

75. Structure-Activity Relations for Imidazo-pyridine-Type Inhibitors of β -D-Glucosidases

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Dedicated to Prof. Dr. *Hans Paulsen* on the occasion of his 75th birthday

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The triazole **7** and the known *gluco*- and *manno*-configured imidazoles **10** and **11** have been prepared by annulation of theazole ring to the aldonothiolactam **14** in a $\text{Hg}(\text{OAc})_2$ -promoted reaction with either hydrazine-carbaldehyde or aminoacetaldehyde dimethyl acetal. Depending upon the reaction conditions, the synthesis of the imidazoles yielded mostly the *gluco*-imidazole **19** or a mixture of the *gluco*/*manno* epimers **19/20**. In contrast to the triazole **4**, the isomeric triazole **7** proved a good inhibitor of retaining β -glucosidases from sweet almonds and from *Caldocellum saccharolyticum*. This observation and the qualitative correlation between basicity and inhibitory power of the tetrahydropyridozoles provide further evidence for the hypothesis of the 'lateral protonation' of glycosides by (some) retaining β -glucosidases.

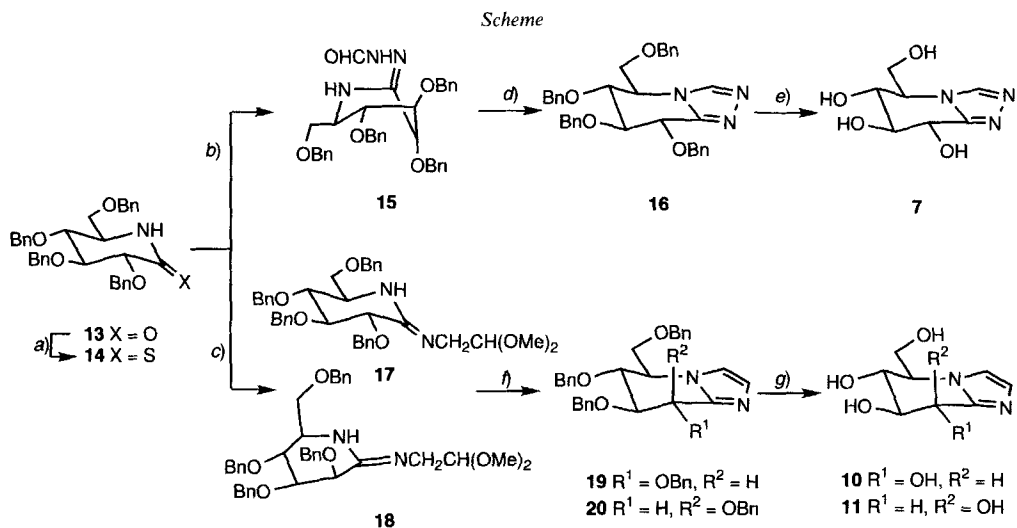
Introduction. – We have compared the inhibition of some retaining β -D-glycosidases by the tetrazoles **1** [1] and **2** [2], on the one hand, and the triazoles **4** and **5** [3], on the other hand. The tetrazoles, but not the triazoles, proved good inhibitors of at the least some retaining β -glucosidases [3]. We have suggested that the cleavage of β -glycosides by these enzymes involves protonation at O–C(1) of the substrate in the plane of the pyranose ring [3] rather than perpendicular to it as suggested by the lysozyme paradigm [4]. This interpretation is based on the presence of a N-atom in the tetrazole, but not in the triazole, corresponding to O–C(1) of a glycoside, and thus on the availability for partial protonation, by the catalytic carboxy group of these enzymes, of a doubly occupied nonbonding orbital in the sigma plane of the tetrazole ring.

The difference of the inhibitory power of the triazoles and the tetrazoles might also (partially) reflect the more favorable interaction of the carboxylate group of the catalytic machinery, situated below the plane of the ring, with the more highly electronegative tetrazoles. This rationalization, however, is at variance with the report that the imidazole **10** [5] is a much stronger inhibitor than the tetrazole **1** [6]. Nonetheless, a comparison of the inhibition by the isomeric triazoles **4** and **7** of very similar electronegativity would allow an easier evaluation of the importance of the 'lateral protonation'; this should be corroborated by a correlation of the relative basicity and inhibitory activity of pyrido-imidazoles, -triazoles, and -tetrazoles.

The *manno*- and *galacto*-configured triazoles **8** and **9** have been prepared by *Tatsuta* and coworkers [7]. They followed a strategy similar to the one used by *Streith* and coworkers [8], *Grierson* and coworkers [9], and *Burgess* and *Chaplin* [10], involving the addition of a *N*-protected triazole derivative to pentofuranoses followed by intramolec-

ular *N*-alkylation as the key steps. We considered that annulation of an azole ring [11] to the easily accessible lactam **13** [12] might be advantageous and provide a general access to carbohydrate-derived pyridozoles. We have examined this approach by synthesizing the triazole **7** and the known *gluco*- and *manno*-configured imidazoles **10** and **11**.

Synthesis. – For the synthesis of the triazole **7**, we used a variant of the method of Pellizzari [13] (Scheme). The required aldonothiolactam **14** [14] was obtained in an improved yield of 99 % from the readily prepared 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-gluconolactam (**13**)¹ [12] [15] by using Lawesson's reagent at 25° rather than at higher temperature. While hydrazinecarbaldehyde did not react with **14** in THF at reflux, *in situ* activation of the thiolactam with Hg(OAc)₂² at 5° gave the amidrazone **15** which cyclized smoothly under acidic or basic conditions to the 1,2,4-triazole **16** in 85 (from **14**) and 91 % (from **15**) yields, respectively.



a) Lawesson's reagent, toluene; 99 %. b) H₂NNHCHO, Hg(OAc)₂, THF; > 99 %. c) H₂NCH₂CH(OMe)₂; 82 % of **17/18** 2:1; or H₂NCH₂CH(OMe)₂, Hg(OAc)₂, THF; ca. 90 % of **17**. d) Crude **15**, toluene, TsOH · H₂O; 85 % from **14**; or piperidine, CDCl₃; 91 % from **15**. e) Pd(OH)₂, H₂, AcOH/MeOH; 58 %. f) Crude **17/18** 2:1, toluene, TsOH · H₂O; ca. 75 % (**19/20** 70:30 to 25:75); or crude **17**, toluene, H₂O, TsOH · H₂O; 76 % of **19**. g) Pd(OH)₂, H₂, AcOH/MeOH; 64 %.

For the synthesis of the corresponding imidazole **19**, we treated **14** with the more highly nucleophilic aminoacetaldehyde dimethyl acetal. This led in 82 % yield to a 2:1 mixture of the *gluco*/*manno*-configured amidines **17/18**. The amidines were separated by chromatography. They were epimerized individually by treatment with TsOH · H₂O in CDCl₃. This led, after one week, to a 60:40 *gluco*/*manno* mixture and to traces of the corresponding lactams [12] [15] and further by-products.

¹) The yield of **13** from 2,3,4,6-tetra-*O*-benzyl-D-glucose has been increased to ca. 75 % (see *Exper. Part*).

²) Mercury salts have been used in the synthesis of amidines from thiolactams [16] and from thioamides [17] [18], and of guanidines from thioureas [19–24]. Of several salts tested, Hg(OAc)₂ proved most advantageous.

Epimerization during the synthesis of the amidine was circumvented by again activating **14** with $\text{Hg}(\text{OAc})_2$ in THF at 5°. However, cyclization of the crude amidine under acidic conditions ($\text{TsOH} \cdot \text{H}_2\text{O}$, toluene, 60°) yielded 78% of a 82:18 mixture of the *gluco/manno*-configured imidazoles **19/20**. Cyclization of the amidine in the presence of additional H_2O reduced the amount of the *manno*-imidazole to less than 10%. Under these conditions, **19** was obtained in 76% overall yield from the thiolactam **14**. Cyclization of **17/18** in more highly concentrated solutions and in the absence of additional H_2O proceeded more slowly and led to mixtures enriched in the *manno*-configured imidazole **20**. The **19/20** ratio depended critically upon the exact conditions of the reaction and varied between 60:40 and 25:75.

Hydrogenolytic debenzoylation of **16**, **19**, and **20** gave the deprotected **7**, **10**, and **11** respectively. This strategy provided **7** and **10** in 11 steps from methyl α -D-glucopyranoside, each in an overall yield of 22%, and similarly the *manno*-configured imidazole **11** in 11%. The availability of the starting material, the relatively short synthesis, and the satisfactory overall yields speak in favor of this strategy for the preparation of tetrahydropyridoimidazoles and -triazoles³⁾.

The amidrazone **15** is characterized by a *s* ($\text{C}=\text{N}$) at 147.17 and a *d* at 165.96 ($\text{C}=\text{O}$) ppm in its ^{13}C -NMR spectrum. The $J(\text{H},\text{H})$ values ($J(2,3) = 2.2$, $J(3,4) = 3.7$, $J(4,5) = 9.7$ Hz) indicate a $B_{2,5}$ conformation. The amidino group of **17** and **18** gives rise to a *s* at 157.14 and 156.95 ppm, respectively, and to a strong IR band at 1650 cm^{-1} . The $J(\text{H},\text{H})$ values for **17** ($J(2,3) = 9.0$, $J(3,4) = 7.9$, $J(4,5) = 8.7$ Hz) evidence the *gluco*-configuration and the 4C_1 conformation, while the $J(\text{H},\text{H})$ values of **18** ($J(2,3) = 3.1$, $J(3,4) = 3.1$, $J(4,5) = 3.6$ Hz) are in keeping with a *manno*-configuration and a flattened 5S_3 conformation. An exocyclic $\text{C}=\text{N}$ bond in **15**, **17**, and **18** is indicated by the absence of an observable coupling between the two NH in **15** and between the NH and the CH_2N group in **17** and **18**; this is in agreement with the NH IR bands of **17** and **18** [26]. The configuration of the newly formed $\text{C}=\text{N}$ bond was tentatively assigned as (*Z*) based on the analogy with the gluconhydroximolactams [14].

The *gluco*-configuration of the benzyl-protected **16** and **19** and the corresponding deprotected **7** and **10** and the *manno*-configuration of **20** and **11** were assigned on the basis of the $J(\text{H},\text{H})$ values of the corresponding tetrazoles [1] [2] (*cf. Table*) and confirmed by an X-ray analysis of $\mathbf{10} \cdot \text{HCl}^4)$ (*Fig. 1*) that also shows the 5H_6 conformation of $\mathbf{10} \cdot \text{HCl}$ in the solid state. The torsion angle $\text{C}(5)-\text{N}(4)-\text{C}(8a)-\text{C}(8)$ (systematic numbering) is -9.9° , somewhat larger than in the corresponding tetrazole (-4.5°). As shown by the $J(\text{H},\text{H})$ values collected in the *Table*, the imidazoles, triazoles, and tetrazoles adopt a similar conformation in D_2O (6H_7 , except for the *manno*-configured imidazole **11** which adopts a flattened E_7 conformation). Protonation of the *gluco*-configured imidazole **10** shifts the signals of $\text{H}-\text{C}(8)$, $\text{H}-\text{C}(5)$, $\text{H}-\text{C}(2)$, and $\text{H}-\text{C}(3)$ (systematic numbering) to lower field⁵⁾, but does not affect the conformation of the piperidine ring.

The triazole **7** inhibits competitively the β -glucosidases from sweet almonds and from *Caldocellum saccharolyticum* ($K_i = 19$ and $0.17\text{ }\mu\text{M}$, resp., pH 6.8, 37°). As reported by Tatsuta and coworkers [6], the imidazole **10** is a strong inhibitor of the sweet-almond

³⁾ A similar strategy has been used for an advantageous preparation of the tetrazole **1** from the benzylated gluconolactam **13** [25].

⁴⁾ Crystallographic data have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EW, England.

⁵⁾ Comparison of the chemical shifts values in the ^1H -NMR spectra of **10** and $\mathbf{10} \cdot \text{HCl}$ with those reported by Tatsuta and coworkers [6] indicates that the data in [6] are of a partially protonated **10**.

Table. Coupling Constants J [Hz] of the Tetrazoles **1** [1] [3], **2** [2], and **3** [27], Triazoles **4** [3], **5** [3], **7**, **8** [7], and **9** [7], and Imidazoles **10**, **10** · HCl, and **11** in D_2O . The conventional carbohydrate numbering is used for convenience.

	1	4	7	10	10 · HCl	2	5	8	11	3	9
$J(2,3)$	8.4	8.9	8.7	8.7	9.0	4.1	4.2	4.0	3.7	9.0	9.0
$J(3,4)$	9.5	10.1	9.5	9.7	10.0	9.0	10.4	9.0	8.1	2.1	2.0
$J(4,5)$	8.5	9.3	9.2	9.0	8.7	7.5	9.0	8.0	6.1	2.4	3.0
$J(5,6)$	2.3	2.3	4.1	2.5	3.0	2.8	2.8	5.0	4.2	6.3	
$J(5,6')$	2.5	2.6	1.9	2.2	1.5	2.5	3.1	3.0	3.1	5.5	
$J(6,6')$	12.1	12.6	12.8	12.8	13.0	12.5	14.0	13.0	12.5	11.9	

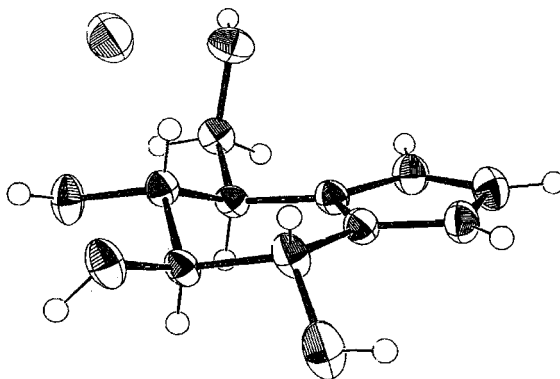
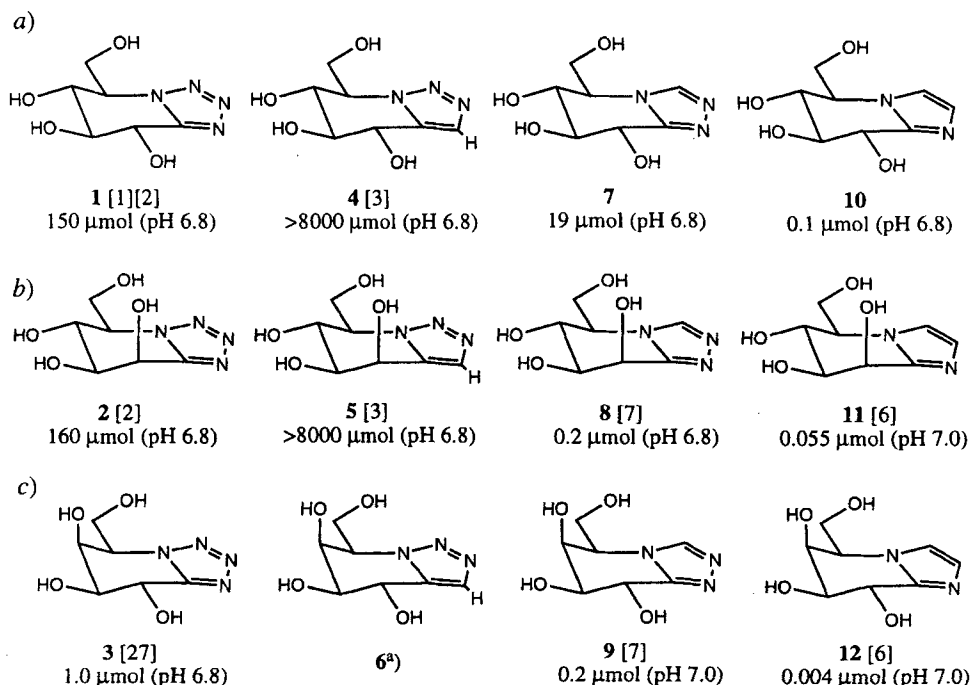


Fig. 1. X-Ray analysis of **10** · HCl

β -glucosidases ($K_i = 0.1 \mu\text{M}$, pH 6.8, 37°); while this enzyme was inhibited competitively, the β -glucosidase from *Caldocellum saccharolyticum* was inhibited in a mixed fashion ($K_i = 0.02 \mu\text{M}$, $\alpha = 3.2$, pH 6.8, 55°). These results are in keeping with the contention that the 'lateral protonation', and not the interaction of the azole ring with the cation-stabilizing carboxylate group is the dominating factor for the inhibition. As shown in Fig. 2, there is a convincing correlation between basicity and inhibitory activity not only for the *gluco*- and *manno*-configured tetrahydropyridoozoles, but also for the *galacto*-configured tetrahydropyridoozoles **3** [27], **9** [7], and **12** [6]; as it is evidenced from the Table, there are only minor conformational differences between the azoles possessing the same configuration.

We also tested the inhibition by **7** and **10** of brewer's yeast α -glucosidase. In keeping with recently reported observations [28], the more strongly basic imidazole **10** inhibited this enzyme 15 times more effectively than the triazole **7** (**7**: $K_i = 870 \mu\text{M}$, **10**: $K_i = 59 \mu\text{M}$, pH 6.8, 37° , competitive inhibition for both compounds).

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^a) This compound has not yet been described.

Fig. 2. K_i Values of gluco-, manno-, and galacto-configured tetrahydropyridoazoles against a) sweet-almonds β -glucosidases, b) snail- β -mannosidase, and c) *E. coli* β -galactosidase

Experimental Part

General. See [29]. β -Glucosidase from *Caldocellum saccharolyticum* and α -glucosidase from brewer's yeast were purchased from Sigma Chemical Co. and used without further purification.

Improved Procedure for the Preparation of 5-Amino-2,3,4,6-tetra-O-benzyl-5-deoxy-D-glucono-1,5-lactam (13). At 25°, a mixture of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (60.1 g, 111 mmol), Ac_2O (113 ml), and DMSO (170 ml) was stirred for 19 h, evaporated (35°, 0.05 Torr), and dried *i. v.* for 24 h. A soln. of the crude was dissolved in Et_2O (1 l), treated within 1.5 h with condensed ammonia (200 ml) at -60° , and kept at reflux for 2 h. After removal of the cooling trap, NH_3 and Et_2O were evaporated. The residue was dried *i. v.* for 12 h, dissolved in DMSO (450 ml) and treated with Et_3N (120 ml, 861 mmol) and then, dropwise, at $T < 25^\circ$, within 1.5 h with a soln. of pyridine $\cdot \text{SO}_3$ (102 g, 641 mmol) in DMSO (450 ml, addition starting 15 min after mixing pyridine $\cdot \text{SO}_3$ and DMSO at r.t.). The soln. was stirred for further 5 h at $T < 25^\circ$ and poured into toluene/ H_2O 20:3 (3 l). The layers were separated, and the aq. phase was extracted with toluene. Drying (MgSO_4) of the combined org. layers, filtration, and evaporation gave a thick oil which was dried *i. v.* for 3 h. A soln. of the residue in CHCl_3 (500 ml) was treated with AcOH (25 ml, 437 mmol), stirred for 4 d at 25°, and treated with sat. aq. NaHCO_3 soln. (300 ml). The aq. phase was extracted with CH_2Cl_2 (2×150 ml), and the combined org. phases were dried (MgSO_4), filtered, and evaporated. The residue was dried *i. v.*, dissolved in CH_2Cl_2 (1.2 l), and added at 0° within 1.5 h to a soln. of Et_3SiH (86 ml, 541 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (68 ml, 541 mmol) in MeCN (1.2 l). The mixture was stirred for further 15 min, treated with sat. aq. NaHCO_3 soln. (400 ml), and diluted with CH_2Cl_2 (500 ml). The layers were separated, and the aq. phase was extracted with CH_2Cl_2 (2×300 ml). The combined org. phases were dried (MgSO_4), filtered, and evaporated. Recrystallization of the residue in boiling MeOH gave **13** (45 g, 75%). Colorless needles. M.p. $102\text{--}103^\circ$.

5-Amino-2,3,4,6-tetra-O-benzyl-5-deoxy-D-gluconothio-1,5-lactam (**14**). A mixture of **13** (4.4 g, 8.18 mmol) and Lawesson's reagent (2.5 g, 6.18 mmol) in toluene (130 ml) was stirred at 25° for 28 h. Evaporation and FC (Et₂O/hexane 0:1 → 1:3) gave **14** (4.5 g, 99%). M.p. 85°. $[\alpha]_D^{25} = 136.0$ ($c = 0.5$, CHCl₃).

2-(2,3,4,6-Tetra-O-benzyl-5-deoxy-1,5-imino-D-glucopyranosylidene)hydrazine-1-carbaldehyde (**15**). At 5°, a soln. of **14** (1.25 g, 2.26 mmol) in THF (12 ml, freshly distilled) was treated with hydrazinecarbaldehyde (630 mg, 10.5 mmol) and Hg(OAc)₂ (890 mg, 2.8 mmol), and kept for 40 min at 5°. Filtration through *Celite* and normal workup afforded **15** (1.32 g, > 99%). White solid. R_f (AcOEt) 0.54. IR (CHCl₃): 3369m, 3189w, 3067w, 3008m, 2922m, 1695s, 1656s, 1497m, 1454m, 1388w, 1363m, 1291s, 1093s, 1074s, 911w. ¹H-NMR (CDCl₃): 3.63 (dd, $J = 5.9$, 9.7, irradi. at 3.89 → d , $J \approx 9.0$, H-C(6)); 3.66 (dd, $J = 3.7$, 9.7, irradi. at 3.97 → d , $J \approx 9.6$, H-C(4)); 3.80 (dd, $J = 2.5$, 9.7, irradi. at 3.89 → d , $J \approx 9.7$, H'-C(6)); 3.85–3.93 (m, H-C(5)); 3.97 (dd, $J = 2.2$, 3.7, irradi. at 4.14 → d , $J \approx 3.7$, H-C(3)); 4.14 (d, $J = 2.2$, irradi. at 3.97 → s , H-C(2)); 4.42 (d, $J = 11.5$, PhCH); 4.46 (d, $J = 12.5$, PhCH); 4.56 (d, $J = 12.1$, PhCH); 4.58 (d, $J = 11.5$, PhCH); 4.59 (d, $J = 11.8$, PhCH); 4.61 (d, $J = 12.1$, PhCH); 4.66 (d, $J = 11.8$, PhCH); 4.76 (d, $J = 12.1$, PhCH); 6.04 (br. s, exchange with CD₃OD, NH); 7.15–7.23 (m, 2 arom. H); 7.23–7.50 (m, 18 arom. H); 8.51 (d, $J = 8.7$, addn. of CD₃OD → s , CHO); 10.84 (d, $J = 9.0$, exchange with CD₃OD, NHCHO). ¹³C-NMR (CDCl₃): 52.53 (d, C(5)); 69.15 (t, C(6)); 70.88 (t, PhCH₂); 71.82 (t, PhCH₂); 72.51 (t, PhCH₂); 73.63 (t, PhCH₂); 76.61 (d); 80.31 (d); 82.22 (d); 128.00–128.75 (several d); 137.82 (s); 138.02 (s); 138.21 (2s); 147.17 (s, C(1)); 165.96 (d, CHO). FAB-MS: 581 (44, $[M + 1]^+$), 580 (90, $[M]^+$), 563 (51, $[M + 1 - H_2O]^+$), 562 (100, $[M - H_2O]^+$).

(5R,6R,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyridine (**16**). a) *Acidic Conditions*: At 25°, a soln. of crude **15** (1.32 g, 2.26 mmol) in toluene (30 ml) was treated with TsOH · H₂O (250 mg, 1.3 mmol) and stirred at 40° for 24 h. Normal workup and FC (AcOEt/hexane 0:1 → 9:1) gave **16** (1.076 g, 85% from **14**).

b) *Basic Conditions*: At 25°, a soln. of crude **15** (26 mg, 0.04 mmol) in CDCl₃ (0.6 ml) was treated with piperidine (0.02 ml, 0.2 mmol) and kept at 25° for 5 d. Normal workup and FC (AcOEt/hexane 0:1 → 9:1) gave **16** (23 mg, 91%). R_f (AcOEt) 0.47. UV (CHCl₃): 242(3.0), 252(3.0), 258(3.0). IR (CHCl₃): 3090w, 3068w, 3043w, 3008m, 2869m, 1497m, 1455m, 1362m, 1334w, 1248w, 1151w, 1097s, 1071s, 986w. ¹H-NMR (CDCl₃): 3.64 (dd, $J = 6.9$, 10.4, HC-C(5)); 3.77 (t, $J = 7.2$, H-C(6)); 3.81 (dd, $J = 2.8$, 10.5, HC-C(5)); 4.14 (dd, $J = 5.3$, 7.2, H-C(7)); 4.25 (dt, $J = 2.8$, 6.9, H-C(5)); 4.42 (d, $J = 11.8$, PhCH); 4.476 (d, $J = 10.7$, PhCH); 4.481 (d, $J = 11.8$, PhCH); 4.63 (d, $J = 11.2$, PhCH); 4.78 (d, $J = 11.0$, PhCH); 4.81 (d, $J = 11.2$, PhCH); 4.85 (d, $J = 5.3$, H-C(8)); 4.91 (d, $J = 11.5$, PhCH); 5.17 (d, $J = 11.8$, PhCH); 7.16–7.46 (m, 20 arom. H); 8.32 (s, H-C(3)). ¹³C-NMR (CDCl₃): 57.58 (d, C(5)); 68.57 (t, CH₂-C(5)); 71.40 (t, PhCH₂); 72.74 (d, C(8)); 73.62 (t, PhCH₂); 74.10 (t, PhCH₂); 74.13 (t, PhCH₂); 75.59, 80.83 (2d, C(6), C(7)); 128.10–128.90 (several d); 137.08 (s); 137.39 (s); 137.65 (s); 137.76 (s); 141.84 (d, C(3)); 150.39 (s, C(8a)). FAB-MS: 562 (100, $[M + 1]^+$).

(5R,6R,7S,8S)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-1,2,4-triazolo[4,3-a]pyridine-6,7,8-triol (**7**). A soln. of **16** (193 mg, 0.34 mmol) in AcOEt/AcOH/H₂O 1.4:1:0.4 (1.4 ml) at 25° was added to a suspension of 20% Pd(OH)₂ (200 mg) in MeOH (1.8 ml) and hydrogenated at 6 bar for 4 d. The suspension was filtered through *Celite*. Evaporation of the filtrate, followed by HPLC (H₂O/MeOH; Merck LiChrosorb RP-18 (7 μm) 250 × 25 mm) gave **7** as a colorless oil which crystallized *i. v.* (40 mg, 58%). M.p. 224°. R_f (AcOEt/MeOH/H₂O 7:2:1) 0.1. $[\alpha]_D^{25} = -21.5$ ($c = 0.48$, H₂O). ¹H-NMR (D₂O): 3.82 (t, $J \approx 9.5$, H-C(7)); 3.90 (t, $J \approx 9.2$, H-C(6)); 4.02 (dd, $J = 4.1$, 12.8, HC-C(5)); 4.09–4.14 (m, H-C(5)); 4.24 (dd, $J = 1.9$, 12.8, HC-C(5)); 4.47 (d, $J = 8.7$, H-C(8)); 8.64 (s, H-C(3)). ¹H-NMR (CD₃OD): 3.75 (dd, $J = 7.8$, 9.3, irradi. at 4.64 → d , $J \approx 9.4$, H-C(7)); 3.82 (dd, $J = 7.5$, 9.3, H-C(6)); 3.92 (dd, $J = 5.3$, 11.8, HC-C(5)); 4.03 (ddd, $J = 2.2$, 5.3, 7.5, H-C(5)); 4.21 (dd, $J = 2.5$, 11.8, HC-C(5)); 4.64 (d, $J = 7.8$, H-C(8)); 8.65 (s, H-C(3)). ¹³C-NMR (D₂O): 61.87 (t, CH₂-C(5)); 62.58 (d, C(5)); 69.26, 70.13, 76.99 (3d, C(6), C(7), C(8)); 145.38 (d, C(3)); 156.36 (s, C(8a)). FAB-MS: 202 (100, $[M + 1]^+$). Anal. calc. for C₇H₁₁N₃O₄ (201.18): C 41.79, H 5.51, N 20.89; found: C 41.86, H 5.50, N 20.96.

2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1-[(2',2'-dimethoxyethyl)imino]-1,5-imino-D-glucitol (**17**). At 5°, a soln. of **14** (100 mg, 0.18 mmol) in THF (1 ml, freshly distilled) was treated with aminoacetaldehyde dimethyl acetal (0.1 ml, 0.93 mmol) and Hg(OAc)₂ (80 mg, 0.25 mmol) and kept for 50 min at 5°. Normal workup afforded **17** (110 mg, 97%). R_f (AcOEt) 0.10. IR (CHCl₃): 3437m, 3367w, 3067w, 3008m, 2929s, 2870s, 1650s, 1497s, 1454s, 1362m, 1263w, 1096s, 909s. ¹H-NMR (CDCl₃): 3.34 (dd, $J = 6.2$, 14.0, irradi. at 4.46 → d , $J \approx 14.0$, CHN=C); 3.35 (s, MeO); 3.36 (s, MeO); 3.42 (dd, $J \approx 6.2$, 14.8, irradi. at 4.46 → d , $J \approx 13.7$, CHN=C); 3.62–3.68 (m, irradi. at 3.70 → d , $J \approx 6.9$, H-C(5)); 3.68–3.72 (m, irradi. at 3.65 → br. s, 2H-C(6)); 3.85 (dd, $J = 7.9$, 8.7, irradi. at 3.65 → d , $J \approx 7.5$, irradi. at 3.96 → change, H-C(4)); 3.96 (t, $J = 9.0$, irradi. at 4.18 → d , $J \approx 7.5$, H-C(3)); 4.18 (d, $J = 9.0$, irradi. at 3.96 → change, H-C(2)); 4.46 (t, $J \approx 5.5$, irradi. at 3.38 → s , CH(OMe)₂); 4.51 (d, $J = 12.1$, PhCH); 4.58 (d, $J = 12.1$, PhCH); 4.60 (d, $J = 12.1$, PhCH); 4.65 (d, $J = 11.5$, PhCH);

4.84 (*d*, *J* = 12.1, PhCH); 4.85 (*d*, *J* = 11.2, PhCH); 4.88 (*d*, *J* = 11.2, PhCH); 4.94 (*d*, *J* = 11.2, PhCH); 5.00–5.30 (br. *s*, exchange with CD₃OD, NH); 7.15–7.45 (*m*, 20 arom. H). ¹³C-NMR (CDCl₃): 42.79 (*t*, CH₂N); 53.87 (*q*, 2MeO); 60.25 (*d*, C(5)); 70.69 (*t*, C(6)); 72.92 (*t*, PhCH₂); 73.58 (*t*, PhCH₂); 73.99 (*t*, 2PhCH₂); 76.94 (*d*, C(2)); 78.44, 82.15 (2*d*, C(3), C(4)); 102.12 (*d*, CH(OMe)₂); 127.00–128.40 (several *d*); 136.91 (*s*); 137.77 (2*s*); 138.03 (*s*); 157.14 (*s*, C(1)). FAB-MS: 625 (100, [*M* + 1]⁺), 517 (85, [*M* + 1 – BnOH]⁺).

Reaction of 14 in Neat Aminoacetaldehyde Dimethyl Acetal. A soln. of **14** (99 mg, 0.18 mmol) in aminoacetaldehyde dimethyl acetal (0.3 ml, 2.78 mmol) was kept for 27 h at 25°. Evaporation afforded 105 mg of crude **17/18** 69:31 (¹H-NMR). FC (AcOEt/hexane 1:1 → 1:0) gave **17** (29 mg, 26%), **17/18** 2:1 (51 mg, 46%), and **18** (11 mg, 10%).

Data of 2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1-[(2',2'-dimethoxyethyl)imino]-1,5-imino-D-mannitol (18): *R*_f (AcOEt) 0.03. IR (CHCl₃): 3443*m*, 3067*w*, 3008*m*, 2928*s*, 2867*s*, 1649*s*, 1516*s*, 1497*s*, 1454*s*, 1362*m*, 1073*s*. ¹H-NMR (CDCl₃): 3.34 (*s*, MeO); 3.36 (*s*, MeO); 3.38 (*dd*, *J* = 6.2, 14.0, irradi. at 4.48 → *d*, *J* ≈ 14.0, CHN); 3.45 (*dd*, *J* = 5.6, 14.0, irradi. at 4.48 → *d*, *J* ≈ 14.0, CHN); 3.53–3.62 (*m*, irradi. at 3.71 → change, irradi. at 3.81 → change, H–C(5), H–C(6)); 3.67–3.74 (*m*, *J* = 4.4, 8.1, irradi. at 3.55 → change, irradi. at 3.59 → change, H'–C(6)); 3.81 (*t*, *J* = 3.6, irradi. at 3.55 → br. *s*, H–C(4)); 3.88 (*t*, *J* = 3.1, irradi. at 3.81 → change, irradi. at 4.23 → *d*, *J* ≈ 3.1, H–C(3)); 4.23 (*d*, *J* = 3.1, H–C(2)); 4.43 (*d*, *J* = 11.8, PhCH); 4.48 (*t*, *J* = 5.6, irradi. at 3.35 → change, irradi. at 3.41 → change, CH(OMe)₂); 4.48 (*d*, *J* = 11.3, PhCH); 4.49–4.58 (*m*, 3PhCH); 4.56 (*d*, *J* = 11.5, PhCH); 4.59 (*d*, *J* = 11.8, PhCH); 4.62 (*d*, *J* = 12.1, PhCH); 5.00–5.30 (br. *s*, exchange with CD₃OD, NH); 7.15–7.40 (*m*, 20 arom. H). ¹³C-NMR (CDCl₃): 42.29 (*t*, CH₂N); 54.02 (*q*, 2MeO); 58.88 (*d*, C(5)); 71.77 (*t*, C(6)); 71.87 (*t*, PhCH₂); 72.14 (*t*, PhCH₂); 73.23 (*t*, 2PhCH₂); 73.76, 74.71, 76.20 (3*d*, C(2), C(3), C(4)); 102.91 (*d*, CH(OMe)₂); 127.00–128.40 (several *d*); 137.50 (*s*); 138.50 (2*s*); 139.20 (*s*); 156.95 (*s*, C(1)). FAB-MS: 625 (100, [*M* + 1]⁺), 517 (14, [*M* + 1 – BnOH]⁺).

Isomerization of 17. At 25°, a soln. of crude **17** (20 mg, 0.032 mmol) in CDCl₃ (0.6 ml) was treated with TsOH · H₂O (16 mg, 0.08 mmol) and kept at 25° for one week → **17/18** 60:40 (¹H-NMR).

Isomerization of 18. Similarly as for **17**, with **18** (20 mg, 0.032 mmol) and TsOH · H₂O (16 mg, 0.08 mmol) → **17/18** 60:40 (¹H-NMR).

(5*R*,6*R*,7*S*,8*S*)- and (5*R*,6*R*,7*S*,8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimida-zo[1,2-*a*]pyridine (**19** and **20**, resp.). **a**) A soln. of **14** (127 mg, 0.23 mmol) in aminoacetaldehyde dimethyl acetal (1 ml, 9.25 mmol) was kept for 28 h at 25°, evaporated, and dried. The residue (¹H-NMR **17/18** 69:31) was dissolved in toluene (5 ml), treated with TsOH · H₂O (80 mg, 0.42 mmol), and stirred at 60° for 12 h. Normal workup afforded **19/20** 7:3 (105 mg, ¹H-NMR). FC (AcOEt/hexane/Et₃N 0:97:3 → 97:97:6) gave **19** (61 mg, 47%), **19/20** 2:1 (12 mg, 9%), and **20** (26 mg, 20%).

b) Similarly as **a**, a soln. of **17/18** 69:31 and TsOH · H₂O (80 mg, 0.42 mmol) in toluene (1 ml) was stirred for 2 d at 50°, diluted with toluene (4 ml), and stirred for further 12 h at 50°. Normal workup and FC afforded **19/20** 50:50 (96 mg, 75%)⁶⁾.

c) At 5°, a soln. of **14** (101 mg, 0.18 mmol) in THF (1 ml, freshly distilled) was treated with aminoacetaldehyde dimethyl acetal (0.1 ml, 0.93 mmol) and Hg(OAc)₂ (82 mg, 0.26 mmol), and kept for 2 h at 5°. After normal workup and drying, the residue was dissolved in toluene (5 ml), treated with TsOH · H₂O (95 mg, 0.5 mmol), and stirred at 70° for 21 h. Normal workup afforded **19/20** 82:18 (100 mg, ¹H-NMR). FC (AcOEt/hexane/Et₃N 0:97:3 → 97:97:6) gave **19** (66 mg, 65%) and **19/20** 41:59 (13 mg, 13%).

d) Similarly as **c**, after normal workup and drying, the residue was dissolved in toluene (5.2 ml) and H₂O (0.5 ml), treated with TsOH · H₂O (90 mg, 0.47 mmol), and stirred at 65° for 18 h. Normal workup afforded **19/20** > 90:10 (100 mg, ¹H-NMR). FC (AcOEt/hexane/3% Et₃N) gave **19** (77.4 mg, 76%).

Data of 19: *R*_f (AcOEt/hexane 1:1) 0.57. UV (CHCl₃): 243(3.7), 259(3.5), 283(2.8). IR (CHCl₃): 3090*w*, 3067*w*, 3008*m*, 2868*m*, 1497*m*, 1455*s*, 1362*m*, 1262*w*, 1094*s*, 1151*w*, 1028*s*, 912*w*. ¹H-NMR (CDCl₃): 3.76 (*dd*, *J* = 5.3, 10.6, irradi. at 4.20 → *d*, *J* ≈ 10.3, HC–C(5)); 3.877 (*dd*, *J* = 2.8, 10.6, irradi. at 4.20 → *d*, *J* ≈ 10.0, HC–C(5)); 3.881 (*t*, *J* = 7.8, irradi. at 4.20 → *d*, *J* ≈ 7.5, H–C(6)); 4.11 (*dd*, *J* = 5.9, 7.5, irradi. at 4.77 → *d*, *J* ≈ 7.8, H–C(7)); 4.20 (*ddd*, *J* = 2.8, 5.3, 7.8, H–C(5)); 4.46 (*d*, *J* = 12.1, PhCH); 4.50 (*d*, *J* = 12.5, PhCH); 4.53 (*d*, *J* = 11.2, PhCH); 4.72 (*d*, *J* = 11.2, PhCH); 4.77 (*d*, *J* = 5.6, H–C(8)); 4.85 (*d*, *J* = 11.2, PhCH); 4.87 (*d*, *J* = 11.2, PhCH); 4.90 (*d*, *J* = 11.8, PhCH); 5.21 (*d*, *J* = 11.5, PhCH); 7.07, 7.14 (2*d*, each *J* = 0.9, H–C(2), H–C(3)); 7.17–7.24 (*m*, 2 arom. H); 7.26–7.41 (*m*, 16 arom. H); 7.43–7.48 (*m*, 2 arom. H). ¹³C-NMR (CDCl₃): 58.21 (*d*, C(5)); 68.50 (*t*, CH₂–C(5)); 72.89 (*t*, PhCH₂); 73.44 (*t*, PhCH₂); 74.24 (*t*, PhCH₂); 74.44 (*t*, PhCH₂); 74.46 (*d*, C(8)); 76.20, 82.30 (2*d*, C(6), C(7)); 117.57 (*d*, C(3)); 127.9–128.8 (several *d*); 129.62 (*d*, C(2)); 137.60 (*s*); 137.92 (*s*); 138.18 (*s*); 138.54 (*s*); 144.30 (*s*, C(8a)). FAB-MS: 561 (100, [*M* + 1]⁺).

⁶⁾ Repetitions of this experiment led in ca. 75% yield to **19/20** 60:40 to 25:75.

Data of 20: R_f (AcOEt/hexane 1:1) 0.40. UV (CHCl₃): 243(3.6), 259(3.5), 283(3.4). IR (CHCl₃): 3090w, 3067w, 3008m, 2868m, 1496m, 1454s, 1364m, 1262m, 1099s, 1028s, 915w. ¹H-NMR (CDCl₃): 3.63 (dd, $J = 7.2$, 10.0, irradi. at 4.15 $\rightarrow d$, $J \approx 9.8$, HC–C(5)); 3.77 (dd, $J = 3.1$, 10.0, irradi. at 4.15 $\rightarrow d$, $J \approx 9.7$, HC–C(5)); 3.87 (dd, $J = 3.1$, 9.3, irradi. at 4.81 $\rightarrow d$, $J \approx 9.3$, H–C(7)); 4.15 (dt, $J = 2.8$, 7.0, H–C(5)); 4.30 (dd, $J = 7.2$, 9.3, irradi. at 4.15 $\rightarrow d$, $J \approx 8.7$, H–C(6)); 4.47 (s, PhCH₂); 4.58 (d, $J = 11.8$, PhCH); 4.63 (d, $J = 11.8$, PhCH); 4.67 (d, $J = 11.8$, 2PhCH); 4.75 (d, $J = 12.5$, PhCH); 4.81 (d, $J = 3.1$, H–C(8)); 5.01 (d, $J = 11.2$, PhCH); 7.07 (d, $J = 1.3$), 7.18 (d, $J = 0.9$, H–C(2), H–C(3)); 7.22–7.37 (m, 18 arom. H); 7.39–7.45 (m, 2 arom. H). ¹³C-NMR (CDCl₃): 59.93 (d, C(5)); 68.26 (d, C(8)); 70.56 (t, CH₂–C(5)); 71.19 (t, PhCH₂); 71.80 (t, PhCH₂); 73.35 (t, PhCH₂); 75.05 (t, PhCH₂); 74.36, 80.30 (2d, C(6), C(7)); 119.61 (d, C(3)); 127.8–128.8 (several d); 129.54 (d, C(2)); 137.81 (s); 138.10 (s); 138.33 (s); 138.39 (s); 143.15 (s, C(8a)). FAB-MS: 561 (100, $[M + 1]^+$).

(5R,6R,7S,8S)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)imidazo[1,2-a]pyridine-6,7,8-triol (**10**). A soln. of **19** (334 mg, 0.60 mmol) in AcOEt/MeOH/H₂O 5:17:3 (2.3 ml) was treated with AcOH (1 ml) and 20% Pd(OH)₂/C (314 mg) and hydrogenated at 6 bar for 1 d. The suspension was filtered through Celite. Evaporation of the filtrate, followed by HPLC (H₂O/MeOH, Merck LiChrosorb RP-8 (7 μ m) 250 $\times$ 25 mm) gave **10** (77 mg, 65%). Colorless oil. R_f (AcOEt/MeOH/H₂O 7:2:1) 0.1. $[\alpha]_D^{25} = -9.3$ ($c = 1.1$, MeOH; $[\eta]_D^{25} = -8.0$ (MeOH)). UV (MeOH): 218(3.9). ¹H-NMR (D₂O): 3.76 (t, $J \approx 9.2$, irradi. at 4.58 $\rightarrow d$, $J \approx 9.7$, H–C(7)); 3.91 (dd, $J = 9.0$, 9.7, H–C(6)); 3.99 (td, $J = 2.4$, 9.0, H–C(5)); 4.05 (dd, $J = 2.5$, 12.8 HC–C(5)); 4.21 (dd, $J = 2.2$, 12.8, HC–C(5)); 4.58 (d, $J = 8.7$, H–C(8)); 7.09, 7.25 (2s, H–C(2), H–C(3)). ¹³C-NMR (D₂O): 61.35 (t, CH₂–C(5)); 63.06 (d, C(5)); 70.08, 70.80, 77.51 (3d, C(6), C(7), C(8)); 120.56, 131.48 (2d, C(2), C(3)); 149.19 (s, C(8a)).

(5R,6R,7S,8S)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)imidazo[1,2-a]pyridine-6,7,8-triol Hydrochloride (**10** · HCl). A soln. of **10** (60 mg, 0.3 mmol) in MeOH (5 ml) was treated with 2N HCl (1 ml) and evaporated. Recrystallization from EtOH gave **10** · HCl (40 mg, 56%). White crystals suitable for X-ray analysis. M.p. 141°. R_f (AcOEt/MeOH/H₂O 7:2:1) 0.1. ¹H-NMR (D₂O): 3.90 (t, $J = 9.3$, irradi. at 4.85 $\rightarrow d$, $J \approx 10.0$, H–C(7)); 4.01 (dd, $J = 8.7$, 10.0, H–C(6)); 4.10 (dd, $J = 3.0$, 12.9, HC–C(5)); 4.19–4.26 (m, H–C(5)); 4.28 (dd, $J = 1.5$, 13.1, HC–C(5)); 4.85 (d, $J = 9.0$, H–C(8)); 7.52, 7.62 (2s, H–C(2), H–C(3)). ¹³C-NMR (D₂O): 61.04 (t, CH₂–C(5)); 64.96 (d, C(5)); 69.18, 69.66, 76.01 (3d, C(6), C(7), C(8)); 122.61, 123.59 (2d, C(2), C(3)); 148.21 (s, C(8a)).

X-Ray Analysis of 10 · HCl. Crystals were obtained from EtOH. Monoclinic P2₁; $a = 7.843(1)$, $b = 7.9996(1)$, $c = 8.588(2)$ $\beta = 113.751(6)$; $V = 493.18(13)$ Å³; $D_{\text{calc}} = 1.594$ Mg/m³; $Z = 2$. The reflexions were measured on an Enraf-Nonius-CAD4 diffractometer (graphite monochromator, MoK α , $\lambda = 0.71073$) at 293 K. $R = 0.03$, $R_w = 0.0796$. The structures were solved with the direct-methods routine of SHELX-86, and the refinement was performed with SHELXL-92 [30].

(5R,6R,7S,8R)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)imidazo[1,2-a]pyridine-6,7,8-triol (**11**). As described for **10**, with **20** (229 mg, 0.41 mmol): **11** (51 mg, 63%). Colorless oil. R_f (AcOEt/MeOH/H₂O 7:2:1) 0.1. UV (MeOH): 216 (3.6). ¹H-NMR (D₂O): 4.07 (dd, $J = 4.2$, 12.6, irradi. at 4.27 $\rightarrow d$, $J \approx 11.8$, HC–C(5)); 4.15 (dd, $J = 3.7$, 8.1, irradi. at 5.20 $\rightarrow d$, $J \approx 8.4$, H–C(7)); 4.21 (dd, $J = 3.1$, 12.5, irradi. at 4.27 $\rightarrow d$, $J \approx 13.1$, HC–C(5)); 4.24–4.29 (m, H–C(5)); 4.34 (dd, $J = 6.1$, 7.9, irradi. at 4.27 $\rightarrow d$, $J \approx 7.5$, H–C(6)); 5.20 (d, $J = 3.7$, H–C(8)); 7.54, 7.64 (2s, H–C(2), H–C(3)). ¹³C-NMR (D₂O): 62.50 (t, CH₂–C(5)); 64.37 (d, C(5)); 65.91, 68.39, 71.77 (3d, C(6), C(7), C(8)); 123.30, 123.49 (2d, C(2), C(3)); 146.40 (s, C(8a)).

Inhibition Studies. Determinations of the inhibition constants (K_i) were performed in the presence of a range of the inhibitor concentrations (typically 4–6 concentrations) which bracket the K_i value.

a) Inhibition of Sweet-Almond β -Glucosidases. Inhibition constants (K_i) were determined at 37°, using a 0.08M KH₂PO₄/K₂HPO₄ buffer (pH 6.8) and 4-nitrophenyl β -D-glucopyranoside as substrate. Measurements were started by addition of the substrate. The increase of absorption per min at 400 nm was taken as velocity for the hydrolysis of the substrate. The increase was linear during all measurements (3 min). K_i values were determined by taking the slopes from the Lineweaver-Burk plots [31] and plotting them vs. the inhibitor concentrations [32]. After fitting the data to a straight line, the negative $[I]$ -intercept of this plot gave the appropriate K_i .

b) Inhibition of Caldocellum saccharolyticum β -Glucosidase. Similarly as *a*. The inhibition constants were determined at 55°.

c) Inhibition of Brewer's Yeast α -Glucosidase. Similarly as *a*. The inhibition constants were determined using 0.025M KH₂PO₄/K₂HPO₄/NaCl buffer (pH 6.8), and 4-nitrophenyl α -D-glucopyranoside as substrate.

REFERENCES

- [1] P. Ermert, A. Vasella, *Helv. Chim. Acta* **1991**, *74*, 2043.
- [2] P. Ermert, A. Vasella, M. Weber, K. Rupitz, S. G. Withers, *Carbohydr. Res.* **1993**, *250*, 113.

- [3] T. D. Heightman, M. Locatelli, A. Vasella, *Helv. Chim. Acta* **1996**, 79, 2190.
- [4] D. C. Phillips, *Sci. Am.* **1966**, 215, 78.
- [5] K. Tatsuta, S. Miura, S. Ohta, H. Gunji, *Tetrahedron Lett.* **1995**, 36, 1085.
- [6] K. Tatsuta, S. Miura, S. Ohta, H. Gunji, *J. Antibiot.* **1995**, 48, 286.
- [7] K. Tatsuta, Y. Ikeda, S. Miura, *J. Antibiot.* **1996**, 49, 836.
- [8] A. Frankowski, C. Seliga, D. Bur, J. Streith, *Helv. Chim. Acta* **1991**, 74, 934.
- [9] P. Kefalas, D. S. Grierson, *Tetrahedron Lett.* **1993**, 34, 3555.
- [10] K. Burgess, D. A. Chaplin, *Heterocycles* **1994**, 37, 673.
- [11] D. H. Hua, F. Zhang, J. Chen, P. D. Robinson, *J. Org. Chem.* **1994**, 59, 5084.
- [12] R. Hoos, A. B. Naughton, A. Vasella, *Helv. Chim. Acta* **1993**, 76, 1802.
- [13] G. Pellizzari, *Gazz. Chim. Ital.* **1894**, 222.
- [14] R. Hoos, A. B. Naughton, W. Thiel, A. Vasella, W. Weber, K. Rupitz, S. G. Withers, *Helv. Chim. Acta* **1993**, 76, 2666.
- [15] H. S. Overkleeft, J. van Wiltenburg, U. K. Pandit, *Tetrahedron* **1994**, 50, 4215.
- [16] J. Marchand-Brynaert, M. Moya-Portuguez, I. Huber, L. Ghosez, *J. Chem. Soc., Chem. Commun.* **1983**, 818.
- [17] K. Suzuki, T. Fujii, K. Sato, H. Hashimoto, *Tetrahedron Lett.* **1996**, 37, 5921.
- [18] M. Avalos, B. Reyes, P. Cintas, J. D. Carlos, J. L. Jimenez, J. C. Palacios, *Tetrahedron* **1995**, 51, 8043.
- [19] R. de B. Ashworth, A. F. Crowther, F. H. S. Curd, F. L. Rose, *J. Chem. Soc.* **1948**, 581.
- [20] A. F. Crowther, F. H. S. Curd, F. L. Rose, *J. Chem. Soc.* **1948**, 586.
- [21] F. Micheel, W. Brunkhorst, *Chem. Ber.* **1955**, 88, 481.
- [22] O. Buchardt, U. Ehrbar, C. Larsen, J. Moller, P. E. Nielsen, T. Thomsen, F. Wätjen, J. B. Hansen, *J. Org. Chem.* **1984**, 49, 4123.
- [23] H. A. Moynihan, S. M. Roberts, H. Weldon, G. H. Allcock, E. E. Anggard, T. D. Warner, *J. Chem. Soc., Perkin Trans. 1* **1994**, 769.
- [24] P. Deprez, J.-P. Vevert, *Synth. Commun.* **1996**, 26, 4299.
- [25] S. Vonhoff, A. Vasella, unpublished results.
- [26] H. U. Sieveking, W. Lüttke, *Liebigs Ann. Chem.* **1977**, 2, 189.
- [27] T. D. Heightman, P. Ermert, D. Klein, A. Vasella, *Helv. Chim. Acta* **1995**, 78, 514.
- [28] R. Hoos, A. Vasella, K. Rupitz, S. G. Withers, *Carbohydr. Res.* **1997**, 298, 291.
- [29] T. Granier, A. Vasella, *Helv. Chim. Acta* **1995**, 78, 1738.
- [30] G. M. Sheldrick, *Acta Crystallogr.* **1990**, 46, 467.
- [31] H. Lineweaver, D. Burk, *J. Am. Chem. Soc.* **1934**, 56, 658.
- [32] I. H. Segel, 'Enzyme Kinetics', Wiley, New York, 1975.