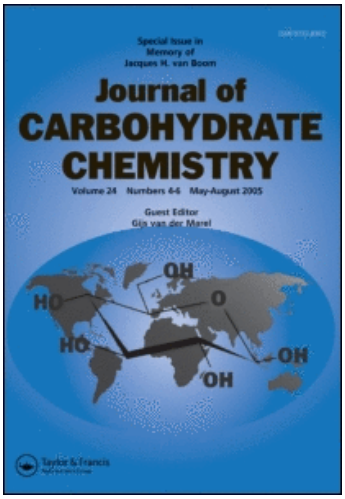

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Synthesis of *N*-[2-S -(2-Acetamido-2,3-dideoxy-D-glucopyranose-3-y1)-2-Thio-D-Lactoyl]-L-alanyl-D-isoglutamine

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SYNTHESIS OF N-[2-S-(2-ACETAMIDO-2,3-DIDEOXY-D-GLUCOPYRANOSE-3-yl)-2-THIO-D-LACTOYL]-L-ALANYL-D-ISOGLUTAMINE*

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ABSTRACT

N-[2-S-(2-Acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine, in which the oxygen atom at C-3 of N-acetylmuramoic acid moiety in N-acetylmuramoyl-L-alanyl-D-isoglutamine (MDP) has been replaced by sulfur, was synthesized from allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (1).

Treatment with sodium acetate of the 3-O-mesylate, derived from 1 by 4,6-O-isopropylidenation and subsequent mesylation, gave allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-allopyranoside (4). When treated with potassium thioacetate, the 3-O-mesylate, derived from 4, afforded allyl 2-acetamido-3-S-acetyl-2-deoxy-4,6-

* Studies on Immunoadjuvant Active Compounds, Part 26. For Part 25, see ref. 1.

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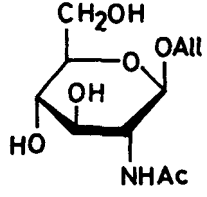
O-isopropylidene-β-D-glucopyranoside (6). S-Deacetylation of 6, condensation with 2-L-chloropropanoic acid, and subsequent esterification, gave the 3-S-[D-1-(methoxycarbonyl)ethyl]-3-thio-glucopyranoside derivative (7). Coupling of the acid, derived from 7, with the methyl ester of L-alanyl-D-isoglutamine, and subsequent hydrolysis, yielded the title compound.

INTRODUCTION

In the previous papers, we have demonstrated that not only is the restricted configuration of the sugar moiety in N-acetylmuramoyl-L-alanyl-D-isoglutamine,[2,3] which is the minimal, adjuvant active structure of bacterial, cell-wall peptidoglycans, important for the activity,[4] but also that the chemical modifications[1,5-8] of the functional groups in the carbohydrate moiety produce various, important effects on the manifestation of the activity. In view of these facts, we now describe the synthesis of N-acetyl-3-thiomuramoyl-L-alanyl-D-isoglutamine, in which the oxygen atom at C-3 of N-acetylmuramoic acid moity in MDP is replaced by sulfur, and its immunoadjuvant activity.

RESULTS AND DISCUSSION

Isopropylidenation[9] of allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (1) with 2,2-dimethoxypropane in N,N-dimethylformamide in the presence of p-toluenesulfonic acid gave the 4,6-O-isopropylidene derivative 2 in good yield. Treatment of 2 with methanesulfonyl chloride in pyridine afforded the 3-O-mesyl derivative 3, which was converted, in 92% yield, into allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-allopyranoside (4) by heating with sodium acetate in aqueous 95% 2-methoxyethanol. Methanesulfonylation of 4 gave the 3-O-mesylate 5; significant signals in the ^{1}H NMR spectrum were a one-proton triplet at δ 4.95 ($J_{2,3} = J_{3,4} = 2.5$ Hz, H-3) and S-Me absorption at δ 2.97. Other NMR data are given in the Experimental section, and are consistent with structure 5.



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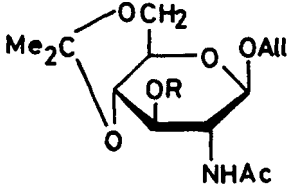
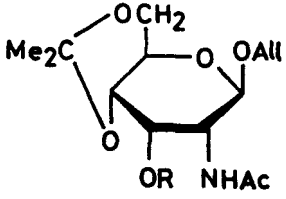
All = CH_2=CH-CH_2-



2 R = H

3 R = Ms

Ms = $MeSO_2$



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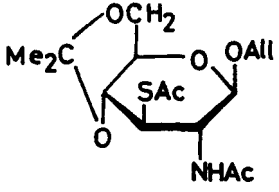
5 R = Ms



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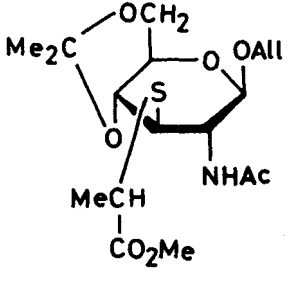

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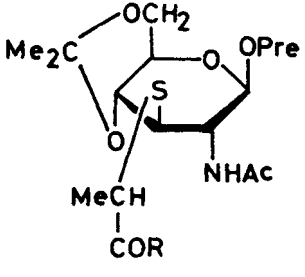
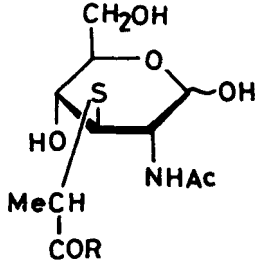


8 R = OH

9 R = a

Pre = CH_3CH=CH-

a = L-Ala-D-isoGln-OMe



10 R = b

11 R = a

b = L-Ala-D-isoGln

On treatment with potassium thioacetate in N,N-dimethylformamide for 50 h at 80-85 °C under nitrogen atmosphere, compound 5 afforded allyl 2-acetamido-3-S-acetyl-2-deoxy-4,6-O-isopropylidene-3-thio-β-D-glucopyranoside (6) in 60% yield; whose IR and ^{1}H-NMR spectra showed the characteristic, S-acyl absorption at ν 1690 cm^{-1} and at δ 2.38, respectively. The sodium salt of 6, formed by addition of sodium methoxide in methanol, was condensed with L-2-chloropropanoic acid in dry 1,4-dioxane at room temperature, to afford the 3-S-(D-1-carboxyethyl) derivative, which was converted, in 93% yield, into allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-S-[D-1-(methoxycarbonyl)ethyl]-3-thio-β-D-glucopyranoside (7) by addition of diazomethane. Treatment[10] of 7 with tris(triphenylphosphine)-rhodium chloride in the presence of 1,4-diazabicyclo[2,2,2]octane

TABLE I

Immunoadjuvant Activity of N-Acetyl-3-thiomuramoyl-L-alanyl-D-isoglutamines on the Induction of Delayed-type Hypersensitivity to ABA-N-acetyltyrosine in Guinea-pigs.

Compound	Dose (μg)	Skin Reaction with ABA-BSA[a] (50 μg) (diam. in mm)[b] at	
		24 h	48 h
10	100	13.6 ± 0.5	(3.5 ± 1.4)
11	100	16.6 ± 1.0	(12.5 ± 1.6)
MDP	100	20.9 ± 0.9	22.4 ± 1.0
Control[c]		0	0

[a]Azobenzenearsonate-N-acetyl-L-tyrosine-bovine serum albumin. [b]The data indicate the average diameter ± the standard error of the skin reaction (induration) of four guinea-pigs; the values in parentheses indicate the size of erythema. [c]ABA-N-acetyltyrosine in Freund's incomplete adjuvant.

in aqueous 10% ethanol, and subsequent hydrolysis gave propenyl 2-acetamido-3-S-(D-1-carboxyethyl)-2-deoxy-4,6-O-isopropylidene-3-thio-β-D-glucopyranoside (8) in 74% yield, without affecting other functional groups; the ^{1}H-NMR spectrum showed the characteristic absorptions due to the propenyl group at δ 1.45 (=CH-Me) and 6.12 (-O-CH=). Coupling of 8 with L-alanyl-D-isoglutamine methyl ester, using dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (HOSu) as the activating agents, afforded the dipeptide derivative 9 in 92% yield. Hydrolytic removal of the protecting groups in 9 under mild, acidic conditions afforded the desired N-[2-S-(2-acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine (10) in 81% yield. When treated with diazomethane, compound 10 gave the methyl ester 11.

The immunoadjuvant activities of compounds 10 and 11 on the induction of the delayed type of hypersensitivity to N-acetyl-L-tyrosine-3-azobenzene-4'-arsonate (ABA-N-acetyltyrosine) in guinea-pigs were examined[11] (see Table I). Both of the compounds have a distinct, but week, immunoadjuvant activity as compared to that of MDP, indicating that the oxygen atom on C-3 in carbohydrate moiety of MDP seems to be important for the activity.

EXPERIMENTAL

General procedures. Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Evaporations were conducted in vacuo. Preparative chromatography was performed on silica gel (Waco Co.; 200 mesh) with the solvent systems specified. Specific rotations were determined with a Union PM-201 polarimeter, and IR spectra were recorded with a Jasco A-100 spectrophotometer. ^{1}H NMR spectra were recorded at 90 MHz with a Hitachi R-22 spectrometer.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (2). To a solution of allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside[12] (1; 150 mg) in N,N-dimethyl-

formamide (10 mL) were added 2,2-dimethoxypropane (1 mL) and p-toluenesulfonic acid monohydrate (15 mg). The mixture was stirred for 1 h at room temperature, treated with Amberlite IR-410 (OH^-) resin to remove the acid, and then evaporated. The crystalline residue was recrystallized from ethanol-ether to give 2 (158 mg, 91 %) as needles; mp 150-152 °C, $[\alpha]_D^{25}$ - 68.0° (c 0.2, methanol); IR (Nujol) 3450 (OH), 3250 (NH), 1650 and 1570 (amide), and 860 cm^{-1} (Me_2C); NMR (in 1:1 $CDCl_3$-CD_3OD) δ 1.42, 1.52 (2 s, 6 H, Me_2C), 2.00 (s, 3 H, AcN), 4.56 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.88-5.35 (m, 3 H, $=CH_2$, H-3), 5.67-6.10 (m, 1 H, =CH-), and 7.28 (d, 1 H, $J_{NH,2}$ 6.8 Hz, NH).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.73; H, 7.58; N, 4.59.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-O-mesyl-β-D-glucopyranoside (3). To an ice-cooled solution of 2 (3.0 g) in dry pyridine (20 mL) was added methanesulfonyl chloride (1 mL), and the mixture was kept for 3 h at 0 °C. The mixture was evaporated, the residue extracted with chloroform, and the extract successively washed with 2 M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to give a crystalline product. Recrystallization from ethyl acetate-hexane afforded 3 (3.4 g, 89.5%) as needles; mp 118 °C, $[\alpha]_D^{25}$ - 40° (c 0.2, chloroform); IR (Nujol) 3350 (NH), 1660 and 1530 (amide), 1180 (SO_2), and 860 cm^{-1} (Me_2C); NMR (in $CDCl_3$) δ 1.40, 1.50 (2 s, 6 H, Me_2C), 2.02 (s, 3 H, AcN), 3.06 (s, 3 H, MeS), 4.93 (t, 1 H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3), 4.95 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.12-5.38 (m, 2 H, $=CH_2$), 5.70-6.09 (m, 1 H, =CH-), and 6.55 (d, 1 H, $J_{NH,2}$ 8.4 Hz, NH).

Anal. Calcd for $C_{15}H_{25}NO_8S$: C, 47.48; H, 6.64; N, 3.69. Found: C, 47.51; H, 6.48; N, 3.80.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-β-D-allopyranoside (4). To a solution of 3 (960 mg) in aqueous 95% 2-methoxyethanol (8 mL) was added sodium acetate (1.86 g), and the mixture was refluxed overnight, and then evaporated. Chloroform (50 mL) was added to the residue; the precipitates was filtered off and washed with chloroform. The filtrate and washings were combined,

and evaporated to a syrup which was chromatographed on a column of silica gel (50 g) with chloroform, and then with 100:1 chloroform-methanol. The latter eluate gave 4 (700 mg, 92%) as needles; mp 168-170 °C, $[\alpha]_D^{25}$ - 103° (c 0.22, methanol); IR (Nujol) 3450 (OH), 3300 (NH), 1660 and 1550 (amide), and 860 cm^{-1} (Me_2C); NMR (in 1:1 $CDCl_3$-CD_3OD) δ 1.41, 1.50 (2 s, 6 H, Me_2C), 2.01 (s, 3 H, AcN), 4.71 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.05-5.38 (m, 3 H, $=CH_2$, H-3), 5.60-6.22 (m, 1 H, =CH-), and 6.88 (d, 1 H, $J_{NH,2}$ 8.2 Hz, NH).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.72; H, 7.52; N, 4.58.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-O-mesyl-β-D-allopyranoside (5). Mesylation of 4 (1.0 g) with methanesulfonyl chloride (0.35 mL)-pyridine (7 mL) as described for 3, gave 5 (1.1 g, 85%) as needles; mp 172-173 °C, $[\alpha]_D^{25}$ - 91.5° (c 0.2, chloroform); IR (Nujol) 3250 (NH), 1650 and 1560 (amide), 1185 (SO_2), and 860 cm^{-1} (Me_2C); NMR (in $CDCl_3$) δ 1.39, 1.51 (2 s, 6 H, Me_2C), 2.02 (s, 3 H, AcN), 3.11 (s, 3 H, MeS), 4.70 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1) 5.06-5.38 (m, 3 H, $=CH_2$, H-3), 5.67-6.02 (m, 1 H, =CH-), and 6.15 (d, 1 H, $J_{NH,2}$ 8.0 Hz, NH).

Anal. Calcd for $C_{15}H_{25}NO_8S$: C, 47.48; H, 6.64; N, 3.69. Found: C, 47.39; H, 6.63; N, 3.52.

Allyl 2-acetamido-3-S-acetyl-2-deoxy-4,6-O-isopropylidene-3-thio-β-D-glucopyranoside (6). To a solution of 5 (200 mg) in N,N-dimethylformamide (4 mL) was added potassium thioacetate (390 mg), and the mixture was heated, with stirring, for 50 h at 80-85 °C under nitrogen atmosphere. The mixture was evaporated to a syrup which was chromatographed on a column of silica gel (20 g) with chloroform and then with 100:1 chloroform-methanol. The latter eluate gave compound 6 (114 mg, 60%) as needles, after recrystallization from ether; mp 147-148 °C, $[\alpha]_D^{25}$ - 94° (c 0.2, chloroform); IR (Nujol) 3230 (NH), 1690 (AcS), 1650 and 1550 (amide), and 850 cm^{-1} (Me_2C) ; NMR (in $CDCl_3$) δ 1.40, 1.46 (2 s, 6 H, Me_2C), 1.93 (s, 3 H, AcN), 2.38 (s, 3 H, AcS), 4.51 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.51 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.08-5.38 (m, 2 H, $=CH_2$), and 5.55-6.06 (m, 3 H, =CH-, NH).

Anal. Calcd for $C_{16}H_{25}NO_6S$: C, 53.46; H, 7.01; N, 3.90. Found: C, 53.33; H, 6.91; N, 3.98.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-S-[D-1-(methoxycarbonyl)ethyl]-3-thio-β-D-glucopyranoside (7). To a solution of 6 (80 mg) in dry methanol (4 mL) was added sodium metal (10 mg), and the mixture was kept for 30 min at room temperature, and then evaporated to dryness. To a stirred solution of the residue in dry 1,4-dioxane (5 mL) were added sodium hydride in oil suspension (10 mg, 50% of sodium hydride by weight) and L-2-chloropropanoic acid (30 mg), and the mixture was stirred for 1.5 h at room temperature. Amberlite IRC-50 (H^+) resin was added to the mixture until pH 4 was reached, and triethylamine was added, with stirring, to pH 8; the resin was filtered off and washed with chloroform. The filtrate and washings were combined, and evaporated. To a solution of the residue in 1:3 chloroform-methanol (6 mL) was added an excess of diazomethane in ether; after 10 min, the reaction was complete. The product, purified by chromatography on a column of silica gel (15 g) with 100:1 chloroform-methanol, was obtained as needles; wt. 84 mg (93%), mp 157-160 °C, $[\alpha]_D^{25}$ + 14° (c 0.28, chloroform); IR (Nujol) 3340 (NH), 1740 (ester), 1660 and 1540 (amide), and 860 cm^{-1} (Me_2C); NMR (in $CDCl_3$) δ 1.41 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeCH), 1.41, 1.51 (2 s, 6 H, Me_2C), 2.02 (s, 3 H, AcN), 4.13 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CHMe), 4.76 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.04-5.35 (m, 2 H, $=CH_2$), 5.65-6.06 (m, 1 H, =CH-), and 6.37 (d, 1 H, $J_{NH,2}$ 7.0 Hz, NH).

Anal. Calcd for $C_{18}H_{29}NO_7S$: C, 53.58; H, 7.24; N, 3.47. Found: C, 53.45; H, 7.13; N, 3.46.

Propenyl 2-acetamido-3-S-(D-1-carboxyethyl)-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranoside (8). To a solution of 7 (60 mg) in aqueous 10% ethanol (5 mL) were added tris(triphenylphosphine)-rhodium chloride (20 mg) and diazabicyclo[2,2,2]octane (7 mg), and the mixture was refluxed, with stirring, for 4 h. The precipitates were filtered off, and the filtrate was evaporated. The residue was chromatographed on a column of silica gel (10 g) with chloroform and 200:1 chloroform-methanol. The latter eluate gave the propenyl

glycoside as a syrup. To a solution of the glycoside in 1,4-dioxane (3 mL) was added 0.1M potassium hydroxide (2 mL), and the mixture was stirred for 10 min at room temperature, and then treated with Amberlite IR-120 (H^+) resin to remove the base. The resin was filtered off and washed with methanol, and the filtrate and washings were combined, and evaporated. The residue was chromatographed on a column of silica gel (10 g) with (a) 200:1, and (b) 20:1 chloroform-methanol. Eluant (b) afforded 8 (43 mg, 74%) as a syrup; $[\alpha]_D^{25}$ -7.8° (c 0.54, chloroform); IR (film) 3300 (NH), 1730 (C=O), 1650 and 1560 (amide), and 850 cm^{-1} (Me_2C); NMR (in $CDCl_3$) δ 1.45 (m, 3 H, =CHMe), 1.42, 1.51 (2 s, 6 H, Me_2C), 2.04 (s, 3 H, AcN), 6.12 (m, 1 H, =CH-) and 6.78 (m, 2 H, NH, COOH).

Anal. Calcd for $C_{17}H_{27}NO_7S$: C, 52.42; H, 6.99; N, 3.60. Found: C, 52.25; H, 7.21; N, 3.53.

N-[2-S-(Propenyl 2-acetamido-2,3-dideoxy-4,6-O-isopropylidene-β-D-glucopyranoside-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine methyl ester (9). To a solution of 8 (40 mg) in dry 1,4-dioxane (2 mL) were added N-hydroxysuccinimide (18 mg) and dicyclohexylcarbodiimide (32 mg), and the mixture was stirred for 30 min at room temperature. L-Alanyl-D-isoglutamine methyl ester trifluoroacetate (46 mg) and triethylamine (0.1 mL) were added to the mixture, and it was stirred for 3 h at room temperature, and then evaporated. The residue was purified by chromatography on a column of silica gel (10 g) with (a) 100:1 and (b) 20:1 chloroform-methanol. Eluant (b) gave compound 9 (59 mg, 95%) as an amorphous mass; $[\alpha]_D^{25}$ + 1.2° (c 0.5, 1:1 chloroform-methanol); IR (KBr) 3300 (NH), 1740 and 1250 (ester), 1660 and 1550 (amide), and 860 cm^{-1} (Me_2C); NMR (in 1:1 $CDCl_3$-CD_3OD) δ 1.26-1.58 (15 H, Me_2C, 3 MeCH), 1.96 (s, 3 H, AcN), 3.73 (s, 3 H, MeO), 4.68 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), and 6.11-6.33 (m, 1 H, =CH-).

Anal. Calcd for $C_{26}H_{42}N_4O_{10}S$: C, 51.88; H, 7.02; N, 9.30. Found: C, 51.62; H, 7.30; N, 9.29.

N-[2-S-(2-Acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine (10). A solution of 9 (41 mg) in acetone (3 mL) and 1M hydrochloric acid (0.2 mL) was refluxed for 2 h, cooled, and treated with Amberlite IR-410 (OH^-) resin to remove

the acid, and then evaporated. The residue was purified by chromatography on a column of silica gel (5 g) with (a) 50:1 and (b) 5:1 chloroform-methanol, to give compound 10 (28.2 mg, 76%) from the eluant (b); amorphous, $[\alpha]_D^{25}$ + 1.8° (c 0.3, methanol; equil.); IR (KBr) 3450-3300 (OH, NH), 1720 (C=O), and 1650 and 1570-1540 cm^{-1} (amide); NMR (in CD_3OD) δ 1.26-1.47 (6 H, 2 MeCH), 1.89 (s, 3 H, AcN), and 7.22, 7.34, and 7.70 (3 H, 3 NH).

Anal. Calcd for $C_{22}H_{36}N_4O_{10}S$: C, 48.17; H, 6.62; N, 10.22. Found: C, 47.99; H, 6.85; N, 10.05.

N-[2-S-(2-Acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine methyl ester (11). To a solution of 10 (16 mg) in methanol (4 mL) was added an excess of diazomethane in ether; after 10 min, the reaction was complete. The mixture was evaporated to afford 11 (16 mg, quantitative), amorphous mass; $[\alpha]_D^{25}$ + 3.4° (c 0.3, methanol; equil.); IR (KBr) 3500-3300 (OH, NH), 1740 and 1230 (ester), and 1660 and 1560-1540 cm^{-1} (amide); NMR (in D_2O) δ 1.26-1.47 (6 H, 2 MeCH), 1.90 (s, 3 H, AcN), and 3.75 (s, 3 H,MeO)

Anal. Calcd for $C_{23}H_{38}N_4O_{10}S$: C, 49.10; H, 6.81; N, 9.96. Found: C, 48.85; H, 7.03; N, 9.95.

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