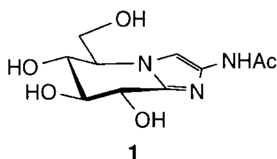
# Very Strong Inhibition of Glucosidases by *C(2)*-Substituted Tetrahydroimidazopyridines

by **Narendra Panday**, **Yves Canac**, and **Andrea Vasella***

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

The C(2)-substituted imidazoles **11**, **15**–**17**, **19**, **21**, **23/24**, **28**–**31**, **37**, and **38** have been prepared from the known 2,3-unsubstituted imidazole **7** *via* the iodoimidazole **10**, and tested as inhibitors of $\beta$- and $\alpha$-glucosidases. Introduction of hydrophobic and flexible substituents, such as in **28** and **29**, led to a very strong inhibition of $\beta$-glucosidases, with $K_i$ values for **29** of 1.2 and 0.11 nM against $\beta$-glucosidases from almonds and *Caldocellum saccharolyticum*, respectively. A slow onset of the inhibition was observed for the strongly inhibiting **16**, **28**–**31**, **37**, and **38**. While the introduction of a hydroxymethyl or a phenethyl substituent as in **17** and **30** led to stronger inhibition, the 1′-hydroxyphenethyl derivatives **37** and **38** were weaker inhibitors than **16** and **29**. This result is interpreted in the light of a conformational change of the substrate on the way to the transition state. The substituent at C(2) has only a moderate influence on the selectivity of the inhibition of two $\beta$- and one $\alpha$-glucosidases, increasing it by a maximal factor of *ca.* 10 (**16**), or decreasing it by a maximal factor of *ca.* 15 (**37**).

**Introduction.** – Tetrahydropyridoimidazoles are the strongest glycosidase inhibitors of the pyridoazole type [1–3], interacting most favourably with both the catalytic acid and the catalytic nucleophile at the active site [4]. Still stronger inhibitors may result from the introduction of aglycon mimicking substituents into the imidazole ring. A $pK_{HA}/K_i$ correlation of the 2- and 3-acetamido D-*gluco*- and D-*manno*-imidazopyridines **1**–**4** has shown that the acetamido group at C(3) interacts unfavourably with retaining $\beta$-glycosidases of family 1, while the acetamido group at C(2) does not noticeably influence the inhibition [5]. This result is in agreement with molecular modeling, which indicates that only substituents at C(2) project into the aglycon binding subsite of such $\beta$-glycosidases, while substituents at C(3) interact unfavourably with the active site. Hence, introducing substituents at C(2) may lead to stronger inhibitors.



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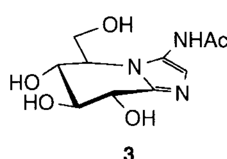

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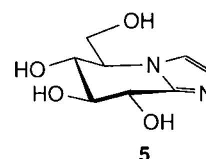

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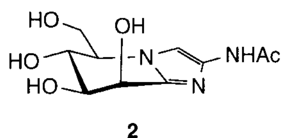

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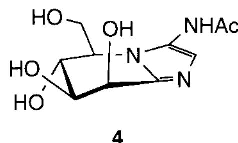

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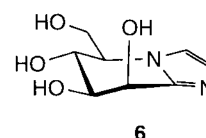

**6**

Aglycon-mimicking groups may be introduced by *N*-acylation of the 2-aminoimidazoles that were prepared as intermediates in the synthesis of **1** and **2** [5]. However, 2-acylamino substituents lower the basicity as evidenced by the $pK_{HA}$ values of **1**, **2**, **5**, and **6** [5]. Lowering the basicity impairs the interaction of the azole moiety with the catalytic acid and the catalytic nucleophile, with a negative effect on the inhibition. According to the *Hammett* $\sigma$ constant of the amino group, 2-(alkylamino)-imidazopyridines should be more strongly basic than **5** or **6**, but we had reasons to suspect that they would not be sufficiently stable [5]. We have, therefore, prepared and tested the imidazoles **11**, **15**–**17**, **19**, **21**, **23/24**, **28**–**31**, **37**, and **38** (*Scheme*) which possess a range of hydrophilic and hydrophobic substituents at C(2). They should be readily accessible from the known imidazole **7**.

**Synthesis.** – The tetrabenzylated 2,3-unsubstituted imidazole **7** [2] was transformed into the 2-iodoimidazole **10**[1]) by analogy with the procedure described by *Tatsuta et al.* for the preparation of a protected *galacto*-configured 2-bromoimidazole [6]. Treatment of **7** with 10 equiv. of NIS at 70° in DMF gave the 2,3-diiodoimidazole **8** in 83–92% yield. Milder conditions (5 equiv. of NIS, 60°) led mainly to the 3-iodoimidazole **9** (63%, besides 24% of **8**), in agreement with the known reactivity of imidazoles [6–8]. Regioselective deiodination of **8** at C(3) by sequential treatment with EtMgBr[2]) and $H_2O$ at −10° followed by crystallization gave the desired 2-iodoimidazole **10** (82–94%). The deprotected 2-iodoimidazole **11** was obtained in 63% yield by $BCl_3$-promoted debenzylation [9] of **10**.

The structure of the diiodoimidazole **8** was established by X-ray analysis (*Fig. 1*). This imidazole adopts a conformation between $^{6}H_{7}$[3]) and a sofa with C(7) below the ring plane, as conditioned by the 1,5-interaction between the I substituent at C(3) and the $BnOCH_2$ group at C(5)[4]). The position of the I substituent in **9** and **10** has been assigned on the basis of the upfield shift of the $^{13}$C-NMR signal of the iodinated C-atom and by comparison of the *J*(H,H) values of **9** and **10** to those of the diiodide **8** and the parent **7** [2] (*Table 1*). *J*(H,H) Values of **8** and **9** show that in solution both piperidines adopt a sofa conformation, similar to that found for **8** in the solid state. The coupling constants of the 2-iodoimidazole **10**, however, agree well with those of **7** ($^{7}H_{6}$/$^{6}H_{7}$ 2:1 [2]), confirming that **8** was de-iodinated at C(3).

To prepare the hydroxymethylated and the aminomethylated imidazoles **16** and **17**, we treated the organomagnesium derivative of **10** with either DMF or TsCN [10–15]. This yielded 85% of the 2-formylimidazole **12** and 89% of the imidazole-2-carbonitrile **13**, respectively. Reduction of the aldehyde **12** with $LiAlH_4$ provided 87% of the (hydroxymethyl)imidazole **14**. Its deprotection by hydrogenolysis was accompanied by deoxygenation of the $HOCH_2$ group, yielding 71% of the 2-methylimidazole **15** that

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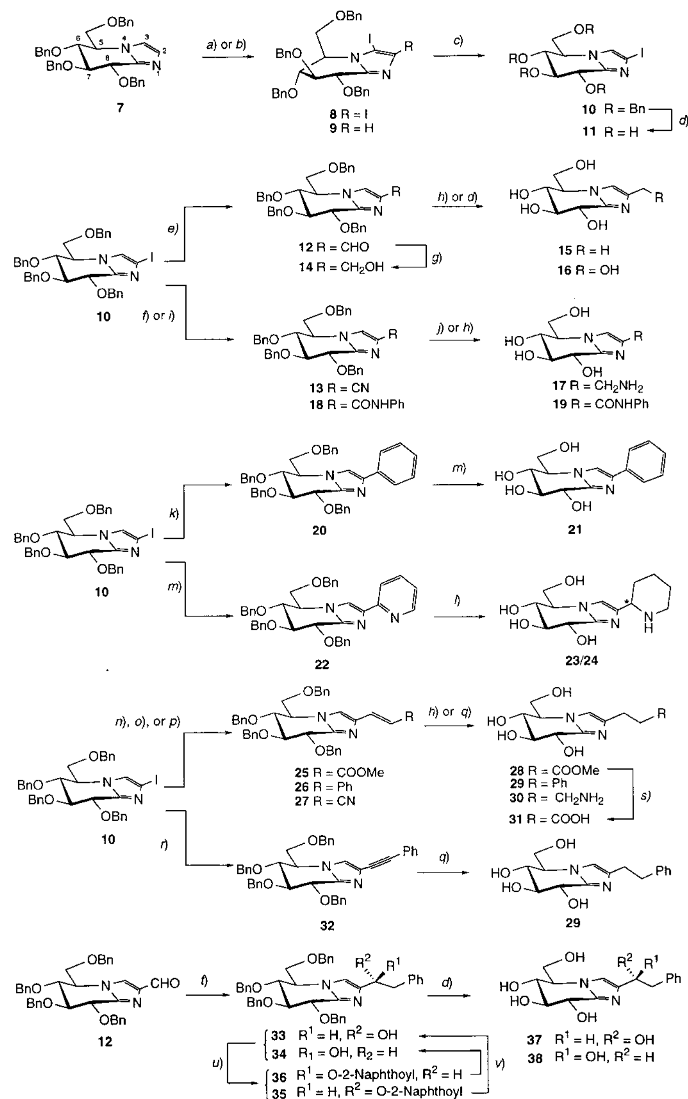
1) Exploratory metal/halogen exchange reactions and Pd-mediated coupling of the corresponding 2-bromoimidazole were much less satisfactory.

2) Similar results were obtained when **8** was treated with BuLi at −78°.

3) Since the direction of numbering of azolopyridines (*cf.* **7** in the *Scheme*) is opposite to that of pyranosides, the sides above and below the plane of the imidazopyridines, as defined by the clockwise and counterclockwise numbering, are interchanged with those defined according to carbohydrate numbering.

4) A similar 1,5 interaction has been noticed between the 3-acetamido group and the $BnOCH_2$ group at C(5) of the protected *gluco*- and *manno*-configured 3-acetamidoimidazoles [5].

*Scheme*




*a*) *N*-Iodosuccinimide (NIS), DMF, 80°; 83–92% of **8**. *b*) NIS, DMF, 60°; 63% of **9**, 24% of **8**. *c*) EtMgBr, THF of $CH_2Cl_2$, 0°; 82–94%. *d*) $BCl_3$, $CH_2Cl_2$, $-78° \to 0°$; 63% of **11**, 83% of **16** from **14**; 74% of **37**/**38** from **33**/**34**; 73% of **37** from **33**; 71% of **38** from **34**. *e*) 1. EtMgBr, 2. DMF 85%. *f*) 1. EtMgBr, 2. TsCN; 89%. *g*) $LiAlH_4$/THF, $-78°$; 87%. *h*) $H_2$, AcOEt/MeOH/AcOH, Pd/C; 63% of **15**, 85% of **19**, 82% of **28**. *i*) 1. EtMgBr, 2. PhNCO; 95%. *j*) AcOH/TFA 1:1, Pd/C, $H_2$; 79%. *k*) 1. EtMgBr, 2. $ZnBr_2$, 3. $[Pd(PPh_3)_4]$, PhI; 72%; *l*) MeOH, $H_2O$, AcOH 9:2:1, Pd/C (10%), $H_2$; 55% of **21**, 60% of **23**/**24**. *m*) 1. EtMgBr, 2. $ZnBr_2$, 3. $[Pd(PPh_3]_4]$, 2-Bromopyridine; 77%. *n*) Methyl acrylate, $Pd(OAc)_2[P(2\text{-Tolyl})_3]_2$, $K_2CO_3$, DMF; 92% of **25**. *o*) Styrene, $Pd(OAc)_2[P(2\text{-Tolyl})_3]_2$, $K_2CO_3$, DMF/$H_2O$ 6:1; 59% of **26**. *p*) Acrylonitrile, $Pd(OAc)_2$, $Ph_3P$, $K_2CO_3$, DMF; 41% of **27**. *q*) 1. Pd/C, $H_2$, 2. $BCl_3$, $CH_2Cl_2$; 88% from **26**. *r*) Phenylacetylene, $Pd(PPh_3)_4$, CuI, $Et_3N$, DMF; 82% of **32**. *s*) Aq. HCl, 40°; quant. *t*) BnLi, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA); 64%. *u*) 2-Naphthoyl chloride, pyridine; **35**: 32%; **36**: 36%. *v*) NaOMe, 60°, 98% of **33**, 96% of **34**.

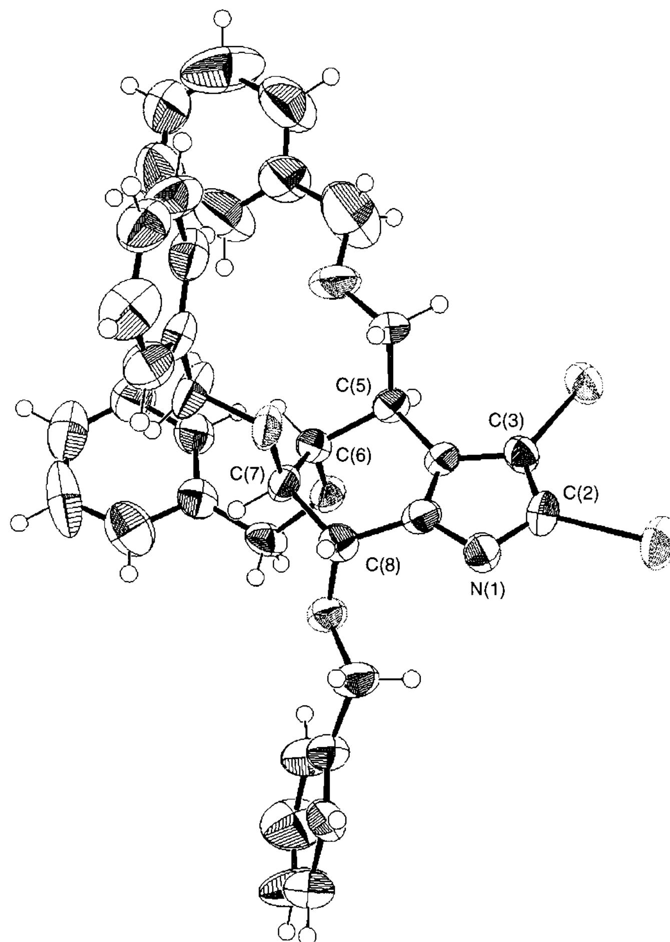



Fig. 1. *ORTEP Representation of the diiodoimidazole* **8**

Table 1. *Selected* [13]*C-NMR Chemical Shifts and* J*(H,H) Values of the Protected 2,3-Unsubstituted Imidazole* **7** *and the Protected Iodoimidazoles* **8**–**10**

| Compound | C(2) | C(3) | *J*(5,6) | *J*(6,7) | *J*(7,8) |
|---|---|---|---|---|---|
| **7** | 129.62 | 117.57 | 7.5 | 7.5 | 5.3 |
| **8** | 81.28 | 97.07 | 1.9 | 4.1 | 3.8 |
| **9** | 130.04 | 102.15 | 2.0 | 4.2 | 3.7 |
| **10** | 81.77 | 122.88 | 7.5 | 7.5 | 5.4 |

was also obtained (63%) by hydrogenolysis of the aldehyde **12**. However, $BCl_3$-promoted deprotection of **14** gave the desired (hydroxymethyl)imidazole **16** in 83% yield. The $CH_2NH_2$ derivative **17** was prepared by hydrogenolysis at 6 bar of the imidazole-carbonitrile **13** in $AcOH/CF_3CO_2H$ 1:1 (79%). Hydrogenolysis in the absence of $CF_3CO_2H$ considerably prolonged the reaction (32 instead of 8 h), but still led to the

desired (aminomethyl)imidazole (78%). In MeOH, however, hydrogenolysis of **13** remained incomplete even after 76 h, and was accompanied by reductive deamination of the $NH_2CH_2$ group, as evidenced by the $^1$H-NMR spectrum of the crude.

The (phenylcarbamoyl)imidazole **19** was obtained by treatment of the organomagnesium derivative of **10** with PhNCO (95% of **18**), followed by hydrogenolytic debenzylation (85%). The protected 2-phenyl- and 2-pyridylimidazoles **20** and **22** were prepared according to a method described by *Minato et al.* [16] for bromomagnesiumpyrroles. Following their protocol, the organomagnesium derivative of **10** was treated with $ZnBr_2$ and then with either PhI or 2-bromopyridine in the presence of [$Pd(PPh_{3)4}$] to yield 72% of **20** and 77% of **22**, respectively. The phenylimidazole **20** was hydrogenolytically deprotected to the tetrol **21** (68%), while hydrogenolysis of **22** also reduced the piperidine moiety and led to a 1:1 mixture of the diastereoisomeric piperidinylimidazoles **23** and **24** (60%).

To prepare the [(methoxycarbonyl)ethyl]-, the (phenethyl)-, the (aminopropyl)- and the (carboxyethyl)imidazoles **28**–**31**, respectively, we subjected the 2-iodoimidazole **10** [5]) to standard *Heck* conditions ($Pd(OAc)_2$, $Ph_3P$, $Et_3N$, or $K_2CO_3$, DMF 60–80°) with methyl acrylate, styrene, and acrylonitrile. This gave the coupling products **25**–**27** in 63, 42, and 41% yield, respectively, along with variable amounts of **7** and of starting material **10**. Attempts to improve the yields by using other commercially available Pd catalysts, varying the base, or adding tetrabutylammonium salts [6]) remained unsuccessful. A black precipitate ($Pd^0$?) appeared at elevated temperatures (>100°), independently of the catalyst used. Addition of excess $Ph_3P$ or trifurylphosphine led to 10–15% of the phosphonium salts **39** or **40** [7]), and reduced the yield of the desired coupling products. Addition of $H_2O$ (14% (*v*/*v*)) [28] increased the yield of the (phenylvinyl)imidazole **26** from 43 to 51%, but had no influence on the yield of either the (cyanovinyl)imidazole **27** or the [(methoxycarbonyl)vinyl]imidazole **25**. However, replacing $Pd(OAc)_2/PPh_3$, by *Herrmann*'s palladacycle [29] improved the yield of **25** from 63 to 92%. This catalyst also improved the yield of the (phenylvinyl)imidazole **26** from 51 to 59% but had no effect on the yield of the (cyanovinyl)imidazole **27**.

Hydrogenation of **25** and **27** (Pd/C in AcOH) gave the deprotected [(methoxycarbonyl)ethyl]- and (aminopropyl)imidazoles **28** and **30** in 82 and 59% yield, respectively. Under the same conditions, the C=C bond of the stilbene analogue **26** was readily reduced, while debenzylation proceeded very slugglishly, even after adding fresh catalyst and increasing the $H_2$ pressure. Debenzylation was completed by treating the crude in $CH_2Cl_2$ with $BCl_3$, providing 88% of the deprotected (phenethyl)imidazole **29**. The overall yield of **29** from the iodoimidazole **10** was significantly increased by proceeding *via* the (phenylethynyl)imidazole **32**, obtained in 82% by *Sonogashira* coupling of **10** with ethynylbenzene. The propionic acid **31** was obtained quantitatively as the hydrochloride by hydrolysis of the methyl propionate **28** in 1M HCl.

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[5]) For examples of *Heck* reactions with iodoimidazoles, see [17–24]. In most cases, the coupling products have been obtained in moderate yields.

[6]) The rate- and yield-increasing influence of tetraalkylammonium salts in *Heck* reactions has been documented [25].

[7]) Formation of tetraarylphosphonium salts by $Pd^{II}$-mediated coupling of halogenoarenes with triarylphosphines is known [26][27]. As the crude reaction was worked up with sat. aq. $NH_4Cl$, **39** and **40** are assumed to have chloride counterions.

Considering the strong inhibition (see below) by the (hydroxymethyl)imidazole **16** and the phenethyl derivative **29**, we also prepared the diastereoisomeric ($\alpha$-hydroxyphenethyl)imidazoles **37** and **38**. Addition of BnLi to the formylimidazole **12** gave a 45:55 mixture of the ($\alpha$-hydroxyphenethyl)imidazoles **33** and **34** (64%, along with 12% of **7**), which could not be separated by crystallization, FC, or HPLC. The 2-naphthoates **35** and **36**, however, were separated by TLC and isolated by HPLC (32% of **35** and 36% of **36**). Attempts to crystallize either **35** or **36** from various solvents failed, but the diastereoisomeric alcohols **33** and **34**, obtained in 98% and 96% yield by denaphthoylation of **35** and **36**, crystallized readily from $Et_2O$/hexane. They were debenzylated ($BCl_3$) to **37** (73%) and **38** (71%). X-Ray analysis of the (*R*)-alcohol **33**[8]) at low temperature (*Fig. 2*) established the configuration at C(1′) of **33** and thereby also of **34**–**38**.

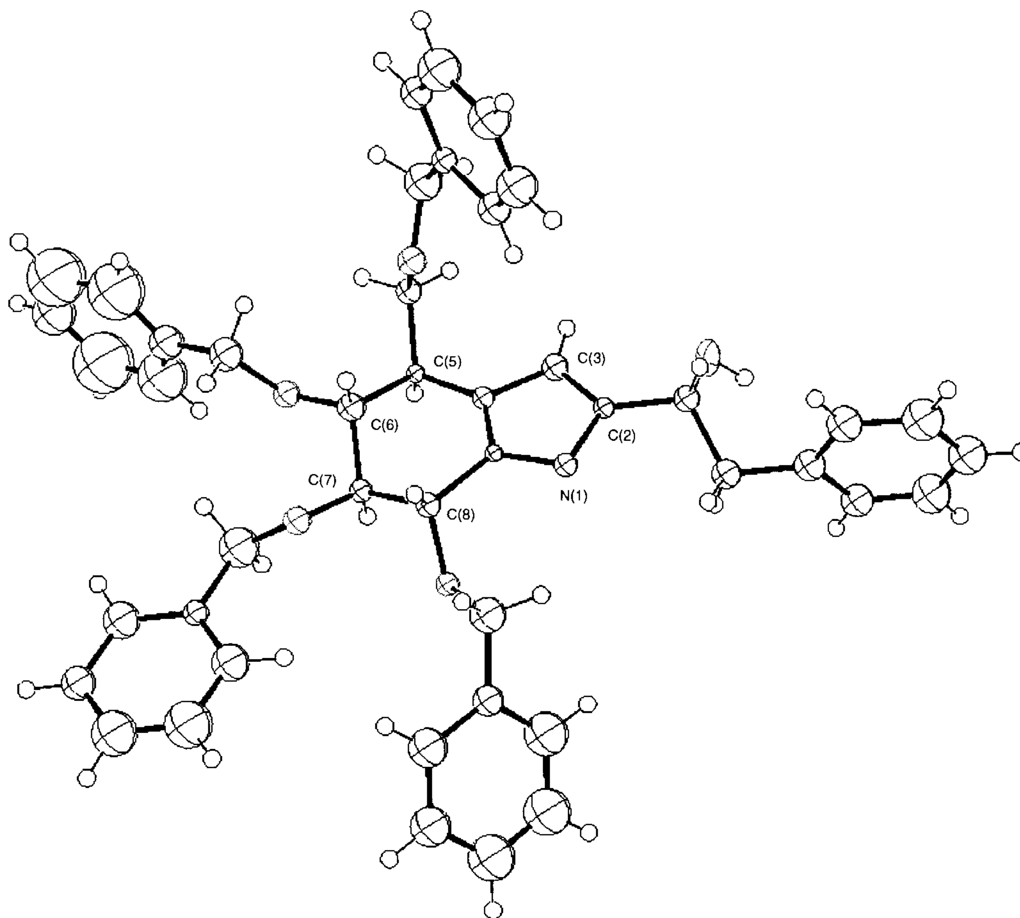


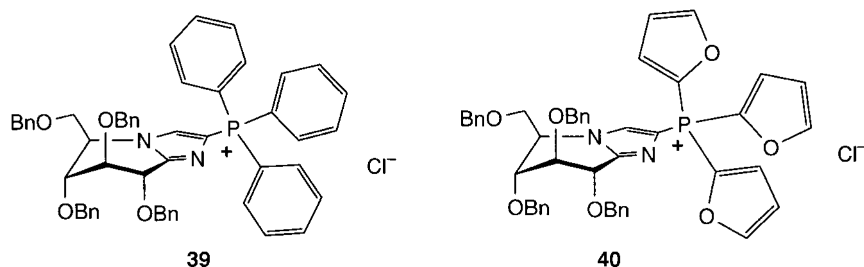

Fig. 2. *ORTEP Representation of (α-hydroxyphenethyl)imidazole* **33**. Non-H-atoms are refined isotropically (*cf. Exper. Part*)

[8]) The (*S*)-alcohol **34** gave cotton-like crystals that were not suitable for X-ray analysis.

With the exception of the additional signals of the functional groups at C(2) and their influence on the chemical shifts of H−C(3), C(2), and C(3), the $^1$H-NMR and $^{13}$C-NMR spectra of the protected and unprotected *C(2)*-functionalized imidazoles **12**–**38** closely resemble those of the 2,3-unsubstituted imidazoles **4** and **7**. Thus, the protected *C(2)*-functionalized imidazoles exist as 2:1 mixtures of the $^7H_6$ and $^6H_7$ conformers, while the deprotected imidazoles adopt the expected $^7H_6$-conformation. The H−C(5), H−C(6), $CH_2C(5)$-, and H−C(3) signals of the phosphonium salts **39** and **40** are strongly shielded as compared to those of **7**, while the H−C(8) signal of **39** and **40** is strongly deshielded (*Table 2*). The $J(5,6)$, $J(6,7)$, and $J(7,8)$ values of **39** and **40** indicate a conformation close to $^6H_7$.

Table 2. *Selected $^1$H-NMR Chemical Shifts and* J*(H,H) Values of the Protected 2,3-Unsubstituted Imidazole* **7** *and the Phosphonium Salts* **39** *and* **40**

| Compound | H−C(5) | H−C(6) | H−C(7) | H−C(8) | CH−C(5) | CH′−C(5) | $J$(5,6) | $J$(6,7) | $J$(7,8) |
|---|---|---|---|---|---|---|---|---|---|
| **7** | 4.20 | 3.88 | 4.11 | 4.77 | 3.76 | 3.88 | 7.8 | 7.8 | 5.6 |
| **39** | 3.92 | 3.64 | 4.01 | 6.06 | 2.54 | 3.11 | 4.7 | 4.6 | 2.8 |
| **40** | 3.99 | 3.75 | 4.13 | 6.14 | 3.02 | 3.28 | 4.7 | 4.5 | 3.2 |




**Enzymatic Tests and Discussion.** – The *C(2)*-functionalized imidazoles **11**, **15**–**17**, **19**, **21**, **23/24**, **28**–**31**, **35**, and **36** inhibit $\beta$-glucosidases from almonds and *Caldocellum saccharolyticum*, and the $\alpha$-glucosidase from yeast in a competitive, mixed, or non-competitive fashion (*Table 3*). The two $\beta$-glucosidases are inhibited about as strongly by the methylimidazole **15** as by the 2,3-unsubstituted imidazole **5**, indicating that the Me group of **15** does not significantly interact with the aglycon binding subsite. The almost isosteric iodoimidazole **11** inhibits the two $\beta$-glucosidases some 5–7 times less strongly than **15** and **5**, in agreement with its reduced basicity. The (hydroxymethyl)-imidazole **16** inhibits the $\beta$-glucosidases from almonds *ca.* 10 times and the $\beta$-glucosidase from *C. saccharolyticum ca.* 4 times more strongly than **5** or **15**. This is very likely due to H-bonding. Such an interaction appears particularly probable in view of the lower p$K_{HA}$ of the hydroxymethylated **16**, relative to that of **5**. A probable H-bond acceptor is the carbonyl O-atom of the catalytic acid. This assumption is supported by fitting the (hydroxymethyl)imidazole **16** into the active site of the $\beta$-glycosidase from *Sulfolobus solfataricus* [9]) (*Fig. 3*), another member of the family 1 glycosidases.

[9]) X-Ray structure of the native enzyme solved at 2.6-Å resolution by *Aguilar et al.* [30].

Table 3. *Inhibition Constants Measured at pH 6.8 and p$K_{HA}$ of* C(2)*-Functionalized Imidazoles Compared to Those of the 2,3-Unsubstituted Parent Imidazole* **5**

| Compound | p$K_{HA}$ | $\beta$-Glucosidases from almonds[a]) | $\beta$-Glucosidase from *Caldocellum s.*[b]) | $\alpha$-Glucosidase from brewer's yeast[a]) |
|---|---|---|---|---|
| **5** | 6.12 | 100 nM | 20 nM($\alpha$ = 3.2) | 59 µM |
| **11** | 4.62 | 1280 nM[c]) | 170 nM | 1850 µM[c]) |
| **15** | 6.46 | 260 nM[c]) | 25 nM[c]) | 72 µM[c]) |
| **16** | 5.22 | 11 nM | 5 nM | 69 µM[c]) |
| **17** | 4.08/ > 9.0 | 1600 nM[c]) | 150 nM[c]) | 2060 µM[c]) |
| **19** | < 3.0 | 3000 nM | 140 nM | 2150 µM[c]) |
| **21** | 4.99 | 100 nM ($\alpha$ = 7.0) | 18 nM | 554 µM[c]) |
| **23/24** | [e]) | 3000 nM[c]) | 600 nM | > 3400 µM[c]) |
| **28** | 6.17 | 9.9 nM[d]) | 1.8 nM ($\alpha$ = 2.5) | 25 µM[c]) |
| **29** | 6.03 | 1.2 nM | 0.11 nM ($\alpha$ = 15) | 0.5 µM[c]) |
| **30** | 5.32/ > 9.0 | 70 nM[c]) | 25 nM[c]) | 185 µM[c]) |
| **31** | 4.06/7.05 | 55 nM[c]) | 18 nM[c]) | 242 µM[c]) |
| **37** | [e]) | 63 nM | 16 nM | 3 µM |
| **38** | [e]) | 41 nM | 7 nM | 10 µM |

[a]) At 37°. [b]) At 55°. [c]) $IC_{50}$. [d]) Non-competitive inhibition. [e]) Not determined.

In contrast to the effect of the $CH_2OH$ group at C(2), the $CH_2NH_2$ group at C(2) reduces the inhibition considerably, as evidenced by the $IC_{50}$ values of **17**. This may be due to unfavourable interactions of the ammonium group with the enzyme, the lower basicity of the imidazole, and/or H-bonding with the imidazole N(1)-atom that impair the interaction with the catalytic acid. In keeping with the weak inhibition by the (aminomethyl)imidazole **17**, the diastereoisomeric piperidinylimidazoles **23/24** (1:1) inhibit the $\beta$-glucosidases also much less strongly than **5**.

In spite of its lower p$K_{HA}$ value, the phenylimidazole **21** inhibits the $\beta$-glucosidases as strongly as **5**, indicating a favourable interaction of the Ph group with the aglycon binding subsite that compensates for the effects of the lower basicity. Such a compensation is not observed for the (phenylcarbamoyl)imidazole **19** (p$K_{HA}$ < 3)[10]) as reflected by its weaker inhibition of the $\beta$-glucosidases.

A very significant increase of the inhibitory strength is observed for the [(methoxycarbonyl)ethyl]imidazole **28** and particularly for the (phenethyl)imidazole **29**. To the best of our knowledge, the phenethyl derivative **29** is the strongest inhibitor of a $\beta$-glucosidase described so far. This competitive inhibition of the almond $\beta$-glucosidases and the almost competitive inhibition of the *C. saccharolyticum* $\beta$-glucosidase most probably results from the interaction of the substituent at C(2) with the aglycon binding subsite. The strong inhibitory properties of **28** and **29**, as compared to those of the phenylimidazole **21** or the (phenylcarbamoyl)imidazole **19**, may reflect the higher flexibility of the substituents at C(2) of **27** and **28**. The (aminopropyl)imidazole **30** and the carboxylic acid **31** inhibit the two $\beta$-glucosidases 5–227 times less strongly than the [(methoxycarbonyl)ethyl]imidazole **28** and the (phenethyl)imidazole **29**. It is tempting to conclude that these $\beta$-glucosidases prefer hydrophobic aglyca. However, the inhibition has only been determined at pH 6.8, where both the

[10]) No inflection of the titration curve was observed between pH values of 3.0 and 9.0 upon attempted determination of the p$K_{HA}$ of **21**. It is, therefore, assumed that its p$K_{HA}$ is below 3.0.

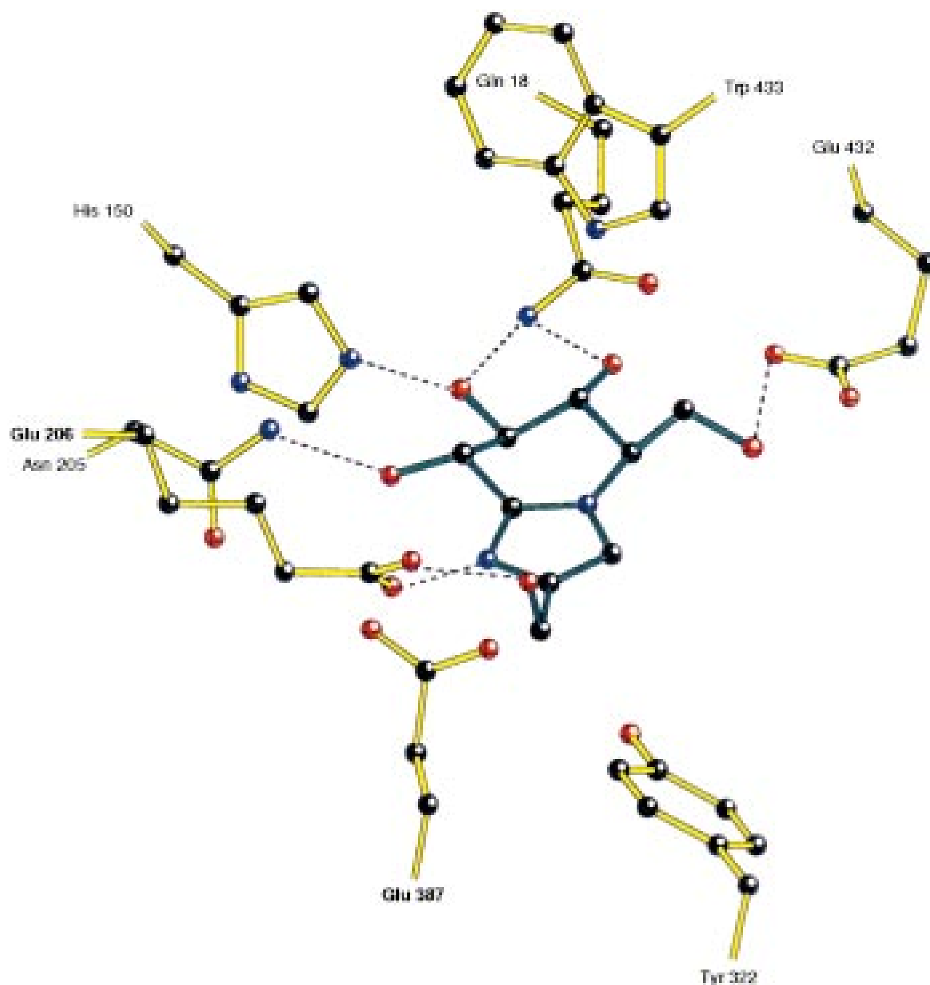
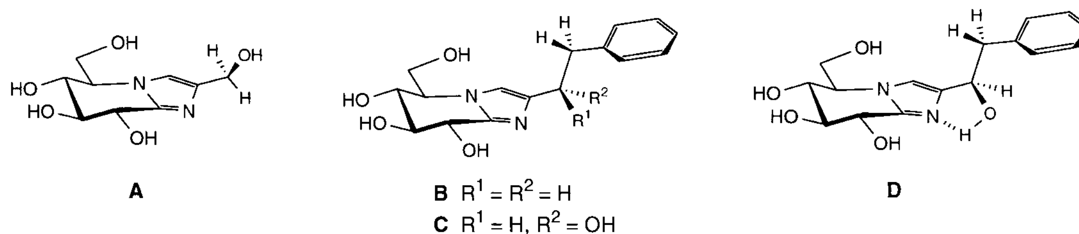



Fig. 3. *(Hydroxymethyl)imidazole* **16** *fitted into the active site of β-Glucosidase from* Sulfolobus solfataricus

monoammonium salt of **30** and the carboxylic acid **31** are expected to form a strong intramolecular H-bond to N(1) that may have to be cleaved upon binding of the enzyme. Indeed, while sweet almond β-glucosidases prefer hydrophobic aglycons [31], this is presumably not so for the β-glucosidase from *C. saccharolyticum*, natural substrate of which appears to be cellobiose [32]. Irrespective of these considerations, the strong inhibition by the phenethyl derivative **29** may reflect hydrophobic interactions of the substituent at C(2) with putative aromatic residues close to the aglycon binding site of the glucosidases. Aromatic residues at this site have, *e.g.*, been demonstrated in cellobiohydrolase I of *Trichoderma reesei* [33][11]).

[11]) The importance of hydrophobic interactions in the binding of biologically active compounds to their receptors has recently been reviewed by *Teague* and *Davis* [34].

The difference between the inhibition of the two diastereoisomeric hydroxyphenethyl derivatives **37** and **38** is small, the (1′*S*)-diastereoisomer **38** inhibiting the two enzymes slightly more strongly than the (1′*R*)-configured **37**. Remarkably, both the hydroxyphenethyl derivatives **37** and **38** inhibit the $\beta$-glucosidases from almonds and *C. saccharolyticum* 34–145 times less strongly than the phenethyl derivative **29** and 1.4–5.7 times less strongly than the hydroxymethyl derivative **16**. To rationalize this finding, we considered the change of the ring conformation of the glycon in the course of the enzymatic glycoside hydrolysis. A conformational change is required for the pseudoaxial orientation of the scissile bond, as postulated by the theory of stereoelectronic control [35] and evidenced by X-ray analysis of two *endo*-$\beta$-glucosidases [36][37]. This conformational change implies that, on the way to the transition state, the glycosidic O-atom is shifted above the average plane of the $-1$ site [38] of the undistorted substrate. The position of the catalytic acid should change in a complementary fashion. For *anti*-protonating [39] $\beta$-glucosidases, this suggests that **A** represents the relevant conformer of the hydroxymethyl derivative **16**. The 'upward' shift of the pseudoaxial aglycon would be mimicked by conformer **B** of the phenethyl derivative **29**. It is not possible to combine the hypothetically preferred conformers **A** and **B** while maintaining the optimal position of both the OH and the phenethyl group, as in conformers **A** and **B**. The small difference between the inhibition of the diastereoisomeric hydroxyphenethyl derivatives **37** and **38** may indicate that the position of the OH group in conformer **C** of **38** is sterically less favourable than the position of the OH group in conformer **D** of **37** but that **D** may form an intramolecular H-bond, as shown below, impairing the interaction of the N(1)-atom with the catalytic acid.




The imidazoles **16**, **28**–**31**, **37**, and **38** are slow binding inhibitors of the two $\beta$-glucosidases, as evidenced by the asymptotic activity curve (initial burst after addition of the $\beta$-glucosidase to the substrate/inhibitor solution and gradual decrease of the enzymatic activity) (*Fig. 4*). According to the activity curves, the steady-state kinetics was reached after a period of *ca.* 20 min. For the determination of the $IC_{50}$ and $K_i$ values, the enzymatic reaction was started by addition of the substrate after preincubating the $\beta$-glucosidase in the presence of the inhibitor for 30 min[12]).

Slow inhibition is a well-documented phenomenon [40–44] that has also been observed for some inhibitors of glycosidases [45][46]. It has been attributed to the isomerization of the initial enzyme-inhibitor complex (EI) into a complex (EI*) which binds the inhibitor much more tightly. Approximate values for $k_3$ (forward isomeri-

[12]) Almost identical $IC_{50}$ or $K_i$ values were obtained after preincubation for 1 h.

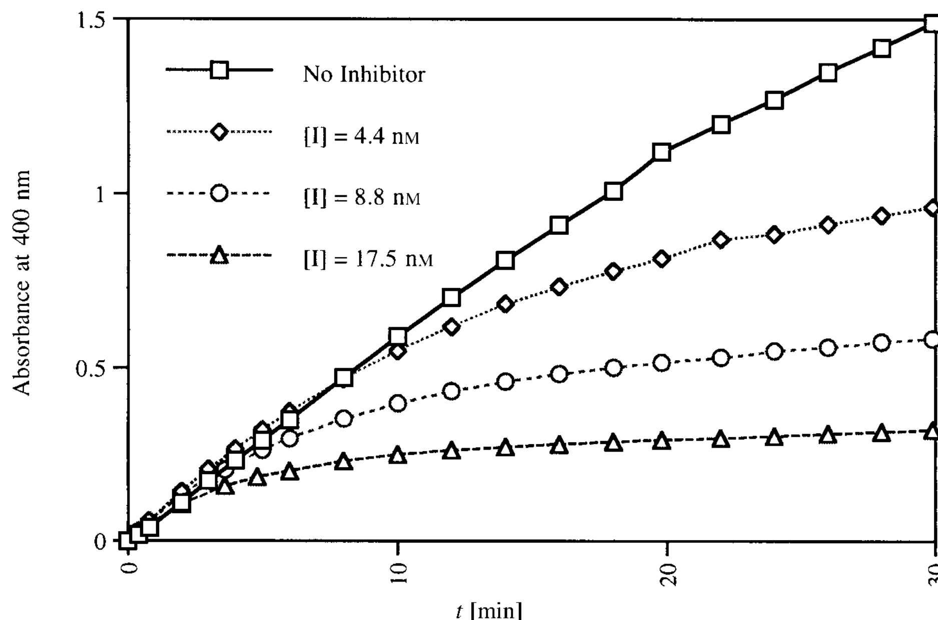



Fig. 4. *Time-dependent decrease of the activity of the β-Glucosidase from* Caldocellum saccharolyticum *in the presence of* **28**

zation rate of EI) and $k_4$ (reverse isomerization rate of EI*) were determined for **28** and **29** (*Table 4*) by a procedure given in [43] (*cf. Exper. Part*). According to the ratio $k_3/k_4$, the inhibition increases with time by a factor of 79–400 compared to the initial inhibition. This ratio correlates with the lifetime of EI* and is significant in view of a potential *in vivo* application of the inhibitor, since the reverse isomerization rate of EI* ($k_4$) is not affected by the inhibition-induced upstream accumulation of the substrate [43].

Table 4. *Rate Constants* $k_3$ *and* $k_4$ *for* **28** *and* **29** *According to* Eqn. 1 *and* $K_i$ *Values Determined with and without Preincubation of the Enzyme and the Inhibitor*

$$E + I \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EI \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EI^* \quad (1)$$

| Compound | β-Glucosidase | $k_3$ | $k_4$ | $k_3/k_4$ | $K_i$(initial)[a]) | $K_i$(end)[b]) |
|---|---|---|---|---|---|---|
| **28** | Almonds | 0.0597 $s^{-1}$ | 0.00015 $s^{-1}$ | 400 | 1.0 μM | 0.0099 μM |
| **29** | Almonds | 0.0325 $s^{-1}$ | 0.00041 $s^{-1}$ | 80 | 0.1 μM | 0.0012 μM |
| **29** | *Caldocellum* | 0.0400 $s^{-1}$ | 0.00023 $s^{-1}$ | 174 | 0.01 μM | 0.0001 μM |

[a]) No preincubation of enzyme and inhibitor. [b]) Preincubation of enzyme and inhibitor during 30 min.

The 2,3-unsubstituted imidazole **5**, like other basic inhibitors of the lactone type, inhibits both β- and α-glucosidases. This lack of selectivity has been rationalized by pointing out that the less favourable steric relation, in α-glucosidases, between the basic site and the catalytic acid may be compensated by coulombic interactions resulting from (partial) protonation of the inhibitor [47]. One, therefore, expects the basic

character of the *C(2)*-substituted imidazoles to be particularly important for the inhibition of $\alpha$-glucosidases. The orientation of the substituent at C(2) in the plane of the imidazole ring is expected to be unfavourable for the inhibition of $\alpha$-glucosidases and may lead to an improved selectivity of *C(2)*-substituted imidazoles towards $\beta$-glucosidases. However, the $IC_{50}$ values (*Table 3*) determined against yeast $\alpha$-glucosidase show that the substituent at C(2) may also favourably interact with this enzyme. Thus, the (hydroxymethyl)imidazole **16** inhibits the $\alpha$-glucosidase about as strongly as the more highly basic **5** and **15**, suggesting that C(1′)–OH is again involved in H-bonding. The [(methoxycarbonyl)ethyl]imidazole **27**, the (phenethyl)imidazole **29**, and the two diastereoisomeric ($\alpha$-hydroxyphenethyl)imidazoles **37** and **38**[13]) are significantly stronger inhibitors than **5** or **15**. This may result from the conformational flexibility of the substituent at C(2) of **28**, **29**, **37**, and **38**. The stronger inhibition by the [(methoxycarbonyl)ethyl]imidazole **28** and the (phenethyl)imidazole **29** as compared to that of the (aminopropyl)imidazole **30** and the carboxylic acid **31** suggests that hydrophobic interactions contribute significantly to the binding of the inhibitors. The importance of the basicity of the imidazoles is illustrated by the 26-fold weaker inhibition of the yeast $\alpha$-glucosidase by the iodoimidazole **11** than by the isosteric, but more strongly basic methylimidazole **15**. Also the (phenylcarbamoyl)imidazole **19** and the phenylimidazole **21** are weaker inhibitors than **5**. In contradistinction to the inhibition of the $\beta$-glucosidases, where **21** and **5** are about equipotent, the lower basicity of **21** is not compensated by a favourable interaction of the Ph group with the yeast $\alpha$-glucosidase. The amines **17** and **23/24** are again weak inhibitors, possibly for reasons analogous to those discussed above.

As expected for inhibitors designed for $\beta$-glucosidases, **5** and all *C(2)*-functionalized imidazoles described here inhibit the $\beta$-glucosidases significantly more strongly than yeast $\alpha$-glucosidase, with the (hydroxymethyl)imidazole **16** and the phenylimidazole **21** showing the highest and the ($\alpha$-hydroxyphenethyl)imidazoles **37** and **38** the lowest selectivities. High selectivity for the $\beta$-glucosidases, particularly for the *C. saccharolyticum* $\beta$-glucosidase, is also observed for the rather weakly inhibiting (aminomethyl)imidazole **17**, the 1:1 mixture of the piperidinylimidazoles **23/24**, and the (phenylcarbamoyl)imidazole **19**, while the selectivity of the strongly inhibiting (phenethyl)imidazole is not higher than that of the 2,3-unsubstituted imidazole **5**. As compared to the selectivity of **5**, which inhibits $\beta$-glucosidases from almonds 590 times and $\beta$-glucosidase from *C. saccharolyticum* 2950 times more strongly than $\alpha$-glucosidase from yeast, the introduction of a substituent at C(2) reduces the selectivity by a maximal factor of *ca.* 15 (**37**) and enhances it by a maximal factor of *ca.* 10 (**16**). We take these low values as an indication that the inhibition of $\beta$-glucosidases, and the selectivity may be further improved by judicious choice of the side chain at C(2).

We thank Dr. *B. Schweizer* for the determination of the X-ray structures of **8** and **33**, Dr. *I. Billault* for providing crystals of **8**, *J. Schneider* and *D. Manser* for the $pK_{HA}$ determinations, *M. Terinek* for a generous sample of **7**, Dr. *B. Bernet* for checking the experimental part, and the *Swiss National Science Foundation* and *Oxford Glycosciences Ltd.*, Abingdon (UK), for generous support.

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[13]) The diastereoisomeric hydroxyphenethyl derivatives **37** and **38** inhibit the $\alpha$-glucosidase from yeast 6–10 times less strongly than **29**. In contradistinction to the inhibition of the $\beta$-glucosidases, the (1′*R*)-diastereoisomer **37** is a slightly stronger inhibitor than the (1′*S*)-diastereoisomer **38**.

## Experimental Part

*General*. Solvents were distilled before use. Normal workup implies distribution of the crude product between $Et_2O$ and sat. aq. soln. of $NH_4Cl$, and ice, unless indicated otherwise, drying of the org. layer ($MgSO_4$), filtration, and evaporation of the filtrate. M.p.: uncorrected. TLC: *Merck* silica gel *60F-254* plates; detection by heating with mostain (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 *Fluka 60* (0.04 – 0.063 mm). IR Spectra: KBr or 3% $CHCl_3$ soln. $^1$H-NMR (300 MHz, if not indicated otherwise) and $^{13}$C-NMR (75 MHz, if not indicated otherwise) were measured at 25°: Chemical shifts $\delta$ in ppm and coupling constants $J$ in Hz. FAB- and CI-MS: 3-nitrobenzyl alcohol and $NH_3$ as matrix, resp., unless indicated otherwise.

*(5*R*,6*R*,7*S*,8*S*)-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2,3-diiodo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine and (5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-3-iodo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**8** and **9**, resp.). *a*) A soln. of **7** (290 mg, 0.52 mmol) in DMF (3.5 ml) was treated with *N*-iodosuccinimide (NIS; 1.16 g, 5.18 mmol) and kept at 80° for 6 h. The brown mixture was diluted with $Et_2O$, washed successively with a sat. aq. $NH_4Cl$ soln., a 5% aq. $NaS_2O_3$ soln., and $H_2O$, dried ($MgSO_4$), and filtered. Evaporation and FC (hexane/AcOEt 9:1) gave **8** (389 mg, 92%), which was recrystallized in hexane/$Et_2O$ (colourless crystals, suitable for X-ray analysis). Reaction performed on a larger scale (2.70 g, 4.82 mmol) gave **8** (3.23 g, 83%).

*b*) A soln. of **7** (96 mg, 0.171 mmol) in DMF (1 ml) was treated with NIS (192 mg, 0.855 mmol) and kept at 60° for 8 h. Workup and FC as described in *a* gave **9** (74 mg, 63%) and **8** (33 mg, 24%).

*Data of* **8**: $R_f$ (hexane/$Et_2O$ 1:1) 0.65. M.p. 76 – 77°. UV ($CHCl_3$): 269 (3.2). IR ($CHCl_3$): 3008*w*, 2959*w*, 2927*s*, 2856*s*, 1727*w*, 1683*w*, 1602*w*, 1455*m*, 1376*w*, 1262*s*, 1097*s*, 1016*s*, 864*w*. $^1$H-NMR ($CDCl_3$): 3.63 (*dd*, $J = 9.3$, 4.4 CH–C(5)); 3.71 (*dd*, $J = 9.7$, 8.7, CH′–C(5)); 4.07 (*t*, $J = 4.1$, irrad. at 4.68 → *d*, $J \approx 4.0$, H–C(7)); 4.33 (*dd*, $J = 4.4$, 1.9, irrad. at 4.07 → *d*, $J \approx 1.5$, H–C(6)); 4.41 (*s*, PhC*H*$_2$); 4.45 (*ddd*, $J = 8.7$, 4.7, 1.9, H–C(5)); 4.47 (*d*, $J = 11.8$, PhC*H*); 4.55 (*d*, $J = 11.8$, PhC*H*); 4.57 (*d*, $J = 11.8$, PhC*H*); 4.67 (*d*, $J = 12.1$, PhC*H*); 4.68 (*d*, $J = 3.8$, H–C(8)); 4.81 (*d*, $J = 12.1$, PhC*H*); 5.10 (*d*, $J = 12.1$, PhC*H*); 7.17 – 7.43 (*m*, 20 arom. H). $^{13}$C-NMR ($CDCl_3$): 60.88 (*d*, C(5)); 69.49 (*t*, *C*H$_2$–C(5)); 72.32, 72.92, 73.10, 73.27 (4*t*, 4 Ph*C*H$_2$); 72.16, 73.27, 78.13 (3*d*, C(6), C(7), C(8)); 81.28 (*s*, C(2)); 97.09 (*s*, C(3)); 127.87 – 128.72 (several *d*); 137.60, 137.78, 137.81, 138.37 (4*s*); 149.26 (*s*, C(8a)). CI-MS ($NH_3$): 813 (3, $[M+1]^+$), 685 (1, $[M-I]^+$), 599 (1), 493 (6), 91 (100).

*X-Ray Analysis of* **8**: Orthorhombic *P*21; $a = 9.571(7)$, $b = 10.995(4)$, $c = 32.009(6)$; $V = 3368(3)$ Å$^3$, $D_{calc} = 1.507$ Mg/m$^3$, $Z = 4$. The reflexions were measured on an *Enraf-Nonius-CAD4*-diffractometer (graphite monochromator, Mo$K_\alpha$, $\lambda = 0.71073$) at 293 K. $R = 0.0908$, $R_w = 0.2061$. Part of the structure was solved by direct methods, the remaining non-H-atoms were found from a difference *Fourier* map with SHELXS-96. The non-H-atoms were refined anisotropically with SHELX-97. H-Atoms were calculated at idealized positions and included in the structure factor calculation with fixed isotropic displacement parameters.

*Data of* **9**: $R_f$ ($Et_2O$/hexane 1:1) 0.59. UV ($CHCl_3$): 296 (2.9). IR ($CHCl_3$): 3008*w*, 2928*w*, 2857*s*, 1734*w*, 1603*w*, 1497*w*, 1455*m*, 1362*w*, 1262*m*, 1096*s*, 1028*m*, 908*w*, 607*w*. $^1$H-NMR ($CDCl_3$): 3.63 (*dd*, $J = 9.9$, 4.6, CH–C(5)); 3.72 (*t*, $J = 9.6$, CH′–C(5)); 4.07 (*t*, $J = 4.2$, 3.7, irrad. at 4.69 → *d*, $J \approx 4.0$, H–C(7)); 4.35 (*dd*, $J = 4.2$, 2.0, H–C(6)); 4.41 (*s*, PhC*H*$_2$); 4.42 – 4.51 (*m*, H–C(5)); 4.48 (*d*, $J = 11.2$, PhC*H*); 4.56 (*d*, $J = 12.0$, PhC*H*); 4.59 (*d*, $J = 11.6$, PhC*H*); 4.67 (*d*, $J = 11.4$, PhC*H*); 4.69 (*d*, $J = 3.7$, H–C(8)); 4.84 (*d*, $J = 12.0$, PhC*H*); 5.10 (*d*, $J = 12.0$, PhC*H*); 7.07 – 7.39 (*m*, 20 arom. H, H–C(2)). $^{13}$C-NMR ($CDCl_3$): 58.13 (*d*, C(5)); 69.33 (*t*, CH$_2$–C(5)); 72.40, 72.19, 73.32, 73.39 (4*t*, 4 Ph*C*H$_2$); 72.50, 73.39, 78.42 (3*d*, C(6), C(7), C(8)); 102.15 (*s*, C(3)); 127.83 – 128.72 (several *d*); 130.04 (*d*, C(2)); 137.76, 137.84, 137.92, 138.50 (4*s*); 145.20 (*s*, C(8a)).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2-iodo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**10**). A soln. of **8** (515 mg, 0.63 mmol) in THF (10 ml) was treated at 0° with a 1M soln. of EtMgBr in THF (0.95 ml), stirred for 10 min, and treated with a sat. aq. $NH_4Cl$ soln. (1 ml). Workup and FC (hexane/AcOEt 85:15) gave **10** (407 mg, 94%) as a solid. The reaction performed on a larger scale (3.20 g, 3.94 mmol) gave **10** (2.22 g, 82%) after recrystallization in $Et_2O$/hexane (colourless crystals). $R_f$ (hexane/$Et_2O$ 1:1) 0.57. M.p. 89°. $[\alpha]_D^{20} = +39.4$ ($c = 1$, $CHCl_3$). UV ($CHCl_3$): 269 (2.72). IR ($CHCl_3$): 3159*w*, 3067*w*, 3008*s*, 2915*m*, 2869*m*, 1953*w*, 1878*w*, 1811*w*, 1603*w*, 1497*s*, 1454*s*, 1424*m*, 1362*m*, 1334*w*, 1152*w*, 1097*s*, 1028*s*, 946*m*, 912*w*, 629*w*, 608*w*. $^1$H-NMR ($CDCl_3$, 200 MHz): 3.71 (*dd*, $J = 10.4$, 5.4, CH–C(5)); 3.81 (*t*, $J = 7.5$, irrad. at 4.11 → *d*, $J \approx 7.0$, H–C(6)); 3.81 (*dd*, $J = 10.3$, 2.9, CH′–C(5)); 4.11 (*dd*, $J = 7.5$, 5.4, irrad. at 4.74 → *d*, $J \approx 7.5$, H–C(7)); 4.21 (*ddd*, $J = 7.9$, 5.4, 2.9, H–C(5)); 4.45 (*d*, $J = 12.0$, PhC*H*); 4.50 (*d*, $J = 11.6$, PhC*H*); 4.52 (*d*, $J = 12.0$, PhC*H*); 4.67 (*d*, $J = 11.2$, PhC*H*); 4.74 (*d*, $J = 5.4$, irrad. at 4.11 → *s*, H–C(8)); 4.81 (*d*, $J = 11.6$, PhC*H*); 4.83 (*d*, $J = 11.2$, PhC*H*); 4.85 (*d*, $J = 11.6$, PhC*H*); 5.16 (*d*, $J = 11.6$, PhC*H*); 7.15 (*s*, H–C(3)); 7.17 – 7.44 (*m*, 20 arom. H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 57.93 (*d*, C(5)); 67.80 (*t*, *C*H$_2$–C(5)); 72.22, 72.88, 73.42, 73.61 (4*t*, 4 Ph*C*H$_2$); 73.11, 75.39, 80.95 (3*d*, C(6), C(7), C(8)); 81.77 (*s*, C(2)); 122.88 (*d*, C(3)); 127.6 – 128.22 (several *d*); 136.76, 137.07, 137.30, 137.68 (4*s*);

145.45 (*s*, C(8a)). CI-MS ($NH_3$): 687 (5, $M^+$), 561 (2), 473 (3), 347 (11), 239 (23), 132 (15), 108 (74), 91 (100). Anal. calc. for $C_{36}H_{35}IN_2O_4$ (686.16): C 62.98, H 5.14, N 4.08; found: C 63.03, H 5.03, N 4.03.

*(5*R*,6*R*,7*S*,8*S*)-5-(Hydroxymethyl)-2-iodo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol* (**11**). A soln. of **10** (20 mg, 0.029 mmol) in $CH_2Cl_2$ at $-78°$ was treated with a 1M soln. of $BCl_3$ in $CH_2Cl_2$ (0.4 ml), stirred until the mixture had reached a temp. of 23° (*ca.* 3 h), cooled to $-78°$, and treated with $H_2O$ (2 ml). Evaporation of the solvent and FC (AcOEt/MeOH 10 : 1) gave **11** (6 mg, 63%). $R_f$ (AcOEt/MeOH) 0.12. $^1$H-NMR ($CD_3OD$): 3.64 (*dd*, *J* = 9.3, 8.9, H–C(7)); 3.76 (br. *t*, *J* = 9.0, 8.5, H–C(6)); 3.84–3.91 (*m*, H–C(5), CH–C(5)); 4.08–4.14 (*m*, CH–C(5)); 3.89 (*d*, *J* = 8.2, H–C(8)); 7.40 (*s*, H–C(3)). $^1$H-NMR ($CD_3OD$ + 2 equiv. $CF_3CO_2H$): 3.77 (*dd*, *J* = 9.6, 8.3, H–C(8)); 3.90 (br. *t*, *J* = 9.0, H–C(6)); 3.99 (*dd*, *J* = 12.1, 4.2, CH–C(5)); 4.10–4.19 (*m*, H–C(5)); 4.22 (*dd*, *J* = 12.0, 2.5, H–C(5)); 4.71 (*dd*, *J* = 8.3, H–C(8)); 7.84 (*s*, H–C(3)). $^{13}$C-NMR ($CDCl_3$): 61.06 (*t*, $CH_2$–C(5)); 63.89 (*d*, C(5)); 68.45, 68.54, 74.65 (3*d*, C(6), C(7), C(8)); 125.85 (*d*, C(3)); 150.52 (*s*, (C(8a)). Anal. calc. for $C_8H_{11}IN_2O_4$ (326.09): C 29.47, H 3.40, N 8.59; found: C 29.34, H 3.20, N 8.79.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-carbaldehyde* (**12**). A soln. of **10** (200 mg, 0.3 mmol) in THF (5 ml) was treated at 0° with a 1M soln. of EtMgBr in THF (0.5 ml, 0.5 mmol), stirred for 5 min, treated with DMF (5 ml), and stirred for 90 min. The mixture was cooled to $-30°$ and treated with a sat. aq. $NH_4Cl$ soln. Workup and FC (hexane/AcOEt 2 : 1) gave **12** (150 mg, 85%). $R_f$ (AcOEt/hexane 1 : 1) 0.72. UV ($CHCl_3$): 268 (3.9). IR ($CHCl_3$): 3067*w*, 3007*m*, 2869*m*, 2236*m*, 1688*s*, 1539*m*, 1497*m*, 1455*w*, 1363*w*, 1338*w*, 1112*s*, 1028*m*, 909*m*. $^1$H-NMR ($CDCl_3$): 3.75 (*dd*, *J* = 10.6, 5.6, CH–C(5)); 3.84 (*dd*, *J* = 8.1, 6.9, H–C(6)); 3.85 (*dd*, *J* = 10.6, 2.8, CH′–C(5)); 4.12 (*dd*, *J* = 6.9, 5.0, H–C(7)); 4.26 (*ddd*, *J* = 8.1, 5.6, 2.8, H–C(5)); 4.44 (*d*, *J* = 12.1, PhC*H*); 4.47 (*d*, *J* = 11.2, PhC*H*); 4.50 (*d*, *J* = 12.1, PhC*H*); 4.63 (*d*, *J* = 11.5, PhC*H*); 4.76 (*d*, *J* = 5.0, H–C(8)); 4.77 (*d*, *J* = 11.8, PhC*H*); 4.79 (*d*, *J* = 11.5, PhC*H*); 4.84 (*d*, *J* = 11.8, PhC*H*); 5.10 (*d*, *J* = 11.5, PhC*H*); 7.06–7.46 (*m*, 20 arom. H); 7.75 (*s*, H–C(3)); 9.90 (*s*, CHO). $^{13}$C-NMR ($CDCl_3$): 58.68 (*d*, C(5))9, 67.98 (*t*, $CH_2$–C(5)); 72.74, 73.55, 73.81, 74.02 (4*t*, 4 Ph$CH_2$); 73.29, 76.06, 81.19 (3*d*, C(6), C(7), C(8)); 124.25 (*d*, C(3)); 128.05–128.09 (several *d*); 137.18, 137.55, 137.71, 137.99 (4*s*); 142.26 (*s*, C(2)); 146.14 (*s*, C(8a), 186.47 (*d*, CHO). FAB-MS: 589 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-carbonitrile* (**13**). A soln. of **10** (100 mg, 0.15 mmol) in THF (0.5 ml) was treated at 0° with a 1M soln. of EtMgBr in THF (0.5 ml), stirred for 5 min, and treated with a suspension of TsCN (300 mg, 1.66 mmol) in THF (2 ml). After stirring for 30 min, the mixture was cooled to $-30°$ and treated with a sat. aq. soln. of $NH_4Cl$. Workup and FC (hexane/AcOEt 2 : 1) gave **13** (79 mg; 89%). $R_f$ ($Et_2O$/hexane 1 : 1) 0.12. UV ($CHCl_3$): 283 (3.8). IR ($CHCl_3$): 3067*w*, 3001*m*, 2926*m*, 2871*m*, 2236*m*, 1626*s*, 1530*w*, 1497*w*, 1454*w*, 1423*w*, 1362*w*, 1098*s*, 1028*m*, 909*w*. $^1$H-NMR ($CDCl_3$): 3.67 (*dd*, *J* = 10.6, 6.2, CH–C(5)); 3.77 (*dd*, *J* = 10.9, 2.5, CH′–C(5)); 3.79 (*t*, *J* = 7.2, H–C(6)); 4.08 (*dd*, *J* = 6.9, 5.3, H–C(7)); 4.20 (*td*, *J* = 6.2, 2.8, H–C(5)); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.46 (*d*, *J* = 11.2, PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.61 (*d*, *J* = 11.5, PhC*H*); 4.67 (*d*, *J* = 5.0, H–C(8)); 4.74 (*d*, *J* = 12.1, PhC*H*); 4.78 (*d*, *J* = 11.5, PhC*H*); 4.81 (*d*, *J* = 11.8, PhC*H*); 5.06 (*d*, *J* = 11.8, PhC*H*); 7.15–7.45 (*m*, 20 arom. H); 7.54 (*s*, H–C(3)). $^{13}$C-NMR ($CDCl_3$): 59.02 (*d*, C(5)); 68.24 (*t*, $CH_2$–C(5)); 72.85 (br. *t*, 2 Ph$CH_2$); 73.57, 73.95 (2*t*, 2 Ph$CH_2$); 73.98, 75.60, 80.70 (3*d*, C(6), C(7), C(8)); 114.45 (*s*, CN): 126.92 (*d*, C(3)); 128.13–128.93 (several *d*); 130.64 (*s*, C(2)); 137.00 (*s*); 137.40 (*s*); 137.60 (*s*); 137.76 (*s*); 145.96 (*s*, C(8a)). FAB-MS: 586 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-methanol* (**14**). At $-78°$, a soln. of **12** (100 mg, 0.17 mmol) in THF (5 ml) was treated with a 0.2M suspension of $LiAlH_4$ in THF (1 ml) and stirred until the temp. had reached $-30°$ (*ca.* 1 h). The soln. was cooled to $-78°$ and treated with $H_2O$ (1 ml). Normal workup and FC (AcOEt) gave **14** (88 mg, 87%). Colourless oil that crystallized upon standing. $R_f$ (AcOEt/hexane 1 : 1) 0.13. IR ($CHCl_3$): 3614*w*, 3090*w*, 3066*m*, 2925*s*, 2869*s*, 1946*w*, 1869*w*, 1806*w*, 1468*m*, 1454*m*, 1362*m*, 1240*m*, 1097*s*, 1028*s*, 910*w*, 857*w*, 698*s*. $^1$H-NMR ($CDCl_3$): 2.80–3.20 (br. *s*, exchange with $CD_3OD$, OH); 3.73 (*dd*, *J* = 10.3, 5.3, CH–C(5)); 3.83 (*dd*, *J* = 10.2, 3.1, CH′–C(5)); 3.85 (*dd*, *J* = 8.1, 7.5, C(6)); 4.08 (*dd*, *J* = 7.5, 5.4, H–C(7)); 4.16 (*ddd*, *J* = 8.1, 5.3, 3.1, H–C(5)); 4.44 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 11.8, 2 PhC*H*); 4.62 (*s*, $CH_2$–C(2)); 4.67 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 5.6, H–C(8)); 4.80 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 11.5, 2 PhC*H*); 5.12 (*d*, *J* = 11.8, PhC*H*); 6.98 (*s*, H–C(3)); 7.01–7.58 (*m*, 20 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.18 (*d*, H–C(5)); 58.82 (*t*, $CH_2$–C(2)); 68.49 (*t*, $CH_2$–C(5)); 72.80, 73.42, 74.03, 74.24 (4*t*, 4 Ph$CH_2$), 74.24, 76.14, 81.93 (3*d*, C(6), C(7), C(8)); 114.98 (*d*, C(3)); 127.83–128.78 (several *d*, *s* of C(2)); 137.55 (*s*); 137.87 (*s*); 138.07 (*s*); 138.58 (*s*); 142.45 (*s*, C(8a)). FAB-MS: 591 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-2-Methyl-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol Hydrochloride* (**15** · HCl). A soln. of **12** (20 mg, 0.039 mmol) in AcOEt/MeOH/AcOH 1 : 1 : 1 was treated with 10% Pd/C (10 mg) and hydrogenated at 6 bar for 36 h. Filtration, evaporation, and ion-exchange chromatography

(*Amberlite CG-120*, $H^+$ form, elution with 1M HCl) gave **15** · HCl (86.3 mg, 63%). Colourless hygroscopic resin. $R_f$ (AcOEt/MeOH 5:1) 0.31. $^1$H-NMR ($D_2O$): 2.31 (*s*, Me); 3.87 (*dd*, *J* = 10.0, 8.7, H–C(7)); 3.98 (*dd*, *J* = 10.0, 8.7, H–C(6)); 4.07 (*dd*, *J* = 12.5, 2.9, CH–C(5)); 4.13–4.20 (*m*, H–C(5)); 4.24 (*dd*, *J* = 12.5, 2.1, CH′–C(5)); 4.80 (*d*, *J* = 9.6, H–C(8)); 7.50 (*s*, H–C(3)). $^{13}$C-NMR ($D_2O$): 9.30 (*q*, Me); 58.34 (*t*, $CH_2$–C(5)); 61.96 (*d*, C(5)); 66.50, 66.98, 73.45 (3*d*, C(6), C(7), C(8)); 116.15 (*d*, C(3)); 132.14 (*s*, C(2)); 144.40 (*s*, C(8a)). CI-MS: 215 (65, $[M+1]^+$), 133 (100). Anal. calc. for $C_9H_{14}N_2O_4$ · HCl · 1.5 $H_2O$ (277.70): C 38.93, H 6.53, N 10.99; found: C 38.65, H 6.81, N 9.87.

*(5*R*,6*R*,7*S*,8*S*)-2,5-Bis(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol Hydrochloride* (**16** · HCl). At −78°, a soln. of **14** (85 mg, 0.145 mmol) in $CH_2Cl_2$ (3 ml) was treated dropwise with a 1M soln. of $BCl_3$ in $CH_2Cl_2$ (2 ml, 2 mmol), stirred until the mixture had reached a temp. of 23° (*ca.* 3 h), cooled to −78°, and treated with $H_2O$ (2 ml). Evaporation of the solvent, FC (AcOEt/MeOH 10:1) and ion-exchange chromatography (*Amberlite CG-120*, $H^+$ form, elution with 1M HCl) gave **16** · HCl (32 mg, 83%) as a colourless hygroscopic resin. $R_f$ (AcOEt/MeOH 5:1) 0.13. $^1$H-NMR ($D_2O$): 3.88 (*dd*, *J* = 10.3, 9.0, H–C(7)); 3.98 (*dd*, *J* = 10.0, 8.7, H–C(6)); 4.06 (*dd*, *J* = 12.8, 3.1, CH–C(5)); 4.17–4.20 (*m*, H–C(5)); 4.24 (*dd*, *J* = 12.8, 2.5, CH–C(5)); 4.65 (*s*, $CH_2$–C(2)); 4.83 (*d*, *J* = 8.7, H–C(8)); 7.57 (*s*, H–C(3)). $^1$H-NMR ($D_2O$ in the presence of 5% of $NH_3$): 3.81 (*dd*, *J* = 10.0, 9.0, H–C(7)); 3.93 (*dd*, *J* = 10.0, 9.0, H–C(6)); 4.02–4.07 (*m*, H–C(5), CH–C(5)); 4.19–4.23 (*m*, CH′–C(5)); 4.65 (*s*, $CH_2$–C(2)); 4.68 (*d*, *J* = 8.7, H–C(8)); 7.37 (*s*, H–C(3)). $^{13}$C-NMR ($D_2O$): 56.52 (*t*, $CH_2$–C(2)); 61.13 (*t*, $CH_2$–C(5)); 64.95 (*d*, C(5)); 69.35, 69.70, 76.14 (3*d*, C(6), C(7), C(8)); 120.09 (*d*, C(3)); 137.53 (*s*, C(2)); 148.71 (*s*, C(8a)). FAB-MS: 231 (100, $[M+1]^+$). Anal. calc. for $C_9H_{14}N_2O_5$ · HCl · 1.8 $H_2O$ (299.11): C 36.14, H 6.27, N 9.37; found: C 35.98, H 6.45, N 9.09.

*(5*R*,6*R*,7*S*,8*S*)-2-(Aminomethyl)-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol* (**17**). *a*) A soln. of **13** (28 mg, 0.048 mmol) in AcOH/$CF_3CO_2H$ 1:1 (3 ml) was treated with 10% Pd/C (20 mg) and hydrogenated at 6 bar for 8 h. Filtration, evaporation of the solvent, and ion-exchange chromatography (*Amberlite CG-120*, $NH_4^+$ form, elution with 0.1M aq. $NH_3$) gave **17** (9 mg, 79%). Colourless, hygroscopic foam.

*b*) As described in *a*) but with AcOH instead of the 1:1 AcOH/$CF_3CO_2H$ mixture and hydrogenating during 32 h instead of during 8 h gave **17** (78%).

*c*) As described in *a* but with MeOH instead of the 1:1 AcOH/$CF_3CO_2H$ mixture. The reaction was incomplete after 76 h. According to its $^1$H-NMR, the crude contained **17** and **15** in ratio of *ca.* 3:1.

*Data of* **17**: $R_f$ (AcOEt/MeOH 5:1) 0.06. $^1$H-NMR ($D_2O$): 3.88 (*dd*, *J* = 9.3, 9.0, H–C(7)); 3.89 (br. *s*, $CH_2$–C(2)); 3.96 (*t*, *J* = 9.6, H–C(6)); 4.02–4.15 (*m*, H–C(5), CH–C(5)); 4.25 (*dd*, *J* = 12.8, 2.2, CH′–C(5)); 4.63 (*d*, *J* = 9.3, H–C(8)); 7.26 (*s*, H–C(3)). $^1$H-NMR ($D_2O$, 2 equiv. of $CF_3COOH$): 3.81 (*dd*, *J* = 10.0, 8.7, H–C(7)); 3.93 (*dd*, *J* = 10.0, 8.7, H–C(6)); 4.04–4.08 (*m*, H–C(5), CH–C(5)); 4.18 (*s*, $CH_2$–C(2)); 4.20–4.23 (*m*, CH–C(5)); 4.68 (*d*, *J* = 8.7, H–C(8)); 7.51 (*s*, H–C(3)). $^1$H-NMR ($D_2O$, 2 equiv. of HCl): 3.90 (*dd*, *J* = 10.0, 9.0, H–C(7)); 3.98 (*t*, *J* = 10.0, H–C(6)); 4.04–4.08 (*m*, CH–C(5)); 4.21–4.28 (*m*, H–C(5), CH–C(5)); 4.34 (*s*, $CH_2$–C(2)); 4.86 (*d*, *J* = 9.7, H–C(8)); 7.82 (*s*, H–C(3)). $^{13}$C-NMR ($D_2O$); 35.74 (*t*, $CH_2$–C(2)); 61.28 ($CH_2$–C(5)); 65.41 (*d*, C(5)); 69.26, 69.70, 75.91 (3*d*, C(6), C(7), C(8)); 123.21 (*d*, C(3)); 129.86 (*s*, C(8a)). FAB-MS: 230 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-*N*-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-carboxamide* (**18**). At 0°, a soln. of **10** (50 mg, 0.074 mmol) in THF (2 ml) was treated with a 1M soln. of EtMgBr in THF (0.14 ml, 0.14 mmol), stirred for 10 min, treated with PhNCO (0.1 ml, 0.92 mmol), and warmed to 23° within 30 min. Workup and FC (AcOEt/hexane 1:2) gave **18** (48 mg, 95%). $R_f$ (AcOEt/hexane 1:2) 0.51. UV (MeOH): 263 (3.2). IR ($CHCl_3$): 3380*w*, 3008*m*, 1709*s*, 1597*m*, 1561*m*, 1521*m*, 1499*m*, 1421*s*, 1326*w*, 1098*m*, 1028*w*, 590*w*. $^1$H-NMR ($CDCl_3$): 3.75 (*dd*, *J* = 10.3, 5.0, CH–C(5)); 3.85 (*dd*, *J* = 10.6, 3.4, CH–C(5)); 3.91 (*dd*, *J* = 8.1, 7.5, H–C(6)); 4.10 (*dd*, *J* = 7.5, 5.9, H–C(7)); 4.17–4.21 (*m*, H–C(5)); 4.45 (*s*, PhC*H*$_2$); 4.48 (*d*, *J* = 11.2, PhC*H*); 4.72 (*d*, *J* = 11.5, PhC*H*); 4.73 (*d*, *J* = 5.9, H–C(8)); 4.83 (*d*, *J* = 11.2, 2 PhC*H*); 4.89 (*d*, *J* = 11.5, PhC*H*); 5.15 (*d*, *J* = 11.5, PhC*H*); 7.07–7.58 (*m*, 24 arom. H); 7.71–7.74 (*m*, 1 arom. H); 7.77 (*s*, H–C(3)); 9.00 (*s*, slow exchange with $CD_3OD$, NH). $^{13}$C-NMR ($CDCl_3$): 58.76 (*d*, C(5)); 67.72 (*t*, *C*H$_2$–C(5)); 73.10, 73.58, 74.29, 74.46 (4*t*, 4 Ph*C*H$_2$); 74.16, 75.94, 81.80 (3*d*, C(6), C(7), C(8)); 119.93 (*d*, 2 arom. C); 121.13 (*d*, arom. C); 124.10 (*d*, C(3)); 128.23-129.61 (several *d*); 133.91, 137.35, 137.70, 137.94, 138.39 (5*s*); 144.34 (*s*, C(2)); 149.00 (*s*, C(8a)); 160.86 (*s*, C=O).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Trihydroxy-5-(hydroxymethyl)-*N*-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-carboxamide* (**19**). A soln. of **18** (40 mg, 0.059) in AcOEt/MeOH/AcOH 1:1:1 (2 ml) was treated with 30 mg of Pd/C (10%) and hydrogenated at 6 bar for 12 h. Filtration, evaporation, FC (AcOEt/MeOH/$H_2O$ 20:1:1), and recrystallization in $H_2O$ gave **19** (16 mg, 85%). Colourless solid. $R_f$ (AcOEt/MeOH/$H_2O$ 20:2:1) 0.34. UV (MeOH): 261 (3.1). IR ($CHCl_3$): 3398*m* (br.), 3044*m*, 2923*m*, 2853*m*, 1710*s*, 1596*m*, 1563*m*, 1498*m*, 1401*s*, 1291*m*, 1225*m*, 1072*m*, 751*s*, 689*s*, 589*s*. $^1$H-NMR ($D_2O$): 3.78 (*dd*, *J* = 9.7, 9.0, irrad. at 4.60 → *d*, *J* ≈ 9.5,

H–C(7)); 3.92 (*t*, *J* = 10.0, H–C(6)); 4.04–4.13 (*m*, H–C(5)); 4.05 (*dd*, *J* = 13.7, 3.1, CH–C(5)); 4.24 (*dd*, *J* = 13.4, 2.8, CH–C(5)); 4.60 (*d*, *J* = 8.7, H–C(8)); 7.25 (*tt*, *J* = 7.5, 1.0, 1 arom. H); 7.43 (*t*, *J* = 7.5, 2 arom. H); 7.50 (*dd*, *J* = 7.4, 1.2, 2 arom. H); 7.9 (*s*, H–C(3)). $^{13}$C-NMR ($D_2O$): 61.54 (*t*, $CH_2$–C(5)); 63.69 (*d*, C(5)); 69.99, 70.76, 77.27 (3*d*, C(6), C(7), C(8)); 124.90 (*d*); 125.03 (*d*, 2 arom. C); 128.68 (*d*, C(3)); 132.26 (*d*, 2 arom. C); 138.66 (*s*, arom. C); 139.49 (*s*, C(2)); 150.57 (*s*, C(8a)); 166.02 (*s*, C=O). CI-MS ($NH_3$): 319 (0.2, $[M+1]^+$), 119 (1), 44 (100). Anal. calc. for $C_{15}H_{17}N_3O_5 \cdot 2H_2O$ (355.37): C 50.70, H 5.39, N 11.82, found: C 50.45, H 5.18, N 11.57.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**20**). At 0°, a stirred suspension of **10** (0.150 g, 0.22 mmol) in THF (2 ml) was treated dropwise with a 3M soln. of EtMgBr in $Et_2O$ (0.145 ml, 0.44 mmol) and stirred for 10 min. A suspension of anh. $ZnBr_2$ (0.148 g, 0.65 mmol) in THF (1 ml) was added. The mixture was stirred for 15 min at 0°, treated with $[Pd(PPh_3)_4]$ (0.025 g, 0.022 mmol) and iodobenzene (0.049 ml, 0.44 mmol), allowed to reach r.t., stirred for 2 h, cooled to −30°, and treated with sat. aq. $NH_4Cl$ soln. Workup and FC (hexane/AcOEt 4:1) gave **20** (0.100 g, 72%). Colorless solid. $R_f$ (AcOEt/hexane 1:3) 0.18. UV ($CHCl_3$): 292 (7.2). IR ($CHCl_3$): 3065*w*, 3007*w*, 2961*w*, 2868*w*, 1722*m*, 1607*w*, 1496*w*, 1454*m*, 1437*w*, 1361*w*, 1261*s*, 1156*w*, 1095*s*, 1027*m*, 818*w*. $^1$H-NMR ($CDCl_3$): 3.80 (*dd*, *J* = 10.6, 5.6, irrad. at 4.24 → *d*, *J* ≈ 10.4, CH–C(5)); 3.91 (*t*, *J* = 7.8, irrad. at 4.15 → change, H–C(6)); 3.92 (*dd*, *J* = 10.6, 2.5, irrad. at 4.24 → change, CH′–C(5)); 4.15 (*dd*, *J* = 7.8, 5.6, irrad. at 4.83 → change, H–C(7)); 4.21–4.24 (*m*, H–C(5)); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 5.6, irrad. at 4.15 → *s*, H–C(8)); 4.84 (*d*, *J* = 13.7, PhC*H*); 4.88 (*d*, *J* = 11.2, PhC*H*); 4.97 (*d*, *J* = 11.5, PhC*H*); 5.29 (*d*, *J* = 11.5, PhC*H*); 7.22–7.43 (*m*, 21 arom. H, H–C(3)); 7.51 (br. *d*, *J* = 7.9, 2 arom. H); 7.82 (br. *d*, *J* = 7.5, 2 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.34 (*d*, C(5)); 68.47 (*t*, $CH_2$–C(5)); 72.80, 73.47, 74.27, 74.48 (4*t*, 4 Ph$CH_2$); 74.40, 76.31, 82.27 (3*d*, C(6), C(7), C(8)); 113.49 (*d*, C(3)); 125.28 (*d*, 2 arom. C); 127.00 (*d*, arom. C); 127.97–128.90 (several *d*); 134.84 (*s*, C(2)); 137.71, 138.06, 138.32, 138.71 (4*s*); 142.41 (*s*); 144.65 (*s*, C(8a)). FAB-MS: 637 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2-(pyridin-2-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**22**). A soln. of **10** (250 mg, 0.36 mmol) in THF (3 ml) at 0° under Ar was treated dropwise with a 3M soln. of EtMgBr in $Et_2O$ (0.24 ml, 0.73 mmol), stirred for 10 min, treated with a suspension of anh. $ZnBr_2$ (0.246 g, 1.09 mmol) in THF (1 ml), cooled to 0°, stirred for 15 min, and treated with $[Pd(PPh_3)_4]$ (0.042 g, 0.036 mmol) and 2-bromopyridine (0.071 ml, 0.73 mmol). The soln. was allowed to reach 23°, stirred for 2 h, cooled to −30°, treated with sat. aq. $NH_4Cl$ soln. (5 ml), and warmed to 23°. Workup and FC (hexane/AcOEt 1:3) gave **22** (0.179 g, 77%). Colourless oil. $R_f$ (AcOEt/hexane 3:1) 0.35. UV ($CHCl_3$): 294 (7.7). IR ($CHCl_3$): 3067*w*, 2928*w*, 2855*w*, 1600*s*, 1454*m*, 1261*s*, 1100*s*, 1013*s*, 818*m*. $^1$H-NMR ($CDCl_3$): 3.86 (*dd*, *J* = 10.3, 4.4, irrad. at 4.23 → *d*, *J* ≈ 10.4, CH–C(5)); 3.95 (*dd*, *J* = 10.4, 2.8, irrad. at 4.23 → change, CH′–C(5)); 3.96 (*t*, *J* = 7.8, irrad. at 4.14 → *s*, H–C(6)); 4.14 (*dd*, *J* = 7.8, 5.9, irrad. at 3.96 → change, H–C(7)); 4.21–4.27 (*m*, H–C(5)); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 11.2, PhC*H*); 4.53 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 11.5, PhC*H*); 4.82 (*d*, *J* = 5.9, irrad. at 4.14 → *s*, H–C(8)); 4.86 (*d*, *J* = 11.2, PhC*H*); 4.88 (*d*, *J* = 11.2, PhC*H*); 4.96 (*d*, *J* = 11.5, PhC*H*); 5.29 (*d*, *J* = 11.5, PhC*H*); 7.14 (*td*, *J* = 5.9, 1.1, 1 arom. H); 7.24–7.40 (*m*, 18 arom. H); 7.47–7.52 (*m*, 2 arom. H); 7.72 (*td*, *J* = 8.0, 1.9, 1 arom. H); 7.77 (*s*, H–C(3)); 8.07 (br. *d*, *J* = 8.0, 1 arom. H); 8.57 (br. *d*, *J* = 4.1, 1 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.40 (*d*, C(5)); 67.87 (*t*, $CH_2$–C(5)); 72.75, 73.39, 74.18, 74.36 (4*t*, 4 Ph$CH_2$); 74.37, 76.12, 82.18 (*d*, C(6), C(7), C(8)); 113.76 (*d*, C(3)); 117.09 (*d*, ar. C); 119.19 (*d*, arom. C); 128.11–128.72 (several *d*); 136.71 (*d*, arom. C); 137.57, 137.89, 138.14, 138.46 (4*s*); 142.58 (*s*); 144.84 (*s*); 149.32 (*d*); 153.73 (*s*, C(8a)). FAB-MS: 639 (100, $[M+1]^+$).

*(5*R*,6*R*,7*S*,8*S*)-5-(Hydroxymethyl)-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol* (**21**). A soln. of **20** (320 mg, 0.50 mmol) in MeOH/$H_2O$/AcOH 9:2:1 (2.5 ml) was treated with 10% Pd/C (300 mg), hydrogenated at 6 bar for 3 days, and filtered through *Celite*. Evaporation, FC ($CH_3OH$/AcOEt 1:9), and crystallization from MeOH gave **21** (76 mg, 55%). Colourless crystals. M.p. 194°. $R_f$ (AcOEt/MeOH 8:2) 0.39. UV (MeOH): 291 (4.0). IR (KBr). 3932–3421*s*, 1734*w*, 1718*w*, 1700*w*, 1684*w*, 1654*m*, 1647*w*, 1636*w*, 1609*w*, 1560*w*, 1508*m*, 1458*m*, 1437*w*, 1328*m*, 1081*s*. $^1$H-NMR ($CD_3OD$): 3.74 (*t*, *J* ≈ 8.4, H–C(7)); 3.85 (*t*, *J* ≈ 8.6, irrad. at 3.74 → change, H–C(6)); 3.92–3.96 (*m*, H–C(5)); 3.99 (*dd*, *J* = 11.8, 4.0, CH–C(5)); 4.23 (*dd*, *J* = 11.8, 2.2, CH–C(5)); 4.56 (*d*, *J* = 7.8, irrad. at 3.74 → change, H–C(8)); 7.21 (*td*, *J* = 0.9, 7.5, 1 arom. H); 7.34 (br. *t*, *J* = 7.6, 2 arom. H)); 7.62 (*s*, H–C(3)); 7.77 (*dd*, *J* = 0.9, 7.5, 2 arom. H). $^{13}$C-NMR ($CD_3OD$): 61.64 (*t*, $CH_2$–C(5)); 63.14 (*d*, C(5)); 69.47, 70.08, 76.83 (3*d*, C(6), C(7), C(8)); 114.91 (*d*, C(3)); 126.30 (*d*, 2 arom. C); 128.14 (*d*, 1 arom. C); 129.84 (*d*, 2 arom. C); 135.70 (*s*, C(2)); 143.50 (*s*, 1 arom. C); 148.64 (*s*, C(8a)). FAB-MS: 277 (100, $[M+1]^+$). Anal. calc. for $C_{14}H_{16}N_2O_4 \cdot 0.1\ CH_3OH$ (279.49): C 58.27, H 5.56, N 9.30; found: C 58.52, H 5.48, N 9.42.

*(5R,6R,7S,8S)-5-(Hydroxymethyl)-2-(piperidin-2-yl)-5,6,7,8-tetrahydromidazo[1,2-a]pyridine-6,7,8-triol* (**23/24**). A soln. of **22** (0.120 g, 0.18 mmol) in MeOH/$H_2O$/AcOH 9:2:1 (1.8 ml) was treated with 20% $Pd(OH)_2$/C (100 mg) and hydrogenated at 6 bar for 2 days. The mixture was filtered through *Celite*. Evaporation and ion-exchange chromatography (*Amberlite CG-120*, $NH_4^+$ form, elution with 0.1M aq. $NH_3$) gave **23/24** 1:1 (0.036 g, 60%, ratio determined by the intensities of the $^{13}$C-NMR signals of the piperidinyl substituent): colourless oil crystallizing upon standing. $R_f$ (AcOEt/MeOH 1:1) 0.16. UV ($CH_3OH$): 292 (5.8). $^1$H-NMR ($CD_3OD$): 1.60–2.20 (br. *m*, 6 H); 3.14 (br. *m*, 2 H); 3.43 (br. *m*, 1 H); 3.69 (br. *t*, *J* = 8.1, H–C(7)); 3.81 (br. *t*, *J* = 8.4, irrad. at 3.69 → change, H–C(6)); 3.90–4.30 (br. *m*, $CH_2$–C(5), H–C(5)); 4.49 (br. *d*, *J* = 7.5, irrad. at 3.69 → change, H–C(8)); 7.46 (br. *s*, H–C(3)). $^{13}$C-NMR ($CD_3OD$): 29.61, 29.82 (2*t*); 46.17 (*t*); 55.82, 55.91 (2*d*); 61.44 (*t*, $CH_2$–C(5)); 63.21 (*d*, C(5)); 69.44, 69.87, 76.62 (3*d*, C(6), C(7), C(8)); 117.60 (*d*, C(3)); 139.31 (*s*, C(2)); 148.98 (*s*, C(8a)). EI-MS: 284 (100, $[M+1]^+$).

*Methyl (E-3-{(5R,6R,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]-pyridin-2-yl}prop-2-enoate* (**25**). *Triphenyl{(5R,6R,7S,8S)-6,7,8-tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl}phosphonium Chloride* (**39**), *{(5R,6R,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl}tris[furan-2-yl]phosphonium Chloride* (**40**). *a*) A soln. of **10** (250 mg, 0.364 mmol), $[Pd(OAc)_2(P(2\text{-Tolyl})_3)_2]$ (17 mg, 0.018 mmol), $K_2CO_3$ or (75 mg, 0.546 mmol, 1.5 equiv.), and methyl prop-2-enoate (0.16 ml, 1.8 mmol) in DMF (5 ml) was stirred at 80° for 2 h under Ar. Workup and FC ($Et_2O$/hexane 1:1) gave **25** (216 mg, 92%). Yellowish oil.

*b*) A soln. of **10** (50 mg, 0.073 mmol), $[Pd(OAc)_2]$ (2 mg, 0.0089 mmol), $Ph_3P$ (2.8 mg, 0.0107 mmol), $K_2CO_3$ (75 mg, 0.546 mmol), and methyl prop-2-enoate (0.1 ml, 1.13 mmol) in DMF (1 ml) was stirred at 80° for 8 h. Workup and FC ($Et_2O$/hexane 1:1) gave **25** (30 mg, 63%) and **7** (5 mg, 12%).

*c*) As described in *b*, but with 14 mg (0.0535 mmol) instead of 2.8 mg of $Ph_3P$, **25** (19 mg, 39%) and **39** (8 mg, 13%) were obtained. Colourless oils.

*d*) As described in *b*, but with $P(2\text{-furyl})_3$ instead of $Ph_3P$, **25** (28 mg, 59%) and **7** (4 mg, 10%) were obtained.

*e*) As described in *c* but with $P(2\text{-furyl})_3$ instead of $Ph_3P$, **25** (20 mg, 42%) and **40** (9 mg, 17%) were obtained.

*Data of* **25**: $R_f$ (AcOEt/hexane 1:3) 0.23. UV ($CHCl_3$): 295 (3.3). IR ($CHCl_3$): 3090*m*, 2952*m*, 2868*m*, 1700*s*, 1643*s*, 1603*w*, 1497*m*, 1454*m*, 1438*m*, 1362*m*, 1302*m*, 1263*s*, 1168*s*, 1097*s*, 1028*m*, 979*m*, 912*w*, 866*w*. $^1$H-NMR ($CDCl_3$): 3.71 (*dd*, *J* = 10.4, 5.3, CH–C(5)); 3.79 (*s*, MeO); 3.81 (*dd*, *J* = 10.4, 2.8, CH′–C(5)); 3.82 (*t*, *J* ≈ 7.8, H–C(6)); 4.09 (*dd*, *J* = 7.5, 5.6, H–C(7)); 4.16 (*ddd*, *J* = 8.1, 5.6, 2.8, H–C(5)); 4.43 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 11.2, PhC*H*); 4.67 (*d*, *J* = 11.5, PhC*H*); 4.72 (*d*, *J* = 5.6, H–C(8)); 4.82 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 11.2, PhC*H*); 4.89 (*d*, *J* = 11.5, PhC*H*); 5.18 (*d*, *J* = 11.8, PhC*H*); 6.62 (*dd*, *J* = 15.6, H–C(*α*)); 7.18 (*s*, H–C(3)); 7.19–7.40 (*m*, 18 arom. H); 7.44–7.46 (*m*, 2 arom. H); 7.56 (*d*, *J* = 15.6, H–C(*β*)). $^{13}$C-NMR ($CDCl_3$): 51.55 (*q*, MeO); 58.39 (*d*, C(5)); 68.28 (*t*, $CH_2$–C(5)); 72.82, 73.45, 73.82, 74.15 (4*t*, 4 Ph$CH_2$); 74.31, 75.99, 81.72 (3*d*, C(6), C(7), C(8)); 115.84, 120.45 (2*d*, C(*α*), C(*β*)); 127.97–128.85 (several *d*, including C(3)); 136.85, 137.74, 137.99, 138.23, 138.45 (5*s*, including C(2)); 145.90 (*s*, C(8a)); 168.53 (*s*, C=O). CI-MS: 645 (10, $M^+$), 431 (5), 325 (9), 263 (21), 262 (21), 105 (100), 91 (79).

*Data of* **39**: $R_f$ (AcOEt/hexane 1:5) 0.29. UV ($CHCl_3$): 286 (3.7). IR ($CHCl_3$): 3063*m*, 3007*m*, 2977*w*, 2926*w*, 2865*w*, 1496*m*, 1480*m*, 1454*m*, 1435*s*, 1363*m*, 1329*w*, 1098*s*, 1028*m*, 909*s*, 532*s*. $^1$H-NMR ($CDCl_3$): 2.54 (*dd*, *J* = 10.0, 6.2, CH–C(5)); 3.11 (*dd*, *J* = 10.0, 5.6, CH′–C(5)); 3.64 (*t*, *J* = 4.7, H–C(6)); 3.92 (*td*, *J* = 5.6, 4.5, H–C(5)); 4.01 (*dd*, *J* = 4.6, 2.8, H–C(7)); 4.09 (*s*, PhC$H_2$); 4.34 (*d*, *J* = 11.8, PhC*H*); 4.36 (*d*, *J* = 10.6, PhC*H*); 4.57 (*d*, *J* = 11.6, PhC*H*); 4.99 (*d*, *J* = 10.9, PhC*H*); 5.05 (*d*, *J* = 11.5, PhC*H*); 5.24 (*d*, *J* = 11.5, PhC*H*); 5.86 (*s*, H–C(3)); 6.06 (*d*, *J* = 2.8, H–C(8)), 7.05–7.39 (*m*, 29 arom. H); 7.67–7.81 (*m*, 6 arom. H). $^{31}$P-NMR (121 MHz, $CDCl_3$): +29.82 (*s*). FAB-MS: 791 (100, $M^+$), 627 (7), 453 (8), 91 (70).

*Data of* **40**: $R_f$ (AcOEt/hexane 1:5) 0.34. UV ($CHCl_3$): 276 (3.9). IR ($CHCl_3$): 3089*w*, 3008*m*, 2981*m*, 2922*m*, 2867*m*, 1951*w*, 1880*w*, 1813*w*, 1702*m*, 1672*m*, 1599*m*, 1552*m*, 1496*s*, 1454*s*, 1366*s*, 1097*s*, 1012*s*, 909*s*, 652*w*, 592*s*, 537*s*. $^1$H-NMR ($CDCl_3$): 3.02 (*dd*, *J* = 10.1, 6.1, irrad. at 3.99 → *d*, *J* ≈ 10.0, CH–C(5)); 3.28 (*dd*, *J* = 10.3, 4.7, irrad. at 3.99 → *d*, *J* ≈ 10.0, CH′–C(5)); 3.75 (*t*, *J* = 4.7, irrad. at 3.99 → *d*, *J* ≈ 4.5, irrad. at 4.13 → *d*, *J* ≈ 4.5, H–C(6)); 3.99 (*dt*, *J* = 4.9, 6.0, irrad. at 3.75 → *t*, *J* ≈ 6.0, H–C(5)); 4.03 (*s*, 2 PhC$H_2$); 4.13 (*dd*, *J* = 4.4, 3.4, irrad. at 3.75 → *d*, *J* ≈ 4.5, H–C(7)); 4.38 (*d*, *J* = 11.8, PhC*H*); 4.45 (*d*, *J* = 10.6, PhC*H*); 4.59 (*d*, *J* = 11.2, PhC*H*); 5.43 (*d*, *J* = 11.2, PhC*H*); 5.94 (*s*, H–C(3)); 6.14 (*d*, *J* = 3.2, irrad. at 4.13 → *s*, H–C(8)); 6.16 (*dd*, *J* = 3.4, 1.6, 3 arom. H) 7.02–7.08 (*m*, 4 arom. H); 7.16–7.40 (*m*, 22 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.46 (*d*, C(5)); 70.15 (*t*, $CH_2$–C(5)); 70.63 (*d*, C(8)); 72.41, 72.63, 72.66, 72.79 (4*t*, 4 Ph$CH_2$); 75.36, 78.87 (*d*, C(6), C(7)); 111.13 (*dd*, *J*(P,C) = 8.3, 3 C(3′)); 124.65 (*dd*, *J*(P,C) = 15.48, 3 C(2′)); 127.23–128.36 (several *d*); 137.53 (br. *s*); 137.56 (*s*); 137.97 (*s*); 139.10 (*s*); 142.47 (*s*); 143.73 (*d*, *J*(P,C) = 83.3, 3 C(1′)); 147.65 (*dd*, *J*(P,C) = 5.8, 3 C(4′)). $^{31}$P-NMR (121 MHz, $CDCl_3$): −22.53 (*s*). FAB-MS: 703 (100, $M^+$), 627 (7), 453 (8), 91 (70).

*(5R,6R,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-2-[(E)-2-phenylethenyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine* (**26**). *a*) A soln. of **10** (30 mg, 0.044 mmol), $Pd(OAc)_2$ (1 mg, 6.3 μmol), $Ph_3P$ (2.8 mg, 10.7 μmol), $K_2CO_3$ (9.3 mg, 0.0675 mmol), and styrene (0.1 ml, 0.87 mmol) in DMF (0.7 ml) was stirred at 80° for 12 h. Workup and FC ($Et_2O$/hexane 1:1) gave **26** (14 mg, 42%) and **7** (6 mg, 25%).

*b*) As described in *a*, but with $Pd_2(OAc)_2$(2-tolyl)$_3$ instead of $Pd(OAc)_2$ and $PPh_3$, **26** (17 mg, 51%), was obtained.

*c*) As described in *a* but in DMF/$H_2O$ 6:1, **26** (18 mg, 54%) and **7** (4 mg, 16%) were obtained.

*d*) As described in *c* but with [$Pd_2(OAc)_2$(2-tolyl)$_2$] instead of [$Pd(OAc)_2$] and $PPh_3$, **26** (20 mg, 59%) and **7** (25 mg, 10%) were obtained.

*Data of* **26**: $R_f$ ($Et_2O$/hexane 1:1) 0.31. UV ($CHCl_3$): 311 (4.42), 300 (4.43), 229 (4.30). IR ($CHCl_3$): 3011*w*, 2958*m*, 2858*m*, 1678*w*, 1496*w*, 1467*m*, 1397*w*, 1264*w*, 1110*m*, 909*s*, 818*w*, 651*w*. $^1$H-NMR ($CDCl_3$): 3.76 (*dd*, *J* = 10.6, 5.6, CH–C(5)); 3.86 (*dd*, *J* = 10.6, 2.2, CH'–C(5)); 3.86 (*t*, *J* ≈ 7.8, H–C(6)); 4.11 (*dd*, *J* = 7.2, 5.3, H–C(7)); 4.19 (*ddd*, *J* = 8.1, 5.3, 2.8, H–C(5)); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 12.0, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 5.3, H–C(8)); 4.83 (*d*, *J* = 11.5, 2 PhC*H*); 4.89 (*d*, *J* = 11.8, PhC*H*); 5.22 (*d*, *J* = 11.8, PhC*H*); 7.00 (*d*, *J* = 16.2, 1 olef. H); 7.06 (*s*, H–C(3)); 7.18–7.39 (*m*, 20 arom. H); 7.45–7.52 (5 arom. H, 1 olef. H). $^{13}$C-NMR ($CDCl_3$): 58.16 (*d*, C(5)); 68.47 (*t*, $CH_2$–C(5)); 72.72, 73.40, 74.07, 74.29 (4*t*, 4 Ph$CH_2$); 74.24, 76.30, 82.03 (3*d*, C(6), C(7), C(8)); 115.95 (*d*); 120.93 (*d*); 126.50 (*d*, 2 arom. C); 127.21 (*d*, 2 arom. C); 127.59 (*d*); 128.12–128.81 (several *d*); 137.60, 138.13, 138.18, 138.20, 138.57 (5*s*); 140.93 (*s*, C(2)); 144.73 (*s*, C(8a)). FAB-MS: 636 (100, $[M+1]^+$).

*(E)-3-{(5R,6R,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl}pro-2-enenitrile* (**27**). *a*) A soln. of **10** (60 mg, 0.087 mmol), [$Pd(OAc]_2$] (4 mg, 0.018 mmol), $Ph_3P$ (3.3 mg, 0.0216 mmol), $K_2CO_3$ (75 mg, 0.546 mmol), and acrylonitrile (0.1 ml, 1.50 mmol) in DMF (1 ml) were stirred at 90° for 16 h. Workup and FC ($Et_2O$/hexane 1:1) gave **27** (22 mg, 41%) and **7** (8 mg, 16%).

*b*) As described in *a* but with [$Pd_2(OAc)_2$[P(2-tolyl)$_3$]$_2$] instead of [$Pd(OAc)_2$] and $PPh_3$, **27** (23 mg, 42%) and **7** (7 mg, 14%) were obtained.

*Data of* **27**: $R_f$ ($Et_2O$/hexane 1:1): 0.32. UV ($CHCl_3$): 292 (4.21), 243 (3.67). IR ($CHCl_3$): 3008*m*, 2926*m*, 2869*m*, 2869*w*, 2215*w*, 1952*w*, 1869*w*, 1628*w*, 1497*w*, 1455*w*, 1361*m*, 1336*w*, 1261*w*, 1095*s*, 1028*m*, 958*w*. $^1$H-NMR ($CDCl_3$): 3.70 (*dd*, *J* = 10.3, 5.6, CH–C(5)); 3.80 (*dd*, *J* = 10.3, 2.8, CH'–C(5)); 3.81 (*dd*, *J* = 8.1, 7.5, H–C(6)); 4.07 (*dd*, *J* = 7.2, 5.6, H–C(7)); 4.17 (*ddd*, *J* = 8.1, 5.6, 2.8, H–C(5)); 4.42 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 11.5, 2 PhC*H*); 4.67 (*d*, *J* = 11.2, PhC*H*); 4.69 (*d*, *J* = 5.3, H–C(8)); 4.80 (*d*, *J* = 11.2, PhC*H*); 4.82 (*d*, *J* = 11.8, PhC*H*); 4.86 (*d*, *J* = 11.8, PhC*H*); 5.14 (*d*, *J* = 11.5, PhC*H*); 6.10 (*d*, *J* = 16.2, H–C(α)); 7.14 (*s*, H–C(3)); 7.20 (*d*, *J* = 16.2, H–C(β)); 7.17–7.45 (*m*, 20 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.54 (*d*, C(5)); 68.26 (*t*, $CH_2$–C(5)); 72.95, 73.45, 74.16, 74.28 (4*t*, 4 Ph$CH_2$); 73.68, 75.85, 81.38 (3*d*, C(6), C(7), C(8)); 93.67 (*d*, C(α)); 119.46 (*s*, CN); 120.56 (*d*, C(β)); 128.08–128.86 (several *d*, including C(3)); 137.26 (*s*); 137.66 (br. *s*); 137.86 (*s*); 141.90 (*s*, C(2)); 146.32 (*s*, C(8a)). EI-MS: 612 (2, $[M+1]^+$), 520 (9), 398 (70), 292 (100), 187 (59).

*Methyl (5R,6R,7S,8S)-6,7,8-Trihydroxy-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-propionate* (**28**). A soln. of **25** (110 mg, 0.171 mmol) in MeOH/AcOEt/AcOH 1:1:1 (5 ml) was treated with 10% Pd/C (50 mg) and hydrogenated for 24 h at 6 bar. Filtration and crystallization from $H_2O$ gave **28** (40 mg, 82%). Colourless crystals. $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1) 0.13. UV ($CHCl_3$): 254 (3.3). IR ($CHCl_3$): 3399*m* (br.), 3065*m*, 3044*m*, 2923*m*, 2852*w*, 1710*s*, 1692*s*, 1596*m*, 1498*s*, 1401*s*, 1291*m*, 1071*m*, 689*w*. $^1$H-NMR ($CD_3OD$): 2.66 (*t*, *J* = 7.5, 2 H); 2.87 (*t*, *J* = 7.5, 2 H); 3.63 (*s*, MeO); 3.68 (*t*, *J* ≈ 8.4, irrad. at 4.54 → *d*, *J* ≈ 8.0, H–C(7)); 3.81 (*t*, *J* ≈ 9.3, H–C(6)); 3.90–3.96 (*m*, H–C(5), CH–C(5)); 4.16 (*dd*, *J* = 12.3, 3.1, CH'–C(5)); 4.54 (*d*, *J* = 8.4, H–C(8)); 7.25 (*s*, H–C(3)). $^{13}$C-NMR ($CD_3OD$): 22.80, 34.01 (2*t*); 52.39 (*q*, MeO); 61.12 (*t*, $CH_2$–C(5)); 63.83 (*d*, C(5)); 69.12, 69.18, 76.15 (3*d*, C(6), C(7), C(8)); 116.78 (*d*, C(3)); 138.71 (*s*, C(2)); 147.56 (*s*, C(8a)); 174.92 (*s*, C=O). CI-MS: 287 (2, $[M+1]^+$), 227 (100), 145 (4). Anal. calc. for $C_{12}H_{18}N_2O_6 \cdot 0.5\ H_2O$ (295.29): C 48.55, H 6.48, N 9.49; found: C 48.55, H 6.20, N 9.37.

*(5R,6R,7S,8S)-6,7,8-Trihydroxy-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-propanoic acid Hydrochloride* (**31** · HCl). A soln. of **28** (32 mg, 0.112 mmol) in 1M aq. HCl (1 ml) was stirred for 1 h at 40°. Evaporation of the solvent, dissolution in $H_2O$, and lyophilization gave **31** · HCl (34 mg, 100%). Colourless, hygroscopic resin. $R_f$ (AcOEt/MeOH/$H_2O$ 3:1:1): 0.05. $^1$H-NMR ($D_2O$): 2.73, 2.96 (2*t*, *J* = 7.1, 4 H); 3.84 (*t*, *J* = 9.5, H–C(7)); 3.96 (*t*, *J* = 9.5, H–C(6)); 4.04 (*dd*, *J* = 13.1, 2.8, CH–C(5)); 4.12–4.15 (*m*, H–C(5)); 4.20 (*d*, *J* = 12.8, 1.5, CH'–C(5)); 4.78 (*d*, *J* = 7.8, H–C(8)); 7.38 (*s*, H–C(3)). $^{13}$C-NMR ($D_2O$): 22.39, 35.06 (2*t*); 61.04 (*t*, $CH_2$–C(5)); 64.94 (*d*, C(5)); 69.18, 69.66, 76.07 (3*d*, C(6), C(7), C(8)); 119.24 (*d*, C(3)); 137.11 (*s*, C(2)); 147.61 (*s*, C(8a)); 178.34 (*s*, C=O). EI-MS: 273 (100, $[M+1]^+$).

*(5R,6R,7S,8S)-5-(Hydroxymethyl)-2-(2-phenylethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6,7,8-triol* (**29**). *a*) A soln. of **26** (50 mg, 0.075 mmol) in AcOH (5 ml) was treated with 10% Pd/C (50 mg) and hydrogenated at 6 bar for 68 h. Filtration and evaporation of the solvent gave a mixture ($^1$H-NMR) of partially

debenzylated derivatives of **26** with a reduced double bond. The debenzylation proceeded only insignificantly upon further hydrogenation with fresh catalyst. After filtration and evaporation, the residue was dissolved in $CH_2Cl_2$ (5 ml), treated at $-78°$ with a 1M soln. of $BCl_3$ (0.4 ml) and stirred, until the mixture had attained 23° (*ca.* 3 h). The soln. was cooled to $-78°$, treated with $H_2O$, and warmed to 23°. Evaporation, FC (AcOEt/MeOH/$H_2O$ 20:1:1), and crystallization from AcOEt/MeOH/$H_2O$ 10:1:1 gave **29** (20 mg, 88%).

*b*) As described in *a* for **26**, but with **32**, **29** (21 mg, 91%) was obtained.

*Data of* **29**: $R_f$ (AcOEt/MeOH/$H_2O$ 10:1:1): 0.10. $^1$H-NMR ($CD_3OD$): 2.78–2.92 (*m*, 4 H); 3.66 (*dd*, $J$ = 8.7, 8.1, H–C(7)); 3.78 (*dd*, $J$ = 8.7, 8.1, H–C(6)); 3.82–3.84 (*m*, H–C(5)); 3.87–3.92 (*m*, CH–C(5)); 4.11 (*dd*, $J$ = 11.8, 1.9, CH′–C(5)); 4.49 (*d*, $J$ = 7.8, H–C(8)); 7.04 (*s*, H–C(3)); 7.07–7.25 (*m*, 5 arom. H). $^{13}$C-NMR ($CD_3OD$): 30.56, 36.66 (2*t*); 61.50 (*t*, $CH_2$–C(5)); 63.28 (*d*, C(5)); 69.41, 69.62, 76.59 (3*d*, C(6), C(7), C(8)); 115.72 (*d*, C(3)); 127.32 (*d*); 129.65 (2*d*); 129.69 (2*d*); 141.69 (*s*); 143.15 (*s*); 147.35 (*s*). CI-MS: 305 (100, $[M+1]^+$), 237 (48), 223 (58), 213 (64), 91 (59), 78 (77). Anal. calc. for $C_{16}H_{20}N_2O_4 \cdot 0.7\ H_2O$ (304.35): C 60.63, H 6.80, N 8.84; found: C 60.79, H 6.74, N 8.72.

*(5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)5-[(benzyloxy)methyl]-2-(2-phenylethynyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**32**). *a*) A mixture of **10** (400 mg, 0.58 mmol), $[Pd(PPh_3)_4]$ (34 mg, 0.294 mmol), $Et_3N$ (0.4 ml), CuI (11 mg, 0.058 mmol), and phenylacetylene (0.2 ml, 1.82 mmol) in DMF (10 ml) was stirred for 2 h at 80° under Ar. Workup, FC ($Et_2O$/hexane 1:2), and crystallization from $Et_2O$/hexane gave **32** (315 mg, 82%) and **7** (45 mg, 15%). $R_f$ ($Et_2O$/hexane 1:1) 0.46. M.p. 108°. UV ($CHCl_3$): 285 (3.8), 268 (3.78). IR ($CHCl_3$): 3066*m*, 3008*m*, 2922*w*, 2868*m*, 2220*w*, 1951*w*, 1878*w*, 1810*w*, 1735*w*, 1600*w*, 1496*s*, 1454*s*, 1362*m*, 1337*w*, 1097*s*, 1070*s*, 1028*s*, 913*w*, 863*w*. $^1$H-NMR ($CDCl_3$): 3.76 (*dd*, $J$ = 10.3, 5.3, CH–C(5)); 3.87 (*dd*, $J$ = 10.3, 2.8, CH′–C(5)); 3.88 (*t*, $J$ = 6.9, H–C(6)); 4.14 (*dd*, $J$ = 6.9, 5.0, H–C(7)); 4.23 (*ddd*, $J$ = 7.0, 5.6, 2.8, H–C(5)); 4.47 (*d*, $J$ = 11.8, PhC*H*); 4.51 (*d*, $J$ = 11.2, PhC*H*); 4.53 (*d*, $J$ = 12.1, PhC*H*); 4.68 (*d*, $J$ = 11.5, PhC*H*); 4.76 (*d*, $J$ = 5.3, H–C(8)); 4.81 (*d*, $J$ = 11.5, PhC*H*); 4.83 (*d*, $J$ = 11.5, PhC*H*); 4.88 (*d*, $J$ = 11.5, PhC*H*); 5.10 (*d*, $J$ = 11.5, PhC*H*); 7.01–7.47 (*m*, 23 arom. H, H–C(3)); 7.54–7.59 (*m*, 2 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.42 (*d*, C(5)); 68.49 (*t*, $CH_2$–C(5)); 72.79, 73.47, 73.95, 74.16 (4*t*, 4 Ph$CH_2$); 73.84, 74.16, 81.72 (3*d*, C(6), C(7), C(8)); 83.63, 89.34 (2*s*, C≡C); 122.13 (*d*, C(3)); 123.71 (*s*); 124.62 (*s*); 127.86–128.83 (several *d*); 131.82 (*d*, 2 arom. C); 137.48, 137.81, 138.00, 138.44 (4*s*); 144.47 (*s*, C(8a)). FAB-MS: 661 (100, $[M+1]^+$). Anal. calc. for $C_{44}H_{40}N_2O_4$ (660.01): C 79.98, H 6.10, N 4.24; found: C 79.83, H 6.35, N 4.24.

*(5*R*,6*R*,7*S*,8*S*)-2-(3-Aminopropyl)-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol* (**30**). A soln. of **27** (8 mg, 0.0131 mmol) in MeOH/AcOH 1:1 (2 ml) was treated with 10% Pd/C (10 mg) and hydrogenated for 17 h at 6 bar. Filtration, evaporation of the solvent, dissolution in $H_2O$, lyophylization, and ion-exchange chromatography (*Amberlite CG-50*, $NH_4^+$ form, elution with 0.1M aq. ammonia) gave **30** (2.6 mg, 59%). Hygroscopic colourless solid. $R_f$ (AcOEt/MeOH/$H_2O$ 5:1:1): 0.03. $^1$H-NMR ($D_2O$): 1.89 (*m*, irrad. at 2.62 → *t*, $J \approx 7.0$, irrad. at 2.99 → *t*, $J \approx 7.0$, 2 H–C(2′)); 2.62 (*t*, $J$ = 7.5, irrad. at 1.89 → *s*, 2 H–C(3′)); 2.99 (*dd*, $J$ = 8.1, 7.5, 2 H–C(1′)); 3.74 (*dd*, $J \approx 9.0$, 8.7, H–C(7)); 3.88 (*t*, $J$ = 9.0, H–C(6)); 3.90–3.93 (*m*, H–C(5)); 4.03 (*dd*, $J$ = 12.7, 1.9, CH–C(5)); 4.17 (*dd*, $J$ = 12.5, 2.5, CH′–C(5)); 4.55 (*d*, $J$ = 9.0, H–C(8)); 7.04 (*s*, H–C(3)). $^{13}$C-NMR ($CDCl_3$, 125 MHz): 26.82 (*t*, C(2′)); 29.24 (*t*, C(1)); 41.42 (*t*, C(3′)); 61.23 (*t*, $CH_2$–C(5)); 62.81 (*d*, C(5)); 69.89, 70.65, 77.48 (3*d*, C(6), C(7), C(8)); 116.63 (*d*, C(3); 139.34 (*s*, C(2)); 149.31 (*s*, C(8a)). EI-MS: 258 (100, $[M+1]^+$).

*(*R*)- and (*S*)-2-Phenyl-1-[(5*R*,6*R*,7*S*,8*S*)-6,7,8-tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl]ethanol* (**33** and **34**, resp.). *a*) *Preparation of a* ca. *1.3*M *BnLi Soln*[14]). A 1.6M soln. of BuLi in hexane (5 ml, 8 mmol) at $-78°$ was treated with TMEDA (1.2 ml, 8 mmol) and allowed to reach 0°. The mixture was cooled to $-78°$, and toluene (1 ml) was added dropwise. The mixture was allowed to reach 23° within *ca.* 3 h and stirred for an additional 5 h, when the soln. had adopted a dark orange colour.

*b*) *Preparation of* **33** *and* **34** *by Addition of BnLi to* **12**. A soln. of **12** (257 mg, 0.467 mmol) in THF was treated at $-78°$ with 0.5 ml of the BnLi soln. prepared as described in *a* and allowed to reach 23° within 1 h. The mixture was cooled to $-78°$ and treated with sat. aq. $NH_4Cl$. Workup and FC (AcOEt/Hexane 1:2) gave a *ca.* 45:55 mixture of **33** and **34** (213 mg, 64%), not separable by crystallization, FC or HPLC, and **7** (31 mg, 12%).

*c*) *Preparation of* **33** *by Denaphthoylation of* **35**. A soln. of **35** (32 mg, 0.038 mmol) in MeOH (4 ml) was treated with a 1M soln. of MeONa in MeOH (0.4 ml) and stirred at 60° for 40 min. The mixture was treated with 1M aq. HCl until the pH was slightly acidic (*ca.* 4–5 according to pH-paper), and the solvent was evaporated. Workup and FC (AcOEt/Hexane 2:1) gave **33** (26 mg, 98%), which crystallized from $Et_2O$/hexane. Colourless needles.

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[14]) Similar procedures are given in [48][49].

*d*) *Preparation of* **34** *by Denaphthoylation of* **36**. As described in *c* for **35**, but with **36**, **34** (25 mg, 96%) was obtained. Colourless, cotton-like needles.

*Data of* **33**: M.p.: 117°. $R_f$ (AcOEt/Hexane 1:1) 0.45. IR ($CHCl_3$): 3593*w*, 3443*w* (br.), 3085*w*, 3004*m*, 2923*m*, 2663*m*, 1954*w*, 1613*w*, 1706*w*, 1491*m*, 1454*s*, 1362*m*, 1095*s*, 1026*m*, 909*m*, 602*w*. $^1$H-NMR ($CDCl_3$): 2.57 (br. *d*, *J* = 4.7, exchange with $CD_3OD$, OH); 3.07 (*dd*, *J* = 13.7, 8.4, H–C(2′)); 3.20 (*dd*, *J* = 13.5, 5.0, H–C(2′)); 3.70 (*dd*, *J* = 10.3, 5.3, CH–C(5)); 3.81 (*dd*, *J* = 10.6, 3.1, CH′–C(5)); 3.86 (*t*, *J* = 7.5, H–C(6)); 4.09 (*dd*, *J* = 7.5, 5.6, H–C(7)); 4.14 (*ddd*, *J* = 7.5, 5.1, 3.1, H–C(5)); 4.41 (*d*, *J* = 12.1, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 11.2, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.75 (*d*, *J* = 5.0, H–C(8)); 4.82 (*d*, *J* = 11.5, PhC*H*); 4.83 (*dd*, *J* = 11.2, PhC*H*); 4.84 (*d*, *J* = 11.5, PhC*H*); 4.94 (br. *dt*, *J* ≈ 9.0, 4.7, H–C(1′)); 5.14 (*d*, *J* = 11.5, PhC*H*); 6.83 (*s*, H–C(3)); 7.17–7.38 (*m*, 23 arom. H); 7.41–7.44 (*m*, 2 arom. H). $^{13}$C-NMR ($CDCl_3$): 43.93 (*t*, C(2′)); 58.16 (*d*, C(5)); 68.42 (*t*, $CH_2$C(5)); 70.02 (*d*, C(1′)); 72.64, 73.39, 74.07, 74.25 (4*t*, 4 Ph$CH_2$); 74.24, 76.43, 82.03 (3*d*, C(6), C(7), C(8)); 116.94 (*d*, C(3)); 127.10–128.76 (several *d*); 131.41 (*d*); 137.60, 138.13, 138.49, 138.84 (4*s*), 143.60 (*s*); 145.02 (*s*).

*X-Ray Analysis of* **33**: Monoclinic *P*21; *a* = 5.095(1), *b* = 26.547(10), *c* = 13.365(2); *V* = 1802.0(8)Å$^3$, $D_{calc}$ = 1.255 Mg/m$^3$, *Z* = 2. The reflexions were measured on an *Enraf-Nonius-CAD4* diffractometer (graphite monochromator, Cu$K_\alpha$ radiation, $\lambda$ = 0.71073) at 170 K. *R* = 0.0822, $R_w$ = 0.1823. The structures were solved with the direct-methods routine of SIR97. Because of limited data the non-H-atoms were refined only isotropically with SHELX-97. H-Atoms were calculated at idealized positions and included in the structure-factor calculation with fixed isotropic displacement parameters.

*Data of* **34**: M.p.: 91°. $R_f$ (AcOEt/Hexane 1:1) 0.45. IR ($CHCl_3$: 3594*w*, 3444*w* (br.), 3088*w*, 3007*m*, 2922*m*, 2666*m*, 1951*w*, 1611*w*, 1706*w*, 1496*m*, 1454*s*, 1362*m*, 1095*s*, 1026*m*, 909*m*, 600*w*. $^1$H-NMR ($CDCl_3$): 2.56 (br. *d*, *J* = 4.4, exchange with $CD_3OD$, OH): 3.11 (*dd*, *J* = 13.7, 8.1, H–C(2′)); 3.21 (*dd*, *J* = 13.7, 5.3, H–C(2′)); 3.71 (*dd*, *J* = 10.3, 5.3, CH–C(5)); 3.81 (*dd*, *J* = 10.3, 3.1, CH′–C(5)); 3.85 (*t*, *J* = 7.5, H–C(6)); 4.10 (*dd*, *J* = 7.5, 5.6, H–C(7)); 4.15 (*ddd*, *J* = 7.5, 5.1, 3.1, H–C(5)); 4.42 (*d*, *J* = 12.1, PhC*H*); 4.47 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.2, PhC*H*); 4.70 (*d*, *J* = 11.2, PhC*H*); 4.75 (*d*, *J* = 5.6, H–C(8)); 4.83 (*d*, *J* = 11.2, PhC*H*); 4.84 (*dd*, *J* = 11.2, PhC*H*); 4.85 (*d*, *J* = 11.5, PhC*H*); 4.90–4.96 (*m*, H–C(1′)); 5.14 (*d*, *J* = 11.2, PhC*H*); 6.84 (*s*, H–C(3)); 7.17–7.38 (*m*, 23 arom. H); 7.42–7.45 (*m*, 2 arom. H). $^{13}$C-NMR ($CDCl_3$): 43.89 (*t*, C(2′)); 58.10 (*d*, C(5)); 68.39 (*t*, $CH_2$–C(5)); 69.81 (*d*, C(1′)); 72.56, 73.39, 74.05, 74.21 (4*t*, 4 Ph$CH_2$); 74.21, 76.25, 82.17 (3*d*, C(6), C(7), C(8)); 113.78 (*d*, C(3)); 127.86–128.76 (several *d*); 129.82 (*d*); 137.91, 137.99, 138.52, 138.85 (4*s*), 143.68 (*s*); 144.81 (*s*).

*(1*R*)- and (1*S*)-2-Phenyl-1-{(5*R*,6*R*,7*S*,8*S*)-6,7,8-tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl]}ethyl Naphthalene-2-carboxylate* (**35** and **36**, resp.). A soln. of **33/34** (45:55, 100 mg, 0.147 mmol) in pyridine (3 ml) was treated with 2-naphthoyl chloride (100 mg, 0.52 mmol) and stirred for 6 h at 60°. Workup and FC (AcOEt/hexane 1:4) gave a 45:55 mixture **35/36** (98 mg, 80%). HPLC (*Spherisorb SW*, AcOEt/hexane 1:5) gave **35** (40 m, 32%) and **36** (44 mg, 36%).

*Data of* **35**: $R_f$ (AcOEt/hexane 1:4) 0.21. IR ($CHCl_3$): 3065*m*, 3008*m*, 2928*m*, 2867*m*, 1710*s*, 1632*w*, 1602*m*, 1496*m*, 1454*m*, 1356*m*, 1281*s*, 1095*s*, 1028*m*, 827*w*. $^1$H-NMR ($CDCl_3$): 3.50–3.60 (*m*, 2 H–C(2′)); 3.68 (*dd*, *J* = 10.3, 5.3, CH–C(5)); 3.79 (*dd*, *J* = 10.6, 3.1, CH′–C(5)); 3.86 (*dd*, *J* = 7.8, 7.5, H–C(6)); 4.11 (*dd*, *J* = 7.2, 5.0, H–C(7)); 4.11–4.16 (*m*, H–C(5)); 4.35 (*d*, *J* = 12.1, PhC*H*); 4.40 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.2, PhC*H*); 4.82 (*d*, *J* = 11.5, PhC*H*); 4.84 (*d*, *J* = 5.0, H–C(8)); 4.84 (br. *d*, *J* = 11.2, 2 PhC*H*); 5.15 (*d*, *J* = 11.5, PhC*H*); 6.36 (*t*, *J* = 6.5, H–C(1′)); 6.99 (*s*, H–C(3)); 7.11–7.35 (*m*, 22 arom. H); 7.38–7.42 (*m*, 2 arom. H); 7.49–7.61 (*m*, 3 arom. H); 7.81–7.92 (*m*, 3 arom. H); 8.01–8.09 (*m*, 2 arom. H); 8.59 (*s*, 1 arom. H). $^{13}$C-NMR ($CDCl_3$): 40.53 (*t*, C(2′)); 58.00 (*d*, C(5)); 68.14 (*t*, $CH_2$–C(5)); 72.34 (*d*, C(1′)); 72.36, 73.35, 73.87, 74.18 (4*t*, 4 Ph$CH_2$); 73.89, 76.35, 81.98 (3*d*, C(6), C(7) C(8)); 116.08 (*d*, C(3)); 125.67, 126.58, 126.73, 127.78, 127.96 (5*d*); 128.15–128.68 (several *d*); 129.65 (*d*); 129.91 (*d*, 2 C); 131.40 (*d*); 132.76 (*s*); 135.74 (*s*); 137.48, 137.89, 138.13, 138.49 (4*s*), 140.72 (*s*); 143.89 (*s*, C(8a)); 166.38 (*s*, C=O).

*Data of* **36**: $R_f$ (AcOEt/hexane 1:4) 0.22. IR ($CHCl_3$): 3065*m*, 3008*m*, 2928*m*, 2867*m*, 1951*w*, 1708*s*, 1632*w*, 1602*m*, 1496*m*, 1454*m*, 1356*m*, 1281*s*, 1095*s*, 1028*m*, 955*m*, 866*w*. $^1$H-NMR ($CDCl_3$): 3.56 (*dd*, *J* = 13.4, 7.5, H–C(2′)); 3.62 (*dd*, *J* = 13.5, 7.2, H–C(2′)); 3.72 (*dd*, *J* = 10.3, 5.3, CH–C(5)); 3.83 (*dd*, *J* = 10.3, 2.8, CH–C(5)); 3.85 (*dd*, *J* = 7.7, 7.2, H–C(6)); 4.13 (*dd*, *J* = 7.2, 5.0, H–C(7)); 4.13–4.18 (*m*, H–C(5)); 4.39 (*d*, *J* = 12.1, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.50 (*d*, *J* = 11.5, PhC*H*); 4.68 (*d*, *J* = 11.2, PhC*H*); 4.81 (*d*, *J* = 11.5, PhC*H*); 4.82 (*d*, *J* = 5.0, H–C(8)); 4.83 (*dd*, *J* = 11.2, PhC*H*); 4.84 (*d*, *J* = 11.5, PhC*H*); 5.15 (*d*, *J* = 11.5, PhC*H*); 6.38 (*t*, *J* = 7.2, H–C(1′)); 7.07 (*s*, H–C(3)); 7.11–7.35 (*m*, 22 arom. H); 7.41–7.44 (*m*, 2 arom. H); 7.50–7.61 (*m*, 3 arom. H); 7.83–7.94 (*m*, 3 arom. H); 8.06–8.09 (*m*, 2 arom. H); 8.62 (*s*, 1 arom. H). $^{13}$C-NMR ($CDCl_3$): 39.96 (*t*, C(2′)); 57.92 (*d*, C(5)); 68.22 (*t*, $CH_2$–C(5)); 71.92 (*d*, C(1′)); 72.17, 73.42, 73.79, 74.18 (4*t*, 4 Ph$CH_2$); 74.00, 76.43, 82.24 (3*d*, C(6), C(7), C(8)); 116.94 (*d*, C(3)); 125.76, 126.58, 126.73, 127.30, 127.95 (5*d*);

128.15 – 128.73 (several *d*); 129.64 (*d*); 129.93 (*d*, 2 C); 131.41 (*d*); 132.76 (*s*); 135.74 (*s*), 137.55, 137.90, 138.10, 138.55 (4*s*), 140.33 (*s*); 143.84 (*s*, C(8a)); 166.41 (*s*, C=O).

*(5*R*,6*R*,7*S*,8*S*)-5-(Hydroxymethyl)-2-[(*R*)- and (*S*)-1-hydroxy-2-phenylethyl]-5,6,7,8-tetrahydromidazo[1,2-*a*]-pyridine-6,7,8-triol* (**37** and **38**, resp.). *a*) A soln. of **33** (30 mg, 0.044 mmol) in $CH_2Cl_2$ at $-78°$ was treated dropwise with a 1M soln. of $BCl_3$ (0.3 ml), stirred until the mixture had reached 0° (*ca.* 3 h), cooled to $-78°$, and treated with $H_2O$ (0.5 ml). Evaporation of the solvent, FC (AcOEt/MeOH 10:1), and ion-exchange chromatography (*Amberlite CG-120*, $NH_4^+$ form, elution with 1M $NH_4OH$) gave **37** (10.3 mg, 73%).

*b*) As described in *a* for **33**, but with **34**, **38** (10.0 mg, 71%) was obtained.

*Data of* **37**: $R_f$ (AcOEt/MeOH 5:1): 0.12. $^1$H-NMR (300 MHz, $D_2O$): 3.09 (*dd*, *J* = 13.5, 7.5, H−C(2′)); 3.19 (*dd*, *J* = 13.7, 6.5, H−C(2′)); 3.76 (*t*, *J* = 9.0, H−C(7)); 3.89 (*t*, *J* = 9.0, H−C(6)); 3.93 – 4.04 (*m*, H−C(5), CH−C(5)); 4.13 – 4.17 (*m*, CH′−C(5)); 4.61 (*d*, *J* = 8.4, H−C(8)); 4.97 (br. *t*, *J* = 7.0, H−C(1′)); 7.11 (*s*, H−C(3)); 7.22 – 7.35 (*m*, 5 arom. H). $^{13}$C-NMR (300 MHz, $D_2O$): 44.98 (*t*, C(2′)); 61.43 (*t*, $CH_2$−C(5)); 63.45 (*d*, C(5)); 70.01, 70.59, 71.36, 77.39 (4*d*, C(6), C(7), C(8), C(1′)); 117.81 (*d*, C(3)); 129.70 (*d*, 1 arom. C); 131.58 (*d*, 2 arom. C); 132.83 (*d*, 2 arom. C); 140.86 (*s*, 1 arom. C); 145.30 (*s*, C(2)); 149.05 (*s*, C(8a)). CI-MS: 321 (100, $[M+1]^+$).

*Data of* **38**: $R_f$ (AcOEt/MeOH 5:1): 0.12. $^1$H-NMR (300 MHz, $D_2O$): 3.07 (*dd*, *J* = 13.5, 7.5, H−C(2′)); 3.20 (*dd*, *J* = 13.7, 6.5, H−C(2′)); 3.75 (*t*, *J* = 9.0, H−C(7)); 3.88 (*t*, *J* = 9.0, H−C(6)); 3.95 – 4.05 (*m*, H−C(5), CH−C(5)); 4.15 (*dd*, *J* = 12.6, 2.0, CH′−C(5)); 4.59 (*d*, *J* = 8.7, H−C(8)); 4.95 (br. *t*, *J* = 7.0, H−C(1′)); 7.10 (*s*, H−C(3)); 7.21 – 7.35 (*m*, 5 arom. H). $^{13}$C-NMR (300 MHz, $D_2O$): 44.83 (*t*, C(2′)); 61.42 (*t*, $CH_2$−C(5)); 63.45 (*d*, C(5)); 70.03, 70.57, 71.48, 77.36 (4*d*, C(6), C(7), C(8), C(1′)); 117.79 (*d*, C(3)); 129.68 (*d*, 1 arom. C); 131.51 (*d*, 2 arom. C); 132.56 (*d*, 2 arom. C); 140.86 (*s*, 1 arom. C); 145.31 (*s*, C(2)); 149.00 (*s*, C(8a)). CI-MS: 321 (100, $[M+1]^+$).

*Inhibition Studies.* Determination of the inhibition constants ($K_i$) or the $IC_{50}$ values was performed with a range of inhibitor concentrations (typically 4 – 8 concentrations) which bracket the $K_i$ or $IC_{50}$ value.

a) *Inhibition of Sweet Almonds β-Glucosidases.* Inhibition constants ($K_i$) and $IC_{50}$ values were determined at 37°, using a 0.08M $KH_2PO_4/K_2HPO_4$ buffer (pH 6.8) and 4-nitrophenyl β-D-glucopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme in presence of the inhibitor during 30 min or 1 h by the addition of the substrate. The increase of absorption per min at 400 nm was taken as rate for the hydrolysis of the substrate. The increase was linear during all measurements (2 min). $IC_{50}$ Values were determined by plotting the rate of substrate hydrolysis *vs.* the inhibitor concentration. Determination of the inhibitor concentration corresponding to half the rate measured in absence of the inhibitor gave the appropriate $IC_{50}$ value. $K_i$ Values were determined by taking the slopes from the *Lineweaver-Burk* plots [50] and plotting them *vs.* the inhibitor concentrations [51]. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot provided the appropriate $K_i$ value. To establish whether an inhibitor is slow binding or not, $IC_{50}$ values determined by addition of the substrate after preincubation of the enzyme and the inhibitor during 30 min were compared to those determined by addition of the enzyme to substrate-inhibitor solutions.

b) *Inhibition of* Caldocellum saccharolyticum *β-Glucosidase.* As described in *a*, the inhibition constants ($K_i$) and $IC_{50}$ values were determined at 55°.

c) *Inhibition of* Brewer's Yeast *α-Glucosidase.* As described in *a*, the inhibition constants ($K_i$) were determined using 0.025M $KH_2PO_4/K_2HPO_4$/NaCl buffer (pH 6.8) and 4-nitrophenyl α-D-glucopyranoside as substrate.

d) *Determination of* $k_3$ *and* $k_4$ *Values* (according to the procedure in [43]). The enzymatic reaction was started by the addition of the enzyme to the substrate/inhibitor soln. and monitored during 30 min. Intersection of the tangent to the curve at $t = 0$ min with the asymptote gave an estimate of *k*, whereby $k = v(\text{initial})/[k_4 \cdot v(\text{end})]$. Using the equations $v = V_{max}/(1 + [S]/K_M)$, $K_i = v_i \cdot [I]/(v - v_i)$, and $k_3/k_4 = K_i(\text{initial})/(K_i(\text{end}) - 1)$, the values for $k_3$ and $k_4$, as well as for $K_i$(initial) and $K_i$(end) were determined.

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