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# SYNTHESIS OF HYDROPHOBIC DERIVATIVES OF MURAMYLDIPEPTIDES

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*Methyl esters of the cyclohexyl-, phenethyl-, (2-naphthyl)methyl-, and 2'-(1-naphthyl)ethyl β-glycosides of N-acetylmuramyl-L-alanyl-D-isoglutamine have been synthesized. The corresponding glycosides of N-acetylglucosamine were obtained by glycosylating the alcohols with the peracetate of α-glucosaminyl chloride in the presence of $HgI_2$, followed by deacetylation. Subsequent benzylidenation and alkylation with α-L-chloropropionic acid led to glycosylmuramic acids, the condensation of which with the dipeptide and final debenzylidenation gave the desired glycopeptides.*

One of the traditional approaches to highly active derivatives of N-acetylmuramyl-*L*-alanyl-*D*-isoglutamine (muramyldipeptide, MDP) is the introduction of either a lipophilic component or a fragment of a biologically active compound [1]. In the first case lipophilicity is usually ensured by long hydrocarbon chains present in higher linear or α-branched carboxylic acids, natural mycolic acids, or a phosphatidylethanolamine. Such promising analogs of MDP as MTP-kephalin (MTP-PE) [1, 2], 6-O-stearoyl-MDP [3], B30MDP [4], and MTP-glyceryldipalmitoyl [1] have been constructed in this way. It is considered that the high immunostimulating activity of these lipoglycopeptides is connected with their better incorporation into the membranes of immune cells.

In the second case, fragments of vitamin K, ubiquinone Q, and hydrophobic compounds similar to them are added to the muramyldipeptide molecule [5]. The high antitumoral activity of these conjugates is usually explained just by the combination of two biologically active compounds, although it is possible that the added biologically active compounds fulfil the role of hydrophobic anchors. Of MDP analogs with lipophilic components of cyclic nature, only the benzyl α- and β-glycosides of MDP [6] and the cholesteryl β-glycoside of MDP [7], and also the cholesterol ester of MTP [8], are known.

In order to study the relationship of the structures of MDP derivatives to their biological activities, we have now synthesized glycosides of MDP containing carbocyclic aglycons: cyclohexyl (**1a**), phenethyl (**1b**), (2-naphthyl)methyl (**1c**), and 2-(1-naphthyl)ethyl (**1d**). We have previously obtained MDP glycosides with lipophilic carbochain aglycons [9], some of which — for example, the heptyl and hexadecyl β-glycosides of muramyldipeptide — exhibited a high immunostimulating activity [10].

The key stage in the synthesis of the glycopeptides (**1a-d**) is the formation of the corresponding β-glycosides of N-acetylglucosamine. Such glycosides can be obtained rapidly and with good yields by the use of the chloride (**2**) as a stable and readily available glycosyl donor in the presence of $HgI_2$ [11]. The glycosylation of cyclohexanol, phenethyl alcohol, β-naphthylcarbinol, and α-naphthylethanol was performed with an equivalent amount of the chloride (**2**) in dichloroethane at room temperature with addition of the catalyst and of 3Å molecular sieves.

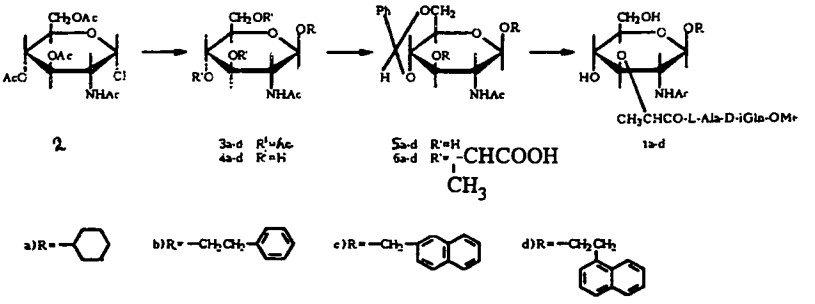


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TABLE 1. PMR Spectra of Glycosides (**3a-d**) and Glycopeptides (**1a-d**)

| | 3a | 3b | 3c | 3d | 1a | 1b | 1c | 1d |
|---|---|---|---|---|---|---|---|---|
| R | 1.15 m; 1.61 m | 7.21 m; 2.89 t | 7.37 m; 7.71 m | 7.29 m; 7.42 m; 7.65 d; 7.77 d; 7.95 d; 3.29 t | 1.14 m; 1.43 m; 1.60 m | 7.23 m; 2.77 t | 7.51 m; 7.88 m | 7.40 m; 7.53 m; 7.83 d; 7.92 d; 8.08 d |
| C(1)-$OCH_2$ | | 3.67 dt; 4.13 dt | 4.66 d; 4.95 d | 3.42 m; 4.17 m | | | | |
| NAc, OAc | 1.83 s; 1.91 s; 1.92 s; 1.97 s | 1.83 s; 2.05 s (6H); 2.08 s | 1.81 s; 1.97 s; 2.01 s (6H) | 1.66 s; 1.92 s (6H); 1.99 s | 1.75 s | 1.72 s | 1.73 s | 1.72 s |
| H-1 ($J_{1,2}$ Hz) | 4.76 d (8.5) | 4.62 d (8.5) | 4.57 d (8.0) | 4.56 d (8.0) | 4.37 d (8.0) | 4.31 d (8.5) | 4.40 d (8.0) | 4.37 d (8.5) |
| NH | 5.48 d | 5.36 d | 5.34 d | 5.23 d | 7.41 d; 7.80 d; 8.18 d | 7.39 d; 7.78 d; 8.13 d | 7.42 d; 7.82 d; 8.10 d | 7.16 d; 7.79 d; 8.08 d |
| C(4)-OH | | | | | 5.26 d | 5.29 d | 5.30 d | 5.32 d |
| C(6)-OH | | | | | 4.57 t | 4.64 t | 4.68 br.t | 4.64 br.t |
| $\underline{CH_3}CH$ | | | | | 1.18 d; 1.24 d | 1.23 d (6H) | 1.23 d (6H) | 1.18 d; 1.23 d |
| β-$CH_2$-*i*Gln | | | | | 1.98 m | 1.99 m | 2.00 m | 1.98 m |
| γ-$CH_2$-*i*Gln | | | | | 2.29 t | 2.29 t | 2.29 t | 2.29 t |
| $CONH_2$-*i*Gln | | | | | 7.12 s; 7.38 s | 7.14 s; 7.37 s | 7.15 s; 7.35 s | 7.14 s; 7.38 s |
| COOMe | | | | | 3.58 s | 3.58 s | 3.58 s | 3.57 s |

*Solvent for compounds (**3a-d**) $CDCl_3$, and for compounds (**1a-d**) DMSO-$d_6$. Working frequency for compounds (**3a—c**) 200 MHz, and for (**3d**) and (**1a-d**) 300 MHz.

After the end of the reactions, glycosides (**3a-d**) were isolated by crystallization with yields of 57-68%. Their structures were shown by their PMR spectra, with complete assignment of the proton signals (see Table 1 and the Experimental part). The presence of one-proton doublets in the 4.56-4.76 ppm regions and SSCCs of 8-8.5 Hz showed the β- configuration of the glycosidic center. The signals of the protons of the glycoside residues in compounds (**3a-d**) had similar chemical shifts and SSCCs.

The structures of the aglycons were confirmed by the presence in the PMR of multiplets of methylene protons with the CSs 1.15 and 1.61 ppm for the cyclohexyl glycosides (**3a**), a multiplet of five aromatic protons with a CS of 7.21 ppm and the triplet of a β-methylene group with a CS of 2.89 ppm for the phenethyl glycoside (**3b**), multiplets of protons of the β-naphthyl fragment with CSs of 7.37 and 7.71 ppm for glycoside (**3c**), and three doublets with CSs of 7.65, 7.77, and 7.95 ppm and two multiplets with CSs of 7.29 and 7.42 ppm for the protons of the α-naphthyl residue, together with a triplet of the β-methylene group, for glycoside (**3d**). The nonequivalence of the protons of the α-methylene groups of the aglycons in compounds (**3b-d**) must be mentioned.

The peracetates (**3a-d**) were subjected to Zemplen deacetylation, and the triols (**4a-d**) were converted by the action of benzaldehyde dimethyl acetal into the acetals (**5a-d**). Alkylation of the hydroxy groups at C-3 in compounds (**5a-d**) with α-*L*-chloropropionic acid in the presence of sodium hydride yielded the benzylidenemuramic acids (**6a-d**). Condensation of the N-hydroxysuccinimide esters of the muramic acids with the methyl ester of *L*-alanyl-*D*-isoglutamine led to the protected glycopeptides. Elimination of the benzylidene protection by acid hydrolysis gave the desired MDP glycosides (**1a-d**). The structures of the final compounds were confirmed by PMR spectroscopy. In the PMR spectra of these compounds, together with the signals of the protons of the carbohydrate moiety, we identified the protons of the characteristic groups of the lactoylpeptide residue (see Table 1 and the Experimental part).

## EXPERIMENTAL

Melting points were determined on a PTP instrument, and optical rotations at 20-22°C on a Polamat-A polarimeter. PMR spectra were obtained on Bruker WP-200 (200 MHz) and Varian VXR-300 (300 MHz) instruments, with tetramethylsilane as internal standard; chemical shifts are given in ppm, δ-scale. TLC was conducted on Silufol-UV-254 plates (Kavalier). The substances were detected by carbonization at 300°C. Column chromatography was performed on Aldrich silica gel, 70-230 mesh. The elementary analyses of the compound synthesized corresponded to the calculated values.

2-Phenylethan-1-ol, (2-naphthyl)methanol, and 2-(1-naphthyl)ethan-1-ol were synthesized by the $LiAlH_4$ reduction of phenylacetic, 2-naphthoic, and (1-naphthyl)acetic acids.

A number of general methods were used.

**Glycosylation.** A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-*D*-glucopyranosyl chloride [12] in dry dichloroethane (25 ml/g) was treated with 1.16 equiv. of mercury(II) iodide and 1 equiv. of an alcohol. The reaction mixture was stirred in the presence of 3-Å molecular sieves until the glycosyl donor had disappeared (monitoring by TLC in the benzene–ethanol (10:1) and (5:1) systems). The molecular sieves and the undissolved catalyst were filtered off, and the filtrate was diluted with chloroform and washed with water. The organic layer was separated off, dried with anhydrous $Na_2SO_4$, and evaporated. The residue was purified by crystallization.

**Zemplen Deacetylation.** A solution of an acetate in dry methanol or a mixture of methanol and dichloromethane (1:1) (10 ml/g) was treated with 0.01-0.05 equiv. of a 0.1 N solution of sodium methanolate in methanol, and the reaction mixture was kept for 12-24 h. Then it was neutralized with KU-2 cation-exchange resin ($H^+$), the resin was washed with methanol, and the filtrate was evaporated

**Benzylidenation.** Benzaldehyde dimethyl acetal (1 ml/g) and a few drops of a 10% solution of sulfuric acid in methanol were added to a suspension of the substance in dry dioxane (2-3 ml/g). The reaction mixture was carefully stirred at 90-95°C for 3-5 min, and then 50-100 ml of hexane was added and the precipitate was triturated to a powder, filtered off, and dried.

**Preparation of Muramic Acids.** With stirring, 4 equiv. of sodium hydride was added to a solution of a saccharide with a free C(3)-OH group in dry dioxane (20 ml/g). The mixture was heated to 95°C and was kept at this temperature for 1 h; after cooling to 65°C, 2 equiv. of α-*L*-chloropropionic acid was added, and the reaction mixture was kept at 65°C for another 3 h. After further cooling, the excess of sodium hydride was decomposed with ethanol, and the mixture was concentrated and was poured into cold water. The resulting solution was acidified with 2 N sulfuric acid to pH 2-3, and the muramic acid was extracted with chloroform. The extract was dried with anhydrous $Na_2SO_4$ and evaporated, and the residue was crystallized.

**Condensation by the N-Hydroxysuccinimide Method.** With stirring, 1.1 equiv. of N-hydroxysuccinimide and 1.1 equiv. of dicyclohexylcarbodimide were added to a solution of an acid in dry dioxane or THF (10-20 ml/g). After 3-5 h, the precipitate of dicyclohexylurea was filtered off and was washed with the solvent. The filtrate was treated with 1 equiv. of N-deblocked dipeptide (obtained by treating the methyl ester of Boc-*L*-alanyl-*D*-isoglutamine with trifluoroacetic acid, followed by evaporation to dryness) and with triethylamine to pH 8. After the end of the reaction, the product was isolated by filtration and was purified by column chromatography.

**Hydrolysis of the Benzylidene Derivatives.** With heating in the boiling water-bath, the alkylidene derivatives were dissolved in 80% acetic acid (10 ml/g), and the solutions were kept at the same temperature for 20-40 min (monitoring by TLC). They were then evaporated to dryness, and the residues were triturated in ether.

### Methyl Ester of O-(Cyclohexyl 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl) -*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1a)

**Cyclohexyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (3a).** The glycosylation of 1.37 g (13.7 mmole) of cyclohexanol with 5.0 g (13.7 mmole) of the chloride (2) gave, after recrystallization from ether, 3.97 g (68%) of glycoside (3a), mp 178°C, $[\alpha]_{546}$ −17.6° (*c* 0.77; chloroform). PMR (200 MHz, $CDCl_3$): 1.15 m, 1.61 m ($CH_2$). 1.83 s, 1.92 s, 1.97 s (12H, NAc and 3 OAc), 3.55 (1H, O-CH), 3.56 m (1H, H-2), 3.59 m (1H, H-5), 3.99 dd and 4.16 dd (2H, 1.91 s, H-6a, H-6b; $J_{5,6a}$ 2.5 Hz, $J_{5,6b}$ 5 Hz, $J_{6a,6b}$ 12 Hz), 4.75 d (1H, H-1; $J_{1,2}$ 8.5 Hz), 4.93 dd (1H, H-4; $J_{4,5}$ 9.5 Hz), 5.29 dd (1H, H-3; $J_{3,4}$ 9.5 Hz, $J_{2,3}$ 10.5 Hz), 5.48 d (1H, NH; $J_{2,NH}$ 8.5 Hz).

**Cyclohexyl 2-Acetamido-2-deoxy-β-*D*-glucopyranoside (4a).** The deacetylation of 2.8 g (6.5 mmole) of the peracetate (**3a**) yielded 1.9 g (96%) of compound (**4a**), mp 167-169°C, $[\alpha]_{546}$ −37.3° (*c* 0.67; methanol).

**Cyclohexyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-*D*-glucopyranoside (5a).** The benzylidenation of 500 mg (1.66 mmole) of the triol (**4a**) gave 500 mg (78%) of the acetal (**5a**), mp 235-237°C (decomp.), $[\alpha]_{546}$ −87° (*c* 0.67; dichloromethane).

**Cyclohexyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-3-O-(*D*-1-carboxyethyl)-β-*D*-glucopyranoside (6a).** The alkylation of 800 mg (2.05 mmole) of compound (**5a**) with chloropropionic acid led to 900 mg (95%) of the muramic acid (**6a**), mp 221-222°C (decomp.), $[\alpha]_{546}$ −18.8° (*c* 0.67; dimethylformamide)

**Methyl Ester of O-(Cyclohexyl 2-acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl)-*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1a).** We condensed 200 mg (0.43 mmole) of the acid (**6a**) with the dipeptide obtained from 142 mg (0.44 mmole) of the corresponding Boc derivative. Then the benzylidene group was removed from the protected glycopeptide, giving 160 mg (62%) of compound (**1a**) in the form of an amorphous powder, $[\alpha]_{546}$ −21.8° (*c* 0.67; methanol). PMR (300 MHz, DMSO-$d_6$): 1.14 m, 1.43 m, 1.60 m ($CH_2$), 1.18 d and 1.24 d (6H, 2 $CH_3CH$), 1.75 s (3H, NAc), 1.98 m (2H, β-$CH_2$-*i*Gln), 2.29 t (2H, γ-$CH_2$-*i*Gln), 3.58 s (3H, COOMe), 4.37 d (1H, H-1; $J_{1,2}$ 8 Hz), 4.57 t (1H, $C_6$-OH), 5.26 d (1H, $C_4$-OH), 7.12 s and 7.38 s (2H, $CONH_2$), 7.41 d, 7.80 d, and 8.12 d (3H, 3 NH).

## Methyl Ester of O-(Phenethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl) -*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1b)

**Phenethyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (3b).** Phenethyl alcohol (335 mg, 2.7 mmole) was glycosylated with 1.0 g (2.7 mmole) of the chloride (**2**), and, after recrystallization from ether, 700 mg (57%) of glycoside (**3b**) was obtained, with mp 119-120°C, $[\alpha]_{546}$ +54.2° (*c* 1.0; dichloroethane). PMR (200 MHz, $CDCl_3$): 1.83 s, 2.05 s (6H), 2.08 s (12 H, NAc and 3 OAc), 2.89 t (−$CH_2$-Ph), 3.67 dt and 4.13 dt (2 H, O-$CH_2$), 3.68 ddd (1H, H-5; $J_{5,6}$ 2.5 Hz, $J_{5,6b}$ 5 Hz), 3.83 ddd (1H, H-2, $J_{2,3}$ 10.5 Hz), 4.11 dd and 4.26 dd (2H, H-6a, H-6b; $J_{6a,6b}$ 13 Hz), 4.62 d (1H, H-1; $J_{1,2}$ 8.5 Hz), 5.06 dd (1H, H-4; $J_{4,5}$ 9.5 Hz), 5.25 dd (1H, H-3; $J_{3,4}$ 9.5 Hz), 5.36 d (1H, NH; $J_2$, NH 8.5 Hz), 7.21 m (5H, Ph).

**Phenethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranoside (4b).** The deacetylation of 500 mg (1.1 mmole) of the peracetate (**3b**) gave 300 mg (90%) of compound (**4b**), mp 162-164°C, $[\alpha]_{546}$ −27.1° (*c* 1.0; methanol).

**Phenethyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-*D*-glucopyranoside (5b).** The benzylidenation of 500 mg (1.54 mmole) of the triol (**4b**) gave 550 mg (87%) of the acetal (**5b**), mp 154-156°C (decomp.), $[\alpha]_{546}$ −77.1° (*c* 1.0; methanol).

**Phenethyl 2-Acetamido-4,6-O-benzylidene-3-O-(*D*-1-carboxyethyl)-2-deoxy-β-*D*-glucopyranoside (6b).** By the alkylation of 1.1 g (2.67 mmole) of compound (**5b**) with 580 mg (5.34 mmole) of chloropropionic acid, we synthesized 1.2 g (93%) of the muramic acid (**6b**), mp 215-217°C (decomp.), $[\alpha]_{546}$ −37.5° (*c* 1.0; dimethylformamide).

**Methyl Ester of O-(Phenethyl 2-acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl)-*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1b).** We condensed 200 mg (0.413 mmole) of the acid (**6b**) with the dipeptide obtained from 136 mg (0.413 mmole) of the corresponding Boc derivative. Then the benzylidene group was removed from the protected dipeptide, giving 250 mg (86%) of compound (**1b**) in the form of an amorphous white powder, $[\alpha]_{546}$ −15.5° (*c* 0.67; methanol). PMR (300 MHz, DMSO-$d_6$): 1.23 d (6H, 2 $CH_3CH$), 1.72 s (3H, NAc), 1.99 m (2H, β-$CH_2$-*i*Gln), 2.29 t (2H, γ-$CH_2$-*i*Gln), 2.77 t (−$CH_2$-Ph), 3.58 s (3H, COOMe), 4.31 (1H, H-1; $J_{1,2}$ 8.5 Hz), 4.64 t (1H, $C_6$-OH), 5.29 d (1H, $C_4$-OH), 7.14 s and 7.37 s (2H, $CONH_2$), 7.39 d, 7.78 d and 8.13 d (3H, 3 NH).

## Methyl Ester of O-[(2-Naphthylmethyl) 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl] -*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1c)

**2-Naphthylmethyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (3c).** The glycosylation of 430 mg (2.7 mmole) of 2-naphthylmethanol with 990 mg (2.7 mmole) of the chloride (**2**), followed by recrystallization from methanol, gave 755 mg (57%) of glycoside (**3c**), mp 175-178°C, $[\alpha]_{546}$-36.9° (*c* 0.62; chloroform). PMR (200 MHz, $CDCl_3$): 1.81 s, 1.97 s, 2.01 s (6H) (12 H, NAc and 3 OAc), 3.57 ddd (1H, H-5; $J_{5.6}$ 2.5 Hz, $J_{5.6b}$ 5 Hz), 3.91 m (1H, H-2; $J_{2.3}$ 10.5 Hz),

4.08 dd and 4.20 dd (2H, H-6a. H-6b; $J_{6a,6b}$ 12 Hz), 4.57 d (1H, H-1; $J_{1,2}$ 8 Hz), 4.66 d and 4.95 d (2H, O-$CH_2$), 5.00 dd (1H, H-4; $J_{4,5}$ 9.5 Hz), 5.08 dd (1H, H-3; $J_{3,4}$ 9.5 Hz), 5.34 d (1H, NH; $J_{2,NH}$ 8.5 Hz), 7.37 m and 7.71 m (7H, CH-arom.).

**2-Naphthylmethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranoside (4c).** The deacetylation of 1.64 g (3.37 mmole) of the peracetate (**3c**) gave 1.05 g (96%) of compound (**4c**), mp 255-256°C decomp., $[\alpha]_{546}$ −74.6° (*c* 0.67; dimethylformamide).

**2-Naphthylmethyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-*D*-glucopyranoside (5c).** The benzylidenation of 600 mg (1.67 mmole) of the triol (**4c**) gave 700 mg (94%) of the acetal (**5c**), mp 255-256°C (decomp.), $[\alpha]_{546}$ −108.8° (*c* 0.67; dimethylformamide).

**Methyl Ester of O-[(2-Naphthylmethyl) 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl]-*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1c).** We condensed 300 mg (0.58 mmole) of the acid (**6c**) with the dipeptide obtained from 190 mg (0.58 mmole) of the corresponding Boc derivative. The benzylidene group was eliminated from the protected dipeptide, giving 290 mg (70%) of compound (**1c**) as an amorphous white powder, $[\alpha]_{546}$ +6° (*c* 0.67; methanol. PMR (300 MHz, DMSO-$d_6$): 1.23 d (6H, 2 $CH_3CH$), 1.73 s (3H, NAc). 2.00 m (2H, β-$CH_2$-*i*Gln), 2.29 t (2H, γ-$CH_2$-*i*Gln), 3.58 s (3H, COOMe) 4.40 d (1H, H-1; $J_{1,2}$ 8 Hz), 4.68 br.t (1H, $C_6$-OH), 5.30 br.d (1H, $C_4$-OH), 7.15 s and 7.35 s (2H, $CONH_2$), 7.42 d, 7.82 d and 8.10 d (3H, 3 NH), 7.51 m and 7.88 m (7H, CH-arom.).

**Methyl Ester of O-[2′-(1-Naphthyl)ethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl]-*D*-lactyl-*L*-alanyl-*D*-isoglutamine (1d)**

**2′-(1-Naphthyl)ethyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-*D*-glucopyranoside (3d).** 2-(1-Naphthyl)ethan-1-ol (390 mg; 2.26 mmole) was glycosylated with 830 mg (2.26 mmole) of the chloride (**2**). Crystallization from ethanol yielded 660 mg (58%) of glycoside (**3d**),mp, 188-189°C, $[\alpha]_{546}$ −14.7° (*c* 1.1; dichloroethane). PMR (300 MHz, $CDCl_3$): 1.66 s, 1.92 s (6H), 1.99 s (12 H, NAc and 3 OAc), 3.29 t (2H, $CH_2$-$\underline{CH_2}$), 3.56 m (1H, H-5; $J_{5,6a}$ 2 Hz, $J_{5,6b}$ 4.5 Hz), 3.72 m (1H, H-2; $J_{2,3}$ 10 Hz), 4.03 dd and 4.18 dd (2H, H-6a, H-6b; $J_{6a,6b}$ 12 Hz), 4.56 d (1H, H-1; $J_{1,2}$ 8 Hz), 3.72 m and 4.17 m (2H, O-$CH_2$), 4.98 dd (1H, H-4; $J_{4,5}$ 9.5 Hz), 5.18 dd (1H, H-3; $J_{3,4}$ 9.5 Hz), 5.23 d (1H, NH; $J_{2,NH}$ 8.5 Hz). 7.29 m, 7.42 m, 7.65 d, 7.77 d, and 7.95 d (7H, CH-arom.).

**2′-(1-Naphthyl)ethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranoside (4d).** The deacetylation of 610 mg (1.21 mmole) of the peracetate (**3d**) gave 435 mg (96) of compound (**4d**), mp 204-205°C, $[\alpha]_{546}$ −31.3° (*c* 0.80; dimethylformamide).

**2′-(1-Naphthyl)ethyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-β-*D*-glucopyranoside (5d).** The benzylidenation of 420 mg (1.12 mmole) of (**4d**) yielded 450 mg (87%) of the acetal (**5d**), mp 220-222°C (decomp.), $[\alpha]_{546}$ −73.7° (*c* 0.93; dimethylformamide).

**2′-(1-Naphthyl)ethyl 2-Acetamido-4,6-O-benzylidene-3-O-(*D*-1-carboxyethyl)-2-deoxy-β-*D*-glucopyranoside (6d).** By the alkylation of 350 mg (0.76 mmole) of compound (**5d**) with chloropropionic acid we synthesized 390 mg (96%) of the muramic acid (**6d**), mp 210-212°C (decomp.), $[\alpha]_{546}$ −63.5° (*c* 1.0; dimethylformamide).

**Methyl Ester of O-[2′-(1-Naphthyl)ethyl 2-Acetamido-2-deoxy-β-*D*-glucopyranosid-3-yl]-*D*-lactoyl-*L*-alanyl-*D*-isoglutamine (1d).** We condensed 390 mg (0.73 mmole) of the acid (**6d**) with the dipeptide obtained from 240 mg (0.73 mmole) of the corresponding Boc derivative. The benzylidene group was eliminated from the protected dipeptide, giving 280 mg (60%) of compound (**1d**) as an amorphous white powder, $[\alpha]_{546}$ +5.5° (*c* 1.1; methanol). PMR (300 MHz, DMSO-$d_6$): 1.18 d, 1.23 d (6H, 2 $CH_3CH$), 1.72 s (3H, NAc), 1.98 m (2H, β-$CH_2$-*i*Gln), 2.29 t (2H, γ-$CH_2$-*i*Gln), 3.57 s (3H, COOMe), 4.37 d (1H, H-1; $J_{1,2}$ 8 Hz), 4.64 br.t (1H, $C_6$-OH), 5.32 br.d (1H, $C_4$-OH), 7.14 s and 7.38 s (2H, $CONH_2$), 7.16 d, 7.79 d and 8.08 d (3H, 3 NH), 7.40 m, 7.53 m, 7.83 d, 7.92 d and 8.08 d (7H, CH-arom.).

## REFERENCES


1. G. Baschang, Tetrahedron, **45**, No. 20, 6331 (1989).
2. S. Sone, S. Mutsuura, M. Ogawara, and E. Tsubura, J. Immunol., **132**, No. 4, 2105 (1984).
3. S. Kusumoto, S. Okada, K. Yamamoto, and T. Shiba, Bull. Chem. Soc. Jpn., **51**, No. 7, 2122 (1978); S. Kotani, F. Kinoshita, I. Morisaki, T. Shimono, T. Okunaga, H. Takada, M. Tsujimoto, Y. Watanabe, K. Kato, T. Shiba, S. Kusumoto, and S. Okada, Biken J., **20**, No. 3-4, 95 (1977); Y. Osada, M. Mitsuyama, T. Une, K. Matsumoto, T. Otani, M. Satoh, H. Ogawa, and K. Nomoto, Infect. Immun., **37**, No. 1, 292 (1982).

4. S. Kusumoto, M. Inage, T. Shiba, I. Azuma, and Y. Yamamura, Tetrahedron Lett., No. 49, 4899 (1978); M. Tsujimoto, S. Kotani, T. Okunaga, Takao Kubo, H. Takada, Takashi Kubo, T. Shiba, S. Kusumoto, T. Takahashi, Y. Goto, and F. Kinoshita, Vaccine, **7**, 39 (1989).
5. S. Kobayashi, T. Fukuda, I. Imada, M. Fujino, I. Azuma, and Y. Yamamura, Chem. Pharm. Bull., **27**, No. 12, 3193 (1979); T. Fukuda, S. Kobayashi, H. Yukimasa, I. Imada, M. Fujino, I. Azuma, and Y. Yamamura, Chem. Pharm. Bull., **29**, No. 8, 2215 (1981).
6. A. Hasegawa, Y. Kaneda, M. Amano, M. Kiso, and I. Azuma, Agric. Biol. Chem., **42**, No. 11, 2187 (1978); C. Merser, P. Sinaÿ, and A. Adam, Biochem. Biophys. Res. Commun., **66**, No. 4, 1316 (1975).
7. V. O. Kur'yanov, O. É. Zemlyakov [A. E. Zemlyakov], and V. Ya. Chirva, in: Abstracts of Lecture at the 17th Ukrainian Conference on Organic Chemistry [in Ukrainian], Kharkov (1995), p. 602.
8. G. M. Barratt, W. P. Yu, H. Fessi, J. P. Devissaguet, J. F. Petit, J. P. Tenu, L. Israel, J. F. Morere, and F. Puisieux, Cancer J., **2**, No. 12, 439 (1989).
9. A. E. Zemlyakov and V. Ya. Chirva, Khim. Prir. Soedin., 714 (1987); V. O. Kur'yanov, A. E. Zemlyakov, and V. Ya. Chirva, Bioorg. Khim., **20**, No. 4, 439 (1994).
10. O. V. Kalyuzhin, B. B. Fuks, N. V. Bovin, A. E. Zemlyakov, and V. Ya. Chirva, Byull. Éksp. Biol., No. 5, 510 (1994).
11. A. E. Zemlyakov, V. O. Kur'yanov, and V. Ya. Chirva, Khim. Prir. Soedin., 367 (1996).
12. D. Horton, in: Methods in Carbohydrate Chemistry, R. L. Whistlrer and J. N. BeMiller (eds.), Academic Press, New York, Vol VI. (1972), pp. 282-285.