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# TRANSFORMATION OF GLYCYRRHIZIC ACID. VII. SYNTHESIS OF TRITERPENE GLYCOPEPTIDES CONTAINING ALKYL ESTERS OF L-AMINO ACIDS

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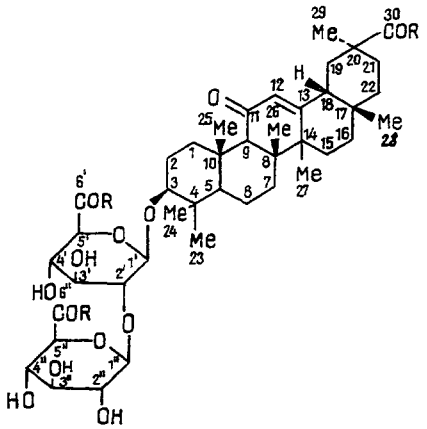
*The synthesis has been effected by the activated N-hydroxy succinimide ester method of new triterpene glycopeptides derived from glycyrrhizic acid, containing fragments of alkyl (ethyl, propyl, butyl) esters of L-amino acids.*

The triterpene glycoside glycyrrhizic acid (GA) (**1**) is the main component of an extract of the root of liquorice, *Glycyrrhizae glabra* L. and *Glycyrrhizae uralensis* F., and is of great interest for pharmacology because of its high and diverse pharmacological activity (antiinflammatory, antiulcerous, antidotal, antiallergic, antiviral, etc.) [1-6].

We have previously proposed the synthesis of triterpene glycopeptides derived from GA containing fragments of methyl esters of L- and D-amino acids which possess immunomodulating and anti-HIV activity [1, 5, 6]. Having continued these investigation, we have achieved the synthesis of new glycopeptides of GA (**2**) using ethyl, propyl, and butyl groups for the protection of the carboxy groups of the amino acids.

The condensation of GA having unsubstituted hydroxy groups in the carbohydrate chain with L-amino esters (amino components) was carried out by the activated-ester method using N-hydroxysuccinimide (HOSu) and N,N'-dicyclohexylcarbodiimide (DCC) in tetrahydrofuran or dioxane.

The amino acid esters (amino components) were obtained in situ from the corresponding hydrochlorides in the presence of a small excess of a base (triethylamine or N-ethylmorpholine) (1-3 mmole). The yields of the desired compounds after purification amounted to 32-48%.



**2**. R=OH
**2a**. R=*L*-Ala(OEt)
**2b**. R=*L*-Val(OEt)
**2c**. R=*L*-Glu(OEt)$_2$
**2d**. R=*L*-Ala(OPr)
**2e**. R=*L*-Glu(OPr)$_2$
**2g**. R=*L*-Ala(OBu)
**2h**. R=*L*-Val(OBu)
**2f**. R=*L*-Glu(OBu)$_2$

The structures of the glycopeptides (**2**) obtained were confirmed by their IR, UV, and $^{13}C$ NMR spectra and the results of elementary analysis. Thus, in the IR spectra of glycopeptides (**2**) the absorption maxima characteristic for OH and NH

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TABLE 1. Hydrochlorides of Alkyl Esters of L-Amino

| Compound | Yield, % | mp, °C | $[\alpha]_D^{20}$, deg (c; MeOH) | Found, % | | | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | Cl |
| 1. Ala-OEt[a] | 64.4 | 75—77 | −10 (0.06) | | | | |
| 2. Glu(OEt)-OEt[b] | 73.7 | 112—114 | +25 (0.08) | | | | |
| 3. Val-OEt[c] | 60.5 | 170—172 | +17 (0.02) | | | | |
| 4. Ala-OPr | 67.0 | 198—200 | +27 (0.08) | 42.45 | 7.92 | 8.85 | 20.68 |
| 5. Glu(OPr)-OPr | 49.5 | 162—165 | +22 (0.08) | 48.63 | 7.80 | 5.82 | 14.02 |
| 6. Ala-OBu | 52.0 | Amorph. | +15 (0.08) | 45.74 | 7.24 | 7.60 | 20.05 |
| 7. Val-OBu | 50.3 | 53—54 | +12.5 (0.08) | 49.97 | 9.88 | 6.61 | 15.59 |
| 8. Glu(OBu)-OBu | 74.0 | Amorph. | +11 (0.08) | 51.95 | 8.31 | 4.20 | 12.56 |

| Compound | Empirical formula | Calculated, % | | | |
|---|---|---|---|---|---|
| | | C | H | N | Cl |
| 4. Ala-OPr | $C_6H_{14}NO_2Cl$ | 42.97 | 8.42 | 8.35 | 21.17 |
| 5. Glu(OPr)-OPr | $C_{11}H_{22}NO_4Cl$ | 49.33 | 8.28 | 5.23 | 13.26 |
| 6. Ala-OBu | $C_7H_{16}NO_2Cl$ | 46.26 | 7.79 | 7.71 | 19.53 |
| 7. Val-OBu | $C_9H_{20}NO_2Cl$ | 51.54 | 9.63 | 6.68 | 16.90 |
| 8. Glu(OBu)-OBu | $C_{13}H_{26}NO_4Cl$ | 52.77 | 8.86 | 4.73 | 12.00 |

[a]Lit. [9]: mp 76°; $[\alpha]_D^{25}$ — 11.4° (2%, 5 N, HCl).
[b]Lit. [9]: mp 113-114°C; $[\alpha]_D^{20}$ + 2.4° (4%, $H_2O$).
[c]Lit. [9]: mp 167.5-168°; $[\alpha]_D^{21}$ + 15.5° (2%, $H_2O$).

groups were observed in the 3600-3200 $cm^{-1}$ region, those of ester groups at 1750-1730 $cm^{-1}$, those of conjugated carbonyl groups ($C_{11}$=O) at 1660-1640 $cm^{-1}$, and those of amide groups in the 1560-1530 $cm^{-1}$ region.

The UV spectra of the compounds synthesized contained the absorption maxima characteristic for a 12-en-11-one system in the region of 249-251 nm [5].

Tables 2 and 3 give the chemical shifts in the $^{13}C$ NMR spectrum of glycopeptide (**2**). The chemical shifts of the signals of the C atoms of the carbohydrate and aglycon moieties of the molecules of the compounds (**2**) investigated (Table 2) were analogous to the NMR $^{13}C$ NMR spectra of GA (**1**) and its aglycon — β-glycyrrhetic acid — which have been considered in detail in the literature [7, 8]. The signals of the glycosidic C-atoms (C1′ and C1″ of the carbohydrate moiety of the molecules of the glycopeptides were observed in the strong-field region at 104-105 ppm (Table 2). The presence of the amino acid fragments in the glycopeptide molecule was detected from the additional signals of the carbonyls of ester groups in the 172-175 ppm region (Table 3).

The alkyl chains of the ester groups gave additional signals (of $CH_3-$ and $-CH_2-$) in the strong-field region.

## EXPERIMENTAL

For TLC we used Silufol plates and the following solvent systems: A) chloroform−methanol−water (45:10:1); B) chloroform−ethanol (5:1). The spots of the substances were revealed with a 20% solution of tungstophosphoric in ethanol with heating at 110-120°C for 2-3 min.

TABLE 2. Chemical Shifts of the Signals of the C-Atoms of the Aglycon and Carbohydrate Moieties in the $^{13}C$ NMR Spectra of Glycopeptides of Glycyrrhizic Acid ($CD_3OD$, δ, ppm, 25°C, 75.5 MHz)

| Atom C | 2a | 2b | 2c | 2d | 2h | 2f |
|---|---|---|---|---|---|---|
| 1 | 40.50 | 39.13 | 40.35 | 40.30 | 40.30 | 40.63 |
| 2 | 27.63 | 27.72 | 27.93 | 27.60 | 27.56 | 27.89 |
| 3 | 91.00 | 88.85 | 90.63 | 90.66 | 90.20 | 90.90 |
| 4 | 40.89 | 40.84 | 40.67 | 40.69 | 40.61 | 40.95 |
| 5 | 56.63 | 56.53 | 56.47 | 56.38 | 56.36 | 56.69 |
| 6 | 18.61 | 18.17 | 18.45 | 18.43 | 18.88 | 18.73 |
| 7 | 34.05 | 32.46 | 33.99 | 33.79 | 33.78 | 34.12 |
| 8 | 44.79 | 45.18 | 44.88 | 44.62 | 44.78 | 44.87 |
| 9 | 63.29 | 61.60 | 63.12 | 63.10 | 63.04 | 63.38 |
| 10 | 38.23 | 37.35 | 38.07 | 38.04 | 38.03 | 38.34 |
| 11 | 202.51 | 200.89 | 202.30 | 202.53 | 202.10 | 202.70 |
| 12 | 129.14 | 127.64 | 128.97 | 128.92 | 128.94 | 129.21 |
| 13 | 172.10 | 170.07 | 171.76 | 171.25 | 171.63 | 171.75 |
| 14 | 46.90 | 45.18 | 46.72 | 46.73 | 46.64 | 47.01 |
| 15 | 27.81 | 27.02 | 27.42 | 27.24 | 26.54 | 27.68 |
| 16 | 28.46 | 27.92 | 27.63 | 27.39 | 27.35 | 27.89 |
| 17 | 33.13 | 32.28 | 32.96 | 32.95 | 32.89 | 33.21 |
| 18 | 48.43 | 47.20 | 48.17 | 47.83 | 48.12 | 48.43 |
| 19 | 42.63 | 42.99 | 42.49 | 42.48 | 42.50 | 42.78 |
| 20 | 45.02 | 43.30 | 45.05 | 44.94 | 44.97 | 45.15 |
| 21 | 32.23 | 32.28 | 32.64 | 32.05 | 32.19 | 32.33 |
| 22 | 39.16 | 38.90 | 39.01 | 39.02 | 39.00 | 38.34 |
| 23 | 28.65 | 28.59 | 28.80 | 28.42 | 28.77 | 28.26 |
| 24 | 17.09 | 16.84 | 17.05 | 17.01 | 16.95 | 17.36 |
| 25 | 17.37 | 17.13 | 17.32 | 17.30 | 17.24 | 17.62 |
| 26 | 19.66 | 18.35 | 19.40 | 19.35 | 19.37 | 19.66 |
| 27 | 24.17 | 24.39 | 23.91 | 23.91 | 23.88 | 24.16 |
| 28 | 29.04 | 28.75 | 28.48 | 28.81 | 28.45 | 29.09 |
| 29 | 29.44 | 29.41 | 29.21 | 28.22 | 29.17 | 29.46 |
| 30 | 180.45 | 178.88 | 180.27 | 180.54 | 180.12 | 180.50 |
| 1' | 104.97 | 104.09 | 104.98 | 105.07 | 104.82 | 105.26 |
| 2' | 79.60 | 81.95 | 81.60 | 81.82 | 81.37 | 81.80 |
| 3' | 75.78 | 74.38 | 75.89 | 75.86 | 75.87 | 76.14 |
| 4' | 73.13 | 71.37 | 73.31 | 73.39 | 73.54 | 73.80 |

TABLE 2 (continued)

| Atom C | 2a | 2b | 2c | 2d | 2h | 2f |
|---|---|---|---|---|---|---|
| 5′ | 77.30 | 75.97 | 77.67 | 77.69 | 77.56 | 77.97 |
| 6′ | 172.10 | 170.53 | 171.43 | 171.25 | 171.34 | 171.75 |
| 1″ | 106.17 | 103.84 | 104.98 | 104.96 | 104.77 | 105.26 |
| 2″ | 76.31 | 72.79 | 75.89 | 75.80 | 75.24 | 76.30 |
| 3″ | 76.39 | 75.40 | 76.09 | 75.98 | 76.14 | 76.36 |
| 4″ | 73.61 | 72.07 | 73.51 | 73.39 | 73.54 | 73.80 |
| 5″ | 77.29 | 75.73 | 77.19 | 77.18 | 77.17 | 77.44 |
| 6″ | 172.60 | 172.30 | 171.61 | 172.90 | 171.42 | 171.93 |

IR spectra were recorded on Specord M80 and UR-20 spectrometers of mulls in paraffin oils. UV spectra were taken on Specord M-40 and Specord M-400 instruments in methanol and ethanol. Melting points were determined on a Boetius microstage. Optical activities were measured on a Perkin-Elmer 241 MC polpolarimeter in a tube 1 dm long. $^{13}C$ NMR spectra were taken on a Bruker AM-300 instrument with a working frequency of 75.7 MHz in deuteromethane, using tetramethylsilane as internal standard.

N-methyl- and N-ethylmorpholines and triethylamine were dried over KOH and were redistilled.

Glycyrrhizic acid containing 95% of the main substances, obtained by the procedure of [5], was used. The elemental analyses of the compounds synthesized corresponded to the calculated figures.

**General Procedure for Obtaining Hydrochlorides of Alkyl Esters of L-Amino Acids.** At 0°C, 20-30 ml of freshly distilled thionyl chloride was added dropwise to a suspension of 5-10 g of an L-amino acid in 300 ml of a dry alcohol (ethanol, *n*-propanol, or *n*-butanol), and the mixture was stirred with cooling for 1-1.5 h and was then left overnight at 20-22°C. The excesses of solvent and $SOCl_2$ were distilled off in vacuum at ~40°C, and the syrupy residue was triturated with dry ether and was then crystallized twice from a mixture of methane and ether or of ethyl acetate and hexane. The properties of the amino acid ester hydrochlorides obtained are given in Table 1.

The IR spectra of the amino acid ester hydrochlorides contained absorption maxima of the ester groups in the regions of 1730-1740, 1610-1600, and 1590-1580 $cm^{-1}$, corresponding to $NH_3^+$groupings.

**3-O-[Glucopyranuronosyl-(1″→2′)-glucopyranuronosyl]glycyrrhizic Acid, Triamide with L-Alanine Ethyl Ester (2a).** At 0°C, 1.2 g (10.4 mmole) of N-hydroxysuccinimide and 1.4 g (6.8 mmole) of N,N′-dicyclohexylcarbodiimide were added to a solution of 1.64 g (2 mmole) of glycyrrhizic acid in 30 ml of dioxane, and the mixture was stirred with cooling for 2 h and at 20-22°C for 2 h. It was then kept in the refrigerator overnight, the precipitate of dicyclohexylurea was filtered off, and the filtrate was cooled in an ice bath and was treated with 1.5 g (9.8 mmole) of the hydrochloride of L-alanine ethyl ester, 1.5 ml (10.9 mmole) of triethylamine, and 20 ml of DMFA, and the resulting mixture was kept at 20-22°C with periodic stirring for 24 h. It was then diluted with 400 ml of cold water and was acidified with citric acid to pH ~ 3, and the precipitate was filtered off, washed with water, and dried. This gave 1.5 g (67.0%). of a crude product, which was reprecipitated from hexane and was chromatographed on a column of silica gel L (40/100 μm) with elution by chloroform–alcohol (100:1), (50:1), (25:1), and (10:1) (v/v). The (50:1) and (25:1) mixtures eluted 0.9 g (40.2%) of the desired product in the form of an amorphous yellowish substance, $R_f$ 0.45 (A), $[\alpha]_D^{20}$ + 55° (s 0.05; EtOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1730 (COOEt); 1660 ($C_{11}$ = O) 1550 (CONH). UV spectrum ($\lambda_{max}^{C_2H_5OH}$, nm): 250 (log ε 4.22). Found %: C 60.51; H 7.78; N 3.35; $C_{57}H_{89}O_{19}$. Calculated %: C 61.10; H 8.00; N 3.75; M 1120.30.

**3-O-[Glucopyranuronosyl-(1″→2′)-glucopyranuronosyl]glycyrrhizic Acid, Triamide with L-Alanine Valine Ethyl Ester (2b).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.4 g (6.8 mmole) of N,N′-dicyclohexylcarbodiimide, 1.5 g (8.3 mmole) of L-valine ethyl ester hydrochloride, and 1.5 ml (10.9 mmole) of triethylamine in 50 ml of dioxane yielded 1.5 g (62.5%) of a crude product, which was reprecipitated from acetone with hexane and was chromatographed on a column of silica gel L (40/100 μm) with elution by chloroform–alcohol (100:1), (50:1), (25:1), (10:1). The (50:1) and (25:1) mixtures eluted 0.8 g (33.3%) of the analytically pure product (**2b**) in the form of an amorphous substance. $R_f$ 0.56 (B), $[\alpha]_D^{20}$ + 26° (s 0.025; EtOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1730 (COOR); 1660 ($C_{11}$ = O); 1545 (CONH). UV spectrum ($\lambda_{max}^{C_2H_5OH}$, nm): 249.5 (log ε 3.97). Found %: C 62.99; H 8.19; N 2.88; $C_{63}H_{101}N_3O_{19}$. Calculated %: C 62.82; H 8.45; N 3.49; M 1204.45.

TABLE 3. Chemical Shifts of the Signals of the C Atoms of the Amino Acid Fragments in the $^{13}C$ NMR Spectra of Glycyrrhizic Acid Glycopeptides ($CD_3OD$; δ, ppm; 25°C; 75.5 MHz)

| Amino acid fragments (compound). | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|
| $^3CH_3{}^2CHNH$ (2a) | 176.19 | 52.62 | 17.49 | | | |
| $^1COOC_2H_5$ | 172.74 | 52.44 | 17.25 | | | $C_2H_5$: 50.14; 50.03; 26.77; 26.68; 26.27 |
| | 172.60 | 51.96 | 17.00 | | | |
| $^4CH_3-{}^3CH-{}^2CHNH$ (2b) | 174.52 | 57.03 | 31.81 | 22.71 | 24.87 | |
| $^5CH_3$ $^1COOC_2H_5$ | 174.52 | 55.11 | 31.43 | 22.65 | 24.46 | $C_2H_5$: 50.21; 50.09; 26.09; 25.98; 25.65; 25.51 |
| | 172.30 | 55.02 | 30.67 | 22.65 | 24.39 | |
| $C_2H_5O^5CO^4CH_2{}^3CH_2{}^2CHNH$ | 173.28 | 53.09 | 28.22 | 31.42 | 174.48 | $C_2H_5$: 52.00; 52.50; 44.62; |
| (2c) $^1COOC_2H_5$ | 173.03 | 52.90 | 27.29 | 31.68 | 174.23 | 44.52; 27.29; 26.59; 26.50; |
| | 172.55 | 52.68 | 27.16 | 31.08 | 174.02 | 26.04 |
| $^3CH_3{}^2CHNH$ (2d) | 174.31 | 53.13 | 17.90 | | | |
| $^1COOC_3H_7$ | 174.17 | 53.08 | 17.84 | 45.07 | 44.62 | $C_3H_7$: 32.93; 32.05; 28.96; 14.48 |
| | 172.90 | 53.04 | 17.30 | 14.35 | 14.04 | |
| $^4CH_3-{}^3CH^2CHNH$ (2h) | 173.13 | 58.84 | 32.64 | 19.43 | 20.18 | $C_4H_9$: 66.18; 66.06; 31.76; |
| $^5CH_3$ $^1COOC_4H_9$ | 172.45 | 58.37 | 32.27 | 19.35 | 20.14 | 26.74; 26.54; 26.40; 26.07; |
| | 172.38 | 58.37 | 32.19 | | 19.52 | 14.07 |
| $C_4H_9O^5CO^4CH_2{}^3CH_2{}^2CHNH$ | 174.39 | 53.30 | 28.71 | 31.97 | 173.15 | $C_4H_9$: 66.80; 65.45; 65.81; |
| (2f) $^1COOC_4H_9$ | 174.11 | 53.20 | 28.71 | 31.69 | 172.98 | 34.12; 32.06; 24.16; 20.43; |
| | 173.38 | 53.08 | 28.26 | 31.36 | 172.98 | 20.39; 20.03; 19.98; 14.35; 14.08; 14.04 |

**3-O-[Glucopyranuronosyl-(1″→2′)-glucopyranuronosyl]glycyrrhizic Acid, Triamide with Glutamic Acid Diethyl Ester (2c).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.4 g (6.5 mmole) of N,N′-dicyclohexylcarbodiimide, 1.92 g (8 mmole) of L-glutamic acid ethyl ester hydrochloride, and 1.2 ml (10.3 mmole) of N-ethylmorpholine in 50 ml of tetrahydrofuran yielded 1.6 g (58.0%) of the crude glycopeptide (**2c**). By reprecipitation from chloroform–ethanol (5:1), 1.1 g (40.5%) of product (**2c**) was obtained, and it was chromatographed on a column of silica gel L (100/250 μl) with elution by chloroform–methanol–water (300:10:1), (200:10:1), and (50:10:1) (v/v). The (100:10:1) mixture eluted 0.6 g (21.4%) of the desired product (**2c**), homogeneous according to TLC. $R_f$ 0.54 (A), $[\alpha]_D^{20}$ + 46° (s 0.12; MeOH). IR spectrum (ν, $cm^{-1}$): 3600-3200 (OH, NH); 1745 (COOEt), 1670 ($C_{11}$ = O); 1545 (CONH), UV spectrum ($\lambda_{max}^{CH_3OH}$, nm): 248 (log ε 4.17). Found %: C 59.54; H 8.05; N 2.82; $C_{69}H_{107}N_3O_{25}$. Calculated %: C 60.10; H 7.87; N 3.05. M 1378.79.

**3-O-[Glucopyranurosyl-(1″→2′)-glucopyranurosyl]glycyrrhizic Acid, Triamide with L-Alanine Propyl Ester) (2d).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.3 g (6 mmole) of N,N′-dicyclohexylcarbodiimide, 1.5 g (9 mmole) of L-alanine propyl ester hydrochloride, and 1.4 ml (10.2 mmole) of triethylamine in 50 ml of dioxane yielded 1.7 g (72.9%) of the crude glycopeptide (**2d**), which was isolated by evaporating off the dioxane in vacuum at a temperature < 50°C, dissolving the residue in methylene chloride (200 ml) and washing the solution successively with 5% HCl, water, 5% $NaHCO_3$ solution, and water again. The solution was dried over $MgSO_4$ and was evaporated in vacuum. A homogeneous product was isolated by chromatography on a column of silica gel L (40/100 μm) with elution by chloroform–methanol (100:1), (50:1), (25:1), (10:1). The (50:1)-(25:1) mixtures eluted 1.1 g (52.5%) of the homogeneous product (**2d**) in the form of an amorphous cream-colored substance. $R_f$ 0.45 (B), $[\alpha]_D^{20}$ + 48° (s 0.05; EtOH).

IR spectrum ($\nu$, $cm^{-1}$: 3600-3200 (OH, NH); 1740 (COOPr); 1660 ($C_{11}$ = O); 1550 (CONH). UV spectrum: $\lambda_{max}^{C_2H_5OH}$, nm: 248 (log$\varepsilon$ 4.00). Found %: C 61.79; H 8.00; N 3.20. $C_{60}H_{95}N_3O_{19}$. Calculated %: C 62.00; H 8.24; N 3.61. M 1162.55.

**3-O-[Glucopyranurosyl-(1″→2′)-glucopyranurosyl]glycyrrhizic Acid, Triamide with L-glutamic Acid Dipropyl Ester Hydrochloride (2e).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.4 g (6.8 mmole) of N,N′-dicyclohexyl carbodiimide, 2.0 g (7.5 mmole) of L-glutamic acid dipropyl ester hydrochloride, and 2.0 ml (14.6 mmole) of triethylamine in a mixture of 50 ml of dioxane and 40 ml of dimethylformamide yielded 1.5 g (52.4%) of the crude glycopeptide (**2e**), which was chromatographed on a column of silica gel L with elution by chloroform–methanol (100:1), (50:1), (25:1), and (10:1). The (50:1) and (25:1) mixtures eluted 0.9 g (31.5%) of the homogeneous product (**2e**) in the form of an amorphous substance. $R_f$ 0.5 (A). $[\alpha]_D^{20}$ + 43° (s 0.03; MeOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1740 (COOPr); 1660 ($C_{11}$ = O); 1540 (CONH). UV spectrum ($\lambda_{max}^{CH_3OH}$, nm): 250 (log$\varepsilon$ 4.18). Found %: C 61.04; H 8.11; N 3.87, $C_{72}H_{119}N_3O_{27}$. Calculated %: C 60.61; H 8.40; N 3.45. M 1458.91.

**3-O-[Glucopyranurosyl-(1″→2′)-glucopyranurosyl]glycyrrhizic Acid, Triamide with L-Alanine Butyl Ester (2g).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.4 g (6.8 mmole) of N,N′-dicyclohexylcarbodiimide, 1.3 g (7 mmole) of L-alanine butyl ester hydrochloride, and 1.4 ml (10.2 mmole) of triethylamine in 50 ml of dioxane yielded 1.7 g (70.8%) of the crude glycopeptide (**2g**), which was reprecipitated from acetone with hexane and was rechromatographed on a column of silica gel L (40/100 $\mu$m) with elution by chloroform–ethanol (50:1), (25:1), (10:1), and (5:1). The (10:1) mixture gave 1.15 g (47.9%) of the homogeneous product (**2g**). $R_f$ 0.54 (A), $[\alpha]_D^{20}$ + 47° (s 0.02; MeOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1745 (COOBu); 1670 ($C_{11}$ = O); 1545 (CONH). UV spectrum ($\lambda_{max}^{CH_3OH}$, nm): 248 (log$\varepsilon$ 3.98). Found %: C 62.78; H 8.40; N 3.44. $C_{63}H_{101}N_3O_{19}$. Calculated %: C 62.82; H 8.45; N 3.44. M 1204.64.

**3-O-[Glucopyranurosyl-(1″→2′)-glucopyranurosyl]glycyrrhizic Acid, Triamide with L-Valine Butyl Ester (2h).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.4 g (6.8 mmole) of N,N′-dicyclohexylcarbodiimide, 1.68 g (8 mmole) of L-valine butyl ester hydrochloride, and 1.2 ml (8.7 mmole) of N-ethylmorpholine in 50 ml of tetrahydrofuran yielded 2.0 g (78.7%) of the crude glycopeptide (**2h**), which was reprecipitated from a mixture of chloroform and ethanol (5:1) with ether. Yield 1.1 g (43.3%). To obtain an analytically pure sample, the product was chromatographed on a column of silica gel L (100/250 $\mu$m) with elution by chloroform–methanol–water (200:10:1), (100:10:1) , (50:10:1), and (25:10:1). The (100:10:1) mixture eluted 0.6 g (23.6%) of the homogeneous glycopeptide (**2h**) in the form of an amorphous substance. $R_f$ 0.6 (A); $[\alpha]_D^{20}$ + 35° (s 0.084 MeOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1745 (COOBu); 1670 ($C_{11}$ = O); 1540 (CONH). UV spectrum ($\lambda_{max}^{CH_3OH}$, nm): 248 (log$\varepsilon$ 4.02). Found %: C 64.42; H 8.37; N 3.99; $C_{69}H_{113}N_3O_{18}$. Calculated %: C 65.10; H 8.96; N 3.30; M 1272.85.

**3-O-[Glucopyranurosyl-(1″→2′)-glucopyranurosyl]glycyrrhizic Acid, Triamide with L-glutamic Acid Dibutyl Ester (2f).** As for experiment (**2a**), 1.64 g (2 mmole) of glycyrrhizic acid, 1.2 g (10.4 mmole) of N-hydroxysuccinimide, 1.3 g (6 mmole) of N,N′-dicyclohexylcarbodiimide, 2.1 g (7 mmole) of L-glutamic acid dibutyl ester dihydrochloride, and 1.5 ml (10.9 mmole) of triethylamine in a mixture of 50 ml of dioxane and 5 ml of dimethylformamide yielded 2.3 g (74.6) of the crude glycopeptide (**2f**), which was chromatographed on a column of silica gel L (100/250 $\mu$m), with elution by chloroform–methanol (50:1), (25:1), and (10:1). The (50:1) and (25:1) mixtures eluted 1.5 g (48.5%) of product (**1**) in the form of an amorphous yellowish substance. $R_f$ 0.5 (A); $[\alpha]_D^{20}$ + 30° (s 0.02; MeOH). IR spectrum ($\nu$, $cm^{-1}$): 3600-3200 (OH, NH); 1740 (COOBu); 1690 (CONH); 1650 ($C_{11}$ = O); 1530 (CONH). UV spectrum ($\lambda_{max}^{CH_3OH}$, nm): 249 (log$\varepsilon$ 4.09). Found %: C 60.19; H 8.24; N 2.73; $C_{81}H_{131}N_3O_{25}$. Calculated %: C 60.30; H 8.53; N 2.72. M 1546.87.

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