Improved Access to Imidazole-phosphonic Acids: Synthesis of D-*manno*-Tetrahydroimidazopyridine-2-phosphonates[1])

by **Miroslav Terinek** and **Andrea Vasella***

Laboratorium für Organische Chemie, ETH-Hönggerberg, Wolfgang-Pauli Strasse 10, CH-8093 Zürich

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 $HgCl_2/Et_3N$-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 $HgCl_2/Et_3N$, 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 acetal[3]) 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 Pd-catalysed 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-coupling[4]) of

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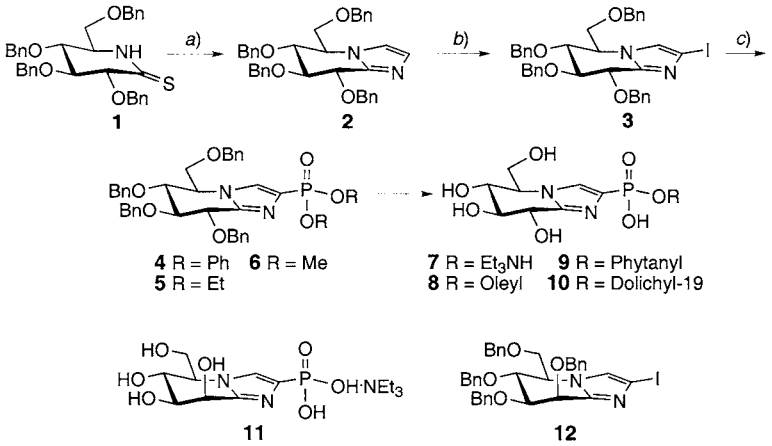
[1]) Presented in part at the XXIst International Carbohydrate Symposium, Cairns, Australia, July 7–12, 2002, Abstract Nr. PP 180.

[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].

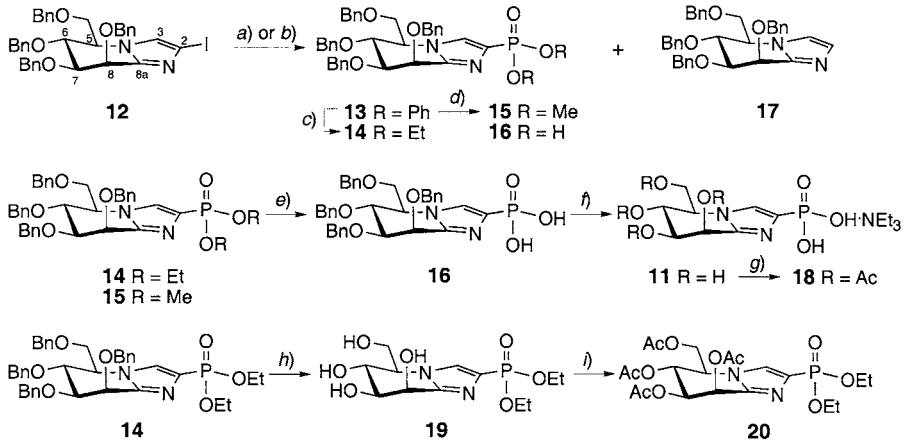
[4]) For further examples of the Pd-catalysed coupling of heteroaryl halides with dialkyl H-phosphonates, *cf.* [15][22–31].

Scheme 1



a) 1. *Lawesson*'s reagent, toluene; 2. $H_2NCH_2CH(OMe)_2$, $Hg(OAc)_2$, THF, 5°; 3. $TsOH \cdot H_2O$, toluene/H_2O, 65°; 75% [20]. *b*) 1. *N*-Iodosuccinimide, DMF, 80°; 2. EtMgBr, THF, 0°; 68–86% [21]. *c*) $HP(O)(OR)_2$, $Pd(PPh_3)_4$, Et_3N, toluene, 95°; 84% of **4**, 62% of **5**, and 31% of **6** [1].

Scheme 2



a) $HP(O)(OR)_2$, $Pd(PPh_3)_4$, Et_3N, 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*) $HP(O)(OSiMe_3)_2$, $Pd(PPh_3)_4$, Et_3N, 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*) Me_3SiBr, CH_2Cl_2. *f*) H_2, $Pd(OH)_2$/C, MeOH/AcOEt/H_2O; (77% from **14**; 83% from **15**). *g*) Ac_2O, pyridine; 96%. *h*) H_2, $Pd(OH)_2$/C, AcOEt/MeOH/H_2O/AcOH; 82%. *i*) Ac_2O, 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$_3$N) led to the desired bis(trimethylsilyl) ester[5]) besides the dehalogenated imidazole **17**. Chromatography (*RP-C18* SiO$_2$; MeOH, H$_2$O) 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 (PtO$_2$) [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 Me$_3$SiBr [45][46], and the resulting crude phosphonic acid **16** was debenzylated (H$_2$, Pd(OH)$_2$). Treating the crude product with 3 equiv. of Et$_3$N, followed by lyophilisation, gave **11** (78% from **14**), mostly as the mono(triethylammonium) salt (1.10 equiv. of Et$_3$N according to ^{1}H-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 Et$_3$N) from **14** and **15**, respectively. According to ^{1}H- and ^{31}P-NMR spectroscopy, the purity of **11** was not affected by chromatography on DEAE-cellulose. Acetylation of **11** (1.60 equiv. of Et$_3$N) gave the tetraacetate **18** in 96% yield (1.62 equiv. of Et$_3$N). We also examined the dealkylation of the acetylated diethyl phosphonate **20** by excess Me$_3$SiBr. 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 acetal[6]) 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 **25**[7]) were prepared similarly to the analogous diethyl acetal corresponding to **23** (diethyl [1-(benzylamino)-2,2-diethoxy-

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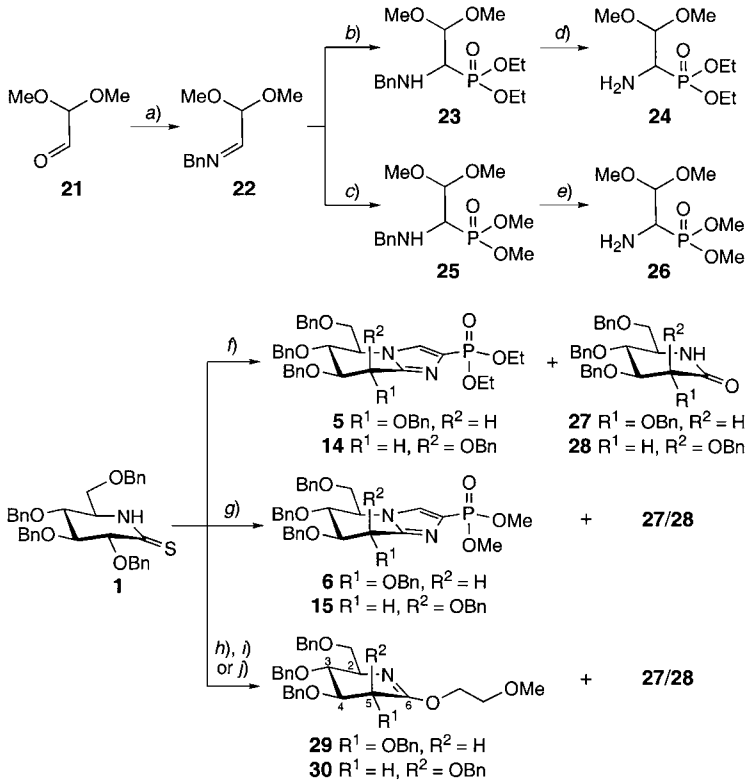
[5]) The iodoimidazole **12** failed to react with the bis[(*tert*-butyl)dimethylsilyl] H-phosphonate; only the dehalogenated imidazole **17** (34%) was isolated. The required H-phosphonate was prepared similarly to HP(O)(OSiMe$_3$)$_2$ [32] by treating phosphoric acid with (*t*-Bu)Me$_2$SiCl in the presence of Et$_3$N 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].

Scheme 3



a) $BnNH_2$, $MgSO_4$, THF, 0°→22°; 90%. *b*) $HP(O)(OEt)_2$, Et_3N, Me_3SiCl, CH_2Cl_2, 0°→22°; 70%. *c*) $HP(O)(OMe)_2$, Et_3N, Me_3SiCl, CH_2Cl_2, 0°→22°; 60%. *d*) H_2, Pd/C, EtOH; 74%. *e*) H_2, Pd/C, MeOH; 73%. *f*) 1. **24**, $HgCl_2$, Et_3N, mol. sieves (3 Å), THF, reflux; 2. $TsOH \cdot H_2O$, toluene, 65°; 45% of **5**/**14** 55:45 and 11% of **27**/**28** 75:25. *g*) 1. **26**, $HgCl_2$, Et_3N, mol. sieves (4 Å), THF, reflux; 2. $TsOH \cdot H_2O$, toluene, 65°; 12% of **6**/**15** 57:43 and 22% of **27**/**28** 71:29. *h*) **24**, $HgCl_2$, Et_3N, mol. sieves (4 Å), 2-methoxyethanol, 80°; 66% of **29**/**30** 64:36 and 16% of **27**/**28** 54:46. *i*) $HgCl_2$, Et_3N, 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 $BnNH_2$ in the presence of $MgSO_4$ 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-to-bulb 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.

$HgCl_2$ 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, $HgCl_2$-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 2-methoxyethanol 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 SiO_2, and addition of Et_3N 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 $HgCl_2/Et_3N$ 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 D-*manno*-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 ($^7H_6$ and $^6H_7$ 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 ^1J(2,P) of 256.3, 246.6, and 245.8 Hz in the ^{13}C-NMR spectra ($CDCl_3$) of **13**–**15**, respectively.

The imine **22** is characterised by a ^{13}C *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 ^{13}C *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*).

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[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 ^{1}H-NMR spectra, ^{13}C *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*).

We thank Dr. *B. Bernet* for checking the experimental part, and the *Swiss National Science Foundation* and *Oxford Glycosciences Ltd.*, Abingdon (UK), for generous support.

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°/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 $CHCl_3$, absorption in cm^{-1}. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra: chemical shifts δ in ppm rel. to TMS (^{1}H and ^{13}C) or H_3PO_4 (^{31}P) 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*-butyl)dimethylsilyl] 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)Me_2SiCl (11.1 g, 73.64 mmol) in Et_2O (120 ml) and Et_3N (10 ml, 71.75 mmol), vigorously stirred for 3 h at 75°, and cooled to 22°. The precipitate (Et_3NCl) was filtered off and washed with Et_2O (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)dimethylsilyl] H-phosphonate (9.81 g, 86%) as a colourless liquid. R_f (AcOEt) 0.08. B.p. (0.5 Torr) 87–89°. IR ($CHCl_3$): 3403*w* (br.), 3001*m*, 2957*s*, 2933*s*, 2887*m*, 2861*m*, 2434*w*, 1634*w*, 1472*m*, 1464*m*, 1393*w*, 1364*w*, 1263*s*, 1055*s*, 1016*s*, 998*s*, 939*w*, 845*s*, 828*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.246 (*s*, 2 MeSi); 0.252 (*s*, 2 MeSi); 0.92 (*s*, 2 Me_3CSi); 6.86 (*d*, ^1J(H,P) = 697.9, HP=O). ^{13}C-NMR ($CDCl_3$, 75 MHz): −3.79 (*q*, 2 MeSi); −3.64 (*q*, 2 MeSi); 17.80 (*d*, ^3J(C,P) = 1.8, 2 Me_3CSi); 25.16 (*q*, 2 Me_3CSi). ^{31}P-NMR ($CDCl_3$, 121 MHz): −12.67. EI-MS: 309 (<1, $[M-H]^+$), 295 (8, $[M-Me]^+$), 253 (100, $[M-t\text{-}Bu]^+$), 211 (14), 195 (20, $[M-TBDMS]^+$), 179 (6, $[M-TBDMSO]^+$), 169 (8), 135 (24), 73 (53). Anal. calc. for $C_{12}H_{31}O_3Si_2P$ (310.52): C 46.42, H 10.06; found: C 46.24, H 9.93.

*Diphenyl (5*R*,6*R*,7*S*,8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-phosphonate* (**13**). A suspension of **12** (36.7 mg, 0.054 mmol) and $Pd(PPh_3)_4$ (18.0 mg, 15.6 μmol) in freshly distilled and degassed toluene (134 μl) was treated under Ar with Et_3N (52 μl, 0.373 mmol) and $HPO(OPh)_2$ (51 μl, 0.265 mmol), and stirred at 95° for 15 h. The mixture was concentrated and co-evaporated with toluene (4 × 2 ml). The ^{1}H-NMR spectrum of the crude showed **13**, besides $P(O)Ph_3$ and $HPO(OPh)_2$. FC (hexane/AcOEt 8:2 → 6:4 → 0:1), followed by FC (CH_2Cl_2/i-PrOH 10:0.05 → 10:0.3), gave **13** (36.5 mg, 86%). Colourless oil. R_f (hexane/AcOEt 1:1) 0.44. $[\alpha]_D^{25} = -35.3$ (c = 0.99, $CHCl_3$). UV ($CHCl_3$): 259 (3.15). IR ($CHCl_3$): 3151*w*, 3066*w*, 2926*m*, 2868*m*, 1952*w*, 1875*w*, 1812*w*, 1728*w*, 1593*m*, 1490*s*, 1455*m*, 1363*w*, 1272*s*, 1161*s*, 1113*s*, 1026*s*, 941*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): see *Table 1*; additionally, 3.51 (irrad. at 3.68 → change); 3.68 (irrad. at 3.51 → change); 3.86 (irrad. at 4.84 → *d*, J = 9.3); 4.11 (irrad. at 3.51 → change); 4.26 (irrad. at 3.86 → *d*, $J \approx 7.0$); 4.36 (*d*, J = 12.1, PhC*H*); 4.39 (*d*, J = 12.1, PhC*H*); 4.586 (*d*, J = 11.2, PhC*H*); 4.590 (*d*, J = 12.1, PhC*H*); 4.60 (*d*, J = 11.9, PhC*H*); 4.67 (*d*, J = 11.9, PhC*H*); 4.68 (*d*, J = 12.1, PhC*H*); 4.84 (irrad. at 3.86 → *s*); 4.96 (*d*, J = 11.2, PhC*H*); 7.05–7.36 (*m*, 30 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): see *Table 2*; additionally, 70.59, 71.91, 73.22, 74.96 (4*t*, 4 PhCH_2); 120.93 (*dd*, ^3J(C,P) = 4.5, C(2) and C(6) of PhO); 120.95 (*dd*, ^3J(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 (2*s*); 137.75 (2*s*); 150.46 (*d*, ^2J(C,P) = 7.5, C(1) of PhO); 150.48 (*d*, ^2J(C,P) = 7.1, C(1) of PhO). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 1*. FAB-MS: 1585 (2, $[2M+H]^+$), 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.

Table 1. *Selected ^1H- and ^{31}P-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** $CDCl_3$	**14** C_6D_6	**15** $CDCl_3$	**16** CD_3OD	**18** CD_3OD	**20** $CDCl_3$	**11** D_2O	**19** D_2O	**19** CD_3OD
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
P	5.01	12.21	12.06	14.91	– 1.37	0.04	11.22	– 1.92	14.86	13.39

[a]) $^3J(H,P) = 1.9$ Hz. [b]) $^3J(H,P) = 0.9$ Hz. [c]) Not assigned.

Table 2. *Selected ^{13}C-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_6D_6	**15** $CDCl_3$	**16** CD_3OD	**18** CD_3OD	**20** $CDCl_3$	**11** D_2O	**19** D_2O	**19** CD_3OD
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[c])	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[c])	66.38[c])	65.44[c])	67.79[c])	64.49[c])	67.21[c])
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[c])	63.64[c])	65.67[c])
C(8a)	146.06	145.99	145.85	145.91	146.70	142.99	142.49	147.96	148.63	150.47
^1J(2,P)	256.3	246.6	242.9	245.8	[e])	233.9	246.6	197.9	246.0	246.6
^2J(3,P)	39.7	37.9	[e])	36.6	20.8	34.2	37.2	21.9	36.6	36.6
^3J(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 Ph*C*H_2 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 Et_3N (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 H_2O (100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated. The ^{1}H-NMR spectrum of the crude showed a mixture of **14**/**17** *ca.* 62:38, $P(O)Ph_3$, and $HPO(OEt)_2$. FC (hexane/AcOEt/Et_3N 5:5:0.3 → 3:7:0.3 → 0:1:0.03) gave **17**

(296 mg, 40%) [20] as a pale yellow oil and a mixture containing mainly **14** and $P(O)Ph_3$ (739 mg). FC (*RP-C18* silica gel, MeOH/H_2O 7:3 → 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 μmol), KF (8.9 mg, 0.153 mmol), and 18-crown-6 (2 mg, 7.57 μmol) in EtOH (0.5 ml) was refluxed for 45 min and evaporated. A soln. of the residue in AcOEt (5 ml) was washed with H_2O (3 × 5 ml) and brine (5 ml), dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 1:1 → 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* $HgCl_2$. A suspension of **1** (100 mg, 0.181 mmol), $HgCl_2$ (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 Et_3N (50 μl, 0.359 mmol), warmed to 80°, stirred for 8 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 combined filtrate and washing was washed with sat. NH_4Cl soln. (3 × 20 ml). The combined aq. layers were extracted with Et_2O (2 × 25 ml). The combined org. layers were washed with H_2O (40 ml) and brine (40 ml), dried ($MgSO_4$), and evaporated. A soln. of the residue (121 mg) in toluene (5 ml) was treated with $TsOH \cdot H_2O$ (115 mg, 0.605 mmol), stirred for 7 h at 65°, cooled to 22°, diluted with Et_2O (50 ml), and washed with sat. NH_4Cl soln. (3 × 20 ml). The combined aq. layers were extracted with Et_2O (2 × 20 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), dried ($MgSO_4$), 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 (5*R*,6*R*,7*S*,8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-phosphonate* (**14**). R_f (hexane/AcOEt 1:1) 0.09. $[\alpha]_D^{25} = -27.9$ ($c = 1.05$, $CHCl_3$). UV ($CHCl_3$): 265 (2.77). IR ($CHCl_3$): 3152*w*, 3065*w*, 2908*m*, 2869*m*, 1954*w*, 1812*w*, 1727*w*, 1603*w*, 1516*m*, 1453*m*, 1393*w*, 1364*m*, 1253*s*, 1100*s*, 1028*s*, 972*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 1*; additionally, 1.32 (br. *t*, J = 7.2, *Me*CH_2O); 1.35 (br. *t*, $J = 6.9$, *Me*CH_2O); 3.58 (irrad. at 3.73 → change); 3.73 (irrad. at 3.58 → change); 3.87 (irrad. at 4.84 → *d*, $J \approx 9.1$); 4.04–4.25 (*m*, irrad. at 3.58 → change, 2 MeCH_2O, H–C(5)); 4.29 (irrad. at 3.87 → change); 4.45 (br. *s*, PhCH_2); 4.59 (*d*, $J = 11.2$, PhC*H*); 4.62 (*d*, $J = 12.1$, PhC*H*); 4.65 (*d*, $J = 12.1$, PhC*H*); 4.68 (*d*, $J = 11.8$, PhC*H*); 4.73 (*d*, $J = 12.1$, PhC*H*); 4.84 (irrad. at 3.87 → *s*); 4.98 (*d*, $J = 10.9$, PhC*H*); 7.22–7.36 (*m*, 20 arom. H). ^{1}H-NMR (C_6D_6, 300 MHz): see *Table 1*; additionally, 1.17 (*t*, $J = 7.2$, *Me*CH_2O); 1.19 (*t*, $J = 7.2$, *Me*CH_2O); 3.28 (irrad. at 3.77 → *d*, $J = 9.7$); 3.44 (irrad. at 3.28 → change, irrad. at 3.77 → change); 3.77 (irrad. at 3.28 → change); 4.02 (*d*, $J = 12.1$, PhC*H*); 4.07 (*d*, $J = 12.1$, PhC*H*); 4.15–4.35 (*m*, 2 MeCH_2O); 4.20 (*d*, $J = 10.9$, PhC*H*); 4.24 (irrad. at 3.77 → change); 4.35 (*d*, $J = 11.8$, PhC*H*); 4.39 (*d*, $J = 11.2$, PhC*H*); 4.80 (*d*, $J = 12.1$, PhC*H*); 4.85 (irrad. at 3.46 → *s*); 4.86 (*d*, $J \approx 12.8$, PhC*H*); 4.89 (*d*, $J = 11.5$, PhC*H*); 7.03–7.19 (*m*, 16 arom. H); 7.23–7.28 (*m*, 2 arom. H); 7.43–7.48 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 2*; additionally, 16.39 (*dq*, ^3J(C,P) ≈ 7.3, *Me*CH_2O); 16.45 (*dq*, ^3J(C,P) ≈ 6.1, *Me*CH_2O); 62.41 (*dt*, ^2J(C,P) ≈ 8.6, Me*C*H_2O); 62.48 (*dt*, ^2J(C,P) ≈ 7.3, Me*C*H_2O); 70.90, 72.04, 73.35, 75.10 (4*t*, 4 Ph*C*H_2); 127.84–128.78 (several *d*); 137.57, 137.97, 138.10, 138.23 (4*s*). ^{13}C-NMR (C_6D_6, 75 MHz): see *Table 2*; additionally, 16.75 (*dq*, ^3J(C,P) = 6.1, 2 *Me*CH_2O); 62.21 (*dt*, ^2J(C,P) = 4.9, Me*C*H_2O); 62.28 (*dt*, ^2J(C,P) = 5.5, Me*C*H_2O); 70.95, 71.64, 73.14, 74.90 (4*t*, 4 Ph*C*H_2); 127.79–129.31 (several *d*, incl. C(3)); 137.92, 138.50, 138.59, 138.70 (4*s*). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 1*. ^{31}P-NMR (C_6D_6, 121 MHz): see *Table 1*. FAB-MS: 1393 (3, $[2M + H]^+$), 697 (86, $[M + H]^+$), 589 (5, $[M - BnO]^+$), 377 (7), 91 (100, $C_7H_7^+$). HR-MALDI-MS: 735.2650 (2, $[M + K]^+$, $C_{40}H_{45}KN_2O_7P^+$; 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, $[M - BnO]^+$, $C_{33}H_{38}N_2O_6P^+$; calc. 589.2467), 561.2177 (14), 533.1867 (8), 515.1754 (7). Anal. calc. for $C_{40}H_{45}N_2O_7P$ (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 Et_3N (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 ^{1}H-NMR spectrum of the crude showed a mixture **15**/**17** *ca.* 50:50, besides $P(O)Ph_3$ and $HPO(OMe)_2$. FC (hexane/AcOEt 8:2 → 5:5 → 3:7 → 1:9 → 0:1) gave **17** (4 mg, 23%) [20] and crude **15** as colourless oils. FC (*RP-C18* silica gel, MeOH/H_2O 6:4 → 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 H_2O (3 × 5 ml) and brine (5 ml), dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 1:1 → 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. NH_4Cl 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 (Na_2SO_4), and evaporated. A soln. of the residue (74 mg) in toluene (2.5 ml) was treated with $TsOH \cdot H_2O$ (60 mg, 0.315 mmol), stirred for 12 h at 65°, diluted with Et_2O (40 ml), and washed with sat. NH_4Cl soln. (3 × 20 ml). The combined aq. layers were extracted with Et_2O (2 × 20 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 3:1 → 1:1 → 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 (5*R,*6*R,*7*S,*8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-phosphonate* (**15**). Colourless oil. R_f (AcOEt) 0.18. $[\alpha]_D^{25} = -35.7$ ($c = 0.99$, $CHCl_3$). UV ($CHCl_3$): 259 (2.91). IR ($CHCl_3$): 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*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 1*; additionally, 3.57 (irrad. at 3.72 → change); 3.72 (irrad. at 3.57 → change); 3.80 (*d*, ^3J(H,P) = 11.2, MeO); 3.81 (*d*, ^3J(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*, PhC*H*$_2$); 4.59 (*d*, *J* = 11.2, PhC*H*); 4.61 (*d*, *J* = 12.1, PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.67 (*d*, *J* = 12.1, PhC*H*); 4.72 (*d*, *J* = 12.1, PhC*H*); 4.82 (irrad. at 3.86 → *s*); 4.97 (*d*, *J* = 10.9, PhC*H*); 7.21–7.36 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 2*; additionally, 52.84 (*dq*, ^2J(C,P) = 6.1, MeO); 53.05 (*dq*, ^2J(C,P) = 6.1, MeO); 70.86, 71.93, 73.22, 74.98 (4*t*, 4 PhC*H*$_2$); 127.61–128.57 (several *d*); 137.24, 137.64, 137.76, 137.90 (4*s*). ^{31}P-NMR ($CDCl_3$, 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. 561.2154), 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.

*(5*R,*6*R,*7*S,*8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-phosphonic Acid* (**16**). A suspension of **12** (16.6 mg, 24.2 μmol) and $Pd(PPh_3)_4$ (8.2 mg, 7.10 μmol) in freshly distilled and degassed toluene (61 μl) was treated under Ar with Et_3N (24 μl, 0.172 mmol) and $HPO(OSiMe_3)_2$ (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/H_2O 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/H_2O 9:1) 0.32. IR ($CHCl_3$): 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*. ^{1}H-NMR (CD_3OD, 300 MHz): see *Table 1*; additionally, 3.73 (irrad. at 3.81 → change); 3.81 (irrad. at 3.73 → change); 4.15 (irrad. at 4.29 → *d*, *J* = 3.1, irrad. at 5.17 → *d*, *J* = 6.2); 4.29 (irrad. at 4.15 → change); 4.41 (*d*, *J* = 12.1, PhC*H*); 4.45 (*d*, *J* = 12.8, PhC*H*); 4.52–4.62 (*m*, irrad. at 4.29 → change, H–C(5)); 4.53 (*d*, *J* = 11.5, PhC*H*); 4.58 (*d*, *J* = 11.8, PhC*H*); 4.60 (*d*, *J* = 11.8, PhC*H*); 4.63 (*d*, *J* = 11.5, PhC*H*); 4.76 (*d*, *J* = 11.5, PhC*H*); 4.81 (*d*, *J* = 11.8, PhC*H*); 5.17 (irrad. at 4.15 → *s*); 7.17–7.37 (*m*, 18 arom. H); 7.41–7.44 (*m*, 2 arom. H). ^{13}C-NMR (CD_3OD, 75 MHz): see *Table 2*; additionally, 74.42 (3*t*), 74.45 (2*t*) (*C*H$_2$–C(5), 4 PhC*H*$_2$); 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 ppm. ^{31}P-NMR (CD_3OD, 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, $[M+Na]^+$), 641 (100, $[M+H]^+$), 561 (1, $[M-HPO_3]^+$), 533 (5, $[M-BnO]^+$), 91 (90, $C_7H_7^+$).

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 Me_3SiBr (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/H_2O 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/H_2O 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 DEAE-cellulose column (*Cellex-D*, *Bio-Rad*, 15 × 1.5 cm, 0.5–0.7 bar; ^{1}H-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 Et_3NH^+, 77%).

b) Similarly as *a*, a soln. of **14** (100 mg, 0.144 mmol) in CH_2Cl_2 (1.4 ml) was treated with Me_3SiBr (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/H_2O 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 H_2O (1 ml) and treated with Et_3N (50 µl, 0.359 mmol). The soln. was evaporated and co-evaporated with toluene (4 × 2 ml). The residue was taken up in MeOH/H_2O 1:1 (2 ml), treated with activated charcoal, and filtered. Evaporation and lyophilisation (3×) gave **11** (44 mg, 1.10 equiv. of Et_3NH^+, 78%).

c) Similarly as *a*, a soln. of **15** (360 mg, 0.538 mmol) in CH_2Cl_2 (5.5 ml) was treated with Me_3SiBr (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/H_2O 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 Et_3NH^+, 83%).

*Data of Triethylammonium Hydrogen (5*R*,6*R*,7*S*,8*R*)-6,7,8-Trihydroxy-5-(hydroxymethyl)-5,6,7,8-tetrahydroi midazo[1,2-*a*]pyridine-2-phosphonate* (**11**). R_f (MeOH/NH_3/H_2O 4:3:1) 0.50. IR (KBr): 3394*s* (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*. ^{1}H-NMR (D_2O, 400 MHz, 1.60 equiv. of Et_3N): see *Table 1*; additionally, 1.23 (*t*, *J* = 7.3, 1.60 ($MeCH_2$)$_3$NH); 3.15 (*q*, *J* = 7.3, 1.60 (MeCH_2)$_3$NH); 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); 4.28 (irrad. at 4.07 → change); 5.13 (irrad. at 4.07 → *s*). ^{13}C-NMR (D_2O, 100 MHz, 1.60 equiv. of Et_3N): see *Table 2*; additionally, 10.91 (*q*, 1.60 ($MeCH_2$)$_3$NH); 49.34 (*t*, 1.60 (MeCH_2)$_3$NH). ^{31}P-NMR (D_2O, 121 MHz, 1.60 equiv. of Et_3N): see *Table 1*. ESI-MS (MeOH/H_2O 1:1, negative mode): 581 (13, $[2M - 2\,H + Na]^-$), 559 (15, $[2M - H]^-$), 375 (22), 339 (25), 325 (80), 311 (100, $[M + MeO]^-$), 297 (26, $[M + HO]^-$), 279 (63, $[M - H]^-$), 255 (26), 213 (63).

*Triethylammonium Hydrogen (5*R*,6*R*,7*S*,8*R*)-6,7,8-Triacetoxy-5-[(acetoxy)methyl]-5,6,7,8-tetrahydroimid-azo[1,2-*a*]pyridine-2-phosphonate* (**18**). A suspension of **11** (50 mg, 1.60 equiv. of Et_3NH^+, 0.113 mmol) in distilled pyridine (1.3 ml) was treated with distilled Ac_2O (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 × 2 ml). The residue was dissolved in H_2O (10 ml) and washed with AcOEt (4 × 3 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/H_2O 8:4:1) 0.41. IR (KBr): 3414*m* (br.), 2976*m*, 2938*s*, 2739*m*, 2678*s*, 2492*m*, 1748*s*, 1641*w*, 1517*w*, 1476*m*, 1434*m*, 1398*m*, 1372*s*, 1232*s*, 1171*m*, 1141*m*, 1070*s*, 950*m*, 924*m*, 849*w*, 805*w*. ^{1}H-NMR (CD_3OD, 400 MHz): see *Table 1*; additionally, 1.31 (*t*, *J* = 7.3, 1.62 ($MeCH_2$)$_3$NH); 2.03, 2.07, 2.12, 2.13 (4*s*, 4 AcO); 3.21 (*q*, *J* = 7.3, 1.62 (MeCH_2)$_3$NH). ^{13}C-NMR (CD_3OD, 100 MHz): see *Table 2*; additionally, 9.22 (*q*, 1.62 ($MeCH_2$)$_3$NH); 20.50, 20.55, 20.59, 20.61 (4*q*, 4 Me); 47.81 (*t*, 1.62 (MeCH_2)$_3$NH); 171.07, 171.24, 171.36, 171.86 (4*s*, 4 C=O). ^{31}P-NMR (CD_3OD, 121 MHz): see *Table 1*. FAB-MS: 923 (2, $[2M + 2\,Na - H_3O]^+$), 901 (6, $[2M + Na - H_2O]^+$), 897 (2, $[2M + H]^+$), 879 (2, $[2M - OH]^+$), 693 (6, $[M - 3\,H + 2\,Et_3N + 2\,Na]^+$), 614 (9, $[M - 4\,H + Et_3N + 3\,Na]^+$), 592 (38, $[M - 3\,H + Et_3N + 2\,Na]^+$), 550 (10, $[M + Et_3NH]^+$), 535 (9, $[M - 5\,H + 4\,Na]^+$), 529 (10), 513 (46, $[M - 4\,H + 3\,Na]^+$), 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, Et_3NH^+).

*Diethyl (5*R*,6*R*,7*S*,8*R*)-6,7,8-Trihydroxy-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-phosphonate* (**19**). A soln. of **14** (103 mg, 0.148 mmol) in AcOEt/MeOH/H_2O 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/H_2O 8:4:1), and lyophilization gave **19** (41 mg, 82%) as a white powder. R_f (AcOEt/i-PrOH/H_2O 8:4:1) 0.26. $[\alpha]_D^{25} = -18.9$ (*c* = 0.75, MeOH). UV (MeOH): 211 (3.97), 193 (3.21). UV (H_2O): 210 (3.98). IR (KBr): 3700–2000*s* (br.), 2987*m*, 2924*m*, 1643*w*, 1522*m*, 1476*w*, 1440*w*, 1394*m*, 1218*s*, 1163*m*, 1097*s*, 1051*s*, 1023*s*, 976*m*, 902*w*, 794*m*, 768*m*, 663*m*. ^{1}H-NMR (CD_3OD, 300 MHz): see *Table 1*; additionally, 1.31 (*t*, *J* = 7.2, $MeCH_2O$); 1.32 (*t*, *J* = 7.2, $MeCH_2O$); 3.85 (irrad. at 4.86 → *d*, *J* = 8.7); 3.95 (irrad. at 3.89 → change); 4.01–4.23 (*m*, H–C(6), 2 MeCH_2O); 4.17 (irrad. at 3.89 → change, irrad. at 3.95 → change); the signal of H–C(8) is partially hidden by the signal of HDO. ^{1}H-NMR (D_2O, 300 MHz): see *Table 1*; additionally, 1.15 (br. *t*, *J* = 7.2, 2 $MeCH_2O$); 3.98 (br. *q*, *J* ≈ 6.8, MeCH_2O); 4.00 (br. *q*, *J* ≈ 7.2, MeCH_2O); 4.05–4.15 (*m*, H–C(5), CH′–C(5)). ^{13}C-NMR (CD_3OD, 75 MHz): see *Table 2*; additionally, 16.56 (*dq*, ^3J(C,P) = 6.7, 2 $MeCH_2O$); 63.90 (*dt*, ^2J(C,P) ≈ 5.3, MeCH_2O);

63.93 (*dt*, ^2J(C,P) ≈ 5.1, Me*C*H$_2$O). ^{13}C-NMR (D$_2$O, 75 MHz): see *Table 2*; additionally, 15.43 (*dq*, ^3J(C,P) = 6.1, 2 *Me*CH$_2$O); 63.99 (*dt*, ^2J(C,P) = 4.9, Me*C*H$_2$O); 64.05 (*dt*, ^2J(C,P) = 4.3, Me*C*H$_2$O). ^{31}P-NMR (CD$_3$OD, 121 MHz): see *Table 1*. ^{31}P-NMR (D$_2$O, 121 MHz): see *Table 1*. HR-MALDI-MS: 375.0730 (4, $[M+K]^+$, $C_{12}H_{21}KN_2O_7P^+$; calc. 375.0723), 359.0981 (100, $[M+Na]^+$, $C_{12}H_{21}N_2NaO_7P^+$; calc. 359.0984), 337.1158 (72, $[M+H]^+$, $C_{12}H_{22}N_2O_7P^+$; calc. 337.1165), 332.1834 (15), 309.0840 (7), 276.1209 (5), 210.1482 (15). Anal. calc. for $C_{12}H_{21}N_2O_7P \cdot 0.5\ H_2O$ (345.29): C 41.74, H 6.42, N 8.11; found C 42.09, H 6.79, N 8.01.

*Diethyl (5*R*,6*R*,7*S*,8*R*)-6,7,8-Triacetoxy-5-[(acetoxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-phosphonate* (**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 Ac_2O (26 μl, 0.275 mmol), stirred for 16 h, and treated with sat. NH_4Cl 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 (Na_2SO_4), evaporated, and co-evaporated with toluene (3 × 5 ml). FC (AcOEt/Et$_3$N 1:0.03) yielded **20** (17.1 mg, 76%). Colourless oil. R_f (AcOEt/Et$_3$N 1:0.03) 0.13. R_f (AcOEt) 0.10. $[\alpha]_D^{25} = -39.6$ (c = 1.00, $CHCl_3$). UV ($CHCl_3$): 239 (2.43). IR ($CHCl_3$): 2997*m*, 2931*w*, 2856*w*, 1755*s*, 1602*w*, 1516*w*, 1427*w*, 1370*m*, 1239*s*, 1133*m*, 1053*s*, 1028*s*, 974*m*, 953*m*, 916*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 1*; additionally, 1.35 (*t*, J = 7.2, 2 *Me*CH$_2$O); 2.05, 2.11, 2.12, 2.13 (4*s*, 4 AcO); 4.07–4.26 (*m*, 2 MeC*H*$_2$O); 4.30 (irrad. at 4.56 → change); 4.35 (irrad. at 4.56 → change, irrad. at 5.59 → change); 4.50–4.62 (*m*, J_{gem} = 11.2, CH′–C(5)); 5.41 (irrad. at 5.59 → change, irrad. at 6.39 → *d*, J = 8.7); 5.59 (irrad. at 5.41 → change); 6.39 (irrad. at 5.41 → *s*). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 2*; additionally, 16.29 (*dq*, ^3J(C,P) = 6.7, *Me*CH$_2$O); 16.31 (*dq*, ^3J(C,P) = 6.7, *Me*CH$_2$O); 20.52 (*q*, Me); 20.66 (*q*, 2 Me); 20.73 (*q*, Me); 62.59 (*dt*, ^2J(C,P) = 4.9, MeCH$_2$O); 62.65 (*dt*, ^2J(C,P) = 4.9, MeCH$_2$O); 169.29, 169.36, 169.49, 170.06 (4*s*, 4 C=O). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 1*. HR-MALDI-MS: 543.1141 (2, $[M+K]^+$, $C_{20}H_{29}KN_2O_{11}P^+$; calc. 543.1146), 527.1397 (43, $[M+Na]^+$, $C_{20}H_{29}N_2NaO_{11}P^+$; calc. 527.1406), 505.1586 (100, $[M+H]^+$, $C_{20}H_{30}N_2O_{11}P^+$; calc. 505.1587), 385.1158 (9), 343.1049 (9), 325.0945 (19), 252.5781 (7).

Benzyl[(2,2-dimethoxy)ethylidene]amine (**22**). A suspension of $BnNH_2$ (16.95 g, 0.158 mol) and $MgSO_4$ (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 → 22°. The solid was filtered off and washed with Et_2O (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_f (hexane/AcOEt 1:1) 0.48. B.p. (0.3 Torr) 80–84°. IR ($CHCl_3$): 3085*w*, 3066*w*, 3029*w*, 3012*m*, 2966*m*, 2938*m*, 2895*m*, 2836*m*, 1950*w*, 1872*w*, 1808*w*, 1744*w*, 1676*w*, 1604*w*, 1496*w*, 1453*m*, 1376*m*, 1298*w*, 1256*w*, 1169*w*, 1136*m*, 1099*s*, 1067*s*, 994*m*, 961*m*, 915*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 3*; additionally, 3.41 (*s*, 2 MeO); 4.65 (br. *s*, $w_{1/2}$ ≈ 3.5, PhC*H*$_2$); 7.21–7.35 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 53.87 (*q*, 2 MeO); 64.43 (*t*, Ph*C*H$_2$); 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, $C_7H_7^+$). Anal. calc. for $C_{11}H_{15}NO_2$ (193.25): C 68.37, H 7.82, N 7.25; found: C 68.36, H 8.05, N 7.42.

Table 3. *Selected ^{1}H-, ^{13}C-, and ^{31}P-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Imine* **22** *and the Amines* **23**–**26** *in $CDCl_3$*

	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
^2J(1,P)	–	15.3	15.6	14.9	15.6
^3J(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
^1J(1,P)	–	153.5	154.4	153.8	154.4
^2J(2,P)	–	8.6	6.1	8.5	6.1
P	–	25.76	25.70	28.17	28.17

[a]) ^4J(1,CH$_2$) = 1.6 Hz.

Diethyl [1-(Benzylamino)-2,2-dimethoxyethyl]phosphonate (**23**). A soln. of $HPO(OEt)_2$ (6.70 ml, 52.0 mmol) and Et_3N (8.0 ml, 57.4 mmol) in CH_2Cl_2 (1 l) was cooled to 0°, treated dropwise within 15 min with Me_3SiCl (7.40 ml, 58.3 mmol), stirred for 15 min, treated with a soln. of **22** (10.03 g, 51.9 mmol) in CH_2Cl_2 (15 ml), stirred for 20 min at 0° and for 16 h at 22°, and poured into H_2O (500 ml). The layers were separated and the aq. phase was extracted with CH_2Cl_2 (2 × 200 ml). The combined org. layers were washed with brine (350 ml), dried ($MgSO_4$), 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 ($CHCl_3$): 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*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 3*; additionally, 1.315 (*t*, $J = 7.2$, *Me*CH_2O); 1.320 (*t*, $J = 7.2$, *Me*CH_2O); 1.90–2.00 (br. *s*, exchange with CD_3OD, NH); 3.35, 3.39 (2*s*, 2 MeO); 3.94 (br. *d*, $J = 13.4$, $w_{1/2} \approx 2.1$, PhC*H*′); 4.01 (br. *d*, $J = 13.4$, $w_{1/2} \approx 2.1$, PhC*H*′); 4.01–4.21 (*m*, 2 MeCH_2O); 7.18–7.36 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 16.41 (*dq*, ^3J(C,P) ≈ 5.7, *Me*CH_2O); 16.47 (*dq*, ^3J(C,P) ≈ 5.2, *Me*CH_2O); 52.77 (*dt*, ^3J(C,P) = 6.7, Ph*C*H_2); 55.18 (*q*, MeO); 55.60 (*q*, MeO); 61.94 (*dt*, ^2J(C,P) = 6.7, Me*C*H_2O); 62.40 (*dt*, ^2J(C,P) = 6.7, Me*C*H_2O); 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). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 3*. ESI-MS: 685 (3, $[2M + Na]^+$), 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, $[M - PO_3Et_2]^+$). HR-ESI-MS: 685.3011 (100, $[2M + Na]^+$, $C_{30}H_{52}N_2NaO_{10}P_2^+$; calc. 685.2995), 370.1209 (< 1, $[M + K]^+$, $C_{15}H_{26}KNO_5P^+$; calc. 370.1186), 354.1438 (12, $[M + Na]^+$, $C_{15}H_{26}NNaO_5P^+$; calc. 354.1446), 332.1640 (2, $[M + H]^+$, $C_{15}H_{27}NO_5P^+$; calc. 332.1627), 300.1374 (1, $[M - MeO]^+$, $C_{14}H_{23}NO_4P^+$; calc. 300.1365). Anal. calc. for $C_{15}H_{26}NO_5P$ (331.35): C 54.37, H 7.91, 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 H_2 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_f (AcOEt/MeOH 7:1) 0.24. B.p. (0.4 Torr) 130°. IR ($CHCl_3$): 3394*w*, 3026*w*, 2995*s*, 2938*m*, 2911*m*, 2837*w*, 2472*w*, 1598*w* (br.), 1445*w*, 1392*w*, 1369*w*, 1244*m*, 1163*m*, 1119*m*, 1055*s*, 1028*s*, 977*s*, 881*w*, 828*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 3*; additionally, 1.31 (*t*, $J = 7.2$, *Me*CH_2O); 1.32 (*t*, $J = 7.2$, *Me*CH_2O); 1.43–1.64 (br. *s*, exchange with CD_3OD, NH_2); 3.42, 3.44 (2*s*, 2 MeO); 4.12 (br. *q*, $J = 7.2$, $w_{1/2} = 3.6$, MeCH_2O); 4.14 (br. *q*, $J = 7.2$, $w_{1/2} = 3.6$, MeCH_2O). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 16.37 (*q*, *Me*CH_2O); 16.45 (*q*, *Me*CH_2O); 55.10 (*q*, MeO); 55.51 (*q*, MeO); 62.17 (*dt*, ^2J(C,P) = 6.7, Me*C*H_2O); 62.40 (*dt*, ^2J(C,P) = 6.7, Me*C*H_2O). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 3*. HR-ESI-MS: 533.2383 (13), 505.2061 (100, $[2M + Na]^+$, $C_{16}H_{40}N_2NaO_{10}P_2^+$; calc. 505.2056), 483.2248 (14, $[2M + H]^+$, $C_{16}H_{41}N_2O_{10}P_2^+$; calc. 483.2236), 280.0726 (8, $[M + K]^+$, $C_8H_{20}KNO_5P^+$; calc. 280.0716), 264.0971 (31, $[M + Na]^+$, $C_8H_{20}NNaO_5P^+$; calc. 264.0977), 252.6343 (3), 242.1167 (3, $[M + H]^+$, $C_8H_{21}NO_5P^+$; calc. 242.1157), 210.0900 (14). Anal. calc. for $C_8H_{20}NO_5P$ (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 Et_3N (0.80 ml, 5.74 mmol) in CH_2Cl_2 (100 ml) was cooled to 0°, treated dropwise within 3 min with Me_3SiCl (0.74 ml, 5.83 mmol), stirred for 10 min, treated with a soln. of **22** (1.03 g, 5.33 mmol) in CH_2Cl_2 (5 ml), stirred for 5 min at 0° and for 3 h at 22°, and poured into H_2O (100 ml). The layers were separated, and the aq. phase was extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layers were washed with brine (100 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt) afforded **25** (976 mg, 60%) and **22** (103 mg, 10%) as colourless oils.

Data of **25**: R_f (AcOEt) 0.08. IR ($CHCl_3$): 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*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 3*; additionally, 1.89–2.01 (br. *s*, exchange with CD_3OD, NH); 3.36, 3.38 (2*s*, 2 MeO); 3.74 (*d*, ^3J(H,P) = 10.6, MeOP); 3.79 (*d*, ^3J(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). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 52.74 (*dq*, ^2J(C,P) = 7.3, MeOP); 52.82 (*dt*, ^3J(C,P) = 6.7, PhCH_2); 53.27 (*dq*, ^2J(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). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 3*. HR-ESI-MS: 657.2688 (6), 629.2406 (100, $[2M + Na]^+$, $C_{26}H_{44}N_2NaO_{10}P_2^+$; calc. 629.2369), 342.0887 (1, $[M + K]^+$, $C_{13}H_{22}KNO_5P^+$; calc. 342.0873), 326.1125 (10, $[M + Na]^+$, $C_{13}H_{22}NNaO_5P^+$; calc. 326.1133), 304.1331 (< 1, $[M + H]^+$, $C_{13}H_{23}NO_5P^+$; calc. 304.1314). Anal. calc. for $C_{13}H_{22}NO_5P$ (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_f (AcOEt/MeOH 7:1) 0.24. B.p. (0.3 Torr) 130°. IR ($CHCl_3$): 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*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 3*; additionally, 1.43–1.63 (br. *s*, exchange with CD_3OD, NH_2); 3.45, 3.47 (2*s*, 2 MeO); 3.79 (*d*, ^3J(H,P) = 10.6, MeOP); 3.80 (*d*, ^3J(H,P) = 10.6, MeOP). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 3*; additionally, 52.82 (*dq*, ^2J(C,P) = 6.1, MeOP); 53.11 (*dq*, ^2J(C,P) = 6.7, MeOP); 54.99 (*q*, MeO); 55.58 (*q*, MeO). ^{31}P-NMR ($CDCl_3$, 121 MHz): see *Table 3*. HR-ESI-MS: 449.1425 (17, $[2M + Na]^+$, $C_{12}H_{32}N_2NaO_{10}P_2^+$; calc. 449.1430), 427.1626 (1, $[2M + H]^+$, $C_{12}H_{33}N_2O_{10}P_2^+$; calc. 427.1610), 326.1129 (5), 236.0655 (100, $[M + Na]^+$, $C_6H_{16}NNaO_5P^+$; calc. 236.0664), 182.0578 (5, $[M - MeO]^+$, $C_5H_{13}NO_4P^+$; calc. 182.0582). Anal. calc. for $C_6H_{16}NO_5P$ (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 Et_3N (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. $NaHCO_3$ soln. (3 × 20 ml) and brine (30 ml), dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt/Et_3N 3:1:0.12 → 2:1:0.09 → 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 (2*R*,3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-2-[(benzyloxy)methyl]-6-[2-(methoxy)ethoxy]-2,3,4,5-tetrahydropyridine* (**29**). Colourless oil. R_f (hexane/AcOEt/Et_3N 2:1:0.09) 0.48. $[\alpha]_D^{25} = +95.6$ (c = 1.02, $CHCl_3$). UV ($CHCl_3$): 259 (2.91). IR ($CHCl_3$): 3089*w*, 3067*w*, 3032*w*, 3012*m*, 2875*m*, 1951*w*, 1875*w*, 1810*w*, 1751*w*, 1675*s*, 1604*w*, 1496*w*, 1454*m*, 1402*w*, 1360*m*, 1296*m*, 1267*w*, 1232*m*, 1126*s*, 1094*s*, 1028*m*, 913*w*, 844*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.42 (*s*, MeO); 3.54 (*dtd*, *J* ≈ 1.9, 3.1, 8.7, H–C(2)); 3.67–3.79 (*m*, MeOCH_2CH_2O, CH_2–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*, MeOCH$_2$CH_2O); 4.51 (*d*, *J* = 12.5, PhC*H*); 4.54 (*d*, *J* = 11.2, PhC*H*); 4.58 (*d*, *J* = 12.5, PhC*H*); 4.70 (*d*, *J* = 10.9, PhC*H*); 4.81 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 10.6, PhC*H*); 4.87 (*d*, *J* = 10.6, PhC*H*); 5.00 (*d*, *J* = 10.6, PhC*H*); 7.21–7.24 (*m*, 2 arom. H); 7.25–7.38 (*m*, 16 arom. H); 7.39–7.43 (*m*, 2 arom. H). ^{1}H-NMR (C_6D_6, 300 MHz): 3.09 (*s*, MeO); 3.39 (*t*, *J* = 5.3, MeOCH_2CH$_2$O); 3.64 (*dtd*, *J* ≈ 1.9, 2.8, 8.7, irrad. at 4.09 → *td*, *J* = 2.8, 8.7, H–C(2)); 3.79 (*dd*, *J* = 2.5, 9.0, irrad. at 3.64 → *d*, *J* = 9.0, CH–C(2)); 3.83 (*dd*, *J* = 3.1, 9.0, irrad. at 3.64 → *d*, *J* = 9.0, CH′–C(2)); 3.89 (*t*, *J* ≈ 9.0, irrad. at 3.64 → *d*, *J* ≈ 9.0, H–C(3)); 3.98 (*dd*, *J* = 7.2, 9.3, irrad. at 4.09 → *d*, *J* = 9.3, H–C(4)); 4.09 (*dd*, *J* = 1.9, 6.9, irrad. at 3.64 → *d*, *J* = 7.2, irrad. at 3.98 → *d*, *J* ≈ 1.3, H–C(5)); 4.27–4.41 (*m*, irrad. at 3.39 → change, MeOCH$_2$CH_2O); 4.37 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 4.62 (*d*, *J* = 11.5, PhC*H*); 4.63 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 11.5, PhC*H*); 4.80 (*d*, *J* = 11.5, PhC*H*); 4.93 (*d*, *J* = 11.2, PhC*H*); 5.03 (*d*, *J* = 11.2, PhC*H*); 7.04–7.20 (*m*, 12 arom. H); 7.24–7.32 (*m*, 6 arom. H); 7.41–7.45 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 58.95 (*q*, MeO); 60.47 (*d*, C(2)); 64.65 (*t*, MeO*C*H$_2$); 70.36, 70.74 (2*t*, *C*H$_2$–C(2), *C*H$_2$O–C(6)); 73.16, 74.64, 74.74, 74.87 (4*t*, 4 PhCH$_2$); 77.06, 79.05, 83.18 (3*d*, C(3), C(4), C(5)); 127.35–128.25 (several *d*); 137.87, 138.19, 138.32, 138.42 (4*s*); 160.89 (*s*, C(6)). ^{13}C-NMR (C_6D_6, 75 MHz): 58.63 (*q*, MeO), 61.07 (*d*, C(2)); 65.03 (*t*,

MeO*C*H$_2$); 70.92, 71.04 (2*t*, *C*H$_2$–C(2), *C*H$_2$O–C(6)); 73.46, 74.49, 74.54, 74.88 (4*t*, 4 Ph*C*H$_2$); 77.58, 79.36, 83.82 (3*d*, C(3), C(4), C(5)); 127.57–128.52 (several *d*); 138.96 (*s*); 139.29 (2*s*); 139.41 (*s*); 161.62 (*s*, C(6)). HR-MALDI-MS: 652.2678 (1, $[M+K+H_2O]^+$, $C_{37}H_{43}KNO_7^+$; calc. 652.2676), 636.2932 (15, $[M+Na+H_2O]^+$, $C_{37}H_{43}NNaO_7^+$; calc. 636.2937), 614.3110 (100, $[M+H+H_2O]^+$, $C_{37}H_{44}NO_7^+$; calc. 614.3118), 596.3015 (4, $[M+H]^+$, $C_{37}H_{42}NO_6^+$; calc. 596.3012), 560.2415 (2), 538.2584 (2), 506.2541 (10). Anal. calc. for $C_{37}H_{41}NO_6$ (595.73): C 74.60, H 6.94, N 2.35; found: C 74.65, H 6.81, N 2.52.

*Data of (2*R*,3*R*,4*S*,5*S*)-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/Et$_3$N 2:1:0.09) 0.41. R_f (CH$_2$Cl$_2$/MeOH/Et$_3$N 1:0.01:0.01) 0.23 (**30**) and 0.13 (impurity). IR ($CHCl_3$): 3391*w* (impurity), 3089*w*, 3066*w*, 3028*w*, 3012*w*, 2928*w*, 2861*w*, 1951*w*, 1875*w*, 1810*w*, 1706*m* (impurity), 1677*s*, 1602*m*, 1496*w*, 1455*m*, 1410*w*, 1363*w*, 1319*w*, 1265*m*, 1097*s*, 1013*m*, 911*w*, 823*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.14–3.22 (*m*, impurity); 3.38 (*s*, MeO); 3.41 (*s*, impurity); 3.54–3.64 (*m*, H–C(2), CH$_2$–C(2)); 3.65–3.69 (*m*, MeOC*H*$_2$CH$_2$O); 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*, MeOCH$_2$C*H*$_2$O); 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, PhC*H*); 4.53 (*s*, impurity); 4.575 (*d*, *J* = 12.1, PhC*H*); 4.582 (*d*, *J* = 12.1, PhC*H*); 4.59 (*d*, *J* = 11.2, PhC*H*); 4.63 (*d*, *J* = 12.1, PhC*H*); 4.78 (*d*, *J* = 12.1, PhC*H*); 4.86 (*d*, *J* = 10.9, PhC*H*); 4.87 (*d*, *J* = 12.1, PhC*H*); 5.24 (*d*, *J* = 5.9, impurity); 7.21–7.38 (*m*, 18 arom. H); 7.40–7.44 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 58.94 (*q*, MeO); 61.76 (*d*, C(2)); 64.60 (*t*, MeO*C*H$_2$); 70.68, 71.48 (2*t*, *C*H$_2$–C(2), *C*H$_2$O–C(6)); 71.57 (*d*, C(3)), 71.84 (*t*, Ph*C*H$_2$); 73.07 (*t*, 2 Ph*C*H$_2$), 74.25 (*t*, Ph*C*H$_2$), 74.42 (*d*, C(5)); 79.43 (*d*, C(4)); 127.25–128.23 (several *d*); 138.12, 138.14, 138.44, 138.60 (4*s*); 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, $[M+H+H_2O]^+$, $C_{37}H_{44}NO_7^+$; 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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