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Note

Synthesis of some carbohydrate analogs of *N*-acetylmuramoyl-L-alanyl-D-isoglutamine*

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In earlier papers[1–12] in this series, we have investigated the structural requirements of the carbohydrate moiety in *N*-acetylmuramoyl-L-alanyl-D-isoglutamine[13] (MDP) for the immunoadjuvant activity. The present communication deals with a continuation of these studies. We now describe the synthesis of some MDP analogs in which we have modified the substituents at C-4, and at C-4 and C-6, of the carbohydrate moiety in MDP.

Treatment of benzyl 2-acetamido-2,6-dideoxy-3-*O*-[D-(1-methoxycarbonyl)-ethyl]-α-D-glucopyranoside (**2**), derived[6a] from its 4-acetate (**1**) by *O*-deacetylation, with methanesulfonyl chloride in pyridine afforded the 4-*O*-mesyl derivative **3**, which was converted into benzyl 2-acetamido-4-azido-2,4,6-trideoxy-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-galactopyranoside (**11**) by heating with sodium azide in dry *N*,*N*-dimethylformamide. On treatment with sodium azide in *N*,*N*-dimethylformamide for 5 h at 80°, benzyl 2-acetamido-2-deoxy-6-*O*-mesyl-3-*O*-[D-1-(methoxycarbonyl)-ethyl]-α-D-glucopyranoside[6a] (**4**) afforded the azide derivative **5** in good yield; compound **5** was mesylated with methanesulfonyl chloride in pyridine to afford the 4-*O*-mesyl derivative **6**.

On the other hand, reduction of the azide group in **5** (in ethanol) with hydrogen in the presence of 10% Pd–C catalyst, and subsequent *N*-acetylation, gave benzyl 2,6-di(acetamido)-2,6-dideoxy-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-glucopyranoside (**7**) in 92% yield; this was converted into the 4-*O*-mesyl derivative **8**. Methanesulfonylation of benzyl 2-acetamido-6-*O*-benzoyl-2-deoxy-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-glucopyranoside[14] (**9**) gave compound **10**. On being heated at 100° with sodium azide in *N*,*N*-dimethylformamide, the mesyloxy group in compounds **6**, **8**, and **10** was exchanged, to afford the corresponding 4-azide derivatives (**12**, **13**, and **14**), with inversion of the configuration of C-4. Treatment of **15**, derived from **14** by debenzoylation, with methanesulfonyl chloride in pyridine afforded benzyl 2-

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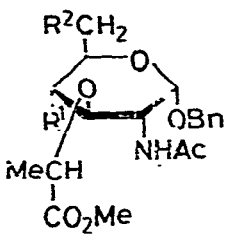
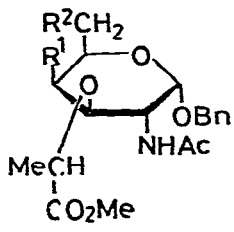
acetamido-4-azido-2,4-dideoxy-6-*O*-mesyl-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-galactopyranoside (**16**).

Saponification of **11** with 0.1M aqueous potassium hydroxide in 1,4-dioxane gave the free acid, which was used for the next reaction without purification. Coupling of the acid with L-alanyl-D-isoglutamine benzyl ester was conducted with dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu) as the activating agents, to afford benzyl 2-acetamido-4-azido-2,4,6-trideoxy-3-*O*-(D-2-propanoyl-L-alanyl-D-isoglutamine benzyl ester)-α-D-galactopyranoside (**17**) in almost quantitative

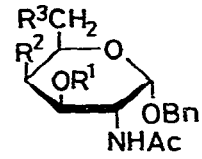


1 R^1 = OAc, R^2 = H
2 R^1 = OH, R^2 = H
3 R^1 = OMs, R^2 = H
4 R^1 = OH, R^2 = OMs
5 R^1 = OH, R^2 = N_3
6 R^1 = OMs, R^2 = N_3
7 R^1 = OH, R^2 = NHAc
8 R^1 = OMs, R^2 = NHAc
9 R^1 = OH, R^2 = OBz
10 R^1 = OMs, R^2 = OBz

Ac = MeCO ; Bn = $PhCH_2$
Bz = PhCO ; Ms = $MeSO_2$



11 R^1 = N_3, R^2 = H
12 R^1 = R^2 = N_3
13 R^1 = N_3, R^2 = NHAc
14 R^1 = N_3, R^2 = OBz
15 R^1 = N_3, R^2 = OH
16 R^1 = N_3, R^2 = OMs



17 R^1 = a, R^2 = N_3, R^3 = H
18 R^1 = a, R^2 = R^3 = N_3
19 R^1 = a, R^2 = N_3, R^3 = NHAc
20 R^1 = a, R^2 = N_3, R^3 = OBz
21 R^1 = a, R^2 = N_3, R^3 = OH
22 R^1 = a, R^2 = N_3, R^3 = OMs
23 R^1 = b, R^2 = NH_2, R^3 = H
24 R^1 = b, R^2 = R^3 = NH_2
25 R^1 = b, R^2 = R^3 = NHAc
26 R^1 = b, R^2 = NH_2, R^3 = NHAc
27 R^1 = b, R^2 = NH_2, R^3 = OH
28 R^1 = b, R^2 = NH_2, R^3 = OMs

a = -CH(Me)CO-L-Ala-D-isoGln-OBn
b = -CH(Me)CO-L-Ala-D-isoGln

yield. In the same way, coupling of the acids, derived from compounds **12**, **13**, **14**, and **16** (by hydrolysis), with the L-alanyl-D-isoglutamine derivative yielded the corresponding dipeptides (**18**, **19**, **20**, and **22**) in excellent yields. Treatment of **20** with sodium methoxide in methanol gave benzyl 2-acetamido-4-azido-2,4-dideoxy-3-*O*-(D-2-propanoyl-L-alanyl-D-isoglutamine benzyl ester)-α-D-galactopyranoside (**21**).

Hydrogenolytic removal of the benzyl group and reduction of the azide group in **17**, in 15:1 (v/v) methanol–acetic acid, with hydrogen in the presence of 10% Pd–C catalyst at room temperature gave benzyl 2-acetamido-4-amino-2,4,6-trideoxy-3-*O*-(D-2-propanoyl-L-alanyl-D-isoglutamine)-α-D-galactopyranoside (**23**) in good yield. By essentially the same procedure, compound **18** yielded **24**. *N*-Acetylation of **24** gave the 2,4,6-tri-*N*-acetyl derivative **25**. In the same way, hydrogenation of compounds **19**, **21**, and **22** afforded the corresponding 4-amino derivatives (**26**, **27**, and **28**) in high yields.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a Union PM-201 polarimeter, and i.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. N.m.r. data were recorded at 90 MHz with a Hitachi R-22 spectrometer, and were confirmed by use of decoupling techniques. Preparative chromatography was performed on silica gel (Waco Co.; 300 mesh) with the solvent systems specified. Evaporations were conducted *in vacuo*.

Benzyl 2-acetamido-2,6-dideoxy-3-O[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**2**). — To a solution of benzyl 2-acetamido-4-*O*-acetyl-2,6-dideoxy-3-*O*-[D-1-(methoxycarbonyl)ethyl]-α-D-glucopyranoside[6a] (**1**; 700 mg) in methanol (20 mL) was added sodium methoxide (30 mg), and the solution was kept for 2 h at room temperature, and then treated with Amberlite IR-120 (H^+) ion-exchange resin to remove the base; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated, to give a crystalline product. Recrystallization from ether afforded **2** (470 mg, 75%) as needles, m.p. 155–156°, $[\alpha]_D^{25}$ +164° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3360 and 3320 (OH, NH), 1720 and 1230 (ester), 1650 and 1540 (amide), and 740 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.22 (d, 3 H, $J_{5,Me}$ 6.0 Hz, Me), 1.36 (d, 3 H, $J_{Me,CH}$ 6.4 Hz, MeC), 1.98 (s, 3 H, AcN), 3.71 (s, 3 H, MeO), 4.53, 4.76 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 4.65 (q, 1 H, $J_{CH,Me}$ 6.4 Hz, CH), 5.16 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 7.26 (s, 5 H, Ph), and 7.41 (d, 1 H, $J_{2,NH}$ 5.0 Hz, NH).

Anal. Calc. for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.85; H, 7.18; N, 3.65.

Benzyl 2-acetamido-2,6-dideoxy-4-O-mesyl-3-O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**3**). — To a solution of **2** (300 mg) in dry pyridine (5 mL) was added methanesulfonyl chloride (500 mg), and the mixture was kept overnight at 0°, and evaporated, the residue extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated, to give a crystalline mass. Recrystallization from ether afforded **3** (340 mg, 94%) as needles, m.p. 154°, $[\alpha]_D^{25}$ +104° (*c* 0.9, chloroform); ν_{max}^{Nujol} 3300 (NH), 1750 and 1230 (ester), 1640 and 1540 (amide), 1170 (SO_2), and 740 and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{20}H_{29}NO_9S$: C, 52.27; H, 6.36; N, 3.05. Found: C, 52.31; H, 6.29; N, 3.12.

Benzyl 2-acetamido-6-azido-2,6-dideoxy-3-O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**5**). — To a solution of[6a] **4** (1.84 g) in dry *N*,*N*-dimethylformamide (15 mL) was added sodium azide (1.8 g), and the mixture was heated, with stirring, for 5 h at 80°, evaporated, and the residue extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (50 g) with chloroform and then 100:1 chloroform–methanol.

The latter eluate afforded **5** (1.19 g, 73%) as needles, m.p. 141–142°, $[\alpha]_D^{25}$ +147° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3440 (OH), 3260 (NH), 2080 (N_3), 1720 and 1220 (ester), 1640 and 1540 (amide), and 740 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found: C, 54.21; H, 6.19; N, 13.09.

Benzyl 2-acetamido-6-azido-2,6-dideoxy-4-O-mesyl-3-O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**6**). — A sample of **5** (1.1 g) was mesylated with methanesulfonyl chloride (1.1 g)–pyridine (10 mL) overnight at −10°, and the mixture was processed as described before. The product crystallized from ether, to give **6** (1.2 g, 92%) as needles, m.p. 145°, $[\alpha]_D^{25}$ +120° (*c* 0.2, chloroform); ν_{max}^{Nujol} 3250 (NH), 2070 (N_3), 1740 and 1240 (ester), 1640 and 1530 (amide), 1170 (SO_2), and 720 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{20}H_{28}N_4O_9S$: C, 47.99; H, 5.64; N, 11.19. Found: C, 47.83; H, 5.51; N, 11.09.

Benzyl 2,6-di(acetamido)-2,6-dideoxy-3-O-[D-*1-(methoxycarbonyl)ethyl*)-α-D-*glucopyranoside* (**7**). — A solution of **5** (200 mg) in methanol (60 mL) was hydrogenated with hydrogen in the presence of 10% Pd–C catalyst (50 mg) for 40 min at room temperature. The catalyst was removed by filtration, acetic anhydride (0.5 mL) was added to the filtrate, and after being kept for 30 min at room temperature, the solution was evaporated to a syrup which crystallized from ether–hexane, to afford **7** (190 mg, 92%) as needles, m.p. 158°, $[\alpha]_D^{25}$ +66° (*c* 0.55, chloroform); ν_{max}^{Nujol} 3280 (OH, NH), 1730 and 1230 (ester), 1640, 1620, and 1550 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.40 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.00, 2.02 (2 s, 6 H, 2 AcN), 3.73 (s, 3 H, MeO), 4.44, 4.60 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 4.76 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CH), 5.33 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 6.60, 7.68 (broad s, 2 H, 2 NH), and 7.27 (s, 5 H, Ph).

Anal. Calc. for $C_{21}H_{30}N_2O_8$: C, 57.52; H, 6.90; N, 6.39. Found: C, 57.48; H, 6.90; N, 6.44.

Benzyl 2,6-di(acetamido)-2,6-dideoxy-4-O-mesyl-3-O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**8**). — A sample of **7** (500 mg) was mesylated with methanesulfonyl chloride (300 mg)–dry pyridine (10 mL) overnight at 0°. Processing in the usual way gave the 4-mesylate (540 mg, 92%) as needles, m.p. 170°, $[\alpha]_D^{25}$ +158° (*c* 0.25, methanol); ν_{max}^{Nujol} 3300 (NH), 1750, 1735, and 1260–1240 (ester), 1640 and 1540 (amide), 1180 (SO_2), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.45 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.00, 2.02 (2 s, 6 H, 2 AcN), 3.24 (s, 3 H, MeS), 3.75 (s, 3 H, MeO), 4.55 (s, 2 H, benzyl methylene), 4.61 (t, 1 H, $J_{3,4} = J_{4,5}$ = 7.8 Hz, H-4), 5.30 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.85, 8.05 (broad d, 2 H, 2 NH), and 7.30 (s, 5 H, Ph).

Anal. Calc. for $C_{22}H_{32}N_2O_{10}S$: C, 51.15; H, 6.24; N, 5.42. Found: C, 51.30; H, 6.23; N, 5.49.

Benzyl 2-acetamido-6-O-benzoyl-2-deoxy-4-O-mesyl-3-O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*glucopyranoside* (**10**). — To an ice-cooled solution of[14] **9** (2.0 g) in dry pyridine (10 mL) was added methanesulfonyl chloride (1.0 g), and the mixture

was kept for 2 h at 20°. Processing in the usual way gave the 4-mesylate **10** (2.15 g, 93%) as needles, m.p. 138°, $[\alpha]_D^{25}$ +97° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3300 (NH), 1740 and 1280–1260 (ester), 1650 and 1550 (amide), 1190 (SO_2), and 730 and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{27}H_{33}NO_{11}S$: C, 55.95; H, 5.74; N, 2.42. Found: C, 55.81; H, 5.70; N, 2.42.

*Benzyl 2-acetamido-4-azido-2,4,6-trideoxy-3-*O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*galactopyranoside* (**11**). — To a solution of **3** (260 mg) in dry *N,N*-dimethylformamide (4 mL) was added sodium azide (500 mg), and the mixture was heated, with stirring, for 15 h at 90°. It was then cooled, the salts were filtered off, and the filtrate was evaporated to a syrup which was extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (20 g) with chloroform and then 30:1 chloroform–methanol. The latter eluate gave unreacted starting-material (130 mg, 50%) and **11** (95 mg, 41%); m.p. 127–128°, $[\alpha]_D^{25}$ +142° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3280 (NH), 2100 (N_3), 1750 and 1240 (ester), 1650 and 1550 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.21 (d, 3 H, $J_{5,Me}$ 6.6 Hz, Me), 1.46 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.00 (s, 3 H, AcN), 3.78 (s, 3 H, MeO), 4.18 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CH), 4.47, 4.60 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.28 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), and 7.26 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{26}N_4O_6$: C, 56.16; H, 6.45; N, 13.79. Found: C, 56.24; H, 6.43; N, 13.56.

*Benzyl 2-acetamido-4,6-diazido-2,4,6-trideoxy-3-*O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*galactopyranoside* (**12**). — To a solution of **6** (700 mg) in dry *N,N*-dimethylformamide (8 mL) was added sodium azide (700 mg), and the mixture was heated, with stirring, for 10 h at 100°. The same procedure as that described for **11** gave unreacted starting-material (240 mg, 34%) and **12** (370 mg, 59%); m.p. 110°, $[\alpha]_D^{25}$ +141° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3260 (NH), 2100 and 2070 (N_3), 1740 and 1270 (ester), 1640 and 1530 (amide), and 720 and 680 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.48 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.01 (s, 3 H, AcN), 3.35 (m, 2 H, H-6,6'), 3.78 (s, 3 H, MeO), 4.22 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CH), 4.50, 4.65 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.35 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.22 (d, 1 H, $J_{2,NH}$ 4.0 Hz, NH), and 7.29 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{25}N_7O_6$: C, 51.00; H, 5.63; N, 21.91. Found: C, 51.21; H, 5.79; N, 21.58.

*Benzyl 2,6-di(acetamido)-4-azido-2,4,6-trideoxy-3-*O-[D-*1-(methoxycarbonyl)ethyl*]-α-D-*galactopyranoside* (**13**). — To a solution of **8** (500 mg) in dry *N,N*-dimethylformamide (10 mL) was added sodium azide (500 mg), and the mixture was heated, with stirring, for 6.5 h at 100°; the mixture was processed as already described, to give **13** (220 mg, 49%) as needles, m.p. 180–181°, $[\alpha]_D^{25}$ +161° (*c* 0.4, chloroform); ν_{max}^{Nujol} 3270 (NH), 2080 (N_3), 1740 and 1230 (ester), 1645 and 1540 (amide), and 730 and 680 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.44 (d, 3 H, $J_{Me,CH}$

7.0 Hz, MeC), 1.98, 2.01 (2 s, 6 H, 2 AcN), 4.42 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CH), 4.32, 4.55 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.29 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), and 7.24 (s, 5 H, Ph).

Anal. Calc. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.36; H, 6.20; N, 15.03.

*Benzyl 2-acetamido-4-azido-6-*O*-benzoyl-2,4-dideoxy-3-*O*-[*D*-1-(methoxycarbonyl)ethyl]-α-*D*-galactopyranoside* (**14**). — To a solution of **10** (1.0 g) in dry *N*,*N*-dimethylformamide (10 mL) was added sodium azide (1.0 g), and the mixture was heated, with stirring, for 8 h at 100°; the mixture was processed as already described, to give **14** (310 mg, 34%) as needles. The unreacted starting-material **10** (330 mg, 33%) was also recovered. Compound **14** had m.p. 164–166°, $[\alpha]_D^{25}$ +103° (*c* 0.2, chloroform); ν_{max}^{Nujol} 3300 (NH), 2120 (N_3), 1740 and 1220 (ester), 1660 and 1560 (amide), and 740 and 705 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.47 (d, 3 H, $J_{Me,CH}$ 7.2 Hz, MeC), 2.02 (s, 3 H, AcN), 3.76 (s, 3 H, MeO), 4.44, 4.62 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.38 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.22 (s, 5 H, Ph), and 7.25–8.10 (m, 5 H, Ph).

Anal. Calc. for $C_{26}H_{30}N_4O_8$: C, 59.31, H, 5.74; N, 10.64. Found: C, 59.26; H, 5.69; N, 10.51.

*Benzyl 2-acetamido-4-azido-2,4-dideoxy-3-*O*-[*D*-1-(methoxycarbonyl)ethyl]-α-*D*-galactopyranoside* (**15**). — To a solution of **14** (300 mg) in methanol (20 mL) was added sodium methoxide (30 mg), and the mixture was kept for 30 min at room temperature, and then treated with Amberlite IR-120 (H^+) resin to remove the base. The solution 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 eluant gave compound **15** (220 mg, 91%) as a syrup, $[\alpha]_D^{25}$ +134° (*c* 0.3, chloroform); ν_{max}^{film} 3320–3280 (OH, NH), 2090 (N_3), 1740 and 1220 (ester), 1650 and 1530 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.48 (s, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.02 (s, 3 H, AcN), 3.78 (s, 3 H, MeO), 4.24 (q, 1 H, $J_{CH,Me}$ 7.0 Hz, CH), 4.46, 4.64 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.35 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), and 7.27 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found: C, 54.13; H, 6.18; N, 13.11.

*Benzyl 2-acetamido-4-azido-2,4-dideoxy-6-*O*-mesyl-3-*O*-[*D*-1-(methoxycarbonyl)ethyl]-α-*D*-galactopyranoside* (**16**). — To an ice-cooled solution of **15** (300 mg) in pyridine (3 mL) was added methanesulfonyl chloride (300 mg), and the mixture was kept for 2 h at 20°. Processing in the usual way gave **16** (350 mg, 98%) as needles, m.p. 155°, $[\alpha]_D^{25}$ +131° (*c* 0.4, chloroform); ν_{max}^{Nujol} 3280 (NH), 2100 (N_3), 1760, 1740, and 1220 (ester), 1650 and 1540 (amide), 1170 (SO_2), and 720 and 680 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.49 (d, 3 H, $J_{Me,CH}$ 7.0 Hz, MeC), 2.02 (s, 3 H, AcN), 3.02 (s, 3 H, MeS), 3.78 (s, 3 H, MeO), 4.46, 4.62 (2 d, 2 H, J_{gem} 12.0 Hz, benzyl methylene), 5.35 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), and 7.28 (s, 5 H, Ph).

Anal. Calc. for $C_{20}H_{28}N_4O_9S$: C, 47.99; H, 5.64; N, 11.19. Found: C, 47.76; H, 5.51; N, 11.35.

*Benzyl 2-acetamido-4-azido-2,4,6-trideoxy-3-*O-(D-*2-propanoyl*-L-*alanyl*-D-*isoglutamine benzyl ester*)-α-D-*galactopyranoside* (**17**). — To a solution of **11** (40 mg) in 1,4-dioxane (3 mL) was added 0.1M potassium hydroxide (1.7 mL), and the solution was stirred for 5 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. The filtrate and washings were combined, and evaporated, to afford the crystalline, free acid which was used for the next reaction without purification. To a solution of the acid in dry 1,4-dioxane (2 mL) were added, with stirring, *N*-hydroxysuccinimide (HOSu) (14 mg), and dicyclohexylcarbodiimide (DCC) (31 mg), and the mixture was stirred for 50 min at room temperature; at that time, the starting material had been converted into the activated ester. L-Alanyl-D-isoglutamine benzyl ester trifluoroacetate (55 mg) and triethylamine (0.05 mL) were added to the mixture, and it was stirred for 1.5 h at room temperature, and then evaporated. The residue was chromatographed on a column of silica gel (10 g) with chloroform and then 50:1 chloroform–methanol. The latter eluate afforded **17** (60 mg, 90%) as crystals, m.p. 254°, $[\alpha]_D^{25}$ +63° (*c* 0.55, acetic acid); ν_{max}^{Nujol} 3260 (NH), 2100 (N_3), 1720 and 1260 (ester), 1670, 1640, and 1540 (amide), and 720, 710, and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{33}H_{43}N_7O_9$: C, 58.09; H, 6.36; N, 14.38. Found: C, 58.14; H, 6.32; N, 14.29.

*Benzyl 2-acetamido-4,6-diazido-2,4,6-trideoxy-3-*O-(D-*2-propanoyl*-L-*alanyl*-D-*isoglutamine benzyl ester*)-α-D-*galactopyranoside* (**18**). — Hydrolysis of **12** (300 mg) with 0.1M potassium hydroxide (10 mL) in 1,4-dioxane (10 mL), with processing as already described, gave the free acid. Coupling of the acid with the L-alanyl-D-isoglutamine derivative (367 mg) in dry 1,4-dioxane (5 mL) by using HOSu (93 mg), DCC (207 mg), and triethylamine (0.2 mL), as described for **17**, gave **18** (470 mg, 97%) as crystals, m.p. 200–205° (dec.), $[\alpha]_D^{25}$ +43° (*c* 1.0, acetic acid); ν_{max}^{Nujol} 3260 (NH), 2100 and 2080 (N_3), 1720 and 1260 (ester), 1660, 1630, and 1540 (amide), and 720, 710, and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{33}H_{42}N_{10}O_9$: C, 54.84; H, 5.86; N, 19.38. Found: C, 54.85; H, 5.83; N, 19.09.

*Benzyl 2,6-di(acetamido)-4-azido-2,4,6-trideoxy-3-*O-(D-*2-propanoyl*-L-*alanyl*-D-*isoglutamine benzyl ester*)-α-D-*galactopyranoside* (**19**). — Hydrolysis of **13** (70 mg) with 0.1M potassium hydroxide (3.2 mL) in 1,4-dioxane (4 mL), as described for **17**, gave the free acid, which was condensed with the dipeptide (82 mg) in dry 1,4-dioxane (2 mL) by using HOSu (21 mg), DCC (46 mg), and triethylamine (0.1 mL) as already described, to give **19** (110 mg, 98%) as crystals, m.p. 215–218° (dec.), $[\alpha]_D^{25}$ +48° (*c* 0.8, acetic acid); ν_{max}^{Nujol} 3260 (NH), 2100 (N_3), 1720 and 1260 (ester), 1670, 1640, 1620, and 1540 (amide), and 720 and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{35}H_{46}N_8O_{11}$: C, 56.90; H, 6.28; N, 15.17. Found: C, 56.88; H, 6.31; N, 15.02.

*Benzyl 2-acetamido-4-azido-6-*O-*benzoyl-2,4-dideoxy-3-*O-(D-*2-propanoyl*-L-*alanyl*-D-*isoglutamine benzyl ester*)-α-D-*galactopyranoside* (**20**). — Hydrolysis of **14** (180 mg) with 0.1M potassium hydroxide (5 mL) in 1,4-dioxane (6 mL) in the usual

way gave the corresponding free acid. Coupling of the acid with the dipeptide (200 mg) in dry 1,4-dioxane (4 mL), by using HOSu (50 mg), DCC (100 mg), and triethylamine (0.1 mL) as already described, afforded compound **20** (240 mg, 88%) as crystals, m.p. 221–223°, $[\alpha]_D^{25}$ +49.5° (*c* 0.9, acetic acid); ν_{max}^{Nujol} 3270 (NH), 2100 (N_3), 1730 and 1270 (ester), 1670, 1640, and 1540 (amide), and 720–690 cm^{-1} (phenyl).

Anal. Calc. for $C_{40}H_{47}N_7O_{11}$: C, 59.91; H, 5.91; N, 12.23. Found: C, 59.76; H, 6.20; N, 12.05.

*Benzyl 2-acetamido-4-azido-2,4-dideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine benzyl ester)-α-*D*-galactopyranoside* (**21**). — To a solution of **20** (150 mg) in dry methanol (30 mL) was added sodium methoxide (20 mg); after 30 min, the mixture was processed as described for **15**, to give compound **21** (110 mg, 84%), m.p. 172–173°, $[\alpha]_D^{25}$ +56° (*c* 0.9, acetic acid); ν_{max}^{Nujol} 3400–3270 (OH, NH), 2100 (N_3), 1740 and 1260 (ester), 1640 and 1530–1520 (amide), and 720 and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{33}H_{43}N_7O_{10}$: C, 56.80; H, 6.21; N, 14.05. Found: C, 56.69; H, 6.25; N, 13.88.

*Benzyl 2-acetamido-4-azido-2,4-dideoxy-6-*O*-mesyl-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine benzyl ester)-α-*D*-galactopyranoside* (**22**). — Hydrolysis of **16** (290 mg) with 0.1M potassium hydroxide (8.7 mL) in 1,4-dioxane (10 mL), as described for **17**, gave the free acid, which was condensed with the dipeptide (318 mg) in dry 1,4-dioxane (5 mL), by using HOSu (80 mg), DCC (180 mg), and triethylamine (0.3 mL) as already described, to give **22** (410 mg, 91%) as crystals, m.p. 195–200° (dec.). $[\alpha]_D^{25}$ +58° (*c* 1.0, acetic acid); ν_{max}^{Nujol} 3270 (NH), 2100 (N_3), 1730 and 1260 (ester), 1660, 1630, and 1530 (amide), and 720, 710, and 680 cm^{-1} (phenyl).

Anal. Calc. for $C_{34}H_{45}N_7O_{12}S$: C, 52.63; H, 5.85; N, 12.64. Found: C, 52.59; H, 5.90; N, 12.58.

*Benzyl 2-acetamido-4-amino-2,4,6-trideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**23**). — Compound **17** (55 mg) was dissolved in a mixture of methanol (15 mL) and acetic acid (1 mL), 10% Pd–C catalyst (80 mg) was added, and hydrogen was bubbled through while the mixture was stirred for 1 h at room temperature, the course of the reaction being monitored by t.l.c. The catalyst was removed by filtration, and the filtrate was lyophilized, to give a hygroscopic, amorphous mass (45 mg, quantitative yield) which showed a single spot in t.l.c.; $[\alpha]_D^{25}$ +89° (*c* 0.2, methanol); ν_{max}^{KBr} 3400–3200 (OH, NH), 1720 C=O), 1650 and 1530 (amide), and 740 and 690 cm^{-1} (phenyl); n.m.r. data (in D_2O): δ 1.23 (d, 3 H, $J_{5,Me}$ 6.4 Hz, Me), 1.34, 1.40 (2 d, 6 H, $J_{Me,CH}$ 7.2 Hz, 2 MeC), 1.92 (s, 3 H, AcN), 4.94 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 7.38 (s, 5 H, Ph).

Anal. Calc. for $C_{26}H_{39}N_5O_9$: C, 55.21; H, 6.95; N, 12.38. Found: C, 54.83; H, 7.33; N, 12.15.

*Benzyl 2-acetamido-4,6-diamino-2,4,6-trideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**24**). — Compound **18** (300 mg) in methanol (30 mL)–acetic acid (1 mL) was hydrogenated in the presence of 10% Pd–C catalyst (300 mg), as described in the preparation of **23**, to give **24** (220 mg, 92%) as an amorphous material, $[\alpha]_D^{25}$ +78° (*c* 0.3, methanol); ν_{max}^{KBr} 3400–3250 (NH), 1720

(C=O), 1660–1640, and 1530 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in D_2O): δ 1.35, 1.44 (2 d, 6 H, $J_{Me,CH}$ 7.2 Hz, 2 MeC), 1.88 (s, 3 H, AcN), 5.04 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), and 7.40 (s, 5 H, Ph).

Anal. Calc. for $C_{26}H_{40}N_6O_9$: C, 53.78; H, 6.94; N, 14.48. Found: C, 53.41; H, 7.35; N, 14.19.

*Benzyl 2,4,6-tri(acetamido)-2,4,6-trideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**25**). — *N*-Acetylation of **24** (50 mg) with acetic anhydride (100 mg) in dry methanol (5 mL) gave **25** (55 mg, quantitative yield) as an amorphous material, $[\alpha]_D^{25}$ +74° (*c* 0.2, methanol); ν_{max}^{KBr} 3400–3250 (NH), 1720 (C=O), 1640 and 1530 (amide), and 740 and 690 cm^{-1} (phenyl); n.m.r. data (in D_2O): δ 1.29, 1.40 (2 d, 6 H, $J_{Me,CH}$ 7.2 Hz, 2 MeC), 1.98 (s, 6 H, 2 AcN), 2.09 (s, 3 H, AcN), 5.08 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 7.37 (s, 5 H, Ph).

Anal. Calc. for $C_{30}H_{44}N_6O_{11}$: C, 54.20; H, 6.67; N, 12.64. Found: C, 53.86; H, 6.98; N, 12.35.

*Benzyl 2,6-di(acetamido)-4-amino-2,4,6-trideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**26**). — Hydrogenation of **19** (82 mg) in methanol (20 mL)–acetic acid (1 mL) with hydrogen in the presence of 10% Pd–C catalyst (100 mg), according to the procedure already described, gave **26** (65 mg, 94%) as an amorphous material; $[\alpha]_D^{25}$ +64° (*c* 0.3, methanol); n.m.r. data (in D_2O): δ 1.25, 1.37 (2 d, 6 H, $J_{Me,CH}$ 7.2 Hz, 2 MeC), 1.90, 1.98 (2 s, 6 H, 2 AcN), 4.98 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 7.38 (s, 5 H, Ph).

Anal. Calc. for $C_{28}H_{42}N_6O_{10}$: C, 54.01; H, 6.80; N, 13.50. Found: C, 53.65; H, 7.21; N, 13.36.

*Benzyl 2-acetamido-4-amino-2,4-dideoxy-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**27**). — Hydrogenation of **21** (90 mg) in methanol (15 mL)–acetic acid (1 mL) in the presence of 10% Pd–C catalyst (100 mg), as already described, gave **27** (69 mg, 92%) as an amorphous material; $[\alpha]_D^{25}$ +22° (*c* 0.74, methanol); ν_{max}^{KBr} 3400–3250 (OH, NH), 1720 (C=O), 1650 and 1520 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in D_2O): δ 1.35, 1.37 (2 d, 6 H, $J_{Me,CH}$ 7.2 Hz, 2 MeC), 1.89 (s, 3 H, AcN), 5.00 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), and 7.38 (s, 5 H, Ph).

Anal. Calc. for $C_{26}H_{39}N_5O_{10}$: C, 53.69; H, 6.76; N, 12.04. Found: C, 53.58; H, 6.92; N, 11.75.

*Benzyl 2-acetamido-4-amino-2,4-dideoxy-6-*O*-mesyl-3-*O*-(*D*-2-propanoyl-*L*-alanyl-*D*-isoglutamine)-α-*D*-galactopyranoside* (**28**). — Hydrogenation of **22** (400 mg) in methanol (50 mL) and acetic acid (2 mL) in the presence of 10% Pd–C catalyst (400 mg) for 1 h at room temperature gave compound **28** (315 mg, 93%) as an amorphous material; $[\alpha]_D^{25}$ +61° (*c* 0.4, methanol); ν_{max}^{KBr} 3370–3230 (NH), 1720 (C=O), 1650 and 1520 (amide), 1170 (SO_2), and 730 and 690 cm^{-1} (phenyl); n.m.r. data (in D_2O): δ 1.41 (d, 6 H, $J_{Me,CH}$ 7.0 Hz, 2 MeC), 1.98 (s, 3 H, AcN), 3.15 (s, 3 H, MeS), 5.01 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 7.33 (s, 5 H, Ph).

Anal. Calc. for $C_{27}H_{41}N_5O_{12}S$: C, 49.15; H, 6.26; N, 10.62. Found: C, 48.92; H, 6.53; N, 10.49.

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