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Aminosubstituted α-D-glucosylmethylbenzenes (benzyl α-*C*-glucosides) and an *N*-(*C*-α-D-glucosylmethyl)aniline (anilinomethyl α-*C*-glucoside); novel α-D-glucosidase inhibitors

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ABSTRACT

D-Glucose was transformed via 3,4,5,7-tetra-*O*-benzyl-1,2-dideoxy-D-*gluco*-hept-1-enitol (**5**) into 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-phenyl-D-*erythro*-L-*ido*-heptitol (**9**) the structure of which was determined by X-ray analysis of the per-*O*-acetylated derivative **12**. 1-*O*-Mesylation of **9** and azide displacement gave only low yields of 2,6-anhydro-7-azido-1,3,4,5-tetra-*O*-benzyl-7-deoxy-7-*C*-phenyl-D-*erythro*-L-*gulo*-heptitol (**16**). Therefore, **9** was oxidized to 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-phenyl-D-*glycero*-D-*ido*-heptose (**15**) and thence transformed into the (*E*/*Z*)-oximes **17h,l** which, with $LiAlH_4$ as reducing agent, gave 7-amino-2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7-deoxy-7-*C*-phenyl-D-*erythro*-L-*gulo*-heptitol (**19**), 7-amino-2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7-deoxy-7-*C*-phenyl-L-*threo*-L-*gulo*-heptitol (**23**), and 2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7-deoxy-7-phenylamino-D-*glycero*-L-*gulo*-heptitol (**27**) in 1:1:1 ratios. Their *N*-protection, hydrogenolytic *O*-debenzylation, and *N*-deprotection afforded the desired target molecules 7-amino-2,6-anhydro-7-deoxy-7-*C*-phenyl-D-*erythro*-L-*gulo*-heptitol (**1a**), 7-amino-2,6-anhydro-7-deoxy-7-*C*-phenyl-L-*threo*-L-*gulo*-heptitol (**2a**), and 2,6-anhydro-7-deoxy-7-phenylamino-D-*glycero*-L-*gulo*-heptitol (**4a**). Hydrogenolysis of **15** furnished directly 2,6-anhydro-7-deoxy-7-*C*-phenyl-D-*glycero*-L-*gulo*-heptitol (**3a**). Inhibition studies with α-D-glucosidase from yeast with *p*-nitrophenyl α-D-glucopyranoside as substrate exhibited, for **1a** and **4a**, K_i values of the same order as found for 1-deoxynojirimycin.

INTRODUCTION

The finding that amino sugar-based glycosidase inhibitors have potential as anti-HIV, diabetes, and cancer therapeutic agents has led to a wide interest and a demand for such compounds[1–6]. Because phenyl glycosides are generally accepted as substrates by glycosidases, we planned to investigate novel aminosubstituted α- and β-D-glucopyranosylmethylbenzenes of the structure **1a, b** and **2a, b** (Scheme 1) as potential glucosidase inhibitors. These diastereomers should also provide infor-

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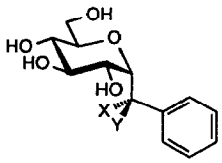
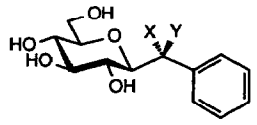


1a X = H, Y = NH_2

2a X = NH_2, Y = H

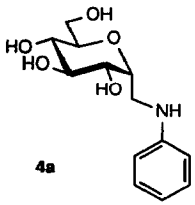
3a X = Y = H



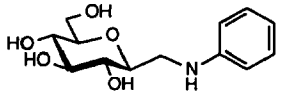
1b X = H, Y = NH_2

2b X = NH_2, Y = H

3b X = Y = H



4a



4b

Scheme 1.

mation about the mechanism of action and the topography of the active site of the enzyme[7–10]. Their inhibitory action can be compared with that of the corresponding *C*-glucosyl compounds **3a,b**, and the anilino derivatives **4a,b**. Aniline itself[11] and aniline *N*-substituted with a galactopyranosylmethylene group[12] have already been shown to be inhibitors of glycosidases. In a previous publication[9], we described syntheses and kinetic properties of the β anomers **1b–3b**. In this paper, we report our results with the α anomers **1a–4a**.

RESULTS AND DISCUSSION

Synthesis.—For the synthesis of the target molecules **1a–4a**, the hydroxy-substituted α-D-glucosylmethylbenzene **9** was envisaged as starting material. To this end, the readily available 2,3,4,6-tetra-*O*-benzyl-D-glucose[13] was transformed by a Wittig reaction into the known open-chain methylene derivative **5**[14,15] (Scheme 2). Subsequent ring closure by oxymercuration ($\rightarrow$ **6**) and oxidative demercuration following known procedures[14,16] afforded exclusively *C*-α-D-glucopyranosylmethanol (**7**)[14,17]. Oxidation under Swern conditions[18] furnished the configurationally labile aldehyde **8** which, without isolation, was immediately treated with phenylmagnesium bromide in THF to furnish the benzylic alcohol **9** in good yield exclusively as the (*1S*)-diastereomer. Compound **9** was characterized as its *O*-acetyl derivative **10**. The configuration of the newly formed stereocenter at C-1 was assigned by X-ray structure analysis of the per-*O*-acetylated derivative **12** (Fig. 1). This compound was obtained by hydrogenolytic *O*-debenzylation of **9** with palla-

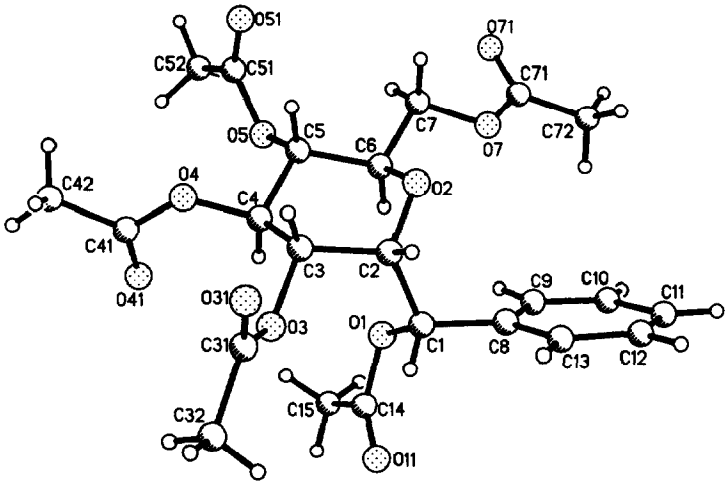
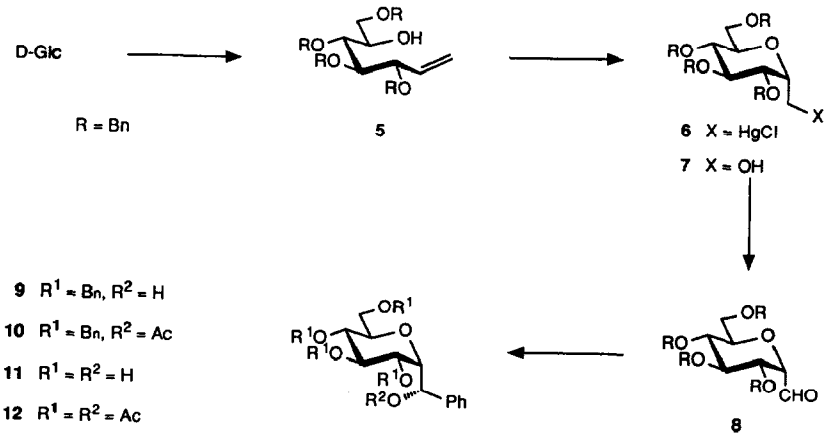


Fig. 1. Structure of 1,3,4,5,7-penta-*O*-acetyl-2,6-anhydro-1-*C*-phenyl-D-*erythro*-L-*ido*-heptitol (**12**) as found in the crystal.

dium-on-carbon as catalyst, furnishing the fully *O*-deprotected compound **11**, followed by *O*-acetylation with acetic anhydride in pyridine.

The X-ray structure analysis of **12** exhibits slight chair deformation in order to avoid unfavourable 1,3-diaxial interactions of the axial α-hydroxybenzyl group at C-2 with the axial hydrogen atoms at C-4 and C-6, thus leading to a half-chair-like conformation. Comparison of the ^{1}H NMR coupling constants of pyranose ring protons shows that tertiary groups at the anomeric centre of *C*-glycosyl compounds generally tend to switch over from an axial into an equatorial position[19]. Contrastingly, substitution of the glycosidic oxygen by a methylene group induces practically



Scheme 2.

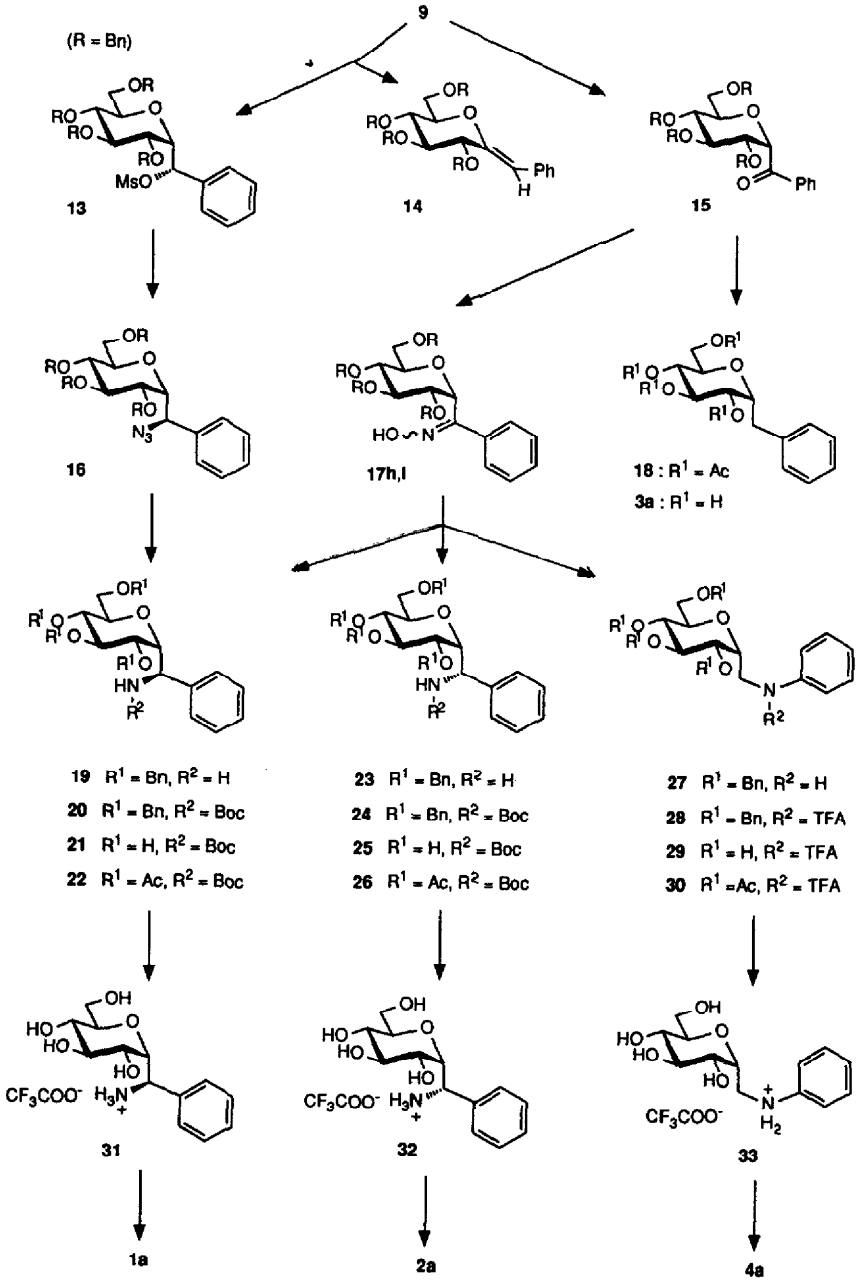
no ring deformation as found for the *C*-α-D-glucopyranosylmethylbenzene **18** (see below) and in previous studies[20,21].

For the introduction of the amino group, phenylcarbinol derivative **9** was activated by 1-*O*-mesylation to afford **13** (Scheme 3). Under standard reaction conditions (methanesulfonyl chloride–pyridine, one equivalent each in CH_2Cl_2), no reaction took place. Replacement of the solvent by pyridine gave exclusively the known elimination product **14**[17]. Best results for the synthesis of **13** were obtained with 4-dimethylaminopyridine and a twentyfold excess of methanesulfonyl chloride in CCl_4. Treatment of **13** with tetramethylguanidinium azide in DMF afforded azido compound **16** together with **14** as major products. Other reaction conditions for the synthesis of **16** did not lead to improved results. For analytical purposes, the azido group was reduced with lithium aluminium hydride ($LiAlH_4$) in THF to give the *C*-α-D-glucopyranosylbenzylamine **19**.

Because of low yields and accessibility of only one diastereoisomer, a second approach for the synthesis of compounds **1a** and **2a** was investigated. Swern oxidation of **9** yielded heptose derivative **15** in high yield. Treatment of **15** with hydroxylammonium chloride in pyridine furnished quantitatively the diastereomeric oximes **17h,l** in a 1 : 1 ratio. The distinction **h/l** (*h*igh and *l*ow) refers to the difference in their R_f values; the absolute configuration of the (*E*/*Z*)-oximes **17h,l** was not established since a mixture was sufficient in the following step. Complex hydrides are known to reduce oximes to amines with partial rearrangement to the corresponding *N*,*N*-disubstituted amine (via Beckmann rearrangement and reduction)[22]; thus, not only access to the target molecules **1a** and **2a** but also to **4a** was expected via such a route. Indeed, reduction of **17h,l** with $LiAlH_4$ in THF afforded the diastereomeric amines **19** and **23** together with the rearranged anilino derivative **27** (~ 1 : 1 : 1 ratios) in good overall yield.

According to our experience, hydrogenolytic *O*-debenzylation of sugars in the presence of unprotected amino groups often causes difficulties and ends up in partial debenzylation[23]. Therefore, the following reaction sequence was chosen: **19** was *N*-protected by the *tert*-butoxycarbonyl (Boc) group under standard conditions, affording urethane **20**; its hydrogenolytic *O*-debenzylation with palladium-on-carbon gave pure **21** which was isolated as its per-*O*-acetylated derivative **22**. Acid-catalyzed cleavage of the Boc protecting group in **21** furnished the target molecule which was isolated as the trifluoroacetate **31** in quantitative yield. Its treatment with basic ion-exchange resin provided the aminosubstituted α-D-glucopyranosylmethylbenzene **1a**. The same reaction sequence was applied, starting from **23**, to obtain the Boc-protected urethane **24**, the *O*-debenzylated intermediate **25**, and its per-*O*-acetylated derivative **26**. Cleavage of the Boc protecting group in **25** and then release of the amino group, as described above, afforded the diastereoisomers **32** and **2a**, respectively, in quantitative yields.

In the case of the *N*-(*C*-glucosylmethyl)aniline **27**, we took advantage of the trifluoroacetyl (TFA) protecting group, because Boc-protected secondary amines sometimes underwent side reactions during acid cleavage[23]. Therefore, **27** was



Scheme 3.

treated with trifluoroacetic anhydride and pyridine in CH_2Cl_2 to give **28** in high yield. Hydrogenolysis under standard conditions afforded the *O*-debenzylated intermediate **29** which was transformed into **30** upon *O*-acetylation. Treatment of

TFA-protected **29** with sodium carbonate in aqueous methanol furnished the target molecule, which was isolated as the trifluoroacetate **33**. The amino group was again released by treatment with basic ion-exchange resin to yield the *N*-(*C*-glucosylmethyl)aniline **4a**.

The desired α-D-glucosylmethylbenzene **3a** was readily obtained by direct hydrogenolytic *O*-debenzylation of **15** with palladium-on-carbon as catalyst which results also, as previously observed for the β anomer[9], in removal of the oxygen next to the phenyl group. *O*-Acetylation of the crude product with acetic anhydride in pyridine furnished the deoxy compound **18**, which was treated with methanolic sodium methoxide to afford compound **3a**.

The ^{1}H NMR data of the intermediates and of the final products are in accordance with the assigned structures. All target molecules are stable in aqueous solution.

Inhibition studies.—The assay method was based on measuring the continuous release of *p*-nitrophenol from *p*-nitrophenyl α-D-glucopyranoside (PNPG) by the action of yeast α-D-glucosidase (maltase)[24]. The Michaelis–Menten constant (K_M) at pH 6.5 was determined to be $2 \cdot 10^{-4}$ M. For practical reasons, instead of the free amines **1a**, **2a**, and **4a**, their trifluoroacetic acid salts **31–33** were used. The kinetic parameters were determined by Lineweaver–Burk plots[25]. Table 1 summarizes the resulting inhibition constants (K_i) together with those of some important known inhibitors. As expected, the α-D-glucosylmethylbenzene **3a** showed only low inhibition and there is a clear distinction between the diastereomeric α-amino-substituted derivatives **1a** and **2a** with a relatively strong inhibition for isomer **1a**. However, it is remarkable that the *N*-(*C*-glucosylmethyl)aniline **4a** yields a K_i value practically identical to that of 1-deoxynojirimycin. These observations give an indication of the relative position of acid groups in the active site of the enzyme which participate in the glycosidic cleavage.

EXPERIMENTAL

General methods.—Melting points are uncorrected. Optical rotations were measured at 22°C with a Perkin–Elmer 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ (internal standard Me_4Si) with a Bruker AC 250 Cryospec instrument. R_f values refer to TLC performed on Silica Gel 60 F_{254} (Merck). Column chromatography was performed under normal pressure with silica gel (Merck, 70–230 mesh ASTM and 230–400 mesh ASTM for flash chromatography) and under elevated pressure with LiChroprep Si 60 (Merck, 15–25 μm). The bp of the light petroleum was 35–65°C. UV spectra were recorded with a Philips PU 8740 UV/VIS spectrophotometer. IR spectra were recorded with a Mattson Polaris FT-IR spectrometer.

2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1*-C-*phenyl*-D-erythro-L-ido-*heptitol* (**9**).—A solution of oxalyl chloride (370 μL, 23.8 mmol) in dry CH_2Cl_2 (10 mL) was cooled to −60°C and a solution of dry Me_2SO (670 μL, 51.9 mmol) in dry CH_2Cl_2 (2 mL)

TABLE I

Type of inhibition and inhibition constants (K_i)[a]

Compound	pH	Inhibition type	K_i[M]	Ref
Maltose	6.8	(substrate)	$3.5 \cdot 10^{-2}$ [b]	24
3a	6.5	competitive	$1.3 \cdot 10^{-3}$	
2a	6.5	competitive	$1.1 \cdot 10^{-3}$	
Phenyl α-D-glucopyranoside	6.8	(substrate)	$4.0 \cdot 10^{-3}$ [b]	24
N-Methyldeoxynojirimycin	6.5	competitive	$3.7 \cdot 10^{-4}$	26
1a	6.5	competitive	$3.8 \cdot 10^{-5}$	
4a	6.5	competitive	$1.1 \cdot 10^{-5}$	
Deoxynojirimycin	6.5	competitive	$0.9 \cdot 10^{-5}$	26

[a] For method, see Experimental. [b] With respect to PNPG as substrate.

was added dropwise during ca. 5 min. Stirring was continued at −60°C for 10 min, followed by addition of a solution of 2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-D-*glycero*-L-*gulo*-heptitol[14–16] (**7**; 2.18 g, 3.93 mmol) in dry CH_2Cl_2 (4 mL) during ca. 5 min. The mixture was stirred for 15 min followed by addition of Et_3N (2.7 mL, 19.6 mmol) during ca. 5 min. After 10 min, the cold mixture was diluted with CH_2Cl_2 (50 mL) and poured into aq NH_4Cl (50 mL), and the organic layer was collected. The aqueous phase was re-extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The crude aldehyde was dissolved in dry diethyl ether (40 mL) and added dropwise to a Grignard solution (20 mL of a 0.3 M solution in diethyl ether) prepared from bromobenzene and magnesium. After warming at 35°C for 30 min, the mixture was cooled and then decomposed by adding, with stirring, aq 20% NH_4Cl (50 mL). The aqueous phase was re-extracted with diethyl ether (20 mL), and the combined organic layers were washed successively with aq NH_4Cl (40 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (4:1 light petroleum–EtOAc) of the residue yielded **9** (1.98 g, 80%), isolated as a colorless oil; $[\alpha]_D$ +39.5° (*c* 1, $CHCl_3$), R_f 0.33 (3:1 light petroleum–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.55 (bs, 1 H, OH), 3.55 (dd, 1 H, *J* 4.7, 6.1 Hz, H-3), 3.64 (dd, 1 H, *J* 6.1, 8.2 Hz, H-5), 3.63–3.73 (m, 2 H, H-7a,7b), 3.99–4.05 (m, 2 H, H-2,4), 4.17 (d, 1 H, *J* 11.5 Hz, C*H*$_2$Ph), 4.18–4.27 (m, 1 H, H-6), 4.44–4.71 (m, 7 H, C*H*$_2$Ph), 5.08 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 7.15–7.36 (m, 25 H, 5 Ph). Anal. Calcd for $C_{41}H_{42}O_6 \cdot 0.5H_2O$: C, 76.96; H, 6.77. Found: C, 76.97; H, 6.82.

1-O-Acetyl-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-C-phenyl-D-erythro-L-ido-*heptitol* (**10**).—To a solution of **9** (40 mg, 0.063 mmol) in dry pyridine (5 mL) was added Ac_2O (5 mL), and the mixture was left at room temperature overnight. When the reaction was complete as shown by TLC [R_f 0.37 (4:1 light petroleum–EtOAc)], the mixture was coevaporated with toluene (3 × 20 mL). Flash chromatography (6:1 light petroleum–EtOAc) of the residue gave **10** (42 mg, 98%) isolated as a colorless oil; $[\alpha]_D$ +59° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.04 (s, 3 H, OAc), 3.60–3.70 (m, 4 H, H-3,4,7a,7b), 3.99 (t, 1 H, *J* 7.2 Hz, H-4), 4.11–4.17 (m, 1

H, H-6), 4.22 (t, 1 H, *J* 6.4 Hz, H-2), 4.20–4.77 (m, 8 H, CH_2Ph), 6.19 (d, 1 H, *J* 6.4 Hz, H-1), 7.17–7.31 (m, 25 H, 5 Ph). Anal. Calcd for $C_{43}H_{44}O_7$: C, 76.76; H, 6.59. Found: C, 76.37; H, 6.56.

2,6-Anhydro-1-C-phenyl-D-erythro-L-ido-*heptitol* (**11**).— To a solution of **12** (140 mg, 0.291 mmol) in dry MeOH (25 mL) was added sodium methoxide (0.2 mL of a 0.2 M solution in MeOH). After 5 h at room temperature, the mixture was neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 $CHCl_3$–MeOH) of the residue gave **11** (75 mg, 96%) as a colorless oil; $[\alpha]_D$ +80° (*c* 1, MeOH); R_f 0.08 (9:1 $CHCl_3$–MeOH); ^{1}H NMR (250 MHz, D_2O): δ 3.31 (t, 1 H, *J* 7.8 Hz, H-5), 3.40 (dd, 1 H, $J_{2,3}$ 5.1, $J_{3,4}$ 7.6 Hz, H-3), 3.55 (dd, 1 H, $J_{6,7a}$ 3.5, J_{gem} 12.5 Hz, H-7a), 3.62 (dd, 1 H, $J_{6,7b}$ 5.7, J_{gem} 12.5 Hz, H-7b), 3.83 (t, 1 H, *J* 7.6 Hz, H-4), 3.89–3.95 (m, 2 H, H-2,6), 4.93 (d, 1 H, *J* 6.4 Hz, H-1), 7.18–7.26 (m, 5 H, Ph).

1,3,4,5,7-Penta-O-acetyl-2,6-anhydro-1-C-phenyl-D-erythro-L-ido-*heptitol* (**12**).— To a solution of **9** (1.5 g, 2.38 mmol) in EtOAc (35 mL) and MeOH (35 mL) was added palladium-on-carbon (10%, 150 mg). After hydrogenolysis for 6 h, the mixture was filtered and concentrated under reduced pressure. The residue was dissolved in dry pyridine (20 mL) and treated with Ac_2O (20 mL), and the mixture was left at room temperature overnight. When the reaction was complete as shown by TLC [R_f 0.5 (1:1 light petroleum–EtOAc)], the mixture was coevaporated with toluene (3 × 50 mL). Flash chromatography (3:1 → 2:1 light petroleum–EtOAc) of the residue yielded **12** (800 mg, 70%) as a colorless oil that crystallized on standing; $[\alpha]_D$ +56° (*c* 1, $CHCl_3$). Careful recrystallization from light petroleum–EtOAc gave crystals, mp 147°C, which were suitable for X-ray analysis; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.78 (s, 3 H, OAc), 1.99 (s, 6 H, 2 OAc), 2.02, 2.19 (2 s, 6 H, 2 OAc), 3.96 (dd, 1 H, $J_{6,7a}$ 2.4, J_{gem} 11.6 Hz, H-7a), 4.13 (dd, 1 H, $J_{6,7b}$ 5.8, J_{gem} 11.6 Hz, H-7b), 4.23 (ddd, 1 H, $J_{5,6}$ 8.4, $J_{6,7a}$ 2.4, $J_{6,7b}$ 5.8 Hz, H-6), 4.54 (t, 1 H, *J* 6.4 Hz, H-2), 4.93–5.01 (m, 2 H, H-3,5), 5.58 (t, 1 H, *J* 8.7 Hz, H-4), 6.10 (d, 1 H, *J* 6.4 Hz, H-1), 7.24–7.34 (m, 5 H, Ph). Anal. Calcd for $C_{23}H_{28}O_{11}$: C, 57.50; H, 5.88. Found: C, 57.50; H, 5.90.

2,6-Anhydro-3,4,5,7-tetra-O-benzyl-1-O-methanesulfonyl-1-C-phenyl-D-erythro-L-ido-*heptitol* (**13**).—To a solution of **9** (125 mg, 0.198 mmol) in dry CCl_4 (5 mL) were added 4-dimethylaminopyridine (50 mg) and methanesulfonyl chloride (200 μL). The mixture was stirred for 6 days at 50°C, then allowed to come to room temperature, diluted with diethyl ether (50 mL), and extracted with water (20 mL). The organic layer was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), and evaporated to dryness. Flash chromatography (19:1 toluene–EtOAc) yielded **13** (77 mg, 55%) as a colorless oil; $[\alpha]_D$ +58° (*c* 1, $CHCl_3$); R_f 0.45 (9:1 toluene–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.85 (s, 3 H, CH_3), 3.30 (t, 1 H, *J* 4.7 Hz, H-3), 3.61 (dd, 1 H, $J_{4,5}$ 5.0, $J_{5,6}$ 7.5 Hz, H-5), 3.65 (dd, 1 H, $J_{6,7a}$ 3.4, J_{gem} 10.4 Hz, H-7a), 3.73 (dd, 1 H, $J_{6,7b}$ 5.4, J_{gem} 10.4 Hz, H-7b), 3.87 (t, 1 H, *J* 5.0 Hz, H-4), 4.00 (d, 1 H, *J* 11.2 Hz, CH_2Ph), 4.21–4.28 (m, 2 H, H-2,6), 4.36 (d, 1 H, *J* 11.2 Hz, CH_2Ph), 4.44–4.63 (m, 6 H, CH_2Ph), 5.80 (d, 1 H, *J* 7.5 Hz, H-1),

7.14–7.35 (m, 25 H, 5 Ph). Anal. Calcd for $C_{42}H_{44}O_8S$: C, 71.16; H, 6.22. Found: C, 71.05; H, 6.32.

2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1*-C-*phenyl*-D-glycero-D-ido-*heptose* (**15**).—A solution of oxalyl chloride (95 μL, 1.11 mL) in dry CH_2Cl_2 (5 mL) was cooled to −60°C and a solution of dry Me_2SO (170 μL, 2.39 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise during ca. 5 min. Stirring was continued at −60°C for 15 min followed by addition of a solution of **9** (450 mg, 0.713 mmol) in dry CH_2Cl_2 (2 mL) during ca. 10 min. The mixture was stirred for 30 min, then Et_3N (700 μL, 5.05 mmol) was added dropwise during ca. 5 min and the solution was allowed to attain room temperature. The mixture was diluted with CH_2Cl_2 (60 mL), then extracted with aq NH_4Cl (4 × 20 mL), and the organic layer was concentrated in vacuo. Flash chromatography (5:1 light petroleum–EtOAc) yielded **15** (410 mg, 92%) as a colorless oil; $[\alpha]_D$ +22° (*c* 1, $CHCl_3$); R_f 0.48 (3:1 light petroleum–EtOAc); ^1H NMR (250 MHz, $CDCl_3$): δ 3.57 (dd, 1 H, $J_{6,7a}$ 1.9, J_{gem} 10.7 Hz, H-7a), 3.70 (dd, 1 H, $J_{6,7b}$ 3.2, J_{gem} 10.7 Hz, H-7b), 3.75 (dd, 1 H, $J_{4,5}$ 8.3, $J_{5,6}$ 9.7 Hz, H-5), 3.84–3.90 (m, 1 H, H-6), 3.95 (dd, 1 H, $J_{2,3}$ 6.1, $J_{3,4}$ 8.9 Hz, H-3), 4.39–4.61 (m, 5 H, CH_2Ph, H-4), 4.77–5.03 (m, 4 H, CH_2Ph), 5.22 (d, 1 H, *J* 6.1 Hz, H-2); 7.12–7.96 (m, 25 H, 5 Ph); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.95 (Ph*C*O). Anal. Calcd for $C_{41}H_{40}O_6$: C, 78.32; H, 6.41. Found: C, 78.16; H, 6.43.

2,6-Anhydro-7-azido-1,3,4,5-tetra-O-*benzyl-7-deoxy-7*-C-*phenyl*-D-erythro-L-gulo-*heptitol* (**16**).—To a solution of **13** (40 mg, 0.056 mmol) in dry DMF (3 mL) was added tetramethylguanidinium azide (89 mg, 0.56 mmol). The mixture was stirred at 70°C for 7 days, then diluted with water (50 mL), and extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with water (4 × 15 mL) and concentrated under reduced pressure. Flash chromatography (50:1 toluene–EtOAc) of the residue yielded **16** (7.5 mg, 20%) as a colorless oil; $[\alpha]_D$ −21° (*c* 0.5, $CHCl_3$); R_f 0.44 (19:1 toluene–EtOAc); $\nu_{max}^{CCl_4}$ 2106.9 cm^{-1} (N_3); ^1H NMR (250 MHz, $CDCl_3$): δ 3.36 (dd, 1 H, J_{gem} 10.7, $J_{1a,2}$ 3.8 Hz, H-1a), 3.45 (dd, 1 H, J_{gem} 10.7, $J_{1b,2}$ 4.6 Hz, H-1b), 3.63 (dd, 1 H, *J* 4.8, *J* 7.4 Hz, H-3); 3.81–3.92 (m, 3 H, H-2,4,5), 4.07 (dd, 1 H, $J_{5,6}$ 3.0, $J_{6,7}$ 9.6 Hz, H-6), 4.14–4.72 (m, 8 H, CH_2Ph), 4.82 (d, 1 H, $J_{6,7}$ 9.6 Hz, H-7), 7.06–7.38 (m, 25 H, 5 Ph).

(E/Z)-*2,6-Anhydro-3,4,5,7-tetra*-O-*benzyl-1*-C-*phenyl*-D-glycero-D-ido-*heptose oxime* (**17h,l**).—To a solution of **15** (7.67 g, 11.9 mmol) in dry pyridine (100 mL) was added hydroxylammonium chloride (2.48 g, 35.7 mmol). After warming for 5 h at 40°C, the mixture was concentrated under reduced pressure, diluted with toluene (50 mL), and evaporated to dryness. Filtration over silica gel (9:1 toluene–acetone) yielded **17h,l** (7.7 g, quant; *E*:*Z* = 1:1) as a colorless oil, which was used as the *E*/*Z*-mixture in the next step. Separation of the *E*/*Z* isomers was possible by flash chromatography (83:16:1 → 74:25:1 light petroleum–EtOAc–Et_3N).

Compound **17h**: R_f 0.26 (83:16:1 light petroleum–EtOAc–Et_3N); $[\alpha]_D$ +26° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 3.49 (dd, 1 H, J_{gem} 10.5, $J_{6,7a}$ 1.8 Hz, H-7a), 3.60 (dd, 1 H, J_{gem} 10.5, $J_{6,7b}$ 4.0 Hz, H-7b), 3.64 (dd, 1 H, *J* 8.8, 9.8 Hz, H-5), 3.86–3.91 (m, 1 H, H-6), 3.90 (dd, 1 H, $J_{2,3}$ 6.4, $J_{3,4}$ 9.5 Hz, H-3), 4.27–5.12

(m, 10 H, CH_2Ph, H-2,4), 4.72 (d, 1 H, *J* 6.4 Hz, H-2), 7.08–7.46 (m, 25 H, 5 Ph), 9.22 (bs, 1 H, NOH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 152.8 (CNOH). Anal. (for **17h**) Calcd for $C_{41}H_{41}NO_6$: C, 76.49; H, 6.42; N, 2.18. Found: C, 76.74; H, 6.53; N, 2.20.

Compound **17l**: R_f 0.19 (83:16:1 light petroleum–EtOAc–Et_3N); $[\alpha]_D$ +7.0° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.48 (dd, 1 H, J_{gem} 10.7, $J_{6,7a}$ 2.9 Hz, H-7a), 3.54 (dd, 1 H, J_{gem} 10.7, $J_{6,7b}$ 3.6 Hz, H-7b), 3.84–3.94 (m, 3 H, H-4,5,6), 4.32–4.63 (m, 9 H, CH_2Ph, H-3), 5.69 (d, 1 H, *J* 3.6 Hz, H-2), 7.18–7.37 (m, 23 H, Ph), 7.67–7.71 (m, 2 H, Ph), 9.26 (bs, 1 H, NOH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 161.1 (CNOH). Anal. (for **17l**) Calcd for $C_{41}H_{41}NO_6$: C, 76.49; H, 6.42; N, 2.18. Found: C, 76.43; H, 6.50; N, 2.23.

1,3,4,5-Tetra-O-*acetyl-2,6-anhydro-7-deoxy-7-C-phenyl*-D-glycero-L-gulo-*heptitol* (**18**).—To a solution of **15** (170 mg, 0.27 mmol) in EtOAc (5 mL) and MeOH (5 mL) was added palladium-on-carbon (10%, 70 mg). After hydrogenolysis for 3 h, the mixture was filtered and concentrated under reduced pressure. A mixture of the residue, dry pyridine (5 mL), and Ac_2O (5 mL) was left for 3 h at room temperature. Then, the mixture was coevaporated with toluene (3 × 25 mL). Flash chromatography (3:1 light petroleum–EtOAc) of the residue yielded **18** (80 mg, 70%) as white crystals; mp 79°C; $[\alpha]_D$ +85° (*c* 1, Et_2O); R_f 0.64 (1:1 light petroleum–EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.00, 2.01, 2.07, 2.09 (4 s, 12 H, 4 OAc), 2.94 (dd, 1 H, $J_{6,7a}$ 5, J_{gem} 14.9 Hz, H-7a), 3.10 (dd, 1 H, $J_{6,7b}$ 9.9, J_{gem} 14.9 Hz, H-7b), 4.02–4.10 (m, 2 H, H-1a,1b), 4.18–4.26 (m, 1 H, H-2), 4.55 (ddd, 1 H, $J_{5,6} = J_{6,7a} = 5$, $J_{6,7b}$ 9.9 Hz, H-6), 5.01 (t, 1 H, *J* 9 Hz, H-3), 5.15 (dd, 1 H, $J_{4,5}$ 9, $J_{5,6}$ 5 Hz, H-5), 5.47 (t, 1 H, *J* 9 Hz, H-4), 7.21–7.36 (m, 5 H, Ph). Anal. Calcd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.20. Found: C, 59.72; H, 6.28.

7-Amino-2,6-anhydro-1,3,4,5-tetra-O-*benzyl-7-deoxy-7-C-phenyl*-D-erythro-L-gulo-*heptitol* (**19**), *7-amino-2,6-anhydro-1,3,4,5-tetra*-O-*benzyl-7-deoxy-7-C-phenyl*-L-threo-L-gulo-*heptitol* (**23**), *and 2,6-anhydro-1,3,4,5-tetra*-O-*benzyl-7-deoxy-7-phenylamino*-D-glycero-L-gulo-*heptitol* (**27**).—*Procedure (a)*. To a suspension of $LiAlH_4$ (350 mg) in dry THF (110 mL) was added dropwise a solution of **17h,l** (3.7 g, 5.75 mmol) in dry THF (40 mL) at room temperature. The mixture was heated under reflux (bath temperature, 75°C) for 60 min, then allowed to attain room temperature, and filtered. The filtrate was treated successively with wet diethyl ether (10 mL) and water (3 mL). The mixture was again filtered, and the filtrate was washed with aq NH_4Cl (100 mL). The aqueous phase was re-extracted with diethyl ether (100 mL), and the combined organic layers were concentrated under reduced pressure and coevaporated with toluene (2 × 50 mL). Flash chromatography (100:2 → 95:5 → 9:1 $CHCl_3$–MeOH) yielded **19** (1.04 g, 29%) as a yellowish oil that crystallized on standing, **23** (880 mg, 24%) as a colorless oil, and crude **27** (900 mg). Compound **27** was purified further by flash chromatography (9:1 light petroleum–EtOAc), followed by MPLC (4:1 light petroleum–EtOAc), to give pure **27** (725 mg, 20%) as a colorless oil. Compound **19** could be recrystallized

from light petroleum–EtOAc and from hot EtOH to form colorless needles; mp 113°C.

Procedure (b) for **19**. To a suspension of $LiAlH_4$ (5 mg) in dry THF (1 mL) was added dropwise a solution of **16** (7.5 mg, 11.6 μmol) in dry THF (1 mL) with stirring. The mixture was heated under reflux for 90 min, then allowed to attain room temperature, and successively treated with wet diethyl ether (5 mL) and water (1 drop). The solution was filtered (Celite), the filter cake was washed with diethyl ether (10 mL), and the combined filtrates were evaporated to dryness. Flash chromatography (74:25:1 light petroleum–EtOAc–Et_3N) yielded **19** (4 mg, 56%) as a colorless oil.

Compound **19**: R_f 0.34 (100:2 $CHCl_3$–MeOH); $[\alpha]_D$ +22.5° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.74 (bs, 2 H, NH_2), 3.21 (dd, 1 H, J_{gem} 10.7, $J_{1a,2}$ 2.2 Hz, H-1a), 3.46 (dd, 1 H, J_{gem} 10.7, $J_{1b,2}$ 3.4 Hz, H-1b), 3.60–3.71 (m, 2 H, H-2,3), 3.93 (dd, 1 H, $J_{4,5}$ 7, $J_{5,6}$ 4.4 Hz, H-5), 4.00 (t, 1 H, *J* 7 Hz, H-4), 4.14–4.88 (m, 10 H, 4 CH_2Ph, H-6,7), 4.20 (dd, 1 H, $J_{5,6}$ 4.4, $J_{6,7}$ 9.2 Hz, H-6), 4.40 (d, 1 H, *J* 9.2 Hz, H-7), 7.12–7.40 (m, 25 H, 5 Ph). Anal. (for **19**) Calcd for $C_{41}H_{43}NO_5$: C, 78.19; H, 6.88; N, 2.22. Found: C, 77.94; H, 6.95; N, 2.42.

Compound **23**: R_f 0.22 (100:2 $CHCl_3$–MeOH); $[\alpha]_D$ +28° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.84 (bs, 2 H, NH_2), 3.32 (dd, 1 H, $J_{4,5}$ 5.3, $J_{5,6}$ 3.6 Hz, H-5), 3.63 (dd, 1 H, $J_{2,3}$ 7.4, $J_{3,4}$ 5.3 Hz, H-3), 3.71–3.73 (m, 2 H, H-1a,1b), 3.82 (t, 1 H, *J* 5.3 Hz, H-4), 3.92 (d, 1 H, *J* 11.3 Hz, C*H*HPh), 4.03 (dd, 1 H, $J_{5,6}$ 3.6, $J_{6,7}$ 9.2 Hz, H-6), 4.08–4.15 (m, 1 H, H-2), 4.25 (d, 1 H, *J* 11.3 Hz, CH*H*Ph), 4.35 (d, 1 H, *J* 9.2 Hz, H-7), 4.47–4.65 (m, 6 H, 3 CH_2Ph), 7.04–7.32 (m, 25 H, 5 Ph). Anal. (for **23**) Calcd for $C_{41}H_{43}NO_5 \cdot 0.25H_2O$: C, 77.64; H, 6.91; N, 2.21. Found: C, 77.64; H, 6.98; N, ca. 2.50.

Compound **27**: R_f 0.86 (100:2 $CHCl_3$–MeOH); $[\alpha]_D$ +44.5° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 3.40 (dd, 1 H, $J_{6,7a}$ 10.9, J_{gem} 12.7 Hz, H-7a), 3.48 (dd, 1 H, $J_{6,7b}$ 4.9, J_{gem} 12.7 Hz, H-7b), 3.64–3.92 (m, 6 H, H-1a, 1b, 2, 3, 4, 5), 4.31–4.39 (m, 1 H, H-6), 4.49–5.00 (m, 8 H, 4 CH_2Ph), 6.59–6.62 (m, 2 H, Ph), 6.71–6.76 (m, 1 H, Ph), 7.14–7.38 (m, 22 H, Ph). Anal. (for **27**) Calcd for $C_{41}H_{43}NO_5$: C, 78.19; H, 6.88; N, 2.22. Found: C, 78.21; H, 6.95; N, 2.17.

2,6-Anhydro-1,3,4,5-tetra-O-*benzyl-7*-tert-*butoxycarbonylamino-7-deoxy-7*-C-*phenyl*-D-erythro-L-gulo-*heptitol* (**20**).—To a solution of **19** (125 mg, 0.198 mmol) in dioxane (10 mL) was added (*t*-BuOCO)$_2$O (160 mg, 0.733 mmol) and Et_3N (1 mL). The mixture was left for 4 h at room temperature, then concentrated under reduced pressure and coevaporated with toluene (25 mL). Flash chromatography (7:1 → 5:1 light petroleum–EtOAc) yielded **20** (100 mg, 69%) as a colorless glassy solid; mp 109°C; $[\alpha]_D$ +21° (*c* 1, $CHCl_3$); R_f 0.41 (4:1 light petroleum–EtOAc). ^1H NMR (250 MHz, $CDCl_3$): δ 1.37 [s, 9 H, C$(CH_3)_3$], 3.53–3.68 (m, 3 H, H-1a, 1b,5), 3.57 (dd, 1 H, J_{gem} 10.7, $J_{1a,2}$ 3.1 Hz, H-1a), 3.65 (dd, 1 H, J_{gem} 10.7, $J_{1b,2}$ 3.8 Hz, H-1b), 3.74 (dd, 1 H, $J_{2,3}$ 8.2, $J_{3,4}$ 6 Hz, H-3), 3.91 (t, 1 H, *J* 6 Hz, H-4), 3.93–4.00 (m, 1 H, H-2), 4.15 (dd, 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 6.7 Hz, H-6), 4.36–4.70 (m, 8 H, 4 CH_2Ph), 5.14 (bt, 1 H, *J* 7 Hz, H-7), 5.93 (bd, 1 H, *J* 7 Hz, NH), 7.16–7.37

(m, 25 H, 5 Ph). Anal. Calcd for $C_{46}H_{51}NO_7$: C, 75.69; H, 7.04; N, 1.92. Found: C, 75.40; H, 7.05; N, 1.70.

*2,6-Anhydro-7-*tert*-butoxycarbonylamino-7-deoxy-7-C-phenyl-*D*-erythro-*L*-gulo-heptitol* (**21**).—To a solution of **20** (220 mg, 0.301 mmol) in EtOAc (6 mL) and MeOH (6 mL) was added palladium-on-carbon (10%, 20 mg). After hydrogenolysis for 18 h, the mixture was filtered and concentrated under reduced pressure. Flash chromatography (9:1 $CHCl_3$–MeOH) yielded **21** (110 mg, 99%) as a colorless glassy solid; $[\alpha]_D$ +10.5° (*c* 1, MeOH); R_f 0.33 (9:1 $CHCl_3$–MeOH); ^1H NMR (250 MHz, CD_3OD): δ 1.31 [bs, 9 H, $C(CH_3)_3$], 3.42–3.77 (m, 6 H, H-1a,1b,2,3,4,5), 4.01 (dd, 1 H, $J_{5,6}$ 2.6, $J_{6,7}$ 7.3 Hz, H-6), 4.90 (d, 1 H, *J* 6.7 Hz, H-7), 7.12–7.33 (m, 5 H, Ph).

*1,3,4,5-Tetra-O-acetyl-2,6-anhydro-7-*tert*-butoxycarbonylamino-7-deoxy-7-C-phenyl-*D*-erythro-*L*-gulo-heptitol* (**22**).—To a solution of **21** (38 mg, 0.102 mmol) in dry pyridine (2 mL) was added Ac_2O (2 mL), and the mixture was left at room temperature overnight. When the reaction was complete as shown by TLC [R_f 0.5 (100:2 $CHCl_3$–MeOH)], the mixture was coevaporated with toluene (3 × 20 mL). Flash chromatography (100:2 $CHCl_3$–MeOH) yielded **22** (55 mg, quant) as a colorless crystalline solid; mp 209°C (with dec); $[\alpha]_D$ +16° (*c* 0.125, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.36 [s, 9 H, $C(CH_3)_3$], 1.84, 2.04, 2.07, 2.09 (4 s, 12 H, 4 OAc), 3.89 (dd, 1 H, J_{gem} 11.7, $J_{1a,2}$ 3.8 Hz, H-1a), 3.97–4.08 (m, 1 H, H-2), 4.22–4.30 (m, 2 H, H-1b,5), 4.78–4.84 (m, 2 H, H-3,7), 5.02 (t, 1 H, *J* 9.3 Hz, H-6), 5.06 (dd, 1 H, $J_{3,4}$ 4.3, $J_{4,5}$ 3.1 Hz, H-4), 5.18 (m, 1 H, NH), 7.23–7.35 (m, 5 H, Ph).

*2,6-Anhydro-1,3,4,5-tetra-O-benzyl-7-*tert*-butoxycarbonylamino-7-deoxy-7-C-phenyl-*L*-threo-*L*-gulo-heptitol* (**24**).—Compound **23** (63 mg, 0.1 mmol) in dioxane (5 mL) was treated with $(t\text{BuOCO})_2O$ (71 mg) and Et_3N (0.5 mL) as described for **20**. Flash chromatography (7:1 → 5:1 light petroleum–EtOAc) yielded **24** (66 mg, 90%) as a colorless oil; $[\alpha]_D$ +27° (*c* 1, $CHCl_3$); R_f 0.42 (4:1 light petroleum–EtOAc); ^1H NMR (250 MHz, $CDCl_3$): δ 1.31 [bs, 9 H, $C(CH_3)_3$], 3.46 (dd, 1 H, $J_{4,5}$ 5.9, $J_{5,6}$ 4.0 Hz, H-5), 3.63–3.76 (m, 3 H, H-1a,1b,3), 3.90 (t, 1 H, *J* 5.9 Hz, H-4), 3.90 (d, 1 H, *J* 11.4 Hz, C*H*HPh), 3.97 (m, 1 H, H-2), 4.13 (dd, 1 H, $J_{5,6}$ 4.0, $J_{6,7}$ 9.4 Hz, H-6), 4.23 (d, 1 H, *J* 11.4 Hz, CH*H*Ph), 4.45–4.70 (m, 6 H, 3 CH_2Ph), 4.90 (bs, 1 H, H-7), 5.25 (bd, 1 H, *J* 4.8 Hz, NH), 7.04–7.35 (m, 25 H, 5 Ph). Anal. Calcd for $C_{46}H_{51}NO_7$: C, 75.69; H, 7.04; N, 1.92. Found: C, 75.25; H, 7.07; N, 1.78.

*2,6-Anhydro-7-*tert*-butoxycarbonylamino-7-deoxy-7-C-phenyl-*L*-threo-*L*-gulo-heptitol* (**25**).—Compound **24** (210 mg, 0.288 mmol) in EtOAc (6 mL) and MeOH (6 mL) was treated with palladium-on-carbon (10%, 20 mg) as described for **21**. Flash chromatography (9:1 $CHCl_3$–MeOH) of the residue yielded **25** (99 mg, 93%) as a colorless foam; $[\alpha]_D$ +39.5° (*c* 1, $CHCl_3$); R_f 0.26 (9:1 $CHCl_3$–MeOH); ^1H NMR (250 MHz, CD_3OD): δ 1.40 [bs, 9 H, $C(CH_3)_3$], 3.16–3.21 (m, 1 H, H-5), 3.58 (ddd, 1 H, $J_{2,3} = J_{3,4} = 4$, $^4J_{3,5}$ 0.7 Hz, H-3), 3.67 (dd, 1 H, J_{gem} 11.9, $J_{1a,2}$ 3.5 Hz, H-1a), 3.79 (t, 1 H, *J* 4 Hz, H-4), 3.97 (ddd, 1 H, $J_{1a,2} = J_{2,3} = 4$, $J_{1b,2}$ 8 Hz, H-2), 4.03 (dd, 1 H, $J_{5,6}$ 1.9, $J_{6,7}$ 10.2 Hz, H-6), 4.11 (dd, 1 H, J_{gem} 11.9, $J_{1b,2}$ 8 Hz, H-1b), 4.90 (d, 1 H, *J* 10.2 Hz, H-7), 7.27–7.45 (m, 5 H, Ph).

1,3,4,5-Tetra-O-*acetyl-2,6-anhydro-7*-tert-*butoxycarbonylamino-7-deoxy-7*-C-*phenyl*-L-threo-L-gulo-*heptitol* (**26**).—Compound **25** (31 mg, 83.7 μmol) was treated with dry pyridine (2 mL) and Ac_2O (2 mL) as described for **22**. Flash chromatography (1:1 light petroleum–EtOAc) of the residue yielded **26** (45 mg, quant) as a colorless glassy foam; $[\alpha]_D$ +39° (*c* 1, $CHCl_3$); R_f 0.55 (1:1 light petroleum–EtOAc); ^1H NMR (250 MHz, $CDCl_3$): δ 1.34 [s, 9 H, $C(CH_3)_3$], 1.61, 1.99, 2.05, 2.11 (4 s, 12 H, 4 OAc), 3.96 (dd, 1 H, J_{gem} 12, $J_{1a,2}$ 2.5 Hz, H-1a), 4.13 (ddd, 1 H, $J_{1a,2}$ 2.5, $J_{1b,2} = J_{2,3} = 6.5$ Hz, H-2), 4.33 (dd, 1 H, $J_{3,4}$ 9.9, $J_{4,5}$ 3.9 Hz, H-4), 4.55 (dd, 1 H, J_{gem} 12, $J_{1b,2}$ 6.5 Hz, H-1b), 4.63 (dd, 1 H, $J_{4,5}$ 4, $J_{5,6}$ 7 Hz, H-5), 4.85 (t, 1 H, *J* 4 Hz, H-3), 4.85–4.98 (m, 1 H, H-7), 5.26–5.32 (m, 2 H, H-6, NH), 7.20–7.33 (m, 5 H, Ph).

2,6-Anhydro-1,3,4,5-tetra-O-*benzyl-7-deoxy-7-(*N-*phenyltrifluoroacetamido)*-D-glycero-L-gulo-*heptitol* (**28**).—To a solution of **27** (164 mg, 0.26 mmol) in dry CH_2Cl_2 (25 mL) was added trifluoroacetic anhydride (100 μL, 0.708 mmol) with stirring at 0°C. Then, dry pyridine (100 μL, 1.24 mmol) was added dropwise and the mixture was allowed to attain room temperature overnight. When TLC (4:1 light petroleum–EtOAc) showed the absence of starting material, the mixture was diluted with toluene and coevaporated (2 × 25 mL). Flash chromatography (6:1 light petroleum–EtOAc) of the residue yielded **28** (174 mg, 92%) as a colorless oil; $[\alpha]_D$ +24° (*c* 1, $CHCl_3$); R_f 0.48 (4:1 light petroleum–EtOAc); ^1H NMR (250 MHz, $CDCl_3$): δ 3.42 (dd, 1 H, J_{gem} 10.4, $J_{1a,2}$ 1.3 Hz, H-1a), 3.52–3.78 (m, 5 H, H-1b,2,3,4,5), 3.93–4.05 (m, 1 H, H-6), 4.29–4.40 (m, 2 H, H-7a,7b), 4.43–4.94 (m, 8 H, 4 CH_2Ph), 7.09–7.40 (m, 25 H, 5 Ph); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 46.84 (C-7), 68.25, 71.27, 72.04, 73.16, 73.45, 74.96, 75.45, 77.56, 78.77, 82.25 (10 C, 4 CH_2Ph, C-1,2,3,4,5,6), 116.31 (q, 1 C, $^2J_{C,F}$ 288.4 Hz, CF_3), 127.58–129.21 (m, 25 C, *o*-, *m*-, *p*-Ph), 137.65, 137.86, 138.13, 138.54, 138.90 (5 C, *ipso*-Ph), 157.09 (q, 1 C, $^3J_{C,F}$ 35.7 Hz, $COCF_3$). Anal. Calcd for $C_{43}H_{43}F_3NO_6$: C, 71.06; H, 5.96; N, 1.93. Found: C, 71.13; H, 5.87; N, ca. 2.00.

*2,6-Anhydro-7-deoxy-7-(*N-*phenyltrifluoroacetamido)*-D-glycero-L-gulo-*heptitol* (**29**).—To a solution of **28** (106 mg, 0.146 mmol) in EtOAc (2.5 mL) and MeOH (2.5 mL) was added palladium-on-carbon (10%, 11 mg). After hydrogenolysis for 2 h, the mixture was filtered and concentrated under reduced pressure. Flash chromatography (9:1 $CHCl_3$–MeOH) of the residue yielded **29** (53.3 mg, quant) as a colorless foam; $[\alpha]_D$ +45.5° (*c* 1, $CHCl_3$); R_f 0.24 (9:1 $CHCl_3$–MeOH); ^1H NMR (250 MHz, CD_3OD): δ 3.41 (dd, 1 H, *J* 8.7, 9.2 Hz, H-3/4), 3.52–3.75 (m, 5 H, H-1a,1b,2,3/4,5), 3.81 (dd, 1 H, $J_{6,7a}$ 2.8, J_{gem} 14.4 Hz, H-7a), 4.13 (ddd, 1 H, $J_{5,6}$ 6.0, $J_{6,7a}$ 2.8, $J_{6,7b}$ 11.6 Hz, H-6), 4.63 (dd, 1 H, $J_{6,7b}$ 11.6, J_{gem} 14.4 Hz, H-7b), 7.45–7.53 (m, 5 H, Ph).

1,3,4,5-Tetra-O-*acetyl-2,6-anhydro-7-deoxy-7(*N-*phenyltrifluoroacetamido)*-D-glycero-L-gulo-*heptitol* (**30**).—Compound **29** (30 mg, 0.082 mmol) was treated with dry pyridine (2.5 mL) and Ac_2O (2.5 mL) as described for **22**. Flash chromatography (2:1 light petroleum–EtOAc) of the residue yielded **30** (44 mg, quant), as a colorless oil; $[\alpha]_D$ +54° (*c* 1, $CHCl_3$); R_f 0.57 (1:1 light petroleum–EtOAc); ^1H

NMR (250 MHz, $CDCl_3$): δ 1.95, 1.98, 1.99, 2.04 (4 s, 12 H, 4 OAc), 3.53 (dd, 1 H, $J_{6,7a}$ 2.7, J_{gem} 14.4 Hz, H-7a), 3.92–4.02 (m, 2 H, H-1a, 2), 4.13 (dd, 1 H, J_{gem} 12.0, $J_{1b,2}$ 4.9 Hz, H-1b), 4.29 (ddd, 1 H, $J_{5,6}$ 6, $J_{6,7a}$ 2.7, $J_{6,7b}$ 11.5 Hz, H-6), 4.59 (dd, 1 H, $J_{6,7b}$ 11.5, J_{gem} 14.4 Hz, H-7b), 4.95 (t, 1 H, *J* 9 Hz, H-3), 5.11 (dd, 1 H, $J_{4,5}$ 9, $J_{5,6}$ 6 Hz, H-5), 5.28 (t, 1 H, *J* 9 Hz, H-4), 7.25–7.29 (m, 2 H, Ph), 7.38–7.43 (m, 3 H, Ph). Anal. Calcd for $C_{23}H_{26}F_3NO_{10}$: C, 51.78; H, 4.91; N, 2.63. Found: C, 51.12; H, 4.62; N, 2.45.

7-Ammonio-2,6-anhydro-7-deoxy-7-C-phenyl-D-erythro-L-gulo-*heptitol trifluoroacetate* (**31**).—To a solution of **21** (92 mg, 0.255 mmol) in $CHCl_3$ (5 mL) was added trifluoroacetic acid (1 mL), and the mixture was left at room temperature. When TLC (8:2 $CHCl_3$–MeOH) showed the absence of starting material (ca. 2.5 h), the mixture was diluted with $CHCl_3$ (15 mL), concentrated in vacuo, and coevaporated again with $CHCl_3$ (2 × 20 mL), to give **31** (98 mg, quant) as a colorless oil that crystallized on standing. For enzymic studies, **31** was subjected to preparative HPLC chromatography (9:1 H_2O + 0.1% trifluoroacetic acid–MeCN; flow: 12 mL/min; t_R 8.9 min; 86 bar), concentrated in vacuo, and lyophilized; $[\alpha]_D$ +38.5° (*c* 0.7, H_2O); ^1H NMR (250 MHz, D_2O): δ 3.16–3.36 (m, 4 H, H-1a,1b,2,3), 3.69 (t, 1 H, *J* 8.8 Hz, H-4), 3.79 (dd, 1 H, $J_{4,5}$ 8.8, $J_{5,6}$ 5.2 Hz, H-5), 4.34 (dd, 1 H, $J_{5,6}$ 5.2, $J_{6,7}$ 9.9 Hz, H-6), 4.73 (d, 1 H, *J* 9.9 Hz, H-7), 7.30–7.37 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{20}F_3NO_7 \cdot 0.5H_2O$: C, 45.92; H, 5.40; N, 3.57. Found: C, 45.95; H, 5.33; N, 3.71.

7-Ammonio-2,6-anhydro-7-deoxy-7-C-phenyl-L-threo-L-gulo-*heptitol trifluoroacetate* (**32**).—Compound **25** (85 mg, 0.23 mmol) in $CHCl_3$ (5 mL) was treated with trifluoroacetic acid (1 mL) as described for **31**, to give **32** (88 mg, quant) as a colorless oil that crystallized on standing. For enzymic studies, **32** was subjected to preparative HPLC (9:1 H_2O + 0.05% trifluoroacetic acid–MeCN; flow: 9 mL/min; t_R 11.77 min; 59 bar), concentrated in vacuo, and lyophilized; $[\alpha]_D$ +26° (*c* 0.87, H_2O); ^1H NMR (250 MHz, D_2O): δ 3.18 (dd, 1 H, $J_{4,5}$ 4.1, $J_{5,6}$ 2.4 Hz, H-5), 3.49 (t, 1 H, *J* 4.8 Hz, H-3), 3.54–3.58 (m, 1 H, H-1a), 3.63 (t, 1 H, *J* 4.8 Hz, H-4), 3.80–3.90 (m, 2 H, H-1b,2), 4.20 (dd, 1 H, $J_{5,6}$ 2.4, $J_{6,7}$ 9.5 Hz, H-6), 4.47 (d, 1 H, *J* 9.5 Hz, H-7), 7.31 (bs, 5 H, Ph). Anal. Calcd for $C_{15}H_{20}F_3NO_7 \cdot 0.5H_2O$: C, 45.92; H, 5.40; N, 3.57. Found: C, 45.82; H, 5.51; N, 3.60.

2,6-Anhydro-7-deoxy-7-phenylammonio-D-glycero-L-gulo-*heptitol trifluoroacetate* (**33**).—To a solution of **29** (67 mg, 0.183 mmol) in MeOH (5 mL) and H_2O (0.33 mL) was added Na_2CO_3 (100 mg) with stirring. After 4 h at room temperature, the mixture was filtered and the filter cake washed with MeOH (5 mL). The combined filtrates were neutralized with Amberlite IR-120 (H^+) resin, filtered, and evaporated to dryness. Preparative HPLC (9:1 H_2O + 0.05% trifluoroacetic acid–MeCN; flow: 15 mL/min; t_R 8.32 min, λ_{max} 207.5 nm), concentration in vacuo, and lyophilisaton yielded **33** (68 mg, 97%); $[\alpha]_D$ +44° (*c* 0.5, MeOH); λ_{max}^{MeOH} 205.8, 245.0, 292.8 nm; ^1H NMR (250 MHz, D_2O): δ 3.19 (t, 1 H, *J* 9.2 Hz, H-3), 3.35 (t, 1 H, *J* 9.2 Hz, H-4), 3.39–3.51 (m, 1 H, H-2), 3.54–3.62 (m, 4 H, H-1a,1b,5,7a), 3.74 (dd, 1 H, $J_{6,7b}$ 11, J_{gem} 13.7 Hz, H-7b), 4.14 (ddd, 1 H, $J_{5,6}$ 6.1, $J_{6,7a}$ 2.6, $J_{6,7b}$ 11

Hz, H-6), 7.28–7.38 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{20}F_3NO_7 \cdot H_2O$: C, 44.78; H, 5.02; N, 3.49. Found: C, 44.54; H, 4.88; N, 3.88.

7-Amino-2,6-anhydro-7-deoxy-7-C-phenyl-D-erythro-L-gulo-*heptitol* (**1a**).—A solution of **31** (25 mg, 0.065 mmol) in water was chromatographed through a short column charged with Amberlite IRA-400 (OH^-) resin. Evaporation of the solvent yielded **1a** (17.5 mg, quant) as a colorless oil; ^1H NMR (250 MHz, D_2O): δ 3.17–3.33 (m, 4 H, H-1a,1b,2,3), 3.72–3.76 (m, 2 H, H-4,5), 4.00–4.05 (m, 1 H, H-6), 4.25 (d, 1 H, J 10.3 Hz, H-7), 7.19–7.29 (m, 5 H, Ph).

7-Amino-2,6-anhydro-7-deoxy-7-C-phenyl-L-threo-L-gulo-*heptitol* (**2a**).—Compound **32** (20 mg, 52.2 μmol) was treated as described for **1a**, to give **2a** (14 mg, quant) as a colorless oil; ^1H NMR (250 MHz, D_2O): δ 3.28 (dd, 1 H, $J_{4,5}$ 6.4, $J_{5,6}$ 3.6 Hz, H-5), 3.38 (t, 1 H, J 6.5 Hz, H-3), 3.59–3.73 (m, 3 H, H-1a,2,4), 3.79 (dd, 1 H, J_{gem} 11.1, $J_{1b,2}$ 6.6 Hz, H-1b), 3.94 (dd, 1 H, $J_{5,6}$ 3.6, $J_{6,7}$ 9.9 Hz, H-6), 4.08 (d, 1 H, J 9.9 Hz, H-7), 7.19–7.26 (m, 5 H, Ph).

2,6-Anhydro-7-deoxy-7-C-phenyl-D-glycero-L-gulo-*heptitol* (**3a**).—To a solution of **18** (35 mg, 82.8 μmol) in dry MeOH (10 mL) was added sodium methoxide (0.15 mL of a 0.2 M solution in MeOH). After 2.5 h at room temperature, the mixture was neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 $CHCl_3$–MeOH) of the residue yielded **3a** (21 mg, quant) as a colorless oil; $[\alpha]_D$ +133° (c 1, MeOH); R_f 0.14 (9:1 $CHCl_3$–MeOH); ^1H NMR (250 MHz, CD_3OD): δ 2.93–3.05 (m, 2 H, H-7a,7b), 3.34–3.42 (m, 1 H, H-2), 3.63–3.78 (m, 5 H, H-1a,1b,3,4,5), 4.12–4.19 (m, 1 H, H-6), 7.18–7.31 (m, 5 H, Ph).

2,6-Anhydro-7-deoxy-7-phenylamino-D-*glycero*-L-gulo-*heptitol* (**4a**).—Compound **33** (18.5 mg, 48.1 μmol) was treated as described for **1a**, to give **4a** (13 mg, quant) as a colorless oil; R_f 0.3 (85:15 $CHCl_3$–MeOH); ^1H NMR (250 MHz, D_2O): δ 3.17–3.34 (m, 3 H, H-3,7a,7b), 3.37–3.44 (m, 1 H, H-2), 3.49 (t, 1 H, J 9.4 Hz, H-4), 3.51–3.68 (m, 3 H, H-1a,1b,5), 4.07 (ddd, 1 H, $J_{5,6} = J_{6,7a} = 5.1$, $J_{6,7b}$ 7.8 Hz, H-6), 6.70–6.74 (m, 3 H, Ph), 7.09–7.16 (m, 2 H, Ph).

Inhibition studies.—(*a*) *Materials.* Buffer substances were purchased from Fluka and used as received. α-D-Glucosidase (yeast, EC 3.2.1.20) and *p*-nitrophenyl α-D-glucopyranoside (PNPG) were obtained from Boehringer Mannheim.

(b) Preparation of solutions. The buffer consisted of 0.01 M piperazine 1,4-bis(2-ethanesulfonic acid) (PIPES), 0.02 M NaOAc, and 0.1 mM EDTA[3]. The pH was adjusted to 6.5 with NaOH (10 M). PNPG was dissolved in the buffer solution for enzyme assays. 0.95 mg of α-D-glucosidase lyophilisate [ca. 8.4 U/mg (30°C, PNPG as substrate)] was dissolved in 1 mL of buffer solution and used for assays without further dilution. For each inhibitor, inhibitor concentrations ranging from 0 to 3 K_i, were generally used to determined the K_i value. At each inhibitor concentration, six substrate concentrations, spanning 0.4 K_M to 4 K_M, were used.

(c) Procedure for enzyme assays. To a 1-mL disposable cuvette was added buffer solution (940 μL), inhibitor solution (20 μL), and PNPG-solution (20 μL). The solution was thermally equilibrated at 30°C and the reaction was started by

addition of 20 μL of α-D-glucosidase solution. Liberation of *p*-nitrophenol ($\epsilon_{ONP^-, pH\ 6.5}$ 3204.5 M^{-1} cm^{-1})[26] was monitored, using a Philips PU 8740 UV/VIS-spectrophotometer, for 60 s, and the initial hydrolysis rate was calculated.

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