Carbohydrate Research, 82 (1980) 141–148

Note

Novel analogs of glycopeptides

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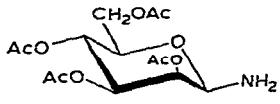
(Received November 2nd, 1979; accepted for publication, December 28th, 1979)

In a preceding paper[1], we reported the synthesis of a number of *N*-substituted D-mannosylamines that exhibit interesting biological activities. The importance of carbohydrates in various immunological processes that involve membrane receptor, surface antigen, mediators of delayed hypersensitivity, and glycoprotein biosynthesis has been well recognized[2]. Novel analogs of 2-acetamido-*N*-(L-aspart-4-oyl)-2-deoxy-β-D-glucopyranosylamine, the glycopeptide junction in immunoglobulins, were explored[3] as potential regulators of the biosynthesis, secretion, and function of immunoglobulins. Glycosylamine linkages occur widely in the region linking carbohydrate and protein moieties in proteoglycans and glycoproteins[4]. As an extension of work on amino-alkyl and -aryl glycosides having insulin-like activity[5–7], we now report the synthesis of a group of novel analogs of glycopeptides having ω-aminoalkanoic acids or heterocyclic groups linked to the sugar carrier, D-mannose, through an amide linkage.

Crystalline 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine[8] (**1**) was obtained in good yield from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl azide by catalytic reduction with Raney nickel. Condensation of **1** with 7-(benzyloxycarbonylamino)-heptanoic acid[9] in dichloromethane containing dicyclohexylcarbodiimide (DCC) gave 2,3,4,6-tetra-*O*-acetyl-*N*-[7-(benzyloxycarbonylamino)heptanoyl]-β-D-mannopyranosylamine (**2**) in low yield, but the *N*-acylurea **7** was isolated as the major product[10,11]. However, when **1** was coupled with 7-(benzyloxycarbonylamino)heptanoyl chloride in the presence of 4-(dimethylamino)pyridine[12], compound **2** was isolated in 60% yield. Zemplén deacetylation of **2** afforded **3**, which was hydrogenated in the presence of 10% palladium-on-charcoal, to give *N*-(7-aminoheptanoyl)-β-D-mannopyranosylamine (**4**). The two homologs **5** and **6** were prepared, as for **4**, from **1** and the respective, *N*-protected ω-aminoalkanoic acids[9]. The insulin-like activities of the *N*-(7-aminoheptanoyl) ($n = 6$) and *N*-(8-aminooctanoyl) ($n = 7$) derivatives (**4** and **5**, respectively) were about the same, and were much greater than that of the *N*-(6-aminohexanoyl) ($n = 5$) analog **6**. These biological activities have already been discussed[5].

Analogs of 2-acetamido-*N*-(L-aspart-4-oyl)-2-deoxy-β-D-glucopyranosylamine



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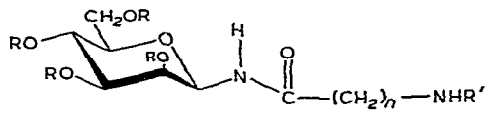
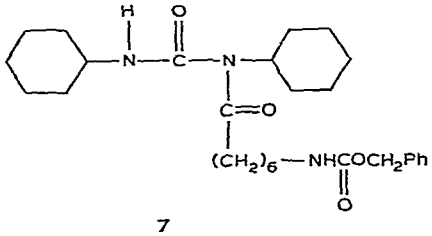


2 R = Ac, R′ = $COOCH_2Ph$, n = 6
3 R = H, R′ = $COOCH_2Ph$, n = 6
4 R = R′ = H, n = 6
5 R = R′ = H, n = 7
6 R = R′ = H, n = 5



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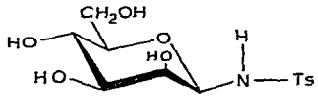

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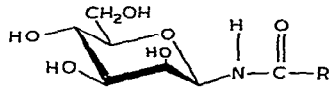

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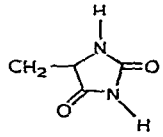
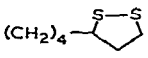
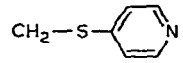
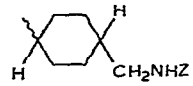
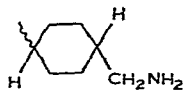
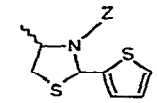
10 R = 

11 R = 

12 R = 

13 R = 

14 R = 

15 R = 

Z = $COCH_2Ph$

having the 2-amino and the free 1-carboxyl group in the L-aspart-4-oyl group replaced by hydantoin and toluenesulfonamide groups were reported previously[3]. We have now prepared *N*-*p*-tolylsulfonyl-β-D-mannopyranosylamine[13] (**8**), the *N*-benzoyl derivative[14,15] (**9**), and the *N*-(5-hydantoinacetyl) analog (**10**) for additional biological

evaluation. Several acyl groups were selected on the basis of their types of chemical structure; the possibility of biological activities associated with them was discussed previously[3].

In view of the well known, biological role of lipoic acid[16,17] in animal metabolism, the preparation of *N*-lipoyl-β-D-mannopyranosylamine (**11**) from **1** and DL-α-lipoic acid was also carried out. Other novel analogs of glycopeptides prepared in this study are **12–15**. Removal of the benzyloxycarbonyl protecting group in **13** and **15** was surprisingly sluggish. Compounds **8–15** were found to be inactive in the insulin, fat-cell bioassay[5,18].

EXPERIMENTAL

General methods. — Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. Optical rotations were measured at 27° with a Zeiss polarimeter. Thin-layer chromatography (t.l.c.) was performed on 250-μm Silica Gel GF_{254} (Analtech) plates, and detection was effected with a ceric sulfate (1%)–sulfuric acid (10%) spray. Column chromatography was conducted with Silica Gel No. 7734 (70–230 mesh ASTM; E. Merck). N.m.r. spectra were recorded for solutions in chloroform-*d* (unless stated otherwise) at 60 or 100 MHz with Varian T-60 and HA-100 n.m.r. spectrometers, respectively. Conventional processing consisted in drying solutions with anhydrous sodium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

*2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl azide.* — Stannic tetrachloride (2 mL) was added to a solution of D-mannopyranose pentaacetate (8 g) and trimethylsilyl azide (2.6 mL) in dichloromethane (180 mL). After 6 h, the solution was washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to a syrup which crystallized on standing (7.6 g, quantitative yield). Recrystallization from 2-propanol afforded pure material, m.p. 52–54°, $[\alpha]_D^{27}$ +116° (*c* 1.02, chloroform); lit.[19] $[\alpha]_D^{23}$ +91.0° (*c* 1.0, 1,4-dioxane); ν_{max}^{KBr} 2125 cm^{-1} (N_3).

Anal. Calc. for $C_{14}H_{19}N_3O_9$: C, 45.04; H, 5.13; N, 11.26. Found: C, 45.41; H, 5.26; N, 11.12.

*2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosylamine* (**1**). — A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl azide (3.0 g) in ethyl acetate (40 mL) was hydrogenated at atmospheric pressure in the presence of Raney nickel. After 6.5 h, the suspension was filtered, and the filtrate was evaporated to a syrup which crystallized on standing in the cold. Recrystallization from 2-propanol afforded **1** (1.7 g, 61%), m.p. 145–147°, $[\alpha]_D^{27}$ −9.8° (*c* 1.02, methanol); lit.[8] m.p. 155.5°, $[\alpha]_D^{21}$ −12.7° (*c* 1.0, chloroform).

Anal. Calc. for $C_{14}H_{21}NO_9$: C, 48.41; H, 6.09; N, 4.03. Found: C, 48.42; H, 6.21; N, 3.76.

*2,3,4,6-Tetra-*O*-acetyl-*N*-[7-(benzyloxycarbonylamino)heptanoyl]-β-D-mannopyranosylamine* (**2**). — (*a*) *From the acid and DCC.* A solution of DCC (0.68 g,

3.3 mmol) in dichloromethane (20 mL) was added to a solution of **1** (0.87 g, 2.5 mmol) and 7-(benzyloxycarbonylamino)heptanoic acid [m.p. 79–81° (aq. ethanol); lit.[9] m.p. 90°] (0.7 g, 2.5 mmol) in dichloromethane (40 mL). The solution was kept for 16 h at room temperature, the suspension was filtered, and the filtrate was concentrated to a small volume, and refiltered. The filtrate was chromatographed on a column of silica gel with 1:1 ethyl acetate–chloroform as the eluant. Compound **2** was isolated as a foam (0.4 g, 26%), $[\alpha]_D^{27}$ −7.6 ±0.6° (*c* 1.0, chloroform).

Anal. Calc. for $C_{29}H_{40}N_2O_{12}$: C, 57.23; H, 6.62; N, 4.60. Found: C, 57.22; H, 6.68; N, 4.32.

N-[7-(Benzyloxycarbonylamino)heptanoyl]dicyclohexylurea (**7**) was isolated as the major product, m.p. 95–96.5° (petroleum ether).

Anal. Calc. for $C_{28}H_{43}N_3O_4$: C, 69.25; H, 8.92; N, 8.65. Found: C, 69.03; H, 9.07; N, 8.55.

(*b*) *From the acid chloride.* 4-(Dimethylamino)pyridine[12] (0.062 g, 0.51 mmol) was added to a stirred solution of **1** (0.87 g, 2.5 mmol) and 7-(benzyloxycarbonylamino)heptanoyl chloride (0.75 g, 2.5 mmol) [obtained from 7-(benzyloxycarbonylamino)heptanoic acid and thionyl chloride] in dichloromethane (20 mL). After 1 h at room temperature, the solution was washed successively with M hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to a residue which was chromatographed, as before, to give **2** (0.92 g, 60%).

N-[*7-(Benzyloxycarbonylamino)heptanoyl*]-*β*-D-*mannopyranosylamine* (**3**). — Sodium methoxide (0.05 g) was added to a solution of **2** (1.13 g) in dry methanol (25 mL). After 2 h, the solution was deionized with acidic resin, the suspension filtered, and the filtrate evaporated to a crystalline mass. Recrystallization from methanol afforded **3** (0.76 g, 93%), m.p. 169–172°, $[\alpha]_D^{27}$ −7.4 ±0.3° (*c* 1.0, methanol).

N-(*7-Aminoheptanoyl*)-*β*-D-*mannopyranosylamine* (**4**). — A solution of **3** (200 mg) in aq. methanol (10 mL) containing 10% palladium-on-charcoal (80 mg) was hydrogenated for 1 h at room temperature. The catalyst was filtered off and washed with aqueous methanol, and the filtrates were combined and evaporated to a crystalline mass. Recrystallization from ethanol afforded **4** (125 mg, 90%), m.p. 162° (dec.), $[\alpha]_D^{27}$ −19.4 ±0.5° (*c* 1.59, water); R_F 0.23 (2:2:1 chloroform–methanol–ammonium hydroxide).

Anal. Calc. for $C_{13}H_{26}N_2O_6 \cdot H_2CO_3$: C, 45.65; H, 7.66; N, 7.60. Found: C, 45.31; H, 7.53; N, 7.50.

N-(*8-Aminooctanoyl*)-*β*-D-*mannopyranosylamine* (**5**). — 2,3,4,6-Tetra-*O*-acetyl-*N*-[(8-benzyloxycarbonylamino)octanoyl]-*β*-D-mannopyranosylamine was prepared from **1** and 8-(benzyloxycarbonylamino)octanoyl chloride [obtained from 8-(benzyloxycarbonylamino)octanoic acid, m.p. 58–60° (MeOH) (lit.[9] m.p. 58–60°) and thionyl chloride] in 89% yield. Deacetylation of this material afforded *N*-[(8-benzyloxycarbonylamino)octanoyl]-*β*-D-mannopyranosylamine, $[\alpha]_D^{27}$ −9.0 ±1.1° (*c* 1.0, methanol).

Anal. Calc. for $C_{22}H_{34}N_2O_8$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.08; H, 7.28; N, 6.10.

Hydrogenolysis of the foregoing compound gave **5**, m.p. 210–212°, $[\alpha]_D^{27}$ −30.1 ±1.1° (*c* 0.93, water).

Anal. Calc. for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.75. Found: C, 52.09; H, 8.66; N, 8.41.

N-(*6-Aminohexanoyl*)-*β*-D-*mannopyranosylamine* (**6**). — 2,3,4,6-Tetra-*O*-acetyl-*N*-[(6-benzyloxycarbonylamino)hexanoyl]-*β*-D-mannopyranosylamine was prepared from **1** and 6-(benzyloxycarbonylamino)hexanoyl chloride [obtained from 6-(benzyloxycarbonylamino)hexanoic acid, m.p. 55–56° (lit.[9] m.p. 55–57°) and thionyl chloride] in 58% yield. Deprotection of this material afforded *N*-[(6-benzyloxycarbonylamino)hexanoyl]-*β*-D-mannopyranosylamine, m.p. 159–161°. Hydrogenolysis of the latter compound gave **6**, m.p. 210°, $[\alpha]_D^{27}$ −28.9 ±0.6° (*c* 1.6, water).

Anal. Calc. for $C_{12}H_{24}N_2O_6$: C, 49.30; H, 8.27; N, 9.59. Found: C, 49.35; H, 8.09; N, 9.10.

N-p-*Tolylsulfonyl*-*β*-D-*mannopyranosylamine* (**8**). — Compound **8** was prepared by tosylation of **1**, followed by deacetylation; m.p. 200–203° (dec.), $[\alpha]_D^{27}$ +18.9 ±1.0° (*c* 1.03, water).

Anal. Calc. for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.75; N, 4.20; S, 9.62. Found: C, 46.49; H, 5.93; N, 3.94; S, 9.26.

N-*Benzoyl*-*β*-D-*mannopyranosylamine* (**9**). — A solution of **1** (800 mg) and 4-(dimethylamino)pyridine (100 mg) in benzoyl chloride (2 mL) was stirred for 16 h at room temperature. The reaction mixture was processed in the usual way, to give 2,3,4,6-tetra-*O*-acetyl-*N*-benzoyl-*β*-D-mannopyranosylamine (600 mg), $[\alpha]_D^{27}$ −19.9 ±0.7° (*c* 1.3, chloroform); lit.[14] $[\alpha]_D^{27}$ −28.8° (*c* 1.2, chloroform).

Anal. Calc. for $C_{21}H_{25}NO_{10}$: C, 55.87; H, 5.58; N, 3.10. Found: C, 55.84; H, 5.53; N, 2.91.

Deacetylation of this compound afforded **9** in 76% yield, m.p. 256–258° (70% ethanol), $[\alpha]_D^{27}$ −9.1° (*c* 1.0, Me_2SO); lit.[14,15] m.p. 253–254°, $[\alpha]_D^{25}$ +6.4° (*c* 0.2, pyridine).

N-(*5-Hydantoinacetyl*)-*β*-D-*mannopyranosylamine* (**10**). — A suspension of **1** (3.5 g, 10 mmol), 5-hydantoinacetic acid (2.0 g, 13 mmol), and DCC (3.0 g, 13 mmol) in *N*,*N*-dimethylformamide (DMF, 10 mL) and acetonitrile (60 mL) was stirred for 18 h at room temperature. The mixture was filtered, and the filtrate was evaporated to a residue which crystallized from methanol–ether. Recrystallization from methanol afforded 2,3,4,6-tetra-*O*-acetyl-*N*-(5-hydantoinacetyl)-*β*-D-mannopyranosylamine (3.5 g, 72%), m.p. 208–210°, $[\alpha]_D^{27}$ −16.4 ±1.0° (*c* 1.06, methanol); R_F 0.7 (40:20:1 chloroform–methanol–water).

Anal. Calc. for $C_{19}H_{25}N_3O_{12}$: C, 46.82; H, 5.17; N, 8.62. Found: C, 46.82; H, 5.40; N, 8.75.

This compound was deacetylated with sodium methoxide in methanol, to give **10**, which was isolated as a foam in 73% yield; $[\alpha]_D^{27}$ −24.7 ±0.3° (*c* 1.54, water); R_F 0.26 (6:4:1 chloroform–methanol–water); *m/e* 823 M^+, silylated, 7 Me_3Si).

Anal. Calc. for $C_{11}H_{17}N_3O_8$: C, 41.38; H, 5.37; N, 13.16. Found: C, 41.05; H, 5.70; N, 12.76.

N-*Lipoyl-β-*D-*mannopyranosylamine* (**11**). — A suspension of **1** (3.4 g, 4.8 mmol), DL-α-lipoic acid (2.06 g, 10 mmol), and DCC (3 g, 13 mmol) in DMF (10 mL) and acetonitrile (60 mL) was stirred for 16 h at room temperature. The mixture was filtered, and the filtrate was evaporated to a residue which was chromatographed on a column of silica gel with 1:9 ethyl acetate–chloroform as the eluant. The desired fractions were combined, and evaporated, to give 2,3,4,6-tetra-*O*-acetyl-*N*-lipoyl-β-D-mannopyranosylamine (1.9 g), $[\alpha]_D^{27}$ −24.9 ±0.9° (*c* 1.0, chloroform).

Anal. Calc. for $C_{22}H_{33}NO_{10}S_2 \cdot 0.5\ H_2O$: C, 48.51; H, 6.29; N, 2.57; S, 11.77. Found: C, 48.51; H, 6.70; N, 2.62; S, 11.61.

Deprotection of this compound with sodium methoxide in methanol afforded **11**, which crystallized from the medium in 61% yield; m.p. 165–170° (dec.). Recrystallization from methanol afforded pure material, m.p. 187–189°, $[\alpha]_D^{27}$ −31.0° (*c* 1.0, water).

Anal. Calc. for $C_{14}H_{25}NO_6S_2$: C, 45.76; H, 6.86; N, 3.81; S, 17.45. Found: C, 45.59; H, 7.12; N, 3.98; S, 17.55.

N-(*4-Pyridylthio)acetyl-β-*D-*mannopyranosylamine* (**12**). — A suspension of **1** (3.5 g, 10 mmol), (4-pyridylthio)acetic acid (2.0 g, 11.5 mmol), and DCC (3 g, 14 mmol) in DMF (10 mL) and acetonitrile (60 mL) was stirred for 24 h at room temperature. The mixture was filtered, and the filtrate was evaporated, to give crude 2,3,4,6-tetra-*O*-acetyl-*N*-(4-pyridylthio)acetyl-β-D-mannopyranosylamine (2.4 g), R_F 0.8 (40:10:1 chloroform–methanol–water). Deprotection of this compound afforded **12**, which crystallized from the medium. Recrystallization from water gave pure **12** (0.7 g), m.p. 213° (dec.), $[\alpha]_D^{27}$ −8.7 ±1.0° (*c* 1.0, water).

Anal. Calc. for $C_{13}H_{18}N_2O_6S$: C, 47.26; H, 5.49; N, 8.48; S, 9.71. Found: C, 47.36; H, 5.65; N, 8.29; S, 9.70.

N-[*4-*trans-(*Aminomethyl)cyclohexylcarbonyl*]-β-D-*mannopyranosylamine* (**14**). — A solution of **1** (1.46 g) and 4-*trans-N*-(benzyloxycarbonylamino)methylcyclohexylcarbonyl chloride (1.75 g) [prepared from 4-*trans*-(benzyloxycarbonylamino)methylcyclohexylcarboxylic acid, m.p. 107–110°, and thionyl chloride in benzene] in dichloromethane (50 mL) containing 4-(dimethylamino)pyridine (0.22 g) was stirred for 2 h at room temperature. Dichloromethane (100 mL) was added, and the solution was washed with cold M HCl, aq. sodium hydrogencarbonate, and water, dried, and evaporated to a syrup which crystallized on trituration with ethyl ether–petroleum ether to give 2.6 g of crystalline product. Recrystallization from 2-propanol afforded 2,3,4,6-tetra-*O*-acetyl-*N*-[4-*trans-N*-(benzyloxycarbonylamino)methylcyclohexylcarbonyl]-β-D-mannopyranosylamine (1.7 g), m.p. 195–198°, $[\alpha]_D^{27}$ −12.9 ±0.3° (*c* 1.55, chloroform).

Anal. Calc. for $C_{30}H_{40}N_2O_{12}$: C, 58.05; H, 6.50; N, 4.51. Found: C, 57.92; H, 6.60; N, 4.26.

This compound was deacetylated, to give *N*-[4-*trans-N*-(benzyloxycarbonylamino)methylcyclohexylcarbonyl]-β-D-mannopyranosylamine (**13**), which crystallized from the medium in 89% yield; m.p. 243–244° (dec.), $[\alpha]_D^{27}$ −2.9 ±1.0° (*c* 1.0, 50% methanol).

Anal. Calc. for $C_{22}H_{32}N_2O_8$: C, 58.39; H, 7.12; N, 6.19. Found: C, 58.01; H, 7.01; N, 5.98.

Hydrogenolysis of **13** in ethanol containing 10% palladium-on-charcoal at 60° and 40 lb.in.$^{-2}$ afforded a large proportion of unreacted **13**, and **14**, R_F 0.13 (5:5:1 chloroform–methanol–ammonium hydroxide); *m/e* 750 (M^+, silylated).

N-[N-(*Benzyloxycarbonyl*)-*2*-(*2-thienyl*)-L-*thiazolidine-4-carbonyl*]-β-D-*manno-pyranosylamine* (**15**). — A solution of **1** (650 mg, 1.87 mmol) in dichloromethane (5 mL) was added, with stirring, to *N*-(benzyloxycarbonyl)-2-(2-thienyl)-L-thiazolidine-4-carboxylic acid (650 mg, 1.86 mmol) in dichloromethane (5 mL) containing DCC (500 mg, 2.43 mmol). After 16 h, the mixture was filtered, and the solid was washed with dichloromethane. The filtrates were combined, washed with water, dried, and evaporated to a syrup which was triturated with ethyl ether to give 2,3,4,6-tetra-*O*-acetyl-*N*-[*N*-(benzyloxycarbonyl)-2-(2-thienyl)-L-thiazolidine-4-carbonyl]-β-D-mannopyranosylamine (800 mg, 64%) as a foam. An analytical sample was obtained by chromatography; $[\alpha]_D^{27}$ +6.0 ±0.3° (*c* 1.54, chloroform); R_F 0.5 (2:1 chloroform–ethyl acetate); *m/e* 678 (M^+) and 543 ($M^+ - COOCH_2Ph$).

Anal. Calc. for $C_{30}H_{34}N_2O_{12}S_2$: C, 52.38; H, 5.39; N, 3.94; S, 9.02. Found: C, 52.70; H, 5.32; N, 3.86; S, 8.74.

Deprotection of this compound (500 mg) gave **15** (260 mg, 69%), $[\alpha]_D^{27}$ +35.9 ±0.3° (*c* 1.51, methanol); R_F 0.6 (10:3 chloroform–methanol); *m/e* 798 (M^+, silylated) and 663 (silylated $M^+ - COOCH_2Ph$).

Anal. Calc. for $C_{22}H_{26}N_2O_8S_2$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.96; H, 5.30; N, 5.41.

ACKNOWLEDGMENTS

The authors thank Dr. H. M. Katzen and his associates of this Institute for their suggestions and collaboration during this research, Mr. J. Smith for mass-spectral measurements, and Mr. J. P. Gilbert and his associates for microanalyses.

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