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Oxazolidines from sugars: conformationally restricted derivatives of muramic acid

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ABSTRACT

The syntheses are described of four conformationally restricted derivatives of muramic acid based on the α-D-glucopyrano[2,3-*d*]oxazolidine ring system.

INTRODUCTION

Muramic acid (**1**) is a constituent of the peptidoglycan from bacterial cell walls [1] and the immunostimulant muramyldipeptide [2] (**2**, MDP). Many derivatives and analogues of MDP have been synthesised [3–7], seeking to minimise such side effects as pyrogenicity [8], thrombocytolysis [9], and somnogenicity [10].

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, rigid analogues of MDP are of interest, as a first step, we have synthesised some conformationally restricted derivatives (**3–7**) of muramic acid. This rigidity is achieved by the formation of an oxazolidine ring between N-2 and O-3.

RESULTS AND DISCUSSION

Reaction of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside [11] (**7**) with dichloroacetic acid in boiling dioxane in the presence of sodium hydride afforded 3-acetyl-2-carboxy-(benzyl 4,6-*O*-benzylidine-2,3-dideoxy-α-D-glucopyranosido)[2,3-*d*]oxazolidine (**16**, 89%), which was converted into the methyl

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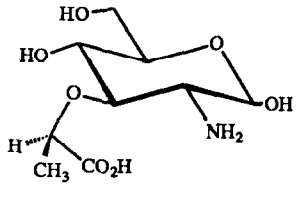

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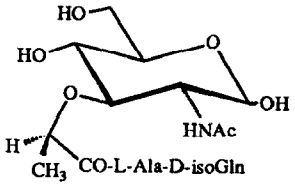

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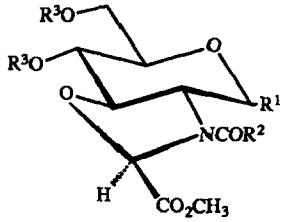


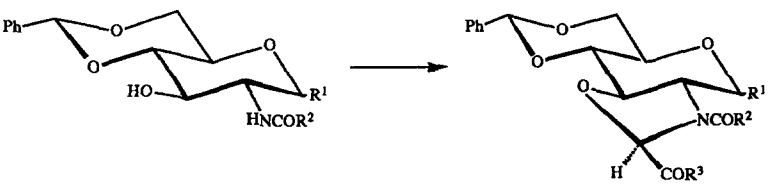
3 R^1= OH, R^2= Me, R^3= H

4 R^1= OH, R^2= Hep, R^3= H

5 R^1= H, R^2= Me, R^3= H

6 R^1= αOMe, R^2= Me, R^3= Bu

ester **17** by treatment with ethereal diazomethane. Similarly, benzyl 4,6-*O*-benzylidene-2-deoxy-2-octanamido-α-D-glucopyranoside [12] (**8**) yielded 2-carboxy-3-octanoyl-(benzyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-*d*]oxazolidine (**18**) and its methyl ester **19** (91%). Likewise, 3-acetyl-2-methoxycarbonyl-(1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-glucitolo)[2,3-*d*]oxazolidine (**20**) was obtained from **9** in high yield.



7 R^1= αOBn, R^2= Me

8 R^1= αOBn, R^2= Hep

9 R^1= H, R^2= Me

10 R^1= αOBn, R^2= ^{t}Bu

11 R^1= αOBn, R^2= O^{t}Bu

12 R^1= αOBn, R^2= Ph

13 R^1= αOMe, R^2= Me

14 R^1= βOBn, R^2= Me

15 R^1= βOMe, R^2= Me

16 R^1= αOBn, R^2= Me, R^3= OH

17 R^1= αOBn, R^2= Me, R^3= OMe

18 R^1= αOBn, R^2= Hep, R^3= OH

19 R^1= αOBn, R^2= Hep, R^3= OMe

20 R^1= H, R^2= Me, R^3= OMe

21 R^1= αOBn, R^2= ^{t}Bu, R^3= OMe

22 R^1= αOBn, R^2= O^{t}Bu, R^3= OMe

23 R^1= αOBn, R^2= Ph, R^3= OMe

24 R^1= αOMe, R^2= Me, R^3= OMe

25 R^1= βOBn, R^2= Me, R^3= OMe

26 R^1= βOMe, R^2= Me, R^3= OMe

27 R^1= αOBn, R^2= Me, R^3= NH_2

28 R^1= αOBn, R^2= Me, R^3= GlyOEt

29 R^1= αOBn, R^2= Me, R^3= L-AlaOEt

30 R^1= αOBn, R^2= Me, R^3= L-ValOEt

31 R^1= αOBn, R^2= Hep, R^3= GlyOEt

32 R^1= αOBn, R^2= Hep, R^3= L-AlaOEt

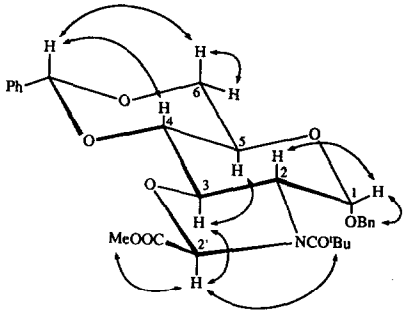


Fig. 1. Observed NOE for **21**.

When the oxazolidine ring was formed, only one of two possible isomers was obtained. Although the ^{1}H-NMR spectra of **16–20** contained twin peaks for the resonances of H-1,2,3 (sugar skeleton), COOMe, Ac, and H-2′ (oxazolidine ring), they collapsed to singlets on heating, reflecting the existence of rotational isomers.

In order to determine the configuration of the newly created chiral carbon, **21–26** were synthesised by the above-mentioned procedure: only one isomer was obtained in each synthesis.

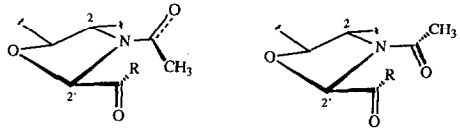
The ^{1}H-NMR spectrum of **21**, recorded at room temperature, did not contain any twin peaks and it was possible to carry out a NOESY experiment in order to determine the configuration at C-2′. Since there was, amongst others, NOE between H-3 and H-2′ (Fig. 1), the configuration at C-2′ was *R* (cf. ref. 13).

The reactions of the acids **16** and **18** with dicyclohexylcarbodi-imide and *N*-hydroxysuccinimide and subsequent reactions with ammonia or amino acids were undertaken as a preliminary study of the synthesis of the rigid analogues of MDP. Thus, **16**, in the subsequent reactions with ammonia or the ethyl esters of glycine, L-alanine, or L-valine, afforded **27** (75%), **28** (72%), **29** (82%), and **30** (78%), respectively, after column chromatography. Similarly, with **18**, the subsequent reactions with the ethyl esters of glycine or L-alanine yielded **31** (72%) and **32** (76%), respectively.

In solution at room temperature, the methyl ester **17** existed as a 2:1 mixture of conformers in which the *anti* form preponderated, whereas the proportion of conformers for the amide **27** was 3:1 in favour of the *syn* form. The *anti* / *syn* conformations were assigned as follows. (*a*) According to Levy and Nelson [14] the higher-field ^{13}C resonance of amides corresponds to the carbon *syn* to the carbonyl group. Table I contains the δ values for the C-2′ and C-2 resonances of **17** and **27**. These values for the major conformer of **17** are 86.71 and 52.72 ppm, respectively, whereas, for the minor conformer, they are 85.62 and 53.59 ppm, respectively. Hence, in the major isomer, C-2′ is *anti* to the carbonyl group. The situation for **27** is reversed and the major conformer has C-2′ *syn* to the carbonyl group. (*b*) According to Stewart and Siddall [15], for *N*-isopropylamides, the hydrogen *anti* to the carbonyl group will resonate at higher field. The data in Table I

TABLE I

Selected chemical shifts for *syn* / *anti* conformers [a]



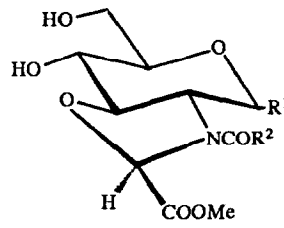
	17 (R=OMe)			27 (R=NH_2)		
	C-2′	C-2	H-2′	C-2′	C-2	H-2′
Major conformer	86.71	52.72	5.42	86.74	60.41	5.44
Minor conformer	85.62	53.59	5.83	87.84	60.17	5.24

[a] δ in ppm for solutions in Me_2SO-d_6.

show that the H-2′ resonance of the major conformer of **17** is at higher field, whereas it is at lower field for the major conformer of **27**, confirming the conclusions in (*a*).

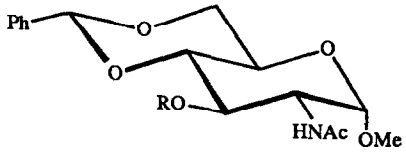
This inversion in the ratio of conformers may reflect the formation of a hydrogen bond in **27** between the NH_2 and CO functions at positions 2 and 3 of the oxazolidine ring, which would give rise to a seven-membered ring as found in peptides [16]. A similar hydrogen bond has been observed in natural MDP [17].

Hydrogenation (Pd–C) of **17** or **25** in methanol at room temperature afforded the same compound, namely, 3-acetyl-2-methoxycarbonyl-(2,3-dideoxy-D-glucopyrano)[2,3-*d*]oxazolidine (**3**). The reaction of **17** (at 100 psi) required 96 h and the yield was 64%, whereas **25** at 40 psi required 40 h and gave 80% of **3**. Likewise, hydrogenation (100 psi) of **19** afforded 68% of 2-methoxycarbonyl-3-octanoyl-(2,3-dideoxy-D-glucopyrano)[2,3-*d*]oxazolidine (**4**) and of **20** (at 40 psi) gave 62% of 3-acetyl-2-methoxycarbonyl-(1,5-anhydro-2,3-dideoxy-D-glucitolo)[2,3-*d*]oxazolidine (**5**). Controlled hydrogenation of **17** or **19** at 40 psi gave the benzyl α-glycosides **33**

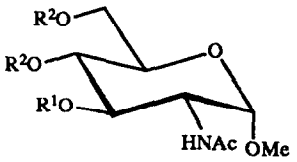


33 R^1= αOBn, R^2= Me

34 R^1= αOBn, R^2= Hep



35 R = Bn



36 R^1 = Bn, R^2 = H

37 R^1 = Bn, R^2 = Bu

38 R^1 = H, R^2 = Bu

(98%) and **34** (96%), respectively. This control was not possible for the β-glycoside **25**.

Compound **6** was obtained by the following route. Reaction of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**13**) with benzyl bromide–sodium hydride yielded the 3-*O*-benzyl derivative **35**, mild hydrolysis of which with acid removed the benzylidene group and gave **36**. Treatment of **36** with butyl bromide–sodium hydride gave methyl 2-acetamido-3-*O*-benzyl-4,6-di-*O*-butyl-2-deoxy-α-D-glucopyranoside (**37**), hydrogenolysis of which gave methyl 2-acetamido-4,6-di-*O*-butyl-2-deoxy-α-D-glucopyranoside (**38**). The conversion of **38** into 3-acetyl-2-methoxycarbonyl-(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*d*]oxazolidine (**6**, 60%) was effected by the above-mentioned procedure.

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 and 80 MHz; internal Me_4Si) were recorded with Varian XL-200 and Bruker WP-80-SY instruments. Mass spectra (EI at 70 eV; CI with isobutane) were obtained with a Kratos MS-80-RFA spectrometer. Solvents were evaporated in vacuo. Preparative chromatography was performed on Silica Gel 60 (Merck).

3-Acetyl-2-carboxy-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine (**16**).—To a solution of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**; 5 g, 12.5 mmol) in dry 1,4-dioxane (350 mL) was added NaH (2.4 g, 100 mmol), and the mixture was stirred for 15 min at 80°. A solution of dichloroacetic acid (3.1 mL, 37.5 mmol) in dry 1,4-dioxane (15 mL) was added dropwise, the mixture was stirred for 3 h at 80°, then cooled, and water was added until the suspension disappeared. M HCl was added to pH 8, and

the solution was concentrated in vacuo to one-third volume, diluted with water (~ 150 mL), and washed thrice with hexane. The aqueous solution was acidified to pH 3 with M HCl, and the precipitate was collected, washed with water, and subjected to column chromatography ($CHCl_3$, 30:1 and 10:1 $CHCl_3$–MeOH). The last solvent gave **16** (5.84 g, 89%), mp 210° (dec), $[\alpha]_D$ +126° (*c* 0.27, $CHCl_3$); ν_{max} 3360–2525 (b, OH), 1620 cm^{-1} (CO). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 7.39 (m, 10 H, 2 Ph), 5.89 and 5.65 (2 bs, H-1), 5.73 (s, 1 H, PhC*H*), 5.76 and 5.29 (2 s, H-2′), 4.69 (m, 2 H, PhCH_2), 1.95 and 1.86 (2 s, Ac).

Anal. Calcd for $C_{24}H_{25}NO_8$; C, 63.29; H, 5.53; N, 3.08. Found: C, 63.10; H, 5.58; N, 3.17.

*3-Acetyl-2-methoxycarbonyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine* (**17**).—To a cold solution of **16** (1 g, 2.2 mmol) in MeOH (100 mL) was added ethereal diazomethane until the yellow colour persisted. The solvent was evaporated to afford solid **17** (1.03 g, quantitative yield). Recrystallisation from MeOH gave **17** with mp 176–177° (dec), $[\alpha]_D$ +136° (*c* 0.83, $CHCl_3$); ν_{max} 3067 and 3034 (Ar), 1748 (CO, ester), 1674 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 150°): δ 7.36 (m, 10 H, 2 Ph), 5.83 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 5.71 (s, 1 H, PhC*H*), 5.58 (s, 1 H, H-2′), 4.73 (AB q, 2 H, ^2J 11.8 Hz, PhCH_2), 3.77 (s, 3 H, COOMe), 1.92 (s, 3 H, Ac). Mass spectrum (CI): *m/z* 470 (100%) $[M + H]^+$.

Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 64.26; H, 5.59; N, 3.25.

*2-Carboxy-3-octanoyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine* (**18**).—Reaction of benzyl 4,6-*O*-benzylidene-2-deoxy-2-octanamido-α-D-glucopyranoside (**8**; 4.3 g, 9 mmol) with dichloroacetic acid, as described for the preparation of **16**, yielded crude **18**. Recrystallisation from 1,4-dioxane–water gave **18** (4.4 g, 91%), mp 136°, $[\alpha]_D$ +118° (*c* 0.89, $CHCl_3$); ν_{max} 3500 (OH), 3066 and 3034 (Ar), 1662 cm^{-1} (CO).

Anal. Calcd for $C_{30}H_{37}NO_8$: C, 66.77; H, 6.91; N, 2.60. Found: C, 66.53; H, 6.73; N, 2.79.

*2-Methoxycarbonyl-3-octanoyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine* (**19**).—Treatment of a solution of **18** (2.5 g, 4.6 mmol) in MeOH (240 mL) with diazomethane and evaporation of the solvents gave **19** (2.6 g) as a white solid. Recrystallisation from MeOH afforded **19** (2.3 g, 91%), mp 142–143°, $[\alpha]_D$ +119° (*c* 1, $CHCl_3$); ν_{max} 3060 and 3035 (Ar), 1747 (CO, ester), 1675 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 7.38 (m, 10 H, 2 Ph), 5.93 and 5.71 (2 d, H-1), 5.84 and 5.42 (2 s, H-2′), 5.74 (s, 1 H, PhC*H*), 4.67 (m, 2 H, PhCH_2), 3.78 and 3.66 (2 s, COOMe), 0.85 (t, 3 H, CH_3). Mass spectrum (CI): *m/z* 554 (100%) $[M + H]^+$.

Anal. Calcd for $C_{31}H_{39}NO_8$: C, 67.25; H, 7.10; N, 2.53. Found: C, 66.99; H, 6.76; N, 2.82.

*3-Acetyl-2-methoxycarbonyl-(1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-*D*-glucitolo)[2,3-*d*]oxazolidine* (**20**).—Compound **9** [18] (1.3 g, 4.4 mmol) was treated with

dichloroacetic acid as described for **7**. The resulting acid was esterified with diazomethane and the crude solid product was subjected to column chromatography (hexane, CH_2Cl_2, and 50:1 CH_2Cl_2–MeOH). The last solvent gave **20** (0.9 g, 58.2%), mp 155°, $[\alpha]_D$ +11° (*c* 1.2, $CHCl_3$); ν_{max} 1750 (CO, ester), 1666 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, $CDCl_3$, 20°): δ 5.59 (s, 1 H, PhC*H*), 5.54 and 5.51 (2 s, H-2′), 3.83 (s, COOMe), 3.71 (t, 1 H, *J* 10.2 Hz, H-1*ax*), 2.06 and 1.97 (2 s, Ac). Mass spectrum (CI): *m/z* 364 (100%) $[M + H]^+$.

Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.11; H, 5.93; N, 3.61.

2-Methoxycarbonyl-3-pivaloyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine (**21**).—Prepared from **10**, as described above *, **21** (62%) had mp 101°, $[\alpha]_D$ +117° (*c* 1.1, $CHCl_3$); ν_{max} 1760 (CO, ester), 1650 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, $CDCl_3$, 20°): δ 7.35 (m, 10 H, 2 Ph), 6.00 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 5.75 (s, 1 H, H-2′), 5.58 (s, 1 H, PhC*H*), 3.79 (s, 3 H, COOMe) 3.62 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{2,3}$ 9.8 Hz, H-2), 1.15 (s, 9 H, ^{t}Bu). Mass spectrum (EI): *m/z* 511 (0.6%) $[M]^+$.

Anal. Calcd for $C_{28}H_{33}NO_8$: C, 65.74; H, 6.50; N, 2.73. Found: C, 65.20; H, 6.69; N, 2.89.

*2-Methoxycarbonyl-3-*tert*-butoxycarbonyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine* (**22**).—Prepared from **11**, as described above *, **22** (51%) had mp 128°, $[\alpha]_D$ +103° (*c* 1, $CHCl_3$); ν_{max} 3065 and 3033 (Ar), 1763 (CO, ester), 1710 cm^{-1} (CO, urethane). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 7.37 (m, 10 H, 2 Ph), 5.72 (s, 1 H, PhC*H*), 5.70 and 5.49 (2 d, H-1), 5.35 and 5.33 (2 s, H-2′), 3.74 and 3.35 (2 s, COOMe), 1.35 and 1.32 (2 s, ^{t}Bu). Mass spectrum (EI): *m/z* 527 (0.5%) $[M]^+$.

Anal. Calcd for $C_{28}H_{33}NO_9$: C, 63.74; H, 6.30; N, 2.65. Found: C, 63.45; H, 6.59; N, 2.51.

3-Benzoyl-2-methoxycarbonyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine (**23**).—Prepared from **12**, as described above, **23** (89.5%) had mp 142°, $[\alpha]_D$ +128° (*c* 1.4, $CHCl_3$); ν_{max} 3061 and 3030 (Ar), 1747 (CO, ester), 1640 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 7.53 (bs, 5 H, COPh), 7.25 (m, 10 H, 2 Ph), 5.89 (bs, 2 H, H-1,2′), 5.73 (s, 1 H, PhC*H*), 3.35 and 3.33 (2 s, COOMe). Mass spectrum (CI): *m/z* 532 (100%) $[M + H]^+$.

Anal. Calcd for $C_{30}H_{29}NO_8$: C, 67.79; H, 5.50; N, 2.63. Found: C, 67.21; H, 5.57; N, 2.64.

3-Acetyl-2-methoxycarbonyl-(methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine (**24**).—Prepared from **13**, as described above, **24** (80%) had mp 173–174°, $[\alpha]_D$ +131° (*c* 0.22, $CHCl_3$); ν_{max} 3040(Ar), 1747 (CO,

* Compounds **10** and **11** were obtained from benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[11] by *N*-acylation in the usual way.

ester), 1669 cm^{-1} (CO, amide). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 7.38 (m, 5 H, Ph), 5.72 and 5.34 (2 d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.60 (s, 1 H, PhC*H*), 5.47 (s, H-2′), 3.79 (s, 3 H, COOMe), 3.47 (s, 3 H, OMe), 2.06 and 1.93 (2 s, Ac). Mass spectrum (CI): *m/z* 394 (20%) $[M + H]^+$.

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.00; H, 5.89; N, 3.56. Found: C, 58.12; H, 6.26; N, 3.25.

3-Acetyl-2-methoxycarbonyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine (**25**).—Prepared from **14**, as described above, **25** (89%) had mp 169–170°, $[\alpha]_D$ −29° (*c* 1.8, $CHCl_3$); ν_{max} 1750 (CO, ester), 1674 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 60°): δ 7.40 (m, 10 H, 2 Ph), 5.71 (s, 1 H, PhC*H*), 5.58 (s, 1 H, H-2′), 5.34 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.81 (AB q, 2 H, ^2J 11.6 Hz, PhCH_2), 3.69 (s, 3 H, COOMe), 2.06 (s, 3 H, Ac). Mass spectrum (CI): *m/z* 470 (100%) $[M + H]^+$.

Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 63.85; H, 5.54; N, 2.89.

3-Acetyl-2-methoxycarbonyl-(methyl 4,6-O-benzylidene-2,3-dideoxy-β-D-glucopyranosido)[2,3-d]oxazolidine (**26**).—Prepared from **15**, as described above, **26** (78%) had mp 191–192°, $[\alpha]_D$ −54° (*c* 0.1, $CHCl_3$); ν_{max} 3060 and 3036 (Ar), 1762 (CO, ester), 1658 cm^{-1} (CO, amide). ^{1}H-NMR data (200 MHz, Me_2SO-d_6, 20°): δ 7.38 (m, 5 H, Ph), 5.72 (s, 1 H, PhC*H*), 5.58 (s, 1 H, H-2′), 5.13 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 3.72 (s, 3 H, COOMe), 3.50 (s, 3 H, OMe), 2.11 (s, 3 H, Ac). Mass spectrum (CI): *m/z* 394 (80%) $[M + H]^+$.

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.00; H, 5.89; N, 3.56. Found: C, 57.78; H, 6.16; N, 3.41.

3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carboxamide (**27**).—To a solution of **16** (0.96 g, 2.1 mmol) in dry 1,4-dioxane (30 mL) were added *N*-hydroxysuccinimide (304 mg, 2.6 mmol) and dicyclohexylcarbodi-imide (523 mg, 2.5 mmol), and the mixture was stirred for 30 min at room temperature. The dicyclohexylurea was collected and washed with 1,4-dioxane, and a stream of ammonia was bubbled into the combined filtrate and washings for 10 min. The mixture was poured into water (100 mL), the white solid was filtered-off and washed with water, and a suspension in warm EtOH (100 mL) was left overnight. The resulting white solid (**27**; 717 mg, 75%) was collected and recrystallised from EtOH to give **27**, mp 281–282°, $[\alpha]_D$ +114° (*c* 0.34, Me_2SO); ν_{max} 3338 and 3151 (NH), 3065 and 3033 (Ar), 1698 (CO, amide), 1551 cm^{-1} (NH). ^{1}H-NMR data (80 MHz, Me_2SO-d_6, 20°): δ 7.92 and 7.62 (2 bs, 2 H, NH_2), 7.40 (m, 10 H, 2 Ph), 5.88 (d, $J_{1,2}$ 2.8 Hz, H-1), 5.72 (s, 1 H, PhC*H*), 5.44 and 5.24 (2 s, H-2′), 4.65 (m, 2 H, PhCH_2), 1.90 and 1.84 (2 s, Ac). Mass spectrum (EI): *m/z* 454 (1%) $[M]^+$.

Anal. Calcd for $C_{24}H_{26}N_2O_7$: C, 63.43; H, 5.77; N, 6.16. Found: C, 63.20; H, 6.01; N, 5.85.

3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine-2-carbonylglycine ethyl ester (**28**).—To a solution of **16** (600 mg, 1.32

mmol) in dry 1,4-dioxane (10 mL) were added *N*-hydroxysuccinimide (186 mg, 1.65 mmol) and dicyclohexylcarbodi-imide (326 mg, 1.58 mmol), and the mixture was stirred for 30 min at room temperature. The dicyclohexylurea was collected and washed with 1,4-dioxane (5 mL), and, to the combined filtrate and washings, were added glycine ethyl ester hydrochloride (184 mg, 1.32 mmol) and triethylamine (0.18 mL, 1.32 mmol). The mixture was stirred overnight at room temperature, then poured into water (25 mL), the precipitate was collected, a suspension in warm EtOH (40 mL) was left to cool, then filtered to give **28** (512 mg, 72%) as a white solid. Recrystallisation from $CHCl_3$–EtOAc gave **28**, mp 269–270°, $[\alpha]_D$ +93° (*c* 0.4, $CHCl_3$); ν_{max} 3292 (NH), 3066, 3034 (Ar), 1746 (CO, ester), 1671 (CO, amide), 1562 cm^{-1} (NH). ^{1}H-NMR data (80 MHz, Me_2SO-d_6, 20°): δ 8.93 (t, 1 H, $J_{H\alpha,NH}$ 8.0 Hz, NH), 7.35 (m, 10 H, 2 Ph), 5.89 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 5.72 (s, 1 H, PhC*H*), 5.59 (s, 1 H, H-2′), 4.66 (AB q, 2 H, ^2J 11.8 Hz, PhCH_2), 4.10 (q, 2 H, *J* 7.1 Hz, COOCH_2CH$_3$), 1.90 (s, 3 H, Ac), 1.20 (t, 3 H, *J* 7.1 Hz, COOCH$_2$ CH_3). Mass spectrum (EI): *m/z* 540 (0.5%) $[M]^+$.

Anal. Calcd for $C_{28}H_{32}N_2O_9$: C, 62.21; H, 5.97; N, 5.18. Found: C, 62.60; H, 6.05; N, 5.29.

*3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine-2-carbonyl-*L*-alanine ethyl ester* (**29**).—Prepared from **16**, as described above, **29** (82%) had mp 246–248° (dec), $[\alpha]_D$ +81° (*c* 1.1, $CHCl_3$); ν_{max} 3296 (NH), 3064, 3033 (Ar), 1740 (CO, ester), 1674 (CO, amide), 1553 cm^{-1} (NH). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 7.35 (m, 10 H, 2 Ph), 6.82 (d, 1 H, $J_{H\alpha,NH}$ 7.4 Hz, NH), 6.02 (bs, 1 H, H-1), 5.60 (s, 1 H, PhC*H*), 5.44 (s, 1 H, H-2′), 4.21 (q, 2 H, *J* 7.1 Hz, COOCH_2CH$_3$), 2.01 (s, 3 H, Ac), 1.28 (t, 3 H, *J* 7.1 Hz, COOCH$_2$CH_3). Mass spectrum (EI): *m/z* 554 (2%) $[M]^+$.

Anal. Calcd for $C_{29}H_{34}N_2O_9$: C, 62.80; H, 6.17; N, 5.05. Found: C, 62.45; H, 5.87; N, 5.34.

*3-Acetyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine-2-carbonyl-*L*-valine ethyl ester* (**30**).—Prepared from **16**, as described above, **30** (78%) had mp 228–230° (dec), $[\alpha]_D$ +91° (*c* 0.55, $CHCl_3$); ν_{max} 3283 (NH), 3065, 3032 (Ar), 1737 (CO, ester), 1670 (CO, amide), 1556 cm^{-1} (NH). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 7.35 (m, 10 H, 2 Ph), 6.77 (d, 1 H, $J_{H\alpha,NH}$ 8.5 Hz, NH), 6.05 (bs, 1 H, H-1), 5.61 (s, 1 H, PhC*H*), 5.48 (s, 1 H, H-2′), 4.22 (q, 2 H, *J* 7.1 Hz, COOCH_2CH$_3$), 2.12 (bs, 4 H, Ac and C*H*Me$_2$), 1.28 (t, 3 H, *J* 7.1 Hz, COOCH$_2$CH_3), 0.94 and 0.92 (2 d, 6 H, CH*Me*$_2$). Mass spectrum (EI): *m/z* 582 (2.5%) $[M]^+$.

Anal. Calcd for $C_{31}H_{38}N_2O_9 \cdot 0.5H_2O$: C, 62.93; H, 6.47; N, 4.73. Found: C, 62.95; H, 6.48; N, 4.81.

*3-Octanoyl-(benzyl 4,6-O-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido)[2,3-*d*]oxazolidine-2-carbonylglycine ethyl ester* (**31**).—Prepared from **18**, as described above, **31** (72%) had mp 225–226° (dec), $[\alpha]_D$ +95° (*c* 0.29, $CHCl_3$); ν_{max} 3291 (NH), 3067, 3035 (Ar), 1747 (CO, ester), 1669 (CO, amide), 1557 cm^{-1} (NH). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 7.35 (m, 10 H, 2 Ph), 6.83 (t, 1 H, J_{NH,CH_2}

8.5 Hz, NH), 6.02 (bs, 1 H, H-1), 5.60 (s, 1 H, PhC*H*), 5.54 (s, 1 H, H-2'), 4.22 (q, 2 H, *J* 6.8 Hz, COOCH_2CH$_3$), 1.29 (t, 3 H, *J* 6.8 Hz, COOCH$_2$CH_3), 0.87 (t, 3 H, Me). Mass spectrum (EI): *m/z* 624 (1.5%) $[M]^+$.

Anal. Calcd for $C_{34}H_{44}N_2O_9$: C, 65.37; H, 7.10; N, 4.48. Found: C, 65.27; H, 7.19; N, 4.40.

3-Octanoyl-(benzyl 4,6-O-benzylidine-2,3-dideoxy-α-D-glucopyranosido)[2,3-d] oxazolidine-2-carbonyl-L-alanine ethyl ester (**32**).—Prepared from **18**, as described above, **32** (76%) had mp 231–233° (dec), $[\alpha]_D$ +86° (*c* 1.18, $CHCl_3$); ν_{max} 3285 (NH), 3067, 3034 (Ar), 1744 (CO, ester), 1672 (CO, amide), 1557 cm^{-1} (NH). Mass spectrum (EI): *m/z* 638 (1.4%) $[M]^+$.

*A*nal. Calcd for $C_{35}H_{46}N_2O_9$: C, 65.81; H, 7.26; N, 4.38. Found: C, 66.08; H, 7.25; N, 4.43.

3-Acetyl-2-methoxycarbonyl-(benzyl 2,3-dideoxy-α-D-glucopyranosido)[2,3-d] oxazolidine (**33**).—To a solution of **17** (500 mg, 1.25 mmol) in MeOH (50 mL) was added 10% Pd–C (150 mg), and the suspension was hydrogenated at 40 psi at room temperature until TLC (10:1 $CHCl_3$–MeOH) indicated that all **17** had been consumed (~ 15 h). The catalyst was collected on Celite, the filter cake was washed with MeOH, and the combined filtrate and washings were concentrated to dryness. A solution of the residue in CH_2Cl_2 (50 mL) was washed with water (4 × 25 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated, to give amorphous **33** (409 mg, 98%), which showed a single spot in TLC and had mp 146°, $[\alpha]_D$ +220° (*c* 0.50, MeOH); ν_{max} 3333 (OH), 3065, 3034 (Ar), 1758 (CO, ester), 1670 cm^{-1} (CO, amide). ^{1}H-NMR data (80 MHz, Me_2SO-d_6, 20°): δ 7.35 (m, 5 H, Ph), 5.74 and 5.55 (2 d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 5.70 and 5.30 (2 s, H-2'), 5.6 and 4.65 (2 bs, OH), 4.65 (m, 2 H, PhCH_2), 3.76 and 3.65 (2 s, COOMe), 1.88 and 1.82 (2 s, Ac). Mass spectrum (CI): *m/z* 382 (20%) $[M + H]^+$.

Anal. Calcd for $C_{18}H_{23}NO_8 \cdot 0.5\ H_2O$: C, 55.38; H, 6.19; N, 3.59. Found: C, 55.32; H, 6.23; N, 3.66.

2-Methoxycarbonyl-3-octanoyl-(benzyl 2,3-dideoxy-α-D-glucopyranosido)[2,3-d] oxazolidine (**34**).—To a solution of **19** (1 g, 1.8 mmol) in 3:1 MeOH–1,4-dioxane (100 mL) was added 10% Pd–C (200 mg), and the suspension was hydrogenated at 40 psi for 16 h at room temperature. After work-up, as described for **33**, and recrystallisation from MeOH–water, **34** (810 mg, 96%) was obtained with mp 105–106°, $[\alpha]_D$ +232° (*c* 0.87, MeOH); ν_{max} 3500–3300 (OH), 1750 (CO, ester), 1650 cm^{-1} (CO, amide). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 7.35 (m, 5 H, Ph), 5.98 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 5.70 and 5.50 (s, H-2'), 4.64 (m, 2 H, PhCH_2), 3.71 (s, COOMe), 0.87 (t, Me). Mass spectrum (EI): *m/z* 465 (0.5%) $[M]^+$.

Anal. Calcd for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58; N, 3.01. Found: C, 62.05; H, 7.64; N, 2.81.

3-Acetyl-2-methoxycarbonyl-(2,3-dideoxy-D-glucopyrano)[2,3-d]oxazolidine (**3**).—(*a*) *From* **17**. To a solution of **17** (500 mg, 1.25 mmol) in MeOH (50 mL) was added 10% Pd–C (150 mg), and the suspension was hydrogenated at 100 psi for 96 h at

room temperature. After the usual work-up and column chromatography (50:1 and 15:1 $CHCl_3$–MeOH), **3** (198 mg, 64%) was obtained as a syrup.

(b) From **25**. Compound **25** was hydrogenated for 40 h as described above. After column chromatography, **3** (80%) was obtained as a syrup, $[\alpha]_D$ +8° (0.23, MeOH); ν_{max} 3420–3310 (OH), 1748 (CO, ester), 1642 cm^{-1} (CO, amide). Mass spectrum (CI): *m/z* 292 (70%) $[M + H]^+$.

Anal. Calcd for $C_{11}H_{17}NO_8 \cdot H_2O$: C, 42.72; H, 6.19; N, 4.53. Found: C, 43.07; H, 5.92; N, 4.82.

2-Methoxycarbonyl-3-octanoyl-(2,3-dideoxy-D-glucopyrano)[2,3-d]oxazolidine (**4**). —To a solution of **19** (1 g, 1.8 mmol) in 1:1 MeOH–1,4-dioxane (150 mL) was added 10% Pd–C (250 mg), and the suspension was hydrogenated at 100 psi for 96 h at room temperature. After work-up, as described for **33**, and column chromatography (15:1 $CHCl_3$–MeOH), **4** (460 mg, 68%) was obtained with mp 87–88°, $[\alpha]_D$ +11°(*c* 0.35, MeOH); ν_{max} 3456 (OH), 1745 (CO, ester), 1631 cm^{-1} (CO, amide). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 5.62 (bs, H-1), 5.20 (s, H-2′), 3.64 (s, COOMe), 0.82 (t, Me). Mass spectrum (EI): *m/z* 375 (5.3%) $[M]^+$.

Anal. Calcd for $C_{17}H_{29}NO_8$: C, 54.39; H, 7.79; N, 3.73. Found: C, 54.08; H, 8.16; N, 3.47.

3-Acetyl-2-methoxycarbonyl-(1,5-anhydro-2,3-dideoxy-D-glucitolo)[2,3-d]oxazolidine (**5**).—A solution of **20** (640 mg, 1.76 mmol) in MeOH (50 mL) was hydrogenated as described for **33**. After column chromatography, amorphous **5** (300 mg, 62%) was obtained with $[\alpha]_D$ +9° (*c* 0.6, MeOH); ν_{max} 3450 (OH), 1750 (CO, ester), 1660 cm^{-1} (CO, amide). Mass spectrum (CI): *m/z* 276 (100%) $[M + H]^+$; high-resolution EI for $C_{11}H_{17}NO_7$, 275.1012 (2.7 ppm).

Methyl 2-acetamido-3-O-benzyl-4,6-di-O-butyl-2-deoxy-α-D-glucopyranoside (**37**). —To a solution of methyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside [19] (**36**; 4 g, 12.3 mmol) in dry 1,4-dioxane (250 mL) was added NaH (0.72 g, 30 mmol), and the mixture was stirred for 15 min at 80°. Freshly distilled butyl bromide (5.5 mL, 51.2 mmol) was added, the mixture was stirred for 4 h at 80°, and water was added dropwise until the evolution of gas ceased. The suspension was filtered, concentrated to one-third volume, and poured into ice–water (400 mL), and the precipitate was collected and washed with water. Recrystallisation from EtOH gave **37** (4.9 g, 92%), mp 148–149°, $[\alpha]_D$ +107° (*c* 0.7, $CHCl_3$); ν_{max} 3302 (NH), 3065, 3034 (Ar), 1648 (CO, amide), 1555 cm^{-1} (NH).

Anal. Calcd for $C_{24}H_{39}NO_6$: C, 65.88; H, 8.98; N, 3.20. Found: C, 66.12; H, 8.71; N, 3.49.

Methyl 2-acetamido-4,6-di-O-butyl-2-deoxy-α-D-glucopyranoside (**38**).—To a solution of **37** (3 g, 6.8 mmol) in 1:1 MeOH–1,4-dioxane (100 mL) was added 10% Pd–C (200 mg). After hydrogenation at 40 psi for 7 h at room temperature, the mixture was filtered through Celite and concentrated. Column chromatography ($CHCl_3$) of the residue gave **38** (1.92 g, 81%), mp 128–129°, $[\alpha]_D$ +56° (*c* 1, $CHCl_3$); ν_{max} 3600–3150 (OH), 3289 (NH), 1643 (CO, amide), 1558 cm^{-1} (NH).

Anal. Calcd for $C_{17}H_{33}NO_6$: C, 58.77; H, 9.57; N, 4.03. Found: C, 59.06; H, 9.23; N, 4.12.

3-Acetyl-2-methoxycarbonyl-(methyl 4,6-di-O-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-d]oxazolidine (**6**).—To a solution of **38** (1.85 g, 5.33 mmol) in dry 1,4-dioxane (200 mL) was added NaH (1 g, 43 mmol), and the mixture was stirred for 15 min at 80°. A solution of dichloroacetic acid (1.32 mL, 16 mmol) in 1,4-dioxane (10 mL) was added dropwise. The mixture was stirred for 6 h at 80°, then cooled, and water was added until the evolution of gas ceased. The biphasic system was concentrated to one-third volume, then diluted with water (200 mL), and M HCl was added to pH 3.5. The aqueous suspension was extracted with $CHCl_3$ (4 × 50 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 (hexane and CH_2Cl_2) of the residue gave **6** (1.36 g, 60%), isolated as a syrup, $[\alpha]_D$ +149° (*c* 1.26, $CHCl_3$); ν_{max} 1762 (CO, ester), 1666 cm^{-1} (CO, amide). ^{1}H-NMR data (80 MHz, $CDCl_3$, 20°): δ 5.70 and 5.30 (2 d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 5.45 (s, H-2′), 3.81 and 3.77 (2 s, COOMe), 3.42 and 3.40 (2 s, OMe), 2.05 and 1.93 (2 s, Ac), 0.92 (t, 3 H, Me). Mass spectrum (EI): *m/z* 417 (1%) $[M]^+$.

Anal. Calcd for $C_{20}H_{35}NO_8$: C, 57.54; H, 8.45; N, 3.35. Found: C, 57.62; H, 8.31; N, 3.24.

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