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Synthesis of DL-2-amino-2-deoxyvalidamine and its three diastereoisomers*

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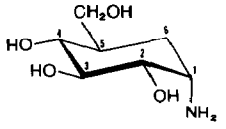
ABSTRACT

DL-2-Amino-2-deoxyvalidamine (**5**), 2-amino-5a-carba-2-deoxy-α-DL-glucopyranosylamine, and related 2-amino-5a-carba-2-deoxy-DL-hexopyranosylamines having the *β-gluco* (**6**), and α- (**7**) and *β-manno* configurations (**8**) have been synthesized from two 1,2-anhydro-3,4-di-*O*-benzyl-5-benzyloxymethyl-1,2,3,4-cyclohexanetetrols (**11** and **12**) by introduction of amino functions essentially *via* azidolysis and reduction. Compounds **5**, **6**, **7**, and **8** were assayed for inhibitory activity against three hydrolases: α- and β-D-glucosidases, and α-D-mannosidase. Compound **8** was shown to possess relatively higher activity against α-D-mannosidase, although it was very weak compared to nojirimycin.

INTRODUCTION

Validamine[2] (**1**), which may be termed 5a-carba-α-D-glucopyranosylamine*, and its synthetic 1- (**2**) (ref. 3) and 2-epimers[4] (**3**) show inhibitory activity against some



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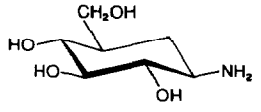

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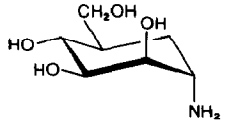

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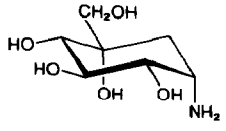

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All synthetic compounds described in this paper are racemic, but for convenience, only single enantiomers are depicted.

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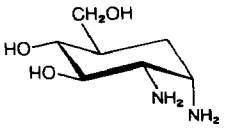
* This nomenclature for the so-called pseudo-sugars follows standard IUPAC practice for a carbocycle for modification of a heterocyclic compound that has an established trivial name. The prefix "carba" is used, with an appropriate locant, to generate a related name for an analog in which the hetero atom is replaced by carbon: for example, "pseudo-α-D-glucopyranose" and aristeromycin may be named 5a-carba-α-D-glucopyranose and 4'a-carba-adenosine, respectively. It is recognized that the formal cyclitol nomenclature is normally used, but the present terminology is useful for comparisons with the sugar analogs.

enzymes[5], such as insect trehalase. The structurally related, branched-chain aminocyclitol valiolamine[6] (**4**) possesses strong inhibitory activity against alpha-amylase, and hence, its chemical modification has been studied[7] extensively for clinical purposes.

Syntheses of 2-amino-5a-carba-2-deoxy-DL-hexopyranosylamines having the *α*-(**5**) and *β-gluco* (**6**), and *α*- (**7**) and *β-manno* configurations (**8**) have now been carried out in order to provide possible enzyme-inhibitors against hydrolases of oligo- and polysaccharides, especially those containing amino sugars. Furthermore, it may be of interest to introduce synthetically the 2-acetamido-5a-carba-2-deoxy-*β*-D-gluco- and manno-pyranose residues into lipid- or protein-linked oligosaccharides, replacing the corresponding true sugar residues by use of a reactive intermediate aziridine (**33**) or the protected amines derived from the diazides **20** or **35**.



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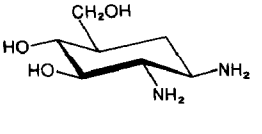

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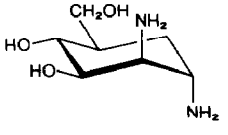

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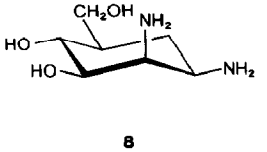

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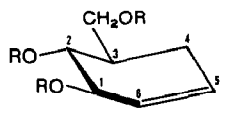
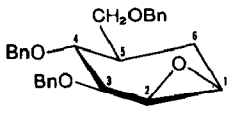
RESULTS AND DISCUSSION

Oxidation of DL-(1,3/2)-3-hydroxymethyl-5-cyclohexene-1,2-diol[8] (**9**) with *m*-chloroperoxybenzoic acid in dichloromethane at room temperature and successive benzylation of the products with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide gave the epoxides **11** (69%) and **12** (9.4%) in 7:1 ratio. Alternatively **9** was initially converted into the tribenzyl ether (**10**), which was similarly oxidized to give a 1:4 ratio of **11** (17%) and **12** (72%). The ^{1}H-n.m.r. spectra of **11** and **12** contained doublets of doublets (δ 3.83, J 1.9, 8 Hz) and (δ 3.78, J ~0, 8 Hz), respectively, attributable to H-3, suggesting that the epoxide group is oriented *cis* to the 2-OBn group in **11**. These results may be explained by the *cis*-directing effect[9] of the 1-OH group of **9** in epoxidation with peroxy acid.

Reaction of **11** with an excess of sodium azide in *N*,*N*-dimethylformamide at 100° gave preferential diaxial cleavage of the epoxide ring to afford 86% of a single azide (**13**), which was convertible into the mesylate **14** (93%) and the triflate **15** (92%). The structure of **15** was supported by its ^{1}H-n.m.r. spectrum, which contained a doublet of doublets (δ 5.01, J 2.5, 6.2 Hz) attributable to H-3. Similarly, **12** was subjected to azidolysis in aqueous 90% *N*,*N*-dimethylformamide at 100° to give two azides [**16**



9 R = H
10 R = Bn



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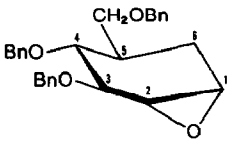

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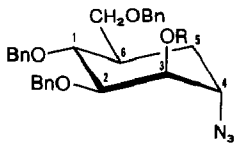
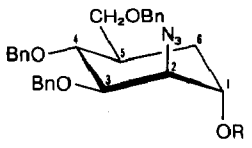
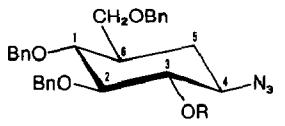


13 R = H
14 R = Ms
15 R = Tf



16 R = H
17 R = Ms

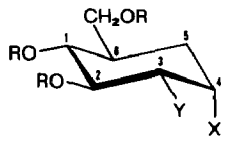


18 R = H
19 R = Ms

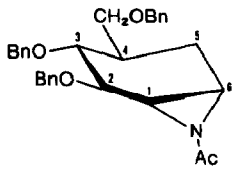
(49%) and **18** (48%)], which were characterized as the respective mesylates **17** (~ 100%) and **19** (88%), the structures of which were differentiated on the basis of their ^{1}H-n.m.r. spectra.

Although azidolysis of **14** did not give rise to any azido product, compound **15** smoothly reacted with azide anion by direct SN2 fashion to yield the diazide **20** (97%). Hydrogenolysis of **20** with Raney nickel[10] T-4 in ethanol containing acetic anhydride gave 44% of the di-*N*-acetyl derivative **21**. The use of triphenylphosphine as a reducing agent[11] improved the yield of this transformation, **21** being obtained in 67% yield after acetylation. *O*-Debenzylation of **21** under Hannesian's conditions [cyclohexene and $Pd(OH)_2/C$ in boiling ethanol] produced the diamine, which was conventionally acetylated to the penta-*N*,*O*-acetyl derivative (**24**) of **3** in 82% overall yield. The structure of **24** was fully established by its ^{1}H-n.m.r. spectrum, which contained a triplet (δ 5.03, J 9.5 Hz), a triplet (δ 5.10, J 9.5 Hz), and a doublet of doublets of doublets (δ 4.22, J 4, 8.8, 9.5 Hz), attributable to H-1,2, and 3, respectively. Attempted selective reduction of the azido groups of **20** by use of a limited amount of triphenylphosphine (1 molar equiv) gave no selectivity, and two mono amino compounds were obtained in almost equal proportion; they were characterized as the *N*-acetyl derivatives **22** (31%) and **23** (24%), the structures of which were deduced on the basis of ^{1}H-n.m.r. spectra, and finally established by formation of **22** (29% overall yield) from **15** through a nucleophilic displacement reaction with potassium phthalimide, followed by hydrazinolysis and acetylation.

Treatment of **14** with lithium aluminum hydride in tetrahydrofuran at 0° resulted in ring formation to give (after conventional acetylation) 78% of the *N*-acetylaziridine **25**, the structure of which was confirmed by i.r. (ν_{max} 1700 cm^{-1}, amide) and ^{1}H-n.m.r. spectral data. On similar azidolysis, **25** was readily converted into two azides **26** (51%) and **29** (31%), the structures of which were determined by the ^{1}H-n.m.r. spectral data. In



	R	X	Y
20	Bn	N_3	N_3
21	Bn	NHAc	NHAc
22	Bn	N_3	NHAc
23	Bn	NHAc	N_3
24	Ac	NHAc	NHAc



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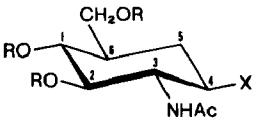
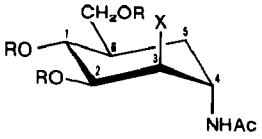
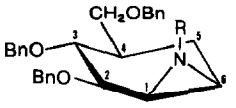


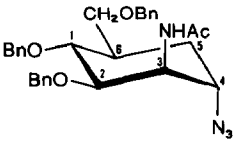
26 R = Bn, X = N_3
27 R = Bn, X = NHAc
28 R = Ac, X = NHAc



29 R = Bn, X = N_3
30 R = Bn, X = NHAc
31 R = Ac, X = NHAc



32 R = H
33 R = Ac



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the former spectrum, well-resolved signals for the 5-methylene protons established the configuration at C-4, and in the latter a broad doublet (δ 3.99, J 4.8 Hz) due to H-3 supported the axial orientation of the azido group.

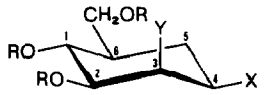
Compound **26** was hydrogenated with Raney nickel in ethyl acetate–ethanol containing acetic anhydride to give the di-*N*-acetyl derivative (**27**), similar hydrogenolysis of which with $Pd(OH)_2$-on-carbon followed by acetylation gave the penta-*N*,*O*-acetyl derivative **28** in quantitative yield. The structure of **28** was firmly confirmed by the ^{1}H-n.m.r. spectrum, which contained a triplet (δ 5.04, J 9.9 Hz), a triplet (δ 4.91, J 9.9 Hz), and a triplet of doublets (δ 4.05, J 1.5, 9.9, 9.9 Hz), due to H-2,3, and 4, respectively.

Likewise, compound **29** was transformed via the di-*N*-acetyl derivative **30** into the penta-*N*,*O*-acetyl derivative **31** (85%), whose ^{1}H-n.m.r. spectrum contained a complex signals for H-1,2 and H-3,4.

Metal hydride reduction of **17** readily gave the aziridine **32** (81%), which was acetylated to the *N*-acetyl derivative **33** ($\sim$ 100%). Compound **32** was rather unreactive toward nucleophiles; however, on similar treatment with azide ion, **33** afforded a sole azido compound **34** in quantitative yield. In contrast, similar reduction of **19** followed by acetylation gave a complex mixture of products instead of **33**. Compound **34** was also convertible into **30** (71%) and then into **31** (71%), identical to **31** obtained before, confirming the structure assigned.

Azidolysis of **19** proceeded smoothly through a SN2 reaction to give, quantitatively, a single diazide (**35**), which was transformed into the di-*N*-acetyl derivative **36** (78%) that was *O*-debenzylated, giving the penta-*N*,*O*-acetyl derivative **38** in quantitative yield. The ^{1}H-n.m.r. spectrum contained a triplet (δ 5.11, J 10.3 Hz) and a doublet of doublets (δ 5.01, J 4, 10.3 Hz) due to H-1,2, supporting the configuration assigned.

Selective reduction of the C-1 equatorial azido group of **35** was successfully effected by use of 1 molar equiv. of triphenylphosphine, and the amine formed was characterized as the *N*-acetyl derivative **37** (51%), the ^{1}H-n.m.r. spectrum of which was accord with the assigned structure.



	R	X	Y
35	Bn	N_3	N_3
36	Bn	NHAc	NHAc
37	Bn	NHAc	N_3
38	Ac	NHAc	NHAc

Compounds **24**, **28**, **31**, and **38** were hydrolyzed with M hydrochloric acid at reflux temperature and then treated with basic resin to give quantitatively the respective free bases **5**, **6**, **7**, and **8**, which were directly assayed against yeast α-D-glucosidase, almond β-D-glucosidase, and Jack bean α-D-mannosidase. Although they all showed only very weak inhibitory activity against these hydrolases (at a final concentration of 2 mg.mL^{-1}) as compared to a reference of nojirimycin[12] (0.1 mg.mL^{-1}), the results may be of some interest for elucidating structure–inhibitory activity relationships. Therefore, the activity against α-D-mannosidase were measured under a high final concentration (4 mg.mL^{-1}, data are listed in Table I). It is noteworthy that, against α-D-mannosidase, the β-gluco and β-manno isomers are more active than the corresponding α anomers.

TABLE I

Inhibitory activity (*I*%) of four 2-amino-5a-carba-2-deoxy-DL-hexopyranosylamines (**5**, **6**, **7**, and **8**)

Compound	α-D-*Glucosidase*[a]	α-D-*Glucosidase*[b]	β-D-*Mannosidase*[c]	
α-gluco **5**	7.5[d]	0[d]	0[d]	14.6[e]
β-gluco **6**	0	0	1.2	73
α-manno **7**	2.0	0	0.7	28.9
β-manno **8**	2.0	0	4.8	94.5
Nojirimycin	80[f]	93.4[f]	10[f]	

[a] Yeast α-D-glucosidase, 0.66mM *p*-nitrophenyl α-D-glucopyranoside, 100mM PBS, pH 6.8. [b] Almond β-D-glucosidase, 0.33mM *p*-nitrophenyl β-D-glucopyranoside, 100mM acetate buffer, pH 5.0. [c] Jack bean α-D-mannosidase, 20mM *p*-nitrophenyl α-D-mannopyranoside, 100mM acetate buffer, pH 4.5. [d] Inhibition (*I*%) determined at the final concentration of 2 mg.mL^{-1}. [e] Inhibition at the final concentration of 4 mg.mL^{-1}. [f] Inhibition at the final concentration of 0.1 mg.mL^{-1}.

EXPERIMENTAL

General methods. — Melting points were determined with a Mel-Temp capillary melting-point apparatus and are uncorrected. I.r. spectra were recorded with a Jasco IR-810 spectrophotometer (neat). ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Jeol JNM FX-90A (90 MHz) or Jeol GSX-270 FT (270 MHz) instruments. T.l.c. was performed on Silica Gel 60 GF (E. Merck) with detection by u.v. light or by charring with H_2SO_4. Column chromatography and preparative t.l.c. were conducted on Wakogel C-300 (300 mesh, Wako Co.) and Silica Gel 60 PF (E. Merck), respectively. Organic solutions were dried over anhydrous Na_2SO_4, and evaporated at $< 50°$ under diminished pressure.

DL-*(1,2,3,5/4)*- (**11**) *and* DL-*(1,2,4/3,5)-1,2-Anhydro-3,4-di*-O-*benzyl-5-benzyloxymethyl-1,2,3,4-cyclohexanetetrol* (**12**). — A. A solution of DL-(1,3/2)-1,2-dihydroxy-3-hydroxymethyl-5-cyclohexene[8] (**7**, 1.00 g, 6.94 mmol) and *m*-chloroperoxybenzoic acid (2.1 g, ~8.3 mmol) in 1,2-dichloroethane (20 mL) was stirred for 30 min at 50°. The mixture was diluted with PhMe and passed through a column of silica gel (40 g) and evaporated to give a mixture (1.2 g) of the epoxides. To a stirred solution of the crude epoxides in *N*,*N*-dimethylformamide (DMF, 10 mL) was added in turn at 0° a slurry of NaH (1.4 g, ~35 mmol) in DMF (15 mL) and, after 45 min, $PhCH_2Br$ (3.0 mL, 25 mmol). The mixture was stirred for 1 h at room temperature, treated with EtOH (5 mL), and then evaporated. The residue was taken up in EtOAc (60 mL), washed with water, dried, and evaporated. The residue was eluted from a column of silica gel (30 g) successively with hexane, PhMe, and EtOAc to give the tribenzyl ethers, which were again chromatographed on a silica gel column (40 g) with 1:30 butanone–PhMe to give **12** (280 mg, 9.4%) and then **11** (2.1 g, 70%) both as syrups; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): for **11**, δ 7.39–7.24 (m, 15 H, 3 Ph), 4.80 (s, 2 H, CH_2Ph), 4.84 and 4.50 (ABq, 2 H, J 10.8 Hz, CH_2Ph), 4.45 (s, 2 H, CH_2Ph), 3.83 (dd, 1 H, $J_{2,3}$ 1.9, $J_{3,4}$ 8 Hz, H-3), 3.64 (m, 1 H, H-4), 3.48 (d, 2 H, $J_{7,7}$ 11 Hz, H-7,7'), and 3.38–3.18 (m, 2 H, H-1,2); for **12**, δ 7.33–7.24 (m, 15 H, 2 Ph), 4.83 and 4.56 (ABq, 2 H, CH_2Ph), 4.75 (m, 2 H) and 4.45 (S, 2 H) (2CH_2Ph), 3.78 (dd, 1 H, $J_{2,3}$ ~0, $J_{3,4}$ 8 Hz, H-3), 3.73 (dd, 1 H, $J_{5,7}$ 4.1, $J_{7,7}$ 9.3 Hz, H-7), 3.43 (dd, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.38 (dd, 1 H, $J_{5,7'}$ 3 Hz, H-7'), 3.23 (m, 1 H, H-1), and 3.15 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-2).

Anal. Calc. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: for **11**, C, 78.05; H, 6.82; for **12**, C, 78.39; H, 6.88.

B. Compound **9** (3.0 g, 20 mmol) was treated with NaH (4.2 g, 100 mmol) in DMF (50 mL) and then with $PhCH_2Br$ (11 mL, 90 mmol) for 2 h at room temperature as just described to give after chromatography the tribenzyl ether **10** (9.4 g, ~100%), which was treated with *m*-chloroperoxybenzoic acid (6.2 g, ~24 mmol) in 1,2-dichloroethane in the presence of phosphate buffer solution (100 mL, pH 8) for 4 h at room temperature. The mixture was diluted with $CHCl_3$ (300 mL) and washed with aq. 20% $Na_2S_2O_3$ and water, dried, and evaporated. The residue was eluted from a column of silica gel (130 g) with 1:40 EtOAc–hexane to give **11** (1.5 g, 17%) and **12** (6.3 g, 72%) both as syrups.

DL-*(1,4/2,3,6)-4-Azido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2,3-cyclohexane-*

triol (**13**). — A mixture of **11** (511 mg, 1.19 mmol), NaN_3 (154 mg, 2.38 mmol), and aq. 95% DMF (3 mL) was stirred for 2 h at 100°, and then evaporated. The residue was digested with EtOAc (50 mL), and the solution was washed with water, dried, and evaporated. The residue was eluted from a column of silica gel (10 g) with 1:8 EtOAc–hexane to give **13** (483 mg, 86%) as a syrup; ν_{max} 2100 cm^{-1} (N_3); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.30 (m, 15 H, 3 Ph), 4.78 and 4.58, and 4.71 and 4.51 (2 ABq, each 2 H, J 11.5 Hz, 2 CH_2Ph), 4.45 (s, 2 H, CH_2Ph), 4.02–3.37 (m, 6 H, H-1,2,3,4,5,7,7'), 2.53 (d, 1 H, J 2.8 Hz, OH).

Anal. Calc. for $C_{28}H_{31}N_3O_4$: C, 71.02; H, 6.60; N, 8.87. Found: C, 71.42; H, 6.55; N, 8.68.

Compound **13** (281 mg, 0.59 mmol) was treated with MsCl (140 μL, 1.8 mmol) in DMF (4 mL) overnight at room temperature. The mixture was diluted with MeOH (2 mL) and toluene evaporated from it. The residue was digested with EtOAc (50 mL), and the solution was washed with water, dried, and evaporated. The residue was eluted from a column of silica gel (10 g) with 1:4 EtOAc–hexane to give the 3-methanesulfonate (**14**) (304 mg, 93%) as a syrup; ν_{max} 2100 (N_3) and 1180 cm^{-1} (mesyl); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.85 (m, 1 H, H-3), 4.73 and 4.48 (ABq, 2 H, J 11 Hz, CH_2Ph), 4.45 and 4.68 (2 s, each 2 H, 2 CH_2Ph), 4.20–3.35 (m, 5 H, H-1,2,4,7,7'), 3.02 (s, 3 H, mesyl), and 2.25–1.70 (m, 3 H, H-5,5',6).

Anal. Calc. for $C_{29}H_{33}N_3O_6S$: C, 63.14; H, 6.03; N, 7.62. Found: C, 63.26; H, 6.09; N, 7.52.

Compound **13** (217 mg, 0.46 mmol) was treated with trifluoromethanesulfonic anhydride (155 μL, 0.91 mmol) in 1,2-dichloroethane (8 mL) containing pyridine (400 μL, 4.6 mmol) for 10 min at −15° under argon. The mixture was poured into saturated aq. $NaHCO_3$ (50 mL) and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was eluted from a column of silica gel (2 g) with 1:4 EtOAc–hexane containing Et_3N (10%) to give the 3-trifluoromethanesulfonate **15** (254 mg, 92%) as a syrup; ν_{max} 3020w, 2900w, 2850w, 2100s, 1440w, 1400s, 1235m, 1200s, 1135m, 1100m, 930m, 900m, 720m, 685m, and 600m cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 5.01 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 6.2 Hz, H-3), 4.71 and 4.53, and 4.66 and 4.45 (2 ABq, each 2 H, J 11.8 Hz, 2 CH_2Ph) and 4.43 (s, 2 H, CH_2Ph), and 4.10–3.40 (m, 5 H, H-1,2,4,7,7'). Compound **15** was not stable enough for elemental analysis.

DL-*(1,4/2,3,5)-2-Azido-3,4-di*-O-*benzyl-5-benzyloxymethyl-1,3,4-cyclohexanetriol* (**16**) *and* DL-*(1,3/2,5,6)-4-azido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2,3-cyclohexanetriol* (**18**). — A mixture of **12** (766 mg, 1.8 mmol), NaN_3 (579 mg, 9.0 mmol), and aq. 90% DMF (10 mL) was stirred for 24 h at 100°, and then evaporated. The residue was digested with EtOAc (70 mL) and the solution was washed with water, dried, and evaporated. The residue was eluted from a column of silica gel (20 g) with 1:12 butanone–PhMe to give **16** (370 mg, 44%) and **18** (403 mg, 48%) both as syrups; ν_{max} for **16**, 2100 cm^{-1} (N_3); for **18**, 2100 cm^{-1} (N_3); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): for **16**, δ 7.3 (m, 15 H, 3 Ph), 4.77 and 4.49 (ABq, 2 H, J 11.3 Hz, CH_2Ph), 4.67 and 4.43 (2 s, each 2 H, 2 CH_2Ph), 4.05–3.45 (m, 6 H, H-1,2,3,4,7,7'), and 2.37–1.50 (m, 4 H, H-5,6,6', OH); for **18**, δ 7.3 (m, 15 H, 3 Ph), 5.05–4.40 (m, 6 H, 3 CH_2Ph), 3.70–3.20 (m, 6 H, H-1,2,3,4,7,7'), 2.53 (bs, 1 H, OH), and 2.15–1.20 (m, 3 H, H-5,5',6).

Anal. Calc. for $C_{28}H_{31}N_3O_4$: C, 71.02; H, 6.60; N, 8.87. Found: for **16**, C, 70.94; H, 6.60; N, 8.75; for **18**, C, 71.25; H, 6.66; N, 8.86.

Compound **16** (880 mg, 1.86 mmol) was treated with MsCl (450 μL, 5.6 mmol) in pyridine (13 mL) for 1 h at room temperature. After conventional workup, the product was purified on a silica gel column (20 g) with 1:5 EtOAc–hexane to give the 1-methanesulfonate (**17**) (1.02 g, ~100%) as a syrup; ν_{max} 2100 (N_3) and 1180 cm^{-1} (mesyl); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.85 (m, 1 H, H-1), 4.70 (m, 2 H, CH_2Ph), 4.51 and 4.80 (ABq, 2 H, J 11 Hz, CH_2Ph), 4.44 (s, 2 H, CH_2Ph), 4.08 (t, 1 H, $J_{1,2} = J_{2,3} = 3.7$ Hz, H-2), 3.91 (dd, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 3.78 (t, 1 H, $J_{4,5}$ 8.4 Hz, H-4), 3.60 (dd, 1 H, $J_{5,7}$ 4.8, $J_{7,7}$ 9.2 Hz, H-7), 3.46 (dd, 1 H, $J_{5,7'}$ 2.9 Hz, H-7'), 2.05 (m, 1 H, H-5), 2.00 (dd, 1 H, $J_{1,6e}$ 2.9, $J_{6,6}$ 10.6 Hz, H-6*e*), and 1.92 (dd, 1 H, $J_{1,6a}$ 4.4 Hz, H-6*a*).

Anal. Calc. for $C_{29}H_{33}N_3O_6S$: C, 63.14; H, 6.03; N, 7.62. Found: C, 63.00; H, 6.01; N, 7.60.

Compound **18** (344 mg, 0.73 mmol) was similarly converted into the 3-methanesulfonate (**19**) (351 mg, 88%) as needles, m.p. 108–109° (from EtOH); ν_{max} 2100 (N_3) and 1180 cm^{-1} (mesyl); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 7.4–7.1 (m, 15 H, 3 Ph), 4.90 and 4.84 (ABq, 2 H, J 10.6 Hz, CH_2Ph), 4.82 and 4.49 (ABq, 2 H, J 11 Hz, CH_2Ph), 4.45 (t, 1 H, $J_{1,2} = J_{2,3} = 9.9$ Hz, H-3), 4.43 (s, 2 H, CH_2Ph), 3.61–3.48 (m, 5 H, H-1,2,4,7, and 7'), 3.04 (s, 3 H, mesyl), 2.17 (ddd, 1 H, J 3.3, J 4.8, $J_{5,5}$ 13 Hz, H-5*e*), 1.78 (m, 1 H, H-6), and 1.62 (q, 1 H, $J_{4,5a} = J_{5a,6} = 13$ Hz, H-5*a*).

Anal. Found: C, 63.14; H, 5.94; N, 7.52.

DL-*(1,3,4/2,6)-3,4-Diazido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**20**). — A mixture of **15** (200 mg, 0.33 mmol), NaN_3 (65 mg, 1.0 mmol), and DMF (3 mL) was stirred for 1 h at room temperature. The mixture was processed conventionally and the product was eluted from a silica gel column with 1:15 EtOAc–hexane to give **20** (160 mg, 97%) as a syrup; ν_{max} 2100 cm^{-1} (N_3); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.87 (s, 2 H, CH_2Ph), 4.85 and 4.51 (ABq, 2 H, J 11 Hz, CH_2Ph), and 4.42 (s, 2 H, CH_2Ph).

Anal. Calc. for $C_{28}H_{30}N_6O_3$: C, 67.45; H, 6.07; N, 16.86. Found: C, 67.71; H, 6.21; N, 16.44.

DL-*(1,3,4/2,6)-3,4-Diacetamido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**21**). — To a solution of **20** (124 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was added Ph_3P (196 mg, 0.75 mmol) and water (2.5 mL), and the mixture was stirred overnight at room temperature and then evaporated. The residue was eluted from a column of silica gel (10 g) with 1:5 EtOH–PhMe and EtOH to give the crude amine, which was acetylated with Ac_2O and pyridine. The product was chromatographed on silica gel with 1:10 EtOH–PhMe to give **21** (88 mg, 67%) as prisms, m.p. 65–65.5° (from $CHCl_3$–hexane); ν_{max} 1650 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 7.00 and 6.59 (2 m, each 1 H, 2 NH), 4.64 and 4.46 (ABq, 2 H, CH_2Ph), 4.57 and 4.47 (2 s, each 2 H, 2 CH_2Ph), 4.40–4.10 (m, 2 H, H-3,4), 3.95–3.55 (m, 4 H, H-1,2,7,7'), 1.91, and 1.82 (2 s, each 3 H, 2 NAc).

Anal. Calc. for $C_{32}H_{38}N_2O_5$ 0.5H_2O: C, 71.22; H, 7.28; N, 5.19. Found: C, 71.42; H, 7.21; N, 5.18.

Selective reduction of **20** *with triphenylphosphine. Preparation of* DL-*(1,3,4/2,6)-3-acetamido-4-azido-* (**22**) *and -4-acetamido-3-azido-1,2-*O*-benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**23**). — A mixture of **20** (100 mg, 0.20 mmol), Ph_3P (53 mg, 0.20 mmol), CH_2Cl_2 (2.5 mL), and water (2 mL) was stirred at room temperature, and then evaporated. The residue was acetylated conventionally and the products were fractionated by preparative t.l.c. with 3:5 butanone–PhMe to give **22** (32 mg, 31%), m.p. 120–122°, and **23** (25 mg, 24%); ν_{max} for **22**, 2100 (N_3), 1640, and 1540 cm^{-1} (amide); for **23**, 2100 (N_3), 1645, and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): for **22**, δ 7.45–7.20 (m, 15 H, 3 Ph), 5.20 (d, 1 H, $J_{3,NH}$ 7 Hz, NH), 4.87 and 4.59 (ABq, 2 H, J 12 Hz), 4.84 and 4.54 (ABq, 2 H, J 11 Hz), and 4.45 (s, 2 H) (3 CH_2Ph), 4.2–3.35 (m, 6 H, H-1,2,3,4,7,7'), 2.25–1.80 (m, 3 H, H-5,5',6), 1.73 (s, 3 H, NAc); data (270 MHz, $CDCl_3$): for **23**, δ 7.34–7.26 (m, 15 H, 3 Ph), 5.43 (d, 1 H, $J_{4,NH}$ 7 Hz, NH), 4.85 (s, 2 H), 4.82 and 4.55 (ABq, 2 H, J 10.6 Hz), and 4.43 (s, 2 H) (3 CH_2Ph), 4.39 (dq, 1 H, $J_{3,4} = J_{4,5a} = J_{4,5e}$ = 3.7 Hz, H-4), 3.69 (dd, 1 H, $J_{6,7}$ 4, $J_{7,7}$ 8.8 Hz, H-7), 3.61 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-3), 3.58 (t, 1 H, $J_{1,2} = J_{1,6}$ = 9.2 Hz, H-1), 3.50 (t, 1 H, H-2), 3.41 (dd, 1 H, $J_{6,7'}$ 2.6 Hz, H-7'), 2.09 (dt, 1 H, $J_{4,5a} = J_{4,5e}$ = 3.7 Hz, $J_{5,5}$ 14.3 Hz, H-5*e*), 2.01 (s, 3 H, NAc), 1.82 (m, 1 H, H-6), and 1.65 (m, 1 H, H-5*a*).

Anal. Calc. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89. Found: for **22**, C, 69.67; H, 6.66; N, 10.53; for **23**, C, 69.89; H, 6.85; N, 10.68.

Preparation of **22** *from* **15**. — A mixture of **15** (271 mg, 0.45 mmol), potassium phthalimide (250 mg, 1.3 mmol), and DMF (3 mL) was stirred overnight at 50°, and then evaporated. The residue was dissolved in EtOAc and the solution was thoroughly washed with water, dried, and evaporated. The residue was eluted from a column of silica gel with 1:20 EtOAc–hexane to give the phthalimide (105 mg, 39%) as a syrup: R_F 0.85 (1:15 butanone–toluene); ν_{max} 2100, 1775, 1715, 1370, 1100, 720, and 700 cm^{-1}. This compound was used without purification in the following step. A 57 mg-portion of the phthalimide was treated with a mixture of hydrazine hydrate (1 mL) and MeOH (3 mL) for 80 min at 70°. The mixture was evaporated and the residue was acetylated conventionally to give a single product (R_F 0.35, 1:5 butanone–PhMe), which was purified by a preparative t.l.c. with 1:8 butanone–PhMe to give **22** (37 mg, 75%), identical to the compound derived from **20** in all respects.

DL-*(1,3,4/2,6)-3,4-Diacetamido-6-acetoxymethyl-1,2-di-*O*-acetyl-1,2-cyclohexanediol* (**24**). — To a solution of **21** (157 mg, 0.29 mmol) in EtOH (2 mL) was added cyclohexene (915 μL, 8.7 mmol) and 20% $Pd(OH)_2$/C (20 mg), and the mixture was refluxed overnight. The mixture was filtered through Celite and the filtrate evaporated. The residue was acetylated conventionally and the product was purified on a silica gel column with 1:5 EtOH–PhMe to give **24** (110 mg, 97%), as a syrup that crystallized from EtOAc–hexane, m.p. 216.5–217°; ν_{max} 1750 (ester), 1650, and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 6.43 (bs, 1 H, 4-NH), 6.27 (bd, 1 H, $J_{3,NH}$ 8.8 Hz, 3-NH), 5.10 (t, 1 H, $J_{1,2} = J_{2,3}$ = 9.5 Hz, H-2), 5.03 (t, 1 H, $J_{1,6}$ 9.5 Hz, H-1), 4.54 (m, 1 H, H-4), 4.22 (ddd, 1 H, $J_{3,4}$ 4 Hz, H-3), 4.12 (dd, 1 H, $J_{6,7}$ 4.8, $J_{7,7}$ 11.4 Hz, H-7), 3.92 (dd, 1 H, $J_{6,7'}$ 3.7 Hz, H-7'), 2.06, 2.03, and 1.94 (3 s, 6, 6, and 3 H, 2 NAc and 3 OAc).

Anal. Calc. for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25. Found: C, 52.44; H, 6.58; N, 7.10.

(*1*SR, *2*RS, *3*RS, *4*RS, *6*SR)-*7-Acetyl-2,3-dibenzyloxy-4-benzyloxymethyl-7-azabicyclo[4.1.0]heptane* (**25**). — To a solution of **14** (70 mg, 0.13 mmol) in tetrahydrofuran (1.5 mL) was added $LiAlH_4$ (25 mg. 0.64 mmol) at 0°, and the mixture was stirred for 45 min at 0°. The excess of reagent was decomposed by addition of MeOH (1 mL) and aq. 15% NaOH (1 mL), and the mixture was filtered through Celite. The filtrate was evaporated and the residue was acetylated conventionally. The product was purified on a column of silica gel (1.7 g) with 1:30 butanone–PhMe to give **25** (42 mg, 78%) as a syrup; ν_{max} 3040w, 2960w, 2910w, 1700s, 1500w, 1460m, 1420m, 1360m, 1270m, 1200m, 1100s, 1050m, 1020m, 740s, and 700s cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.83 and 4.52 (ABq, 2 H, J 11.2 Hz, CH_2Ph), 4.78 and 4.43 (2 s, each 2 H, 2 CH_2Ph), 3.78 (d, 1 H, $J_{2,3}$ 7.8 Hz, H-2), 3.68 (dd, 1 H, $J_{4,8}$ 3.5 $J_{8,8}$ 8.8 Hz, H-8), 3.42 (dd, 1 H, $J_{3,4}$ 10.8 Hz, H-3), 3.42 (dd, 1 H, $J_{4,8'}$ 2.2 Hz, H-8′), 2.74 (m, 2 H, H-3,6), 2.02 (s, 3 H, NAc), and 2.35–1.55 (m, 3 H, H-5,5′,6).

Anal. Calc. for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.67; H, 7.05; N, 2.88.

DL-*(1,3/2,4,6)-3-Acetamido-4-azido-* (**26**) *and* DL-*(1,4/2,3,6)-4-acetamido-3-azido-1,2-di-*O*-benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**29**). — A mixture of **25** (109 mg, 0.23 mmol), NaN_3 (75 mg, 1.2 mmol), and DMF (2 mL) was stirred for 4 h at 100°. The mixture was processed conventionally. The products were eluted from a column of silica gel (5 g) with 1:10 butanone–PhMe to give **26** (61 mg, 51%) and **29** (37 mg, 31%) both as syrups; ν_{max} for **26**, 2100 (N_3), 1650, and 1550 cm^{-1} (amide); for **29**, 2100 (N_3), 1650, and 1545 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): for **26**, δ 7.3 (m, 15 H, 3 Ph), 5.35 (bd, 1 H, $J_{3,NH}$ 8.1 Hz, NH), 4.87, 4.83, 4.62, and 4.53 (2 ABq, each 2 H, J 11 Hz, 2 CH_2Ph), 4.45 (s, 2 H, CH_2Ph), 3.74–3.45 (m, 6 H, H-1,2,3,4,7,7′), 2.08 (dt, 1 H, $J_{4,5e} = J_{5e,6} = 3.8$, $J_{5,5}$ 13 Hz, H-5*e*), 1.86 (s, 3 H, NAc), 1.52 (q, 1 H, $J_{4,5a} = J_{5a,6} = 13$ Hz, H-5*a*); for **29**, δ 7.3 (m, 15 H, 3 Ph), 5.36 (bd, 1 H, $J_{4,NH}$ 7 Hz, NH), 4.77 and 4.49 (ABq, 2 H, J 11.5 Hz, CH_2Ph), 4.77 and 4.49 (ABq, 2 H, J 11 Hz, CH_2Ph), 4.44 (s, 2 H, CH_2Ph), 4.16 (m, 1 H, H-4), 3.99 (bd, 1 H, J 4.8 Hz, H-3), 3.72 (m, 2 H, H-1,2), 3.61 (dd, 1 H, $J_{6,7}$ 3.7, $J_{7,7}$ 8.8 Hz, H-7), 3.48 (dd, 1 H, $J_{6,7'}$ 6.2 Hz, H-7′), 1.93 (s, 3 H, NAc), 2.02–1.85 and 1.67 (2 m, 3 H, H-5,5′,6).

Anal. Calc. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89. Found: for **26**, C, 69.56; H, 6.33; N, 10.57; for **29**, C, 69.73; H, 6.60; N, 10.65.

DL-*(1,3/2,4,6)-3,4-Diacetamido-1,2-di-*O*-benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**27**). — A solution of **26** (42 mg, 0.81 mmol) in EtOAc (2 mL), EtOH (1 mL), and Ac_2O (0.5 mL) was hydrogenated in the presence of Raney nickel T-4 under hydrogen at atmospheric pressure overnight. The solution was filtered and evaporated. The residue was passed through a short column of silica gel with butanone–PhMe then with EtOH to give **23** (42 mg, 99%) as prisms, m.p. 219.5–221° (from EtOH–hexane): ν_{max} 1640 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (90 MHz, $CDCL_3$): δ 7.3 (m, 15 H, 3 Ph), 6.44 (bd, J 5 Hz, NH), 5.55 (bd, J 5 Hz, NH), 4.95–4.35 (m, 6 H, 3 CH_2Ph), 3.95–3.20 (m, 6 H, H-1,2,3,4,7,7′), 1.88 and 1.76 (2 s, each 3 H, 2 NHAc).

Anal. Calc. for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.59; H, 7.12; N, 5.30.

DL-*(1,3/2,4,6)-3,4-Diacetamido-6-acetoxymethyl-1,2-di*-O-*acetyl-1,2-cyclohexanediol* (**28**). — Compound **27** (29 mg, 0.055 mmol) was reduced as in the preparation of **22** to give **28** (21 mg, ~100%) as prisms, m.p. 236.5–237° (from EtOH): ν_{max} 1750 (ester), 1650, and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 6.40 (bd, 1 H, J 7.7 Hz, NH), 6.13 (m, 1 H, NH), 5.04 (t, 1 H, $J_{1,2} = J_{1,6} = 9.9$ Hz, H-1), 4.91 (t, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 4.07 (dd, $J_{6,7}$ 5.1, $J_{7,7}$ 11.4 Hz, H-7), 4.05 (td, $J_{3,4}$ 9.9, $J_{3,5}$ 1.5 Hz, H-3), 3.94 (dd, 1 H, $J_{6,7'}$ 3.3 Hz, H-7'), 3.92 (m, 1 H, H-4), 2.20 (dt, 1 H, $J_{5,NH}$ 13, $J_{4,5e} = J_{5e,6} = 3.7$ Hz, H-5eq), 2.06, 2.04, 1.95, and 1.94 (4 s, 3, 6, 3, and 3 H, 2 NAc and 3 OAc), and 1.41 (q, 1 H, $J_{4,5a} = J_{5a,6} = 13$ Hz, H-5*a*).

Anal. Calc. for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25. Found: C, 52.65; H, 6.40; N, 7.05.

DL-*(1,4/2,3,6)-3,4-Diacetamido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**30**). — Compound **29** (37 mg, 0.072 mmol) was hydrogenated in the presence of Ac_2O as in the preparation of **26** to give **30** (32 mg, 85%) as prisms, m.p. 133–134° (from $CHCl_3$–hexane): ν_{max} 1650 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 6.15–5.75 (m, 2 H, 2 NH), 4.70–4.35 (m, 6 H, 3 CH_2Ph), 4.33–3.45 (m, 6 H, H-1,2,3,4,7,7'), 1.89 and 1.75 (2 s, each 3 H, 2 NAc).

Anal. Calc. for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.31; H, 7.10; N, 5.12.

DL-*(1,4/2,3,6)-3,4-Diacetamido-6-acetoxymethyl-1,2-di*-O-*acetyl-1,2-cyclohexanediol* (**31**). — Compound **30** (23 mg, 0.044 mmol) was reduced as in the preparation of **24** to give **27** (14 mg, 84%) as prisms, m.p. 231–232° (from EtOH): ν_{max} 1740 (ester), 1650, and 1545 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 6.06 (bd, 1 H, J 7.3 Hz) and 5.93 (bd, 1 H, J 8.1 Hz) (2 NH), 5.13–5.06 (m, 2 H, H-1,2), 4.33–4.13 (m, 2 H, H-3,4), 4.27 (dd, 1 H, $J_{6,7}$ 8.8, $J_{7,7}$ 11 Hz, H-7), 4.19 (dd, 1 H, $J_{6,7'}$ 7.7 Hz, H-7'), 2.15, 2.10, 2.07, 1.965 and 1.955 (5 s, each 3 H, 2 NAc and 3 OAc).

Anal. Calc. for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25. Found: C, 52.77; H, 6.63; N, 7.08.

(*1*RS, *2*RS, *3*RS, *4*RS, *6*RS)-*2,3-dibenzyloxy-4-benzyloxymethyl-7-azabicyclo[4.1.0]heptane* (**32**). — Compound **17** (1.02 g, 1.85 mmol) was treated with $LiAlH_4$ in tetrahydrofuran as in the preparation of **25** to give **32** (0.65 g, 81%), as a syrup; ν_{max} 2920w, 2850w, 1500w, 1455w, 1100s, 740s and 700s cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 5.0–4.3 (m, 6 H, 3 CH_2Ph), and 4.0–3.2 (m, 4 H, H-1,2,7,7').

Anal. Calc. for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.57; H, 7.08; N, 3.25.

Compound **32** (0.44 g, 1.0 mmol) was acetylated conventionally to give the *N*-acetyl derivative (**33**) (0.49 g, ~100%) as a syrup, ν_{max} 2930w, 2860w, 1730w, 1700s, 1500w, 1460w, 1100s, 740s, and 700s cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.85 and 4.50 (ABq, 2 H, J 12 Hz, CH_2Ph), 4.82 and 4.41 (2 s, each 2 H, 2 CH_2Ph), 3.85–3.35 (m, 4 H, H-1,2,7,7'), 3.00–2.65 (m, 2 H, H-3,4), 2.15 (s, 3 H, NAc), and 2.2–1.1 (m, 3 H, H-5,5',6).

Anal. Calc. for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.09; H, 6.76; N, 2.96.

DL-*(1,4/2,3,6)-3-Acetamido-4-azido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**34**). — A mixture of **33** (9.4 mg, 0.02 mmol), NaN_3 (15 mg, 0.23 mmol), and DMF (1 mL) was stirred for 1.5 h at 100°. The mixture was processed conventionally and the product was purified on a silica gel column to give **34** (10.2 mg, 99%) as a syrup; ν_{max} 2100 (N_3), 1650, and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 5.64 (bd, $J_{3,NH}$ 7.7 Hz, NH), 4.68 and 4.52, and 4.51 and 4.35 (2 ABq, each 2 H, J 11.4 Hz, 2 CH_2Ph), 4.48 and 4.42 (ABq, 2 H, J 13.2 Hz, CH_2Ph), 4.35 (m, 1 H, H-3), 3.78 (m, 2 H, H-2,4), 3.69 (t, 1 H, $J_{1,2} = J_{1,6} = 6.2$ Hz, H-1), 3.64 (dd, 1 H, $J_{6,7}$ 6.2, $J_{7,7}$ 9.2 Hz, H-7), 3.49 (dd, 1 H, $J_{6,7'}$ 5.5, Hz, H-7'), 2.24 (m, 1 H, H-6), 1.93 (s, 3 H, NAc), and 2.00–1.85 (m, 2 H, H-5,5').

Anal. Calc. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89. Found: C, 70.12; H, 6.66; N, 10.47.

Compound **30** (18 mg, 0.035 mmol) was hydrogenated in the presence of Ac_2O as in the preparation of **27** to give **30** (13 mg, 71%), identical to the compound derived from **29** in all respects.

DL-*(1/2,3,4,6)-3,4-Diazido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**35**). — A mixture of **19** (210 mg, 0.38 mmol), NaN_3 (62 mg, 0.95 mmol), and DMF (4 mL) was stirred overnight at 100°. The mixture was processed conventionally and the product was purified on a column of silica gel with EtOAc–hexane to give **35** (170 mg, 90%) as a syrup; ν_{max} 2150 and 2100 cm^{-1} (N_3); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 4.85 and 4.45 (ABq, 2 H, J 10.5 Hz, CH_2Ph), 4.70 and 4.45 (2 s, each 2 H, 2 CH_2Ph), 4.00 (t, 1 H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3), 3.71 (t, 1 H, $J_{1,2} = J_{1,6} = 9$ Hz, H-1), 3.48 (dd, 1 H, H-2), and 3.26 (m, 1 H, H-4).

Anal. Calc. for $C_{28}H_{30}N_6O_3$: C, 67.45; H, 6.07; N, 16.86. Found: C, 67.22; H, 5.97; N, 16.67.

DL-*(1/2,3,4,6)-3,4-Diacetamido-1,2-di*-O-*benzyl-6-benzyloxymethyl-1,2-cyclohexanediol* (**36**). — Compound **35** (30 mg, 0.06 mmol) was hydrogenated and acetylated as in the preparation of **23** to give **36** hydrate (25 mg, 78%) as prisms; m.p. 50° (from $CHCl_3$–hexane); ν_{max} 1650 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 15 H, 3 Ph), 5.80 (bd, 1 H, J 6 Hz, NH), 2.13 and 1.94 (2 s, each 3 H, 2 NAc).

Anal. Calc. for $C_{32}H_{38}N_2O_5 \cdot H_2O$: C, 70.05; H, 7.34; N, 5.11. Found: C, 70.67; H, 7.08; N, 5.03.

Selective reduction of **35** *with triphenylphosphine.* — A mixture of **35** (256 mg, 0.53 mmol), Ph_3P (135 mg, 0.53 mmol), CH_2Cl_2 (2 mL), and water (2 mL) was stirred overnight at room temperature. The mixture was processed as in the preparation of **22** and **23** to give after acetylation DL-(1/2,3,4,6)-4-acetamido-3-azido-1,2-di-*O*-benzyl-6-benzyloxymethyl-1,2-cyclohexanediol (**37**, 134 mg, 51%), m.p. 132–133° (from acetone–hexane); ν_{max} 2100 (N_3), 1625, and 1555 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 7.35–7.20 (m, 15 H, 3 Ph), 5.68 (d, 1 H, $J_{4,NH}$ 8.8 Hz, NH), 4.87 and 4.49 (ABq, 2 H, J 10.8 Hz), 4.75 and 4.69 (ABq, 2 H, J 11.4 Hz), and 4.44 (s, 2 H) (3 CH_2Ph), 4.13 (t, 1 H, $J_{2,3} = J_{3,4} = 2.9$ Hz, H-3), 4.00 (m, 1 H, H-4), 3.74 (t, 1 H, $J_{1,2} = J_{1,6} = 9.3$ Hz, H-1), 3.66 (dd, 1 H, H-2), 3.58 (dd, 1 H, $J_{6,7}$ 4.4, $J_{7,7}$ 8.8 Hz, H-7), 3.44 (dd, 1 H, $J_{6,7'}$ 4.4 Hz, H-7'), 1.99 (s, 3 H, NAc), and 1.77–1.65 (m, 3 H, H-5,5',6).

Anal. Calc. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89. Found: C, 70.27; H, 6.52; N, 10.93.

DL-*(1/2,3,4,6)-3,4-Diacetamido-6-acetoxymethyl-1,2-di-*O*-acetyl-1,2-cyclohexanediol* (**38**). — Compound **36** (30 mg, 0.056 mmol) was reduced and successively acetylated as in the preparation of **24** to give, after chromatography on silica gel with 3:1 $CHCl_3$–MeOH, **38** (25 mg, ~100%) as prisms, m.p. 194–195° (from EtOAc–hexane); ν_{max} 1750 (ester), 1650, and 1550 cm^{-1} (amide); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 6.99 (bd, 1 H, $J_{4,NH}$ 5.9 Hz, 4-NH), 6.39 (bs, 1 H, 3-NH), 5.11 (t, 1 H, $J_{1,2} = J_{1,6}$ 10.3 Hz, H-1), 5.01 (dd, 1 H, $J_{2,3}$ 4 Hz, H-2), 4.64 (m, 1 H, H-3), 4.04 (dd, 1 H, $J_{6,7}$ 6.3, $J_{7,7}$ 11.4 Hz, H-7), 4.07–4.00 (m, 1 H, H-4), 3.93 (dd, 1 H, $J_{6,7'}$ 4 Hz, H-7'), 2.14, 2.06, 2.00, and 1.95 (4 s, 3, 6, 3, and 3 H, 2 NAc and 3 OAc), 2.3–1.8 (m, 2 H, H-5*e*,6), and 1.46 (q, 1 H, $J_{4,5a} = J_{5,5} = J_{5a,6}$ = 12.5 Hz, H-5*a*).

Anal. Calc. for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25. Found: C, 53.09; H, 6.64; N, 6.95.

DL-*(1,3,4/2,6)-3,4-Diamino-6-hydroxymethyl-1,2-cyclohexanediol* (**5**). — Compound **23** (28 mg, 0.07 mmol) was treated with M HCl (1 mL) for 6 h at 115°. The mixture was evaporated, and the residue was dissolved in water (2 mL) and transferred to a short column of Amberlite CG-50 (NH_4^+) resin. The column was eluted in turn with water (5 mL) and aq. NH_4OH (gradient, 0.5–1.5%, 15 mL). The eluate was evaporated and the residue was passed through a short column of Amberlite IRA 400 (OH^-) resin with MeOH and the effluent evaporated to give **5** (11 mg, 89%) as an amorphous solid, the i.r. spectrum of which supported the structure.

Similarly, DL-(1,3/2,4,6)- (**6**), DL-(1,4/2,3,6)- (**7**), and DL-(1/2,3,4,6)-3,4-diamino-6-hydroxymethyl-1,2-cyclohexanediol (**8**) were prepared from the corresponding penta-*N*,*O*-acetyl derivatives **28**, **31**, and **38**.

The free diamines thus obtained were directly subjected to biological assay.

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