191. Synthesis of a Glucose-Derived Tetrazole as a New β-Glucosidase Inhibitor. A New Synthesis of 1-Deoxynojirimycin

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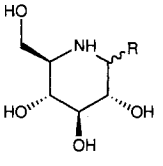
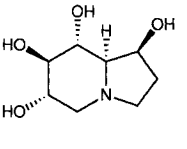
(15.X.91)

The tetrazole **1** is a new β-glucosidase inhibitor ($IC_{50} = 8 \cdot 10^{-5}$ M, *Emulsin*), obtained (92%) by deprotection of **22**, the product of an intramolecular cycloaddition of the azidonitrile **20**. This azidonitrile was formed as an intermediate by treating the L-*ido*-bromide **14** or the L-*ido*-tosylate **19** with NaN_3 at 110–125°. It was isolated in a separate experiment. The yield of **22** from **19** reached 70%; **21** was formed as by-product (10%). The bromide **14** (42%) and the iodide **15** (30–35%) were obtained from the nitrile **13**, together with the 2,5-anhydro-L-idononitrile **16**, which was formed in *ca.* 35–45%. The tosylate **19** was obtained from **18** (97%). To obtain **18**, the nitrile **13** was oxidized according to *Swern* (→ **17**, 92%) and then reduced ($NaBH_4$, $CeCl_3$), leading to **18** and **13** (92%, **18**/**13** 93:7). Reduction of the tetrahydropyridotetrazole **22** with $LiAlH_4$ afforded 83% of the piperidine **23**, which was deprotected to (+)-1-deoxynojirimycin hydroacetate (**2** · AcOH, 86%) and further converted into the corresponding hydrochloride and into the free base **2**.

Introduction. – A number of glycosidase inhibitors, some of them with promising biological properties, have been isolated or designed. Among them are not only polyhydroxylated piperidines (*e.g.* 1-deoxynojirimycin (**2**) [1], nojirimycin (**3**) [2], and related compounds), polyhydroxylated pyrrolidines (*e.g.* DAB 1 [3]) and indolizidines (*e.g.* castanospermine (**4**) [4] and swainsonine [5]), but also analogues of glyconolactones (glucono-1,5-lactone [6], nojirilactame **5** [7], the amidine **6** [8], acylated hydroximolactones **7** [9], and lactone hydrazones **8** [10]).



2 R = H
3 R = OH



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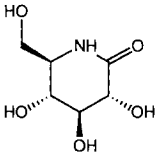

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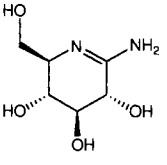

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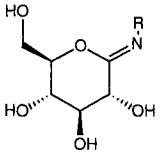
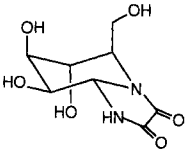


7 R = OCONHPh
8 R = NHCONHPh



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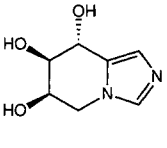

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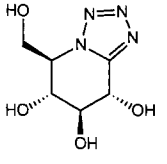
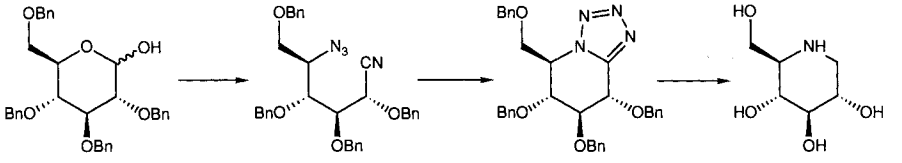


1

In the context of our interest in glucosidase inhibitors [9] [10], we wished to synthesize the tetrazole **1**. This compound is of interest as an analogue of glucono-1,5-lactone; more precisely, it is a nonbasic diazo homologue of the amidin **6**, or an analogue of nojirilactame (**5**), possessing an annulated ring. Several glycosidase inhibitors with a 1,2-annulated five-membered ring, such as kifunensine (**9**) [11], 8-epi-kifunensine [12], allosamidin [13], or the 6-epi-castanospermine analogue **10**, a potential glycosidase inhibitor [14], have recently been isolated and/or prepared.

Scheme 1

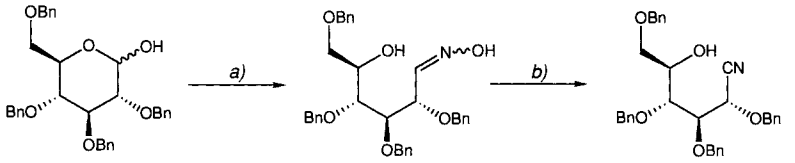


11 **20** **22** **2**

The obvious starting material for the synthesis of the tetrazole **1** and its protected form **22** (*Scheme 1*) is a 5-azido-5-deoxy-glyconononitrile, such as **20**. As a rule, monosaccharide derivatives which are modified at C(5) have been prepared from furanosides, whereas **20** is derived from the pyranose **11**. The synthesis of **1** was of particular interest, as we have started to explore the potential of inter- and intramolecular substitutions at C(5) of acyclic derivatives obtained from pyranoses [15][1]). Finally, to the best of our knowledge, the intramolecular 1,3-dipolar cycloaddition of azidonitriles has not been used to form C,N bonds in the synthesis of carbohydrate-derived piperidinoses[2]), and we wished to demonstrate that tetrazoles such as **22** are convenient precursors of piperidinoses by transforming **22** into 1-deoxynojirimycin (**2**).

Results and Discussion. – The oxime **12** [18], obtained almost quantitatively from the tetra-*O*-benzylglucose **11** [19], was treated with PPh_3 and CBr_4 [20] to yield the nitrile **13** in 75–85% from **11** (*Scheme 2*).

Scheme 2



11 **12** **13**

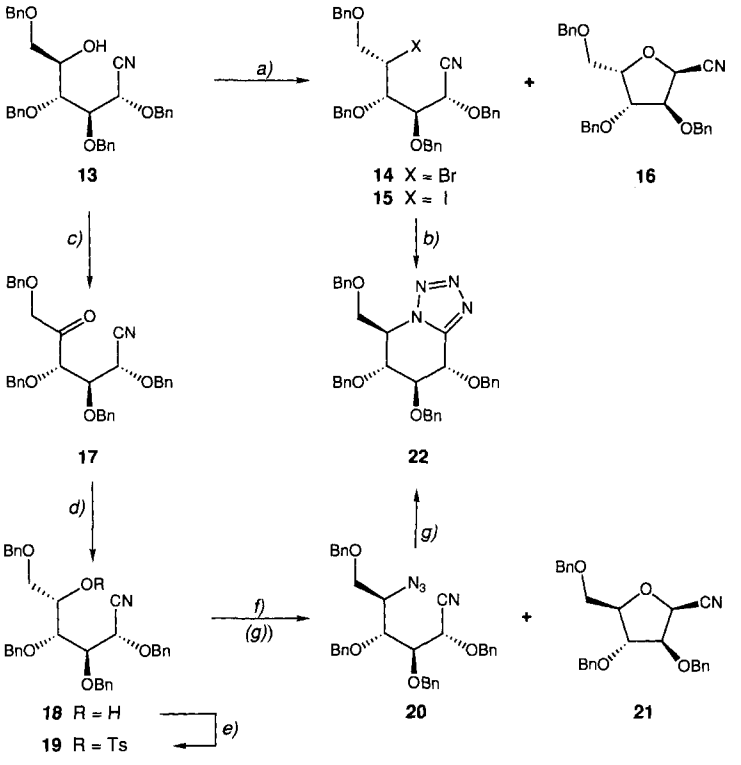
a) NH_2OH, 96% EtOH, 55–60°, 7 h; 99%. *b*) PPh_3, CBr_4, MeCN, r.t., 20 min; 75–85%.

The structure of **13** is evidenced by its elemental analysis and spectroscopic data. The IR spectrum shows an OH band at 3550 cm^{-1}. It shows no CN absorption, like the other nitriles described in this work, and similarly to what has been previously observed for α-alkoxynitriles [21] [22]. The ^{13}C-NMR spectrum indicates the presence of a CN group (*s* at 116.93 ppm). Besides the aromatic C-atoms, 4 CH and 5 CH_2 signals were found. The ^1H-NMR spectrum shows signals for 4 Bn groups, 6 CH of the carbohydrate chain, and 1 CD_3OD-exchangeable OH.

[1]) For examples of related efforts, *cf.* [16].

[2]) The intramolecular azide-alkene cycloaddition, however, is well known [17].

Scheme 3



a) PPh_3, imidazole, Br_2 (or I_2), toluene, 110°, 2 h; 42% of **14** (or 30–35% of **15**). *b*) NaN_3, DMSO, 110–125°, 4 h; 43%. *c*) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; 92%. *d*) $NaBH_4$, $CeCl_3 \cdot 6\,H_2O$, −60 to −40°, 55 min; 86%. *e*) TsCl, pyridine, 40–50°, 20 h; 97%. *f*) NaN_3, DMSO, 110–120°, 5 min; 37% of **20**. *g*) (from **19**) NaN_3, DMSO, 110–125°, 195 min; 70% of **22** and 10% of **21**.

Two routes to the L-*ido*-configurated precursors **14**, **15**, and **19** of the tetrazole **22** were explored (*Scheme 3*), *viz.* double inversion and oxidoreduction. In the first approach, **13** was converted into the L-*ido*-bromide **14** by treatment with an excess of PPh_3/Br_2 and imidazole in boiling toluene [23]. The iodide **15** was obtained in a similar way. A neighboring-group participation of the C(2)–OBn group[3]), leading to the 2,5-anhydro-L-idononitrile **16** is at least partially responsible for the unsatisfactory yield of **14** (42%) and **15** (30–35%). The nitrile **16** was isolated from the product of iodination, while bromination of **13** gave **16** as the main constituent of a mixture of side products, from which it could not be isolated by the usual chromatographic methods.

The MS of **14** shows the peaks for $[M + H]^+$ at m/z 602 and 600 with the characteristic isotope distribution of a bromide; $[M + H]^+$ of **15** occurs at m/z 648. The ^{13}C-NMR spectra of **14** and **15** show the *s* of the CN group at 116.33 and 116.21 ppm, respectively; a *d*, resonating at significantly higher field (51.46 ppm (**14**) and 32.23 ppm (**15**)) as compared to **13**, is assigned to C(5).

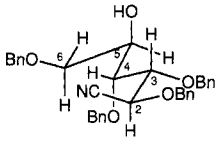
[3]) Substituted benzyl ethers are well known to act as nucleophiles in the synthesis of tetrahydrofurans [27].

Swern oxidation [24] of **13** yielded 92% of the ketone **17**; reduction of **17** with $NaBH_4$ in MeOH in the presence of $CeCl_3 \cdot 6\ H_2O$ [25] gave the desired L-*ido*-hydroxynitrile **18** as the main product, besides **13** (92%; **18**/**13** 93:7); a much lower degree of diastereoselectivity (88%; **18**/**13** = 59:41) was obtained in the absence of $CeCl_3 \cdot 6\ H_2O$. The hydroxynitrile **18** was converted into the tosylate **19** (97%) in the usual way.

Treatment of the bromide **14** with NaN_3 in DMSO at 110–125° [26] led to the tetrazole **22** (43%) and to a mixture of elimination products[4]) (28%). Neither replacement of NaN_3 by NH_4N_3 nor a change of solvent (DMF, HMPT) improved the yields, which were even lower, when **15** was used as the starting material. When the tosylate **19** was exposed to NaN_3 under similar conditions, yields of the tetrazole **22** reached 70%. The major side product was the 2,5-anhydro-D-gluconononitrile **21** (10%) [22]. Monitoring the reaction by TLC indicated the formation of an intermediate, less polar then the tosylate or the tetrazole, which was isolated and identified as the known [28] azidonitrile **20**.

The IR spectrum of **17** is characterized by a CO band at 1735 cm^{-1}; in the ^{13}C-NMR spectrum, *s*'s at 206.53 and 116.22 ppm indicate the presence of a CO and a CN group, respectively. The structure of **18** is evidenced by the disappearance of the CO band and by a new OH absorption at 3570 cm^{-1}. The CN group resonates as a *s* at 116.67 ppm. The values for the chemical shift of 4 *d*, assigned to C(2) to C(5), are nearly identical with those observed for **13**. In the ^1H-NMR spectrum of **18**, H–C(5) (3.82 ppm) resonates at a higher field than H–C(3) (3.94 ppm) and H–C(4) (3.88 ppm), whereas for **13**, the signal of H–C(5) (3.96 ppm) is observed between the signals of H–C(3) (4.06 ppm) and H–C(4) (3.87 ppm). The ^1H-NMR spectrum of **19** shows the resonance of H–C(5), superimposed by Bn signals, in a *m* at 4.63–4.71 ppm and thus at significantly lower field than the corresponding signal of **18**. The structure of **19** is further evidenced by its elemental analysis and the ^{13}C-NMR spectrum, indicating the presence of the CN group (*s* at 116.39 ppm).

The conformations of **13**–**15**, **18**, and **19** may (partially) be deduced and compared, based on the vicinal coupling constants (see the *Table*). For the D-*gluco*-alcohol **13**, large values of $J(2,3)$ and $J(4,5)$, a small value of $J(3,4)$,



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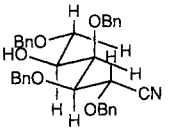
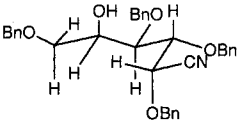
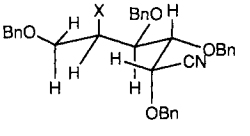


18A



18B

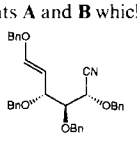


14 X = Br
15 X = I

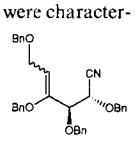
Table. *Selected H,H-Coupling Constants of Compounds* **13**–**15**, **18**, *and* **19**

	$J(2,3)$	$J(3,4)$	$J(4,5)$	$J(5,6)$	$J(5,6')$
13	6.9	3.0	7.7	4.8	4.0
14	4.1	6.6	3.0	6.0	7.4
15	3.9	6.9	2.8	5.9	8.5
18	5.1	5.7	2.8	5.9	6.1
19	5.3	5.1	4.2	5.0	4.2

[4]) In a preliminary experiment, this mixture was separated into two components **A** and **B** which were characterized by their ^1H-NMR spectra, but not further examined. The component **A** showed a *d* at 6.49 ppm (J = 12.9 Hz), assigned to H–C(6), and the component **B** showed at *t* at 5.42 ppm ($J \approx 6.9$ Hz) and a *d* at 4.07 ppm ($J \approx 6.2$ Hz), assigned to H–C(5) and H–C(3), respectively, in keeping with the tentative structures **A** and **B**, respectively.



A



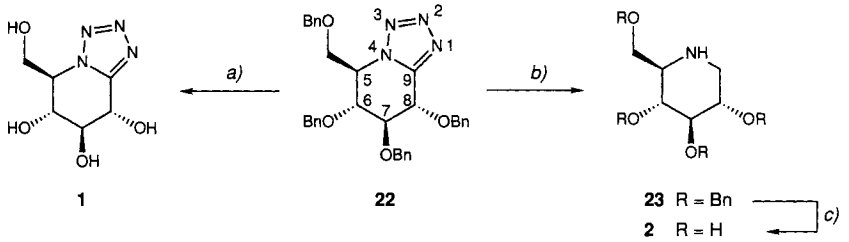
B

and medium-to-small values of $J(5,6)$ and $J(5,6')$ are qualitatively compatible with an extended zig-zag conformation. The L-*ido*-alkohol **18** shows medium values for $J(2,3)$, $J(3,4)$, $J(5,6)$, and $J(5,6')$, while $J(4,5)$ is small, indicating a mixture of conformers and a *gauche*-arrangement of H–C(4) and H–C(5). The coupling constants may be tentatively rationalized by assuming two main conformers, **18A** and **18B**, the former with a zig-zag arrangement of the C-chain, implying a parallel 1,3-arrangement of BnO–C(3) and OH–C(5), perhaps stabilized by an intramolecular H-bond (J(OH,CH) = 6.9 Hz), the latter with a sickle conformation, similar to the dominant conformation of **14** and **15**. For these halides, one finds relatively small values for $J(2,3)$ and $J(4,5)$ and larger ones for $J(3,4)$, $J(5,6)$, and $J(5,6')$. Since both $J(5,6)$ and $J(5,6')$ of **14** and **15** are quite large, a further conformer must contribute to the equilibrium. The vicinal coupling constants of **19** show medium values, indicating a mixture of conformers.

The specific rotation of **20**, the IR and the ^{1}H-NMR spectra are in keeping with the published data, with the exception of the *dd* at 3.8 ppm, for which we find J = 2.4 and 9.2 Hz and not J = 2 and 6.8 Hz [28]. The structures of **16** and **21** are in keeping with their elemental analysis and their spectroscopic data. In the MS of **16** and **21**, $[M + H]^+$ is found at m/z 430; $[M + NH_4]^+$ in the CI-MS (NH_3) of **16** is at m/z 447. The ^{1}H-NMR spectrum of **21** (300 MHz, C_6D_6) is in agreement with the published spectrum (60 MHz, C_6D_6) [22], establishing its configuration, which is as expected from mechanistic consideration. The isomer **16** must then possess the L-*ido*-configuration, which is in agreement with the coupling constants, but which could not unambiguously be derived from them. The structure of **22** is in agreement with the elemental analysis and the MS ($[M + H]^+$ at m/z 563). A *s* at 152.46 ppm and the disappearance of the CN signal evidence the tetrazole ring. The H,H-coupling constants $J(5,6)$ = 7.5, $J(6,7)$ = 8.9, and $J(7,8)$ = 6.9 Hz are in keeping with a *gluco*-configurated piperidinose in a $^6H_7$ conformation; a lower value for $J(7,8)$ would be expected for a $B_{5,8}$ conformation.

Hydrogenolytic debenzylation of **22** afforded the desired tetrazole **1** (92% after chromatography; *Scheme 4*). The structure of **1** was established by X-ray analysis. There

Scheme 4



a) H_2, 10% Pd/C, MeOH, AcOH, r.t., 30 h; 92%. *b*) $LiAlH_4$, Et_2O, reflux, 5 h; 83%. *c*) 1) H_2 (8 bar), 10% Pd/C, AcOH, r.t., 15 h; 86%; 2) MeOH, aq. HCl soln.; 3) *Dowex 1* × *8* (OH^-).

are two crystallographically independent molecules (**I** and **II**, *Fig.*)[5]) in the asymmetric unit, each possessing the same configuration. The configuration at C(5) is *R*, assuming that the chirality at C(2), C(3), and C(4) has not changed. The torsional angle C(5)–N(1)–C(1)–C(2) is −4.5° (molecule **I**) and the torsional angle C(15)–N(11)–C(11)–C(12) −3.4° (molecule **II**); this indicates that the atoms C(5), N(1), C(1), and C(2) or C(15), N(11), C(11), and C(12) are in the same plane. The $^4H_3$ (= $^6H_7$) conformation is clearly visible from the perspective view of the molecules (*Fig.*).

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[5]) Atomic coordinates, bond lengths, and angles were deposited with the *Cambridge Crystallographic Data Center*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. The numbering of the atoms in the *Figure* is different from the systematic numbering (*cf. Scheme 4*) used to discuss the NMR spectra and the conformation.

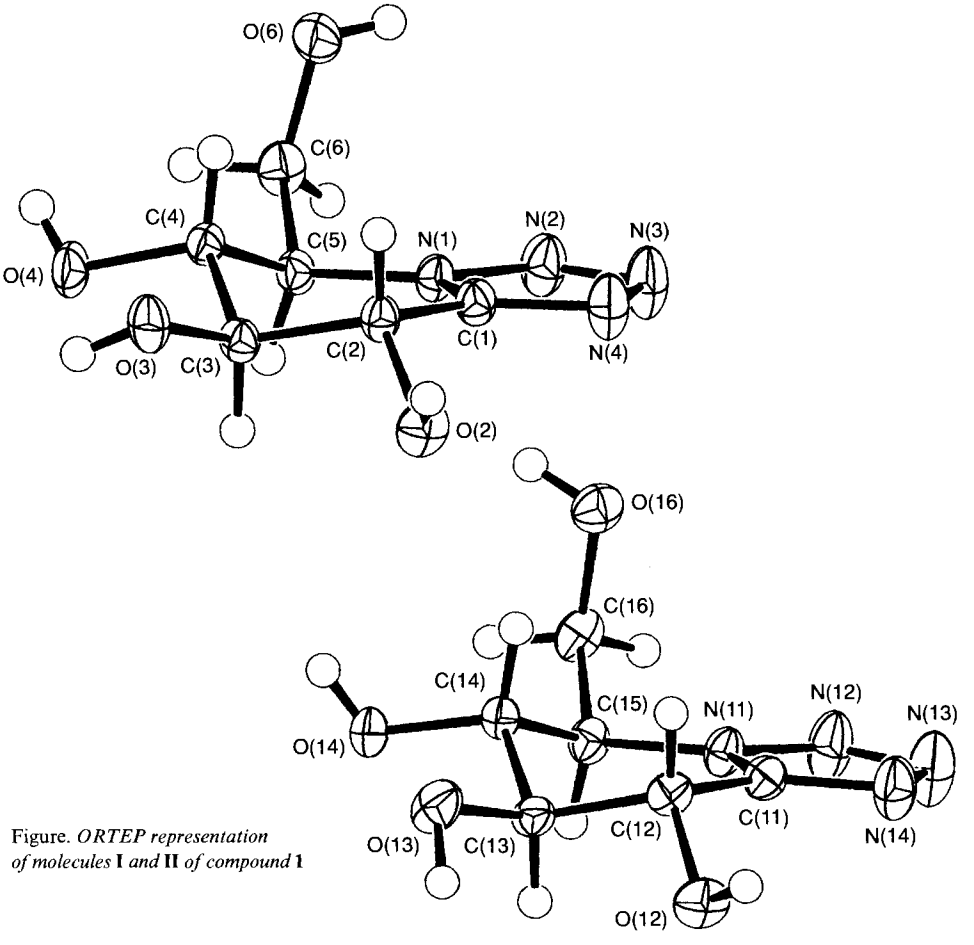

Figure. *ORTEP representation of molecules* **I** *and* **II** *of compound* **1**

The ^{13}C-NMR spectrum of **1** shows the characteristic *s* for the tetrazole ring at 155.52 ppm. In the MS, $[M + H]^+$ is observed as main peak at *m/z* 203. In the ^{1}H-NMR spectrum (CD_3OD), signals corresponding to 6 CH are detected. The large coupling constants of the ring protons ($J(5,6) = 8.5$, $J(6,7) = 9.5$, and $J(7,8) = 8.4$ Hz) indicate a $^6H_7$ conformation. The homoallylic coupling, $J(8,5) \approx 0.7$ Hz, is in agreement with a planar arrangement of C(8), C(9), N(4), and C(5).

Preliminary investigations show an IC_{50} of $0.8 \cdot 10^{-4}$ M for **1** against *Emulsin* (β-glucosidase isoenzyme mixture from almonds) and an IC_{50} of $3 \cdot 10^{-2}$ M, $K_I = 17.9 \cdot 10^{-3}$ M against glucosidase II (an α-glucosidase) in porcine liver extract[6]).

The reductive ring cleavage of 1,5-disubstituted tetrazoles proceeds with loss of three of the ring N-atoms to give secondary amines [29]. Thus, **22** was reduced with an excess of $LiAlH_4$ to yield 83% of the tetra-*O*-benzyldeoxynojirimycin **23** [30] (*Scheme 4*). Hydrogenolysis of **23** (10% Pd/C, AcOH, 8 bar) yielded deoxynojirimycin hydroacetate (**2**·AcOH) in 86% after chromatography. This hydroacetate was converted into the

[6]) Measurements against glucosidase II were carried out at pH 6.5, using the artificial substrate methylumbelliferyl α-D-glucopyranoside; the inhibition was clearly competitive.

corresponding hydrochloride and, hence, by treatment with *Dowex 1 × 8* (OH^-) into the free base **2**.

The benzyl derivative **23** was identified by its m.p. and spectroscopic data. The IR spectrum shows an NH band at 3440 cm^{-1}; $[M + H]^+$ is found in the CI-MS at *m/z* 524. A *ddd* at 2.72 ppm ($J = 2.6$, 5.9, 9.1 Hz) in the ^{1}H-NMR spectrum is assigned to H–C(5); the large coupling constant $J(4,5) = 9.1$ Hz is in keeping with the D-*gluco*-configuration. The large values of $J(1a,2)$, $J(3,4)$, and $J(4,5)$ indicate a $^4C_1$ conformation. The ^{1}H-NMR spectrum of **2** · AcOH shows 8 CH of the piperidinose ring with the characteristic deoxynojirimycinium pattern and a *s* at 1.89 ppm which integrates for 3 H and indicates the presence of the AcO^- anion. In the CI-MS, $[M + H]^+$ occurs at *m/z* 164. The spectroscopic data of **2** · HCl and of the free base **2** match the published data [2] [31].

We thank Dr. *D. Brada,* Zell- und Molekularpathologie, Institut für Pathologie der Universität, 8091 Zürich, for measuring the inhibition constant against glucosidase II, Dr. *A. Linden* for determining the X-ray structure, and the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG,* Basel, for generous support.

Experimental Part

General. Solvents were distilled before use. Normal workup implies distribution of the crude product between the indicated org. solvent and H_2O, drying of the org. layer ($MgSO_4$), filtration, and evaporation of the filtrate. TLC: *Merck* silica gel *60F-254* plates; detection by heating with 5% vanillin in conc. H_2SO_4 or with mostain [32] (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6Mo_7O_{24} \cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Merck 60* (0.04–0.063 mm). M.p.: uncorrected. ^{1}H (300 MHz)- and ^{13}C-NMR (50 MHz): chemical shifts δ in ppm and coupling constants J in Hz.

*2,3,4,6-Tetra-*O*-benzyl-*D*-glucononitrile* (**13**). $NH_2OH \cdot HCl$ (10.26 g, 148 mmol) was added at 55° to a stirred soln. of Na (1.76 g, 76.5 mmol) in 96% aq. EtOH (375 ml). Stirring was continued for 5 min followed by addition of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**11**; 10.0 g, 18.5 mmol). The mixture was stirred for 7 h at 55–60° and filtered. The residue was washed with AcOEt, and the combined filtrate and washings were concentrated. Normal workup (AcOEt) gave crude oxime **12** which crystallized when dried *i.v.* (10.19 g, 99%). CBr_4 (10.39 g, 31.3 mmol) in dry MeCN (40 ml) was added at 20–25° to a stirred soln. of crude **12** (6.96 g, 12.5 mmol) and PPh_3 (6.57 g, 25 mmol) in MeCN (100 ml). Stirring was continued for 20 min, then a soln. of PPh_3 (1.65 g, 6.3 mmol) in MeCN (50 ml) and MeOH (140 ml) was added. After 15 min, the soln. was evaporated and dried *i.v.* FC (hexane/AcOEt 85:15) of the residue afforded **13** (5.11 g, 76%). Yellowish oil. R_f (hexane/AcOEt 1:1) 0.52. $[\alpha]_D^{25} = +61.7$ ($c = 1.29$, $CHCl_3$). IR ($CHCl_3$): 3550*m* (br.), 3090*w*, 3060*w*, 3000*w*, 2920*w*, 2870*w*, 1450*w*, 1345*w*, 1075*s* (br.), 905*w*. ^{1}H-NMR ($CDCl_3$): 2.47 (*d*, $J = 6.6$, exchanged with CD_3OD, OH–C(5)); 3.56 (*dd*, $J = 4.8$, 9.9, H–C(6)); 3.60 (*dd*, $J = 4.0$, 10.0, H′–C(6)); 3.87 (*dd*, $J = 3.0$, 7.7, H–C(4)); 3.96 (*m*, changed after addn. of CD_3OD, H–C(5)); 4.06 (*dd*, $J = 3.0$, 6.9, H–C(3)); 4.42 (*d*, $J = 6.9$, H–C(2)); 4.45–4.54 (*m*, 4 H, PhCH_2); 4.65 (*d*, $J = 11.1$, PhCH_2); 4.68 (*d*, $J = 11.1$, PhCH_2); 4.76 (*d*, $J = 11.3$, PhCH_2); 4.85 (*d*, $J = 11.5$, PhCH_2); 7.20–7.38 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 69.21 (*d*); 69.67 (*d*); 70.52 (*t*); 72.88 (*t*); 73.41 (*t*); 74.30 (*t*); 75.24 (*t*); 77.85 (*d*); 78.70 (*d*); 116.93 (*s*); 127.81–128.85 (several *d*); 135.61 (*s*); 137.43 (*s*); 137.59 (*s*). CI-MS (C_4H_{10}): 628 (20), 539 (38), 538 (100, $[M + H]^+$), 430 (11), 91 (4). Anal. calc. for $C_{34}H_{35}NO_5$ (537.66): C 75.95, H 6.56, N 2.61; found: C 75.77, H 6.80, N 2.55.

*2,3,4,6-Tetra-*O*-benzyl-5-bromo-5-deoxy-*L*-idononitrile* (**14**). A soln. of **13** (10.24 g, 19 mmol) in dry toluene (160 ml) was heated to reflux, slightly cooled, and treated with PPh_3 (19.97 g, 76 mmol), imidazole (5.22 g, 76 mmol), toluene (160 ml), and a soln. of Br_2 (9.11 g, 57 mmol) in toluene (20 ml), causing the formation of a sticky precipitate. The mixture was heated under reflux for 2 h, diluted with toluene (400 ml), and poured onto sat. aq. $NaHCO_3$ soln. (500 ml). The remaining material in the reaction vessel was taken up in toluene/H_2O and added to the bulk of material. The two layers were vigorously mixed, and Br_2 (*ca.* 3 ml) was added until the color of the toluene layer changed from yellow to orange. The mixture was treated with aq. $Na_2S_2O_3$ soln. and vigorously mixed; the org. layer was separated and washed (aq. $Na_2S_2O_3$ soln., H_2O). The H_2O layers were extracted back with toluene. The combined toluene layers were dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 95:5) of the residue yielded **14** as a brown oil (4.82 g, 42%), sufficiently pure for the next step. An anal. sample was further purified by FC to give a yellowish oil. R_f (hexane/AcOEt 8:2) 0.35. $[\alpha]_D^{25} = +39.9$ ($c = 0.845$, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3070*w*, 3040*w*, 3010*w*, 2910*w*, 2870*w*, 1955*w*, 1875*w*, 1810*w*, 1595*w*, 1495*w*, 1450*m*, 1340*m* (br.), 1080*s* (br.), 1025*s*, 910*m*. ^{1}H-NMR ($CDCl_3$): 3.59 (*dd*, $J = 6.0$, 10.1, H–C(6)); 3.78 (*dd*, $J = 7.4$, 10.1, H′–C(6)); 4.00 (*ddd*, $J = 3.0$,

6.0, 7.3, H–C(5)); 4.07 (*dd*, J = 4.1, 6.6, H–C(3)); 4.15 (*dd*, J = 3.1, 6.6, H–C(4)); 4.34 (*d*, J = 4.1, H–C(2)); 4.37 (*d*, J = 12.2, PhCH_2); 4.42 (*d*, J = 12.0, PhCH_2); 4.52 (*d*, J = 11.7, PhCH_2); 4.67 (*d*, J = 11.3, PhCH_2); 4.72 (*d*, J = 10.9, PhCH_2); 4.79 (*d*, J = 10.9, PhCH_2); 4.84 (*d*, J = 11.9, PhCH_2); 4.88 (*d*, J = 11.9, PhCH_2); 7.25–7.36 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 51.46 (*d*); 68.35 (*d*); 70.65 (*t*); 72.67 (*t*); 72.89 (*t*); 74.96 (*t*); 75.38 (*t*); 77.19 (*d*); 80.21 (*d*); 116.33 (*s*); 127.60–128.66 (several *d*); 135.05 (*s*); 137.09 (*s*); 137.54 (*s*); 137.77 (*s*). CI-MS (C_4H_{10}): 603 (32), 602 (97, $[M + H]^+$), 601 (35), 600 (100, $[M + H]^+$), 181 (14), 91 (7). Anal. calc. for $C_{34}H_{34}BrNO_4$ (600.56): C 68.00, H 5.71, N 2.33, Br 13.31; found: C 68.04, H 5.81, N 2.29, Br 13.30.

*2,3,4,6-Tetra-*O*-benzyl-5-deoxy-5-iodo-*L*-idononitrile* (**15**) *and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-*L*-idononitrile* (**16**). A soln. of **13** (500 mg, 0.93 mmol) in dry toluene (25 ml) was heated to reflux, slightly cooled, and treated with PPh_3 (977 mg, 3.72 mmol), imidazole (255 mg, 3.74 mmol), and I_2 (710 mg, 2.79 mmol). The heterogeneous mixture was kept under reflux for 2 h, diluted with toluene (30 ml), and poured onto sat. aq. $NaHCO_3$ soln. (75 ml). The material remaining in the reaction vessel was taken up in a minimal amount of acetone and added to the bulk of material. The mixture was stirred vigorously for 5 min, then I_2 was added in portions until the color of I_2 was no longer discharged. Stirring was continued for 10 min, then crystalline $Na_2S_2O_3$ was added until disappearance of the I_2 color. Normal workup (toluene, aq. $Na_2S_2O_3$ soln., H_2O) and FC (hexane/AcOEt 95:5) afforded **15** (178 mg, 30%) and **16** (178 mg, 44%), both as slightly yellowish oils.

Data of **15**: R_f (hexane/AcOEt 8:2) 0.39. $[\alpha]_D^{25}$ = +33.1 (c = 0.317, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3070*w*, 3030*w*, 3010*w*, 2910*w*, 2870*w*, 1950*w*, 1875*w*, 1810*w*, 1495*w*, 1455*w*, 1400*w*, 1365*w*, 1305*w*, 1240*w*, 1115*s* (br.), 1080*s* (br.), 1030*s*, 915*w*. ^{1}H-NMR ($CDCl_3$): 3.63 (*dd*, J = 5.9, 10.1, H–C(6)); 3.71 (*dd*, J = 2.7, 7.0, H–C(4)); 3.76 (*dd*, J = 8.5, 10.0, H′–C(6)); 4.00 (*dd*, J = 3.9, 6.9, H–C(3)); 4.08 (*ddd*, J = 2.8, 5.8, 8.5, H–C(5)); 4.30 (*d*, J = 3.9, H–C(2)); 4.34 (*d*, J = 11.9, PhCH_2); 4.41 (*d*, J = 11.9, PhCH_2); 4.52 (*d*, J = 11.7, PhCH_2); 4.68 (*d*, J = 11.5, PhCH_2); 4.75 (*d*, J = 10.9, PhCH_2); 4.80 (*d*, J = 10.9, PhCH_2); 4.87 (*d*, J = 11.6, 2 H, PhCH_2); 7.24–7.37 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 32.23 (*d*); 68.23 (*d*); 72.23 (*t*); 72.50 (*t*); 72.60 (*t*); 74.59 (*t*); 75.30 (*t*); 76.75 (*d*); 82.14 (*d*); 116.21 (*s*); 127.51–128.57 (several *d*); 134.91 (*s*); 137.00 (*s*); 137.51 (*s*); 137.88 (*s*). CI-MS (NH_3): 696 (10), 666 (38), 665 (100, $[M + H]^+$), 648 (23, $[M + H]^+$), 447 (14), 431 (13), 313 (13), 308 (39), 295 (18), 200 (11), 108 (16), 91 (14). Anal. calc. for $C_{34}H_{34}INO_4$ (647.56): C 63.06, H 5.29, I 19.60, N 2.16; found: C 63.14, H 5.23, I 19.41, N 2.27.

Data of **16**: R_f (hexane/AcOEt 8:2) 0.25. $[\alpha]_D^{25}$ = 0.0 (c = 0.65, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3060*w*, 3030*w*, 3010*w*, 2930*w*, 2870*m*, 1955*w*, 1875*w*, 1810*w*, 1495*m*, 1455*m*, 1395*w*, 1370*w*, 1355*w*, 1305*w*, 1245*w*, 1105*s*, 1075*s*, 1030*m*, 990*m*, 910*w*. ^{1}H-NMR ($CDCl_3$): 3.63–3.72 (*m*, CH_2(6)); 4.06 (*dd*, J = 2.0, 4.1, H–C(4)); 4.12 (*dd*, J = 2.0, 4.9, H–C(3)); 4.41–4.65 (*m*, 7 H, H–C(5), PhCH_2); 4.85 (*d*, J = 4.9, H–C(2)); 7.18–7.38 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 67.39 (*t*); 69.72 (*d*); 72.42 (*t*); 72.78 (*t*); 73.36 (*t*); 80.26 (*d*); 80.88 (*d*); 81.69 (*d*); 115.77 (*s*); 127.60–128.49 (several *d*); 136.55 (*s*); 137.07 (*s*); 137.77 (*s*). CI-MS (NH_3): 448 (17), 447 (60, $[M + NH_4]^+$), 431 (29), 430 (100, $[M + H]^+$), 338 (15), 108 (13), 91 (23). Anal. calc. for $C_{27}H_{27}NO_4$ (429.52): C 75.50, H 6.34, N 3.26; found: C 75.37, H 6.09, N 3.43.

*2,3,4,6-Tetra-*O*-benzyl-*D*-xylo-hex-5-ulosononitrile* (**17**). Freshly distilled oxalyl chloride (2.12 g, 16.7 mmol) was added dropwise over 12 min to a cooled (−60 to −65°) soln. of dry DMSO (2.6 g, 33.3 mmol) in dry CH_2Cl_2 (30 ml). After 10 min, a soln. of **13** (2.0 g, 3.7 mmol) in CH_2Cl_2 (30 ml) was added over 25 min at this temp. The mixture was stirred for 15 min at −65 to −60°, allowed to warm over 50 min to −20°, maintained for 60 min at −35 to −25°, and again cooled to −65°; Et_3N (20 ml) was then added dropwise over 20 min at −65°. The turbid mixture was warmed over 105 min to 0°, treated with H_2O, and diluted with CH_2Cl_2. Normal workup (CH_2Cl_2, H_2O) and FC (hexane/AcOEt 85:15) yielded **17** (1.84 g, 92%). Yellow, clear oil. R_f (hexane/AcOEt 7:3) 0.42. $[\alpha]_D^{25}$ = +20.2 (c = 0.837, $CHCl_3$). IR (film): 3090*w*, 3060*w*, 3030*m*, 2910*w*, 2870*m*, 1955*w*, 1875*w*, 1815*w*, 1735*s*, 1605*w*, 1585*w*, 1495*m*, 1455*s*, 1400*m*, 1355*m*, 1210*m*, 1095*s*, 1080*s*, 1040*m*, 1030*s*, 910*w*, 820*w*. ^{1}H-NMR ($CDCl_3$): 4.12 (*d*, J = 18.3, H–C(6)); 4.17 (*dd*, $J \approx$ 3.4, 6.5, H–C(3)); 4.21 (*d*, J = 18.3, H′–C(6)); 4.35 (*d*, J = 11.7, PhCH_2); 4.37 (*d*, J = 3.5, 1 H); 4.39 (*d*, J = 7.1, 1 H); 4.42 (*d*, J = 12.2, PhCH_2); 4.49–4.55 (*m*, 3 H, PhCH_2); 4.59 (*d*, J = 11.2, PhCH_2); 4.63 (*d*, J = 11.3, PhCH_2); 4.80 (*d*, J = 11.3, PhCH_2); 7.17–7.37 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 68.20 (*d*); 72.95 (*t*); 73.13 (*t*); 74.27 (*t*); 74.63 (*t*); 74.96 (*t*); 78.93 (*d*); 82.01 (*d*); 116.22 (*s*); 127.79–128.53 (several *d*); 135.13 (*s*); 136.15 (*s*); 136.51 (*s*); 136.96 (*s*); 206.53 (*s*). CI-MS (C_4H_{10}): 537 (36), 536 (91, $[M + H]^+$), 181 (42), 107 (12), 91 (100). Anal. calc. for $C_{34}H_{33}NO_5$ (535.65): C 76.24, H 6.21, N 2.61; found: C 76.22, H 6.48, N 2.47.

*2,3,4,6-Tetra-*O*-benzyl-*L*-idononitrile* (**18**). A soln. of **17** (80 mg, 0.15 mmol) in MeOH (2 ml) was treated with $CeCl_3 \cdot 6\,H_2O$ (53 mg, 0.15 mmol) and cooled to −60° (→ precipitate). $NaBH_4$ (17 mg, 0.45 mmol) was added in portions. The stirred mixture was allowed to warm to −40° over 45 min, then cooled to −60° and stirred for 10 min. The mixture was poured onto phosphate buffer (50 ml; to 10 g of NaH_2PO_4 in 100 ml of H_2O, aq. NaOH was added until pH *ca.* 6) and worked up as usual (AcOEt, phosphate buffer pH 6, H_2O). FC (hexane/AcOEt 85:15) afforded **13** as a yellowish oil (5 mg, 6%) and **18** as a turbid oil which crystallized when dried *i.v.* (69 mg, 86%). An anal.

sample of **18** was recrystallized in Et_2O/hexane. R_f (hexane/AcOEt 7:3) 0.25. M.p. 61–62°. $[\alpha]_D^{25} = +48.15$ ($c = 0.596$, $CHCl_3$). IR ($CHCl_3$): 3570*w*, 3090*w*, 3060*w*, 3030*w*, 3010*w*, 2950*w*, 2870*m*, 1955*w*, 1875*w*, 1810*w*, 1605*w*, 1495*w*, 1455*m*, 1395*w*, 1350*w*, 1305*w*, 1120*s*, 1090*s*, 1030*m*, 915*w*. ^{1}H-NMR ($CDCl_3$): 2.37 (*d*, $J = 6.9$, exchanged with D_2O, OH–C(5)); 3.35 (*dd*, $J = 5.9$, 9.4, H–C(6)); 3.43 (*dd*, $J = 6.1$, 9.4, H′–C(6)); 3.82 (*dq*, $J \approx 2.87$, 6.1, *dt* after addn. of D_2O, H–C(5)); 3.88 (*dd*, $J = 2.8$, 5.7, H–C(4)); 3.94 (*t*, $J \approx 5.4$, H–C(3)); 4.40 (*d*, $J = 11.9$, PhCH_2); 4.45 (*d*, $J = 5.1$, H–C(2)); 4.45 (*d*, $J = 11.9$, PhCH_2); 4.55 (*d*, $J = 11.4$, 2 H, PhCH_2); 4.66 (*d*, $J = 11.2$, PhCH_2); 4.75 (*d*, $J \approx 10.6$, PhCH_2); 4.78 (*d*, $J \approx 10.6$, PhCH_2); 4.88 (*d*, $J = 11.6$, PhCH_2); 7.22–7.37 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 68.69 (*d*); 69.46 (*d*); 70.72 (*t*); 72.67 (*t*); 73.15 (*t*); 74.76 (*t*); 75.02 (*t*); 77.61 (*d*); 78.61 (*d*); 116.67 (*s*); 127.70–128.88 (several *d*); 135.41 (*s*); 137.22 (*s*); 137.62 (*s*); 137.79 (*s*). CI-MS (C_4H_{10}): 538 (21, $[M + H]^+$), 448 (20), 447 (98), 431 (48), 430 (100), 429 (75). Anal. calc. for $C_{34}H_{35}NO_5$ (537.66): C 75.95, H 6.56, N 2.61; found: C 75.84, H 6.36, N 2.64.

*2,3,4,6-Tetra-*O*-benzyl-5-*O*-(4-toluenesulfonyl)-*L*-idononitrile* (**19**). A mixture of 4-toluenesulfonyl chloride (532 mg, 2.79 mmol) and **18** (150 mg, 0.28 mmol) in pyridine (2.5 ml) was stirred at 40–50° for 20 h and then concentrated until formation of a precipitate. The residue was treated with sat. aq. $NaHCO_3$ soln., stirred for 10 min, and worked up as usual ($CHCl_3$, sat. aq. $NaHCO_3$ soln., H_2O). FC (hexane/AcOEt 85:15) yielded **19** (187 mg, 97%). Colorless oil. R_f (hexane/AcOEt 7:3) 0.33. $[\alpha]_D^{25} = +37.8$ ($c = 0.495$, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3060*w*, 3010*w*, 2920*w*, 2870*w*, 1950*w*, 1805*w*, 1595*w*, 1495*w*, 1455*w*, 1400*w*, 1365*m*, 1305*w*, 1235*w*, 1190*m*, 1175*s*, 1120*m*, 1095*s*, 1025*m*, 915*m*, 815*m*. ^{1}H-NMR ($CDCl_3$): 2.37 (*s*, Me); 3.37 (*dd*, $J = 5.0$, 11.0, H–C(6)); 3.60 (*dd*, $J = 4.2$, 11.0, H′–C(6)); 3.81 (*t*, $J \approx 5.1$, 1 H); 4.15 (*t*, $J \approx 4.2$, 1 H); 4.20 (*d*, $J = 12.0$, PhCH_2); 4.29 (*d*, $J \approx 12.6$, PhCH_2); 4.32 (*d*, $J = 5.3$, H–C(2)); 4.50 (*d*, $J = 11.6$, PhCH_2); 4.55 (*d*, $J = 11.2$, PhCH_2); 4.56 (*d*, $J = 11.4$ PhCH_2); 4.63–4.71 (*m*, 3 H, H–C(5), PhCH_2); 4.83 (*d*, $J = 11.6$, PhCH_2); 7.13–7.37 (*m*, 22 arom. H); 7.62 (*d*, $J = 8.34$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 21.56 (*q*); 67.84 (*t*); 68.30 (*d*); 72.67 (*t*); 73.02 (*t*); 74.87 (*t*); 75.16 (*t*); 76.32 (*d*); 77.71 (*d*); 80.32 (*d*); 116.39 (*s*); 127.62–128.65 (several *d*); 129.62 (*d*); 132.20 (*s*); 135.38 (*s*); 136.99 (*s*); 137.41 (*s*); 144.73 (*s*). CI-MS (NH_3): 709 (*ca.* 3, $[M + NH_4]^+$), 537 (5), 448 (24), 447 (80), 430 (12), 281 (16), 280 (100), 108 (28), 91 (12). Anal. calc. for $C_{41}H_{41}NO_7S$ (691.85): C 71.18, H 5.97, N 2.02, S 4.63; found: C 71.22, H 5.72, N 2.07, S 4.51.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydropyrido[1,2-*d*]tetrazole* (**22**) *and 2,5-Anhydro-3,4,6-tri-*O*-benzyl-*D*-glucononitrile* (**21**). *a*) A soln. of **14** (45.28 g, 7.13 mmol) and NaN_3 (4.63 g, 71.2 mmol) in dry DMSO (60 ml) was stirred for 4 h at 110–125°, diluted with H_2O, and worked up as usual (AcOEt, H_2O). FC (hexane/AcOEt 85:15) afforded **22** (1.74 g, 43%). Yellowish, clear oil. R_f (hexane/AcOEt 8:2) 0.18. $[\alpha]_D^{25} = +76.9$ ($c = 0.93$, $CHCl_3$). IR ($CHCl_3$): 3090*w*, 3070*w*, 3000*w*, 2920*w*, 2870*m*, 1955*w*, 1875*w*, 1810*w*, 1600*w*, 1495*w*, 1450*m*, 1355*m*, 1325*m*, 1095*s* (br.), 1025*s*, 905*m*. ^{1}H-NMR ($CDCl_3$): 3.94 (*dd*, $J = 2.6$, 10.3, 1 H, CH_2–C(5)); 4.08 (*dd*, $J = 6.9$, 8.8, H–C(7)); 4.25 (*dd*, $J = 7.5$, 8.9, H–C(6)); 4.28 (*dd*, $J = 3.9$, 10.3, 1 H, CH_2–C(5)); 4.36 (*d*, $J = 11.9$, PhCH_2); 4.43 (*d*, $J = 11.8$, PhCH_2); 4.45 (*m*, H–C(5)); 4.53 (*d*, $J = 11.0$, PhCH_2); 4.77 (*d*, $J = 11.2$, PhCH_2); 4.85–4.89 (*m*, 3 H, H–C(8), PhCH_2); 4.99 (*d*, $J = 11.4$, PhCH_2); 5.30 (*d*, $J = 11.4$, PhCH_2); 7.14–7.47 (*m*, 20 arom. H); irrad. at 4.08 → change at 4.22–4.30 and 4.85–4.89; irrad. at 4.45 → change at 4.22–4.30 and 3.94. ^{13}C-NMR ($CDCl_3$): 60.18 (*d*); 65.74 (*t*); 71.60 (*d*); 73.34 (*t*); 73.49 (*t*); 74.11 (*d*); 74.89 (*t*); 74.99 (*t*); 81.16 (*d*); 127.79–128.42 (several *d*); 136.88 (*s*); 137.04 (*s*); 137.17 (*s*); 137.40 (*s*); 152.46 (*s*). CI-MS (C_4H_{10}): 564 (38), 563 (100, $[M + H]^+$), 473 (14), 359 (13), 279 (13), 107 (40), 91 (31). Anal. calc. for $C_{34}H_{34}N_4O_4$ (562.68): C 72.58, H 6.09, N 9.96; found: C 72.45, H 6.16, N 9.85.

b) A soln. of **19** (49 mg, 0.07 mmol) and NaN_3 (49 mg, 0.75 mmol) in dry DMSO (0.7 ml) was stirred for 195 min at 110–120° and worked up as above. FC (hexane/AcOEt 85:15) afforded **21** (3 mg, 10%) and **22** (28 mg, 70%), both as colorless oils. **21**: R_f (hexane/AcOEt 8:2) 0.27. IR ($CHCl_3$): 3090*w*, 3070*w*, 3040*w*, 3010*w*, 2920*m*, 2870*m*, 1955*w*, 1875*w*, 1810*w*, 1490*w*, 1450*w*, 1360*m*, 1080*s* (br.), 1025*s*, 1000*m*, 910*w*. ^{1}H-NMR ($CDCl_3$): 3.57 (*dd*, $J = 6.5$, 10.1, H–C(6)); 3.65 (*dd*, $J = 5.9$, 10.1, H′–C(6)); 4.06 (*t*, $J = 3.1$, H–C(4)); 4.13–4.18 (*m*, H–C(3), H–C(5)); 4.44–4.63 (*m*, 6 H, PhCH_2); 4.72 (*d*, $J = 4.9$, H–C(2)); 7.21–7.39 (*m*, 15 arom. H). ^{1}H-NMR (C_6D_6): 3.51 (*d*, $J = 6.29$, H–C(6), H′–C(6)); 3.67 (*dd*, $J = 2.7$, 4.9, H–C(3)); 4.04 (*t*, $J \approx 3$, H–C(4)); 4.12 (*dt*, $J = 3.3$, 6.3, H–C(5)); 4.16–4.30 (*m*, 7 H, H–C(2), PhCH_2); 7.04–7.24 (*m*, 15 arom. H). CI-MS (C_4H_{10}): 431 (28), 430 (100, $[M + H]^+$), 338 (34), 181 (43), 91 (39).

*5-Azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-*D*-glucononitrile* (**20**). A soln. of **19** (67 mg, 0.1 mmol) and NaN_3 (67 mg, 1.03 mmol) in dry DMSO (1 ml) was stirred for 5 min at 110–120°. Normal workup (AcOEt, H_2O) and FC (hexane/AcOEt 85:15) afforded **20** (20 mg, 37%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.34. $[\alpha]_D^{25} = +34.8$ ($c = 0.25$, $CHCl_3$; [28]: +37.0 ($c = 0.004$, $CHCl_3$)). IR ($CHCl_3$): 3090*w*, 3060*w*, 3030*w*, 3005*w*, 2920*w*, 2870*m*, 2100*s*, 1950*w*, 1875w, 1810*w*, 1495*w*, 1455*m*, 1395*w*, 1365*w*, 1350*w*, 1265*m*, 1090*s* (br.), 1030*m*, 1000*m*, 910*w*. ^{1}H-NMR ($CDCl_3$): 3.64–3.72 (*m*, CH_2(6)); 3.80 (*dd*, $J \approx 2.4$, 9.2, H–C(4)); 3.90–3.96 (*m*, H–C(3), H–C(5)); 4.34 (*d*, $J = 6.6$, H–C(2)); 4.50 (*s*, 3 H, PhCH_2); 4.55 (*d*, $J = 11.5$, PhCH_2); 4.66 (*d*, $J = 11.3$, PhCH_2); 4.70 (*d*, $J = 11.2$,

PhCH_2); 4.75 (*d*, *J* = 11.3, PhCH_2); 4.85 (*d*, *J* = 11.5, PhCH_2); 7.20–7.40 (*m*, 20 arom. H). CI-MS (NH_3): 581 (29), 580 (78, $[M + NH_4]^+$), 564 (39), 563 (100, $[M + H]^+$), 535 (23), 108 (13).

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)pyrido[1,2-*d*]tetrazole-6,7,8-triol* (**1**). A soln. of **22** (200 mg, 0.36 mmol) in MeOH (7 ml) containing AcOH (*ca.* 0.05 ml) was hydrogenated for 30 h at 1 atm and at r.t. in the presence of 10% Pd/C (275 mg). The suspension was diluted with MeOH and centrifuged. The supernatant was filtered, the pellet was washed with MeOH (twice) and resubjected to centrifugation. The combined filtrates were evaporated. FC (AcOEt/MeOH 17:3) yielded **1** as a colorless oil (66 mg, 92%), which was crystallized from EtOH/AcOEt. R_f (AcOEt/MeOH 3:1) 0.39. M.p. 141–142°. $[\alpha]_D^{25} = -33.9$ (*c* = 0.649, H_2O). IR (KBr): 3060*s* (br.), 2965*w*, 2930*w*, 1635*w*, 1560*w*, 1525*w*, 1505*w*, 1445*m*, 1400*m*, 1360*m*, 1320*m*, 1270*m*, 1260*m*, 1240*w*, 1220*w*, 1195*w*, 1175*m*, 1155*w*, 1125*s*, 1115*s*, 1100*s*, 1065*m*, 1025*m*, 995*m*, 915*m*, 855*m*, 775*w*, 755*m*. ^{1}H-NMR (CD_3OD): 3.69 (*dd*, *J* = 8.4, 9.5, H–C(7)); 3.99 (*t*, *J* = 9.1, H–C(6)); 4.05 (*dd*, *J* = 2.2, 12.1, 1 H, CH_2–C(5)); 4.19 (*dtd*, *J* ≤ 1, 2.1, 8.5, H–C(5)); 4.39 (*dd*, *J* = 2.7, 12.0, 1 H, CH_2–C(5)); 4.63 (*dd*, *J* = 0.7, 8.4, H–C(8)); irrad. at 4.63 → 3.69 (*d*, *J* = 9.5), 4.19 (*dt*, *J* ≈ 2.4, 8.6); irrad. at 4.19 → 3.99 (*d*, *J* = 9.4); 4.05 (*dd*, *J* = 1.1, 11.4), 4.39 (*dd*, *J* = 1.1, 11.0), 4.63 (*d*, *J* = 8.3). ^{13}C-NMR (D_2O): 57.95 (*t*); 62.81 (*d*), 65.68 (*d*); 67.06 (*d*); 74.37 (*d*); 155.52 (*s*). CI-MS (C_4H_{10}): 204 (14), 203 (100, $[M + H]^+$). Anal. calc. for $C_6H_{10}N_4O_4$ (202.17): C 35.65, H 4.99, N 27.71; found: C 35.87, H 5.19, N 27.42.

*2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-*D*-glucitol* (**23**). A soln. of **22** (198 mg, 0.35 mmol) in dry Et_2O (8 ml) was added dropwise to $LiAlH_4$ (162 mg, 4.27 mmol) in Et_2O (5 ml). The mixture was heated under reflux for 5 h and poured onto ice-water (100 ml). Et_2O and dil. NaOH soln. (120 ml; 3.0 g of NaOH in 150 ml of H_2O) were added. Normal workup (Et_2O, H_2O) and FC (hexane/AcOEt 3:7) yielded **23** (153 mg, 83%). Colorless crystals. An anal. sample was recrystallized in dry Et_2O/dry hexane. R_f (hexane/AcOEt 2:8) 0.25. M.p. 46.5–47.5° ([30]: 44–47°). $[\alpha]_D^{25} = +33.1$ (*c* = 0.66, $CHCl_3$). IR ($CHCl_3$): 3340*w*, 3095*w*, 3070*w*, 3005*m*, 2960*m*, 2920*m*, 2870*m*, 1955*w*, 1875*w*, 1815*w*, 1750*w*, 1600*w*, 1495*w*, 1455*m*, 1360*m*, 1095*s* (br.), 1065*s* (br.), 1030*m*, 910*w*. ^{1}H-NMR ($CDCl_3$): 1.66 (*s*, > 1 H, NH); 2.50 (*dd*, *J* = 10.1, 12.2, H_a–C(1)); 2.72 (*ddd*, *J* = 2.6, 5.9, 9.1, H–C(5)); 3.24 (*dd*, *J* = 4.7, 12.2, H_e–C(1)); 3.34 (*t*, *J* = 9.2, H–C(4)); 3.45–3.58 (*m*, H–C(2), H–C(3), H–C(6)); 3.67 (*dd*, *J* = 2.6, 9.0, H′–C(6)); 4.42 (*d*, *J* = 11.8, PhCH_2); 4.47 (*d*, *J* = 11.8, PhCH_2); 4.49 (*d*, *J* = 10.9, PhCH_2); 4.66 (*d*, *J* = 11.7, PhCH_2); 4.70 (*d*, *J* = 11.7, PhCH_2); 4.83 (*d*, *J* = 10.9, PhCH_2); 4.86 (*d*, *J* = 10.9, PhCH_2); 4.98 (*d*, *J* = 10.9, PhCH_2); 7.18–7.36 (*m*, 20 arom. H); irrad. at 3.34 → change at 2.72, 3.45–3.58. ^{13}C-NMR ($CDCl_3$): 48.08 (*t*); 59.69 (*d*); 70.23 (*t*); 72.71 (*t*); 73.32 (*t*); 75.12 (*t*); 75.61 (*t*); 80.05 (*d*); 80.60 (*d*); 87.28 (*d*); 127.46–128.59 (several *d*); 137.91 (*s*); 138.34 (*s*); 138.44 (*s*); 138.84 (*s*). CI-MS (C_4H_{10}): 525 (38), 524 (100, $[M + H]^+$), 416 (15). Anal. calc. for $C_{34}H_{37}NO_4$ (523.68): C 77.98, H 7.12, N 2.67; found: C 77.95, H 7.23, N 2.55.

*(+)-1-Deoxynojirimycin (= 1,5-Dideoxy-1,5-imino-*D*-glucitol;* **2**). A soln. of **23** (42 mg, 0.08 mmol) in AcOH (2 ml) was hydrogenated for 15 h at 8 bar and at r.t. in the presence of 10% Pd/C (53 mg). The suspension was diluted with MeOH and centrifuged, the supernatant filtered and the pellet washed with MeOH (twice) and resubjected to centrifugation. The combined filtrates were evaporated, the residue was co-evaporated with MeOH and dried *i.v.* FC (silica gel, NH_3 in MeOH/$CHCl_3$ 1:1) of the residue afforded **2**·AcOH (15.5 mg, 86%). Colorless oil. R_f (NH_3 in MeOH/$CHCl_3$ 1:1) 0.12. ^{1}H-NMR (D_2O): 1.89 (*s*, AcO); 2.83 (*t*, *J* ≈ 11.9, H_a–C(1)); 3.03 (*ddd*, *J* = 3.2, 5.3, 9.3, H–C(5)), 3.37–3.53 (*m*, 3 H, H_e–C(1), H–C(3), H–C(4)); 3.70 (*ddd*, *J* = 5.2, 9.0, 11.4, H–C(2)); 3.80 (*dd*, *J* = 5.4, 12.5, H–C(6)); 3.90 (*dd*, *J* = 3.2, 12.5, H′–C(6)). CI-MS (C_4H_{10}): 165 (6), 164 (82, $[M + H]^+$), 146 (100).

The hydrochloride of **2** was prepared by repeated (6×) evaporation of a soln. of **2**·AcOH (14.5 mg, 0.07 mmol) in MeOH containing conc. aq. HCl soln. The residue was dissolved in H_2O and lyophilized to give **2**·HCl (13 mg, 100%). ^{1}H-NMR (D_2O): 2.97 (*t*, *J* = 12.0, H_a–C(1)); 3.21 (*ddd*, *J* = 3.3, 5.1, 10.3, H–C(5)); 3.48–3.63 (*m*, H_e–C(1), H–C(3), H–C(4)); 3.78 (*ddd*, *J* = 5.1, 9.1, 11.6, H–C(2)); 3.87 (*dd*, *J* = 5.1, 12.8, H–C(6)); 3.95 (*dd*, *J* = 3.3, 12.8, H′–C(6)). ^{13}C-NMR (D_2O): 46.03 (*t*); 57.86 (*t*); 60.14 (*d*); 67.10 (*d*); 67.94 (*d*); 76.37 (*d*). CI-MS (C_4H_{10}): 164 (65, $[M + H]^+$), 146 (100).

The free base **2** was obtained by treating a soln. of an anal. sample of **2**·HCl in H_2O with ion exchanger (*Dowex 1 × 8*, OH^-; prepared from *Dowex 1 × 8*, Cl^- by treating with 1N NaOH). The ion exchanger was removed and the filtrate lyophilized. $[\alpha]_D^{25} = +35.8$ (*c* = 0.165, H_2O; [2]: +47 (H_2O)). ^{1}H-NMR (D_2O): 2.43 (*dd*, *J* = 10.8, 12.3, H_a–C(1)); 2.52 (*ddd*, *J* = 3.1, 6.3, 9.4, H–C(5)); 3.09 (*dd*, *J* = 5.1, 12.3, H_e–C(1)); 3.21 (*t*, *J* = 9.3, H–C(4)); 3.29 (*t*, *J* = 9.0, H–C(3)); 3.47 (*ddd*, *J* = 5.1, 9.0, 10.7, H–C(2)); 3.60 (*dd*, *J* = 6.3, 11.7, H–C(6)); 3.81 (*dd*, *J* = 3.0, 11.6, H′–C(6)); irrad. at 3.47 → change 2.43, 3.09, and 3.29.

Determination of the Molar Concentration of **1**, *Effecting 50% Inhibition* (IC_{50}) *of* Emulsin. *Emulsin* (from almonds, E.C. 3.2.1.21; *Fluka Biochemica*) and 4-nitrophenyl β-D-glucopyranoside (*Fluka Biochemica*) were used without any further purification. IC_{50} was determined by incubating *Emulsin* (150.7 mU/ml in H_2O; 0.25 ml) with

or without the inhibitor (initial concentrations were $3.02 \cdot 10^{-3}$, $3.02 \cdot 10^{-4}$, $1.81 \cdot 10^{-4}$, or 0; 0.25 ml) and citrate buffer (initial concentration 0.0947M, pH 4.5; 0.25 ml) for 10 min at 37°. Substrate (initial concentrations were $1.98 \cdot 10^{-3}$, $7.95 \cdot 10^{-4}$, $5.96 \cdot 10^{-4}$, and $3.98 \cdot 10^{-4}$ M; 0.25 ml) was added, and the incubation was continued for 2, 4, 6, and 8 min before the reaction was stopped by addition of borate buffer (initial concentration 0.2M, pH 9.2; 0.9 ml). The amount of 4-nitrophenolate liberated was determined from the absorption at 400 nm ($\varepsilon = 15500$).

REFERENCES

[1] K. Daigo, Y. Inamori, T. Takemoto, *Chem. Pharm. Bull.* **1986,** *34,* 2243.

[2] S. Inouye, T. Tsuruoka, T. Ito, T. Niida, *Tetrahedron* **1968,** *24,* 2125.

[3] G. W. J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellows, R. J. Nash, *Tetrahedron Lett.* **1985,** *26,* 3127; R. J. Nash, E. A. Bell, J. M. Williams, *Phytochemistry* **1985,** *24,* 1620.

[4] L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, P. J. Pryce, E. A. Arnold, J. Clardy, *Phytochemistry* **1981,** *20,* 811; R. Saul, J. P. Chambers, R. J. Molyneux, A. D. Elbein, *Arch. Biochem. Biophys.* **1983,** *221,* 593.

[5] S. M. Colgate, P. R. Dorling, C. R. Huxtable, *Aust. J. Chem.* **1979,** *32,* 2257.

[6] E. T. Reese, F. W. Parrish, M. Ettlinger, *Carbohydr. Res.* **1971,** *18,* 381.

[7] M. P. Dale, H. E. Ensley, K. Kern, K. A. R. Sastry, L. D. Byers, *Biochemistry* **1985,** *24,* 3530.

[8] M. K. Tong, G. Papandreou, B. Ganem, *J. Am. Chem. Soc.* **1990,** *112,* 6137.

[9] D. Beer, A. Vasella, *Helv. Chim. Acta* **1986,** *69,* 267.

[10] D. R. Wolk, A. Vasella, F. Schweikart, M. G. Peter, *Helv. Chim. Acta,* accepted.

[11] H. Kayakiri, S. Takase, T. Shibata, M. Okamoto, H. Terano, M. Hashimoto, *J. Org. Chem.* **1989,** *54,* 4015; A. D. Elbein, J. E. Tropea, M. Mitchell, G. P. Kaushal, *J. Biol. Chem.* **1990,** *265,* 15599.

[12] H. Kayakiri, T. Oku, M. Hashimoto, *Chem. Pharm. Bull.* **1990,** *38,* 293.

[13] S. Sakuda, A. Isogai, S. Matsumoto, A. Suzuki, K. Koseki, H. Kodama, Y. Yamada, *Agric. Biol. Chem.* **1988,** *52,* 1615; J. L. Maloisel, A. Vasella, B. M. Trost, D. L. van Vranken, *J. Chem. Soc., Chem. Commun.* **1991,** 1099; D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1991,** *113,* 5863.

[14] A. Frankowski, C. Seliga, D. Bur, J. Streith, *Helv. Chim. Acta* **1991,** *74,* 934.

[15] A. Chaperon, Diplomarbeit, Universität Zürich, 1991.

[16] G. Llewellyn, D. Pickles, J. M. Williams, M. B. Gravestock, 'Eurocarb VI, 6th European Symposium on Carbohydrate Chemistry', Heriot-Watt University, Edinburgh, Scottland, 8–13 Sept., 1991, B.15; N. Chida, Y. Furuno, S. Ogawa, *J. Chem. Soc., Chem. Commun.* **1989,** 1230; B. P. Vaterlaus, J. Kiss, H. Spiegelberg, *Helv. Chim. Acta* **1964,** *47,* 381.

[17] G. Buchanan, A. R. Edgar, B. D. Hewitt, *J. Chem. Soc., Perkin Trans. 1* **1987,** 2371; B. Bernet, A. R. C. Bulusu Murty, A. Vasella, *Helv. Chim. Acta* **1990,** *73,* 940.

[18] B. M. Aebischer, H. W. Hanssen, A. T. Vasella, W. B. Schweizer, *J. Chem. Soc., Perkin Trans. 1* **1982,** 2139.

[19] C. P. J. Glaudemans, H. G. Fletcher, Jr., *Methods Carbohydr. Chem.* **1972,** *6,* 373.

[20] J. N. Kim, K. H. Chung, E. K. Ryu, *Synth. Commun.* **1990,** *20,* 2785.

[21] B. Coxon and H. G. Fletcher, Jr., *J. Am. Chem. Soc.* **1963,** *85,* 2637; *ibid.* **1964,** *86,* 922; R. Meuwly, A. Vasella, *Helv. Chim. Acta* **1985,** *68,* 997.

[22] E. M. Acton, A. N. Fujiwara, L. Goodman, D. W. Henry, *Carbohydr. Res.* **1974,** *33,* 135.

[23] P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980,** 2866.

[24] K. Omura, D. Swern, *Tetrahedron* **1978,** *34,* 1651; A. J. Mancuso, S. L. Huang, D. Swern, *J. Org. Chem.* **1978,** *43,* 2480.

[25] J. L. Luche, *J. Am. Chem. Soc.* **1978,** *100,* 2226; G. Rücker, H. Hörster, W. Gajewski, *Synth. Commun.* **1980,** *10,* 623; A. Krief, D. Surleraux, *Synlett.* **1991,** 273.

[26] J. P. Dulcere, M. Tawil, M. Santelli, *J. Org. Chem.* **1990,** *55,* 571; E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988,** *88,* 297.

[27] S. D. Rychnowsky, D. A. Bartlett, *J. Am. Chem. Soc.* **1981,** *103,* 3963.

[28] P. Bird, D. H. Dolphin, S. G. Withers, *Can. J. Chem.* **1990,** *68,* 317.

[29] R. A. LaForge, C. E. Cosgrove, A. D'Adamo, *J. Org. Chem.* **1956,** *21,* 988.

[30] H. Murai, H. Enomoto, Y. Aoyagi, Y. Yoshikumi, M. Yagi, I. Shirakase, to *Nippon Shinyaku Co. Ltd.*, Belg. 868.329 (CI. C07D), 16. Okt. 1978.

[31] G. W. J. Fleet, N. M. Carpenter, S. Petursson, N. G. Ramsden, *Tetrahedron Lett.* **1990,** *31,* 409; G. W. J. Fleet, L. E. Fellows, P. W. Smith, *Tetrahedron* **1987,** *43,* 979; H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1987,** *52,* 3337.

[32] T. Storz, Diplomarbeit, Universität Konstanz, 1989.