GLYCOSYLATION OF TRITERPENOIDS OF THE DAMMARANE SERIES.

VII. DAMMAR-24-ENE-3α,12β,17α,20(S)-TETRAOL β-D-GLUCOPYRANOSIDES

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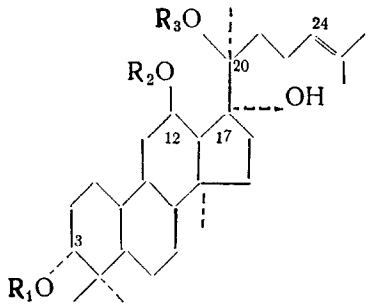
UDC 547.917+547.918+547.597

Glucosides have been synthesized from dammar-24-ene-3α,12β,17α,20(S)-tetraol (betulafolienetetraol), isolated from the leaves of Betula pendula. Condensation with α-acetobromoglucose in the presence of silver oxide and silicate has given acetylated betulafolienetetraol 3- and 12- mono- and 3,12- and 3,20-di-O-β-D-glucopyranosides, the total yield of which amounted to 75-80%. The structures of the semisynthetic glycosides have been established on the basis of the results of IR, $^1H$ and $^{13}C$ NMR spectroscopy.

For a comparative study of the biological activity of dammarane glycosides isolated from ginseng and their closest semisynthetic analogs we have performed a syntheses from dammar-24-ene-3α,12β,17α,20(S)-tetraol (I) – one of the main components of the triterpene fraction of an extract of birch leaves [1]. The tetraol (I) was first isolated by Fischer and Seiler from the leaves of the European white birch Betula alba [2]. Tetraol (I) differs from the native genin of ginsenosides $R_e$, $R_{g1}$, $R_{g2}$, $R_f$ – 20(5)-protopanaxatriol [3] – by the orientation of the hydroxy group at C-3 and the position of one of the four hydroxy groups: in the native genin, a hydroxy group is present at C-6, while in compound (I) it is at C-17.




I. $R_1=R_2=R_3=H$
II. $R_1=Glc(OAc)_4$; $R_2=R_3=H$
III. $R_1=R_3=H$; $R_2=Glc(OAc)_4$
IV. $R_1=R_2=Glc(OAc)_4$; $R_3=H$
V. $R_1=R_3=Glc(OAc)_4$; $R_2=H$

We have previously established that the glycosylation of dammarane triterpenoids with an open side chain under the conditions of the orthoester method and of Helferich's modification is complicated by the competing process of dehydration in the side chain of the aglycon [4] and therefore the condensation of the tetraol (I) with α-acetobromoglucose was effected under the conditions of the classical variant of the Koenigs-Knorr reaction. The results of glycosylation are given in Table 1.

As promoters we used silver oxide, which is traditionally used in the classical variant of the Koenigs-Knorr reaction, and silver silicate, which is a more effective reagent in a number of glycoside syntheses [5].

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Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Branch, USSR Academy of Sciences, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 225-229, March-April, 1988. Original article submitted July 3, 1987; revision submitted October 30, 1987.

 0009-3130/88/2402-0190$12.50 © 1988 Plenum Publishing Corporation

TABLE 1. Conditions and Results of the Condensation of Tetraol (I) with α-Acetobromoglucose in the Presence of Insoluble Silver Compounds

| Experiment No. | Initial substances | | | Reaction products, % | | Recovery of the starting material, % |
|---|---|---|---|---|---|---|
| | alcohol, mmole | α-acetobromoglucose, mmole × n (times) | HBr acceptor, g × n (x) | monoglucosides (II):(III) | diglucosides (IV):(V) | |
| 1 | 1, (I) | 1×3 | $Ag_2O$ 0,234×3 | 62,9 (1:1) | 11,7 (2,5:1) | 9,2 |
| 2 | 1, (I) | 1×4 | Ag silicate 0,750×4 | 62,8 (1:1) | 14,8 (2,5:1) | — |
| 3 | 1, (I) | 1×3 | $Ag_2O$ + 4Å mol, sieve. (0,234+2r)×3 | 49,5 (1:1) | 30,8 (2,5:1) | — |

TABLE 2. $^{13}C$ Chemical Shifts of the Tetraol (I) and Its Glucosides (II)-(V) (δ, ppm relative to PMS)

| C atom | Compound | | | | | C atom | Compound | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | | I | II | III | IV | V |
| 1 | 33,9 | 33,8 | 33,9 | 34,0 | 33,9 | 16 | 37,4 | 37,2 | 38,1 | 38,0 | 37,1 |
| 2 | 25,3 | 20,9 | 25,4 | 20,8 | 21,0 | 17 | 85,6 | 85,3 | 85,1 | 85,1 | 86,2 |
| 3 | 76,1 | 81,6 | 75,9 | 82,1 | 81,9 | 18 | 16,1 | 16,2 | 16,1 | 16,3 | 16,1 |
| 4 | 37,6 | 37,1 | 37,6 | 37,2 | 36,9 | 19 | 16,0 | 16,0 | 15,9 | 15,9 | 16,1 |
| 5 | 49,5 | 49,9 | 49,5 | 49,9 | 49,5 | 20 | 77,3 | 77,4 | 77,0 | 77,0 | 88,5 |
| 6 | 18,3 | 18,0 | 18,3 | 18,0 | 18,1 | 21 | 20,5 | 20,5 | 20,5 | 21,0 | 20,5 |
| 7 | 34,1 | 34,0 | 34,2 | 34,1 | 33,7 | 22 | 36,1 | 36,4 | 36,6 | 36,5 | 36,1 |
| 8 | 40,5 | 40,5 | 40,5 | 40,4 | 40,6 | 23 | 22,7 | 22,7 | 22,6 | 22,6 | 23,1 |
| 9 | 50,0 | 50,3 | 50,0 | 50,0 | 49,8 | 24 | 125,0 | 124,6 | 125,1 | 125,1 | 123,9 |
| 10 | 37,2 | 37,0 | 37,4 | 37,1 | 36,7 | 25 | 131,3 | 131,5 | 131,0 | 130,9 | 131,7 |
| 11 | 32,0 | 31,9 | 27,9 | 27,7 | 30,9 | 26 | 25,8 | 25,6 | 25,7 | 25,7 | 25,6 |
| 12 | 66,9 | 67,3 | 76,5 | 76,4 | 66,2 | 27 | 17,8 | 17,7 | 17,7 | 17,7 | 17,9 |
| 13 | 50,2 | 49,8 | 48,7 | 48,7 | 51,7 | 28 | 28,5 | 28,5 | 28,3 | 28,5 | 28,5 |
| 14 | 51,1 | 51,1 | 51,9 | 51,8 | 51,2 | 29 | 22,2 | 22,0 | 22,1 | 22,0 | 22,1 |
| 15 | 32,0 | 31,9 | 32,1 | 32,1 | 31,7 | 30 | 17,5 | 17,3 | 17,4 | 17,3 | 17,0 |

TABLE 3. Chemical Shifts of the Carbohydrate Components of Glucosides (II)-(V) (δ, ppm relative to TMS)

| Compound | C atom | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| II | 97,7 | 71,6 | 73,0 | 69,1 | 71,5 | 62,2 |
| III | 98,5 | 72,0 | 72,5 | 68,6 | 71,3 | 61,5 |
| IV | 97,9 | 71,6 | 73,0 | 69,0 | 71,8 | 62,1 |
| | 98,4 | 71,3 | 72,4 | 68,6 | 72,0 | 61,5 |
| V | 97,8 | 71,5 | 73,0 | 69,1 | 71,5 | 62,2 |
| | 95,5 | 72,1 | 72,5 | 68,6 | 72,1 | 62,2 |

The reaction was performed at room temperature in dichloroethane with vigorous stirring, and led to a multicomponent mixture of glucosides (II)-(V), the total yield of which amounted to 75-80%, while the replacement of one promoter by the other had no appreciable influence on the composition of the reaction products. Molecular sieves, the use of which in some cases can increase the yield of desired glycosides made possible a slight rise in the yield of diglucosides (IV) and (V) in the glycosylation of the tetraol (I).

The absence of regioselectivity in the glycosylation of unprotected polyols under these conditions, as reported previously [4], greatly complicated the isolation of individual substances which, moreover, on prolonged chromatography were distinguished by instability, and therefore the percentages of the mono- and diglucosides were determined after column chromatography using solvent system 1 and their ratio as the result of rechromatography in system 2.

The structures of the individual glucosides (II)-(V) were established on the basis of the results of an investigation by $^1H$ and $^{13}C$ NMR spectroscopy. The positions of attach-

ment of glucose residues were determined by comparing the $^{13}C$ spectra of the newly obtained glucosides (II)-(V), of the initial tetraol (I), and of betulafolienetriol glucosides obtained previously [4]. The doublet signal of the anomeric glucose proton at C-3 appeared in the $^1H$ spectra of glucosides (II), (IV), and (V) at 4.51-4.53 ppm ($J_{1',2'}$ = 7.5 Hz), that at C-12 for glucosides (III) and (IV) at 4.56-4.60 ppm ($J_{1',2'}$ = 7.5 Hz), and that at C-20 for glucoside (V) at 4.79 ppm ($J_{1',2'}$ = 8.0 Hz). The values of the spin–spin coupling constants show the trans configuration of all the glucosidic bonds.

The deacetylation of the glucosides (II)-(V) obtained with a 0.1 N solution of sodium methanolate in methanol led to the corresponding free glucosides with quantitative yield.

## EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrophotometer in chloroform solution, and $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker WM-250 spectrometer with a working frequency of 250 MHz for $^1H$ and 62.9 MHz for $^{13}C$ at 30°C in deuterochloroform. Chemical shifts are expressed on the δ scale relative to TMS. The accuracy of measurement was ±1.5 Hz for $^{13}C$ and ±0.15 Hz for $^1H$. Optical rotations were determined on a Perkin-Elmer instrument in a cell 10 cm long at 20°C and melting points on a Boëtius stage.

Column chromatography was performed on KSK silica gel (150 mesh) in the systems: 1) benzene–methanol (200:1 → 60:1); and 2) hexane–acetone (8:1 → 4:1).

The individuality of the substances was checked with the aid of TLC in the benzene–chloroform–methanol (6:4:1) and hexane–acetone (3:2) systems. The substances were revealed with 10% $H_2SO_4$ in ethanol followed by heating at 100-200°C. Condensation was performed by the prcedure described previously [4]. Silver silicate was obtained in accordance with [5].

The results of elementary analysis for all the newly obtained compounds coincided with the calculated figures.

Dammar-24-ene-3α,12β,17α,20(S)-tetraol (I) was isolated form the unsaponifiable part of an etheral extract of the leaves Betula pendula followed by chromatography on silica gel and crystallization from acetone; mp 168-170°C. No depression of the melting point was observed for a mixture with an authentic sample.

Dammar-24-ene-3α,12β,17α,20(S)-tetraol 3-O-(2',3',4',6'-Tetra-acetyl-β-D-glucopyranoside) (II). mp 191-193°C (ethanol), $[\alpha]_D^{20}$ +21.0° (c 1.0; chloroform). IR spectrum (ν, $cm^{-1}$): 1594, 1753, 3401, 3611. $^1H$ spectrum (δ, ppm): 0.84 (s, 3H), 0.89 (s, 3H), 0.91 (s, 3H), 0.97 (s, 3H), 1.16 (s, 3H), 1.22 (s, 3H), 1.66 (s, 3H), 1.71 (s, 3H), 2.01-2.09 (s, 12H, 4 × OAc), 2.94 (s, 1H, OH), 3.36 (t, 1H, 2 × J = 2.8 Hz, $H_e$-3), 3.65 (m, 1H, H-5'), 3.85 (d-t, 1H, J = 5.0 Hz; J = 10.0 Hz; J = 10.0 Hz; $H_a$-12), 4.12 (d-d, 1H, J = 2.5 Hz; J = −12.0 Hz, H-6'), 4.22 (d-d, 1H, J = 4.7 Hz; J = − 12.0 Hz, H-6'), 4.53 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 4.91-5.23 (m, H-2', H-3', H-4', H-24).

Dammar-24-ene-3α,12β,17α,20(S)-tetraol 12-O-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranoside) (III). mp 187-189°C (ethanol), $[\alpha]_D^{20}$ −2.94° (c 0.85; chloroform). IR spectrum (ν, $cm^{-1}$): 1594, 1740, 3344, 3593. $^1H$ spectrum (δ, ppm): 0.86 (s, 3H), 0.88 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.19 (s, 6H), 1.66 (s, 3H), 1.71 (s, 3H), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.29 (s, 1H, OH), 3.36 (t, 1H, 2 × J = 1.8 Hz, $H_e$-3), 3.71 (m, 1H, H-5'), 3.86 (t-d, 1H, J = 5.0 Hz) J = 10.0 Hz; J = 10.0 Hz, $H_a$-12), 4.16 (d-d, 1H, J = 5.0 Hz; J = −12.0 Hz, H-6'), 4.26 (d-d, 1H, J = 2.5 Hz; J = −12.0 Hz, H-6'), 4.60 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 4.91-5.22 (m, H-2', H-3', H-4', H-24).

Dammar-24-ene-3α,12β,17α,20(S)-tetraol 3,12-Di-O-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranoside) (IV). mp 145-148°C (ethanol) $[\alpha]_D^{20}$ −17.0° (c 1.0; chloroform). IR spectrum (ν, $cm^{-1}$): 1752, 3463. $^1H$ spectrum (δ, ppm): 0.84 (s, 3H), 0.86 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 1.19 (s, 3H), 1.66 (s, 3H), 1.71 (s, 3H), 2.00-2.11 (s, 24H, 8 × OAc), 3.34 (t, 1H, 2 × J = 1.8 Hz, $H_e$-3), 3.68 (m, 2H, 2H, 2 × H-5'), 3.86 (t-d, 1H, J = 5.0 Hz, J = 10.0 Hz, J = 10.0 Hz, $H_a$-12), 4.22 (m, 4H, 2 × 2H-6'), 4.53 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1' at C-3), 4.56 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1' at C-12), 4.91-5.23 (m, 2H-2', 2H-3', 2H-4', H-24).

Dammar-24-ene-3α,12β,17α,20(S)-tetraol 3,20-Di-O-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranoside) (V). Amorphous, $[\alpha]_D^{20}$ −11.4° (c 0.35; chloroform). IR spectrum (ν, $cm^{-1}$):

1750, 3468. $^1$H spectrum (δ, ppm): 0.84 (s, 3H), 0.89 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.16 (s, 3H), 1.31 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 2.00-2.09 (s, 24H, 8 × OAc), 3.34 (t, 1H, 2 × J = 1.8 Hz, $H_e$-3), 3.68 (m, 3H, 2 × H-5', $H_a$-12), 4.12-4.24 (m, 4H, 2 × H-6'), 4.51 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1' at C-3), 4.79 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1' at C-20), 4.91-5.23 (m, 2H-2', 2H-3', 2H-4', H-24).


## SUMMARY

1. The condensation of dammar-24-ene-3α,12β,17α,20(S)-tetraol (betulalafolienetetraol), isolated from birch leaves, with α-acetobromoglucose in the presence of silver oxide and silicate has been studied.

2. Betulafolienetetraol 3- and 12- mono- and 3,12- and 3,20-di-O-β-D-glucopyranoside — analogs of ginseng glycosides — have been obtained for the first time.


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# TRITERPENE SAPONINS OF Caltha polypetala.

# GLYCOSIDES G and I


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UDC 547.918.547.914.4



From the epigeal organs of the great march marigold (family Ranunculaceae) two triterpene glycosides, a tetra- and a pentaoside of hederagenin, have been isolated. Their chemical structures have been established by chemical methods of investigation and by $^1$H and $^{13}$C NMR spectroscopy. Glycoside G is hederagenin 3-O-α-L-arabinoside 28-O-[O-α-L-rhamnopyranosyl-(1 → 4)-O-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside]. Glycoside I is hederagenin 3-O-[O-β-D-glucopyranosyl-(1 → 2)-α-L-arabinoside 28-O-[O-α-L-rhamnopyranosyl-(1 → 4)-O-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside].


A series of compounds of triterpene nature had previously been isolated from the epigeal organs of Caltha polypetala Hochst. (great marsh marigold), family Ranunculaceae, and the results of investigations of the weakly polar glycosides have been given [1].

In the present paper are considered the results of establishing the structures of the most polar triterpene glycosides — G and I. As shown previously [1], the triterpene glycosides of the great march marigold are hederagenin derivatives and contain in the carbohydrate moiety arabinose and glucose in various ratios. After the acid hydrolysis of glycosides G and I, followed by reduction of the hydrolysates and acetylation, rhamnitol, arabitol, and sorbitol acetates were identified by the GLC method in ratios of 1:1:2 and 1:1:3, respectively. Consequently, glycosides G and I are a hederagenin tetraoside and pentaoside.

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Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 229-236, March-April, 1988. Original article submitted July 20, 1987.




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