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Conformationally restricted analogues of the muramyldipeptide MDP †

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ABSTRACT

The syntheses of eight conformationally restricted analogues of *N*-acetylmuramyl-L-alanyl-D-isoglutamine (MDP) based on the D-glucopyrano[2,3-*d*]oxazolidine ring system are described.

INTRODUCTION

Many derivatives and analogues of the natural immunoadjuvant muramyldipeptide[2] (MDP, **1**) have been synthesised[3–7], seeking to minimise such side effects as pyrogenicity[8], thrombocytolysis[9], and somnogenicity[10]. Although the configurational and constitutional aspects of the MDP molecule have been extensively studied[11], little attention has been paid to the conformational aspect. In this way, the synthesis of a conformationally constrained analogue of MDP was recently described[12], based upon the results of ^{1}H NMR spectroscopic studies[13] of the solution conformation of MDP.

Since MDP is a conformationally flexible molecule, its various biological activities could be due to interactions of different conformations with stereochemically different receptors. For this reason, the synthesis of conformationally restricted analogues of MDP is of interest. This restriction can be achieved by ring formation. As a result of this working hypothesis, the syntheses of eight new analogues of MDP (**2–9**) are described, in which the conformational flexibility is restricted by formation of an oxazolidine ring between the functions at positions 2 and 3 of the D-glucosamine unit. Besides, in these analogues, some successful modifications of the MDP molecule (replacement of the D-isoglutamine residue by alkyl esters of

† Oxazolidines from sugars, Part IV. For Part III, see ref 1.

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D-glutamine[14], elimination[15] or substitution[16] of the anomeric OH function, and/or addition of lipophilic character[17]) have been introduced

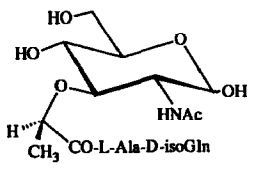
RESULTS AND DISCUSSION

The key step in the syntheses of these MDP analogues was the formation of the oxazolidine ring. This was achieved by reaction of the appropriate D-glucosamine derivatives with dichloroacetic acid in the presence of an excess of sodium hydride in boiling 1,4-dioxane, as previously described[18], affording the 3-acyl-2-carboxy-(D-glucopyrano)[2,3-*d*]oxazolidines **11–16**. Only the (*R*) isomer, at position 2 of the oxazolidine ring, was obtained in each synthesis. In this way, reaction of dodecyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[19] (**10**) with dichloroacetic acid under the above-mentioned conditions gave (2*R*)-3-acetyl-2-carboxy-(dodecyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-*d*]oxazolidine (**17**), which was characterised as its methyl ester (**18**), obtained by reaction with an ethereal solution of diazomethane (70% overall yield).

Condensation of compounds **11–16** with L-alanyl-D-isoglutamine benzyl ester (liberated from the toluene-*p*-sulfonate[20] with triethylamine) was effected with dicyclohexylcarbodiimide and *N*-hydroxysuccinimide as activating agents, affording, after column chromatography, compounds **23–28** in good yields (Table I).

Similarly, coupling of compounds **15–17** with L-alanyl-D-glutamine methyl (or butyl) ester[13] yielded compounds **29–32** (Table I).

Cleavage of the protecting groups was undertaken by hydrogenolysis or hydrolysis. In this way, acid hydrolysis of **28** with 8% HCl afforded **33** in 76% yield.



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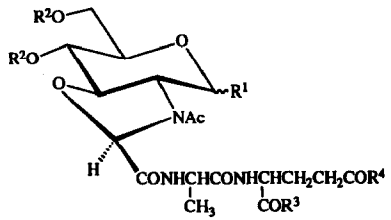
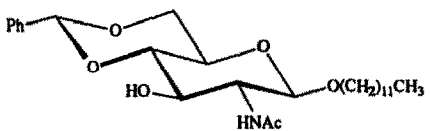


2	R^1 = OH,	R^2 = H,	R^3 = NH_2,	R^4 = OH
3	R^1 = αOMe,	R^2 = ^{n}Bu,	R^3 = NH_2,	R^4 = OH
4	R^1 = βOMe,	R^2 = H,	R^3 = NH_2,	R^4 = OH
5	R^1 = H,	R^2 = H,	R^3 = NH_2,	R^4 = OH
6	R^1 = OH,	R^2 = H,	R^3 = OMe,	R^4 = NH_2
7	R^1 = H,	R^2 = H,	R^3 = OMe,	R^4 = NH_2
8	R^1 = βODodecyl,	R^2 = H,	R^3 = OMe,	R^4 = NH_2
9	R^1 = OH,	R^2 = H,	R^3 = O^{n}Bu,	R^4 = NH_2



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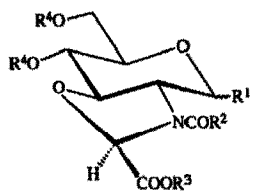
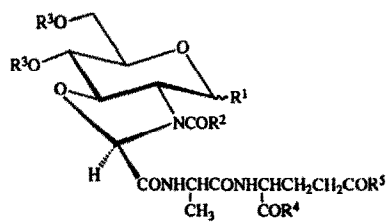


11	R^1 = αOBn	R^2 = Me	R^3 = H	R^4 = PhCH	
12	R^1 = αOBn	R^2 = Hep	R^3 = H	R^4 = PhCH	
13	R^1 = αOMe	R^2 = Me	R^3 = H	R^4 = ^{n}Bu	
14	R^1 = βOMe	R^2 = Me	R^3 = H	R^4 = PhCH	
15	R^1 = βOBn	R^2 = Me	R^3 = H	R^4 = PhCH	
16	R^1 = H	R^2 = Me	R^3 = H	R^4 = PhCH	
17	R^1 = βODodecyl	R^2 = Me	R^3 = H	R^4 = PhCH	
18	R^1 = βODodecyl	R^2 = Me	R^3 = Me	R^4 = PhCH	
19	R^1 = αOBn	R^2 = Me	R^3 = Me	R^4 = PhCH	
20	R^1 = αOBn	R^2 = Hep	R^3 = Me	R^4 = PhCH	
21	R^1 = αOBn	R^2 = Me	R^3 = Me	R^4 = H	
22	R^1 = αOBn	R^2 = Hep	R^3 = Me	R^4 = H	



23	R^1 = αOBn	R^2 = Me	R^3 = PhCH	R^4 = NH_2	R^5 = OBn	
24	R^1 = αOBn	R^2 = Hep	R^3 = PhCH	R^4 = NH_2	R^5 = OBn	
25	R^1 = αOMe	R^2 = Me	R^3 = ^{n}Bu	R^4 = NH_2	R^5 = OBn	
26	R^1 = βOMe	R^2 = Me	R^3 = PhCH	R^4 = NH_2	R^5 = OBn	
27	R^1 = βOBn	R^2 = Me	R^3 = PhCH	R^4 = NH_2	R^5 = OBn	
28	R^1 = H	R^2 = Me	R^3 = PhCH	R^4 = NH_2	R^5 = OBn	
29	R^1 = βOBn	R^2 = Me	R^3 = PhCH	R^4 = OMe	R^5 = NH_2	
30	R^1 = H	R^2 = Me	R^3 = PhCH	R^4 = OMe	R^5 = NH_2	
31	R^1 = βODodecyl	R^2 = Me	R^3 = PhCH	R^4 = OMe	R^5 = NH_2	
32	R^1 = βOBn	R^2 = Me	R^3 = PhCH	R^4 = O^{n}Bu	R^5 = NH_2	
33	R^1 = H	R^2 = Me	R^3 = H	R^4 = NH_2	R^5 = OBn	
34	R^1 = αOBn	R^2 = Me	R^3 = H	R^4 = NH_2	R^5 = OBn	
35	R^1 = αOBn	R^2 = Hep	R^3 = H	R^4 = NH_2	R^5 = OBn	

Likewise, compound **3** was obtained (73%) by mild alkaline hydrolysis of **25** with M NaOH.

On the other hand, hydrogenation of compounds **26–32** with 10% Pd–C for 12–24 h in 1,4-dioxane–methanol (in different ratios according to the solubility of each compound) allowed us to obtain the new conformationally restricted analogues **2** and **4–9**. However, these conditions failed for the hydrogenation of **23** and **24**, because of their lack of solubility in the usual solvents. For them, a different approach was studied. The 4,6-benzylidene acetals present in the methyl esters **19** and **20** were selectively hydrogenolysed with 10% Pd–C, to yield **21** and **22** (ref 18). Subsequent saponification and condensation with L-alanyl-D-isoglutamine benzyl ester, as described above, afforded **34** (63%) and **35** (64%), respectively.

Although these compounds were more soluble than the corresponding 4,6-*O*-benzylidene analogues **23** and **24**, their hydrogenation required more forcing conditions and a longer time for cleavage of the glycosidic α-*O*-benzyl group than those described for compounds **26–32**. In this way, **2** was obtained from **34** after 4 days of reaction with 10% Pd–C at 50°C and 400 psi, in only 51% yield. By comparison, the β-*O*-benzyl group in **27** was hydrogenolysed at 40 psi in 24 h at room temperature, to afford **2** in 81% yield. In contrast, cleavage of this group in compound **35** was not possible, even after exposure to these conditions for 10 days, due possibly to the steric hindrance by the lipohilic amide.

EXPERIMENTAL

General methods.—Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241-MC polarimeter, and IR spectra (KBr discs) were recorded with a Bomem Michelson 100 spectrophotometer. ^{1}H NMR spectra (200 MHz; internal Me_4Si)

TABLE I

Condensation reactions and selected physical data

Compound	Starting material	Dipeptide [a]	Yield (%)	Mp (°C)	$[\alpha]_D$ (°) (c, Me_2SO)
23	**11**	I	84	283–284	+42 (0.3)
24	**12**	I	77	237–238	+30 (0.23)
25	**13**	I	81	191–193	+31 (0.5)
26	**14**	I	76	251–252	−71 (0.4)
27	**15**	I	78	254–255	−33 (0.6)
28	**16**	I	81	238–240	+3 (1.1)
29	**15**	II	63	233–235	+37 (1.3)
30	**16**	II	73	282–283	+2.2 (1.2)
31	**17**	II	72	248–250	−32 (0.9)
32	**15**	III	58	210–212	−35 (0.9)

[a] I, L-Ala-D-isoGln(OBn); II, L-Ala-D-Gln(OMe); III, L-Ala-D-Gln(OBu).

were recorded on a Bruker AC-200 instrument. Mass spectra (CI with isobutane; FAB with thioglycerol matrix) were obtained with a Kratos MS-80-RFA spectrometer. Evaporations were conducted in vacuo. Preparative chromatography was performed on Silica Gel 60 (Merck).

(2R)-3-Acetyl-2-methoxycarbonyl-(dodecyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine (**18**).—To a solution of dodecyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (**10**; 4 g, 8.4 mmol) in dry 1,4-dioxane (400 mL) was added NaH (2.4 g , 100 mmol), and the mixture was stirred for 15 min at 80°C. A solution of dichloroacetic acid (3.2 mL, 40 mmol) in dry 1,4-dioxane (15 mL) was added dropwise, the mixture was stirred for 5 h at 90°C and cooled, and water was added until the suspension disappeared. Hydrochloric acid (1 M) was added to pH 8, the solution was concentrated in vacuo to one-third volume and diluted with water (~ 150 mL), and M HCl was added to pH 3. The aqueous suspension was extracted with $CHCl_3$ (4 × 75 mL), and the combined extracts were dried (Na_2SO_4), filtered, and cooled. This solution was treated with ethereal diazomethane overnight, then concentrated. Column chromatography (2:1 CH_2Cl_2–hexane) of the residue gave **18** (3.2 g, 70%) as a syrup; $[\alpha]_D$ −28.3° (*c* 0.6, $CHCl_3$); ν_{max} 3065, 3031 (Ar), 2926, 2856 (CH), 1761 (CO, ester), 1655 cm^{-1} (CO, amide). ^1H NMR data (200 MHz, Me_2CO-d_6, 20°): δ 7.42 (m, 5 H, Ph), 5.55 (s, 1 H, OCHN), 5.52 (s, 1 H, PhC*H*), 4.89 (br d, 1 H, H-1), 4.29 (dd, 1 H, $J_{5,6eq}$ 4.7, $J_{6ax,6eq}$ 10.2 Hz, H-6*eq*), 3.73 (s, 3 H, COOMe), 2.22 (s, 3 H, Ac), 0.91 [t, 3 H, *J* 9.3 Hz, $O(CH_2)_{11}CH_3$]. Mass spectrum (CI): *m/z* 548 (100%) $[M + H]^+$. Anal. Calcd for $C_{30}H_{45}NO_8$: C, 65.79; H, 8.28; N, 2.56. Found: C, 65.49; H, 8.01; N, 2.82.

(2R)-3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**23**).—To a solution of **11** (1 g, 2.2 mmol) in dry 1,4-dioxane (60 mL) were added *N*-hydroxysuccinimide (316 mg, 2.75 mmol) and dicyclohexylcarbodiimide (525 mg, 2.64 mmol), and the mixture was stirred for 30 min at room temperature. The dicyclohexylurea was collected and washed with 1,4-dioxane (15 mL), and, to the combined filtrate and washings, was added a solution of L-alanyl-D-isoglutamine benzyl ester *p*-toluenesulfonate (1.05 g, 2.2 mmol) and Et_3N (0.3 mL, 2.2 mmol) in 1:3 DMF–1,4-dioxane (25 mL). The mixture was stirred overnight at room temperature, then poured into water (150 mL), the precipitate was collected, and a suspension in warm EtOH (75 mL) was left to cool, then filtered to give **23** (1.38 g, 84%) as a white solid. Recrystallisation from 1,4-dioxane gave **23**; mp 283–284°C; $[\alpha]_D$ +42° (*c* 0.3, Me_2SO); ν_{max} 3289 (NH), 3066, 3034 (Ar), 1736 (CO, ester), 1674, 1648 (CO, amide), 1549 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 20°C): δ 9.04 (d, 1 H, $J_{H^{\alpha},NH}$ 7.5 Hz, N*H* isoGln), 8.32, 7.62 (2 d, 1 H, $J_{H^{\alpha},NH}$ 8.2 Hz, N*H* Ala), 7.48 (m, 15 H, 3 Ph), 7.38, 7.29, 7.21 (3 s, 2 H, NH_2), 5.98, 5.78 (2 br s, 1 H, H-1), 5.84, 5.48 (2 s, 1 H, OCHN), 5.67 (s, 1 H, PhC*H*), 5.18 (s, 2 H, $COOCH_2Ph$), 4.79 (AB q, 2 H, ^2J 11.7 Hz, $PhCH_2$), 1.95 (br s, 3 H, Ac), 1.35 (d, 3 H, *J* 7.2 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 767 (46%) $[M + Na]^+$. Anal. Calcd for $C_{39}H_{44}N_4O_{11}$: C, 62.89; H, 5.95; N, 7.52. Found: C, 63.16; H, 6.21; N, 7.34.

(2R)-3-Octanoyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**24**).—Prepared from **12**, as described above, **24** (77%) had: mp 237–238°C; $[\alpha]_D$ + 30° (*c* 0.23, Me_2SO); ν_{max} 3283 (NH), 3065, 3033 (Ar), 1733 (CO, ester), 1671, 1636 (CO, amide), 1551 cm^{-1} (NH). Mass spectrum (FAB): *m/z* 851 (29%) $[M + Na]^+$. Anal. Calcd for $C_{45}H_{56}N_4O_{11}$: C, 65.20; H, 6.81; N, 6.76. Found: C, 64.96; H, 6.90; N, 6.61.

(2R)-3-Acetyl-(methyl 4,6-di-O-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**25**).—Prepared from **13**, as described above, with subsequent purification by column chromatography (30:1 CH_2Cl_2–MeOH), **25** (81%) had: mp 191–193°C; $[\alpha]_D$ +31° (*c* 0.5, Me_2SO); ν_{max} 3280 (NH), 3067, 3035 (Ar), 1735 (CO, ester), 1681, 1652 (CO, amide), 1551 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 20°C): δ 8.98, 8.93 (2 d, 1 H, $J_{H^\alpha,NH}$ 7.5 Hz, N*H*isoGln), 8.20, 7.50 (2 d, 1 H, $J_{H^\alpha,NH}$ 8.4 Hz, N*H* Ala), 7.34 (s, 5 H, Ph), 7.29, 7.19, 7.16 (3 s, 2 H, NH_2), 5.47, 5.33 (2 s, 1 H, OCHN), 5.45 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.07 (s, 2 H, COOCH_2Ph), 3.38, 3.29 (2 s, 3 H, OMe), 1.88, 1.81 (2 s, 3 H, Ac). Mass spectrum (FAB): *m/z* 715 (41%) $[M + Na]^+$. Anal. Calcd for $C_{34}H_{52}N_4O_{11}$: C, 58.94; H, 7.57; N, 8.09. Found: C, 59.38; H, 7.41; N, 7.78

(2R)-3-Acetyl-(methyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**26**).—Prepared from **14**, as described above, **26** (76%) had: mp 251–252°C; $[\alpha]_D$ −71° (*c* 0.4 Me_2SO); ν_{max} 3282 (NH), 3068, 3038 (Ar), 1734 (CO, ester), 1673, 1649 (CO, amide), 1549 cm^{-1} (NH). ^1H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 8.80 (br s, 1 H, N*H* isoGln), 7.73 (br s, 1 H, N*H* Ala), 7.37 (m, 10 H, 2 Ph), 7.28, 7.12 (2 s, 2 H, NH_2), 5.72 (s, 1 H, PhC*H*), 5.53 (s, 1 H, OCHN), 5.08 (br s, 1 H, H-1), 5.06 (s, 2 H, COOCH_2Ph), 3.46 (s, 3 H, OMe), 2.03 (s, 3 H, Ac). Mass spectrum (FAB): *m/z* 669 (89%) $[M + H]^+$. Anal. Calcd for $C_{33}H_{40}N_4O_{11}$: C, 59.27; H, 6.03; N, 8.38. Found: C, 59.36; H, 5.92; N, 8.69.

(2R)-3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**27**).—Prepared from **15** as described above. After column chromatography (50:1 CH_2Cl_2–MeOH), **27** (78%) had: mp 254–255°C; $[\alpha]_D$ −33.3° (*c* 0.6, Me_2SO); ν_{max} 3306 (NH), 3064, 3035 (Ar), 1741 (CO, ester), 1675, 1652 (CO, amide), 1547 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.29 (d, 1 H, $J_{H^\alpha,NH}$ 6.8 Hz, N*H* isoGln), 7.53 (d, 1 H, $J_{H^\alpha,NH}$ 8.1 Hz, N*H* Ala), 7.32 (m, 15 H, 3 Ph), 6.78 (s, 2 H, NH_2), 5.71 (s, 1 H, PhC*H*), 5.56 (s, 1 H, OCHN), 5.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.06 (s, 2 H, COOCH_2Ph), 4.79 (AB q, 2 H, ^2J 11.4 Hz, PhCH_2), 3.39 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.6 Hz, H-2), 2.36 (t, 2 H, *J* 7.3 Hz, CH_2 γ isoGln), 2.05 (s, 3 H, Ac), 1.28 (d, 3 H, *J* 7.1 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 745 (26%) $[M + H]^+$. Anal. Calcd for $C_{39}H_{44}N_4O_{11}$: C, 62.89; H, 5.95; N, 7.52. Found: C, 62.39; H, 6.12; N, 6.97.

(2R)-3-Acetyl-(1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-D-glucitolo)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**28**).—Prepared from **16**, as described above, **28** (81%) had: mp 238–240°C; $[\alpha]_D$ +3° (*c* 1.1, Me_2SO); ν_{max} 3280 (NH), 3066, 3036 (Ar), 1733 (CO, ester), 1677, 1652 (CO, amide), 1560

cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 135°): δ 8.10 (br d, 1 H, N*H* isoGln), 7.32 (m, 10 H, 2 Ph), 6.57 (br s, 2 H, NH_2), 5.67 (s, 1 H, PhC*H*), 5.53 (s, 1 H, OCHN), 5.08 (s, 2 H, COOCH_2Ph), 4.72 (dd, 1 H, $J_{1eq,2}$ 4.1, $J_{1ax,1eq}$ 10.5 Hz, H-1*eq*), 3 .73 (t, 1 H, $J_{1ax,2}$ 10.4 Hz, H-1*ax*), 2.38 (t, 2 H, *J* 8.2 Hz, CH_2 γ isoGln), 1.90 (s, 3 H, Ac), 1.27 (d, 3 H, *J* 7.2 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 639 (21%) $[M + H]^+$. Anal. Calcd for $C_{32}H_{38}N_4O_{10}$: C, 60.18; H, 6.00; N, 8.77. Found: C, 59.69; H, 5.89; N, 8.54.

(2R)-3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-glutamine methyl ester (**29**).—Reaction of **15** (910 mg, 2 mmol) with L-alanyl-D-glutamine methyl ester hydrochloride (prepared from the benzyloxycarbonyl derivative, according to ref 14), as described for the preparation of **23**, with subsequent column chromatography (40:1 CH_2Cl_2–MeOH), yielded **29** (842 mg, 63%); mp 233–235°C; $[\alpha]_D$ −37.2° (*c* 1.3, Me_2SO); ν_{max} 3317 (NH), 3066, 3033 (Ar), 1742 (CO, ester), 1677, 1664 (CO, amide), 1551 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.27 (d, 1 H, $J_{H^\alpha,NH}$ 7.6 Hz, N*H* Gln), 7.72 (d, 1 H, $J_{H^\alpha,NH}$ 7.7 Hz, N*H* Ala), 7.34 (m, 10 H, 2 Ph), 6.57 (s, 2 H, NH_2), 5.71 (s, 1 H, PhC*H*), 5.59 (s, 1 H, OCHN), 5.37 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.80 (AB q, 2 H, ^2J 11.4 Hz, PhCH_2), 3.63 (s, 3 H, COOMe), 3.38 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.5 Hz, H-2), 2.08 (s, 3 H, Ac), 1.29 (d, 3 H, *J* 7.1 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 669 (100%) $[M + H]^+$. Anal. Calcd for $C_{33}H_{40}N_4O_{11}$: C, 59.27; H, 6.03; N, 8.38. Found: C, 59.78; H, 5.95; N, 7.87.

(2R)-3-Acetyl-(1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-D-glucitolo)[2,3-d]-oxazolidine-2-carbonyl-L-alanyl-D-glutamine methyl ester (**30**).—Prepared from **16**, as described above, **30** (73%) had: mp 282–283°C; $[\alpha]_D$ +2.2° (*c* 1.2, Me_2SO); ν_{max} 3282 (NH), 1741 (CO, ester), 1675, 1659 (CO, amide), 1556 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.32 (br d, 1 H, N*H* Gln), 7.82 (br d, 1 H, N*H* Ala), 7.39 (m, 5 H, Ph), 6.61 (br s, 2 H, NH_2), 5.71 (s, 1 H, PhC*H*), 5.58 (s, 1 H, OCHN), 4.72 (dd, 1 H, $J_{1eq,2}$ 4.4, $J_{1ax,1eq}$ 10.6 Hz, H-1*eq*), 3.72 (t, 1 H, $J_{1ax,2}$ 10.5 Hz, H-1*ax*), 3.64 (s, 3 H, COOMe), 1.92 (s, 3 H, Ac), 1.31 (d, 3 H, *J* 7.3 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 563 (100%) $[M + H]^+$. Anal. Calcd for $C_{26}H_{34}N_4O_{10}$: C, 55.51; H, 6.09; N, 9.96. Found: C, 55.50; H, 6.18; N, 9.62.

(2R)-3-Acetyl-(dodecyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3]-d]oxazolidine-2-carbonyl-L-alanyl-D-glutamine methyl ester (**31**).—Prepared from **17**, as described above, **31** (72%) had: mp 248–250°C; $[\alpha]_D$ −32° (*c* 0.9, Me_2SO); ν_{max} 3280 (NH), 1750 (CO, ester), 1660 (CO, amide), 1553 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.25 (d, 1 H, $J_{H^\alpha,NH}$ 7.1 Hz, N*H* Gln), 7.73 (d, 1 H, $J_{H^\alpha,NH}$ 6.7 Hz, N*H* Ala), 7.37 (m, 5 H, Ph), 5.71 (s, 1 H, PhC*H*), 5.68 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.51 (s, 1 H , OCHN), 3.64 (s, 3 H, COOMe), 1.91 (s, 3 H, Ac), 0.87 [t, 3 H, *J* 6.7 Hz, $O(CH_2)_{11}CH_3$]. Mass spectrum (FAB): *m/z* 747 (62%) $[M + H]^+$. Anal. Calcd for $C_{38}H_{58}N_4O_{11}$: C, 61.11; H, 7.83; N, 7.50. Found: C, 61.11; H, 7.97; N, 7.22.

(2R)-3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-glutamine butyl ester (**32**).—Reaction of **15** (910

mg, 2 mmol) with L-alanyl-D-glutamine butyl ester hydrochloride[14], as described for the preparation of **29**, yielded **32** (823 mg, 58%); mp 210–212°C; $[\alpha]_D$ −35° (*c* 0.9, Me_2SO); ν_{max} 3322 (NH), 3064 (Ar), 1737 (CO, ester), 1679, 1652 (CO, amide), 1560 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 120°C): δ 8.12 (d, 1 H, $J_{H^{\alpha},NH}$ 7.2 Hz, N*H* Gln), 7.63 (d, 1 H, $J_{H^{\alpha},NH}$ 7.4 Hz, N*H* Ala), 7.34 (m, 10 H, 2 Ph), 6.42 (br s, 2 H, NH_2), 5.71 (s, 1 H, PhC*H*), 5.61 (s, 1 H, OCHN), 5.38 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.81 (AB q, 2 H, ^2J 11.5 Hz, PhCH_2), 4.06 [t, 2 H, *J* 6.6 Hz, COOC$H_2(CH_2)_2CH_3$], 2.09 (s, 3 H, Ac), 0.86 [t, 3 H, *J* 7.1 Hz, COO$(CH_2)_3CH_3$]. Mass spectrum (FAB): *m/z* 711 (8%) $[M + H]^+$. Anal. Calcd for $C_{36}H_{46}N_4O_{11}$: C, 60.83; H, 6.52; N, 7.88. Found: C, 60.24; H, 6.62; N, 7.71.

*(2*R*)-3-Acetyl-(1,5-anhydro-2,3-dideoxy-*D*-glucitolo)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-isoglutamine benzyl ester* (**33**).—To a solution of **28** (500 mg, 0.8 mmol) in acetone (150 mL) was added 8% HCl (2 mL), and the mixture was gently warmed for 30 min, then cooled. Lead(II) carbonate basic was added to pH 7, and the mixture was filtered and concentrated to dryness. Recrystallisation of the residue from MeOH–ether gave **33** (335 mg, 76%) as a white solid; mp 256–258°C; $[\alpha]_D$ +20° (*c* 1, Me_2SO); ν_{max} 3425, 3380 (OH), 3267 (NH), 1733 (CO, ester), 1687, 1650 (CO, amide), 1554 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 120°C): δ 8.22 (d, 1 H, $J_{H^{\alpha},NH}$ 6.3 Hz, N*H* isoGln), 7.58 (d, 1 H, $J_{H^{\alpha},NH}$ 6.9 Hz, N*H* Ala), 7.35 (m, 5 H, Ph), 6.71 (br s, 2 H, NH_2), 5.50 (s, 1 H, OCHN), 5.11 (s, 2 H, COOCH_2Ph), 5.01 (d, 1 H, $J_{H,OH}$ 5.1 Hz, OH-4), 4.59 (dd, 1 H, $J_{1eq,2}$ 4.2, $J_{1ax,1eq}$ 10.4 Hz, H-1*eq*), 3.98 (t, 1 H, $J_{H,OH}$ 5.5 Hz, OH-6), 2.40 (t, 2 H, *J* 7.7 Hz, CH_2 γ isoGln), 1.90 (s, 3 H, Ac), 1.29 (d, 3 H, *J* 7.1 Hz, CH_3 Ala). Mass spectrum (FAB): *m/z* 551 (5%) $[M + H]^+$. Anal. Calcd for $C_{25}H_{34}N_4O_{10}$: C, 54.54; H, 6.22; N, 10.18. Found: C, 54.75; H, 6.11; N, 10.19.

*(2*R*)-3-Acetyl-(benzyl 2,3-dideoxy-α-D-glucopyranosido)[2,3-*d*]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester* (**34**).—To a solution of **21** (810 mg, 2.13 mmol) in MeOH (50 mL) was added M NaOH (8 mL), and the solution was left at room temperature for 1 h. Then, the mixture was neutralised with ion-exchange resin (Lewatit S100 G1) and filtered, and the resin was washed with MeOH. The combined filtrate and washings were concentrated to dryness. To a solution of the residue in 1:3 DMF–THF (35 mL) were added *N*-hydroxysuccinimide (306 mg, 2.6 mmol) and dicyclohexylcarbodiimide (527 mg, 2.5 mmol). After 15 min, a solution of L-alanyl-D-isoglutamine benzyl ester *p*-toluenesulfonate (1.02 g, 2.13 mmol) and Et_3N (0.29 mL, 2.1 mmol) in 1:3 DMF–THF (20 mL) was added, and the mixture was stirred overnight. The dicyclochexylurea was filtered-off and washed with DMF. The solution was concentrated in vacuo, and the residue was chromatographed by column (15:1 CH_2Cl_2–MeOH) to give **34** (741 mg, 63%); mp 212–214°C (dec); $[\alpha]_D$ +70° (*c* 0.3, MeOH); ν_{max} 3600–3100 (OH), 3283 (NH), 3066, 3033 (Ar), 1731 (CO, ester), 1679 (CO, amide), 1549 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 145°C): δ 8.22 (d, 1 H, $J_{H^{\alpha},NH}$ 7.5 Hz, N*H* isoGln), 7.40 (d, 1 H, $J_{H^{\alpha},NH}$ 8.0 Hz, N*H* Ala), 7.32 (m, 10 H, 2 Ph), 6.57 (s, 2 H, NH_2), 5.70 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 5.45 (s, 1 H, OCHN), 5.09 (s, 2 H, COOCH_2Ph), 5.00 (d,

1 H, $J_{H,OH}$ 5.9 Hz, OH-4), 4.65 (AB q, 2 H, ^2J 11.5 Hz, PhCH_2), 3.37 (dd, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 2.43 (t, 2 H, J 7.4 Hz, CH_2 γ isoGln), 1.86 (s, 3 H, Ac), 1.27 (d, 3 H, J 7.4 Hz, CH_3 Ala). Mass spectrum (FAB): m/z 657 (100%) $[M+H]^+$. Anal. Calcd for $C_{32}H_{40}N_4O_{11} \cdot H_2O$: C, 56.96; H, 6.27; N, 8.30. Found: C, 56.83; H, 6.26; N, 8.57.

(2R)-3-Octanoyl-(benzyl 2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine benzyl ester (**35**).—Prepared from **22** as described above, **35** (60%) had: mp 209–211°C (dec); $[\alpha]_D$ +64° (*c* 0.36, Me_2SO); ν_{max} 3600–3100 (OH), 3293 (NH), 3065, 3034 (Ar), 1730 (CO, ester), 1648 (CO, amide), 1548 cm^{-1} (NH). Mass spectrum (FAB): m/z 741 (100%) $[M+H]^+$. Anal. Calcd for $C_{38}H_{52}N_4O_{11}$: C, 61.61; H, 7.07; N, 7.56. Found: C, 61.76; H, 6.65; N, 7.92.

(2R)-3-Acetyl-(2,3-dideoxy-D-glucopyrano)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine (**2**).—To a solution of **27** (200 mg, 0.27 mmol) in 1:1 1,4-dioxane–MeOH (200 mL) was added 10% Pd–C (100 mg), and the suspension was hydrogenated at 40 psi for 24 h at room temperature. The catalyst was collected on Celite, the filter cake was washed with MeOH, and the combined filtrate and washings were concentrated to dryness. Column chromatography (1:1 CH_2Cl_2–MeOH) of the residue gave **2** (104 mg, 81%) as a syrup; $[\alpha]_D$ −13° (*c* 1.4, 1:1 MeOH–H_2O); ν_{max} 3600–3000 (OH), 3303 (NH), 1671 (CO, amide), 1566 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 20°C): δ 9.50, 9.22 (2 br d, 1 H, N*H* isoGln), 8.23, 8.05 (2 br d, 1 H, N*H* Ala), 7.33, 6.89 (2 s, 2 H, NH_2), 5.44 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 5.29 (s, 1 H, OCHN), 1.90 (s, 3 H, Ac), 1.25 (d, 1 H, J 7.1 Hz, CH_3 Ala). Anal. Calcd for $C_{18}H_{28}N_4O_{11} \cdot 3H_2O$: C, 40.76 H, 6.46; N, 10.56. Found: C, 40.41; H, 6.59; N, 10.17.

(2R)-3-Acetyl-(methyl 4,6-di-O-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]-oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine (**3**).—To a solution of **25** (500 mg, 0.72 mmol) in MeOH (40 mL) was added M NaOH (1 mL), and the solution was stirred for 20 min at room temperature. Then ion-exchange resin (Lewatit S100 G1) was added to pH 7, and the mixture was filtered and concentrated to dryness. Column chromatography (10:1 CH_2Cl_2–MeOH) of the residue afforded **3** (225 mg, 73%); mp 186–188°C; $[\alpha]_D$ +41° (*c* 0.3, $CHCl_3$); ν_{max} 3700–3100 (OH), 3286 (NH), 1663 (CO), 1558 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 20°C): δ 9.06, 8.97 (2 br d, 1 H, N*H* isoGln), 7.92, 7.60 (2 br d, 1 H, N*H* Ala), 7.35, 6.64 (2 s, 2 H, NH_2), 3.30 (s, 3 H, OMe), 2.00, 1.83 (2 s, 3 H, Ac). Mass spectrum (FAB): m/z 603 (72%) $[M+H]^+$. Anal. Calcd for $C_{27}H_{46}N_4O_{11}$: C, 53.81; H, 7.69; N, 9.30. Found: C, 53.58; H, 8.04; N, 9.14.

(2R)-3-Acetyl-(methyl 2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonyl-L-alanyl-D-isoglutamine (**4**).—To a solution of **26** (265 mg, 0.4 mmol) in 1:1 1,4-dioxane–MeOH (150 mL) was added 10% Pd–C (200 mg), and the suspension was hydrogenated at 50 psi for 24 h at room temperature. After work-up, as described for **2**, and column chromatography (2:1 CH_2Cl_2–MeOH), **4** (130 mg, 67%) was obtained: mp 195–197°C; $[\alpha]_D$ −48° (*c* 0.2, MeOH); ν_{max} 3700–3075 (OH), 3349 (NH), 1673 (CO), 1566 cm^{-1} (NH). ^1H NMR data (200 MHz,

Me_2SO-d_6, 20°C): δ 9.35, 8.88 (2 d, 1 H, $J_{H^{\alpha},NH}$ 7.2 Hz, N*H* isoGln), 8.12, 7.82 (2 d, 1 H, $J_{H^{\alpha},NH}$ 7.8 Hz, N*H* Ala), 7.31, 7.19, 7.00 (3 s, 2 H, NH_2), 5.45, 5.32 (2 s, 1 H, OCHN), 4.46 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 3.20 (s, 3 H, OMe), 2.04 (br s, 3 H, Ac). Anal. Calcd for $C_{19}H_{30}N_4O_{11}$: C, 46.52; H, 6.16; N, 11.42. Found: C, 46.43; H, 6.32; N, 11.19.

*(2R)-3-Acetyl-(1,5-anhydro-2,3-dideoxy-*D*-glucitolo)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-isoglutamine* (**5**).—To a solution of **28** (150 mg, 0.23 mmol) in 1:2 1,4-dioxane–MeOH (40 mL) was added 10% Pd–C (70 mg), and the suspension was hydrogenated at 40 psi overnight at room temperature. After work-up, as described for **2**, and column chromatography (2:1 CH_2Cl_2–MeOH), **5** (95 mg, 88%) was obtained: mp 186–189°C; $[\alpha]_D$ +19° (*c* 0.9, Me_2SO); ν_{max} 3430 (OH), 1673 (CO), 1556 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 120°C); δ 8.25 (br s, 1 H, N*H* isoGln), 7.62 (br s, 1 H, N*H* Ala), 6.70 (br s, 2 H, NH_2), 5.50 (s, 1 H, OCHN), 4.61 (dd, 1 H, $J_{1eq,2}$ 3.9, $J_{1ax,1eq}$ 10.3 Hz, H-1*eq*), 1.91 (s, 3 H, Ac), 1.31 (d, 3 H, *J* 7.0 Hz, C*H*$_3$ Ala). Mass spectrum (FAB): *m/z* 461 (100%) $[M+H]^+$. Anal. Calcd for $C_{18}H_{28}N_4O_{10}$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.46; H, 6.47; N, 11.98.

*(2R)-3-Acetyl-(2,3-dideoxy-*D*-glucopyrano)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-glutamine methyl ester* (**6**).—A solution of **29** (890 mg, 1.3 mmol) in 1:1 1,4-dioxane–MeOH (250 mL) was hydrogenated as described for **5**. After column chromatography (5:1 CH_2Cl_2–MeOH), amorphous **6** (595 mg, 91%) was obtained: mp 138–140°C; $[\alpha]_D$ −11° (*c* 1.1, Me_2SO); ν_{max} 3354 (OH), 1742 (CO, ester), 1670 (CO, amide), 1545 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.79 (br s, 1 H, N*H* Gln), 7.68 (br s, 1 H, N*H* Ala), 6.60 (br s, 2 H, NH_2), 5.59 (s, 1 H, OCHN), 3.65 (s, 3 H, COOMe), 2.03 (s, 3 H, Ac). Mass spectrum (FAB): *m/z* 491 (100%) $[M+H]^+$. Anal. Calcd for $C_{19}H_{30}N_4O_{11}$: C, 46.53; H, 6.16; N, 11.42. Found: C, 46.89; H, 5.82; N, 11.21.

*(2R)-3-Acetyl-(1,5-anhydro-2,3-dideoxy-*D*-glucitolo)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-glutamine methyl ester* (**7**).—A solution of **30** (130 mg, 0. 23 mmol) in 1:1 THF–MeOH (90 mL) was hydrogenated as described for **5**. After column chromatography (5:1 CH_2Cl_2–MeOH), **7** (98 mg, 90%) was obtained: mp 209–210°C; $[\alpha]_D$ +28° (*c* 1, Me_2SO); ν_{max} 3380 (OH), 3278 (NH), 1745 (CO, ester), 1661 (CO, amide), 1554 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 100°C): δ 8.32 (d, 1 H, $J_{H^{\alpha},NH}$ 6.5 Hz, N*H* Gln), 7.81 (br d, 1 H, N*H* Ala), 6.58 (br s, 2 H, NH_2), 5.51 (s, 1 H, OCHN), 4.59 (dd, 1 H, $J_{1eq,2}$ 4.3, $J_{1ax,1eq}$ 10.3 Hz, H-1*eq*), 3.64 (s, 3 H, COOMe), 1.90 (s, 3 H, Ac), 1.30 (d, 3 H, *J* 7.2 Hz, C*H*$_3$ Ala). Mass spectrum (FAB): *m/z* 475 (100%) $[M+H]^+$. Anal. Calcd for $C_{19}H_{30}N_4O_{10}$: C, 48.10; H, 6.37; N, 11.81. Found: C, 48.23; H, 6.61; N 12.09.

*(2R)-3-Acetyl-(dodecyl 2,3-dideoxy-β-*D*-glucopyranosido)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-glutamine methyl ester* (**8**). — A solution of **31** (200 mg, 0.27 mmol) in 3:1 1,4-dioxane–MeOH (40 mL) was hydrogenated as described for **5**. After column chromatography (7:1 CH_2Cl_2–MeOH), **8** (162 mg, 92%) was obtained: mp 208–209°C; $[\alpha]_D$ −72° (*c* 1, Me_2SO); ν_{max} 3414 (OH), 3290 (NH), 1745

(CO, ester), 1661 (CO, amide), 1552 cm^{-1} (NH). ^1H NMR data (200 MHz, Me_2SO-d_6, 120°C): δ 8.20 (d, 1 H, $J_{H^{\alpha},NH}$ 7.5 Hz, N*H* Gln), 7.72 (br, d, 1 H, N*H* Ala), 6.49 (br s, 2 H, NH_2), 5.53 (br d, 1 H, H-1), 5.44 (s, 1 H, OCHN), 3.65 (s, 3 H, COOMe), 1.90 (s, 3 H, Ac). Mass spectrum (FAB): *m/z* 659 (38%) $[M + H]^+$. Anal. Calcd for $C_{31}H_{54}N_4O_{11}$: C, 56.52; H, 8.26; N, 8.50. Found: C, 56.72; H, 8.43; N, 8.37.

*(2R)-3-Acetyl-(2,3-dideoxy-*D*-glucopyrano)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanyl-*D*-glutamine butyl ester* (**9**).—A solution of **32** (170 mg, 0.24 mmol) in 1:1 THF–MeOH (80 mL) was hydrogenated as described for **5**. Recrystallisation from MeOH–ether gave **9** (116 mg, 90%); mp 126–127°C; $[\alpha]_D$ −20° (*c* 0.9, Me_2SO); ν_{max} 3342 (OH), 1741 (CO, ester), 1666 (CO, amide), 1552 cm^{-1} (NH). Mass spectrum (FAB): *m/z* 533 (17%) $[M + H]^+$; high-resolution FAB for $C_{22}H_{38}N_4O_{11}$, 533.2458 (0.2 ppm).

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