# Synthesis of New *C(2)*-Substituted *gluco*-Configured Tetrahydroimidazopyridines and Their Evaluation as Glucosidase Inhibitors

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*Albert Eschenmoser* zum 80. Geburtstag mit herzlichen Glückwünschen zugeeignet.

The *gluco*-configured *C(2)*-substituted tetrahydroimidazopyridines **8**–**14** were prepared and tested as inhibitors of the $\beta$-glucosidases from *Caldocellum saccharolyticum* and from sweet almonds, and of the $\alpha$-glucosidase from brewer's yeast. All new imidazopyridines are nanomolar inhibitors of the $\beta$-glucosidases and micromolar inhibitors of the $\alpha$-glucosidase. The 3-phenylpropyl derivative **14** proved the strongest inhibitor of the *Caldocellum* $\beta$-glucosidase ($K_i = 0.9$ nM), only slightly weaker than the known 2-phenylethyl analogue **7**, and the propyl derivative **13** is the strongest inhibitor of the sweet almond $\beta$-glucosidases ($K_i = 3.2$ nM), again slightly weaker than **7**. There is no strong dependence of the inhibition on the nature of the *C(2)*-substituent and no clear correlation between the inhibitory strength of the known *manno*-configured imidazopyridines **2**–**6** and the *gluco*-analogues **8**–**12**. While most *manno*-imidazopyridines are competitive inhibitors, the *gluco*-analogues proved non-competitive inhibitors of the *Caldocellum* $\beta$-glucosidase and mixed-type or partial mixed-type inhibitors of the sweet almond $\beta$-glucosidases.

**Introduction.** – A recent comparison of the inhibition of retaining $\beta$-glucosidases and snail $\beta$-mannosidase [1–3] by *C(2)*-substituted *manno*- and *gluco*-configured tetrahydroimidazopyridines [4–11] and by appropriately configured isoquinuclidines [12–14] strongly suggested that $\beta$-glucosidases and $\beta$-mannosidases use a different conformational itinerary to attain a similar transition state. In the course of this work, we noticed that the nature of the *C(2)*-substituent of the *gluco*-, *manno*-, and GlcNAc-derived tetrahydroimidazopyridines had a analogous effect on the strength of the inhibition of the $\beta$-glucosidases from *Caldocellum saccharolyticum* [15], $\beta$-mannosidase from snail [8], and *N*-acetyl $\beta$-glucosaminidase from bovine kidney [16], respectively. We also found that the *manno*-configured inhibitors **2**–**6** [17] for which there were no *gluco*-configured counterparts are particularly strong inhibitors of snail $\beta$-mannosidase, *ca.* 3–5 times stronger than **1** ($K_i = 20$ nM) [17], the *manno*-analogue of the *gluco*-configured 2-phenylethyl imidazopyridine **7** that is so far the strongest known inhibitor of a retaining $\beta$-glucosidase ($K_i = 0.1$ nM, *C. saccharolyticum*) [15]. The parallel effect of the *C(2)*-substituents on the strength of the inhibition suggested that the *gluco*-configured imidazopyridines **8**–**12** corresponding to **2**–**6** should be stronger inhibitors than **7**. However, a comparison of the *gluco*- and *manno*-configured *C(2)*-substituted imidazopyridines shows that the analogous effect of the *C(2)*-substituent on the strength of the inhibition is not reflected by a similarity of the type of inhibition (mixed, competitive, or non-competitive), casting some doubt on the validity of the above extrapolation. In view of these considerations and of our interest in very strong glucosidase inhibitors, we decided to prepare the *gluco*-analogues **8**–**12**. Considering the strong inhibition by the

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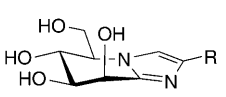
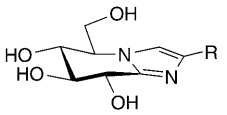
2-phenylethyl derivative **7**, we also wished to synthesise the propyl derivative **13** and the 3-phenylpropyl derivative **14**.



**1** R = $PhCH_2CH_2$
**2** R = PhC≡C
**3** R = PhCH=CH
**4** R = $PhNHCH_2$
**5** R = 3-$NO_2$-$C_6H_4OCH_2$
**6** R = $PhOCH_2$



**7** R = $PhCH_2CH_2$
**8** R = PhC≡C
**9** R = PhCH=CH
**10** R = $PhNHCH_2$
**11** R = 3-$NO_2$-$C_6H_4OCH_2$
**12** R = $PhOCH_2$
**13** R = $CH_3CH_2CH_2$
**14** R = $PhCH_2CH_2CH_2$

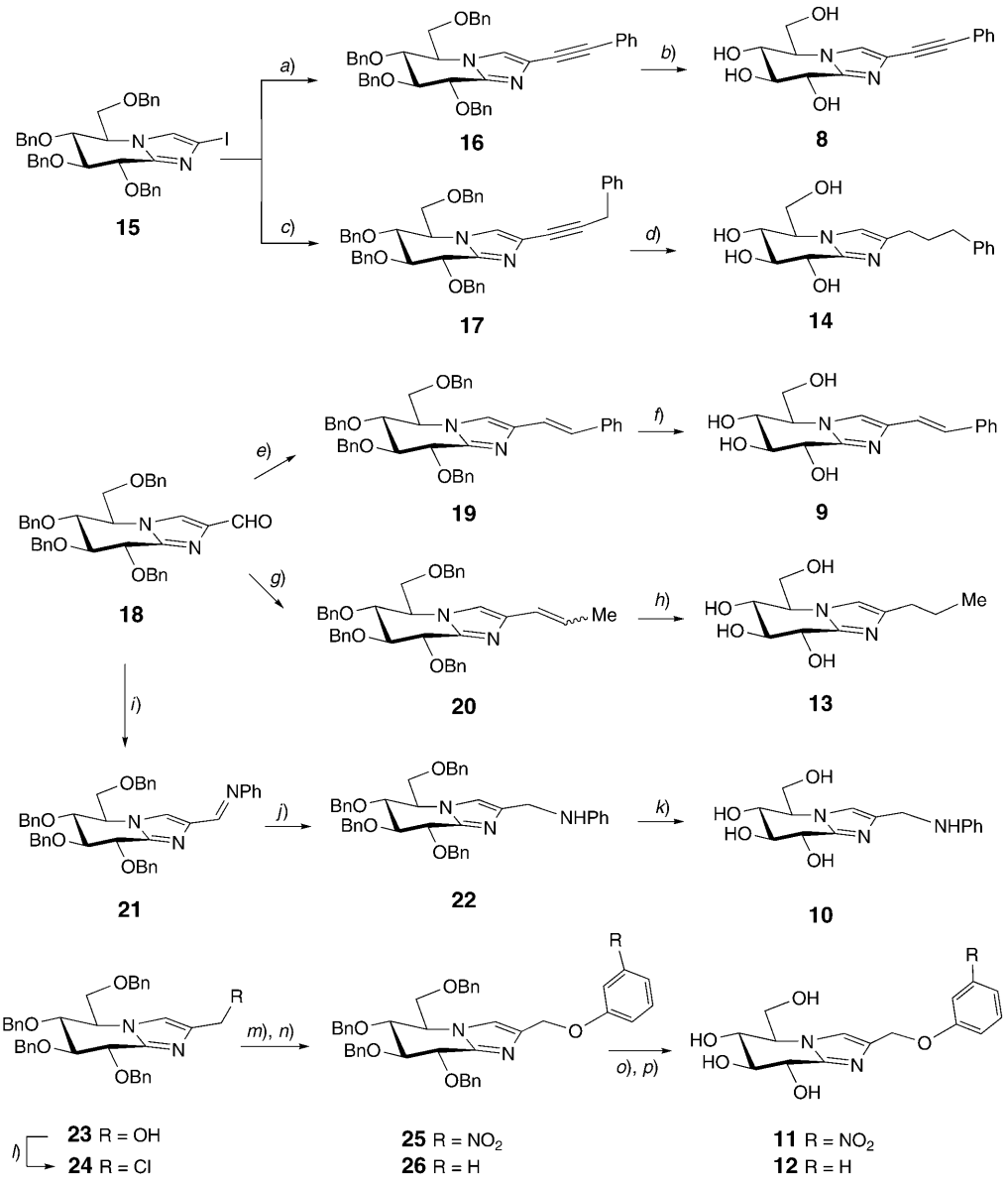
**Synthesis.** – We prepared the *gluco*-analogues **8**–**14** *via* the 2-iodo-imidazopyridine **15**, according to the established synthesis of the corresponding *manno*-imidazopyridines [17]. The compound **15** is available in five steps and in an overall yield of 50–53% from 5-amino-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-gluconolactam [18–20].

*Sonogashira* coupling [21] of **15** (*Scheme*) with phenylacetylene yielded 76% of the known phenylethynyl derivative **16** [15] that was debenzylated ($BCl_3$) to the desired phenylethynyl imidazopyridine **8** (59%). Similarly, the *Sonogashira* coupling of **15** with 3-phenylprop-1-yne yielded **17** that was hydrogenated to the 3-phenylpropyl-imidazopyridine **14** (31% from **15**).

For the synthesis of the remaining inhibitors, we transformed **15** into the known carbaldehyde **18** and the known alcohol **23** [15]. *Wittig–Horner* reaction of **18** with diethyl benzylphosphonate gave the known 2-phenylethenyl derivative **19** [15] that was debenzylated with $AlCl_3$ in the presence of *N*,*N*-dimethylaniline to yield 60% of **9**. *Wittig* olefination of **18** with (ethylidene)(triphenyl)phosphorane yielded 88% of **20** as 45 : 55 (*E*)/(*Z*) mixture that was hydrogenated to provide the propyl-imidazopyridine **13** (82%). The (phenylamino)methyl derivative **10** was obtained by reductive amination of **18** (77%). Treatment of **18** with aniline provided the (phenylimino)methyl derivative **21** that was reduced with $NaBH_4$ and then debenzylated with $BCl_3$ (61%). The (3-nitrophenoxy)methyl derivative **11** was obtained in a yield of 34% by treatment of the hydroxymethyl-imidazopyridine **23** with 1-fluoro-3-nitrobenzene and NaH, followed by debenzylation of the resulting **25** with $AlCl_3$ in the presence of anisole, while the phenoxymethyl derivative **26** was prepared in a yield of 77% by alkylation of phenol with the (chloromethyl)-imidazopyridine **24**, followed by hydrogenolysis (63%). The compound **24** was readily obtained in a yield of 91% from **23** and $SOCl_2$.

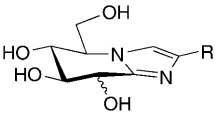
**Enzymatic Tests and Discussion.** – The *gluco*-imidazopyridines **8**–**14** were tested as inhibitors of the $\beta$-glucosidase from *Caldocellum saccharolyticum* (0.08M phosphate buffer, pH 6.8, 55°), the $\beta$-glucosidases from sweet almonds (0.08M phosphate buffer, pH 6.8, 37°), and the $\alpha$-glucosidase from brewer's yeast (0.08M phosphate buffer, pH 6.8, 37°). *Table 1* summarises the results, listing the *manno*- and the corresponding *gluco*-configured imidazopyridines in order of decreasing inhibitory strength of the *manno*-isomers. Although all *gluco*-imidazopyridines are nanomolar inhibitors of the

*Scheme*




*a*) Phenylacetylene, $[Pd(PPh_3)_4]$, CuI, $Et_3N$; 76%. *b*) $BCl_3$, $CH_2Cl_2$; 59%. *c*) 3-Phenylprop-1-yne, $[Pd(PPh_3)_4]$, CuI, $Et_3N$; 58%. *d*) $H_2$, Pd/C, AcOH; 53%. *e*) Diethyl benzylphosphonate, *t*-BuOK, THF; 81%. *f*) $AlCl_3$, $CH_2Cl_2$, *N*,*N*-dimethylaniline; 75%. *g*) Ethyl(triphenyl)phosphonium bromide, BuLi, THF; 88%. *h*) Pd/C, 6 bar of $H_2$, AcOH, 82%. *i*) Aniline, 4-Å mol. sieves, $CH_2Cl_2$. *j*) $NaBH_4$, EtOH; 77% from **18**. *k*) $BCl_3$, $CH_2Cl_2$, $-78°$ to 15°; 61%. *l*) $SOCl_2$, $CH_2Cl_2$; 91%. *m*) 1-Fluoro-3-nitrobenzene, NaH, DMF; 59% of **25**. *n*) PhOH, *t*-BuOK, DMF; 77% of **26**. *o*) $AlCl_3$, anisole, $CH_2Cl_2$; 58% of **11**. *p*) $H_2$, $Pd(OH)_2$/C, AcOEt/MeOH/$H_2O$/AcOH; 63% of **12**.

Table 1. *Inhibition of the β-Glucosidases from* C. saccharolyticum *and Sweet Almonds, the α-Glucosidase from Brewer's Yeast, and the β-Mannosidase from Snail by the the* C(2)*-Substituted* gluco- *and* manno-*Imidazoles*: $K_i$ *and* $pK_{HA}$ *Values*




| | Inhibition of β-mannosidase[a][b] | | | Inhibition of β-glucosidases | | | | Inhibition of α-glucosidase |
|---|---|---|---|---|---|---|---|---|
| R | *manno*-Imidazoles | $pK_{HA}$ | $K_i$ [nM][c] | *gluco*-Imidazoles | $pK_{HA}$ | from *C. sacch.*[d][e] $K_i$ [nM] | from sweet almonds[f][g] $K_i$ [nM]($\alpha$) | from brewer's yeast[f][h] $K_i$ [nM] |
| PhCH=CH | **3** | 4.77 | 6 | **9** | 4.83 | 2.6 | 7.6 (1.3) | 3230 |
| PhC≡C | **2** | [i] | 7 | **8** | [i] | 7.4 | 2.4 (1.1) | 7300 |
| $PhCH_2NH$ | **4** | 5.09[j] | 8 | **10** | 5.62/9.51 | 2.3 | 5.4 (4.4) | 1920 |
| 3-$NO_2$–$C_6H_4OCH_2$ | **5** | 4.36 | 12 | **11** | 4.46 | 2.2 | 6.6 (2.0) | 1770 |
| $PhOCH_2$ | **6** | 4.39 | 12 | **12** | 4.69 | 2.4 | 9.7 (2.0) | 3220 |
| $MeCH_2CH_2$ | | | | **13** | 6.42 | 1.6 | 3.2 (1.1) | 1890 |
| $PhCH_2CH_2CH_2$ | | | | **14** | 6.63 | 0.9 | 8.5 (0.9) | 450 |
| $PhCH_2CH_2$ | **1** | 6.04 | 20 | **7**[k] | 6.03 | 0.11[l] | 1.2 | 500 |

[a]) At 25° and pH 4.5. [b]) Data taken from [17]. [c]) Competitive-type inhibition except for **3**. [d]) At 55° and pH 6.8. [e]) Non-competitive-type inhibition. [f]) At 37° and pH 6.8. [g]) Mixed-type inhibition except for **14** (partial mixed type) [22]. [h]) $IC_{50}$/2. [i]) No inflection of the titration curve was observed within pH 2.1–5.4. [j]) Second p$K$ value not reported. [k]) Data taken from [15]. [l]) Mixed-type inhibition ($\alpha = 15$).

β-glucosidases, none was stronger than the 2-phenylethyl derivative **7**. The strength of the inhibition of the *C. saccharolyticum* β-glucosidase does not vary widely, with $K_i$ values of 0.9 and 7.4 nM for the strongest and weakest inhibitors **14** and **8**, respectively, that correspond to **2**–**6**.

This is also observed for the inhibition of the sweet almond β-glucosidases that were inhibited less strongly than the *Caldocellum* enzyme, as noticed earlier for related imidazopyridines [15]. The extreme $K_i$ values for the *gluco*-analogues of the *manno*-imidazopyridines **2**–**6** are 24 nM for **8** and 5.4 nM for **10**. An even stronger inhibitor is the propyl derivative **13** with a $K_i$ of 1.6 nM for the *Caldocellum* β-glucosidase and 3.2 nM for the sweet almond enzymes. The 3-phenylpropyl derivative **14** proved the strongest inhibitor of the *Caldocellum* β-glucosidase ($K_i = 0.9$ nM). It is, however, a weaker inhibitor of the sweet almond enzyme than **13**. In contradistinction to the inhibition by the *manno*-configured imidazopyridines that is competitive (with an exception for **3**), the *gluco*-analogues showed a non-competitive-type inhibition of the *Caldocellum* and a mixed-type inhibition of the sweet almond β-glucosidases characterised by small α-values with the exception of **14** that proved a partial mixed-type inhibitor. With micromolar $K_i$ values characterising the inhibition of brewer's yeast α-glucosidase the *gluco*-imidazopyridines **7**–**14** are rather selective inhibitors of β-glucosidases. There is no obvious correlation of the strength of the inhibition with basicity. In view of the narrow range of the strength of the inhibition, one may interpret the absence of a clear correspondence of the influence of the nature of the *C(2)*-substituent on the inhibition by the *manno*- and *gluco*-imidazopyridines as denoting the limits of the effect of these aglycon mimics on the strength of the inhibition rather than as indicating a different nature of the reactive intermediates.

We thank Dr. *B. Bernet* for checking the experimental part, *M. Schneider* and *D. Manser* for the p$K_{HA}$ determination, and the *Swiss National Science Foundation* and *F. Hoffmann-La Roche*, Basel, for generous financial support.

## Experimental Part

*General.* See [16].

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-(2-phenylethynyl)imidazo[1,2-*a*]pyridine-6,7,8-triol* (**8**). A soln. of **16** [15] (38 mg, 57.5 μmol) in $CH_2Cl_2$ (1.5 ml) was cooled to −78°, treated with 1M $BCl_3$ in $CH_2Cl_2$ (0.9 ml, 0.923 mmol), and stirred until the mixture had reached 5° (*ca.* 5 h). The mixture was cooled to −78°, treated with $H_2O$ (1 ml), and neutralised with aq. $NH_3$ (1 ml). Evaporation and FC (AcOEt/MeOH/$H_2O$ 1:0:0 → 20:1:1 → 15:1:1) gave **8** (10 mg, 59%). White hygroscopic solid. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.15. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 7.32–7.36 (*m*, H–C(3), H–C(4), and H–C(5) of Ph); 7.45–7.48 (*m*, H–C(2) and H–C(6) of Ph). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*, additionally, 83.39 (*s*, C≡*C*–C(2)); 89.76 (*s*, *C*≡C–C(2)); 124.06 (*d*, C(4) of Ph); 124.60 (*s*, C(1) of Ph, C(2)); 129.06 (2*d*); 131.80 (2*d*);. HR-MALDI-MS: 323.1000 (49, $[M+Na]^+$, $C_{16}H_{16}N_2NaO_4^+$; calc. 323.1008), 301.1183 (58, $[M+H]^+$, $C_{16}H_{17}N_2O_4^+$; calc. 301.1188), 283.1071 (100, $[M-OH]^+$, $C_{16}H_{15}N_2O_3^+$; calc. 283.1083). Anal. calc. for $C_{16}H_{16}N_2O_4\cdot H_2O$ (318.12): C 60.37, H 5.70, N 8.80; found: C 60.24, H 5.64, N 8.78.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-[(3-phenylprop-1-ynyl)-imidazo[1,2-*a*]pyridine* (**17**). A soln. of **15** (172 mg, 0.25 mmol), CuI (5 mg, 0.026 mmol), and $Et_3N$ (174 μl, 1.25 mmol) in degassed DMF (7 ml) was treated with $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), degassed with Ar, treated with $PhCH_2C{\equiv}CH$ (93 μl, 0.75 mmol), heated to 80°, stirred for 2 h, cooled to r.t., diluted with $Et_2O$, washed with sat. $NH_4Cl$ soln. and $H_2O$, dried ($Na_2SO_4$), and evaporated. FC (hexane/AcOEt 3:2) gave **17** (98 mg, 58%). Pale brown oil. $R_f$ (hexane/AcOEt 2:3) 0.52. $[\alpha]_D^{25} = +28.7$ ($c = 0.88$, $CHCl_3$). UV ($CHCl_3$): 295 (3.3), 245 (4.2). IR ($CHCl_3$): 3067*w*, 3023*s*, 3015*s*, 2869*m*, 2123*w*, 1602*m*, 1496*m*, 1454*s*, 1361*m*, 1336*m*, 1095*s*, 1028*s*, 911*w*. $^1$H-NMR ($CDCl_3$, 300 MHz): see *Table 4*; additionally, 3.86 (br. *s*, Ph$CH_2$C≡C); 4.44 (*d*, *J* = 12.1, Ph$CH$); 4.48 (*d*, *J* = 12.3, Ph$CH$); 4.50 (*d*, *J* = 11.8, Ph$CH$); 4.64 (*d*, *J* = 11.3, Ph$CH$); 4.80 (*d*, *J* = 11.3, Ph$CH$); 4.81 (*d*, *J* = 12.3, Ph$CH$); 4.87 (*d*, *J* = 12.1, Ph$CH$); 5.19 (*d*, *J* = 11.5, Ph$CH$); 7.16–7.18 (*m*, 3 arom. H); 7.25–7.37 (*m*, 18 arom. H); 7.43–7.45 (*m*, 4 arom. H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 26.00 (*t*, Ph$CH_2$C≡C); 72.75, 73.28, 73.80, 73.98 (4*t*, 4 Ph$CH_2$); 126.46 (2*d*); 127.49 (2*d*); 127.80–128.44 (several *d*); 136.54, 137.02, 137.32, 137.53, 137.97 (5*s*). HR-MALDI-MS: 697.2989 (23, $[M+Na]^+$, $C_{45}H_{42}N_2NaO_4^+$; calc. 697.3042), 676.3246 (20), 675.3209 (39, $[M+H]^+$, $C_{45}H_{43}N_2O_4^+$; calc. 675.3223), 568.2649 (42), 567.2614 (100, $[M-BnO]^+$, $C_{38}H_{35}N_2O_3^+$; calc. 567.2648).

Table 2. *Selected $^1$H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Deprotected* C(2)-*Substituted* gluco-*Imidazoles* **8**–**14** *in $CD_3OD$*[a])

| Compound | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|
| H–C(3) | 7.59 | 7.38 | 7.16 | 7.43 | 7.37 | 7.12 | 6.99 |
| H–C(5) | 3.89–3.91 | 3.85–3.90 | 3.77–3.82 | 3.87–3.89 | 3.86–3.89 | 3.87–3.89 | 3.80–3.84 |
| H–C(6) | 3.82 | 3.81 | 3.78 | 3.81 | 3.81 | 3.81 | 3.78 |
| H–C(7) | 3.70 | 3.71 | 3.66 | 3.68 | 3.68 | 3.68 | 3.66 |
| H–C(8) | 4.49 | 4.52 | 4.47 | 4.49 | 4.49 | 4.52 | 4.46 |
| CH–C(5) | 3.96 | 3.95 | 3.91 | 3.94 | 3.93 | 3.94 | 3.92 |
| CH′–C(5) | 4.18 | 4.19 | 4.13 | 4.17 | 4.17 | 4.17 | 4.15 |
| *J*(5,6) | 8.7 | 8.4 | 8.4 | 8.6 | 8.7 | 8.4 | 8.1 |
| *J*(6,7) | 8.7 | 8.4 | 8.1 | 8.9 | 8.7 | 8.7 | 8.4 |
| *J*(7,8) | 8.1 | 7.8 | 7.8 | 8.0 | 7.8 | 7.5 | 7.8 |
| *J*(5,CH) | 4.0 | 3.4 | 3.9 | 4.3 | 4.3 | 3.9 | 3.9 |
| *J*(5,CH′) | 2.0 | 1.5 | 2.1 | [b]) | 1.9 | 1.5 | 2.1 |
| *J*(CH,CH′) | 10.8 | 11.8 | 12.0 | 11.0 | 11.5 | 11.5 | 12.0 |

[a]) Assignment based on homodecoupling experiments. [b]) Not assigned.

Table 3. *Selected $^{13}$C-NMR Chemical Shifts* [ppm] *of the* C(2)-*Substituted* gluco-*Imidazoles* **8**–**14**, **16**, **17**, **19**, **20**, **22**, **25**, *and* **26**

| Compd. | Solvent | C(3) | C(5) | $CH_2$–C(5) | C(6) | C(7) | C(8) | C(8a) |
|---|---|---|---|---|---|---|---|---|
| **16** | $CDCl_3$ | 122.13 | 58.42 | 68.49 | 74.16 | 81.72 | 73.84 | 144.47 |
| **17** | $CDCl_3$ | 121.12 | 58.34 | 68.28 | 75.78 | 81.27 | 73.99 | 143.53 |
| **19** | $CDCl_3$ | 115.95 | 58.07 | 68.47 | 76.30 | 82.03 | 74.24 | 144.73 |
| **20**[a]) | $C_6D_6$ | 113.52/116.17 | 58.03/58.11 | 68.46 | 76.27 | 82.50 | 76.17 | 143.79/144.41 |
| **22**[b]) | $CDCl_3$ | 114.42 | 58.07 | 68.23 | 75.93 | 81.85 | 74.29 | 143.56 |
| **25**[b]) | $CDCl_3$ | 117.05 | 58.27 | 68.42 | 75.86 | 81.62 | 73.98 | 144.11 |
| **26**[b]) | $CDCl_3$ | 116.27 | 58.12 | 68.25 | 75.92 | 81.85 | 73.96 | 143.71 |
| **8** | $CD_3OD$ | 122.45 | 62.79 | 61.02 | 69.37 | 76.06 | 68.79 | 148.02 |
| **9** | $CD_3OD$ | 116.50 | 62.53 | 61.08 | 69.47 | 76.23 | 68.87 | 147.96 |
| **10** | $CD_3OD$ | 115.38 | 62.44 | 61.09 | 69.48 | 76.21 | 69.05 | 147.09 |
| **11** | $CD_3OD$ | 117.88 | 62.59 | 61.15 | 69.46 | 76.25 | 68.90 | 147.21 |
| **12** | $CD_3OD$ | 116.57 | 61.70 | 60.28 | 68.63 | 75.44 | 68.09 | 146.88 |
| **13** | $CD_3OD$ | 114.16 | 61.97 | 59.98 | 68.16 | 75.15 | 67.96 | 145.69 |
| **14** | $CD_3OD$ | 113.67 | 61.60 | 60.17 | 68.50 | 75.44 | 68.07 | 145.79 |

[a]) (*Z*)/(*E*) 55 : 45. [b]) Assignment based on a HSQC spectrum.

Table 4. *Selected $^1$H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Protected* C(2)-*Substituted* gluco-*Imidazoles* **16**, **17**, **19**, **20**, **22**, **25**, and **26**

| Compound | **16**[a]) | **17** | **19**[a]) | **20**[b]) | **22**[c]) | **25**[c]) | **26**[c]) |
|---|---|---|---|---|---|---|---|
| H–C(3) | [d]) | 7.19 | 7.06 | 6.82/6.94 | 6.93 | 7.15 | 7.11 |
| H–C(5) | 4.23 | 4.15–4.20 | 4.19 | 3.89–3.92 | 4.12–4.16 | 4.19 | 4.15–4.20 |
| H–C(6) | 3.88 | 3.80–3.84 | 3.86 | 3.66/3.67 | 3.88 | 3.85 | 3.86 |
| H–C(7) | 4.14 | 4.10 | 4.11 | 4.02/4.03 | 4.09 | 4.11 | 4.11 |
| H–C(8) | 4.76 | 4.74 | 4.78 | 4.77 | 4.74 | 4.75 | 4.76 |
| CH–C(5) | 3.76 | 3.72 | 3.75 | 3.40/3.41 | 3.72 | 3.74 | 3.74 |
| CH′–C(5) | 3.87 | 3.82 | 3.86 | 3.49 | 3.82 | 3.85 | 3.85 |
| *J*(5,6) | 6.9 | [e]) | 7.8 | [e]) | 7.6 | 7.2 | 7.8 |
| *J*(6,7) | 6.9 | 7.1 | 7.2 | 8.1 | 7.5 | 7.2 | 7.5 |
| *J*(7,8) | 5.0 | 5.2 | 5.3 | 5.9 | 5.6 | 5.3 | 5.3 |
| *J*(5,CH) | 5.3 | 5.2 | 5.6 | 5.1 | 5.3 | 5.3 | 5.3 |
| *J*(5,CH′) | 2.8 | [e]) | 2.2 | 2.8 | 2.8 | 3.4 | 3.1 |
| *J*(CH,CH′) | 10.3 | 10.5 | 10.6 | 10.3 | 10.3 | 10.9 | 11.5 |

[a]) Data taken from [15]. [b]) (*Z*)/(*E*) 55 : 45 and in solvent $C_6D_6$. [c]) Assignment based on a HSQC spectrum. [d]) Hidden by aromatic signals. [e]) Not assigned.

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-(3-phenylpropyl)imidazo[1,2-*a*]pyridine-6,7,8-triol* (**14**). A soln. of **17** (41 mg, 0.061 mmol) in AcOH (3 ml) was treated with 10% Pd/C (40 mg), hydrogenated for 72 h under 6 bar of $H_2$, diluted with MeOH, and filtered over *Celite*. Evaporation, co-evaporation with toluene, and FC (AcOEt/MeOH/$H_2O$ 10 : 0 : 0 → 10 : 1 : 0 → 10 : 3 : 1) gave **14** (10 mg, 53%). White solid. A sample for microanalysis was dried for 4 d at $10^{-4}$ Torr. $R_f$ (AcOEt/MeOH/$H_2O$ 10 : 1 : 1) 0.22. $[\alpha]_{25}^{+} = -28.4$ ($c = 0.53$, MeOH). UV (MeOH): 209 (4.0). IR (KBr): 3500–3180*s* (br.), 2922*s*, 2851*m*, 1631*w*, 1495*w*, 1452*m*, 1179*w*, 1104*m*, 1018*m*, 870*w*, 747*w*, 699*m*. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 1.12–1.28 (1 H), 1.61–1.71 (1 H), 1.88–1.98 (1 H), 2.48–2.67 (3 H) (4*m*, Ph$CH_2CH_2CH_2$); 3.66 (*t*, $J \approx 8.4$, irrad. 4.15 → *d*, $J \approx 8.1$, H–C(7)); 4.46 (*d*, $J = 7.8$, irrad. 3.66 → *s*, H–C(8)); 7.12–7.26 (*m*, 5 arom. H). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 31.12, 33.36, 35.26 (3*t*, Ph$CH_2CH_2CH_2$); 125.55 (*d*); 128.11 (2*d*); 128.30 (2*d*); 141.59, 142.35 (2*s*, C(2), C(1) of Ph). HR-MALDI-MS: 341.1474 (27, $[M+Na]^+$, $C_{17}H_{22}N_2NaO_4^+$; calc. 341.1477), 325.2114 (55), 320.1690 (25), 319.1649 (100, $[M+H]^+$, $C_{17}H_{23}N_2O_4^+$; calc. 319.1658), 301.1546 (15,

$[M-OH]^+$, $C_{17}H_{21}N_2O_3^+$; calc. 301.1552). Anal. calc. for $C_{17}H_{22}N_2O_4 \cdot H_2O$ (327.37): C 60.88, H 6.91, N 8.35; found: C 60.66, H 6.66, N 8.35.

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-[(*E*)-2-phenylethenyl]imidazo[1,2-*a*]pyridine-6,7,8-triol* (**9**). A soln. of **19** (29 mg, 43.6 μmol) in $CH_2Cl_2$ (1 ml) was treated with $AlCl_3$ (93 mg, 0.69 mmol) and *N*,*N*-dimethylaniline (66 μl, 0.52 mmol), stirred at 23° for 12 h, diluted with AcOEt, and extracted with $H_2O$. Evaporation of the aq. layer and FC (AcOEt/MeOH/$H_2O$ 1:0:0 → 20:1:1 → 15:1:1) gave **9** (10 mg, 75%). White hygroscopic solid. A sample for microanalysis was dried for 4 d at $10^{-4}$ Torr. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.25. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 3.71 (br. *t*, $J \approx 8.4$, H–C(7)); 7.00 (*d*, $J = 17.1$, CH=C*H*); 7.14–7.21 (*m*, H–C(4) of Ph, CH=C*H*); 7.30 (*dd*, $J = 7.8, 7.1$, H–C(3) and H–C(5) of Ph); 7.45–7.48 (*m*, H–C(2) and H–C(6) of Ph). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 120.65 (*d*, PhCH=*C*H); 126.69 (*d*, C(3) and C(5) of Ph); 127.68, 127.72 (2*d*, Ph*C*H=CH, C(4) of Ph); 129.13 (*d*, C(2) and C(6) of Ph); 138.58 (*s*, C(1) of Ph); 141.10 (*s*, C(2)). HR-MALDI-MS: 303.1336 (100, $[M+H]^+$, $C_{16}H_{19}N_2O_4^+$; calc. 303.1345), 285.1230 (24, $[M-OH]^+$, $C_{16}H_{17}N_2O_3^+$; calc. 285.1239). Anal. calc. for $C_{16}H_{18}N_2O_4 \cdot 0.5$ MeOH (318.34): C 62.25, H 6.33, N 8.80; found: C 62.18, H 6.31, N 8.84.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-[(*E*/*Z*)-2-prop-1-enyl]imidazo[1,2-*a*]pyridine* (**20**). A suspension of $EtPPh_3Br$ (137 mg, 0.36 mmol) in $Et_2O$ (5 ml) was cooled to −40°, treated slowly with 1.5M BuLi in hexane (195 μl, 0.29 mmol), stirred for 10 min, warmed to r.t, stirred for 15 min, cooled to −78°, treated with a soln. of **18** (144 mg, 0.25 mmol) in THF (5 ml), warmed to r.t. within 20 min, cooled to −78°, and treated with sat. $NH_4Cl$ soln. Normal workup gave (*Z*)/(*E*)-**20** 55:45 (129 mg, 88%). $R_f$ (hexane/AcOEt 3:2) 0.60. IR ($CHCl_3$): 3089*m*, 3066*s*, 3011*s*, 2918*m*, 2869*m*, 1951*w*, 1603*s*, 1504*s*, 1454*s*, 1430*m*, 1311*m*, 1179*m*, 1070*s*, 1028*m*, 911*m*. $^1$H-NMR ($C_6D_6$, 300 MHz; (*Z*)/(*E*) 55:45): 1.81 (*dd*, $J = 1.5, 6.7$, 1.35 H), 2.23 (*dd*, $J = 1.7, 7.0$, 1.65 H) (Me); 3.40 (*dd*, $J = 5.3, 10.0$, 0.45 H), 3.41 (*dd*, $J = 5.1, 10.2$, 0.55 H) (CH–C(5)); 3.49 (*dd*, $J = 2.8, 10.3$, CH′–C(5)); 3.66 (*t*, $J = 8.1$, 0.45 H), 3.67 (*t*, $J = 8.1$, 0.55 H) (H–C(6)); 3.85–3.92 (*m*, H–C(5)); 4.02, 4.03 (2*dd*, $J = 5.9, 8.1$, H–C(7)); 4.07, 4.12 (2*d*, $J = 11.5$, PhC*H*); 4.33, 4.35 (2*d*, $J = 11.5$, PhC*H*); 4.58 (*d*, $J = 11.5$, PhC*H*); 4.77 (*d*, $J = 5.9$, H–C(8)); 4.78, 4.80 (2*d*, $J = 11.2$, 2 PhC*H*); 5.12 (*d*, $J = 11.8$, PhC*H*); 5.48 (*d*, $J = 11.7$, 0.45 H), 5.51 (*d*, $J = 11.7$, 0.55 H) (PhC*H*); 5.75 (*qd*, $J = 7.8$, 11.5, 0.55 H), 6.77 (*qd*, $J = 7.8$, 15.5, 0.45 H) (CH=C*H*Me); 6.50 (*qd*, $J = 1.5$, 15.5, 0.45 H), 6.70 (*qd*, $J = 1.5$, 11.5, 0.55 H) (C*H*=CHMe); 6.82 (*s*, 0.45 H), 6.94 (*s*, 0.55 H) (H–C(3)); 7.06–7.26 (*m*, 16 arom. H); 7.24 (*d*, $J = 8.1$, 2 arom. H); 7.53 (*d*, $J = 7.8$, 2 arom. H). $^{13}$C-NMR ($C_6D_6$, 75 MHz; (*Z*)/(*E*) 55:45): 15.41, 18.31 (2*q*, Me); 58.03, 58.11 (2*d*, C(5)); 68.46 (*t*, *C*$H_2$–C(5)); 72.56, 73.00, 74.01, 74.05 (4*t*, 4 Ph*C*$H_2$); 76.17 (*d*, C(8)); 76.27 (*d*, C(6)); 82.50 (*d*, C(7)); 113.52, 116.17 (2*d*, C(3)); 123.43, 123.85, 124.05, 124.10 (4*d*, CH=CH); 127.58–128.77 (several *d*); 137.83, 137.88, 138.49, 138.71, 139.01 (5*s*); 141.08, 141.56 (2*s*); 143.79, 144.41 (2*s*, C(8a)). HR-MALDI-MS: 623.2881 (9, $[M+Na]^+$, $C_{39}H_{40}N_2NaO_4^+$; calc. 623.2886), 601.3058 (100, $[M+H]^+$, $C_{39}H_{41}N_2O_4^+$; calc. 601.3066), 509.2427 (10, $[M-Bn]^+$, $C_{32}H_{33}N_2O_4^+$; calc. 509.2440), 493.2483 (99, $[M-BnO]^+$, $C_{32}H_{33}N_2O_3^+$; calc. 493.2491), 387.2059 (11, $[M-2\ BnO+H]^+$, $C_{25}H_{27}N_2O_2^+$; calc. 387.2073).

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-propylimidazo[1,2-*a*]pyridine-6,7,8-triol* (**13**). A soln. of **20** (60 mg, 0.1 mmol) in AcOH (5 ml) was treated with 10% Pd/C (60 mg) and hydrogenated at 6 bar for 68 h, diluted with MeOH, and filtered over *Celite*. Evaporation of the filtrate, co-evaporation with toluene, and FC (AcOEt/MeOH/$H_2O$ 10:0:0 → 10:1:0 → 10:2:1) gave **13** (20 mg, 82%). White hygroscopic solid. A sample for microanalysis was dried for 4 d at $10^{-4}$ Torr. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.20. $[\alpha]_D^{25} = -30.8$ ($c = 0.35$, MeOH). UV (MeOH): 224 (3.7). IR (ATR): 3500–3100*s* (br.), 2959*s*, 2926*s*, 2851*s*, 1505*m*, 1455*s*, 1318*s*, 1254*m*, 1198*m*, 1115*s*, 1026*s*, 867*m*. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 0.96 (*t*, $J = 7.5$, Me); 1.65 (*sext.*, $J = 7.5$, MeC$H_2$CH$_2$); 2.53 (*t*, $J = 7.5$, MeCH$_2$C$H_2$); 4.52 (*d*, $J = 8.0$, irrad. at 3.68 → *s*, H–C(8)). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 12.89 (*q*, Me); 22.30 (*t*, Me*C*H$_2$CH$_2$); 28.96 (*t*, MeCH$_2$*C*H$_2$); 140.38 (*s*, C(2)). HR-MALDI-MS: 265.1156 (5, $[M+Na]^+$, $C_{11}H_{18}N_2NaO_4^+$; calc. 265.1164), 243.1336 (100, $[M+H]^+$, $C_{11}H_{19}N_2O_4^+$; calc. 243.1345). Anal. calc. for $C_{11}H_{18}N_2O_4 \cdot 1/3\ H_2O$ (248.27): C 53.21, H 7.58, N 11.28; found: C 53.12, H 7.28, N 11.28.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-[(phenylimino)methyl]-imidazo[1,2-*a*]pyridine* (**21**). A suspension of **18** (84 mg, 0.142 mmol) and 4-Å activated mol. sieves in $CH_2Cl_2$ (2 ml) was treated with freshly distilled aniline (16 μl, 0.17 mmol), stirred at 23° for 5 h, and filtered. The filtrate was diluted with $Et_2O$, washed with sat. $NaHCO_3$ soln. and brine, dried ($Na_2SO_4$), and evaporated. The $^1$H-NMR spectrum of the residue (105 mg) evidenced **21**. $^1$H-NMR ($CDCl_3$, 300 MHz): 3.81 (*dd*, $J = 5.0, 10.6$, CH–C(5)); 3.88–3.93 (*m*, CH′–C(5), H–C(6)); 4.16 (*dd*, $J = 5.0, 6.8$, H–C(7)); 4.25–4.30 (*m*, H–C(5)); 4.48 (*d*, $J = 12.0$, PhC*H*); 4.50 (*s*, Ph$CH_2$); 4.67 (*d*, $J = 11.0$, PhC*H*); 4.81 (*d*, $J = 10.5$, PhC*H*); 4.82 (*d*, $J = 4.8$, H–C(8)); 4.83, 4.87 (*d*, $J = 11.7$, 2 PhC*H*); 5.15 (*d*, $J = 11.2$, PhC*H*); 7.14–7.45 (*m*, 25 arom. H); 7.72 (*s*, H–C(3)); 8.48 (*s*, C*H*=NPh).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-[(phenylamino)methyl]-imidazo[1,2-*a*]pyridine* (**22**). A soln. of crude **21** (105 mg) in EtOH (10 ml) was treated with $NaBH_4$ (18 mg, 0.5 mmol), stirred at 23° for 3 h, and evaporated. The residue was treated with sat. $NH_4Cl$ soln. and extracted with $Et_2O$. The org. layer was dried ($Na_2SO_4$) and evaporated. FC (hexane/AcOEt 1:1) gave **22** (80 mg, 84% from **18**). White solid. M.p. 94°. $R_f$ (hexane/AcOEt 2:3) 0.40. $[\alpha]_D^{25} = +45.9$ ($c = 0.96$, $CHCl_3$). UV ($CHCl_3$): 295 (3.3), 245 (4.2). IR ($CHCl_3$): 3319*m*, 3059*m*, 3030*s*, 2870*s*, 1954*w*, 1819*w*, 1602*s*, 1508*s*, 1497*m*, 1454*m*, 1435*m*, 1309*s*, 1256*m*, 1069*s*, 989*m*. $^1$H-NMR ($CDCl_3$, 300 MHz; assignment based on a HSQC spectrum): see *Table 4*; additionally, 4.21 (br. *s*, NH); 4.28 (*s*, $CH_2$–C(2)); 4.41 (*d*, *J* = 12.1, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 11.2, PhC*H*); 4.70 (*d*, *J* = 11.2, PhC*H*); 4.81 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 11.2, PhC*H*); 4.84 (*d*, *J* = 11.2, PhC*H*); 5.16 (*d*, *J* = 11.5, PhC*H*); 6.70–6.75 (*m*, 3 arom. H); 7.17–7.34 (*m*, 20 arom. H); 7.43 (*dd*, *J* = 1.5, 7.6, 2 arom. H). $^{13}$C-NMR ($CDCl_3$, 75 MHz; assignment based on a HSQC spectrum): see *Table 3*; additionally, 42.52 (*t*, $CH_2$–C(2)); 72.69, 73.25, 74.01, 74.18 (4*t*, 4 Ph*C*$H_2$); 113.05 (2*d*); 117.31 (*d*); 127.48–129.03 (several *d*); 137.17, 137.48, 137.71, 138.11 (4*s*); 140.18 (*s*, C(2)); 148.23 (*s*, C(1) of NHPh). HR-MALDI-MS: 688.3123 (26, $[M+Na]^+$, $C_{43}H_{43}N_3NaO_4^+$; calc. 688.3151), 666.3319 (29, $[M+H]^+$, $C_{43}H_{44}N_3O_4^+$; calc. 666.3332), 574.2773 (39), 573.2733 (100, $[M-PhNH]^+$, $C_{37}H_{37}N_2O_4^+$; calc. 573.2753). Anal. calc. for $C_{43}H_{43}N_3O_4$ (665.83): C 77.57, H 6.51, N 6.31; found: C 77.53, H 6.73, N 6.24.

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-[(phenylamino)methyl]imidazo[1,2-*a*]pyridine-6,7,8-triol* (**10**). A soln. of **22** (38 mg, 57.1 μmol) in $CH_2Cl_2$ (3 ml) was cooled to −78°, treated with 1M $BCl_3$ in $CH_2Cl_2$ (0.68 ml, 0.685 mmol), stirred until the mixture had reached a temp. of 10°, cooled to −78°, diluted with $H_2O$, and washed with AcOEt. The aq. layer was evaporated. The residue was dissolved in $H_2O$ and applied to ion-exchange chromatography (*Amberlite CG-120*, $H^+$ form, elution with 0.1M $NH_3$). Evaporation, lyophilisation, and drying gave **10** (15 mg, 86%). Hygroscopic white solid. A sample for microanalysis was dried for 4 d at $10^{-4}$ Torr. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1 0.12. $[\alpha]_D^{25} = -25.7$ ($c = 0.44$, MeOH). UV (MeOH): 293 (3.2), 245 (4.1), 205 (4.3). IR (ATR): 3300–3200*s* (br.), 3026*m*, 2882*m*, 1600*s*, 1496*s*, 1318*m*, 1256*m*, 1177*m*, 1087*s*, 1025*s*, 907*m*. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 4.19 (*s*, *C*$H_2$–C(2)); 4.47 (*d*, *J* = 7.8, irrad. at 3.66 → *s*, H–C(8)); 6.60 (*tt*, *J* = 7.3, 0.9, H–C(4) of Ph); 6.67 (*dt*, *J* = 7.5, 0.9, H–C(2) and H–C(6) of Ph); 7.05–7.11 (*m*, H–C(3) and H–C(5) of Ph). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 42.45 (*t*, *C*$H_2$–C(2)); 113.90 (2*d*); 117.84 (*d*); 129.48 (2*d*); 141.03 (*s*, C(2)); 149.41 (*s*, C(1) of Ph). HR-MALDI-MS: 328.1273 (33, $[M+Na]^+$, $C_{15}H_{19}N_3NaO_4^+$; calc. 328.1273), 306.1450 (100, $[M+H]^+$, $C_{15}H_{20}N_3O_4^+$; calc. 306.1454), 213.0871 (43, $[M-PhNH]^+$, $C_9H_{13}N_2O_4^+$; calc. 213.0875). Anal. calc. for $C_{15}H_{19}N_3O_4 \cdot 1/2\ H_2O$ (314.33): C 57.31, H 6.31, N 13.37; found: C 57.01, H 6.06, N 13.19.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2-(chloromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**24**). A soln. of **23** [15] (170 mg, 0.288 mmol) in $CH_2Cl_2$ (7 ml) was treated with $SOCl_2$ (42 μl, 0.58 mmol), stirred at 22° for 25 min, treated with sat. $NaHCO_3$ soln., and extracted with $Et_2O$. The organic layer was washed with sat. $NaHCO_3$ soln. and brine, dried ($Na_2SO_4$), and evaporated affording crude **24** (161 mg, sufficiently pure for the next reaction). FC (hexane/AcOEt 1:1) gave pure **24** (136 mg, 77%). White solid. $R_f$ (hexane/AcOEt 3:2) 0.52. M.p. 80.9°. $[\alpha]_D^{25} = +50.4$ ($c = 0.94$, $CHCl_3$). UV ($CHCl_3$): 240 (3.6). IR ($CHCl_3$): 3067*w*, 3032*m*, 3020*s*, 3013*s*, 2869*m*, 1497*m*, 1454*s*, 1362*m*, 1259*m*, 1216*m*, 1094*s*, 1028*m*. $^1$H-NMR ($CDCl_3$, 300 MHz): 3.76 (*dd*, *J* = 5.3, 10.4, CH–C(5)); 3.86 (*dd*, *J* = 3.1, 10.1, CH′–C(5)); 3.88 (*t*, *J* = 7.5, H–C(6)); 4.14 (*dd*, *J* = 5.6, 7.3, H–C(7)); 4.18–4.21 (*m*, H–C(5)); 4.47 (*d*, *J* = 12.1, PhC*H*); 4.53 (*d*, *J* = 12.1, PhC*H*); 4.63 (*d*, *J* = 12.1, PhC*H*); 4.65 (*s*, $CH_2$–C(2)); 4.71 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 5.4, H–C(8)); 4.84 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 11.5, PhC*H*); 4.88 (*d*, *J* = 11.2, PhC*H*); 5.20 (*d*, *J* = 11.5, PhC*H*); 7.09 (*s*, H–C(3)); 7.22–7.24 (*m*, 2 arom. H); 7.30–7.37 (*m*, 16 arom. H); 7.39–7.47 (*m*, 2 arom. H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 40.36 (*t*, *C*$H_2$–C(2)); 58.35 (*d*, C(5)); 68.45 (*t*, $CH_2$–C(5)); 72.81, 73.46, 74.10 (3*t*, 3 Ph*C*$H_2$); 74.18 (*d*, C(8)); 74.30 (*t*, Ph*C*$H_2$); 76.09 (*d*, C(6)); 81.85 (*d*, C(7)); 116.78 (*d*, C(3)); 127.82–128.79 (several *d*); 137.57, 137.75, 137.97, 138.39, 138.84 (5*s*); 144.33 (*s*, C(8a)). HR-MALDI-MS: 631.2337 (31, $[M+Na]^+$, $C_{37}H_{37}ClN_2NaO_4^+$; calc. 631.2340), 609.2509 (90, $[M+H]^+$, $C_{37}H_{38}ClN_2O_4^+$; calc. 609.2520), 575.2901 (36, $[M-Cl+2\ H]^+$, $C_{37}H_{39}N_2O_4^+$; calc. 575.2910), 501.1942 (100, $[M-BnO]^+$, $C_{30}H_{30}ClN_2O_3^+$; calc. 501.1945). Anal. calc. for $C_{37}H_{37}ClN_2O_4$ (609.16): C 72.95, H 6.12, N 4.60; found: C 73.07, H 6.32, N 4.62.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-[(3-nitrophenoxy)methyl]-imidazo[1,2-*a*]pyridine* (**25**). A suspension of **23** (190 mg, 0.32 mmol) and NaH (60% washed with dry hexane, 23 mg, 0.96 mmol) in degassed DMF (3 ml) was treated with 1-fluoro-3-nitrobenzene (68 μl, 0.64 mmol), stirred for 5 h at 65°, cooled to r.t., diluted with $Et_2O$ (50 ml), and washed with sat. $NH_4Cl$ soln. The combined org. layers were washed with brine, dried ($Na_2SO_4$), filtered, and evaporated. FC (hexane/AcOEt 1:0 → 3:1 → 2:1 → 1:1) gave **25** (130 mg, 57%) and **23** (27 mg, 14%).

*Data of* **25**: Pale yellow solid. $R_f$ (hexane/AcOEt 2:3) 0.71. M.p. 98.5°. $[\alpha]_D^{25} = +39.4$ ($c = 1.04$, $CHCl_3$). UV ($CHCl_3$): 329 (3.3), 269 (3.8), 240 (3.9). IR ($CHCl_3$): 3019*s*, 2976*w*, 2895*w*, 1884*m*, 1728*w*, 1618*w*, 1580*w*, 1529*s*, 1477*m*, 1423*m*, 1391*m*, 1351*m*, 1335*m*, 1046*s*, 928*s*, 877*m*, 849*m*. $^1$H-NMR ($CDCl_3$, 300 MHz; assignment based on a HSQC spectrum): see *Table 4*; additionally, 4.43 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 11.2, PhC*H*); 4.68 (*d*, *J* = 11.5, PhC*H*); 4.82 (*d*, *J* = 11.5, PhC*H*); 4.83 (*d*, *J* = 11.2, PhC*H*); 4.86 (*d*, *J* = 11.8, PhC*H*); 5.08 (*d*, *J* = 11.7, CH–C(2)); 5.13 (*d*, *J* = 11.5, CH′–C(2)); 5.17 (*d*, *J* = 11.5, PhC*H*); 7.17–7.21 (*m*, 2 arom. H); 7.26–7.43 (*m*, 18 arom. H, H–C(6) of $PhNO_2$, H–C(5) of $PhNO_2$); 7.82 (*dt*, *J* = 7.8, 1.8, H–C(4) of $PhNO_2$); 7.95 (*t*, *J* = 2.1, H–C(2) of $PhNO_2$). $^{13}$C-NMR ($CDCl_3$, 75 MHz; assignment based on a HSQC spectrum): see *Table 3*; additionally, 65.14 (*t*, *C*$H_2$–C(2)); 72.69, 73.29 (2*t*, 2 Ph*C*$H_2$); 74.15 (*t*, 2 Ph*C*$H_2$); 109.48 (*d*, C(2) of $PhNO_2$); 115.69 (*d*, C(4) of $PhNO_2$); 121.95 (*d*, C(6) of $PhNO_2$); 127.54–128.46 (several *d*); 129.73 (*d*, C(5) of $PhNO_2$); 136.95, 137.11, 137.38, 137.63, 138.01 (5*s*); 149.02 (*s*, C(3) of $PhNO_2$); 159.21 (*s*, C(1) of $PhNO_2$). HR-MALDI-MS: 712.3008 (9, $[M+H]^+$, $C_{43}H_{42}N_3O_7^+$; calc. 712.3023), 605.2461 (40), 604.2432 (100, $[M-BnO]^+$, $C_{36}H_{34}N_3O_6^+$; calc. 604.2448), 573.2727 (5, $[M-C_6H_4NO_3]^+$, $C_{37}H_{37}N_2O_4^+$; calc. 573.2753), 465.2158 (20, $[M-C_6H_4NO_3-BnOH]^+$, $C_{30}H_{29}N_2O_3^+$; calc. 465.2178), 375.1695 (21, $C_{23}H_{23}N_2O_3^+$, $[M-C_6H_4NO_3-BnO-Bn]^+$; calc. 375.1709), 359.1745 (20, $[M-C_6H_4NO_3-2\,BnO]^+$, $C_{23}H_{23}N_2O_2^+$; calc. 359.1760). Anal. calc. for $C_{43}H_{41}N_3O_7$ (711.81): C 72.56, H 5.81, N 5.90; found: C 72.61, H 5.54, N 6.04.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-2-(phenoxymethyl)imidazo-[1,2-*a*]pyridine* (**26**). A soln. of **24** (49 mg, 0.081 mmol) in DMF (2 ml) was treated with *t*-BuOK (13 mg, 0.12 mmol) and PhOH (11.0 mg, 0.12 mmol), stirred for 3.5 h at 80°, cooled to r.t., diluted with $H_2O$, and extracted with $Et_2O$. The org. layer was washed with 0.5M NaOH and brine, dried ($Na_2SO_4$), and evaporated. FC (hexane/AcOEt 1:1) yielded **26** (41 mg, 77%). Colourless oil. $R_f$ (hexane/AcOEt 3:2) 0.52. $[\alpha]_D^{25} = +37.2$ ($c = 0.865$, $CHCl_3$). UV ($CHCl_3$): 271 (3.3), 240 (3.5). $^1$H-NMR ($CDCl_3$, 300 MHz, assignment based on a HSQC spectrum): see *Table 4*; additionally, 4.43 (*d*, *J* = 12.1, PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.82 (*d*, *J* = 11.8, PhC*H*); 4.84 (*d*, *J* = 12.1, PhC*H*); 4.86 (*d*, *J* = 11.8, PhC*H*); 5.04 (*d*, *J* = 11.8, CH–C(2)); 5.09 (*d*, *J* = 11.8, CH′–C(2)); 5.19 (*d*, *J* = 11.8, PhC*H*); 6.96 (*tt*, *J* = 7.2, 0.9, H–C(4) of PhO); 7.05 (*dt*, *J* = 1.2, 8.9, H–C(3) and H–C(5) of PhO); 7.17–7.24 (*m*, 2 arom. H); 7.25–7.36 (*m*, 18 arom. H); 7.43 (*dd*, *J* = 1.5, 7.8, H–C(2) and H–C(6) of PhO). $^{13}$C-NMR ($CDCl_3$, 75 MHz, assignment based on a HSQC spectrum): see *Table 3*; additionally, 64.63 (*t*, *C*$H_2$–C(2)); 72.61, 73.24, 73.94, 74.15 (4*t*, 4 Ph*C*$H_2$); 114.79 (*d*, C(2) and C(6) of PhO); 120.59 (*d*, C(4) of PhO); 127.73–129.23 (several *d*); 137.11, 137.43, 137.67, 138.09, 138.20 (5*s*); 158.69 (*s*, C(1) of PhO). HR-MALDI-MS: 689.2943 (34, $[M+Na]^+$, $C_{43}H_{42}N_2NaO_5^+$; calc. 689.2991), 667.3159 (100, $[M+H]^+$, $C_{43}H_{43}N_2O_5^+$; calc. 667.3172), 573.2732 (18, $[M-PhO]^+$, $C_{37}H_{37}N_2O_4^+$; calc. 573.2753), 559.2589 (27, $[M-BnO]^+$, $C_{36}H_{35}N_2O_4^+$; calc. 559.2597), 375.1701 (24). Anal. calc. for $C_{43}H_{42}N_2O_5$ (666.82): C 77.45, H 6.35, N 4.20; found: C 77.51, H 6.46, N 4.07.

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-[(3-nitrophenoxy)methyl]imidazo[1,2-*a*]pyridine-6,7,8-triol* (**11**). A soln. of **25** (21.8 mg, 28.1 μmol) in $CH_2Cl_2$ (1.5 ml) was treated with $AlCl_3$ (49 mg, 0.33 mmol) and anisole (53 μl, 0.49 mmol), stirred for 10 h at 23°, and treated with $H_2O$ (20 ml) and AcOEt (15 ml). After separation of the layers, the org. layer was extracted with $H_2O$. The combined aq. layers were evaporated. FC (AcOEt/MeOH/$H_2O$ 1:0:0 → 20:1:1 → 15:1:1) yielded **11** (6.3 mg, 58%). White solid. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.25. $[\alpha]_D^{25} = -23.7$ ($c = 0.435$, MeOH). UV (MeOH): 325 (3.2), 268 (3.7), 213 (4.3). IR (KBr): 3675–2800*s* (br.), 2925*m*, 2853*m*, 1618*m*, 1580*m*, 1528*s*, 1481*m*, 1460*m*, 1350*s*, 1285*m*, 1250*m*, 1177*m*, 1103*m*, 1025*m*, 1008*m*, 871*m*, 829*m*, 801*m*, 738*s*. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally, 4.49 (*d*, *J* = 8.1, irrad. at 3.68 → *s*, H–C(8)); 5.08 (br. *s*, $CH_2$–C(2)); 7.37–7.41 (*m*, H–C(6) of $PhNO_2$); 7.47–7.53 (*m*, H–C(5) of $PhNO_2$); 7.81 (*m*, H–C(2) and H–C(4) of $PhNO_2$). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 65.08 (*t*, *C*$H_2$–C(2)); 109.97 (*d*, C(2) of $PhNO_2$); 116.13 (*d*, C(4) of $PhNO_2$); 122.24 (*d*, C(6) of $PhNO_2$); 130.87 (*d*, C(5) of $PhNO_2$); 136.87 (*s*, C(2)); 149.42 (*s*, C(3) of $PhNO_2$); 159.55 (*s*, C(1) of $PhNO_2$). HR-MALDI-MS: 374.0956 (15, $[M+Na]^+$, $C_{15}H_{17}N_3NaO_7^+$; calc. 374.0964), 358.1011 (27, $[M+Na-O]^+$, $C_{15}H_{17}N_3NaO_6^+$; calc. 358.1015), 352.1139 (28, $[M+H]^+$, $C_{15}H_{18}N_3O_7^+$; calc. 352.1145), 336.1190 (35), 320.1240 (31), 213.0871 (100, $[M-C_6N_4NO_3]^+$, $C_9H_{13}N_2O_4^+$; calc. 213.0875), 195.0763 (39, $[M-C_6N_4NO_3-H_2O]^+$, $C_9H_{11}N_2O_3^+$; calc. 195.077). Anal. calc. for $C_{15}H_{17}N_3O_7$ (351.32): C 51.30, H 5.05, N 11.69; found: C 51.28, H 4.88, N 11.96.

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2-(phenoxymethyl)imidazo[1,2-*a*]pyridine-6,7,8-triol* (**12**). A soln. of **26** (40 mg, 60.1 μmol) in AcOEt/MeOH/$H_2O$ 3:1:1 (2 ml) was treated with 20% Pd/C (20 mg), hydrogenated at amb. pressure for 46 h, and filtered through *Celite* (washing with MeOH). Evaporation of the combined filtrates, FC (AcOEt/MeOH/$H_2O$ 1:0:0 → 20:1:1 → 15:1:1), and drying afforded **12** (11.5 mg, 63%). White hygroscopic solid. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.10. $[\alpha]_D^{25} = +29.2$ ($c = 0.605$, MeOH). UV (MeOH): 277 (3.1), 271 (3.2), 220 (4.1). IR (KBr): 3600–3000*s* (br.), 2926*m*, 1598*m*, 1586*m*, 1458*m*, 1383*w*, 1299*w*, 1240*s*, 1175*m*, 1103*m*, 1028*s*, 874*w*, 754*m*, 691*m*. $^1$H-NMR ($CD_3OD$, 300 MHz): see *Table 2*; additionally,

4.95 (*s*, $CH_2$−C(2)); 6.90 (*tt*, $J$ = 0.9, 7.3, H−C(4) of PhO); 6.94–6.97 (*m*, H−C(2) and H−C(6) of PhO); 7.21–7.27 (*m*, H−C(3) and H−C(5) of PhO). $^{13}$C-NMR ($CD_3OD$, 75 MHz): see *Table 3*; additionally, 63.51 (*t*, $CH_2$−C(2)); 114.56 (*d*, C(2) and C(6) of PhO); 120.65 (*d*, C(4) of PhO); 129.25 (*d*, C(3) and C(5) of PhO); 137.87 (*s*, C(2)); 158.96 (*s*, C(1) of PhO). HR-MALDI-MS: 329.1109 (35, $[M+Na]^+$, $C_{15}H_{18}N_2NaO_5^+$; calc. 329.1113), 307.1290 (88, $[M+H]^+$, $C_{15}H_{19}N_2O_5^+$; calc. 307.1294), 213.0870 (100, $[M-PhO]^+$, $C_9H_{13}N_2O_4^+$; calc. 213.0875). Anal. calc. for $C_{15}H_{18}N_2O_5 \cdot 0.5\ H_2O$ (315.32): C 57.14, H 6.07, N 8.88; found: C 56.90, H 6.43, N 8.73.

*Inhibition Studies.* See [23]. The $\beta$-glucosidase from *Caldocellum saccharolyticum* (EC 3.2.1.21, as lyophilised powder, *Sigma G-6906*), $\beta$-glucosidase from almonds (as lyophilised powder, *Fluka 49290*), $\alpha$-glucosidase from yeast (as lyophilised powder, *Fluka 63412*). 4-nitrophenyl $\beta$-D-glucopyranoside (*Fluka 73676*), and 4-nitrophenyl $\alpha$-D-glucopyranoside (*Fluka 73673*) were used without further purification. The inhibition studies were carried out for $\beta$-glucosidases from *C. saccharolyticum* and sweet almonds, and $\alpha$-glucosidase from brewer's yeast. The results of the inhibition studies are summarised in *Table 1*.

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*Received July 8, 2005*