GLYCOSYLATION OF TRITERPENOIDS OF THE DAMMARANE SERIES

I. 20(S),24(R)-EPOXYDAMMARANE-3α-12β,25-TRIOL 25-O-β-D-GLUCOPYRANOSIDE

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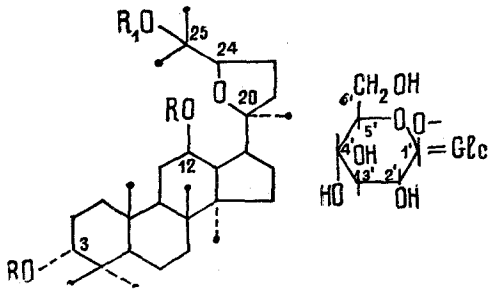
The glycosylation of 3α,12β-diacetoxy-20(S),24(R)-epoxydammaran-25-ol with α-acetobromoglucose under the conditions of Helferich's modification and with D-glucose tert-butyl orthoacetate under the conditions of the orthoester method gives a high yield (60-64%) of the hexacetate of the β-D-glucoside at the tertiary hydroxy group of 20(S),24(R)-epoxydammarane-3α,12β,25-triol (III) with mp 207-209°C (ethanol), $[\alpha]_D^{20}$ −20.9 (c 1.0, $CHCl_3$). Saponification with 10% KOH in methanol gives the free 20(S),24(R)-epoxydammarane-3α,12β,25-triol 25-O-β-D-glucoside (V) (yield 90%) with mp 275-279°C (methanol), $[\alpha]_D^{20}$ +11.4° (c, 1.0, C_5H_5). The results of IR and ^1H and ^{13}C NMR spectroscopy and of elementary analysis are given.

Many triterpene glycosides possess a high biological activity. A special place among them is occupied by the panaxosides — the glycosides of ginseng [1-4]. As has been established, their aglycones are triterpenoids of the dammarane series [5-6]. Consequently, the preparation of glycosides similar in structure to the panaxosides from accessible triterpenoids of the dammarane series is of undoubted interest.

With the aim of approaching the synthesis of analogs of the panaxosides, we have made an attempt to glycosylate the tertiary hydroxy group of 20(S),24(R)-epoxydammarane-3α,12β,25-triol (betulafolienetriol oxide) (I). As is well known, the introduction of a sugar component at a tertiary hydroxyl in complex aglycones is a matter of very great difficulty and usually takes place with low yields [7-9].

We have previously made a comparative study of methods of glycosylating polycyclic alcohols [10], and therefore we rested our choice on two methods. Glycosylation was carried out with D-glucose tert-butyl orthoacetate in chlorobenzene in the presence of 2,4,6-collidinium perchlorate [11] and with α-acetobromoglucose in nitromethane in the presence of mercury cyanide [12]. The initial substance was an acetate derivative of betulafolienetriol oxide (II).



I. R = R₁ = H

II. R = Ac, R₁ = H

III. R = Ac, R₁ = Glc(Ac)₄

IV. R = Ac, R₁ = Glc

V. R = H, R₁ = Glc

As a result of the condensation, in both cases a high yield was obtained of a compound which, according to IR, PMR, and ^{13}C NMR spectroscopy and elementary analysis consisted of the hexaacetate of the β-D-glucoside of betulafolienetriol oxide at C-25 (III). The IR spectrum of compound (III) lacked the absorption band of a hydroxy group that is observed in the spectrum of the initial alcohol (II). In the PMR spectrum of (III) there is a signal of the proton at C_1' of the glucose in the δ 5.06 ppm region in the form of a doublet with

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$J_{1,2}$ = 8.2 Hz, and in the ^{13}C NMR spectrum the shift of the C_1' atom of the carbohydrate component is observed in an unusually high field at δ 95.7 ppm. These facts agree well with the results of Japanese workers [13] and indicate that compound (III) is the β-glucoside of a tertiary alcohol. Furthermore, the downfield shift by Δ 8.1 ppm of the C-25 signal in the ^{13}C NMR spectrum of (III) shows that the carbohydrate moiety is attached to the tertiary hydroxy group.

Below we give the chemical shifts of the signals of some carbon atoms in the ^{13}C NMR spectra of the compound that we have investigated [the spectra of (IV) and (V) were taken in C_5D_5N and the others in $CDCl_3$]:

Compound	*C-3*	*C-12*	*C-20*	*C-24*	*C-25*
I	75.3	71.1	86.7	85.6	70.1
II	78	75.5	85.7	83.4	70.9
III	77.7	75.2	85.4	82.2	79.02
IV	77.8	75.4	85.9	81.9	78.4
V	75.3	71.9	86.4	85.1	76.7

The saponification of compound (III) with sodium methanolate led, according to the results of IR, PMR, and ^{13}C NMR spectroscopy, to the glycoside (IV) retaining two acetate groups in the aglycone moiety. An increase in the time of saponification to 30 days was unsuccessful. Complete saponification was effected with a solution of KOH in methanol. The PMR spectrum of the glycoside (V) obtained lacked the signals of the protons of acetyl groups, and in the ^{13}C NMR spectrum there was no signal of a carbonyl carbon at δ 170 ppm. In the spectrum of compound (V), the C_1' signal of the sugar moiety is observed at δ 98.9 ppm, which confirms the β-configuration of the glycosidic bond [13, 14].

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer and the ^1H and ^{13}C NMR spectra on a Bruker HX-90E spectrometer with tetramethylsilane as internal standard. Optical rotations were determined on a Perkin-Elmer 141 polarimeter at 20°C, and melting points on a Boetius stage. Column chromatography was carried out on KSK silica gel (80-120 mesh). The individuality of the substances was checked by TLC on silica gel in systems 1) hexane–acetone (3:1) and 2) benzene–chloroform–methanol (3:2:1). The spots were detected with 10% sulfuric acid in methanol followed by heating at 100-200°C. Chlorobenzene and nitromethane were purified as described by Kochetkov et al. [11].

20(S),24(R)-Epoxydammarane-3α,12β,25-triol (betulafolienetriol oxide) (I) was isolated from the unsaponifiable fraction of an ethereal extract of the birch *Betula mandshurica*, followed by purification on silica gel. It was crystallized from acetone, mp 235-237°C. According to the literature [15]: mp 237-240°C.

3α,12β-Diacetoxy-20(S),24(R)-epoxydammaran-25-ol (II) was obtained by acetylating compound (I) with acetic anhydride in pyridine at room temperature for a day. It was crystallized from a mixture of petroleum ether and acetone, mp 177-179°C, $[\alpha]_D^{20}$ −12.8° (c 1.0, $CHCl_3$). $C_{34}H_{56}O_6$. According to the literature [16]: mp 178-180°C.

Condensation of the Acetate (II) with α-Acetobromoglucose. A mixture of 0.56 g (1 mmole) of compound (II), 0.82 g (2 mmole) of α-acetobromoglucose, and 0.5 g (2 mmole) of mercury cyanide in 10 ml of absolute nitromethane was stirred at room temperature for 4 h. Then the solution was evaporated, the residue was dissolved in chloroform, and the solution was filtered from mercury salts. The filtrate was washed with water, dried with anhydrous sodium sulfate, and evaporated. The dry residue was chromatographed on silica gel, giving 0.63 g of a chromatographically homogeneous substance (in system 1). Crystallization from ethanol gave the pure hexaacetate of the 25-O-β-D-glucoside of 20(S),24(R)-epoxydammarane-3α,12β,25-triol (III), $C_{48}H_{74}O_{15}$, 0.574 g (64.4%), mp 207-209°C, $[\alpha]_D^{20}$ −20.9° (c 1.0), $CHCl_3$).

IR spectrum ($CHCl_3$, cm^{-1}): 1725, 1754, 1220, 1260 (COOR). PMR spectrum (δ, ppm): 0.84-1.15 (3 H × 8, s), the protons of methyl groups; 2.00-2.09 (3 H × 6, s), the protons of acetate groups; 5.06 (1 H, d, $J_{1,2}$ = 8.2 Hz), at the glucose C_1' atom.

^{13}C NMR (δ, ppm): C_3 77.7; C_{12} 75.2; C_{20} 85.4; C_{24} 82.2; C_{25} 79.02; C_1' 95.7; C_2' 73.0; C_3' 71.3; C_4' 68.6; C_5' 71.3; C_6' 61.2; 168.7 – 170.2 (CH_3CO).

Condensation of the Acetate (II) with α-D-Glucose tert-Butyl Orthoacetate. 2,4,6-Collidium perchlorate (8 mg) was dried by the azeotropic distillation of chlorobenzene from it, and then to the solution was added 0.56 g (1 mmole) of compound (II) and the solvent was distilled off again several times. In two portions with a 10-minute interval, 0.82 g (2 mmole) of α-D-glucose tert-butyl orthoacetate was added and the mixture was heated for another 15 min under the conditions of the azeotropic distillation of the solvent. Then it was evaporated. The dry residue was chromatographed on silica gel. The main fraction was crystallized from ethanol, giving 0.536 g of product (III) (60.2%) with mp 207-209°C.

No depression of the melting point of a mixture with the sample obtained in the preceding experiment was observed.

3α,12β-Diacetoxy-25-β-D-glucopyranosyloxy-20(S),24(R)-epoxydammarane (IV). A solution of 0.2 g of compound (III) in absolute methanol was treated with 1 ml of a 0.1 N solution of sodium methoxide in methanol. After an hour (monitoring by TLC in systems 1 and 2) the initial substance had disappeared. The solution was neutralized with KU-2 cation-exchange resin (H^+ form) and evaporated. This gave 161 mg (99.3%) of the chromatographically homogeneous substance (IV), $[\alpha]_D^{20}$ −29.6° (c 1.0, C_5H_5N).

PMR spectrum (δ, ppm): 0.87-1.18 (3 H ×8, s), 2.00 (3H, s); 2.08 (3 H, s); ^{13}C NMR spectrum (δ, ppm): C_3 77.8; C_{12} 75.4; C_{20} 85.9; C_{24} 81.9; C_{25} 78.4; CH_3CO 170.1; C_1' 98.3; C_2' 75.4; C_3' 77.8; C_4' 71.6; C_5' 77.8; C_6' 62.8.

25-β-Glucopyranosyloxy-20(S),24(R)-epoxydammarane-3α,12β-diol (V). A solution of 0.3 g of compound (III) in methanol was treated with 1 ml of a 10% solution of KOH in methanol. After 1 h the solution was neutralized with KU-2 ion-exchange resion (H^+ form) and was evaporated. The precipitate that deposited was filtered off and dried, giving 195 mg (90%) of compound (V) with mp 275-279°C, $[\alpha]_D^{20}$ +11.4° (c 1.0, C_5H_5N). $C_{36}H_{62}O_9$.

^{13}C NMR spectrum (δ, ppm): C_3 75.3; C_{12} 71.9; C_{20} 86.4; C_{24} 85.1; C_{25} 76.7; C_1' 98.9; C_2' 75.4; C_3' 77.9; C_4' 70.7; C_5' 78.1; C_6' 63.1. The ^{13}C NMR spectra were taken by V. Denisenl and Yu. Kulesh.

SUMMARY

The β-D-glucopyranoside of betulafolienetriol oxide at the tertiary hydroxy group has been obtained in high yield under the conditions of the orthoester method of glycosylation and by Helferich's modification of the acetobromoglucose method.

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