydroxyglucosides 4-6 (Fig. 5).

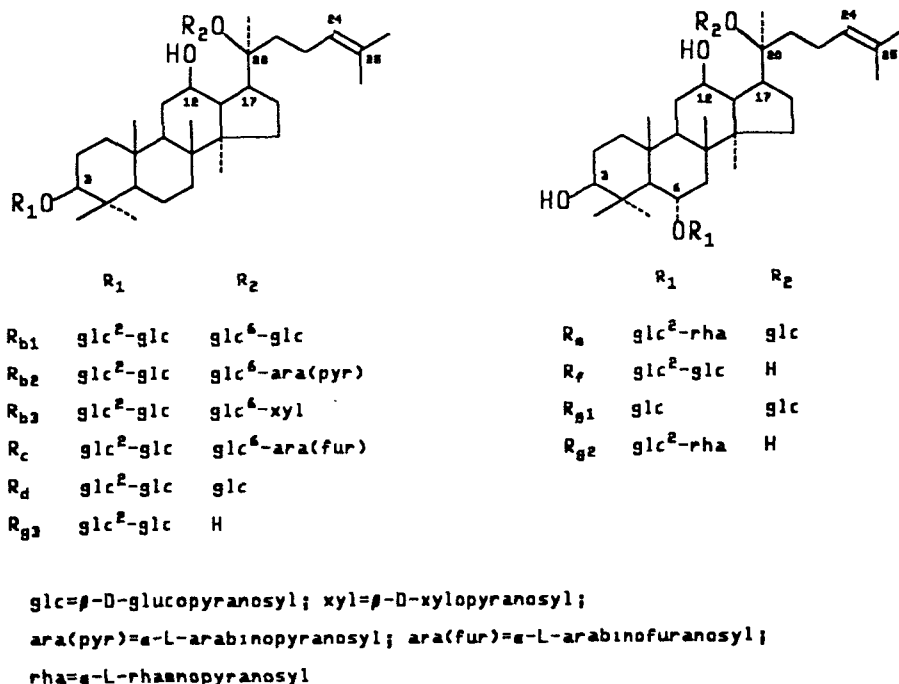


Fig. 3

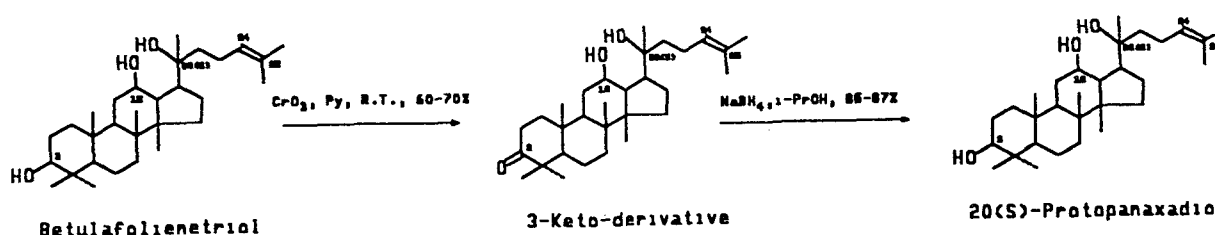


Fig. 4

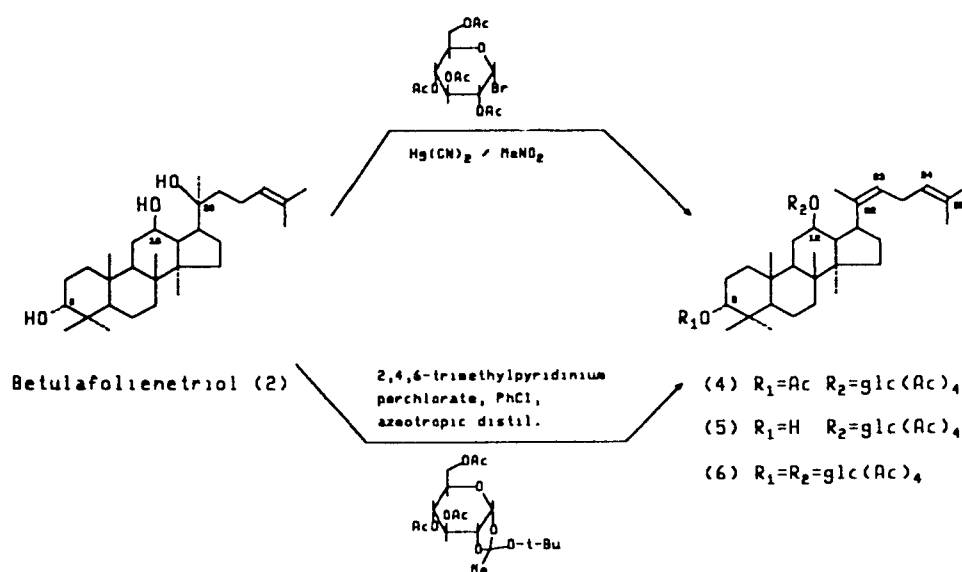


Fig. 5

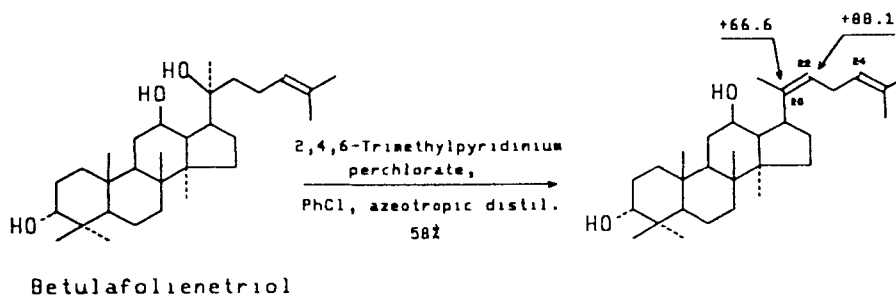


Fig. 6

Attempts of glycosylation of triol 2 with 2, 3, 4, 6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide ( $\alpha$ -acetobromo-glucose) in the presence of mercuric cyanide in nitromethane (Helferich method) were unsuccessful and the 20-dehydroxyglucosides 4 - 6 were obtained, too [Ref. 7]. When triol 2 was heated with a catalytic amount of 2, 4, 6-collidinium perchlorate under the conditions of chlorobenzene azeotropic distillation for 15 min. a mixture of weakly polar products was obtained in which dammar-20(22), 24-diene-3 $\alpha$ , 12 $\beta$ -diol 7, formed via side chain dehydration of the parent alcohol, preponderated (yield 58%) (Fig. 6).

The less reactive tertiary hydroxyl group at C-20 is extremely sensitive to these conditions and the aglycon tends to undergo dehydration. To this reason the use of orthoester and Helferich methods for glycosylating 20-hydroxy-24-ene-type dammarane triterpenes should be avoided.

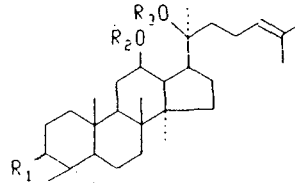
Glycosylation of betulafolienetriol 2 and 20(S)-protopanaxadiol 1 (20-hydroxy-24-ene-type dammarane triterpenes) with  $\alpha$ -acetobromoglucose in the presence of silver

oxide in dichloromethane (Koenigs-Knorr conditions) gives a mixture of the acetylated 3-, 12-, 20-mono-, 3, 12-di- and 3, 20-di-O- $\beta$ -D-glucopyranosyl derivatives 8 - 17 in 83-84.5% total yield (Fig. 7).

Under similar conditions, the 3-O-acetyl derivatives 18, 19 give a mixture of the corresponding 12- and 20-O- $\beta$ -D-glucopyranosides 20 - 23 [Fig. 9] Attempted glycosylation of the diacetates 25, 26 was unsuccessful and gave only unchanged starting material.

The nonstereoselective location of glycosylation of dammarane triols 1 and 2 under Koenigs-Knorr conditions results in the formation of almost all of the possible products (Fig. 8).

However, isolation of the individual compounds in pure state from the prepared glucoside mixtures could not be accomplished as the chromatographic behavior of regioisomeric glucosides did not differ appreciably. For example, the mixture of 12- and 20-O-monoglucoside tetraacetates of 20(S)-protopanaxadiol 14 and 15 was amenable to fractio-



- (8)  $R_1 = \alpha\text{-Oglc}(\text{Ac})_4$   $R_2 = R_3 = \text{H}$   
 (9)  $R_1 = \alpha\text{-OH}$   $R_2 = \text{Oglc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (10)  $R_1 = \alpha\text{-OH}$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (11)  $R_1 = \alpha\text{-Oglc}(\text{Ac})_4$   $R_2 = \text{glc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (12)  $R_1 = \alpha\text{-Oglc}(\text{Ac})_4$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (13)  $R_1 = \beta\text{-Oglc}(\text{Ac})_4$   $R_2 = R_3 = \text{H}$   
 (14)  $R_1 = \beta\text{-OH}$   $R_2 = \text{glc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (15)  $R_1 = \beta\text{-OH}$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (16)  $R_1 = \beta\text{-Oglc}(\text{Ac})_4$   $R_2 = \text{glc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (17)  $R_1 = \beta\text{-Oglc}(\text{Ac})_4$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (18)  $R_1 = \alpha\text{-OAc}$   $R_2 = R_3 = \text{H}$   
 (19)  $R_1 = \beta\text{-OAc}$   $R_2 = R_3 = \text{H}$   
 (20)  $R_1 = \alpha\text{-OAc}$   $R_2 = \text{glc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (21)  $R_1 = \alpha\text{-OAc}$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (22)  $R_1 = \beta\text{-OAc}$   $R_2 = \text{glc}(\text{Ac})_4$   $R_3 = \text{H}$   
 (23)  $R_1 = \beta\text{-OAc}$   $R_2 = \text{H}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (24)  $R_1 = \beta\text{-OAc}$   $R_2 = \text{Ac}$   $R_3 = \text{glc}(\text{Ac})_4$   
 (25)  $R_1 = \alpha\text{-OAc}$   $R_2 = \text{Ac}$   $R_3 = \text{H}$   
 (26)  $R_1 = \beta\text{-OAc}$   $R_2 = \text{Ac}$   $R_3 = \text{H}$   
 (27)  $R_1 = \beta\text{-Oglc}$   $R_2 = \text{H}$   $R_3 = \text{H}$   
 (28)  $R_1 = \beta\text{-OH}$   $R_2 = \text{glc}$   $R_3 = \text{H}$   
 (29)  $R_1 = \beta\text{-OH}$   $R_2 = \text{H}$   $R_3 = \text{glc}$   
 (30)  $R_1 = \beta\text{-Oglc}$   $R_2 = \text{glc}$   $R_3 = \text{H}$   
 (31)  $R_1 = \beta\text{-Oglc}$   $R_2 = \text{H}$   $R_3 = \text{glc}$   
 (32)  $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{H}$   $R_3 = \text{H}$   
 (33)  $R_1 = \alpha\text{-OH}$   $R_2 = \text{glc}$   $R_3 = \text{H}$   
 (34)  $R_1 = \alpha\text{-OH}$   $R_2 = \text{H}$   $R_3 = \text{glc}$   
 (35)  $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{glc}$   $R_3 = \text{H}$   
 (36)  $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{H}$   $R_3 = \text{glc}$

Fig. 7

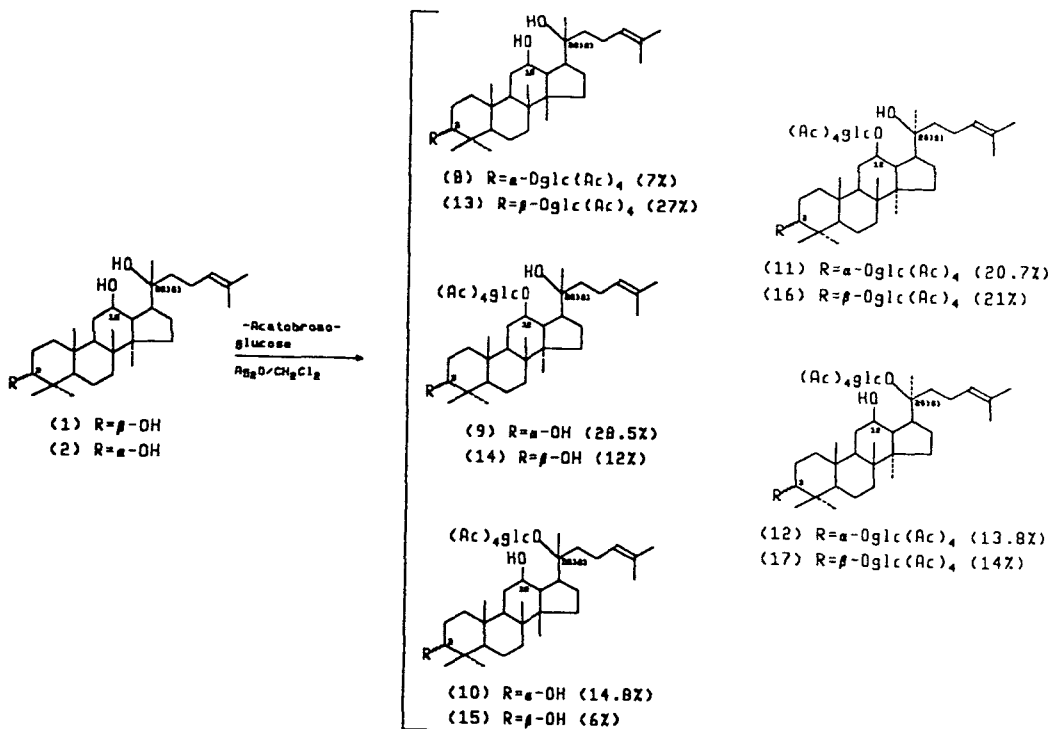


Fig. 8

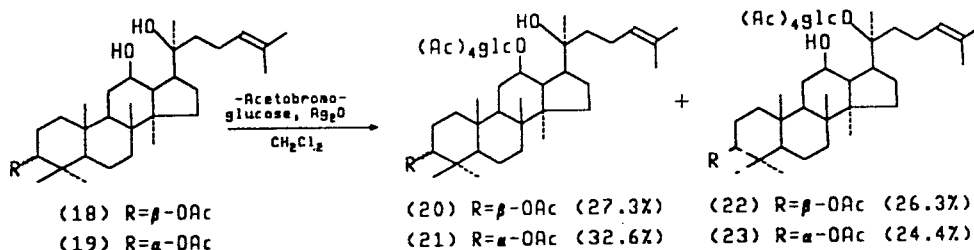


Fig. 9

nation only after supplementary acetylation (to 12-O- $\beta$ -D-glucoside pentaacetate 22 and 20-O- $\beta$ -D-glucoside hexaacetate 24).

The structures of glucosides 8-24 have been established on the basis of IR,  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectroscopy data. The doublets at  $\delta$  4.50-4.85 (J1, 27.8-8.0 Hz) for the anomeric protons of the sugar components of acetylated glucosides are indicative of  $\beta$ -linkages. The locations of the carbohydrate moieties were determined by comparing the  $^{13}\text{C}$ -NMR spectra of the parent triols 1 and 2 with those of the derived glucosides (Fig. 10).

The 20-O- $\beta$ -D-glucopyranoside hexaacetate 24 was identical (by physical constants and spectra) with the

20-O- $\beta$ -D-glucopyranoside hexaacetate of 20(S)-protopanaxadiol (compound K), obtained by enzymatic hydrolysis of ginsenosides -Rb<sub>1</sub>, -Rb<sub>2</sub>, -Rc [Ref. 8].

Deacetylation of glucosides 8-17 with methanolic 0.1N sodium methoxide gave corresponding products 27-36 (Fig. 7) in 90-98% yield.

The 3-O- $\beta$ -D-glucopyranoside 27 and 3, 20-di-O- $\beta$ -D-glucopyranoside 31 were identical (by physical constants and spectra) with the natural ginsenoside -Rh<sub>2</sub>, first obtained by the mild hydrolysis of the ginsenosides -Rb, -Rc and -Rd [Ref. 9], and ginsenoside -F2 isolated from the leaves of *Panax ginseng* [Ref. 10].

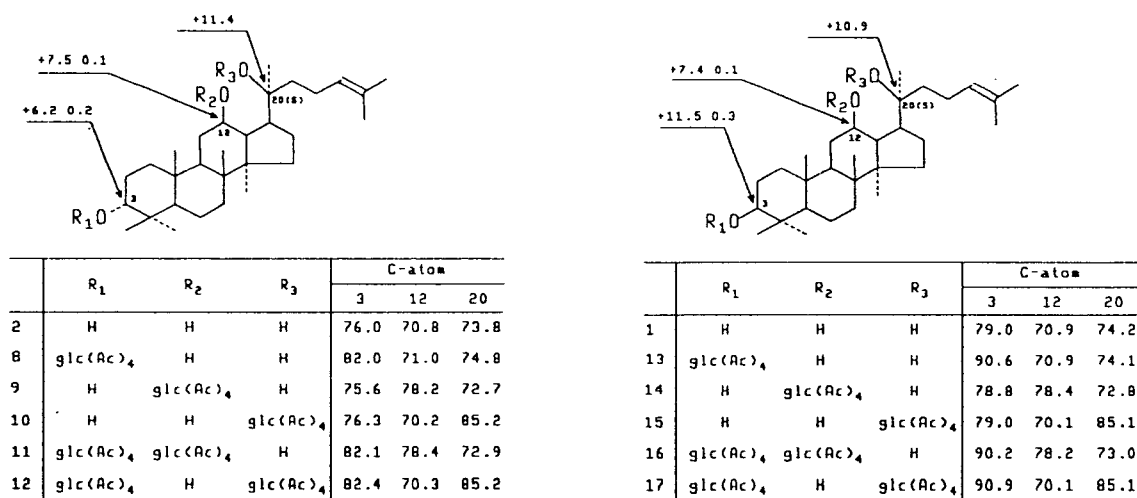


Fig. 10

### REGIO- AND STEREOSELECTIVE SYNTHESIS OF THE 3-O- $\beta$ -D-GLUCOPYRANOSYL-DAMMAR-24-ENE-3 $\beta$ , 12 $\beta$ , 20(S)-TRIOL (GINSENOSE -Rh<sub>2</sub>).

The 3-O- $\beta$ -D-glucopyranosyl derivative of 20(S)-protopanaxadiol (ginsenoside -Rh<sub>2</sub>) 27 has a capacity to inhibit the growth and to induce the redifferentiation of tumor cells [Ref. 11, 12].

As mentioned above, the complications encountered in the separations of glucoside mixtures and isolation of individual

compounds in the pure state were mainly due to nonstereoselective location of glycosylation of the dammarane triols 1 and 2.

12-O-Acetyl derivative of 20(S)-protopanaxadiol 37 is the most convenient aglycon for the regio-selective introduction of carbohydrate residue into C-3 position of triol 1, because the tertiary C-20-hydroxyl group in the compounds having 12 $\beta$ -acetoxy group is sterically hindered and therefore resistant toward glycosylation. However, both the partial acetylation of triol 1 with acetic anhydride in pyridine

and deacetylation of 3, 12 - di - O - acetyl derivative 26 with methanolic 0.1N sodium methoxide gives the 3 - O - acetate 19 (Fig. 11). 12 - O - Acetate 37 has been prepared from betulafolienetriol 2 by the following sequence of reactions (Fig. 12). The triol 2 was oxidized to 3 - ketoderivative 3, which was acetylated with acetic anhydride in pyridine to 3 - keto - 12 - O - acetate 38. NaBH<sub>4</sub> reduction of 3 - keto - 12 - acetate 38 afforded 12 - O - acetyl - 20(S) - protopanaxadiol 37.

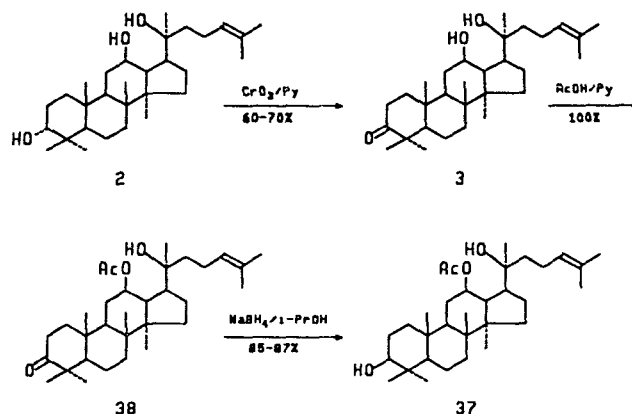


Fig. 12

Condensation of the 12 - O - acetyl derivative 37 with  $\alpha$  - acetobromoglucose in the presence of silver oxide or silver silicate in dichloroethane results in regio - and stereo selective formation of the 3 - O -  $\beta$  - D - glucopyranoside penta - acetate of 20(S) - proto - panaxadiol 39 (yield 50%) (Fig. 13). Moreover, the orthoester 40 isomeric with the glucoside 39 was detected in the reaction mixture (yield 8%). After the removal of the protecting groups the 3 - O -  $\beta$  - D - glucopyranoside of 20(S) - protopanaxadiol 27 identical (by physical constants and spectra) with natural ginsenoside - Rh<sub>2</sub> [Ref. 9] have been obtained.

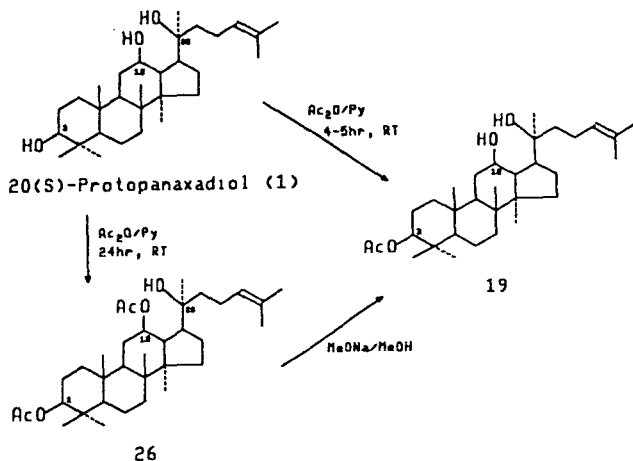


Fig. 11

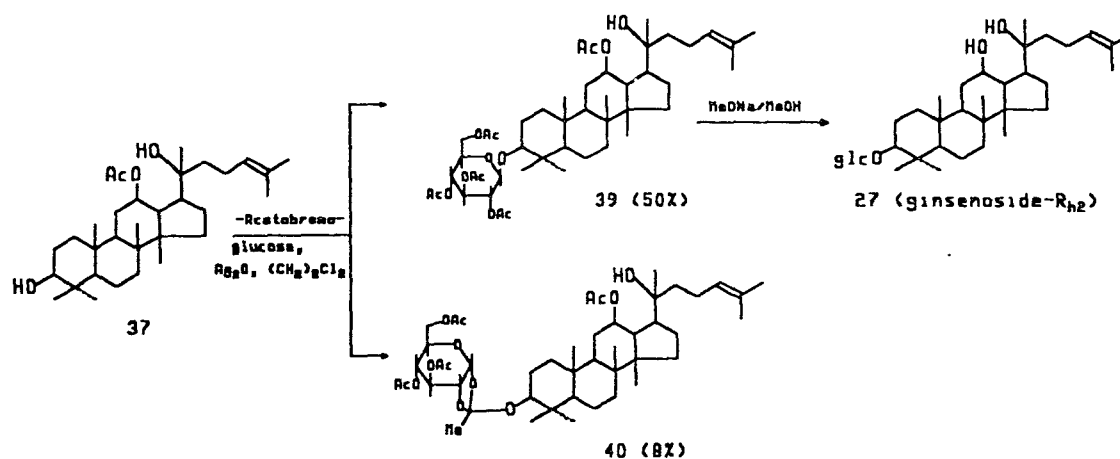


Fig. 13

### SYNTHESIS OF 20 - O - $\beta$ - D - GLUCOPYRANOSIDE OF DAMMAR - 24 - ENE - 3 $\beta$ , 12 $\alpha$ , 20(S) - TRIOL

At present we are studying the various ways for regio - and stereoselective glycosylating the less reactive tertiary C - 20 hydroxyl group in order to simplify the preparations of 20 - O - glycosides of 20(S) - protopanaxadiol.

As mentioned above attempted glycosylation of 3, 12 -

diacetates 26 and 27 was unsuccessful to give only unchanged starting material.

The 3, 12 - diketone of betulafolienetriol 41 may be used as aglycon for regioselective glycosylation of the C - 20 - hydroxyl group. Condensation of diketone 41 with  $\alpha$  - acetobromoglucose results in corresponding 20 - O -  $\beta$  - D - glucopyranoside 42, which after deacetylation and followed NaBH<sub>4</sub> reduction yielded the 20 - O -  $\beta$  - D - glucopyranoside of dammar - 24 - ene - 3 $\beta$ , 12 $\alpha$ , 20(S) - triol 43, 12 $\alpha$  - epimer of 2

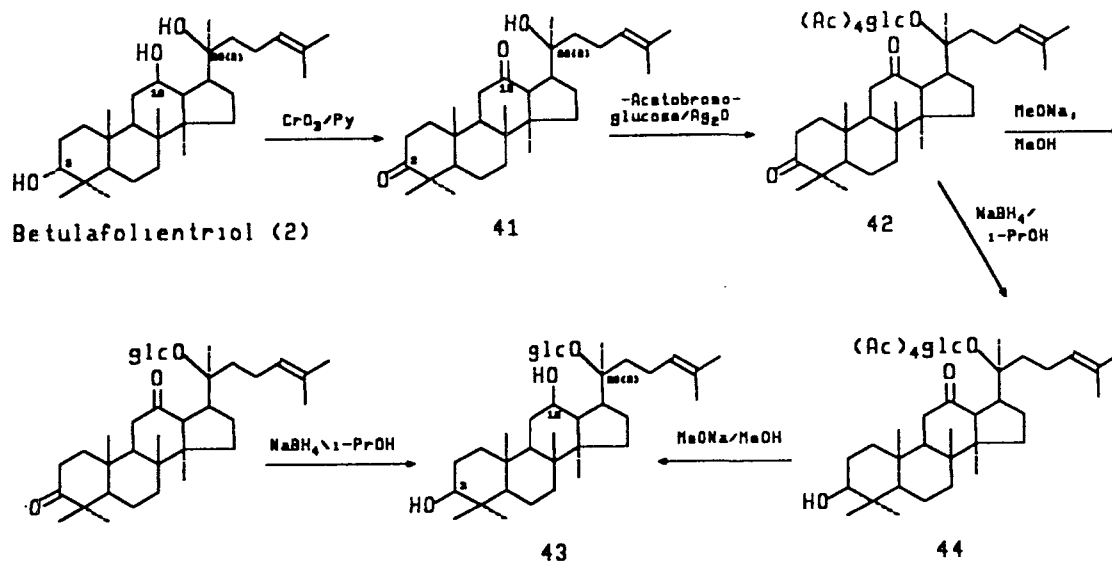


Fig. 14

0(S) - protopanaxadiol (Fig. 14).

It should be noted that the  $\text{NaBH}_4$  treatment of acetylated 20-O-β-D-glucoside 42 gives the 20-O-β-D-glucopyranoside tetraacetate of dammar-24-ene-3β, 20(S)-diol-12-one 44 reducing the 3-keto group only.

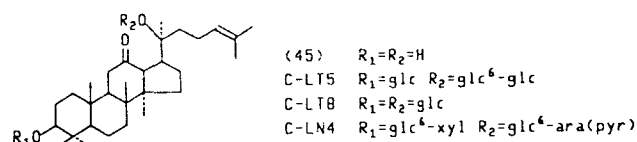


Fig. 15

### SYNTHESIS OF THE 3, 20-DI-O-β-D-GLUCOPYRANOSIDE OF DAMMAR-24-ENE-3β, 20(S)-DIOL-12-ONE (CHIKUSETUSAPONIN-LT8)

The major saponins isolated from the leaves of *Panax Japonicus* collected on the Japan Sea coast and named chikusetsusaponins-LT5, -LT8, -LN4 [Ref. 13] were based on 12-ketone of 20(S)-protopanaxadiol 45 (Fig. 15).

12-Ketone 45 has been used as aglycon in synthesis of 3, 20-di-O-β-D-glucopyranoside 46, identical to natural chikusetsusaponin-LT8.

We prepared the 12-ketoderivative of 20(S)-protopanaxadiol 45 from betulafolienetriol 2 by the following sequence of reactions (Fig. 16). Betulafolienetriol 2, constituent of

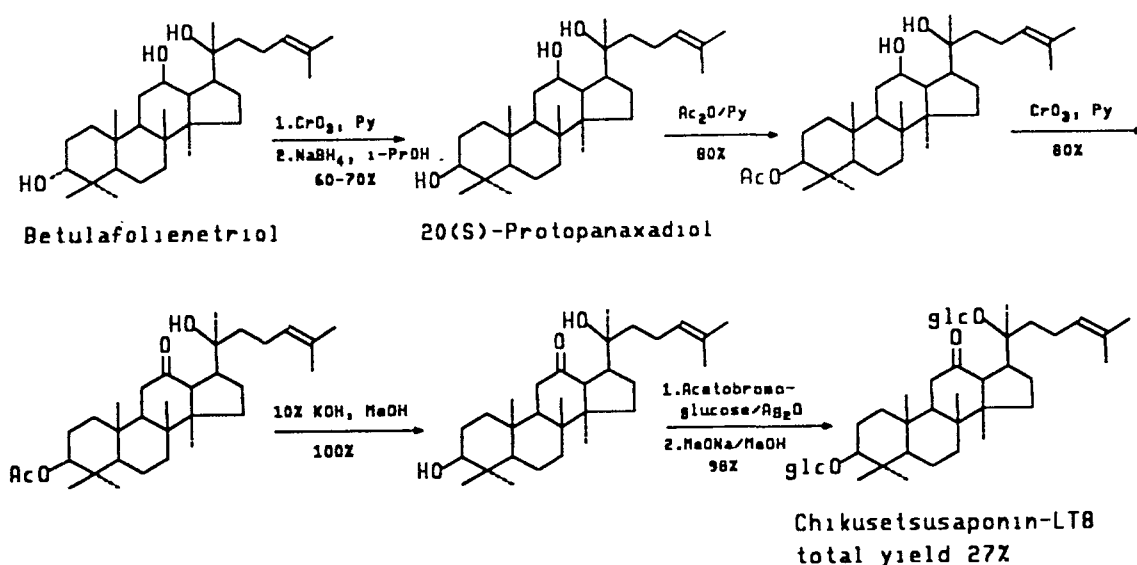
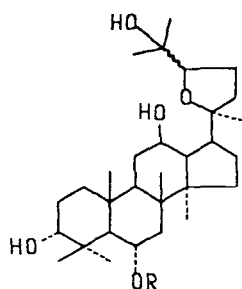


Fig. 16

*Betula* leaves, was converted into 20(S) - protopanaxadiol 1 by the procedure described earlier (Fig. 4). Acetylation of triol 1 under the usual conditions afforded the 3 - monoacetate 47 which was oxidized to the 3 - O - acetyl - 12 - ketone 48. Treatment of 48 with 10% methanolic KOH resulted in the 12 - ketone of 20(S) - protopanaxadiol 45.

Condensation of the 12 - ketone 45 with  $\alpha$  - acetobromoglucose under Koenigs - Knorr conditions gave the 3, 20 - di - O -  $\beta$  - D - glucopyranoside octaacetate of dammar - 24 - ene - 3 $\beta$ , 20(S) - diol - 12 - one, which was deacetylated with sodium methoxide yielding 3, 20 - diglucoside 46 quantitatively.



R = Glc<sup>2</sup> - Glc, 24(S)

R = Glc<sup>2</sup> - Xyl, 24(S)

R = Glc<sup>2</sup> - Rha, 24(R)

R = Glc<sup>2</sup> - Xyl, 24(R)

R = Glc, 24(S)

R = Glc, 24(R)

Majonoside-R1

Majonoside-R2

Pseudoginsenoside-F11

Pseudoginsenoside-RT2

Pseudoginsenoside-RT4

Pseudoginsenoside-RTE

Glc =  $\beta$ -D-Glucopyranosyl

Xyl =  $\beta$ -D-Xylopyranosyl

Rha =  $\alpha$ -L-Rhamnopyranosyl

Fig. 17

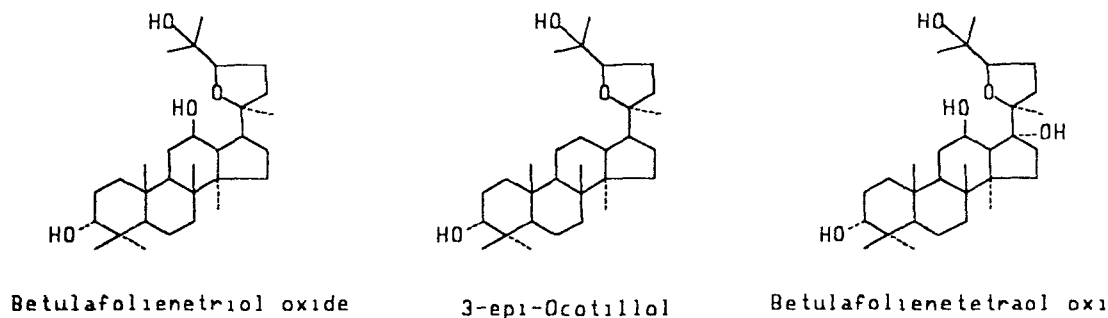


Fig. 18

tetriol(20 - hydroxy - 24 - ene - type triterpenes).

Ocotillol - type glucosides have been obtained using as the Koenigs - Knorr, Helferich as orthoester methods. The results of numerous experiments indicate that the formation of the 12 - mono - , 12, 25 - di - , 3, 12, 25 - tri - O -  $\beta$  - D - glucopyranosides took place under the orthoester and Helferich conditions whereas 3 - mono - and 3, 12 - di - O -  $\beta$  - D - glucosides preponderated when Koenigs - Knorr conditions were applied (Fig. 19).

It should be noted that the presence of the strong hydrogen bonding between the 12 $\beta$  - hydroxyl group and the oxygen of

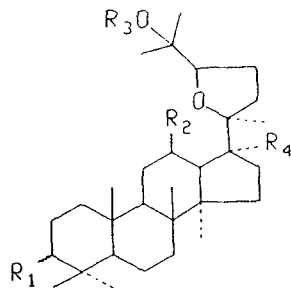
## SEMISYNTHETIC OCOTILLOL - TYPE GLUCOSIDES

Synthesis of ocotillol - type glucosides, analogs of natural pseudoginsenosides and majonosides [Ref. 14] (Fig. 17), is of interest in connection with studies on the behaviour of dammarane polyols in glycosilation reaction.

Dammarane polyols having the cyclized side chain of a substituted tetrahydrofuran ring (20, 24 - epoxy - type ; ocotillol - type), betulafolienetriol oxide 49, betulafolienetriol 50, 3 - epi - ocotillol 51 (Fig. 18) have also been isolated from the *Betula* leaves along with betulafolienetriol and betulafoliene-

the tetrahydrofuran ring of the 20(S), 24(R) - epoxy - dammarane - 3, 12 $\beta$ , 25 - triols 49 and 52 allowed to obtain 12 - O -  $\beta$  - D - glucosides 54, 55 without partial protection of the C - 3 - and C - 25 - hydroxyl groups. Glycosylation of triols 49 and 52, containing free hydroxyl groups, with equimolar amounts of mercury cyanide and acetobromoglucose in dry nitromethane at 90°C was regio - and stereo - selective yielding corresponding 20 - O -  $\beta$  - D - glucosides 54, 55 (yield 72 - 73%) [Ref. 15] (Fig. 20). In the first stage the interaction of triols 49 and 52 with mercury cyanide, probably, results in the formation of intermediate (ion pair) 53 increasing the nu-





$R_1 = \alpha\text{-OH}$   $R_2 = \text{Oglc}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \beta\text{-OH}$   $R_2 = \text{Oglc}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{OH}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \beta\text{-Oglc}$   $R_2 = \text{OH}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \alpha\text{-OH}$   $R_2 = \text{OH}$   $R_3 = \text{glc}$   $R_4 = \text{H}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \beta\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = R_4 = \text{H}$   
 $R_1 = \alpha\text{-OH}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{H}$   
 $R_1 = \beta\text{-OH}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{H}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{H}$

$R_1 = \alpha\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{H}$   
 $R_1 = \beta\text{-Oglc}$   $R_2 = \text{OH}$   $R_3 = \text{H}$   $R_4 = \text{OH}$   
 $R_1 = \alpha\text{-OH}$   $R_2 = \text{glc}$   $R_3 = \text{H}$   $R_4 = \text{OH}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = \text{H}$   $R_4 = \text{OH}$   
 $R_1 = \alpha\text{-OH}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{OH}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = \text{Oglc}$   $R_3 = \text{glc}$   $R_4 = \text{OH}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = R_3 = R_4 = \text{H}$   
 $R_1 = \alpha\text{-OH}$   $R_2 = R_4 = \text{H}$   $R_3 = \text{glc}$   
 $R_1 = \alpha\text{-Oglc}$   $R_2 = R_4 = \text{H}$   $R_3 = \text{glc}$

Fig. 19

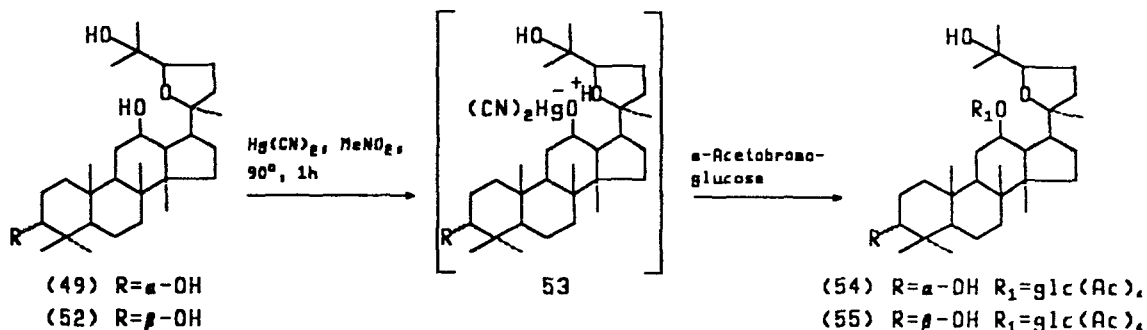


Fig. 20

cleophilic reactivity of the C-12-oxygen atom at the glycosylation reaction.

### BIOLOGICAL ACTIVITIES OF DAMMARANE GLYCOSIDES

Antimicrobial, membranotropic and cytostatic activities of the dammarane glycosides have been studied in order to elucidate the structure-activity relationship [Ref. 16, 17]. Some of the compounds studied inhibit *in Vitro* the reproduction of grampositive bacteria *Staphylococcus aureus* strain 209 and the growth of *Ehrlich carcinoma* cells and affect on the sta-

bility of lipid membranes. All the activities were shown to be dependent on the type of side chain in aglycon and on number and positions of the carbohydrate residues. Glucosides having an open side chain (20-hydroxy-24-ene-type) in their aglycons are more active than glucosides whose aglycons have the cyclized side chain (20, 24-epoxy-type). At this configuration of the hydroxyl group at C-3 doesn't have a considerable influence upon their activities. Most of the semisynthetic dammarane glucosides are usually more active than corresponding polyols.

Glucosides having one glucose residue are usually more active than those which have two glucose residues. These

results are in good agreement with literature data according to which the ginsenosides having less sugar moieties are more intense in antihepatotoxic and antitumor activities as composed with those having more sugar moieties[18].

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