Inhibitors of *endo*-α-mannosidase. Part II.[1] 1-Deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin and congeners modified in the mannojirimycin unit

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The syntheses of 1-deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin (**9**) and its 2-deoxy, 2-*O*-methyl, 4-deoxy, 4-*O*-methyl, 6-deoxy, 6-*O*-methyl, *N*-methyl, and *N*-propyl congeners are described. Since **9** was previously shown to effectively inhibit *endo*-α-D-mannosidase, a glycoprotein-processing hydrolase, these chemical modifications were designed to assist in the assessment of intermolecular hydrogen bonds of the inhibitor–enzyme complex. The previously reported data require that all hydroxyl groups of the deoxymannojirimycin unit of **9**, namely, OH-2, OH-4, OH-6, and also the NH-5 group, interact with charged and polar groupings of the enzyme, since deoxygenations and alkylations abolished or significantly reduced activities. Conformational analysis of **9** and some of its congeners based on NMR chemical shifts, experimental and theoretical nuclear Overhauser enhancements, and HSEA calculations were performed. The chemical modifications of the glucose unit of **9** are described in the accompanying paper.

ULRIKE SPOHR, MIMI BACH et ROBERT G. SPIRO. Can. J. Chem. **71**, 1928 (1993).

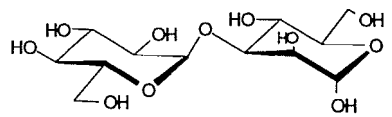
On décrit la synthèse de la 1-désoxy-3-*O*-(α-D-glucopyranosyl)mannojirimycine (**9**) et de ses dérivés 2-désoxy, 2-*O*-méthyle, 4-désoxy, 4-*O*-méthyle, 6-désoxy, 6-*O*-méthyle, *N*-méthyle et *N*-propyle. Puisqu'il a été démontré antérieurement que le composé **9** inhibe d'une façon efficace l'*endo*-α-D-mannosidase, une hydrolase conduisant à des glycoprotéines, les modifications chimiques réalisées avaient pour but d'aide à évaluer les liaisons hydrogènes impliquées dans le complexe inhibiteur–enzyme. Les données rapportées antérieurement (les désoxygénations et les alkylations éliminent ou réduisent fortement les activités) suggèrent que tous les groupes hydroxyles de l'unité désoxymannojirimycine du composé **9**, soit les groupes OH en 2, 4 et 6 ainsi que le groupe NH en 5, interagissent avec les groupes chargés et polaires de l'enzyme. En se basant sur les déplacements chimiques en RMN, sur des effets d'Overhauser nucléaire expérimentaux et théoriques ainsi que sur des calculs HSEA, on a réalisé une analyse conformationnelle du composé **9** et de quelques-uns de ses dérivés. Les modifications chimiques de l'unité glucose du composé **9** sont décrites dans une publication adjointe.

[Traduit par la rédaction]

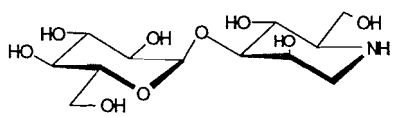
Introduction

The disaccharide 1-deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin (**9**) has been shown to strongly inhibit the action of *endo*-α-D-mannosidase (1), a glycoprotein-processing hydrolase that releases αDGlc(1→3)DMan from incompletely deglucosylated $GlcMan_9GlcNAc_2$ oligosaccharide of immature *N*-linked glycoproteins (2, 3). Although deoxymannojirimycin itself is known to be a strong *exo*-mannosidase inhibitor (4), it was found inactive towards *endo*-mannosidase (3). Apparently, the glucose unit is required for the recognition both of substrates and inhibitors (3) by the enzyme.

It was of interest to further investigate the involvement of the various substituents of inhibitor **9** in the complexation reaction with the enzyme by studying the effect of chemical modifications on the inhibitory properties, thus gaining insights into the topography recognized by the hydrolase. It is to be noted in this regard that extensive protein–oligosaccharide binding studies have been performed with numerous lectins (5–9), monoclonal antibodies (10–12), and enzymes such as amyloglucosidase (13–15) and glycosyltransferases (16–18). The results indicated that in these cases the acceptor protein recognizes only part of the oligosaccharide surface while leaving a considerable portion of the ligand in contact with water. This was confirmed for the complexation of the Lewis b tetrasaccharide by the lectin IV of *Griffonia simplicifolia* (5, 6) by the X-ray crystal structure of the complex (19).



αDGlc(1→3)DMan



9

The approach developed by Lemieux and co-workers (5, 6) for protein–oligosaccharide binding studies, namely, the use of all monodeoxy and mono-*O*-methyl congeners of the parent compound for the appreciation of intermolecular hydrogen bonds, was applied in this investigation, and the bi-

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ological results were recently published (1). The present communication reports on the syntheses and properties of **9** and its congeners modified in the 1-deoxymannojirimycin unit.

Discussion

Synthesis

For the synthesis of 1-deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin (**9**) (Scheme 1), the 1-deoxymannojirimycin derivative **1** reported by Fleet et al. (20) was used as the starting material. Diol **1** was protected at the 6-position either by selective acetylation with acetyl chloride at −78°C to provide **2** (75% yield) or by conversion of **1** into the oxazolidone derivative **13** (91% yield) by treatment with sodium methoxide. The ^{1}H NMR spectrum of acetate **2** showed very broad signals and duplication of the acetyl signal due to the hindered rotation of the *N*-benzyloxycarbonyl grouping about the N—C amide bond at room temperature. The ^{13}C NMR spectrum also displayed signal duplications. The 3-hydroxyl group of acetate **2** proved to be of very low reactivity in comparison to OH-3 of oxazolidone derivative **13**. No glucosidation of **2** was achieved under halide ion catalyzed conditions using bromide **14** (21). Therefore, the glucosidation was carried out with chloride **3** (22) and mediated by silver trifluoromethanesulfonate at −10°C to produce an α:β-mixture of **4** and **5** in the ratio 3.5:1. Repeated column chromatography provided the α-anomer **4** in 66% and the β-anomer **5** in 19% yield. An easier separation of the anomers was achieved after deacetylation of the anomeric mixture of **4** and **5** with triethylamine in aqueous methanol for 7 days to provide the anomers **6** and **7**. Under these conditions oxazolidone formation could be avoided. The anomeric assignments for **6** and **7** followed from the coupling constants $J_{C1',H1'}$ 168.0 Hz for **6** and $J_{C1',H1'}$ 160.5 Hz for **7** in the C–H coupled ^{13}C NMR spectrum (23). **6** was hydrogenolyzed in the presence of 5% palladium-on-carbon and 1 equivalent of hydrochloric acid to afford the target compound **9**. The ^{1}H and ^{13}C NMR data are presented in Tables 1 and 2 and are in full agreement with the structural assignment.

In contrast to acetate **2**, oxazolidone derivative **13** could be glucosylated with bromide **14** under halide ion catalysis, leading to **15** (60% yield). **15** was also obtained by treatment of **4** with sodium methoxide (81% yield). **15** was hydrogenolyzed to the oxazolidone derivative **16**, which showed the CO signal at 160.66 ppm in the ^{13}C NMR spectrum. Saponification of the cyclic carbamate in **15** with ethanolic potassium hydroxide provided **17**, the debenzylation of which also led to **9**.

6-*O*-Methyl congener **10** was prepared from the 6-hydroxy disaccharide **6** by treatment with methyl iodide and silver oxide in toluene (**8**, 91% yield) followed by hydrogenolytic debenzylation.

Disaccharide **9** was converted into the *N*-methyl and *N*-propyl derivatives **11** and **12** in high yields by reductive amination using formaldehyde in the presence of palladium/hydrogen and propionaldehyde in the presence of sodium cyanoborohydride (24).

The synthesis of the 6-deoxy congener **21** is outlined in Scheme 2. Although the 6-position of disaccharide **6** could be methylated under mild conditions to give **8** (Scheme 1), the benzyloxycarbonyl group proved unsuitable in attempts to halogenate or mesylate this position. Therefore this group was replaced by a benzyl group by treating amine **17** (Scheme 2) with benzyl bromide in the presence of potassium carbonate to produce **18** in 94% yield. Mesylation of **18** with methanesulfonyl chloride in pyridine at temperatures as low as −20°C produced a mixture of presumably the 6-*O*-methanesulfonyl ester and the 6-chloro-6-deoxy derivative **19** while a complete conversion into **19** (80% yield) was achieved on heating at 50°C for 1 h. **19** was then reduced with tributyltin hydride to the 6-deoxy derivative **20** (63% yield), which was debenzylated by catalytic hydrogenation over 5% palladium-on-carbon to afford **21** in high yield.

The syntheses leading to the 2-*O*-methyl and 2-deoxy congeners of **9**, namely, **36** and **37**, are presented in Scheme 3. The 4-*O*-benzyl-*N*-benzyloxycarbonyl-2-*O*-methyl derivative of 1-deoxymannojirimycin (**28**) was synthesized in a reaction sequence analogous to the one developed by Fleet et al. for the preparation of the 2,4-di-*O*-benzyl derivative **1** (20). Conventional methylation of 6-azido-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (25) gave the 5-*O*-methyl ether **22**, which was methanolyzed to the methyl glycosides **23** in high yield. Conversion into the trifluoromethanesulfonyl ester (intermediate **24**) followed by reduction of the azido group with triphenylphosphine, cyclization with inversion of configuration at C-2 (intermediate **25**), and *N*-benzyloxycarbonylation led to the bicyclic furanoside **26** in 68% yield. **26** was hydrolyzed to the reducing sugar (intermediate **27**) with subsequent reduction using sodium borohydride to produce **28** in 51% yield. The synthesis of the corresponding 1,2-dideoxy fagomine derivative **29** was reported by Fleet and Smith (26).

Both **28** and **29** were converted into the oxazolidones **30** and **31** in high yields by treatment with sodium methoxide. Glucosylation of **30** and **31** with bromide **14** under halide ion catalyzed conditions led to the α-linked disaccharides **32** and **33**, which were isolated in yields of 67 and 65%, respectively. Saponification of **32** and **33** using ethanolic potassium hydroxide to give **34** and **35** was followed by catalytic hydrogenolysis and provided the 2-*O*-methyl and 2-deoxy disaccharides **36** and **37** in high yields.

In the synthesis of the 4-*O*-methyl and 4-deoxy congeners of **9**, namely, **52** and **53** (Scheme 4), the 4-*O*-allyl disaccharide **45** served as an intermediate for both structures. The synthesis started from 3-*O*-allyl-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (27), which was converted conventionally into the methyl glycosides **38** by azide replacement, benzylation, and methanolysis. 1-Deoxymannojirimycin derivative **43** was then prepared from **38** as reported for **1** (20) and applied to the preparation of **28** via triflate **39**, which was reduced and cyclized with inversion of configuration at C-2 followed by *N*-benzyloxycarbonylation to give **41** (55%). Hydrolysis of the glycoside and subsequent reduction with sodium borohydride led to **43** (59% yield) from which **44** was obtained by treatment with sodium methoxide. Halide-ion catalyzed α-glucosidation of **44** with **14** provided disaccharide **45** in 61% yield. The 4-position of **45** was then liberated by isomerization of the allyl group to a 1-propenyl group with tris(triphenylphosphine)-rhodium(I)chloride (28), which was hydrolyzed using mercuric chloride to give alcohol **46** in 94% yield. **46** was converted into the 4-*O*-methyl derivative **47** with methyl iodide and sodium hydride (88% yield). For conversion into the 4-deoxy derivative **49**, the methyl xanthate **48** was prepared from **46** using sodium hydride, carbon disulfide, and

SCHEME 1

TABLE 1. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (Hz) for αDGlc(1→3)-1-DMJ (**9**) and related structures[a]

		Derivatives of **9**								
	9	2-Deoxy **37**	2-OMe **36**	4-Deoxy- **53**	4-OMe **52**	6-Deoxy **21**	6-OMe **10**	*N*-Me **11**	*N*-Propyl **12**[d]	*N*,6-*O*-Carbonyl **16**
1-DMJ unit										
H-1 ($J_{1,2}$)	3.42 (2.5)	3.47 (2.5)	3.75	3.46 (3.5)	3.38 (2.5)	3.36 (3.0)	3.42 (3.0)	3.53 (3.0)	3.51 (2.5)	3.73
H-1′ ($J_{1',1}$)	3.29 (13.5)	3.13 (13.0)	3.20 (13.5)	3.22 (13.5)	3.23 (13.5)	3.25 (13.5)	3.29 (13.5)	3.48 (13.5)	3.44 (13.5)	3.27 (14.5)
H-2 ($J_{1',2}$)	4.45 (<1)	2.40 (3.0)[b]	4.09 (<1)	4.34 (<1)	4.38 (<1)	4.42 (<1)	4.47 (<1)	4.41 (1)	4.43	4.32 (1.5)
H-3 ($J_{3,4}$)	3.81 (10.0)	3.83	3.85 (10.0)	4.03 (11.5)	3.89	3.76 (9.5)	3.82 (10.0)	3.84 (10.0)	3.81 (10.0)	3.74 (9.5)
H-4 ($J_{4,5}$)	4.08 (10.0)	3.78 (10.0)	4.01 (10.0)	1.87 (12.5)[c]	3.77	3.87 (9.5)	4.11 (10.0)	4.18 (10.0)	4.18 (10.0)	3.94 (9.5)
H-5 ($J_{5,6}$)	3.21 (3.0)	3.19 (4.0)	3.23 (3.0)	3.38 (3.5)	3.21 (2.5)	3.15 (6.5)	3.34 (3.2)	3.13 (<1)	3.21 (1.0)	3.78 (8.5)
H-6 ($J_{6,6'}$)	4.00 (12.5)	3.93 (0)	3.99 (12.5)	3.82 (12.5)	3.99 (12.5)	1.44	3.83	4.13 (13.5)	4.11 (13.5)	4.75 (8.5)
H-6′ ($J_{5,6'}$)	3.89 (6.7)	3.93 (4.0)	3.86 (6.5)	3.69 (7.2)	3.89	—	3.80 (6.5)	4.01 (2.7)	4.00 (2.0)	4.39 (4.5)
CH_3	—	—	3.46	—	3.59	—	3.45	2.99	0.98	—
αDGlc unit										
H-1 ($J_{1,2}$)	5.25 (4.0)	5.21 (3.5)	5.23 (3.5)	5.11 (3.5)	5.21 (3.5)	5.26 (3.5)	5.26 (3.7)	5.25 (3.5)	5.25 (4.0)	5.23 (3.7)
H-2 ($J_{2,3}$)	3.58 (10.0)	3.56 (10.0)	3.57 (10.0)	3.56 (9.5)	3.59	3.57 (9.5)	3.59 (10.0)	3.55 (10.0)	3.58 (9.5)	3.56 (10.0)
H-3 ($J_{3,4}$)	3.78 (9.5)	3.71 (9.5)	3.75 (9.0)	3.72 (9.0)	3.78 (9.0)	3.77 (9.0)	3.79	3.76 (9.0)	3.77 (9.0)	3.78 (9.5)
H-4 ($J_{4,5}$)	3.43 (9.5)	3.41 (9.0)	3.44 (9.5)	3.42 (9.5)	3.43 (9.5)	3.42 (9.5)	3.44	3.43 (9.5)	3.42 (9.0)	3.43 (9.5)
H-5 ($J_{5,6}$)	3.81	3.84 (9.5)	3.75	3.76	3.83	3.80	3.82	3.80	3.80	3.83
H-6	3.86	*	*	*	*	*	*	*	*	3.85
H-6′	*	*	*	*	*	*	*	*	*	*

[a]Measured at 360 MHz and 295 K using 0.03 M solutions in D_2O with acetone as internal standard at 2.225 ppm. The assignments were based on homonuclear shift-correlated 2-D experiments (COSY).

[b]H-2a 1.87 ppm. $J_{2a,2e}$ 14.5 Hz, $J_{2a,1}$ 4.5 Hz, $J_{2a,1'}$ 13.0 Hz.

[c]H-4e 2.11 ppm, $J_{4a,4e}$ 13.5 Hz, $J_{4e,5}$ 3.5 Hz, $J_{4e,3}$ 4.5 Hz.

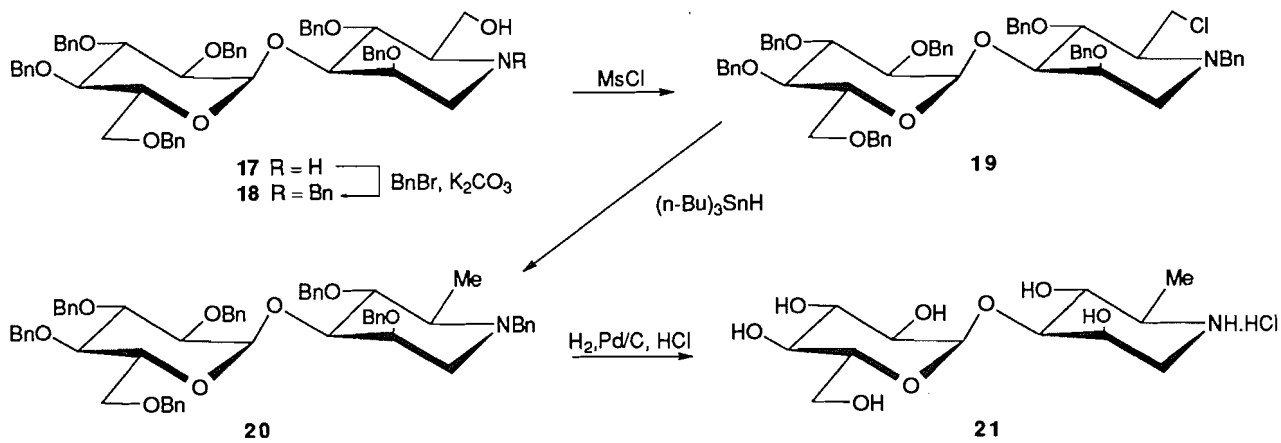
[d]CH_3CH_2 1.74, CH_2O 3.26 ppm, J 7.5 Hz.

*Could not be assigned.

TABLE 2. ^{13}C NMR chemical shifts (δ, ppm) for αDGlc(1→3)-1-DMJ (**9**) and related structures[a]

		Derivatives of **9**								
	9	2-Deoxy **37**	2-OMe **36**	4-Deoxy **53**	4-OMe **52**	6-Deoxy **21**	6-OMe **10**	*N*-Me **11**	*N*-Propyl **12**	*N*-6-*O*-Carbonyl **16**[c]
1-DMJ unit										
C-1	48.44	42.45	43.57	48.77	48.02	48.45	48.27	54.74	55.41[b]	46.28
C-2	66.37[b]	28.64	76.21	65.34	66.79	66.77	66.52[b]	66.41[b]	66.31[c]	69.80[b]
C-3	81.67	79.59	81.09	73.66	79.36	80.67	80.86	80.89	80.82	82.28
C-4	67.24[b]	69.36	66.08	24.82	76.26	70.51	66.02[b]	68.66[b]	66.31[c]	68.97[b]
C-5	61.12	60.83	61.08	57.68	60.44[b]	56.32	59.67[c]	64.92[b]	65.32[c]	58.59
C-6	59.31	58.49	58.82	62.10	58.62	15.33	69.08	59.38	55.49[b]	67.53
CH_3	—	—	57.90	—	61.53[b]	—	59.27[c]	41.79	10.68[d]	—
αDGlc unit										
C-1	101.50	100.86	101.89	97.78	101.11	101.38	101.45	101.44	101.42	101.48
C-2	72.49	72.36	72.44	72.01	72.15	72.46	72.45	72.43	72.43	72.59
C-3	73.57	73.63	73.56	73.57	73.42	73.57	73.54	73.56	73.54	73.62
C-4	70.35	70.41	70.32	70.35	70.47	70.37	70.35	70.35	70.35	70.37
C-5	73.27	73.15	73.47	73.15	73.31	73.31	73.32	73.35	73.35	73.21
C-6	61.34	61.42	61.36	61.37	61.40	61.38	61.36	61.38	61.37	61.34

[a]0.05 M solutions in D_2O with dioxane as internal reference at 67.4 ppm were measured at 75 MHz and 295 K. The assignments were made by inspection and are tentative.
[b,c]The assignments are tentative and may be reversed.
[d]NCH_2 54.94, CH_2 16.39 ppm.
[e]CO 160.66 ppm.



SCHEME 2

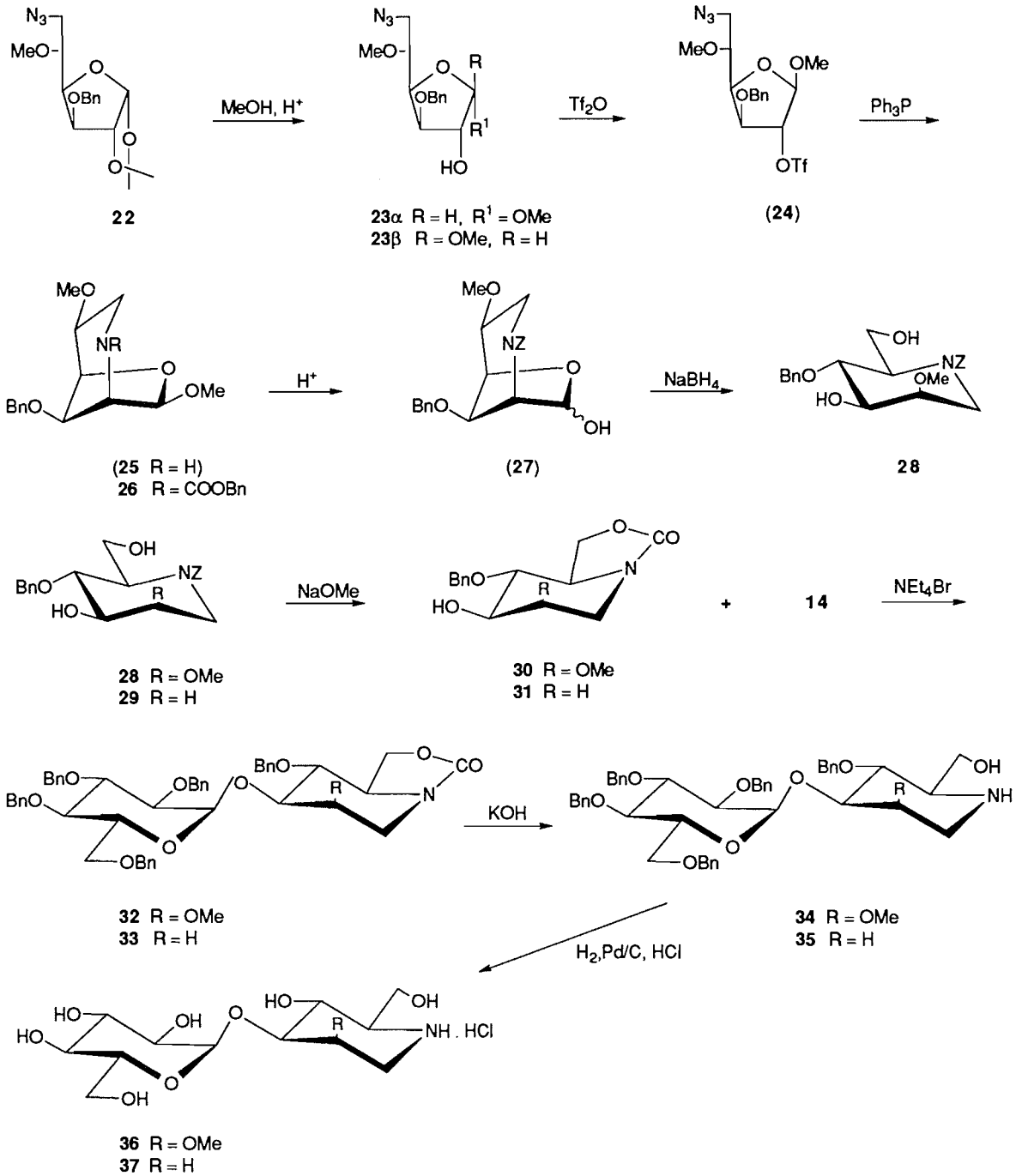
methyl iodide (29). This intermediate was reduced with tributyltin hydride to provide **49** in 79% yield. Saponification of the cyclic carbamate in **47** and **49** followed by catalytic hydrogenolysis of the benzyl groups then led to the 4-*O*-methyl and 4-deoxy disaccharides **52** and **53** in high yields.

NMR and conformational studies

The ^1H and ^{13}C NMR parameters for αDGlc(1→3)-1-DMJ (**9**) are reported in Tables 1 and 2 together with those for structural modifications involving changes of the 1-DMJ unit. The data are in full accord with the structural assignments. The ^1H NMR vicinal coupling constants of both units are typical for the $^4C_1$ conformation of pyranoid rings. Some flattening, though, in the DMJ-piperidine ring of the bicyclic derivative **16** may be expected.

HSEA calculations (30) predict for **9** a conformational preference with minimum energy at $\phi/\psi = -50°/-10°$. In this conformer, H-1′ is found at a close distance across the glycosidic linkage to H-3 (2.40 Å) and to O-4 (2.74 Å), while H-5′ is in nonbonded interaction to H-2 (2.27 Å). The nonbonded interaction of H-1′ to O-4 accounts for the intermediate deshielding of 0.14 ppm with respect to the chemical shift of H-1′ in the 4-deoxy congener **53** (31). NOE experiments with irradiation of H-1′ of **9** resulted in a strong intraunit enhancement of H-2′ and interunit enhancement to H-3 (Table 3, Fig. 1). Irradiation of H-2 caused an interunit NOE to H-5′, the signal of which, however, overlapped with the also enhanced H-3 signal. Relative theoretical NOE values were derived for the low-energy conformer of $\phi/\psi = -45°/-15°$ ($E = -1.7$) and provided a better agreement with the experimental data than those derived for the minimum energy conformer of $\phi/\psi = -50°/-10°$ ($E = -1.8$), particularly, with respect to the internuclear distance between H-2 and H-5′.

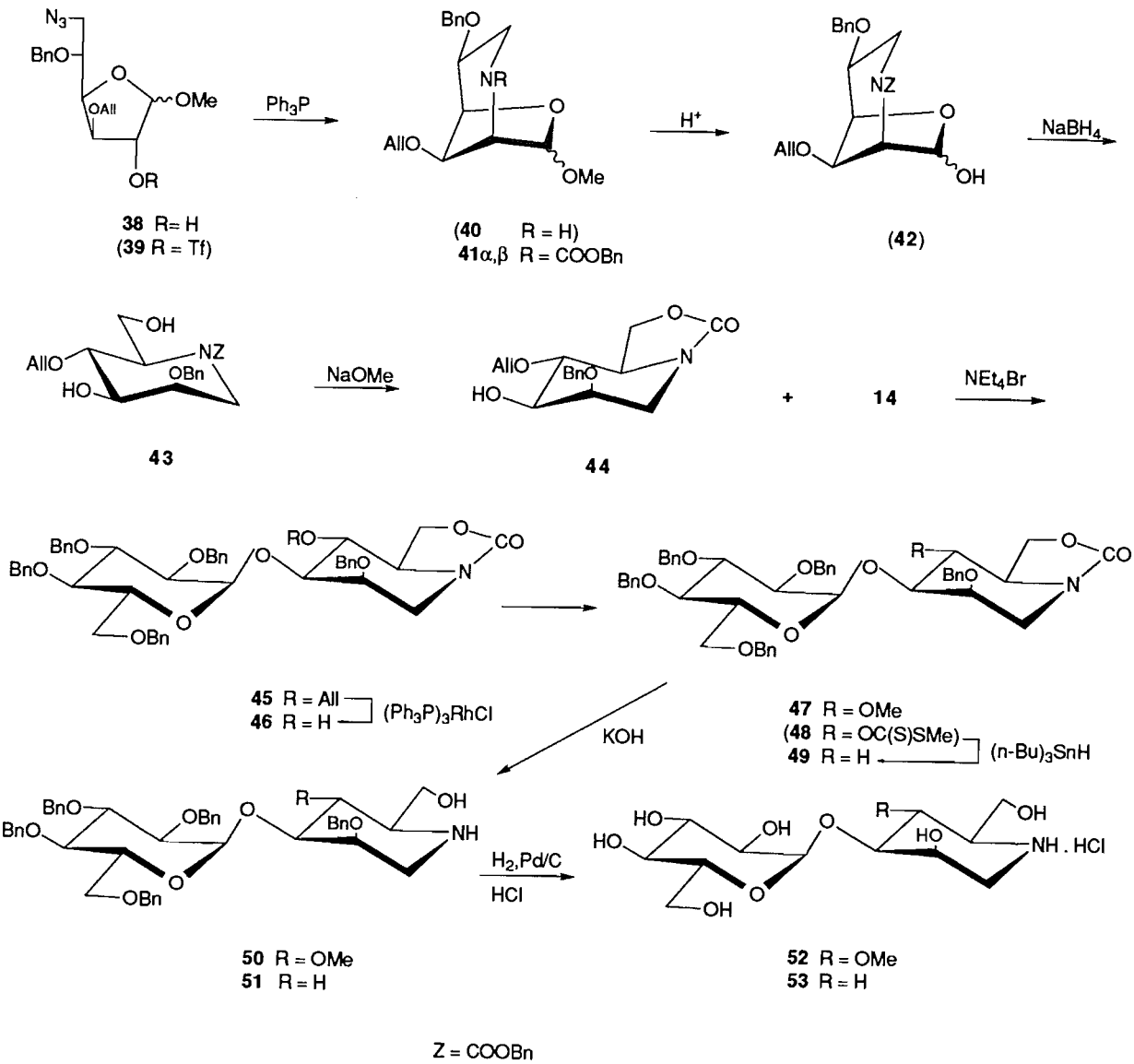
4-Deoxy congener **53** allowed additional NOE experi-



SCHEME 3

ments, since not only H-1′ and H-2, but also H-3 and H-4e provided well-separated signals in the ^{1}H NMR spectrum. HSEA calculations indicate somewhat more flexibility about the glycosidic bond and predict an energy minimum for conformations of $\phi/\psi = -55°$, $-50°/-25°$, $-20°$ ($E = -1.9$) in which H-1′ is in interunit nonbonded interaction to H-3 and H-4e, and H-5′ to H-2. Indeed, irradiation of H-1′ resulted in enhancements of H-3 and H-4e (Table 3), and, conversely, irradiation of H-3 and H-4e caused signal enhancements of H-1′ and also a smaller enhancement of H-5′ in the case of H-3. H-5′ was also enhanced when the H-2 signal was saturated. A reasonably good agreement of the experimental NOE data with the theoretical values was achieved when those were derived for the low-energy conformer of $\phi/\psi = -45°/-25°$ ($E = -1.7$), which appears to approximately represent the average internuclear proton distances of the conformers in equilibrium.

HSEA calculations for the 2-deoxy congener **37** indicate



SCHEME 4

that the conformational preference of the parent compound **9** also applies to **35**, since in contrast to O-4, the axial O-2 of **9** is not involved in interunit nonbonded interactions. In fact, since none of the structural modifications, except deoxygenation of the 4-position, had marked effects on the ^1H and ^{13}C NMR chemical shift of the glucose unit (Tables 1 and 2), the interglycosidic conformational properties of **9** appear maintained in these congeners.

The biological data of this investigation (1) are discussed in the succeeding paper (32), which reports the syntheses of congeners of **9** modified in the glucose unit.

Experimental

Theoretical methods

Conformational preferences about the glycosidic torsion angles were calculated using the HSEA program (30). The calculations were done in 5° steps for the ϕ and ψ angles. The atomic coordinates were derived from neutron diffraction studies of methyl α-D-glucopyranoside and methyl α-D-mannopyranoside (33) with ω-angles of −60° and 180°, respectively. The deoxy functions were generated by bond modifications of methyl α-D-mannopyranoside using a C—H bond length of 1.10 Å. The internuclear distances provided by the HSEA calculations for a specific conformer (Table 3) were used for the determination of the theoretical nuclear Overhauser enhancements. The computer program developed by Helmut Beierbeck was used for this purpose (34).

NMR spectroscopy

The ^1H NMR spectra were measured at 300 MHz and 360 MHz (Bruker AM 300 and WM 360) with tetramethylsilane as internal standard for $CDCl_3$ solutions. Reference standard for D_2O solutions was acetone (2.225 ppm). The ^{13}C NMR spectra were recorded at 75 MHz with dioxane (67.4 ppm) as reference for D_2O solutions and the $CDCl_3$ signal (77.0 ppm) as reference in $CDCl_3$ solutions. The steady-state NOE experiments were performed at 298 K and 360 MHz with 0.05 M solutions in D_2O. Irradiation time was 5 s and the saturation of signals was achieved by multiple frequency irradiation per signal (35, 36).

General methods

Optical rotations were measured at room temperature (23 ± 1°C) in a 1-dm cell on a Perkin–Elmer 241 polarimeter. Thin-layer chromatography was performed on precoated plates of silica gel (60-F254, E. Merck, Darmstadt) and visualized by spraying with 5% sulfuric acid in ethanol followed by heating. For column chroma-

TABLE 3. Intra- and interunit nuclear Overhauser enhancements for compounds **9** and **53**[a]

Compound	Proton saturated	Signal enhanced	% Enhancement	Relative NOE values	
				Observed	Calculated
9[b]	H-1′	H-2′	16.3	0.54	0.59
		H-3	13.7	0.46	0.39
	H-2	H-1e	4.3	0.20	0.11
		H-1a	4.1	0.19	0.15
		H-3	} 12.6	} 0.60	0.34
		H-5′			0.40
53[c]	H-1′	H-2′	16.5	0.57	0.61
		H-3	8.5	0.29	0.25
		H-4e	3.9	0.13	0.13
	H-2	H-1e	4.2	0.24	0.13
		H-1a	3.8	0.22	0.18
		H-3	5.8	0.33	0.34
		H-5	3.8	0.22	0.34
	H-3	H-1a	3.6	0.12	0.08
		H-2	7.2	0.24	0.31
		H-4e	3.0	0.10	0.10
		H-5	6.1	0.20	0.15
		H-1′	10.3	0.34	0.32
		H-5′	1.4	0.05	0.05
	H-4e	H-3	4.2	0.08	0.11
		H-4a	29.4	0.59	0.55
		H-5	6.8	0.14	0.12
		H-6	2.5	0.05	0.04
		H-1′	7.1	0.14	0.18

[a]The experimental data are the mean of two measurements. Minor calculated or negative NOE values are not listed.
[b]The calculated NOE values were derived for the low-energy conformer of $\phi/\psi = -45°/-15°$.
[c]The calculated NOE values were derived for the low-energy conformer of $\phi/\psi = -45°/-25°$.

tography silica gel 60 (230–400 mesh, E. Merck, Darmstadt) and distilled solvents were used. Solvents and reagents were purified and dried according to standard procedures. Melting points are uncorrected.

6-O-Acetyl-2,4-di-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol (2)

Acetyl chloride (82 μL, 1.15 mmol) was added to a solution of diol **1** (20) (304 mg, 0.64 mmol) in dichloromethane (20 mL) and pyridine (200 μL, 2.5 mmol) at −78°C. After 1 h at this temperature, more acetyl chloride (25 μL, 0.35 mmol) was added. The reaction mixture was kept for another hour at −78°C. Then the excess of reagent was quenched by the addition of methanol (50 μL). The solution was diluted with dichloromethane, washed with water, dried, and evaporated. The crude product was purified on a column of silica gel (hexane – ethyl acetate, 3:1, 2:1) yielding crystallizing acetate **2** (249 mg, 75%). The analytical sample was recrystallized from ether – hexane; mp 69–71°C; $[\alpha]_D$ −19 (*c* 0.6, chloroform). ^{1}H NMR ($CDCl_3$, signals broad, mixture of two rotamers in the ratio ~3:2) δ: 7.4–7.1 (m, 15H, 3Ph), 5.2–5.02 (m, 2H, $COOCH_2Ph$), 4.13 (d, 1H, *J* 11.5 Hz, 1 CH_2Ph), 4.12 (d, 1H, *J* 11.5 Hz, 1 CH_2Ph), 3.86–3.6 (m, 2H, H-1, H-1′), 3.18–3.00 (m, 1H, H-5), 2.35–2.26 (m, 1H, OH), 1.92 and 1.77 (2s, 3H, CH_3CO). ^{13}C NMR ($CDCl_3$, δ for minor rotamer in parentheses) δ: 75.98 (74.81) (C-4),[3] 72.20 (C-2)$^+$, 71.35 (2 CH_2Ph), 68.04 (C-3)$^+$, 67.34 ($COOCH_2Ph$), 61.09 (C-6), 52.18 (51.41) (C-5), (37.43), 36.88 (C-1). Anal. calcd. for $C_{30}H_{33}O_7$: C 69.35, H 6.40, N 2.70; found: 69.55, H 6.58, N 2.66.

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl chloride (3) (22)

Oxalyl chloride (160 μL, 1.83 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (740 mg, 1.37 mmol) and *N*,*N*-dimethylformamide (150 μL, 2.11 mmol) in dichloromethane (15 mL). The mixture was stirred for 20 min and then poured into ice-water. The organic solution was washed with ice-water, dried, and evaporated to provide chloride **3** (quant.) as a syrup.

6-O-Acetyl-2,4-di-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-mannitol (4) and -β-D-glucopyranosyl)-D-mannitol (5)

A solution of chloride **3** (7.92 mmol) in dichloromethane (12 mL) was added at −78°C to a stirred mixture of alcohol **2** (2.0 g, 3.85 mmol), silver trifluoromethanesulfonate (2.31 g, 8.99 mmol), *sym*-collidine (418 μL, 3.16 mmol), and 4 Å molecular sieves (1.5 g) in dichloromethane (5.0 mL). The temperature was gradually raised to −10°C and after 2 h at this temperature, *sym*-collidine (630 μL, 4.97 mmol) was added. The mixture was filtered through Celite, the organic solution was washed with aqueous saturated sodium hydrogen carbonate and water, followed by evaporation. Two column chromatographic separations on silica gel (hexane – ethyl

[3]Tentative assignments are marked with +.

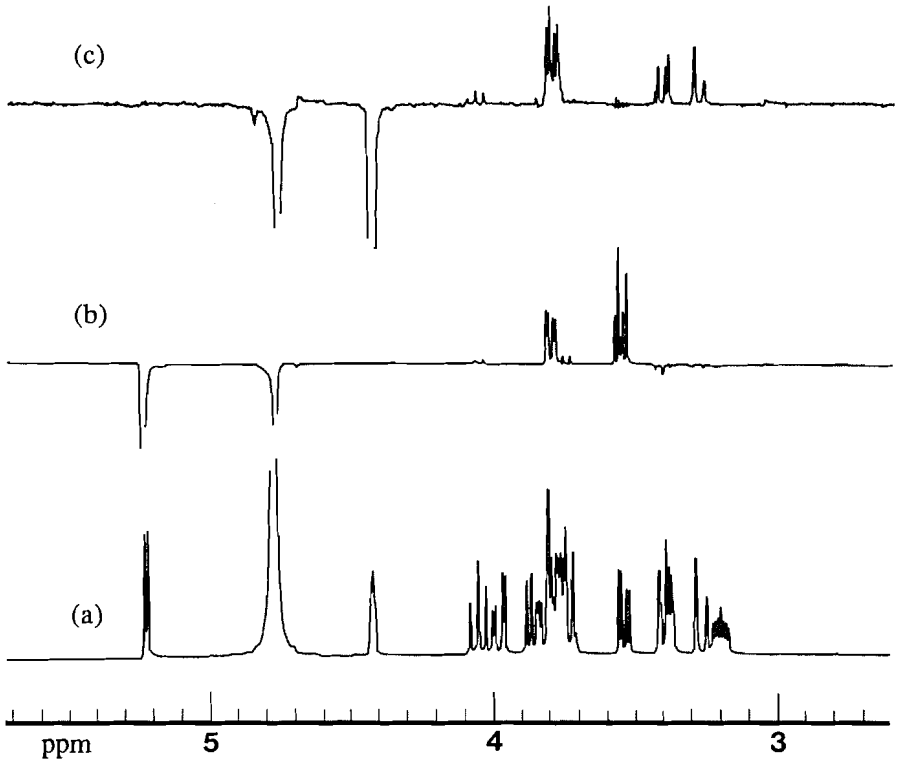


FIG. 1. NOE difference spectra for disaccharide **9**; (*a*) reference spectrum; (*b*) irradiation of H-1′; (*c*) irradiation of H-2.

acetate, 6:1, 5:1) provided the β-isomer **5** (0.774 g, 19%) as a tough syrup; $[\alpha]_D$ +5 (*c* 0.2, chloroform). ^{1}H NMR ($CDCl_3$, broad, mixture of two rotamers in the ratio 3:2) δ: 7.4–7.0 (m, 35H, 7Ph), 5.2–3.1 (complex m, 29H), 1.89 and 1.81 (2s, 3H, CH_3CO). Anal. calcd. for $C_{64}H_{67}NO_{12}$: C 73.76, H 6.48, N 1.34; found: C 74.18, H 7.06, N 1.34. Continued elution of the column provided the α-isomer **4** (2.64 g, 66%) as a tough syrup; $[\alpha]_D$ +33 (*c* 0.4, chloroform). ^{1}H NMR ($CDCl_3$, broad, mixture of two rotamers in the ratio 3:2) δ: 7.40–7.00 (m, 35H, 7Ph), 5.2–2.95 (complex m, 29H), 1.83 and 1.76 (2s, 3H, CH_3CO). Anal. calcd. for $C_{64}H_{67}NO_{12}$: C 73.76, H 6.48, N 1.34; found: C 73.62, H 6.44, N 1.34.

*2,4-Di-*O*-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (6) and -β-D-glucopyranosyl)-D-mannitol (7)*

(*a*) A solution of compound **4** (1.37 g, 1.31 mmol) in methanol (48 mL), triethylamine (20 mL), and water (9.6 mL) was kept at room temperature for 7 days. It was evaporated and the crude product purified on a column of silica gel (hexane – ethyl acetate, 4:1 to 2:1) to provide, in the first fraction, acetate **4** (0.179 g, 13%). Further development gave compound **6** (0.894 g, 68%) as a tough syrup; $[\alpha]_D$ +14.6 (*c* 0.2, chloroform). ^{1}H NMR ($CDCl_3$, broad, mixture of two rotamers) δ: 7.4–6.95 (m, 35H, 7Ph), 5.17–2.83 (complex m, 30H). ^{13}C NMR ($CDCl_3$, δ for minor rotamer in parentheses) δ: 156.10 (CO), 99.24 ($J_{C,H}$ 168.0 Hz, C-1′), 59.14 (C-6), 53.82 (53.34) (C-5), (39.19) 38.63 (C-1). Anal. calcd. for $C_{62}H_{65}NO_{11}$: C 74.45, H 6.55, N 1.40; found: C 74.44, H 6.56, N 1.37.

(*b*) An anomeric mixture of compounds **4** and **5** (415 mg, 0.40 mmol) was deacetylated as described under (*a*). Chromatographic separation on a column of silica gel (hexane – ethyl acetate, 4:1, 3:1) provided, in the first main fraction, the α-isomer **6** (230 mg, 58%). Continued elution provided the β-isomer **7** (51 mg, 13%) as a tough syrup; $[\alpha]_D$ −10.4 (*c* 0.2, chloroform). ^{1}H NMR ($CDCl_3$, mixture of two rotamers, broad) δ: 7.4–7.0 (m, 35H, 7Ph), 5.0–3.1 (complex m, 30H). ^{13}C NMR ($CDCl_3$, δ for minor isomer in parentheses) δ: 156.1 (CO), 105.68 ($J_{C,H}$ 160.5, C-1′), 59.68 (59.53) (C-6), 54.83 (54.50) (C-5), (39.49) 39.04 (C-1). Anal. calcd. for $C_{62}H_{65}NO_{11}$: C 74.45, H 6.55, N 1.40; found: C 74.53, H 6.54, N 1.40.

*2,4-Di-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-6-*O*-methyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (8)*

Methyl iodide (172 μL, 2.76 mmol) was added to a stirred mixture of **6** (150 mg, 0.15 mmol) and silver oxide (320 mg, 1.38 mmol) in toluene (5 mL) at 0°C. After 3 h, the temperature was raised to room temperature and stirring continued for 5 days. More methyl iodide (120 μL, 1.93 mmol) was added, followed by stirring for another day. The solids were removed by filtration and the solvent was evaporated. The remainder was applied to a column of silica gel (hexane–dichloromethane – ethyl acetate, 5:1:1) to provide **8** (137.6 mg, 91%) as a tough syrup; $[\alpha]_D$ +37 (*c* 0.5, chloroform). ^{1}H NMR ($CDCl_3$, broad, mixture of two rotamers) δ: 7.4–7.0 (m, 35H, 7Ph), 5.2–2.9 (complex m, 32H), 3.11 and 3.04 (2s, 3H, CH_3O). Anal. calcd. for $C_{63}H_{67}NO_{11}$: C 74.61, H 6.66, N 1.38; found: C 74.66, H 6.56, N 1.45.

*1,5-Dideoxy-3-*O*-(α-D-glucopyranosyl)-1,5-imino-D-mannitol-hydrochloride (9)*

A mixture of compound **6** (369 mg, 0.37 mmol), 5% palladium-on-carbon (370 mg), methanolic 0.12 N hydrochloric acid (3.8 mL, 0.46 mmol), and methanol (20 mL) was hydrogenated in a hydrogen stream for 1.5 h. The catalyst was removed by filtration and it was codistilled a few times with water. The product was passed through a column of Sephadex LH 20 (ethanol–water, 1:1) and obtained as a white, hygroscopic solid (125 mg, 96%) after freeze-drying its aqueous solution; $[\alpha]_D$ +62.5 (*c* 0.24, water). The ^{1}H and ^{13}C NMR data are reported in Tables 1 and 2. Likewise, **17** can be debenzylated to **9**.

*1,5-Dideoxy-3-*O*-(α-D-glucopyranosyl)-1,5-imino-6-*O*-methyl-D-mannitol-hydrochloride (10)*

A mixture of **8** (159 mg, 0.157 mmol), 5% palladium-on-carbon (112 mg), and methanolic 0.12 N hydrochloric acid (1.65 mL,

0.19 mmol) in methanol (7 mL) was hydrogenated in the hydrogen stream for 2 h. Further processing as described for the preparation of **9** provided the title compound **10** (59 mg, 100%) as a white solid; $[\alpha]_D$ +75.2 (*c* 0.5, water). The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

*1,5-Dideoxy-3-*O*-(α-D-glucopyranosyl)-1,5-imino-*N*-methyl-D-mannitol-hydrochloride (**11**)*

A mixture of **9** (30.8 mg, 0.085 mmol), palladium black (8 mg), methanolic 0.1 N sodium methoxide (851.5 μL), and 37% formaldehyde solution (40 μL, 0.49 mmol) in methanol (2.2 mL) was hydrogenated in the hydrogen stream for 1 day. Then more palladium black (5 mg) and 37% formaldehyde solution (40 μL, 0.49 mmol) were added and hydrogenation continued for another day. The catalyst was removed by filtration and the solution neutralized with methanolic 0.12 N hydrochloric acid (710 μL, 0.085 mmol). It was evaporated and the remainder applied to a column of Sephadex LH 20 (ethanol–water, 1:1). Freeze-drying an aqueous solution of the resultant material provided **11** (27.7 mg, 87%) as a solid; $[\alpha]_D$ +64 (*c* 0.5, water). The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

*1,5-Dideoxy-3-*O*-(α-D-glucopyranosyl)-1,5-imino-*N*-n-propyl-D-mannitol-hydrochloride (**12**)*

Sodium cyanoborohydride (12.8 mg, 0.20 mmol) was added to a stirred mixture of **9** (49.6 mg, 0.14 mmol) and propionaldehyde (56.6 μL, 0.79 mmol) in methanol (2 mL) at room temperature. After 2 h, the solvent was evaporated to provide a milky residue which was applied to a column of Iatrobeads® (chloroform–methanol–water, 65:35:8). The resultant material was dissolved in methanol (1 mL) and methanolic 0.12 N hydrochloric acid solution (1.15 mL, 0.14 mmol) was added, followed by evaporation and codistillation with water. Subsequent gel filtration on a column of Sephadex LH 20 (ethanol–water, 1:1) provided **12** (51 mg, 101%) as a white solid; $[\alpha]_D$ +51.4 (*c* 0.5, water). The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

*2,4-Di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (**13**)*

A solution of **1** (300 mg, 0.63 mmol) in methanolic 0.5 N sodium methoxide (3 mL) was kept at room temperature for 15 h. The solution was made neutral with Amberlite IRC 50 (H^+), filtered, and evaporated. The resulting product was applied to a column of silica gel (dichloromethane – ethyl acetate 4:1, 3:1) to provide **13** (210 mg, 91%) as a white foam; $[\alpha]_D$ +5.9 (*c* 0.4, chloroform). IR ($CHCl_3$): 1755 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–7.25 (m, 10H, 2Ph), 5.03, 4.86, 4.61, 4.37 (2ABq, each 2H, $J_{A,B}$ 11.5 Hz, 2CH_2Ph), 4.33 (dd, 1H, $J_{6A,6B}$ 8.5 Hz, $J_{6A,5}$ 7.2 Hz, H-6A), 4.26 (dd, 1H, $J_{1A,1B}$ 14.0 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 4.03 (dd, 1H, $J_{6B,5}$ 3.0 Hz, H-6B), 3.83 (m, 1H, H-2), 3.70 (bdd, 1H, H-3), 3.59 (t, 1H, $J_{4,5} \sim J_{3,4}$ 9.0 Hz, H-4), 3.51 (m, 1H, H-5), 2.92 (dd, 1H, $J_{1B,2}$ 1.5 Hz, H-1B), 2.48 (bs, 1H, OH). Anal. calcd. for $C_{21}H_{23}NO_5$: C 68.28, H 6.28, N 3.79; found: C 67.98, H 6.21, N 3.77.

*2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**14**) (**21**)*

Oxalyl bromide (200 μL, ~1.85 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (800 mg, 1.48 mmol) in dichloromethane (10 mL) and *N,N*-dimethylformamide (500 μL, 7.0 mmol). After 20 min at room temperature, the mixture was poured into ice-water and the organic solution was washed twice with ice-cold water, dried, and evaporated to provide **14** (quant.) as a syrup.

*2,4-Di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**15**)*

(*a*) A solution of bromide **14** (1.48 mmol) in dichloromethane (2 mL) was transferred into a mixture of alcohol **13** (190 mg, 0.51 mmol), tetraethylammonium bromide (220 mg, 1.05 mmol), *N,N*-dimethylformamide (700 μL), and 4 Å molecular sieves (powdered, 0.5 g) in dichloromethane (1.5 mL). After stirring for 4 days, the reaction was quenched by the addition of methanol (300 μL) and stirring continued for 1 h. The mixture was diluted with dichloromethane, filtered through a pad of Celite, and the solution washed with aqueous sodium bicarbonate and water, followed by drying and evaporation. Purification was achieved by two column chromatographic separations on silica gel (hexane – ethyl acetate, 4:1 to 1:1 and hexane–dichloromethane – ethyl acetate, 5:2:1) to provide **15** (276 mg, 60%) as a slowly crystallizing syrup; $[\alpha]_D$ +15.6 (*c* 0.4, chloroform). ^1H NMR ($CDCl_3$) δ: 7.4–7.1 (m, 30H, 6Ph), 5.05 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.24 (t, 1H, $J_{5,6A} \sim J_{6A,6B}$ 8.5 Hz, H-6A), 4.15 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.2 Hz, H-1A), 3.82 (dd, 1H, $J_{6B,5}$ 3.5 Hz, H-6B), 2.78 (bd, 1H, $J_{1B,2} < 1$ Hz, H-1B). ^{13}C NMR ($CDCl_3$) δ: 157.5 (CO), 100.29 (C-1′), 65.76 (C-6), 57.45 (C-5), 40.82 (C-1). Anal. calcd. for $C_{55}H_{57}NO_{10}$: C 74.05, H 6.44, N 1.57; found: C 74.36, H 6.68, N 1.63.

(*b*) A solution of **4** (190 mg, 0.18 mmol) in methanolic 0.5 N sodium methoxide (1.1 mL) was kept at room temperature for 20 h. The solution was made neutral with Amberlite IRC 50 (H^+), filtered, and evaporated. Chromatographic purification of the remainder on a column of silica gel (hexane – ethyl acetate, 2:1, 1:1) provided a product identical to **15** (132 mg, 81%).

*N,6-O-Carbonyl-1,5-dideoxy-3-*O*-(α-D-glucopyranosyl)-1,5-imino-D-mannitol (**16**)*

A mixture of **15** (125 mg, 0.140 mmol) and 5% palladium-on-carbon (70 mg) in 95% ethanol (4 mL) was hydrogenated in a hydrogen stream for 1.5 h. The catalyst was removed by filtration, followed by evaporation of the solvent. Freeze-drying an aqueous solution provided **16** (50 mg, 102%) as a white solid; $[\alpha]_D$ +70.5 (*c* 0.4, water). The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

*2,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**17**)*

A mixture of **15** (527 mg, 0.59 mmol) in 5% potassium hydroxide in 90% ethanol (15 mL) was heated at 80°C for 4 h. It was neutralized with acetic acid, followed by solvent removal. The material was taken up in dichloromethane and the solution was washed with a little water, dried, and evaporated to provide **17** as a tough syrup (488 mg, 95%). An analytical sample was purified by column chromatography on silica gel (dichloromethane – 3% methanol). ^1H NMR ($CDCl_3$) δ: 7.40–7.10 (m, 30H, 6Ph), 5.00 (bs, 1H, H-1′), 4.04 (overlapped, H-3′), 3.88 (m, H-2), 3.53 (dd, 1H, $J_{2',1'}$ 3.5 Hz, $J_{2',3'}$ 9.5 Hz, H-2′), 3.12 (dd, 1H, $J_{1A,1B}$ 13.5 Hz, $J_{1A,2}$ 4.0 Hz, H-1A), 2.59 (bd, 1H, H-1B).

*N-Benzyl-2,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**18**)*

A mixture of **17** (461 mg, 0.53 mmol), potassium carbonate (50 mg, 0.36 mmol), and benzyl bromide (166 μL, 1.40 mmol) in *N,N*-dimethylformamide (5 mL) was stirred for 2 h at 18°C. The solids were removed by filtration and the solution was concentrated. Column chromatography of the crude product on silica gel (hexane – ethyl acetate, 4:1) provided **18** (480 mg, 94%); $[\alpha]_D$ +38 (*c* 1.3, chloroform). ^{13}C NMR ($CDCl_3$) δ: 98.97 (C-1′), 60.89 (C-5), 58.54, 58.22 (C-1, C-6), 46.63 (NCH_2Ph). Anal. calcd. for $C_{61}H_{65}NO_9$: C 76.62, H 6.85, N 1.47; found: C 76.38, H 6.93, N 1.55.

*N-Benzyl-2,4-di-*O*-benzyl-6-chloro-1,5,6-trideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**19**)*

Methanesulfonyl chloride (50 μL, 0.65 mmol) was added to a solution of **18** (336 mg, 0.35 mmol) in pyridine (5 mL). After 40 min at 22°C, the mixture was heated at 50°C for 1 h. Then it was poured into ice-water and extracted with dichloromethane, followed by washing of the organic solution with water, drying, and evaporation. The resultant material was applied to a column of silica gel (hexane – ethyl acetate, 4:1) to provide **19** (275 mg, 80%) as a tough syrup; $[\alpha]_D$ +31 (*c* 0.7, chloroform). ^1H NMR ($CDCl_3$, broad signals) δ: 7.45–7.05 (m, 35H, 7Ph), 4.90 (overlapped, H-1′), 4.11 (m, 1H, $J_{4',5'}$ 9.5 Hz, H-5′), 4.03 (overlapped, H-3′),

3.88 (overlapped, H-2), 3.60 (t, 1H, $J_{3',4'}$ 9.5 Hz, H-4'), 3.49 (dd, 1H, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 9.5 Hz, H-2'), 3.36 (dd, 1H, $J_{6A',6B'}$ 10.5 Hz, $J_{6A',5'}$ 3.0 Hz, H-6A'), 3.22 (bd, 1H, H-6B'), 2.99 (dd, 1H, $J_{1A,2}$ 6.5 Hz, $J_{1A,1B}$ 12.5 Hz, H-1A), 2.26 (bd, 1H, H-1B). ^{13}C NMR ($CDCl_3$) δ: 98.51 (C-1'), 57.49 (C-1), 47.51 (NCH_2Ph), 42.02 (C-6). Anal. calcd. for $C_{61}H_{64}ClNO_8$: C 75.17, H 6.62, Cl 3.64, N 1.44; found: C 75.07, H 6.60, Cl 4.19, N 1.51.

N-Benzyl-2,4-di-O-benzyl-1,5,6-trideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-mannitol (20)

The chloro compound **19** (254 mg, 0.26 mmol), tributyltin hydride (420 μL, 1.56 mmol), and 2,2'-azobis(isobutyronitrile) (15 mg) in toluene (10 mL) were heated at 95–100°C for 3 h. Evaporation, followed by two column chromatographic purifications on silica gel (toluene – ethyl acetate, 20:1, hexane – ethyl acetate, 6:1) provided **20** (155 mg, 63%); $[\alpha]_D$ +11.3 (*c* 0.2, chloroform). ^{1}H NMR ($CDCl_3$, signals broad) δ: 7.40–7.05 (m, 35H, 7Ph), 5.03 (bs, 1H, H-1'), ~4.09 (m, overlapped, H-3'), 3.50 (dd, 1H, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 9.5 Hz, H-2'), 3.40 (bdd, 1H, $J_{6A',6B'}$ 10.5 Hz, H-6A'), 3.29 (bd, 1H, H-6B'), 1.30 (bd, 3H, $J_{5,6}$ 5.5 Hz, H_3-6). Anal. calcd. for $C_{61}H_{65}NO_8$: C 77.93, H 6.97, N 1.49; found: C 77.93, H 6.82, N 1.46.

1,5,6-Trideoxy-3-O-(α-D-glucopyranosyl)-1,5-imino-D-mannitol-hydrochloride (21)

A mixture of **20** (143 mg, 0.15 mmol), 5% palladium-on-carbon (143 mg), and methanolic 0.12 N hydrochloric acid (1.5 mL, 0.18 mmol) in methanol (5 mL) was hydrogenated in the hydrogen stream for 2 h. Usual processing followed by gel filtration (Sephadex LH 20, ethanol–water, 1:1) provided **21** (52 mg, 99%) as a white powder after freeze-drying an aqueous solution; $[\alpha]_D$ +71 (*c* 0.4, water). The ^{1}H and ^{13}C NMR data are reported in Tables 1 and 2.

6-Azido-3-O-benzyl-6-deoxy-5-O-methyl-1,2-O-isopropylidene-α-D-glucofuranose (22)

Sodium hydride (50% oily suspension, 4.81 g, 0.1 mol) was added slowly to a stirring solution of 6-azido-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (25) (26 g, 0.077 mol) at ice-bath temperature. After 20 min, methyl iodide (9 mL, 0.097 mol) was added and stirring continued for 30 min at ice-bath temperature, then another 30 min at room temperature. The reaction was quenched by the careful addition of methanol at 0°C, followed by evaporation of the solvent. The remainder was taken up in dichloromethane and the organic solution was washed with water, dried, and concentrated. Column chromatographic purification of the crude product on silica gel (hexane – ethyl acetate, 7.5:1) provided **22** (24.2 g, 89%) as an oil; $[\alpha]_D$ −65 (*c* 0.9, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.45–7.25 (m, 5H, Ph), 5.88 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.69 and 4.55 (ABq, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.61 (d, 1H, H-2), 4.19 (dd, 1H, $J_{3,4}$ 2.8 Hz, $J_{4,5}$ 8.5 Hz, H-4), 4.08 (d, 1H, H-3), 3.74 (m, 1H, H-5), 3.68 (dd, 1H, $J_{6,6'}$ 12.5 Hz, $J_{6,5}$ 2.5 Hz, H-6), 3.40 (s, 3H, CH_3O), 3.38 (dd, 1H, $J_{5,6'}$ 4.5 Hz, H-6'), 1.50 and 1.32 (2s, each 3H, $(CH_3)_2C$). Anal. calcd. for $C_{17}H_{23}N_3O_5$: C 58.44, H 6.63, N 12.03; found: C 58.40, H 6.63, N 11.87.

Methyl 6-azido-3-O-benzyl-6-deoxy-5-O-methyl-α- and -β-D-glucofuranoside (23α, 23β)

A solution of **22** (24 g, 0.068 mol) in methanolic 1 N hydrochloric acid (220 mL) was kept overnight at room temperature. It was neutralized with sodium hydrogen carbonate and evaporated. The remainder was taken up in dichloromethane, followed by washing of the organic solution with water, drying, and evaporation. Column chromatographic purification on silica gel (hexane – ethyl acetate, 3.5:1) provided in the first fraction the α-anomer **23α** (5.24 g, 24%) as an oil; $[\alpha]_D$ +41.4 (*c* 0.4, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.25 (m, 5H, Ph), 5.01 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 4.74 and 4.58 (ABq, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.23 (m, 1H, H-2), 4.21 (dd, 1H, $J_{3,4}$ 4.5 Hz, $J_{4,5}$ 7.5 Hz, H-4), 4.03 (dd, 1H, $J_{2,3}$ 2.2 Hz, H-3), 3.70 (m, 1H, H-5), 3.64 (dd, 1H, $J_{5,6A}$ 2.5 Hz, $J_{6A,6B}$ 13.0 Hz, H-6A), 3.49 and 3.40 (2s, each 3H, $2CH_3O$), 3.37 (dd, 1H, $J_{5,6B}$ 4.5 Hz, H-6B), 2.84 (d, 1H, $J_{2,OH}$ 5.5 Hz, OH). Anal. calcd. for $C_{15}H_{21}N_3O_5$: C 55.72, H 6.55, N 12.99; found: C 55.65, H 6.59, N 12.82. Continued elution provided an α,β mixture of **23** (3.31 g, 15%) and finally the pure β anomer **23β** (10.9 g, 49%, total yield 88%) as an oil; $[\alpha]_D$ −71 (*c* 0.4, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.25 (m, 5H, Ph), 4.80 (bs, 1H, $J_{1,2}$ ~ 1 Hz, H-1), 4.67 and 4.62 (ABq, 2H, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.30 (dd, 1H, $J_{3,4}$ 4.7 Hz, $J_{4,5}$ 8.5 Hz, H-4), 4.20 (bs, 1H, H-2), 3.97 (dd, 1H, $J_{2,3}$ 1.6 Hz, H-3), 3.76 (m, 1H, H-5), 3.73 (dd, 1H, $J_{6A,6B}$ 13.0 Hz, $J_{5,6A}$ 2.5 Hz, H-6A), 3.40 (dd, overlapped, $J_{5,6B}$ 4.5 Hz, H-6B), 3.394 and 3.390 (2s, each 3H, $2CH_3O$), 1.67 (d, 1H, $J_{2,OH}$ 3.5 Hz, OH). Anal. calcd. for $C_{15}H_{21}N_3O_5$: C 55.72, H 6.55, N 12.99; found: C 55.73; H 6.27, N 12.88.

Methyl 3-O-benzyl-N-benzyloxycarbonyl-2,6-dideoxy-2,6-imino-5-O-methyl-β-D-glucofuranoside (26)

Trifluoromethanesulfonic anhydride (4.1 mL, 24.4 mmol) was added at −50°C to a stirred solution of **23β** (5.34 g, 16.5 mmol) and pyridine (6 mL, 74.2 mmol) in dichloromethane (100 mL). After 1 h, another portion of the anhydride (1.5 mL, 8.9 mmol) was added and stirring continued for 30 more min at −50°C. The mixture was poured into ice-water, followed by extraction with dichloromethane, washing of the organic solution with water, drying, and evaporation. The remainder (**24**) was taken up in dichloromethane (51 mL) and reduced with triphenylphosphine (5 g, 19 mmol) by refluxing for 2 h. The mixture was allowed to reach room temperature and a solution of saturated aqueous potassium carbonate (10 mL) was added, followed by vigorous stirring overnight. The organic layer was separated, washed with water and evaporated. The resulting product (**25**) was taken up in ether (63 mL). Saturated aqueous sodium hydrogen carbonate (42 mL) and benzyl chloroformate (3.25 mL, 22.8 mmol) were added with vigorous stirring. After 30 min, the organic layer was separated, washed with water, dried, and evaporated. The crude product was applied to a column of silica gel and eluted with hexane-ethyl acetate, 3:1, 2:1 to afford pure **26** (4.6 g, 68%) as a tough syrup; $[\alpha]_D$ −68 (*c* 0.5, chloroform). ^{1}H NMR ($CDCl_3$, duplication of signals due to rotamers, a:b ~ 4:1) δ: 7.40–7.15 (m, 10H, 2Ph), 5.10 (d, overlapped, $J_{1,2}$ 3.0 Hz, H-1a), 5.05 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1b), 4.89 (t, 1H,$J_{2,3}$ 3.5 Hz, H-2a), 4.68 (t, overlapped, $J_{2,3}$ 3.5 Hz, H-2b), 4.46 (dd, 1H, *J* 7.0 and 12.5 Hz, H-5b), 4.40 (overlapped, H-4a), 4.39 (overlapped, H-4b), 4.29 (dd, 1H, *J* 7.0 and 12.0 Hz, H-5a), 4.07 (dd, 1H, H-3a), 3.98 (dd, 1H, H-3b), 3.68–3.60 (m, H-6a, H-6b), 3.494, 3.489 (2s, each 3H, CH_3O-a, CH_3O-b), 3.37, 3.34 (2s, each 3H, CH_3O-a, CH_3O-b), 3.36–3.26 (m, 2H, H-6'a, H-6'b). Anal. calcd. for $C_{23}H_{27}NO_6$: C 66.81, H 6.58, N 3.39; found: C 66.82, H 6.78, N 3.37.

4-O-Benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-2-O-methyl-D-mannitol (28)

A mixture of **26** (2.1 g, 5.07 mmol), dioxane (21.5 mL), trifluoroacetic acid (11 mL), and water (11 mL) was stirred for 3.5 h. Then a solution of sodium acetate (3.6 g) in water (53 mL) was added. The product was extracted with dichloromethane, followed by drying and evaporation of the organic solution. The resultant material (**27**) was dissolved in 95% ethanol (25 mL) and a suspension of sodium borohydride (600 mg, 15.9 mmol) in 50% ethanol (4 mL) was added at 0°C. After stirring for 30 min at room temperature, the reaction was quenched by the addition of ammonium chloride followed by evaporation. The remainder was extracted with dichloromethane, the organic solution was washed with a little water, dried, and evaporated. The reaction product was purified on a column of silica gel (dichloromethane – ethyl acetate, 1:1, 1:2, 1:3, 0:1) to afford **28** (1.044 g, 51%); $[\alpha]_D$ −36 (*c* 0.7, chloroform). Anal. calcd. for $C_{22}H_{27}NO_6$: C 65.82, H 6.78, N 3.49; found: 65.06, H 6.84, N 3.43.

4-O-Benzyl-N,6-O-carbonyl-1,5-dideoxy-1,5-imino-2-O-methyl-D-mannitol (30)

A solution of **28** (520 mg, 1.30 mmol) in methanolic 0.5 N sodium methoxide (4 mL) was kept for 2 h at room temperature. The solution was deionized with Amberlite IRC 50 (H^+), filtered, and evaporated. The remainder was applied to a column of silica gel (dichloromethane – ethyl acetate, 1:1) to afford pure **30** (308 mg, 81%) as a solid; mp 99.5–100.5°C (dichloromethane, ether, hexane); $[\alpha]_D$ +40 (*c* 0.3, chloroform). IR ($CHCl_3$): 1754 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H, Ph), 5.01 and 4.65 (ABq, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.30 (dd, 1H, $J_{6A,6B}$ 9.0 Hz, $J_{6A,5}$ 7.5 Hz, H-6A), 4.17 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.0 Hz, H-1A), 3.96 (dd, 1H, $J_{6B,5}$ 3.0 Hz, H-6B), 3.68 (unres. m, 1H, H-3), 3.60 (bs, 1H, H-2), 3.54 (t, 1H, $J_{3,4} \sim J_{4,5}$ 9.5 Hz, H-4), 3.49 (m, H-5), 3.44 (s, 3H, CH_3O), 2.84 (dd, 1H, $J_{1B,2}$ 1.5 Hz, H-1B), 2.56 (bd, 1H, OH). Anal. calcd. for $C_{15}H_{19}NO_5$: C 61.42, H 6.53, N 4.78; found: C 61.17, H 6.55, N 4.75.

*4-O-Benzyl-N,6-O-carbonyl-1,2,5-trideoxy-1,5-imino-D-*arabino*-hexitol (31)*

A solution of **29** (26) (360 mg, 0.97 mmol) in methanolic 0.5 N sodium methoxide (3.5 mL) was kept at room temperature for 1.5 h. The solution was neutralized with Amberlite IRC 50 (H^+), filtered, and evaporated. Column chromatography on silica gel (dichloromethane – ethyl acetate, 1:1) afforded **31** (227 mg, 89%) as a white solid; $[\alpha]_D$ +76 (*c* 0.3, chloroform). IR ($CHCl_3$): 1794 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–7.25 (m, 5H, Ph), 4.88 and 4.67 (ABq, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.29 (dd, 1H, $J_{6A,6B}$ 8.5 Hz, $J_{6A,5}$ 7.5 Hz, H-6A), 3.89 (dd, $J_{5,6B}$ 5.5 Hz, H-6B), 3.82 (ddd, 1H, $J_{1e,1a}$ 13.5 Hz, $J_{1e,2a}$ 5.5 Hz, $J_{1e,2e}$ 1.5 Hz, H-1e), 3.68 (ddd, 1H, $J_{2a,3}$ 11.5 Hz, $J_{2e,3}$ 4.5 Hz, $J_{3,4}$ 9.0 Hz, H-3), 3.50 (ddd, 1H, $J_{4,5}$ 9.0 Hz, H-5), 3.15 (t, 1H, H-4), 2.93 (bs, 1H, OH), 2.85 (dt, $J_{1a,2a}$ 13.5 Hz, $J_{1a,2e}$ 3.5 Hz, H-1a), 1.95 (m, 1H, $J_{2e,2a}$ 13.0 Hz, H-2e), 1.56 (dq, 1H, H-2a). Anal. calcd. for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32; found: C 63.88, H 6.53, N 5.26.

*4-O-Benzyl-N,6-O-carbonyl-1,5-dideoxy-1,5-imino-2-O-methyl-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-*mannitol *(32)*

A solution of bromide **14** (2.58 mmol) in dichloromethane (4 mL) was transferred into a mixture of **30** (202 mg, 0.69 mmol), tetraethylammonium bromide (300 mg, 1.43 mmol), *N,N*-dimethylformamide (0.7 mL), and 4 Å molecular sieves (powdered, 0.7 g) in dichloromethane (2 mL). After stirring for 3 days, the mixture was processed as described for the preparation of **15** with subsequent column chromatography on silica gel (hexane – ethyl acetate, 4:1 to 1:1) to afford crystalline **32** (377 mg, 67%); mp 114–115°C (dichloromethane, ether, hexane); $[\alpha]_D$ +72 (*c* 0.3, chloroform). ^1H NMR ($CDCl_3$) δ: 7.35–7.10 (m, 25H, 5Ph), 5.14–4.43 (5ABq, 10H, 5CH_2Ph), 4.96 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1'), 4.24 (t, 1H, $J_{6A,6B}$ 8.8 Hz, $J_{6A,5}$ 8.0 Hz, H-6A), 4.10 (overlapped, H-3'), 4.06 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 3.84 (bs, 1H, H-2), 3.79 (dd, 1H, $J_{6B,5}$ 3.0 Hz, H-6B), 3.56 (dd, 1H, $J_{2',3'}$ 9.5 Hz, H-2'), 3.49 (m, 2H, H-3, H-5), 3.28 (s, 3H, CH_3O), 2.71 (bd, 1H, $J_{1B,2} < 1$ Hz, H-1B). ^{13}C NMR ($CDCl_3$) δ: 157.81 (CO), 100.37 (C-1'), 65.77 (C-6), 57.27 (C-5), 56.43 (CH_3O), 40.05 (C-1). Anal. calcd. for $C_{49}H_{53}NO_{10}$: C 72.13, H 6.55, N 1.72; found: C 71.78, H 6.68, N 1.76.

*4-O-Benzyl-N,6-O-carbonyl-1,2,5-trideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-*arabino*-hexitol (33)*

A solution of bromide **14** (2.5 mmol) in dichloromethane (5 mL) was transferred into a mixture of **31** (197 mg, 0.75 mmol), tetraethylammonium bromide (300 mg, 1.43 mmol), *N,N*-dimethylformamide (0.7 mL), and 4 Å molecular sieves (powdered, 0.7 g), in dichloromethane (2 mL). After stirring for 3 days, the mixture was processed as described for **15** with subsequent column chromatography on silica gel (hexane – dichloromethane – ethyl acetate, 4:4:1, 3:5:1, 2:5:1.5) to provide **33** (379 mg, 65%) as a solid. The analytical sample was recrystallized from ethanol; mp 113–114°C, $[\alpha]_D$ +89 (*c* 0.8, chloroform). ^1H NMR ($CDCl_3$) δ: 7.40–7.15 (m, 25H, 5Ph), 5.08 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1'), 5.06–4.43 (5ABq, 10H, 5CH_2Ph), 4.23 (t, 1H, $J_{6A,6B} \sim J_{6A,5}$ 8.0 Hz, H-6A), 4.02 (t, 1H, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 9.0 Hz, H-3'), 3.90 (m, 1H, H-5'), 3.76 (bdd, 1H, $J_{1e,1a}$ 13.5 Hz, $J_{1e,2a}$ 4.5 Hz, $J_{1e,2e} \sim 1$ Hz, H-1e), 3.71 (dd, overlapped, H-6B), ~3.63 (overlapped, H-4'), 3.57 (dd, 1H, H-2'), 3.49 (m, 1H, H-5), 3.22 (t, 1H, $J_{3,4} \sim J_{4,5}$ 9.0 Hz, H-4), 2.78 (dt, 1H, $J_{1a,2a}$ 13.5 Hz, $J_{1a,2e}$ 2.5 Hz, H-1a), 2.25 (m, 1H, $J_{2e,2a}$ 13.0 Hz, H-2e), 1.57 (dq, 1H, H-2a). ^{13}C NMR ($CDCl_3$) δ: 156.67 (CO), 99.64 (C-1'), 65.84 (C-6), 57.17 (C-5), 38.72 (C-1), 31.10 (C-2). Anal. calcd. for $C_{48}H_{51}NO_9$: C 73.36, H 6.54, N 1.78; found: C 73.11, H 6.35, N 1.82.

4-O-Benzyl-1,5-dideoxy-1,5-imino-2-O-methyl-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-mannitol (34)

A mixture of **32** (334 mg, 0.41 mmol) in 5% potassium hydroxide in 90% ethanol (10 mL) was heated at 65°C for 4 h. It was processed as described for **17** followed by column chromatography on silica gel (dichloromethane – 5% methanol) to afford **34** (295 mg, 91%); $[\alpha]_D$ +35 (*c* 0.7, chloroform). ^1H NMR ($CDCl_3$, broad signals) δ: 7.35–7.10 (m, 25H, 5Ph), 4.98 (overlapped, H-1'), 4.15 (overlapped, H-5'), 4.09 (t, overlapped, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 9.0 Hz, H-3'), 3.54 (dd, overlapped, H-2'), 3.27 (s, 3H, CH_3O), 3.15 (bd, 1H, $J_{1A,1B}$ 13.0 Hz, H-1A), 2.48 (H-1B).

*4-O-Benzyl-1,2,5-trideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-*arabino*-hexitol (35)*

A mixture of **33** (306 mg, 0.39 mmol) and potassium hydroxide (0.5 g) in 90% ethanol (10 mL) was heated at 68°C for 1 h. It was processed as described for **17** followed by column chromatography on silica gel (dichloromethane – 5% methanol) to provide **35** (245 mg, 83%); $[\alpha]_D$ +58 (*c* 1.0, chloroform). ^1H NMR ($CDCl_3$) δ: 7.40–7.10 (m, 25H, 5Ph), 5.12–4.42 (5ABq, 10H, 5CH_2Ph), 5.08 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1'), 4.04 (t, 1H, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 9.0 Hz, H-3'), 3.93 (m, 1H, H-5'), 3.72 (overlapped, H-6'), 3.63 (overlapped, H-4'), 3.55 (dd, 1H, H-2'), 3.02 (m, 1H, $J_{1e,1a}$ 12.5 Hz, H-1e), 2.61 (dt, 1H, $J_{1a,2a}$ 13.0 Hz, $J_{1a,2e}$ 1.5 Hz, H-1a), 2.23 (m, 1H, $J_{2a,2e}$ 13.5 Hz, H-2e), 1.59 (dq, 1H, H-2a).

1,5-Dideoxy-3-O-(α-D-glucopyranosyl)-1,5-imino-2-O-methyl-D-mannitol-hydrochloride (36)

A mixture of **34** (140 mg, 0.19 mmol), 5% palladium-on-carbon (145 mg), and methanolic 0.12 N hydrochloric acid (2 mL, 0.24 mmol) in methanol (3 mL) was hydrogenated in the hydrogen stream for 2 h. Usual processing followed by gel filtration as described for **9** provided **36** (68 mg, 98%) as a solid after freeze-drying an aqueous solution; $[\alpha]_D$ +73 (*c* 0.4, water). The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

*1,2,5-Trideoxy-3-O-(α-D-glucopyranosyl)-1,5-imino-D-*arabino*-hexitol-hydrochloride (37)*

A mixture of **35** (242 mg, 0.32 mmol), 5% palladium-on-carbon (240 mg), and methanolic 0.12 N hydrochloric acid (3.34 mL, 0.40 mmol) was hydrogenated in the hydrogen stream for 2 h. Usual work-up and gel filtration as described for **9** provided **37** (104 mg, 94%) as a white solid after freeze-drying an aqueous solution. The ^1H and ^{13}C NMR data are reported in Tables 1 and 2.

Methyl-3-O-allyl-6-azido-5-O-benzyl-6-deoxy-α- and -β-D-glucofuranoside (38)

The title compound was prepared conventionally from 3-*O*-allyl-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (27). Replacement of the *p*-toluenesulfonyloxy group by azide, benzylation of the 5-position, and subsequent methanolysis as described for **23** provided the title compound as an oil. **38** proved labile on storage. α-Anomer: ^1H NMR ($CDCl_3$) δ: 7.35–7.20 (m, 5H, Ph), 5.87 (m, 1H, CH_2=C*H*), 5.28 and 5.17 (2m, 2H, CH_2=CH), 5.02 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 4.71 and 4.59 (ABq, 2H, $J_{A,B}$ 11.5 Hz, CH_2Ph), 4.26 (dd, 1H, $J_{3,4}$ 4.0 Hz, H-4), 4.22–4.15 (m, 2H, H-2, 1CH_2CH=CH_2), 4.00–3.92 (m, 3H, H-3, H-5, 1CH_2CH=CH_2), 3.62 (dd, 1H, $J_{6A,6B}$ 13.5 Hz, $J_{6A,5}$ 2.5 Hz, H-6A),

3.49 (s, 3H, CH_3O), 3.41 (dd, 1H, $J_{5,6B}$ 5.0 Hz, H-6B). β-Anomer: ^{1}H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H, Ph), 5.88 (m, 1H, CH_2=C*H*), 5.27 and 5.18 (2m, 2H, CH_2=CH), 4.82 (d, 1H, $J_{1,2} \sim 1$ Hz, H-1), 4.72 and 4.60 (ABq, 2H, $J_{A,B}$ 11.0 Hz, CH_2Ph), 4.37 (dd, 1H, $J_{3,4}$ 5.2 Hz, $J_{4,5}$ 8.5 Hz, H-4), 4.21 (bs, 1H, H-2), 4.11 and 4.03 (2m, 2H, CH_2CH=CH_2), 4.02 (m, overlapped, H-5), 3.92 (dd, 1H, $J_{3,2}$ 1.2 Hz, H-3), 3.69 (dd, 1H, $J_{6A,6B}$ 13.0 Hz, $J_{6A,5}$ 2.5 Hz, H-6A), 3.42 (dd, 1H, $J_{6B,5}$ 4.5 Hz, H-6B), 3.40 (s, 3H, CH_3O).

*Methyl 3-*O*-allyl-5-*O*-benzyl-*N*-benzyloxycarbonyl-2,6-dideoxy-2,6-imino-α- and -β-*D*-glucofuranoside (**41**α,β)*

Trifluoromethanesulfonic anhydride (2.6 mL, 15.45 mmol) was added at −50 to −40°C to a solution of **38** (3.66 g, 10.5 mmol) and pyridine (3.6 mL, 44.5 mmol) in dichloromethane (70 mL). After 40 min at this temperature, it was processed as described for **26**. The resultant material (**39**) was dissolved in dichloromethane (40 mL) and reduced with triphenylphosphine (3.3 g, 12.6 mmol) for 20 min at room temperature and then for 2 h at reflux temperature. The mixture was allowed to reach room temperature and was vigorously stirred after the addition of saturated aqueous potassium carbonate (10 mL). After 12 h, the organic layer was separated, washed with water, and evaporated. A mixture of the resulting product (**40**), saturated aqueous sodium hydrogen carbonate (30 mL), and benzylchloroformate (2 mL, 14.0 mmol) in ether (45 mL) was vigorously stirred for 20 min. The organic layer was separated, washed with water, and evaporated, followed by column chromatography on silica gel (hexane – ethyl acetate, 3:1) to provide in the first fraction the α-anomer **41**α (330 mg, 7.2%); $[\alpha]_D$ +40 (*c* 0.9, chloroform). ^{1}H NMR ($CDCl_3$, mixture of two rotamers) δ: 7.40–7.15 (m, 10H, 2Ph), 5.83–5.66 (m, 1H, CH_2=C*H*), 4.27 (dd, overlapped, $J_{5,6}$ 6.5 Hz, H-6), 3.37 (s, 3H, CH_3O), 3.01–2.90 (m, H-6′). Anal. calcd. for $C_{25}H_{29}NO_6$: C 68.32, H 6.65, N 3.19; found: C 68.46, H 6.64, N 3.25. Continued elution afforded the β-anomer **41**β (2.21 g, 48%); $[\alpha]_D$ −132 (*c* 0.9, chloroform). ^{1}H NMR ($CDCl_3$, mixture of two rotamers) δ: 5.85–5.66 (m, CH_2=C*H*), 5.10 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1a), 5.06 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1b), 4.78 (t, 1H, $J_{2,3}$ 3.5 Hz, H-2a), 4.41 (dd, H-4a, H-4b), 4.38 (dd, $J_{5,6}$ 7.5 Hz, H-6b), 4.18 (dd, 1H, $J_{5,6}$ 7.0 Hz, $J_{6,6'}$ 12.5 Hz, H-6a), 4.00 (dd, 1H, $J_{3,4}$ 5.7 Hz, H-3a), 3.91 (overlapped, $J_{3,4}$ 5.5 Hz, $J_{2,3}$ 3.5 Hz, H-3b), 3.84–3.76 (m, H-5a, H-5b), 3.50 (s, 3H, CH_3O), 3.40 (H-6′a), 3.37 (H-6′b). Anal. calcd. for $C_{25}H_{29}NO_6$: C 68.32, H 6.65, N 3.19; found: C 68.35, H 6.79, N 3.20.

*4-*O*-Allyl-2-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol (**43**)*

50% Trifluoroacetic acid (25 mL) was added at ice-bath temperature to a solution of **41**β (2.45 g, 5.57 mmol) in dioxane (25 mL). After 4 h at room temperature, a solution of sodium acetate (4.1 g) in water (60 mL) was added. The product was extracted with dichloromethane, followed by drying and evaporation of the organic solution. The remainder was dissolved in 95% ethanol (41 mL) and a suspension of sodium borohydride (720 mg, 19 mmol) in 50% ethanol (6 mL) was added at ice-bath temperature. After 30 min at room temperature, it was worked up as described for **28** with subsequent column chromatography on silica gel (dichloromethane – ethyl acetate, 3:1, 2:1, 1:1) to afford **43** (1.40 g, 59%) as a syrup, $[\alpha]_D$ −22 (*c* 1.8, chloroform). Anal. calcd. for $C_{24}H_{29}NO_6$: C 67.43, H 6.84, N 3.28; found: C 67.57, H 6.92, N 3.30.

*4-*O*-Allyl-2-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (**44**)*

A solution of **43** (1.74 g, 4.07 mmol) in methanolic 0.5 N sodium methoxide (13 mL) was kept at room temperature for 5 h. The solution was made neutral with Amberlite IRC 50 (H^+), filtered, and evaporated. The resultant solid material was purified on a column of silica gel (dichloromethane – ethyl acetate, 3:1, 2:1) to provide **44** (1.15 g, 89%). The analytical sample was recrystallized from dichloromethane, ether, hexane; mp 119.5–120.5°C; $[\alpha]_D$ −49 (*c* 0.4, chloroform). IR ($CHCl_3$): 1760 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.25 (m, 5H, Ph), 5.90 (m, 1H, CH_2=C*H*), 5.26 and 5.19 (2m, 2H, CH_2=CH), 4.84 and 4.36 (ABq, 2H, $J_{A,B}$ 10.5 Hz, CH_2Ph), 4.46 and 4.12 (2m, 2H, CH_2=CH-CH_2), 4.43 (dd, overlapped, 1H, $J_{5,6A}$ 7.5 Hz, H-6A), 4.25 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 4.22 (dd, 1H, $J_{6A,6B}$ 8.5 Hz, $J_{5,6B}$ 2.5 Hz, H-6B), 3.81 (m, 1H, H-2), 3.62 (bdd, 1H, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 8.5 Hz, H-3), 3.49 (m, 2H, H-4, H-5), 2.90 (dd, 1H, $J_{1B,2}$ 1.0 Hz, H-1B). Anal. calcd. for $C_{17}H_{21}NO_5$: C 63.94, H 6.63, N 4.39; found: C 64.10, H 6.60, N 4.40.

*4-*O*-Allyl-2-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**45**)*

A solution of bromide **14** (8.3 mmol) in dichloromethane (15 mL) was added to a mixture of **44** (0.99 g, 3.10 mmol), tetraethylammonium bromide (1.2 g, 5.7 mmol), *N*,*N*-dimethylformamide (2.7 mL), and 4 Å molecular sieves (powdered, 3 g) in dichloromethane (4 mL). After stirring for 3 days, more bromide (2.9 mmol) was added and stirring continued for 2 more days. Usual processing as described for **15** was followed by two column chromatographic purifications on silica gel (hexane – ethyl acetate, 4:1 to 1:2 and hexane–dichloromethane – ethyl acetate, 5:2:1) to provide pure **45** (1.6 g, 61%) as a white foam, $[\alpha]_D$ −1.3, $[\alpha]_{365}$ −32.9 (*c* 0.5, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.15 (m, 25H, 5Ph), 5.73 (m, 1H, CH_2=C*H*), 5.13 and 5.05 (2m, 2H, CH_2=CH), 5.04 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.40 (t, 1H, $J_{6A,6B} \sim J_{5,6A}$ 8.5 Hz, H-6A), 4.19 (dd, 1H, $J_{6B,5}$ 3.5 Hz, H-6B), 4.16 (overlapped, dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 2.79 (bd, 1H, H-1B). ^{13}C NMR ($CDCl_3$) δ: 157.63 (CO), 134.79 (CH_2=*C*H), 116.56 (*C*H_2=CH), 99.96 (C-1′), 65.62 (C-6), 57.32 (C-5), 40.63 (C-1). Anal. calcd. for $C_{51}H_{55}NO_{10}$: C 72.75, H 6.58, N 1.66; found: C 72.65, H 6.70, N 1.69.

*2-*O*-Benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**46**)*

A mixture of **45** (1.2 g, 1.43 mmol), tris(triphenylphosphine)-rhodium(I)chloride (89 mg, 0.096 mmol), 1,4-diazabicyclo[2.2.2]-octane (40 mg, 0.36 mmol), 95% ethanol (84 mL), toluene (36 mL), and water (12 mL) was boiled under reflux for 10 h with stirring. The solvent was removed and the residue dissolved in acetone (116 mL) containing mercuric oxide (24 mg). A solution of mercuric chloride (3.2 g) in acetone–water (9:1, 72 mL) was added and the mixture stirred for 30 min. After solvent removal, the residue was taken up in dichloromethane, the solution washed with aqueous saturated potassium bromide and water, followed by evaporation. Chromatography on a column of silica gel (hexane – ethyl acetate, 2:1, 1:1, 1:2) gave alcohol **46** (1.07 g, 94%) as a white foam; $[\alpha]_D$ 0, $[\alpha]_{365}$ −6.4 (*c* 0.4, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.15 (m, 25H, 5Ph), 4.91 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.39 (t, 1H, $J_{6A,6B} \sim J_{6A,5}$ 8.5 Hz, H-6A), 4.27 (dd, 1H, $J_{5,6B}$ 3.5 Hz, H-6B), 4.20 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.0 Hz, H-1A), 4.04 (t, 1H, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 9.0 Hz, H-3′), 4.02 (t, 1H, $J_{3,4} \sim J_{4,5}$ 9.0 Hz, H-4), 3.91 (m, 1H, H-5′), 3.88 (m, 1H, H-2), 3.59–3.49 (m, 4H, H-5, H-2′, H-4′, H-6A′), 3.45 (dd, 1H, $J_{6A',6B'}$ 10.5 Hz, $J_{5',6B'}$ 2.0 Hz, H-6B′), 3.34 (dd, 1H, $J_{2,3}$ 2.5 Hz, H-3), 2.86 (bd, 1H, H-1B). ^{13}C NMR ($CDCl_3$) δ: 157.60 (CO), 100.41 (C-1′), 65.10 (C-6), 57.26 (C-5), 41.01 (C-1). Anal. calcd. for $C_{48}H_{51}NO_{10}$: C 71.89, H 6.41, N 1.75; found: C 71.48, H 6.37, N 1.79.

*2-*O*-Benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-4-*O*-methyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol (**47**)*

To a solution of **46** (300 mg, 0.37 mmol) in *N*,*N*-dimethylformamide (1.2 mL), sodium hydride (80% oily suspension, 22 mg, 0.73 mmol) was added at ice-bath temperature with stirring. After 15 min, methyl iodide (45 μL, 0.72 mmol) was added and stirring was continued for 30 min at 0°C and then for 1.5 h at room temperature. The reaction was quenched by a few drops of methanol.

It was diluted with dichloromethane, washed with water, dried, and evaporated. The resultant material was applied to a column of silica gel (hexane – ethyl acetate, 2:1, 1:1) to afford **47** (305 mg, 88%); $[\alpha]_D$ −6.3 (*c* 0.3, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.15 (m, 25H, 5Ph), 5.08 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.40 (t, 1H, $J_{5,6A} \sim J_{6A,6B}$ 8.5 Hz, H-6A), 4.17 (overlapped dd, 1H, $J_{5,6B}$ 3.0 Hz, H-6B), 4.14 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 4.02 (overlapped, H-2), 3.52 (s, overlapped, CH_3O), 2.76 (bd, 1H, H-1B). ^{13}C NMR ($CDCl_3$) δ: 157.61 (CO), 99.86 (C-1′), 65.65 (C-6), 61.52 (CH_3O), 57.45 (C-5), 40.60 (C-1). Anal. calcd. for $C_{49}H_{53}NO_{10}$: C 72.13, H 6.55, N 1.72; found: C 72.04, H 6.62, N 1.73.

*2-O-Benzyl-N,6-O-carbonyl-1,4,5-trideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-*lyxo*-hexitol (49)*

Sodium hydride (80% suspension, 52 mg, 1.73 mmol) was added to a solution of **46** (350 mg, 0.44 mmol) and a crystal of imidazole in tetrahydrofuran (5 mL). After 30 min, carbon disulfide (400 μL, 6.65 mmol) was added and, after another 30 min, methyl iodide (110 μL, 1.77 mmol). The mixture was kept stirring for 30 min, was diluted with dichloromethane, followed by washing of the organic solution with water, drying, and evaporation. The resultant yellowish solid (**48**) was taken up in toluene (5 mL) and reduced with tributyltin hydride (350 μL, 1.30 mmol) at reflux temperature for 4 h. The product obtained on evaporation was purified on a column of silica gel (hexane–dichloromethane – ethyl acetate, 5:1:0.5, 5:1:1) to provide pure **49** (270 mg, 79%); $[\alpha]_D$ +7.2 (*c* 0.4, chloroform. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.10 (m, 25H, 5Ph), 4.89 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.38 (t, 1H, $J_{6A,6B} \sim J_{6A,5}$ 8.5 Hz, H-6A), 4.15 (dd, 1H, $J_{1A,1B}$ 14.5 Hz, $J_{1A,2}$ 2.5 Hz, H-1A), 4.01 (t, 1H, $J_{2',3'}$ 9.5 Hz, $J_{3',4'}$ 8.5 Hz, H-3′), 3.97 (dd, 1H, $J_{6B,5}$ 4.5 Hz, H-6B), 3.83 (m, 1H, $J_{5',4'}$ 9.5 Hz, H-5′), 3.77 (m, 1H, H-2), 3.72 (m, 1H, H-5), 3.63 (m, 1H, H-3), 3.60–3.49 (m, 4H, H-4′, H-6A′, H-6B′ and H-2′ at 3.57), 2.75 (bd, 1H, H-1B), 2.13 (q, 1H, $J_{4a,4e} \sim J_{3,4a} \sim J_{4a,5}$ 11 Hz, H-4a), 1.75 (m, 1H, H-4e). ^{13}C NMR ($CDCl_3$) δ: 157.54 (CO), 95.97 (C-1′), 66.84 (C-6), 52.63 (C-5), 42.07 (C-1), 29.47 (C-4). Anal. calcd. for $C_{48}H_{51}NO_9$: C 73.36, H 6.54, N 1.78; found: C 73.06, H 6.49, N 1.84.

2-O-Benzyl-1,5-dideoxy-1,5-imino-4-O-methyl-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-mannitol (50)

A mixture of **47** (245 mg, 0.30 mmol) and potassium hydroxide (500 mg) in 90% ethanol (10 mL) was heated at 75°C for 4 h. The mixture was processed in the usual way and the resulting product purified on a column of silica gel (dichloromethane – 5–7% methanol) to provide **50** (175 mg, 74%) as a tough syrup; $[\alpha]_D$ +31 (*c* 0.7, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.35–7.15 (m, 25H, 5Ph), 5.09 (bs, 1H, H-1′), 3.56 (dd, overlapped, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 9.5 Hz, H-2′), 3.45 (s, 3H, CH_3O), 3.08 (dd, 1H, $J_{1A,1B}$ 14.0 Hz, H-1A), 2.54 (bd, 1H, H-1B).

*2-O-Benzyl-1,4,5-trideoxy-1,5-imino-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-D-*lyxo*-hexitol (51)*

A mixture of **49** (278 mg, 0.35 mmol) and potassium hydroxide (500 mg) in 90% ethanol (10 mL) was heated at 70°C for 10 h. Usual work-up with subsequent column chromatography on silica gel (dichloromethane – 4–6% methanol) provided **51** (239 mg, 89%) as a tough syrup; $[\alpha]_D$ +52 (*c* 0.5, chloroform). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.10 (m, 25H, 5Ph), 4.88 (bs, overlapped, H-1′), 3.96 (t, 1H, $J_{3',4'} \sim J_{2',3'} \sim 9$ Hz, H-3′), 3.58 (dd, overlapped, H-2′).

1,5-Dideoxy-3-O-(α-D-glucopyranosyl)-1,5-imino-4-O-methyl-D-mannitol-hydrochloride (52)

A mixture of **50** (140 mg, 0.18 mmol), 5% palladium-on-carbon (140 mg), and methanolic 0.12 N hydrochloric acid (1.7 mL, 0.20 mmol) in methanol (4 mL) was hydrogenated in the hydrogen stream for 3 h. Usual work-up and gel filtration as described for **9** provided **52** (52.5 mg, 79%) as a white solid after freeze-drying an aqueous solution; $[\alpha]_D$ +92 (*c* 0.4, water). The ^{1}H and ^{13}C NMR data are reported in Tables 1 and 2.

*1,4,5-Trideoxy-3-O-(α-D-glucopyranosyl)-1,5-imino-D-*lyxo*-hexitol (53)*

A mixture of **51** (235 mg, 0.31 mmol), 5% palladium-on-carbon (235 mg), and methanolic 0.12 N hydrochloric acid (2.9 mL, 0.35 mmol) in methanol (5 mL) was hydrogenated in the hydrogen stream for 2.5 h. Usual work-up and gel filtration as described for **9** provided **53** (107 mg, 100%) as a white solid after freeze-drying an aqueous solution; $[\alpha]_D$ +106 (*c* 0.3, water). The ^{1}H and ^{13}C NMR data are reported in Tables 1 and 2.

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