Improved Access to Imidazole-phosphonic Acids: Synthesis of D-manno-Tetrahydroimidazopyridine-2-phosphonates¹)

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The D-manno-tetrahydroimidazopyridine-2-phosphonate **11** was prepared via a high-yielding $Pd(PPh_3)_4$ catalysed diphenylphosphonylation of the manno-iodoimidazole **12**, followed by transesterification to the diethyl phosphonate **14** and dealkylation, providing **11** in eight steps from the thionolactam **1** and in an overall yield of 15%. Alternatively, a more highly convergent synthesis based on the HgCl₂/Et₃N-promoted condensation of the thionolactam **1** with the α -aminophosphonate **24** in THF led to **11** in four steps and in the same overall yield. In the presence of HgCl₂/Et₃N, the thionolactam **1** reacted at 80° with 2-methoxyethanol to provide 66% of a 64:36 mixture of the gluco- and manno-iminoethers **29/30**. Performing the reaction at 22° yielded preferentially the gluco-isomer **29** (86%, 84:16).

Introduction. - We described the synthesis of the gluco-configured tetrahydroimidazopyridine-2-phosphonate 7 (Scheme 1) [1] and its transformation into the oleyl, phytanyl, and dolichyl imidazole-phosphonates 8-10, potential inhibitors of the glucosyl transferase Alg10p $[2]^2$). This enzyme is one of several glucosyl and mannosyl transferases involved in the biosynthesis of N-glycosylated proteins [18]. For the synthesis of the *manno*-configured analogue of the dolichyl ester 10, we required the phosphonate 11. Similarly to the synthesis of 7 from 3, it should be available by phosphonylation of the manno-iodoimidazole 12 [19]. The synthesis of 7, however, has two shortcomings. The iodoimidazole 3 was prepared by a rather long synthesis, *viz*. by a two step condensation of thionolactam 1 with aminoacetaldehyde dimethyl acetal³) to form the imidazole 2 [20], followed by diiodination and regioselective deiodination [21], and the diphenyl phosphonate 4 that was formed in the highest yield by Pdcatalysed phosphonylation of 3 to 4-6 could not be hydrolysed to the phosphonate 7 [1]. We planned to address these issues in the context of the synthesis of **11**, first by elaborating a method for the dephenylation of the *manno*-analogue of 4, and then by designing a shorter synthesis.

Synthesis. – a) *By Phosphonylation of the Iodoimidazole* **12**. The *manno*-configured phosphonates 13-15 (*Scheme 2*) were prepared by Pd-catalysed cross-coupling⁴) of

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²) Several imidazole-derived phosphonates are known. Most of them were prepared by construction of the substituted imidazole ring [3–14]. A few cases describe a phosphonylation [1][15][16], or phosphinylation, followed by oxidation [17] of an imidazole. Two sugar-derived imidazole-phosphonates are known [1][17].

³) Depending on the exact reaction conditions, this condensation provides either the pure *gluco*-imidazole **2**, or a mixture of **2** and the *manno*-isomer **17** [20].

⁴) For further examples of the Pd-catalysed coupling of heteroaryl halides with dialkyl H-phosphonates, cf. [15][22-31].



a) 1. Lawesson's reagent, toluene; 2. H₂NCH₂CH(OMe)₂, Hg(OAc)₂, THF, 5°; 3. TsOH · H₂O, toluene/H₂O, 65°; 75% [20]. b) 1. N-Iodosuccinimide, DMF, 80°; 2. EtMgBr, THF, 0°; 68-86% [21]. c) HP(O)(OR)₂, Pd(PPh₃)₄, Et₃N, toluene, 95°; 84% of **4**, 62% of **5**, and 31% of **6** [1].



a) HP(O)(OR)₂, Pd(PPh₃)₄, Et₃N, toluene, 95°; R = Ph: 86% of **13**; R = Et: 58% of **14** and 40% of **17**; R = Me: 24% of **15** and 23% of **17**. *b*) HP(O)(OSiMe₃)₂, Pd(PPh₃)₄, Et₃N, toluene, 95°; 65% of **16** and 4% of **17**. *c*) KF, 18-crown-6, EtOH, reflux; 90%, or CsF, EtOH, reflux; 84%. d) KF, 18-crown-6, MeOH, reflux; 84%, or CsF, MeOH, reflux; 88%. *e*) Me₃SiBr, CH₂Cl₂. *f*) H₂, Pd(OH)₂/C, MeOH/AcOEt/H₂O; (77% from **14**; 83% from **15**). *g*) Ac₂O, pyridine; 96%. *h*) H₂, Pd(OH)₂/C, AcOEt/MeOH/H₂O/AcOH; 82%. *i*) Ac₂O, DMAP, pyridine; 76%.

the iodoimidazole **12** [19] with diphenyl, diethyl, and dimethyl H-phosphonate, respectively. Like in the *gluco*-series [1], phosphonylation with diphenyl H-phosphonate $(Pd(PPh_3)_4, Et_3N)$ led to the highest yield and the cleanest transformation, providing 86% of **13**, while diethylphosphonylation yielded 58% of **14**, and the use of

dimethyl H-phosphonate resulted in only 24% of **15**. The formation of **14** and **15** was accompanied by significant dehalogenation of **12** to **17** [20]. The only difference to the phosphonylation of the *gluco*-imidazole **3** was the effect of the amine. 1,2,2,6,6-Pentamethylpiperidine or $EtN(i-Pr)_2$ increased the yield of the diethylphosphonylation of **3**, but lowered the yield of the diethylphosphonylation of **12** (from 58 to 51 and 43%, resp.).

Phosphonylation of **12** with bis(trimethylsilyl) H-phosphonate should readily lead to the desired phosphonic acid **16**. Indeed, this phosphonylation $(Pd(PPh_3)_4, Et_3N)$ led to the desired bis(trimethylsilyl) ester⁵) besides the dehalogenated imidazole **17**. Chromatography (*RP-C18* SiO₂; MeOH, H₂O) provided 65% of the phosphonic acid **16**. We did, however, not pursue this reaction. In addition to the high price of bis(trimethylsilyl) H-phosphonate, scale-up proved difficult, and the separation of the acid cumbersome.

Hydrolysis of the diphenyl phosphonate **13** failed under acidic and basic conditions [33-38]. Hydrogenolysis of **13** in the presence of *Adams'* catalyst (PtO₂) [39-43] provided an inseparable mixture. However, CsF-induced transesterification [39] of **13** in boiling EtOH or MeOH gave the diethyl and dimethyl phosphonates **14** (84%) and **15** (88%), respectively. Similar results (90% of **14** and 84% of **15**) were obtained when CsF was replaced by KF and 18-crown-6 [39][44].

The diethyl and dimethyl phosphonates **14** and **15** were dealkylated with Me₃SiBr [45][46], and the resulting crude phosphonic acid **16** was debenzylated (H₂, Pd(OH)₂). Treating the crude product with 3 equiv. of Et₃N, followed by lyophilisation, gave **11** (78% from **14**), mostly as the mono(triethylammonium) salt (1.10 equiv. of Et₃N according to ¹H-NMR). Chromatography of the crude hydrogenolysis product on DEAE-cellulose (elution with aq. triethylammonium hydrogencarbonate), followed by lyophilisation, provided 77 and 83% of the phosphonate **11** (1.19–1.25 equiv. of Et₃N) from **14** and **15**, respectively. According to ¹H- and ³¹P-NMR spectroscopy, the purity of **11** was not affected by chromatography on DEAE-cellulose. Acetylation of **11** (1.60 equiv. of Et₃N) gave the tetraacetate **18** in 96% yield (1.62 equiv. of Et₃N). We also examined the dealkylation of the acetylated diethyl phosphonate **20** by excess Me₃SiBr. The acetate **20** was obtained from the tetrol **19**, resulting from hydrogenolytic debenzylation of **14**. Unfortunately, this attempted dealkylation led to a complex mixture, and we did not pursue this route to **18**.

b) By Condensation of the Thionolactam 1 with the α -Aminophosphonate 24. Condensation of the gluco-thionolactam 1 with the aminophosphonates 24 or 26 instead of aminoacetaldehyde dimethyl acetal⁶) should allow for a more convergent, shorter synthesis of the gluco- and manno-phosphonates 7 and 11 (Scheme 3). The α -aminophosphonate dimethyl acetals 23 and 25⁷) were prepared similarly to the analogous diethyl acetal corresponding to 23 (diethyl [1-(benzylamino)-2,2-diethoxy-

⁵) The iodoimidazole **12** failed to react with the bis[(*tert*-butyl)dimethylsilyl] H-phosphonate; only the dehalogenated imidazole **17** (34%) was isolated. The required H-phosphonate was prepared similarly to HP(O)(OSiMe₃)₂ [32] by treating phosphoric acid with (*t*-Bu)Me₂SiCl in the presence of Et₃N in 86% yield.

⁶) The synthesis of imidazoles by condensation of thionolactams with aminoacetaldehyde dimethyl acetal is well precedented [20] [47–49]; the use of substituted aminoacetals is less well documented [50].

⁷⁾ For reviews on the preparation of α -aminophosphonic acids and their derivatives, cf. [51][52].



a) BnNH₂, MgSO₄, THF, 0° → 22°; 90%. b) HP(O)(OEt)₂, Et₃N, Me₃SiCl, CH₂Cl₂, 0° → 22°; 70%.
c) HP(O)(OMe)₂, Et₃N, Me₃SiCl, CH₂Cl₂, 0° → 22°; 60%. d) H₂, Pd/C, EtOH; 74%. e) H₂, Pd/C, MeOH; 73%. f) 1. 24, HgCl₂, Et₃N, mol. sieves (3 Å), THF, reflux; 2. TsOH · H₂O, toluene, 65°; 45% of 5/14 55:45 and 11% of 27/28 75:25. g) 1. 26, HgCl₂, Et₃N, mol. sieves (4 Å), THF, reflux; 2. TsOH · H₂O, toluene, 65°; 12% of 6/15 57:43 and 22% of 27/28 71:29. h) 24, HgCl₂, Et₃N, mol. sieves (4 Å), 2-methoxyethanol, 80°; 66% of 29/30 64:36 and 16% of 27/28 54:46. i) HgCl₂, Et₃N, mol. sieves (4 Å), 2-methoxyethanol, 22°; 86% of 29/30 84:16 and 7% of 27/28 65:35. j) As *i*, but 80°; 75% of 29/30 68:32 and 12% of 27/28 58:42.

ethyl]phosphonate) [53]. Treatment of glyoxal 1,1-dimethyl acetal (**21**) with BnNH₂ in the presence of MgSO₄ yielded 90% of the imine **22**. Addition of *in situ* generated diethyl or dimethyl trimethylsilyl phosphite [32][54–63] provided the phosphonates **23** (70%) and **25** (60%), respectively. The debenzylated aminophosphonates **24** and **26** were obtained by hydrogenolysis (10% Pd/C) of **23** and **25**, and isolated by bulb-tobulb distillation under reduced pressure in 74 and 73% yield, respectively.

The aminophosphonate **24** proved much less reactive than aminoacetaldehyde dimethyl acetal (*cf.* [20] [47]). Thus, the thionolactam **1** did not react with excess **24** up to 90° and decomposed at 120° . Hg(OAc)₂ led to partial hydrolysis and epimerisation at C(2) (*cf.* [64–66]), providing a mixture of the known lactams **27** and **28**. HgO promoted the condensation of **1** and **24**, as evidenced by the formation of the *gluco*- and *manno*-configured imidazoles **5** and **14** (17%, 55:45) upon acid treatment of the crude.

HgCl₂ in boiling THF proved more useful, but the addition of 2 equiv. of Et_3N and of molecular sieves was required to suppress the formation of **27/28** and to provide (after acid treatment of the crude) a 55:45 mixture of the desired imidazoles **5** and **14** (45%), besides 11% of **27/28** (3:1). This mixture was readily separated by chromatography to give **5** (25%) and **14** (20%). Not surprisingly, HgCl₂-promoted condensation of the thionolactam **1** with the dimethyl aminophosphonate **26** provided the *gluco-* and *manno*-configured imidazoles **6** and **15** in only 12% yield.

Unexpectedly, under otherwise identical conditions, **1** reacted with **24** in 2methoxyethanol at 80° to provide cleanly the *gluco/manno*-iminoether mixture **29/30**⁸) (64:36), isolated in 66% yield besides 16% of **27/28** (54:46). Separation of **29** and **30** proved difficult. While the *gluco*-isomer **29** was obtained pure, the *manno*-isomer **30** could not be completely separated from an unknown impurity. The iminoethers decomposed partially during chromatography on SiO₂, and addition of Et₃N was required to minimize their hydrolysis to the lactams **27/28**. The iminoethers **29/30** (75%, 68:32) and lactams **27/28** (12%, 58:42) were also obtained when **1** was treated with HgCl₂/Et₃N in 2-methoxyethanol at 80° in the absence of the aminophosphonate **24**. Performing the reaction at 22° led preferentially to the *gluco*-isomer **29** (86% of **29/30**, 84:16). Attempted debenzylation of the iminoether **29** under *Birch* conditions [71][72] resulted in a complex mixture.

In conclusion, both improved routes proved useful for the synthesis of the Dmanno-tetrahydroimidazopyridine-2-phosphonate **11**. The high-yielding diphenylphosphonylation of **12**, followed by transesterification to **14** and dealkylation, provided the phosphonate **11** in eight steps from **1** and an overall yield of 15%, while the analogous route involving a diethylphosphonylation of **12** led to **11** in 11% over seven steps. The more highly convergent synthesis, based on the two step condensation of **1** with **24**, provided **11** in four steps and an overall yield also of 15%. This appears to be the first example of the formation of an imidazole by condensation of a thionolactam and an acceptor-substituted aminoacetaldehyde acetal.

The introduction of the phosphonate group has no influence on the solution conformation (${}^{7}H_{6}$ and ${}^{6}H_{7}$ 2:1; see *Table 1* in *Exper. Part*)⁹) of the protected and unprotected *manno*-imidazoles **11**, **13**–**16**, and **18**–**20** [20][73]. The ${}^{13}C$ signals of C(5)–C(8) of **14** (*Table 2* in *Exper. Part*) were assigned on the basis of HSQC-GRASP spectrum; those of the other imidazoles were assigned by analogy. The C(2)–P bond in the phosphonates **13–15** is evidenced by ${}^{1}J(2,P)$ of 256.3, 246.6, and 245.8 Hz in the ${}^{13}C$ -NMR spectra (CDCl₃) of **13–15**, respectively.

The imine **22** is characterised by a ¹³C *doublet* at 161.18 ppm and a weak IR band at 1676 cm⁻¹ (C=N). The formation of C(1)–P bond in the phosphonates **23–26** is evidenced by ¹³C *dd*'s at 56.23, 51.60, 56.19, and 51.38 ppm, showing ¹J(1,P) of 153.5, 154.4, 153.8, and 154.4 Hz, respectively (see *Table 3* in *Exper. Part*).

⁸⁾ Glyconolactam-derived iminoethers were mostly prepared by treatment of the lactams with *Meerwein's* salt [67-69]. For the preparation of iminoethers by HgO-promoted solvolysis of thioacetamides, see [70].

⁹⁾ The direction of numbering of imidazopyridines (cf. 12 in Scheme 2) is opposite to that of pyranosides. Thus, the sides above and below the plane of the imidazoles, as defined by the clockwise and counterclockwise numbering, are interchanged relative to those defined by carbohydrate nomenclature.

The formation of the iminoethers **29** and **30** is confirmed by the disappearance of the NH signal in their ¹H-NMR spectra, ¹³C *singlets* at 160.89 (**29**) and 160.23 ppm (**30**), and strong IR bands at 1675 and 1677 cm⁻¹ (C=N) of **29** and **30**, respectively. The assignment of the *gluco-* and *manno-*configuration to **29** and **30** is based on the values of J(4,5) (7.8 and 3.7 Hz, resp.; *cf. Scheme 3*).

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Experimental Part

General. Solvents were distilled before use: THF and toluene from Na and benzophenone, CH_2Cl_2 from P_2O_5 , 2-methoxyethanol from CaH_2 . Reactions were carried out under Ar, unless stated otherwise. Molecular sieves were dried at $150^{\circ}/0.05$ Torr for 12 h. Qual. TLC: precoated silica-gel plates (*Merck* silica gel 60 F_{254}); 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), unless indicated otherwise. Optical rotations: 1-dm cell at 25°, 589 nm. UV Spectra (*ca*. 0.2 mM solns.): in 1-cm cell at 25° in the range of 190 to 500 nm (log ε values in parenthesis). FT-IR Spectra: KBr or *ca*. 2% soln. in CHCl₃, absorption in cm⁻¹. ¹H-, ¹³C-, and ³¹P-NMR spectra: chemical shifts δ in ppm rel. to TMS (¹H and ¹³C) or H₃PO₄ (³¹P) as external standard, and coupling constants *J* in Hz. FAB-MS and HR-MALDI-MS: 3-nitrobenzyl alcohol (NOBA) and gentisic acid (=2,5-dihydroxybenzoic acid (DHB)) as matrix, respectively.

Bis[(tert-*buty*])*dimethylsily*]] *H-Phosphonate*. A soln. of $H_3PO_4^{10}$) (3.0 g, 36.59 mmol) in THF (25 ml) was treated with a soln. of (*t*-Bu)Me₂SiCl (11.1 g, 73.64 mmol) in Et₂O (120 ml) and Et₃N (10 ml, 71.75 mmol), vigorously stirred for 3 h at 75°, and cooled to 22°. The precipitate (Et₃NCl) was filtered off and washed with Et₂O (3 × 60 ml). The combined filtrate and washings were evaporated, and the residual oil was distilled at 0.5 Torr to give bis[(*tert*-butyl)dimethylsily]] H-phosphonate (9.81 g, 86%) as a colourless liquid. *R*₁ (AcOEt) 0.08. B.p. (0.5 Torr) 87–89°. IR (CHCl₃): 3403w (br.), 3001m, 2957s, 2933s, 2887m, 2861m, 2434w, 1634w, 1472m, 1464m, 1393w, 1364w, 1263s, 1055s, 1016s, 998s, 939w, 845s, 828s. ¹H-NMR (CDCl₃, 300 MHz): 0.246 (*s*, 2 MeSi); 0.252 (*s*, 2 MeSi); 0.92 (*s*, 2 Me₃CSi); 6.86 (*d*, ¹J(H,P) = 697.9, HP=O). ¹³C-NMR (CDCl₃, 75 MHz): – 3.79 (*q*, 2 MeSi); -3.64 (*q*, 2 MeSi); 17.80 (*d*, ³J(C,P) = 1.8, 2 Me₃CSi); 25.16 (*q*, 2 *Me*₃CSi). ³¹P-NMR (CDCl₃, 121 MHz): – 12.67. EI-MS: 309 (<1, [*M* – H]⁺), 295 (8, [*M* – Me]⁺), 253 (100, [*M* – *t*-Bu]⁺), 211 (14), 195 (20, [*M* – TBDMS]⁺), 179 (6, [*M* – TBDMSO]⁺), 169 (8), 135 (24), 73 (53). Anal. calc. for C₁₂H₃₁O₃Si₂P (310.52): C 46.42, H 10.06; found: C 46.24, H 9.93.

Diphenyl (5R,6R,7S,8R)-6,7,8-Tris(benzyloxy)-5-f (benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2a]pyridine-2-phosphonate (13). A suspension of 12 (36.7 mg, 0.054 mmol) and Pd(PPh₃)₄ (18.0 mg, 15.6 µmol) in freshly distilled and degassed toluene (134 µl) was treated under Ar with Et₃N (52 µl, 0.373 mmol) and HPO(OPh)₂ (51 μ l, 0.265 mmol), and stirred at 95° for 15 h. The mixture was concentrated and co-evaporated with toluene (4×2 ml). The ¹H-NMR spectrum of the crude showed **13**, besides P(O)Ph₃ and HPO(OPh)₂. FC (hexane/AcOEt $8:2 \rightarrow 6:4 \rightarrow 0:1$), followed by FC (CH₂Cl₂/i-PrOH $10:0.05 \rightarrow 10:0.3$), gave **13** (36.5 mg, 86%). Colourless oil. $R_{\rm f}$ (hexane/AcOEt 1:1) 0.44. $[a]_{\rm D}^{25} = -35.3$ (c = 0.99, CHCl₃). UV (CHCl₃): 259 (3.15). IR (CHCl₃): 3151w, 3066w, 2926m, 2868m, 1952w, 1875w, 1812w, 1728w, 1593m, 1490s, 1455m, 1363w, 1272s, 1161s, 1113s, 1026s, 941s. ¹H-NMR (CDCl₃, 400 MHz): see *Table 1*; additionally, 3.51 (irrad. at 3.68 → change); 3.68 (irrad. at $3.51 \rightarrow$ change); 3.86 (irrad. at $4.84 \rightarrow d$, J = 9.3); 4.11 (irrad. at $3.51 \rightarrow$ change); 4.26 (irrad. at $3.86 \rightarrow d$, d = 100); 4.11 (irrad. at $3.51 \rightarrow$ change); 4.26 (irrad. at $3.86 \rightarrow d$, d = 100); 4.11 (irrad. at $3.81 \rightarrow d$); 4.11 (irrad. at 3 $J \approx 7.0$; 4.36 (d, J = 12.1, PhCH); 4.39 (d, J = 12.1, PhCH); 4.586 (d, J = 11.2, PhCH); 4.590 (d, J = 12.1, PhCH); 4.59 (d, J = 124.60 (d, J = 11.9, PhCH); 4.67 (d, J = 11.9, PhCH); 4.68 (d, J = 12.1, PhCH); 4.84 (irrad. at 3.86 \rightarrow s); 4.96 (d, J = 12.1, PhCH); 11.2, PhCH); 7.05-7.36 (m, 30 arom. H). ¹³C-NMR (CDCl₃, 100 MHz): see Table 2; additionally, 70.59, 71.91, 73.22, 74.96 (4t, 4 PhCH₂); 120.93 (dd, ${}^{3}J(C,P) = 4.5$, C(2) and C(6) of PhO); 120.95 (dd, ${}^{3}J(C,P) = 4.5$, C(2) and C(6) of PhO); 125.01 (br. d, 2 C(4) of 2 PhO); 127.69–128.55 (several d); 129.53 (br. d, C(3) and C(5) of PhO); 129.56 (br. d, C(3) and C(5) of PhO); 137.15, 137.62 (2s); 137.75 (2s); 150.46 (d, ²J(C,P) = 7.5, C(1) of PhO); $150.48 (d, {}^{2}J(C,P) = 7.1, C(1) \text{ of PhO}). {}^{31}P-NMR (CDCl_{3}, 121 \text{ MHz}): \text{see Table 1. FAB-MS}: 1585 (2, [2M + H]^+), (2M + M) = 100 \text{ MHz})$ 793 (100, $[M + H]^+$), 685 (6, $[M - BnO]^+$), 579 (5), 473 (5), 91 (90, $C_7H_7^+$). HR-MALDI-MS: 831.2528 (1,

¹⁰) Commercially available H_3PO_3 (99%; *Aldrich 21,511-2*) was co-evaporated with toluene (3 × 20 ml) before use.

	13	14	14	15	16	18	20	11	19	19
	CDCl ₃	CDCl ₃	C_6D_6	CDCl ₃	CD ₃ OD	CD ₃ OD	CDCl ₃	D_2O	D_2O	CD ₃ OD
H-C(3)	7.86	7.80	8.00	7.81	7.91 ^a)	7.71	7.69 ^b)	7.64	7.80	7.94
H-C(5)	4.11	4.04-4.25	3.77	4.13	4.52-4.62	4.62	4.35	4.16	4.05 - 4.15	3.95
H-C(6)	4.26	4.29	4.24	4.28	4.29	5.71	5.59	4.28	3.91	4.01-4.23
H-C(7)	3.86	3.87	3.46	3.86	4.15	5.50	5.41	4.07	3.86	3.85
H-C(8)	4.84	4.84	4.85	4.82	5.17	6.37	6.39	5.13	4.82	4.80-4.90
CH-C(5)	3.51	3.58	3.28	3.57	3.73	4.40	4.30	4.04	3.90	3.89
CH' - C(5)	3.68	3.73	3.44	3.72	3.81	4.67	4.50 - 4.62	4.21	4.05 - 4.15	4.17
J(5,6)	7.1	7.5	6.5	7.2	3.1	6.7	5.9	6.8	5.9	6.2
J(6,7)	9.3	9.3	9.7	9.3	6.4	9.4	9.0	8.9	10.0	9.0
J(7,8)	3.1	3.1	3.1	3.1	3.1	3.7	3.7	3.7	3.7	3.7
J(5,CH)	7.1	7.2	6.5	7.2	7.2	4.8	6.5	3.6	4.1	6.2
J(5,CH')	3.1	3.1	3.1	3.1	4.4	3.4	2.8	2.9	^c)	2.5
J(CH,CH')	10.2	10.0	10.0	10.3	10.3	12.2	11.2	12.6	16.2	11.2
Р	5.01	12.21	12.06	14.91	-1.37	0.04	11.22	-1.92	14.86	13.39
^{a)} ${}^{3}J(H,P) = 1.9$ Hz. ^b) ${}^{3}J(H,P) = 0.9$ Hz. ^c) Not assigned.										

Table 1. Selected ¹H- and ³¹P-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the Protected Imidazoles **13–16**, **18**, and **20** and of the Deprotected Imidazoles **11** and **19**

 Table 2. Selected ¹³C-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the Protected Imidazoles

 13-16, 18, and 20 and of the Deprotected Imidazoles 11 and 19

	13 CDCl ₃	14 ^a) CDCl ₃	14 C ₆ D ₆	15 CDCl ₃	16 CD ₃ OD	18 CD ₃ OD	20 CDCl ₃	11 D ₂ O	19 D ₂ O	19 CD ₃ OD
C(2)	128.83	130.83	132.48	129.19	^b)	138.37	132.56	135.67	127.06	129.70
C(3)	130.57	129.18	^b)	129.46	127.75	127.28	127.86	125.95	128.44	130.04
C(5)	60.35	60.36	60.28	60.29	62.40	58.81	57.93	64.59°)	61.51	64.33
$CH_2 - C(5)$	70.08	70.38	69.97	70.16	^d)	63.57	63.48	62.11	59.47	63.07
C(6)	73.70	73.97	73.64	73.74	73.92°)	66.38 ^c)	65.44 ^c)	67.79°)	64.49°)	67.21°)
C(7)	79.81	80.15	80.49	79.90	75.68	70.23	68.63	72.02	70.56	72.78
C(8)	68.21	68.66	68.23	68.56	70.36 ^c)	64.40 ^c)	63.08 ^c)	65.38°)	63.64 ^c)	65.67°)
C(8a)	146.06	145.99	145.85	145.91	146.70	142.99	142.49	147.96	148.63	150.47
${}^{1}J(2,\mathbf{P})$	256.3	246.6	242.9	245.8	e)	233.9	246.6	197.9	246.0	246.6
$^{2}J(3,\mathbf{P})$	39.7	37.9	e)	36.6	20.8	34.2	37.2	21.9	36.6	36.6
³ <i>J</i> (8a,P)	23.7	22.0	22.0	22.0	8.5	20.8	22.6	7.3	21.4	20.7

^a) Assignment based on a HSQC-GRASP spectrum. ^b) Hidden by the aromatic signals at 127.79-130.12 ppm. ^c) Assignment may be interchanged. ^d) Hidden by the PhCH₂ signals at 74.42 and 74.45 ppm. ^e) Not assigned.

 $[M + K]^+$, $C_{48}H_{45}KN_2O_7P^+$; calc. 831.2601), 815.2817 (36, $[M + Na]^+$, $C_{48}H_{45}N_2NaO_7P^+$; calc. 815.2862), 793.3026 (100, $[M + H]^+$, $C_{48}H_{46}N_2O_7P^+$; calc. 793.3042), 685.2450 (18, $[M - BnO]^+$, $C_{41}H_{38}N_2O_6P^+$; calc. 685.2467), 397.1549 (3). Anal. calc. for $C_{48}H_{45}N_2O_7P$ (792.87): C 72.71, H 5.72, N 3.53; found: C 72.71, H 6.00, N 3.51.

Preparation of **5** and **14**. a) By $Pd(PPh_3)_4$ -Catalysed Phosphonylation of **12**. A suspension of **12** (900 mg, 1.31 mmol) and Pd(PPh_3)_4 (456 mg, 0.395 mmol) in freshly distilled and degassed toluene (3.25 ml) was treated under Ar with Et₃N (1.26 ml, 9.04 mmol) and HPO(OEt)_2 (0.85 ml, 6.60 mmol), warmed to 95°, stirred for 19 h, cooled to 22°, diluted with AcOEt (15 ml), and filtered through *Celite* (the solid was washed with 300 ml of AcOEt). The combined yellow filtrate and washing was concentrated to 100 ml, washed with H₂O (100 ml) and brine (100 ml), dried (MgSO₄), and evaporated. The ¹H-NMR spectrum of the crude showed a mixture of **14/17** *ca.* 62:38, P(O)Ph₃, and HPO(OEt)₂. FC (hexane/AcOEt/Et₃N 5:5:0.3 \rightarrow 3:7:0.3 \rightarrow 0:1:0.03) gave **17**

(296 mg, 40%) [20] as a pale yellow oil and a mixture containing mainly **14** and P(O)Ph₃ (739 mg). FC (*RP-C18* silica gel, MeOH/H₂O 7:3 \rightarrow 9:1) of this mixture gave pure **14** (534 mg, 58%).

b) By KF-Induced Transesterification of **13**. A suspension of **13** (12 mg, 15.1 μ mol), KF (8.9 mg, 0.153 mmol), and 18-crown-6 (2 mg, 7.57 μ mol) in EtOH (0.5 ml) was refluxed for 45 min and evaporated. A soln. of the residue in AcOEt (5 ml) was washed with H₂O (3 × 5 ml) and brine (5 ml), dried (MgSO₄), and evaporated. FC (hexane/AcOEt 1:1 \rightarrow 1:3) gave **14** (9.4 mg, 90%).

c) *By CsF-Induced Transesterification of* **13**. A soln. of **13** (18.5 mg, 23.3 µmol) and CsF (9 mg, 59.2 µmol) in EtOH (0.5 ml) was refluxed for 150 min. Workup and FC, as described in *b*, afforded **14** (12.9 mg, 80%). This experiment was repeated on a large scale: a soln. of **13** (1.13 g, 1.43 mmol) and CsF (0.54 g, 3.55 mmol) in EtOH (30 ml) was refluxed for 6 h. Workup and FC gave **14** (831 mg, 84%). Colourless oil.

d) By Treatment of **1** with the Aminophosphonate **24** and HgCl₂. A suspension of **1** (100 mg, 0.181 mmol), HgCl₂ (71 mg, 0.262 mmol), and molecular sieves (3 Å, 100 mg) in THF (2 ml) was treated successively with **24** (90 mg, 0.373 mmol) and Et₃N (50 µl, 0.359 mmol), warmed to 80°, stirred for 8 h, cooled to 22°, diluted with Et₂O (10 ml), and filtered over *Celite* (the solid was washed with 30 ml of Et₂O). The combined filtrate and washing was washed with sat. NH₄Cl soln. (3 × 20 ml). The combined aq. layers were extracted with Et₂O (2 × 25 ml). The combined org. layers were washed with H₂O (40 ml) and brine (40 ml), dried (MgSO₄), and evaporated. A soln. of the residue (121 mg) in toluene (5 ml) was treated with sat. NH₄Cl soln. (3 × 20 ml). The combined org. layers were washed with Et₂O (2 × 20 ml). The combined aq. layers were extracted with sat. NH₄Cl soln. (3 × 20 ml) in toluene (5 ml) was treated with TsOH +H₂O (115 mg, 0.605 mmol), stirred for 7 h at 65°, cooled to 22°, diluted with Et₂O (2 × 20 ml). The combined aq. layers were extracted with Et₂O (50 ml) and brine (50 ml), dried (MgSO₄), and evaporated. FC (hexane/AcOEt 3 : 1 → 1 : 1 → 0 : 1) gave **27/28** 75 : 25 (10.7 mg, 11%) [74][75], **5** (18.3 mg, 15%) [1], **5/14** 41 : 59 (30.7 mg, 24%), and **14** (7.9 mg, 6%).

Data of Diethyl (5R,6R,7S,8R)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-phosphonate (14). $R_{\rm f}$ (hexane/AcOEt 1:1) 0.09. $[\alpha]_{25}^{25} = -27.9$ (c = 1.05, CHCl₃). UV (CHCl₃): 265 (2.77). IR (CHCl₃): 3152w, 3065w, 2908m, 2869m, 1954w, 1812w, 1727w, 1603w, 1516m, 1453m, 1393w, 1364m, 1253s, 1100s, 1028s, 972s. ¹H-NMR (CDCl₃, 300 MHz): see Table 1; additionally, 1.32 (br. t, J = 7.2, $MeCH_2O$; 1.35 (br. $t, J = 6.9, MeCH_2O$); 3.58 (irrad. at 3.73 \rightarrow change); 3.73 (irrad. at 3.58 \rightarrow change); 3.87 (irrad. at $4.84 \rightarrow d$, $J \approx 9.1$); 4.04 - 4.25 (*m*, irrad. at $3.58 \rightarrow$ change, $2 \text{ MeCH}_2\text{O}$, H-C(5)); 4.29 (irrad. at $3.87 \rightarrow 10^{-10}$); 4.04 - 4.25 (*m*, irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (*m*, irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); 4.04 - 4.25 (irrad. at $3.58 \rightarrow 10^{-10}$); $4.29 \rightarrow 10^{-10}$); $4.29 \rightarrow 10^{-10}$); $4.29 \rightarrow 10^{-10}$ (irrad. at $3.58 \rightarrow 10^{-10}$); $4.29 \rightarrow 10^{-1$ change); 4.45 (br. s, PhCH₂); 4.59 (d, J = 11.2, PhCH); 4.62 (d, J = 12.1, PhCH); 4.65 (d, J = 12.1, PhCH); 4.68 (d, J = 11.8, PhCH); 4.73 (d, J = 12.1, PhCH); 4.84 (irrad. at 3.87 → s); 4.98 (d, J = 10.9, PhCH); 7.22 - 7.36 (m, 20) arom. H). ¹H-NMR (C₆D₆, 300 MHz): see *Table 1*; additionally, 1.17 (t, J = 7.2, $MeCH_2O$); 1.19 (t, J = 7.2, $MeCH_2O$; 3.28 (irrad. at 3.77 \rightarrow d, J = 9.7); 3.44 (irrad. at 3.28 \rightarrow change, irrad. at 3.77 \rightarrow change); 3.77 (irrad. at 3.28 \rightarrow ch $3.28 \rightarrow$ change); 4.02 (d, J = 12.1, PhCH); 4.07 (d, J = 12.1, PhCH); $4.15 - 4.35 (m, 2 \text{ MeCH}_2\text{O})$; 4.20 (d, J = 10.9, C); 4.20 (d,PhCH); 4.24 (irrad. at 3.77 -> change); 4.35 (d, J = 11.8, PhCH); 4.39 (d, J = 11.2, PhCH); 4.80 (d, J = 12.1, PhCH); 4.85 (irrad. at $3.46 \rightarrow s$); 4.86 (d, $J \approx 12.8$, PhCH); 4.89 (d, J = 11.5, PhCH); 7.03 – 7.19 (m, 16 arom. H); 7.23-7.28 (m, 2 arom. H); 7.43-7.48 (m, 2 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): see Table 2; additionally, 16.39 (dq, ${}^{3}J(C,P) \approx 7.3$, $MeCH_{2}O$); 16.45 (dq, ${}^{3}J(C,P) \approx 6.1$, $MeCH_{2}O$); 62.41 (dt, ${}^{2}J(C,P) \approx 8.6$, $MeCH_{2}O$); 62.48 (dt, ${}^{2}J(C,P) \approx 7.3$, MeCH₂O); 70.90, 72.04, 73.35, 75.10 (4t, 4 PhCH₂); 127.84 – 128.78 (several d); 137.57, 137.97, 138.10, 138.23 (4s). ¹³C-NMR (C_6D_6 , 75 MHz): see *Table 2*; additionally, 16.75 (*dq*, ³*J*(C,P) = 6.1, 2 $MeCH_{2}O$; 62.21 (dt, ²J(C,P) = 4.9, MeCH_{2}O); 62.28 (dt, ²J(C,P) = 5.5, MeCH_{2}O); 70.95, 71.64, 73.14, 74.90 (4t, 4 PhCH₂); 127.79-129.31 (several d, incl. C(3)); 137.92, 138.50, 138.59, 138.70 (4s). ³¹P-NMR (CDCl₃, 121 MHz): see Table 1. ³¹P-NMR (C₆D₆, 121 MHz): see Table 1. FAB-MS: 1393 (3, [2M + H]⁺), 697 (86, [M + $H]^{+}), 589 (5, [M - BnO]^{+}), 377 (7), 91 (100, C_{7}H_{7}^{+}). HR-MALDI-MS: 735.2650 (2, [M + K]^{+}, C_{40}H_{45}KN_{2}O_{7}P^{+}; C_{40}H_{45}KN_{2}O_{7}N^{+}; C_{40}H_{4}KN_{2}$ calc. 735.2601), 719.2876 (62, $[M + Na]^+$, $C_{40}H_{45}N_2NaO_7P^+$; calc. 719.2862), 697.3045 (100, $[M + H]^+$, $C_{40}H_{46}N_2O_7P^+$; calc. 697.3043), 669.2740 (8), 645.2135 (4), 623.2344 (3), 607.2547 (2), 589.2479 (19, [*M*-0.2547]) BnO]⁺, C₃₃H₃₈N₂O₆P⁺; calc. 589.2467), 561.2177 (14), 533.1867 (8), 515.1754 (7). Anal. calc. for C₄₀H₄₅N₂O₇P (696.78): C 68.95, H 6.51, N 4.02; found: C 68.76, H 6.72, N 3.97.

Preparation of **6** and **15**. a) By $Pd(PPh_3)_4$ -Catalysed Phosphonylation of **12**. A suspension of **12** (21.7 mg, 31.6 µmol) and Pd(PPh_3)_4 (12.4 mg, 10.7 µmol) in freshly distilled and degassed toluene (79 µl) was treated under Ar with Et₃N (31 µl, 0.222 mmol) and HPO(OMe)₂ (15 µl, 0.164 mmol), warmed to 95°, and stirred for 22 h. The mixture was concentrated and co-evaporated with toluene (3 × 5 ml). The ¹H-NMR spectrum of the crude showed a mixture **15/17** *ca*. 50:50, besides P(O)Ph₃ and HPO(OMe)₂. FC (hexane/AcOEt 8:2 \rightarrow 5:5 \rightarrow 3:7 \rightarrow 1:9 \rightarrow 0:1) gave **17** (4 mg, 23%) [20] and crude **15** as colourless oils. FC (*RP-C18* silica gel, MeOH/H₂O 6:4 \rightarrow 1:0) gave pure **15** (5 mg, 24%).

b) By KF-Induced Transesterification of 13. A suspension of 13 (14 mg, 17.7 μmol), KF (10 mg, 0.172 mmol), and 18-crown-6 (2.5 mg, 9.46 μmol) in MeOH (0.5 ml) was refluxed for 90 min and evaporated.

A soln. of the residue in AcOEt (5 ml) was washed with H₂O (3×5 ml) and brine (5 ml), dried (MgSO₄), and evaporated. FC (hexane/AcOEt $1:1 \rightarrow 0:1$) gave **15** (9.9 mg, 84%).

c) By CsF-Induced Transesterification of **13**. A soln. of **13** (16.5 mg, 20.8 µmol) and CsF (12 mg, 79.0 µmol) in MeOH (0.5 ml) was refluxed for 90 min. Workup and FC, as described in *b*, yielded **15** (13.0 mg, 94%). This experiment was repeated on a large scale: a soln. of **13** (490 mg, 0.618 mmol) and CsF (230 mg, 1.51 mmol) in MeOH (15 ml) was refluxed for 17 h. Workup and FC afforded **15** (362 mg, 88%).

d) By Treatment of **1** with the Aminophosphonate **26** and $HgCl_2$. At 22°, a suspension of **1** (50 mg, 90.3 µmol), $HgCl_2$ (35 mg, 0.129 mmol), and molecular sieves (4 Å; 50 mg) in THF (1 ml) was treated successively with **26** (45 mg, 0.211 mmol) and Et_3N (25 µl, 0.179 mmol), warmed to 80°, stirred for 9 h, cooled to 22°, diluted with Et_2O (10 ml), and filtered over *Celite* (the solid was washed with 30 ml of Et_2O). The filtrate was washed with sat. NH₄Cl soln. (3 × 20 ml). The combined aq. layers were extracted with Et_2O (3 × 15 ml). The combined org. layers were washed with H_2O (30 ml) and brine (30 ml), dried (Na₂SO₄), and evaporated. A soln. of the residue (74 mg) in toluene (2.5 ml) was treated with TsOH + H₂O (60 mg, 0.315 mmol), stirred for 12 h at 65°, diluted with Et_2O (2 × 20 ml). The combined org. layers were washed with H_2O (30 ml) and brine (30 × 20 ml). The combined aq. layers (50 ml) and brine (50 ml), dried (Na₂SO₄), and evaporated. FC (hexane/AcOEt 3:1 \rightarrow 1:1 \rightarrow 0:1) gave **27/28** 71:29 (10.7 mg, 22%) [74][75], **6** (3.7 mg, 6%) [1], **6/15** 39:61 (1.5 mg, 2%), and **15** (2.5 mg, 4%).

Data of Dimethyl (5R,6R,7S,8R)-6,7,8-*Tris*(*benzyloxy*)-5-[(*benzyloxy*)*methyl*]-5,6,7,8-*tetrahydroimidazo*[1,2-*a*]*pyridine*-2-*phosphonate* (**15**). Colourless oil. $R_{\rm f}$ (AcOEt) 0.18. $[a]_{\rm D}^{25} = -35.7$ (*c* = 0.99, CHCl₃). UV (CHCl₃): 259 (2.91). IR (CHCl₃): 3151*w*, 3065*w*, 2954*m*, 2864*m*, 1954*w*, 1879*w*, 1813*w*, 1602*w*, 1516*m*, 1455*m*, 1363*m*, 1259*s*, 1110*s*, 1035*s*, 913*w*, 832*m*. ¹H-NMR (CDCl₃, 300 MHz): see *Table 1*; additionally, 3.57 (irrad. at 3.72 → change); 3.72 (irrad. at 3.57 → change); 3.80 (*d*, ³*J*(H,P) = 11.2, MeO); 3.81 (*d*, ³*J*(H,P) = 11.2, MeO); 3.86 (irrad. at 4.28 → change, irrad. at 4.82 → *d*, *J* = 9.3); 4.13 (irrad. at 3.57 → *dd*, *J* = 3.2, 7.2, irrad. at 4.28 → change); 4.28 (irrad. at 3.86 → change); 4.45 (br. *s*, PhCH₂); 4.59 (*d*, *J* = 11.2, PhCH); 4.61 (*d*, *J* = 12.1, PhCH); 4.64 (*d*, *J* = 11.3, PhCH); 4.67 (*d*, *J* = 12.1, PhCH); 4.72 (*d*, *J* = 12.1, PhCH); 4.82 (irrad. at 3.86 → *s*); 4.97 (*d*, *J* = 10.9, PhCH); 7.21 − 7.36 (*m*, 20 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): see *Table 2*; additionally, 52.84 (*dq*, ²*J*(C,P) = 6.1, MeO); 53.05 (*dq*, ³*J*(C,P) = 6.1, MeO); 70.86, 71.93, 73.22, 74.98 (*d*, 4 PhCH₂); 127.61 − 128.57 (several *d*); 137.24, 137.76, 137.90 (*4s*). ³¹P-NMR (CDCl₃, 121 MHz): see *Table 1*. HR-MALDI-MS: 707.2287 (5, $[M + K]^+$, $C_{38}H_{41}KN_2O_7P^+$; calc. 707.2288), 691.2553 (62, $[M + Na]^+$, $C_{38}H_{41}N_2NaO_7P^+$; calc. 691.2549), 669.2725 (100, $[M + H]^+$, $C_{38}H_{42}N_2O_7P^+$; calc. 669.2729), 561.2164 (22, $[M - BnO]^+$, $C_{31}H_{34}N_2O_6P^+$; calc. 501.2154), 334.6364 (5). Anal. calc. for $C_{38}H_{41}N_2O_7P$ (668.72): C 68.25, H 6.18, N 4.19; found: C 68.09, H 6.30, N 4.25.

(5R,6R,7S,8R)-6,78-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,78-tetrahydroimidazo[1,2-a]pyridine-2-phosphonic Acid (**16**). A suspension of **12** (16.6 mg, 24.2 µmol) and Pd(PPh₃)₄ (8.2 mg, 7.10 µmol) in freshly distilled and degassed toluene (61 µl) was treated under Ar with Et₃N (24 µl, 0.172 mmol) and HPO(OSiMe₃)₂ (28 µl, 0.120 mmol), warmed to 95°, and stirred for 44 h. The mixture was concentrated and co-evaporated with toluene (4 × 5 ml). FC (*RP*-*C18* silica gel, MeOH/H₂O 6:4 → 1:0) gave **16** (10.1 mg, 65%) and **17** (0.6 mg, 4%) [20].

Data of **16**: White foam. R_f (*RP C18*, MeOH/H₂O 9:1) 0.32. IR (CHCl₃): 3500-2100*m* (br.), 3162*w*, 3066*m*, 2961*m*, 2871*m*, 1952*w*, 1875*w*, 1812*w*, 1723*w*, 1601*w*, 1536*w*, 1497*m*, 1454*m*, 1365*m*, 1332*w*, 1261*s*, 1098*s*, 1015*s*, 916*m*, 870*w*. ¹H-NMR (CD₃OD, 300 MHz): see *Table 1*; additionally, 3.73 (irrad. at 3.81 → change); 3.81 (irrad. at $3.73 \rightarrow$ change); 4.15 (irrad. at $4.29 \rightarrow d$, J = 3.1, irrad. at $5.17 \rightarrow d$, J = 6.2); 4.29 (irrad. at $4.15 \rightarrow$ change); 4.41 (*d*, J = 12.1, PhCH); 4.45 (*d*, J = 12.8, PhCH); 4.52 – 4.62 (*m*, irrad. at 4.29 → change, H−C(5)); 4.53 (*d*, J = 11.5, PhCH); 4.58 (*d*, J = 11.8, PhCH); 4.63 (*d*, J = 11.5, PhCH); 4.76 (*d*, J = 11.5, PhCH); 4.81 (*d*, J = 11.8, PhCH); 5.17 (irrad. at $4.15 \rightarrow s$); 7.17 – 7.37 (*m*, 18 arom. H); 7.41 – 7.44 (*m*, 2 arom. H). ¹³C-NMR (CD₃OD, 75 MHz): see *Table 2*; additionally, 74.42 (3*t*), 74.45 (2*t*) (CH₂–C(5), 4 PhCH₂); 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals at 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals at 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals at 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals at 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals at 129.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals (12.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals (12.35 – 130.12 (several *d*); 138.57, 138.91, 138.96, 139.00 (4*s*); *d* of C(2) is hidden by signals (12.35 – 130.12 pm. ³¹P-NMR (CD₃OD, 121 MHz): see *Table 1*. FAB-MS: 1960 (3, [3M + K]⁺), 1944 (2, [3M + Na]⁺), 1922 (3, [3M + H]⁺), 1319 (2, [2M + K]⁺), 1303 (2, [2M + Na]⁺), 1281 (22, [2M + H]⁺), 679 (1, [M + K]⁺), 663 (7,

Deprotection of 14 and 15. a) A soln. of 14 (603 mg, 0.865 mmol) in CH_2Cl_2 (8.5 ml) was cooled to 0°, treated with Me₃SiBr (670 µl, 5.18 mmol), stirred for 1 h, warmed to 23°, and stirred for 19 h. The mixture was concentrated and co-evaporated with toluene (4 × 4 ml). The residue was taken up in MeOH/H₂O 9:1 (20 ml), evaporated, and co-evaporated with toluene (2 × 4 ml) to afford a white foam (crude 16). A soln. of crude 16 (568 mg) in MeOH/AcOEt/H₂O 3:1:1 (15 ml) was treated with 20% Pd(OH)₂/C (210 mg) and hydrogenated for 43 h at atmospheric pressure and 23°. The suspension was filtered through *Celite* (washing with 30 ml MeOH/

 H_2O 9:1). Evaporation gave crude **11** (280 mg), which was taken up in 2 ml of H_2O and applied to a DEAEcellulose column (*Cellex-D*, *Bio-Rad*, 15 × 1.5 cm, 0.5 – 0.7 bar; ¹H-NMR detection). The column was washed with H_2O (100 ml), and **11** was eluted with a triethylammonium hydrogen carbonate buffer (pH *ca.* 7.4; 5 mM, 100 ml; 10 mM, 100 ml; 15 mM, 100 ml; 20 mM, 100 ml; 25 mM, 100 ml). The fractions containing **11** were combined and lyophilized (3 ×) to give **11** (270 mg, 1.25 equiv. of Et₃NH⁺, 77%).

b) Similarly as *a*, a soln. of **14** (100 mg, 0.144 mmol) in CH_2Cl_2 (1.4 ml) was treated with Me₃SiBr (110 µl, 0.851 mmol), and stirred for 15 min at 0° and for 20 h at 23°. Workup gave crude **16** (77 mg), which was dissolved in MeOH/AcOEt/H₂O 3 :1:1 (1.5 ml), treated with 20% Pd(OH)₂/C (65 mg), and hydrogenated for 26 h. Filtration over *Celite*, evaporation of the filtrate, and lyophilisation yielded crude **11** (36 mg), which was dissolved in H₂O (1 ml) and treated with Et₃N (50 µl, 0.359 mmol). The soln. was evaporated and co-evaporated with toluene (4 × 2 ml). The residue was taken up in MeOH/H₂O 1:1 (2 ml), treated with activated charcoal, and filtered. Evaporation and lyophilisation (3 ×) gave **11** (44 mg, 1.10 equiv. of Et₃NH⁺, 78%).

c) Similarly as *a*, a soln. of **15** (360 mg, 0.538 mmol) in CH_2Cl_2 (5.5 ml) was treated with Me₃SiBr (420 µl, 3.25 mmol), and stirred for 15 min at 0°, and for 15 h at 23°. Workup gave crude **16** (365 mg), which was dissolved in MeOH/AcOEt/H₂O 3:1:1 (8 ml), treated with 20% Pd(OH)₂/C (350 mg), and hydrogenated for 36 h. Filtration over *Celite* and evaporation of the filtrate yielded crude **11** (199 mg). Ion-exchange chromatography and lyophilisation gave **11** (179 mg, 1.19 equiv. of Et₃NH⁺, 83%).

Data of Triethylammonium Hydrogen (5R,6R,7S,8R)-6,7,8-*Trihydroxy-5-(hydroxymethyl)-5*,6,7,8-*tetrahydroi midazo*[1,2-a]*pyridine-2-phosphonate* (11). $R_{\rm f}$ (MeOH/NH₃/H₂O 4:3:1) 0.50. IR (KBr): 3394s (br.), 2975*m*, 2937*s*, 2738*s*, 2678*s*, 2492*m*, 1640*w*, 1476*m*, 1434*m*, 1398*m*, 1092*s*, 1036*m*, 804*w*. ¹H-NMR (D₂O, 400 MHz, 1.60 equiv. of Et₃N): see *Table 1*; additionally, 1.23 (*t*, *J* = 7.3, 1.60 (*Me*CH₂)₃NH); 3.15 (*q*, *J* = 7.3, 1.60 (MeCH₂)₃NH); 4.04 (irrad. at 4.21 → change); 4.07 (irrad. at 5.13 → *d*, *J* ≈ 9.0); 4.16 (irrad. at 4.04 → change); 4.21 (irrad. at 4.04 → change); 5.13 (irrad. at 4.07 → *s*). ¹³C-NMR (D₂O, 100 MHz, 1.60 equiv. of Et₃N): see *Table 2*; additionally, 10.91 (*q*, 1.60 (*Me*CH₂)₃NH); 49.34 (*t*, 1.60 (MeCH₂)₃NH). ³¹P-NMR (D₂O, 121 MHz, 1.60 equiv. of Et₃N): see *Table 1*. ESI-MS (MeOH/H₂O 1:1, negative mode): 581 (13, [2*M* − 2 H + Na]⁻), 559 (15, [2*M* − H]⁻), 375 (22), 339 (25), 325 (80), 311 (100, [*M* + MeO]⁻), 297 (26, [*M* + HO]⁻), 279 (63, [*M* − H]⁻), 255 (26), 213 (63).

Triethylammonium Hydrogen (5R,6R,7S,8R)-6,7,8-Triacetoxy-5-[(acetoxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-phosphonate (18). A suspension of 11 (50 mg, 1.60 equiv. of Et₃NH⁺, 0.113 mmol) in distilled pyridine (1.3 ml) was treated with distilled Ac₂O (390 µl, 4.13 mmol) and stirred under Ar at 23°. After 2 h, the suspension changed to a clear soln., which was stirred for next 34 h, evaporated, and co-evaporated with toluene $(4 \times 2 \text{ ml})$. The residue was dissolved in H₂O (10 ml) and washed with AcOEt $(4 \times 3 \text{ ml})$. The aq. layer was concentrated in vacuo and lyophilised to give 18 (66.1 mg, 1.62 equiv. of Et_3NH^+ ; 96%). R_f (AcOEt/MeOH/ H₂O 8:4:1) 0.41. IR (KBr): 3414m (br.), 2976m, 2938s, 2739m, 2678s, 2492m, 1748s, 1641w, 1517w, 1476m, 1434m, 1398m, 1372s, 1232s, 1171m, 1141m, 1070s, 950m, 924m, 849w, 805w. ¹H-NMR (CD₃OD, 400 MHz): see Table 1; additionally, 1.31 (t, J = 7.3, 1.62 (MeCH₂)₃NH); 2.03, 2.07, 2.12, 2.13 (4s, 4 AcO); 3.21 (q, J = 7.3, 1.62 (MeCH₂)₃NH). ¹³C-NMR (CD₃OD, 100 MHz): see Table 2; additionally, 9.22 (q, 1.62 (MeCH₂)₃NH); 20.50, 20.55, 20.59, 20.61 (4q, 4 Me); 47.81 (t, 1.62 (MeCH₂)₃NH); 171.07, 171.24, 171.36, 171.86 (4s, 4 C=O). ³¹P-NMR $[2M + H]^+$, 879 (2, $[2M - OH]^+$), 693 (6, $[M - 3H + 2E_{13}N + 2Na]^+$), 614 (9, $[M - 4H + E_{13}N + 3Na]^+$), 592 $(38, [M-3H+Et_3N+2Na]^+), 550 (10, [M+Et_3NH]^+), 535 (9, [M-5H+4Na]^+), 529 (10), 513 (46, [M-4Ma]^+), 529 (10), 513 (46, [M-4Ma]^+), 513 (46, [M-4Ma]^+)$ $H + 3 Na^{+}$, 491 (4, $[M - 3 H + 2 Na^{+}]$, 487 (10, $[M + K^{+}]$, 471 (28, $[M + Na^{+}]$, 453 (36, $[M + Na - H_2O^{+}]$; 449 (31, $[M + H]^+$); 102 (100, Et₃NH⁺).

Diethyl (5R,6R,7S,8R)-6,7,8-Trihydroxy-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2phosphonate (19). A soln. of 14 (103 mg, 0.148 mmol) in AcOEt/MeOH/H₂O 1:6:1 (0.8 ml) and AcOH (0.4 ml) was treated with 20% Pd(OH)₂/C and hydrogenated for 24 h at 23° and at the atmospheric pressure. The mixture was filtered through *Celite* (washing with 20 ml of MeOH). Evaporation, FC (AcOEt/i-PrOH/H₂O 8:4:1), and lyophilization gave 19 (41 mg, 82%) as a white powder. R_t (AcOEt/i-PrOH/H₂O 8:4:1) 0.26. $[\alpha]_D^{25} = -18.9 (c = 0.75, MeOH)$. UV (MeOH): 211 (3.97), 193 (3.21). UV (H₂O): 210 (3.98). IR (KBr): 3700–2000s (br.), 2987m, 2924m, 1643w, 1522m, 1476w, 1440w, 1394m, 1218s, 1163m, 1097s, 1051s, 1023s, 976m, 902w, 794m, 768m, 663m. 'H-NMR (CD₃OD, 300 MHz): see *Table 1*; additionally, 1.31 (t, $J = 7.2, MeCH_2O$); 3.85 (irrad. at 3.89 \rightarrow change, irrad. at 3.95 \rightarrow change); the signal of H–C(8) is partially hidden by the signal of HDO. 'H-NMR (D₂O, 300 MHz): see *Table 1*; additionally, 1.15 (br. t, $J = 7.2, MeCH_2O$); 3.98 (br. q, $J \approx 6.8, MeCH_2O$); 4.00 (br. q, $J \approx 7.2, MeCH_2O$); 4.00 (br. q, $J \approx 7.2, MeCH_2O$); 4.07 (hr. q, $J \approx 7.2, MeCH_2O$); 4.00 (br. q, $J \approx 7.2, MeCH_2O$); 4.05 –4.15 (m, H–C(5), CH'–C(5)). ¹³C-NMR (CD₃OD, 75 MHz): see *Table 2*; additionally, 1.56 (dq, ³J(C,P) = 6.7, 2 MeCH₂O); 6.390 (dt, ²J(C,P) $\approx 5.3, MeCH_2O$); 63.93 (dt, ²*J*(C,P) \approx 5.1, MeCH₂O). ¹³C-NMR (D₂O, 75 MHz): see *Table 2*; additionally, 15.43 (dq, ³*J*(C,P) = 6.1, 2 *M*eCH₂O); 63.99 (dt, ²*J*(C,P) = 4.9, MeCH₂O); 64.05 (dt, ²*J*(C,P) = 4.3, MeCH₂O). ³¹P-NMR (CD₃OD, 121 MHz): see *Table 1*. ³¹P-NMR (D₂O, 121 MHz): see *Table 1*. HR-MALDI-MS: 375.0730 (4, [M + K]⁺, C₁₂H₂₁KN₂O₇P⁺; calc. 375.0723), 359.0981 (100, [M + Na]⁺, C₁₂H₂₁N₂NaO₇P⁺; calc. 359.0984), 337.1158 (72, [M + H]⁺, C₁₂H₂₂N₂O₇P⁺; calc. 337.1165), 332.1834 (15), 309.0840 (7), 276.1209 (5), 210.1482 (15). Anal. calc. for C₁₂H₂₁N₂O₇P⁺0.5 H₂O (345.29): C 41.74, H 6.42, N 8.11; found C 42.09, H 6.79, N 8.01.

Diethyl (5R,6R,7S,8R)-6,7,8-Triacetoxy-5-[(acetoxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2phosphonate (20). A soln. of 19 (15 mg, 44.6 µmol) and DMAP (1.2 mg, 9.82 µmol) in pyridine (0.4 ml) was treated with Ac₂O (26 µl, 0.275 mmol), stirred for 16 h, and treated with sat. NH₄Cl soln. (2 ml). The mixture was diluted with CH_2Cl_2 (30 ml) and washed with sat. NH_4Cl soln. (3 × 20 ml). The combined aq. layers were extracted with CH_2Cl_2 (2 × 20 ml). The combined org. extracts were washed with H_2O (40 ml) and brine (40 ml), dried (Na₂SO₄), evaporated, and co-evaporated with toluene (3×5 ml). FC (AcOEt/Et₃N 1:0.03) yielded **20** (17.1 mg, 76%). Colourless oil. R_f (AcOEt/Et₃N 1:0.03) 0.13. R_f (AcOEt) 0.10. $[\alpha]_D^{25} = -39.6$ (c = -39.6) 1.00, CHCl₃). UV (CHCl₃): 239 (2.43). IR (CHCl₃): 2997m, 2931w, 2856w, 1755s, 1602w, 1516w, 1427w, 1370m, 1239s, 1133m, 1053s, 1028s, 974m, 953m, 916w. ¹H-NMR (CDCl₃, 300 MHz): see Table 1; additionally, 1.35 (t, $J = 7.2, 2 MeCH_{2}O$; 2.05, 2.11, 2.12, 2.13 (4s, 4 AcO); 4.07-4.26 (m, 2 MeCH₂O); 4.30 (irrad. at 4.56 \rightarrow change); 4.35 (irrad. at 4.56 \rightarrow change, irrad. at 5.59 \rightarrow change); 4.50 - 4.62 (*m*, $J_{gem} = 11.2$, CH'-C(5)); 5.41 (irrad. at $5.59 \rightarrow$ change, irrad. at $6.39 \rightarrow d$, J = 8.7); 5.59 (irrad. at $5.41 \rightarrow$ change); 6.39 (irrad. at $5.41 \rightarrow s$). ¹³C-NMR (CDCl₃, 75 MHz): see Table 2; additionally, 16.29 (dq, ³J(C,P) = 6.7, MeCH₂O); 16.31 (dq, ³J(C,P) = 6.7, $MeCH_2O$; 20.52 (q, Me); 20.66 (q, 2 Me); 20.73 (q, Me); 62.59 (dt, ${}^2J(C,P) = 4.9$, $MeCH_2O$); 62.65 (dt, 2M_2O); 62.65 (dt, 2M_2 ²*I*(C,P) = 4.9, Me*C*H₂O); 169.29, 169.36, 169.49, 170.06 (4s, 4 C=O). ³¹P-NMR (CDCl₃, 121 MHz): see *Table 1*. $C_{20}H_{29}N_2NaO_{11}P^+; \ calc. \ 527.1406), \ 505.1586 \ (100, \ [M+H]^+, \ C_{20}H_{30}N_2O_{11}P^+; \ calc. \ 505.1587), \ 385.1158 \ (9), \ (9), \ (9), \ (100, \ [M+H]^+, \ C_{20}H_{20}N_2O_{11}P^+; \ C_{20}H_{20}N_2$ 343.1049 (9), 325.0945 (19), 252.5781 (7).

Benzyl[(2,2-*dimethoxy*)*ethylidene*]*amine* (**22**). A suspension of BnNH₂ (16.95 g, 0.158 mol) and MgSO₄ (19.67 g, 0.163 mol) in THF (280 ml) was cooled to 0°, treated dropwise over 10 min with *ca*. 45% glyoxal 1,1-dimethyl acetal in *t*-BuOMe (34.5 ml, 0.134 mol), stirred for 4 h at 0° and for another 12 h at $0 \rightarrow 22^\circ$. The solid was filtered off and washed with Et₂O (50 ml). Evaporation of the combined filtrate and washing (→ yellowish oil) and distillation (micro-distillation apparatus) at 0.3 Torr gave **22** (23.45 g, 90%). Colourless liquid. *R*_r (hexane/AcOEt 1:1) 0.48. B.p. (0.3 Torr) 80–84°. IR (CHCl₃): 3085w, 3066w, 3029w, 3012m, 2966m, 2938m, 2895m, 2836m, 1950w, 1872w, 1808w, 1744w, 1676w, 1604w, 1496w, 1453m, 1376m, 1298w, 1256w, 1169w, 1136m, 1099s, 1067s, 994m, 961m, 915w. ¹H-NMR (CDCl₃, 300 MHz): see *Table 3*; additionally, 3.41 (*s*, 2 MeO); 4.65 (br. *s*, $w_{12} \approx 3.5$, PhCH₂); 7.21 – 7.35 (*m*, 5 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): see *Table 3*; additionally, 53.87 (*q*, 2 MeO); 64.43 (*t*, PhCH₂); 127.05 (*d*, C(4) of Ph); 127.98 (*d*, C(2) and C(6) of Ph); 128.40 (*d*, C(3) and C(5) of Ph); 138.00 (*s*, C(1) of Ph). ESI-MS: 354 (9), 295 (18), 264 (8, [*M* + MeOH + K]⁺), 248 (88, [*M* + MeOH + Na]⁺), 226 (85, [*M* + MeOH + H]⁺), 216 (28, [*M* + Na]⁺), 194 (100, [*M* + H]⁺), 162 (16, [*M* - MeO]⁺), 108 (28), 91 (12, C₇H⁺). Anal. calc. for C₁₁H₁₅NO₂ (193.25): C 68.37, H 7.82, N 7.25; found: C 68.36, H 8.05, N 7.42.

Table 3. Selected ¹H-, ¹³C-, and ³¹P-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the Imine 22 and the Amines 23-26 in CDCl₃

	22	23	24	25	26
H-C(1)	7.60 ^a)	3.11	3.23	3.14	3.28
H-C(2)	4.74	4.54	4.51	4.57	4.53
J(1,2)	4.4	4.4	4.7	4.4	4.7
$^{2}J(1,\mathbf{P})$	-	15.3	15.6	14.9	15.6
$^{3}J(2,P)$	-	4.7	4.1	5.0	4.1
C(1)	161.18	56.23	51.60	56.19	51.38
C(2)	102.96	104.56	104.09	104.42	103.94
${}^{1}J(1,\mathbf{P})$	-	153.5	154.4	153.8	154.4
$^{2}J(2,\mathbf{P})$	-	8.6	6.1	8.5	6.1
P	_	25.76	25.70	28.17	28.17

Diethyl [1-(Benzylamino)-2,2-dimethoxyethyl]phosphonate (23). A soln. of HPO(OEt)₂ (6.70 ml, 52.0 mmol) and Et₃N (8.0 ml, 57.4 mmol) in CH₂Cl₂ (11) was cooled to 0° , treated dropwise within 15 min with Me₃SiCl (7.40 ml, 58.3 mmol), stirred for 15 min, treated with a soln. of 22 (10.03 g, 51.9 mmol) in CH₂Cl₂ (15 ml), stirred for 20 min at 0° and for 16 h at 22°, and poured into H₂O (500 ml). The layers were separated and the aq. phase was extracted with CH₂Cl₂ (2 × 200 ml). The combined org. layers were washed with brine (350 ml), dried (MgSO₄), and evaporated. FC (AcOEt) gave 23 (12.0 g, 70%) and 22 (0.83 g, 8%) as colourless oils.

Data of **23**: *R*_f (AcOEt) 0.17. IR (CHCl₃): 3366*w* (br.), 3027*w*, 2994*s*, 2935*m*, 2910*m*, 2867*w*, 2837*w*, 2472*w*, 1950*w*, 1874*w*, 1810*w*, 1751*w*, 1603*w*, 1495*w*, 1454*m*, 1391*w*, 1369*w*, 1242*m*, 1100*m*, 1055*s*, 1028*s*, 966*s*. ¹H-NMR (CDCl₃, 300 MHz): see *Table 3*; additionally, 1.315 (*t*, *J* = 7.2, *Me*CH₂O); 1.320 (*t*, *J* = 7.2, *Me*CH₂O); 1.90 – 2.00 (br. *s*, exchange with CD₃OD, NH); 3.35, 3.39 (2*s*, 2 MeO); 3.94 (br. *d*, *J* = 13.4, *w*_{1/2} ≈ 2.1, PhC*H*); 4.01 (br. *d*, *J* = 13.4, *w*_{1/2} ≈ 2.1, PhC*H*); 4.01 – 4.21 (*m*, 2 MeCH₂O); 7.18 – 7.36 (*m*, 5 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): see *Table 3*; additionally, 16.41 (*dq*, ³*J*(C,P) ≈ 5.7, *Me*CH₂O); 16.47 (*dq*, ³*J*(C,P) ≈ 5.2, *Me*CH₂O); 52.77 (*dt*, ³*J*(C,P) = 6.7, PhCH₂); 55.18 (*q*, MeO); 55.60 (*q*, MeO); 61.94 (*dt*, ²*J*(C,P) = 6.7, MeCH₂O); 62.40 (*dt*, ²*J*(C,P) = 6.7, MeCH₂O); 126.92 (*d*, C(4) of Ph); 128.17 (*d*, C(2) and C(6) of Ph); 128.47 (*d*, C(3) and C(5) of Ph); 139.83 (*s*, C(1) of Ph.), 31P-NMR (CDCl₃, 121 MHz): see *Table 3*. ESI-MS: 685 (3, [2*M* + Na]⁺), 530 (2), 386 (2, [*M* + MeOH + Na]⁺), 370 (11, [*M* + K]⁺), 354 (100, [*M* + Na]⁺), 332 (27, [*M* + H]⁺), 300 (20, [*M* - MeO]⁺), 194 (2, [*M* - PO₃Et₂]⁺). HR-ESI-MS: 685.3011 (100, [2*M* + Na]⁺, C₁₅H₂₆NNAo₅P⁺; calc. 354.1446), 332.1640 (2, [*M* + H]⁺, C₁₅H₂₆KNO₅P⁺; calc. 370.1186), 354.1438 (12, [*M* + Na]⁺, C₁₅H₂₆NNO₅P⁺; calc. 352.1627), 300.1374 (1, [*M* - MC]⁺; C₁₄H₂₃NO₄P⁺; calc. 354.1446), 332.1640 (2, [*M* + H]⁺, C₁₅H₂₆NO₅P⁺; calc. 354.1446), 332.1640 (2, [*M* + H]⁺, C₁₅H₂₆NO₅P⁺; calc. 374, H 791, N 4.23; found: C 54.27, H 8.05, N 4.41.

Diethyl (1-Amino-2,2-dimethoxyethyl)phosphonate (24). *a*) At the atmospheric pressure and 22° , a suspension of 23 (77 mg, 0.232 mmol) and 20% Pd(OH)₂/C (40 mg) in EtOH (1.5 ml) was stirred under H₂ for 3 h. The catalyst was filtered off over *Celite*, and the filtrate was evaporated to give 24 (38.1 mg, 68%).

b) A soln. of **23** (60 mg, 0.181 mmol) in EtOH (1.5 ml) was treated with 10% Pd/C (30 mg) and hydrogenated at the atmospheric pressure for 3 h. Filtration over *Celite* and evaporation gave **24** (36.9 mg, 84%).

c) A soln. of **23** (5.0 g, 15.1 mmol) in EtOH (100 ml) was treated with 10% Pd/C (500 mg) and hydrogenated for 42 h at the atmospheric pressure and 22°. New portions of the fresh catalyst (5×500 mg) had to be added during the reaction period. After the reaction was complete, the mixture was filtered over *Celite*. Evaporation and bulb-to-bulb distillation at 0.4 Torr gave **24** (2.78 g, 76%).

d) At 22° and 6 bar, a suspension of **23** (800 mg, 2.41 mmol) and 10% Pd/C (400 mg) in EtOH (10 ml) was hydrogenated for 2 h and filtered over *Celite*. Evaporation and distillation according to c gave **24** (429 mg, 74%). Colourless oil.

Data of **24**: $R_{\rm f}$ (AcOEt/MeOH 7:1) 0.24. Bp. (0.4 Torr) 130°. IR (CHCl₃): 3394w, 3026w, 2995s, 2938m, 2911m, 2837w, 2472w, 1598w (br.), 1445w, 1392w, 1369w, 1244m, 1163m, 1119m, 1055s, 1028s, 977s, 881w, 828w. ¹H-NMR (CDCl₃, 300 MHz): see *Table 3*; additionally, 1.31 (t, J = 7.2, $MeCH_2O$); 1.32 (t, J = 7.2, $MeCH_2O$); 1.43 – 1.64 (br. *s*, exchange with CD₃OD, NH₂); 3.42, 3.44 (2s, 2 MeO); 4.12 (br. *q*, J = 7.2, $w_{1/2}$ = 3.6, MeCH₂O); 4.14 (br. *q*, J = 7.2, $w_{1/2}$ = 3.6, MeCH₂O). ¹³C-NMR (CDCl₃, 75 MHz): see *Table 3*; additionally, 16.37 (q, $MeCH_2O$); 16.45 (q, $MeCH_2O$); 55.10 (q, MeO); 55.51 (q, MeO); 62.17 (dt, ²J(C,P) = 6.7, MeCH₂O); 62.40 (dt, ²J(C,P) = 6.7, MeCH₂O). ³¹P-NMR (CDCl₃, 121 MHz): see *Table 3*. HR-ESI-MS: 533.2383 (13), 505.2061 (100, [2M + Na]⁺, C₁₆H₄₀N₂NaO₁₀P⁺; calc. 505.2056), 483.2248 (14, [2M + H]⁺, C₁₆H₄₁N₂O₁₀P⁺; calc. 483.2236), 280.0726 (8, [M + K]⁺, C₈H₂₀KNO₅P⁺; calc. 280.0716), 264.0971 (31, [M + Na]⁺, C₈H₂₀NNaO₅P⁺; calc. 264.0977), 252.6343 (3), 242.1167 (3, [M + H]⁺, C₈H₂₁NO₅P⁺; calc. 242.1157), 210.0900 (14). Anal. calc. for C₈H₂₀NO₅P (241.22): C 39.83, H 8.36, N 5.81; found: C 40.02, H 8.33, N 5.98.

Dimethyl [1-(Benzylamino)-2,2-dimethoxyethyl]phosphonate (25). A soln. of HPO(OMe)₂ (0.48 ml, 5.24 mmol) and Et₃N (0.80 ml, 5.74 mmol) in CH₂Cl₂ (100 ml) was cooled to 0°, treated dropwise within 3 min with Me₃SiCl (0.74 ml, 5.83 mmol), stirred for 10 min, treated with a soln. of 22 (1.03 g, 5.33 mmol) in CH₂Cl₂ (5 ml), stirred for 5 min at 0° and for 3 h at 22°, and poured into H₂O (100 ml). The layers were separated, and the aq. phase was extracted with CH₂Cl₂ (2 × 50 ml). The combined org. layers were washed with brine (100 ml), dried (MgSO₄), and evaporated. FC (AcOEt) afforded 25 (976 mg, 60%) and 22 (103 mg, 10%) as colourless oils.

Data of **25**: $R_{\rm f}$ (AcOEt) 0.08. IR (CHCl₃): 3406*w* (br.), 3028*w*, 3001*m*, 2957*m*, 2853*w*, 2838*w*, 2473*w*, 1950*w*, 1876*w*, 1810*w*, 1753*w*, 1603*w*, 1495*w*, 1454*m*, 1358*w*, 1242*m*, 1103*m*, 1061*s*, 1039*s*, 970*w*, 908*w*, 834*w*. ¹H-NMR (CDCl₃, 300 MHz): see *Table* 3; additionally, 1.89–2.01 (br. *s*, exchange with CD₃OD, NH); 3.36, 3.38 (2*s*, 2 MeO); 3.74 (*d*, ³*J*(H,P) = 10.6, MeOP); 3.79 (*d*, ³*J*(H,P) = 10.6, MeOP); 3.92 (br. *d*, *J* = 13.4, $w_{1/2} \approx 3.0$ Hz,

PhC*H*); 4.00 (br. $d, J = 13.1, w_{1/2} \approx 3.0$ Hz, PhC*H*); 7.19–7.35 (m, 5 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): see *Table 3*; additionally, 52.74 ($dq, {}^{2}J(C,P) = 7.3, MeOP$); 52.82 ($dt, {}^{3}J(C,P) = 6.7, PhCH_2$); 53.27 ($dq, {}^{2}J(C,P) = 7.3, MeOP$); 55.08 (q, MeO); 55.78 (q, MeO); 127.03 (d, C(4) of Ph); 128.25 (d, C(2) and C(6) of Ph); 128.47 (d, C(3) and C(5) of Ph); 139.70 (s, C(1) of Ph). ³¹P-NMR (CDCl₃, 121 MHz): see *Table 3*. HR-ESI-MS: 657.2688 (6), 629.2406 (100, [2M + Na]⁺, $C_{13}H_{22}NNaO_{5}P^{+}$; calc. 629.2369), 342.0887 (1, [M + K]⁺, $C_{13}H_{22}KNO_{5}P^{+}$; calc. 326.1133), 304.1331 ($<1, [M + H]^{+}, C_{13}H_{23}NO_{5}P^{+}$; calc. 304.1314). Anal. calc. for $C_{13}H_{23}NO_{5}P$ (303.29): C 51.48, H 7.31, N 4.62; found: C 51.41, H 7.24, N 4.86.

Dimethyl (1-Amino-2,2-dimethoxyethyl)phosphonate (26). A suspension of 25 (800 mg, 2.64 mmol) and 10% Pd/C (400 mg) in MeOH (10 ml) was hydrogenated at 6 bar and 22° for 3 h, and filtered over *Celite*. Evaporation and bulb-to-bulb distillation of the yellowish oil at 0.3 Torr gave 26 (409 mg, 73%) as a colourless oil.

Data of **26**: $R_{\rm f}$ (AcOEt/MeOH 7:1) 0.24. B.p. (0.3 Torr) 130°. IR (CHCl₃): 3395*w*, 3027*w*, 3001*s*, 2958*m*, 2853*w*, 2838*w*, 2473*w*, 1601*w* (br.), 1447*m*, 1364*w*, 1248*m*, 1178*m*, 1119*m*, 1062*s*, 1039*s*, 974*m*, 835*m*. ¹H-NMR (CDCl₃, 300 MHz): see *Table* 3; additionally, 1.43 – 1.63 (br. *s*, exchange with CD₃OD, NH₂); 3.45, 3.47 (2*s*, 2 MeO); 3.79 (*d*, ³*J*(H,P) = 10.6, MeOP); 3.80 (*d*, ³*J*(H,P) = 10.6, MeOP). ¹³C-NMR (CDCl₃, 75 MHz): see *Table* 3; additionally, 52.82 (*dq*, ²*J*(C,P) = 6.1, MeOP); 53.11 (*dq*, ²*J*(C,P) = 6.7, MeOP); 54.99 (*q*, MeO); 55.58 (*q*, MeO). ³¹P-NMR (CDCl₃, 121 MHz): see *Table* 3. HR-ESI-MS: 449.1425 (17, [2*M* + Na]⁺, C₁₂H₃₂N₂NaO₁₀P₂⁺; calc. 449.1430), 427.1626 (1, [2*M* + H]⁺, C₁₂H₃₃N₂O₁₀P₂⁺; calc. 427.1610), 326.1129 (5), 236.0655 (100, [*M* + Na]⁺, C₆H₁₆NNaO₅P⁺; calc. 236.0664), 182.0578 (5, [*M* – MeO]⁺, C₅H₁₃NO₄P⁺; calc. 182.0582). Anal. calc. for C₆H₁₆NO₅P (213.17): C 33.81, H 7.57, N 6.57; found: C 34.00, H 7.42, N 6.62.

Preparation of **29** and **30**. a) By Treatment of **1** with the Aminophosphonate **24** and $HgCl_2$ in 2-Methoxyethanol at 80°. A suspension of **1** (50 mg, 90.3 µmol), $HgCl_2$ (35 mg, 0.129 mmol), and molecular sieves (4 Å; 50 mg) in 2-methoxyethanol (1 ml) was treated successively with **24** (44 mg, 0.182 mmol) and Et₃N (25 µl, 0.179 mmol), heated for 5 h at 80°, cooled to 22°, diluted with AcOEt (5 ml), and filtered over *Celite* (washing with 40 ml of AcOEt). The combined filtrate and washings were extracted with sat. NaHCO₃ soln. (3 × 20 ml) and brine (30 ml), dried (Na₂SO₄), and evaporated. FC (hexane/AcOEt/Et₃N 3:1:0.12 \rightarrow 2:1:0.09 \rightarrow 1:1:0.06) gave **29** (19.1 mg, 36%), **29/30** 42:58 (8.3 mg, 15%), **30** containing up to 10% of an unidentified impurity (8.3 mg, *ca*. 15%), and **27/28** 54:46 (8.4 mg, 16%) [74][75].

b) By Treatment of 1 with $HgCl_2$ in 2-Methoxyethanol at 22°. A suspension of 1 (50 mg, 90.3 µmol), $HgCl_2$ (35 mg, 0.129 mmol), and molecular sieves (4 Å; 50 mg) in 2-methoxyethanol (1 ml) was treated with Et_3N (25 µl, 0.179 mmol) and stirred for 14 h at 22°. Workup and FC (as described in *a*) gave **29** (37.6 mg, 70%), **29/30** 15:85 (8.6 mg, 16%), and **27/28** 65:35 (3.4 mg, 7%) [74][75].

c) By Treatment of **1** with $HgCl_2$ in 2-Methoxyethanol at 80°. A suspension of **1** (100 mg, 0.181 mmol), $HgCl_2$ (78 mg, 0.287 mmol), and molecular sieves (4 Å, 100 mg) in 2-methoxyethanol (2 ml) was treated with Et_3N (50 µl, 0.359 mmol) and heated for 2 h at 80°. Workup and FC, as described in *a*, gave **29** (33.1 mg, 31%), **29/30** 75:25 (28.6 mg, 27%), **30** containing up to 10% of an unidentified impurity (18.7 mg, *ca*. 17%), and **27/28** 58:42 (11.5 mg, 12%) [74][75].

Data of (2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-[(benzyloxy)methyl]-6-[2-(methoxy)ethoxy]-2,3,4,5-tetra*hydropyridine* (29). Colourless oil. $R_{\rm f}$ (hexane/AcOEt/Et₃N 2:1:0.09) 0.48. $[\alpha]_{\rm D}^{25} = +95.6$ (c = 1.02, CHCl₃). UV (CHCl₃): 259 (2.91). IR (CHCl₃): 3089w, 3067w, 3032w, 3012m, 2875m, 1951w, 1875w, 1810w, 1751w, 1675s, 1604w, 1496w, 1454m, 1402w, 1360m, 1296m, 1267w, 1232m, 1126s, 1094s, 1028m, 913w, 844w. ¹H-NMR (CDCl₃, 300 MHz): 3.42 (s, MeO); 3.54 (dtd, $J \approx 1.9$, 3.1, 8.7, H–C(2)); 3.67–3.79 (m, MeOCH₂CH₂O, CH₂–C(2), H-C(3); 3.93 (dd, J = 7.8, 9.7, H-C(4)); 4.16 (dd, J = 1.9, 7.8, H-C(5)); 4.27-4.30 (m, MeOCH₂CH₂O); 4.51 (d, J = 12.5, PhCH); 4.54 (d, J = 11.2, PhCH); 4.58 (d, J = 12.5, PhCH); 4.70 (d, J = 10.9, PhCH); 4.81 (d, J = 10.9, PhCH 11.2, PhCH); 4.83 (d, J = 10.6, PhCH); 4.87 (d, J = 10.6, PhCH); 5.00 (d, J = 10.6, PhCH); 7.21 - 7.24 (m, 2 arom. H); 7.25 - 7.38 (m, 16 arom. H); 7.39 - 7.43 (m, 2 arom. H). ¹H-NMR (C₆D₆, 300 MHz): 3.09 (s, MeO); 3.39 (t, J = 5.3, MeOCH₂CH₂O); 3.64 (dtd, $J \approx 1.9, 2.8, 8.7$, irrad. at $4.09 \rightarrow td$, J = 2.8, 8.7, H - C(2)); 3.79 (dd, J = 2.5, 9.0, irrad. at $3.64 \rightarrow d, J = 9.0, CH - C(2)$; $3.83 (dd, J = 3.1, 9.0, irrad. at <math>3.64 \rightarrow d, J = 9.0, CH' - C(2)$; $3.89 (t, J \approx 9.0, CH' = 0.0, CH$ irrad. at $3.64 \rightarrow d, J \approx 9.0, H - C(3)$; $3.98 (dd, J = 7.2, 9.3, irrad. at <math>4.09 \rightarrow d, J = 9.3, H - C(4)$; 4.09 (dd, J = 1.9, J); 4.09 (dd, J6.9, irrad. at $3.64 \rightarrow d$, J = 7.2, irrad. at $3.98 \rightarrow d$, $J \approx 1.3$, H - C(5); 4.27 - 4.41 (*m*, irrad. at $3.39 \rightarrow$ change, MeOCH₂CH₂O); 4.37 (d, J = 12.1, PhCH); 4.44 (d, J = 12.1, PhCH); 4.62 (d, J = 11.5, PhCH); 4.63 (d, J = 11.2, PhCH); 4.73 (d, J = 11.5, PhCH); 4.80 (d, J = 11.5, PhCH); 4.93 (d, J = 11.2, PhCH); 5.03 (d, J = 11.2, PhCH); 7.04 - 7.20 (m, 12 arom. H); 7.24 - 7.32 (m, 6 arom. H); 7.41 - 7.45 (m, 2 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): 58.95 (q, MeO); 60.47 (d, C(2)); 64.65 (t, MeOCH₂); 70.36, 70.74 (2t, CH₂-C(2), CH₂O-C(6)); 73.16, 74.64, 74.74, 74.87 (4t, 4 PhCH₂); 77.06, 79.05, 83.18 (3d, C(3), C(4), C(5)); 127.35-128.25 (several d); 137.87, 138.19, 138.32, 138.42 (4s); 160.89 (s, C(6)). ¹³C-NMR (C₆D₆, 75 MHz): 58.63 (g, MeO), 61.07 (d, C(2)); 65.03 (t, $\begin{array}{l} \text{MeOCH}_2); \ 70.92, \ 71.04 \ (2t, \ CH_2 - C(2), \ CH_2 O - C(6)); \ 73.46, \ 74.49, \ 74.54, \ 74.88 \ (4t, \ 4 \ PhCH_2); \ 77.58, \ 79.36, \\ \text{83.82} \ (3d, \ C(3), \ C(4), \ C(5)); \ 127.57 - 128.52 \ (\text{several } d); \ 138.96 \ (s); \ 139.29 \ (2s); \ 139.41 \ (s); \ 161.62 \ (s, \ C(6)). \ HR-\\ \text{MALDI-MS: } \ 652.2678 \ (1, \ [M + K + H_2 O]^+, \ C_{37}H_{43} \text{KNO}^+; \ \text{calc. } \ 652.2676), \ 636.2932 \ (15, \ [M + \text{Na} + H_2 O]^+, \\ \ C_{37}H_{43} \text{NNaO}^+; \ \text{calc. } \ 636.2937), \ 614.3110 \ (100, \ [M + H + H_2 O]^+, \ C_{37}H_{44} \text{NO}^+; \ \text{calc. } \ 614.3118), \ 596.3015 \ (4, \ [M + H]^+, \ C_{37}H_{42} \text{NO}^+; \ \text{calc. } \ 614.3118), \ 596.3015 \ (4, \ [M + H]^+, \ C_{37}H_{42} \text{NO}^+; \ \text{calc. } \ 614.3112), \ 560.2415 \ (2), \ 538.2584 \ (2), \ 506.2541 \ (10). \ \text{Anal. } \ \text{calc. } \ \text{for } \ C_{37}H_{41} \text{NO}_6 \ (595.73): \\ \ C \ 74.60, \ H \ 6.94, \ N \ 2.35; \ \text{found: } \ C \ 74.65, \ H \ 6.81, \ N \ 2.52. \end{array}$

Data of (2R,3R,4S,5S)-3,4,5-Tris(benzyloxy)-2-[(benzyloxy)methyl]-6-[2-(methoxy)ethoxy]-2,3,4,5-tetrahydropyridine (30; containing up to 10% of an unidentified impurity). Colourless oil. R_f (hexane/AcOEt/Et₃N 2:1:0.09) 0.41. R_f (CH₂Cl₂/MeOH/Et₃N 1:0.01:0.01) 0.23 (30) and 0.13 (impurity). IR (CHCl₃): 3391w (impurity), 3089w, 3066w, 3028w, 3012w, 2928w, 2861w, 1951w, 1875w, 1810w, 1706m (impurity), 1677s, 1602m, 1496w, 1455m, 1410w, 1363w, 1319w, 1265m, 1097s, 1013m, 911w, 823w. ¹H-NMR (CDCl₃, 300 MHz): 3.14-3.22 (m, impurity); 3.38 (s, MeO); 3.41 (s, impurity); 3.54–3.64 $(m, \text{H}-\text{C}(2), \text{CH}_2-\text{C}(2))$; 3.65–3.69 $(m, \text{H}-\text{C}(2), \text{CH}_2-\text{C}(2))$; 3.65–3.69 (m, H-C(2), C(2)); 3.65–3.69 $MeOCH_2CH_2O$; 3.73 (dd, J = 3.7, 9.0, H-C(4)); 4.08 (dd, J = 6.8, 9.0, H-C(3)); 4.13 (d, J = 3.7, H-C(5)); 4.17-4.22 (m, MeOCH₂CH₂O); 4.26-4.31 (m, impurity); 4.40 (dd, J=2.5, 5.9, impurity); 4.47 (s, impurity); 4.52 (d, J = 12.1, PhCH); 4.53 (s, impurity); 4.575 (d, J = 12.1, PhCH); 4.582 (d, J = 12.1, PhCH); 4.59 (d, J = 11.2, PPhCH); 4.63 (d, J = 12.1, PhCH); 4.78 (d, J = 12.1, PhCH); 4.86 (d, J = 10.9, PhCH); 4.87 (d, J = 12.1, PhCH); 5.24 (*d*, *J* = 5.9, impurity); 7.21 – 7.38 (*m*, 18 arom. H); 7.40 – 7.44 (*m*, 2 arom. H). ¹³C-NMR (CDCl₃, 75 MHz): 58.94 (q, MeO); 61.76 (d, C(2)); 64.60 (t, MeOCH₂); 70.68, 71.48 (2t, CH₂-C(2), CH₂O-C(6)); 71.57 (d, C(3)), 71.84 (t, PhCH₂); 73.07 (t, 2 PhCH₂), 74.25 (t, PhCH₂), 74.42 (d, C(5)); 79.43 (d, C(4)); 127.25 – 128.23 (several d); 138.12, 138.14, 138.44, 138.60 (4s); 160.23 (s, C(6)). HR-MALDI-MS: 652.2684 (1, $[M + K + H_2O]^+$, $C_{37}H_{43}KNO_{7}^{+}; calc. \ 652.2676), \ 636.2931 \ (12, \ [M + Na + H_2O]^+, \ C_{37}H_{43}NNaO_{7}^+; calc. \ 636.2937), \ 614.3109 \ (100, 100, 100, 100), \ (100, 100, 100), \ (100, 100),$ $[M + H + H_2O]^+$, $C_{37}H_{44}NO_7^+$; calc. 614.3118), 596.3013 (4, $[M + H]^+$, $C_{37}H_{42}NO_6^+$; calc. 596.3012), 560.2415 (3), 506.2541 (9).

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