JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Structural Analogues of Selfotel

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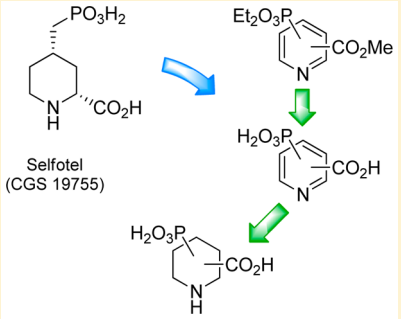
Supporting Information

ABSTRACT: A small library of phosphonopiperidylcarboxylic acids, analogues of NMDA antagonist selfotel (CGS 19755), was synthesized. First, the series of aromatic esters was obtained via a palladium-catalyzed cross-coupling reaction (Hirao coupling) of dialkyl phosphites with bromopyridinecarboxylates, followed by their hydrolysis. Then, hydrogenation of the resulting phosphonopyridylcarboxylic acids over PtO_2 yielded the desired phosphonopiperidylcarboxylic acids. NMR studies indicated that the hydrogenation reaction proceeds predominantly by *cis* addition. Several compounds were obtained as monocrystal structures. Preliminary biological studies performed on cultures of neurons suggest that the obtained compounds possess promising activity toward NMDA receptors.



INTRODUCTION

NMDA (*N*-methyl-D-aspartate) receptors play an important role in the development of the central nervous system (CNS). They are involved in such processes as cognition, learning and memory,[1] and processes of generation of rhythms for breathing[2] and locomotion.[3] Furthermore, they are critical for excitatory synaptic transmission, plasticity, and excitotoxicity in the CNS.[4]

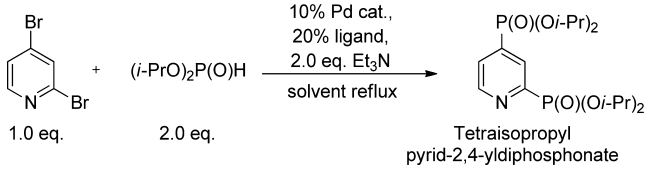
Because of their important role, any malfunction of NMDA receptors results in cognitive defects (decreased activity of the NMDA receptor) or excitotoxicity followed by neurodegeneration (increased activity of the receptor). These dysfunctions are related to many CNS disorders including: stroke, head trauma, ischemia, Huntington's, Parkinson's, and Alzheimer's diseases, epilepsy, neuropathic pain, alcoholism, schizophrenia, mood disorders,[5−9] or tinnitus.[10] Thus, NMDA antagonists are potential agents to treat these diseases. One of the most promising drug candidates, an effective glutamate-site competitive NMDA antagonist, selfotel (CGS 19755), was rejected during clinical trials because of its toxic side effects.[11] The objective of this work was to synthesize a library of NMDA antagonists, analogues of selfotel, in order to estimate their biological activity using culture of neurons.

RESULTS AND DISCUSSION

Chemical Procedures. The well-documented importance of azaheterocylic phosphonates has stimulated intensive studies directed toward methods of their preparation. Numerous studies have indicated that it is a challenging task, and quite frequently, yields of the applied procedures are moderate or even low.[12]

A palladium-catalyzed cross-coupling reaction (Hirao coupling, Scheme 1)[13] has been already applied to the formation of

Scheme 1. Palladium-Catalyzed Cross-Coupling Reaction



aryl phosphonates from dialkyl phosphites and aromatic halides.[14] Although the procedure is well elaborated, both reaction conditions and purification methods required for preparation of phosphorylpyridylcarboxylates needed modification. This was done for preparation of tetraisopropyl pyrid-2,4-yldiphosphonate by using four different catalysts, two ligands and two solvents. The results, shown in Table 1, indicate that the most satisfactory yields have been obtained using Pd_2dba_3 [tris(dibenzylideneacetone)dipalladium(0)] complexed with dppf (1,1-bis(diphenylphosphinyl)ferrocene). $Pd(OAc)_2$ (palladium(II) acetate)/dppf also gave acceptable yields of products, while PPh_3 (triphenylphosphine) was not suitable. The best results have been obtained when 5% of catalyst and 10% of ligand, along with 2.0 equiv of triethylamine per 1.0 equiv of dialkyl phosphite, were used (Scheme 1 and Table 1).

Additionally, the reactivity of three different dialkyl phosphites (dibenzyl, diisopropyl, diethyl) was also studied.

Received: January 31, 2016
Published: May 17, 2016

DOI: 10.1021/acs.joc.6b00220
J. Org. Chem. 2016, 81, 4947−4954

Table 1. Optimization of Reaction Conditions

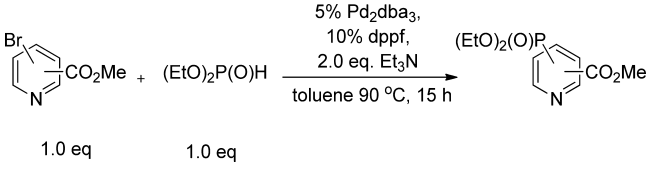
entry	solvent	Pd catalyst	ligand	yield (^{31}P NMR) (%)	isolated yield[a] (%)
1	toluene	$PdBr_2(PPh_3)_2$	PPh_3	–	–
2	toluene	$PdCl_2$	PPh_3	–	–
3	toluene	$Pd(OAc)_2$	PPh_3	7	nd
4	toluene	$PdCl_2$	dppf	40	nd
5	toluene	$Pd(OAc)_2$	dppf	70	54
6	acetonitrile	$PdCl_2$	PPh_3	2	nd
7	acetonitrile	$Pd(OAc)_2$	PPh_3	2	nd
8	toluene	Pd_2dba_3	PPh_3	–	–
9	toluene	Pd_2dba_3	dppf	78	61
10	acetonitrile	Pd_2dba_3	dppf	75	64

[a]Isolated yield of compound after purification. Key: –, no reaction; nd, not determined.

No significant difference was found between the use of diisopropyl and diethyl phosphites, whereas reaction with dibenzyl phosphite did not proceed at all.

The series of phosphorylpyridylcarboxylates and the series of pyridyldiphosphonates were synthesized according to this optimized procedure (Scheme 2). The reaction proceeds readily and afforded the desired compounds **1**–**8** in good isolated yields (Table 2).

Scheme 2. Synthesis of Series of Aromatic Esters



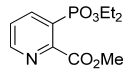
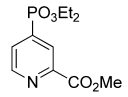
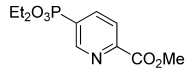
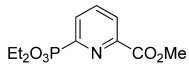
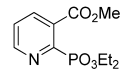
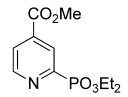
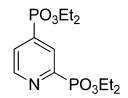
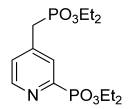
Phosphonic esters were deprotected by hydrolysis with concentrated hydrochloric acid and the resulting acids were hydrogenated to yield the desired analogues of selfotel (Scheme 3). The reversal of order of synthetic steps, namely hydrogenation of esters followed by hydrolysis of phosphorylpyridylcarboxylates (I approach in Scheme 3), appeared to be unsuccessful because of purification of the obtained esters caused significant difficulties.

Hydrogenation of esters was carried out on the basis of the procedure described by Ornstein et al.[15] However, both reaction conditions and purification methods also needed to be optimized for this series of compounds.

In order to select the best reaction conditions, the procedure was optimized for tetraisopropyl pyrid-2,4-yldiphosphonate by varying composition of solvent, molar amount of catalyst, temperature, and time of reaction. The results collected in Table 3 indicate that the optimal conditions are 20% of catalyst, 60 °C, and 48 h of reaction time. An increase in the amount of 2-propanol to 20% resulted in higher solubility of the substrate but did not significantly affect the process.

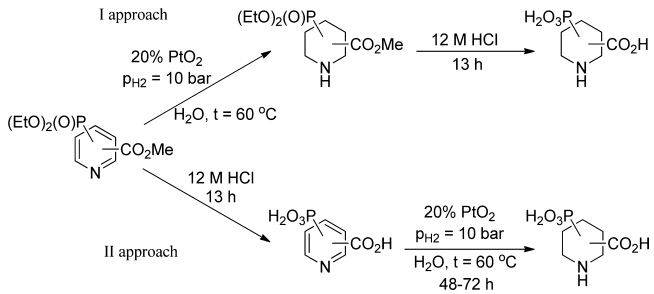
The major problem that arose was the purification of hydrogenation products by silica gel column chromatography because it caused significant loss of this compound. The use of aluminum oxide as stationary phase with precipitation of the product with pentane after column chromatography gave more satisfactory results. Nevertheless, isolated yields were still poor, lower than 23%. Because hydrogenation of the corresponding acids is an alternative procedure for the synthesis of the desired

Table 2. Yields of Aromatic Esters

Entry	Identifier and chemical structure of compound	Yield (^{31}P NMR) (%)	Isolated yield (%)[a]
1.	 **1**	63	31
2.	 **2**	87	70
3.	 **3**	85	75
4.	 **4**	92	72
5.	 **5**	86	65
6.	 **6**	92	73
7.	 **7**	83	49
8.	 **8**	71	37

[a]Isolated yield of compound after purification.

Scheme 3. Overall Scheme for the Synthesis of Analogues of Selfotel



analogues of selfotel, further optimization of purification has not been done.

The series of aromatic acids was obtained upon hydrolysis of the obtained esters with concentrated hydrochloric acid (Scheme 4). This procedure yielded the desired acids almost

DOI: 10.1021/acs.joc.6b00220
J. Org. Chem. 2016, 81, 4947–4954

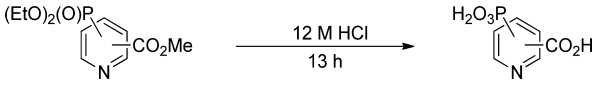
Table 3. Screening for Optimal Reaction Conditions

entry	PtO_2 (%)	solvent	T (°C)	time (h)	yield (^{31}P NMR) (%)	isolated yield[a] (%)
1	15	90% H_2O, 10% *i*-PrOH	40	24	34	nd
2	15	90% H_2O, 10% *i*-PrOH	40	24	72	nd
3	15	90% H_2O, 10% *i*-PrOH	50	24	89	nd
4	15	90% H_2O, 10% *i*-PrOH	50	24	90	4
5	30	90% H_2O, 10% *i*-PrOH	50	48	90	nd
6	20	80% H_2O, 20% *i*-PrOH	60	48	84	23
7	20	80% H_2O, 20% *i*-PrOH	60	55	95	23

[a]Isolated yield of compound after purification; −, means no reaction; nd, not determined.

quantitatively (Table 4), and as usual, the isolated yields were lower.

Scheme 4. Acidic Hydrolysis of Phosphonopyridylcarboxylates[a]



[a]Pyridyldiphosphonic acids were obtained in the same manner. However, **16** was obtained after prolonged (15 h) hydrolysis of ester.

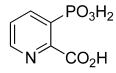
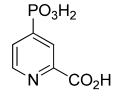
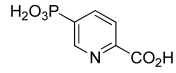
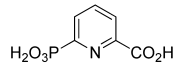
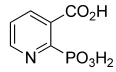
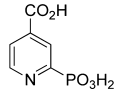
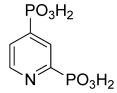
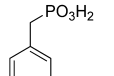
The acids were then hydrogenated based on the procedure (Scheme 5) optimized for esters by changing the solvent from the mixture of water and 2-propanol to pure water. The reaction proceeded smoothly, and the purification of products by means of column chromatography appeared to be unnecessary.

As seen from Table 5, the desired compounds were obtained in moderate to good yields, which are satisfactory from the point of view of their availability for biological studies. NMR studies clearly showed that compounds were obtained as mixtures of stereoisomers with the product of *cis*-addition being the major one (Table 5). This is with the accordance to the general hydrogenation reaction mechanism.

NMR Studies. The NMR spectra of synthesized compounds confirmed their structures. Quite interestingly, we have observed long-range coupling constants via four bonds (11.5 Hz) between two atoms of phosphorus in the ^{31}P NMR spectrum of tetraethyl pyrid-2,4-yldiphosphonate (**7**) (Supporting Information). Moreover, two doublets of doublets found in the ^{13}C NMR spectrum of this compound for both carbon atoms directly connected with phosphorus atoms indicate couplings of each carbon with both phosphorus atoms. This phenomenon, although rare if considering phosphonic acids, is not uncommon, and such long-range couplings have been already reported in the literature.[16]

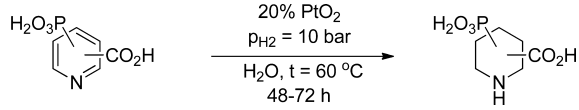
Since the literature data have shown that conformers of piperidinephosphonates could be also seen by NMR, the analysis of the structures of these compounds indicates that they are quite complicated (Supporting Information).[17,18] NMR studies clearly showed that these compounds were obtained as mixtures of stereoisomers with a significant predominance of one of them (Table 5). They also indicated

Table 4. Phosphonopyridinecarboxylic Acids

Entry	Identifier and chemical structure of compound	Yield (^{31}P NMR) (%)	Isolated yield (%)[a]
1.	 **9**	100	84
2.	 **10**	100	72
3.	 **11**	100	92
4.	 **12**	100	86
5.	 **13**	95	90
6.	 **14**	100	72
7.	 **15**	92	76
8.	 **16**	99	81

[a]Isolated yield of compound after purification.

Scheme 5. Preparation of Aliphatic Acids



that the major diastereoisomer is a product of hydrogen *cis*-addition. Additionally, crystallographic studies performed on **19** and **21** demonstrated that the phosphonic group in the *cis*-isomer is in the equatorial position of the six-membered ring. Of course, despite the fact that two enantiomeric mixtures of diastereoisomers are expected to appear, each of the enantiomers may be present in (at least) two conformations.

Crystallographic Studies. The crystals of some of compounds of the series of aromatic acids were obtained. X-ray crystallography confirms their chemical structure. 3-Phosphonopyrid-2-ylcarboxylic acid (**9**), 4-phosphonopyrid-2-ylcarboxylic acid (**10**), 5-phosphonopyrid-2-ylcarboxylic acid (**11**), 2-phosphonopyrid-3-ylcarboxylic acid (in **13**·H_2O), 2-phosphonopyrid-4-ylcarboxylic acid (in **14**·H_2O), pyrid-2,4-

DOI: 10.1021/acs.joc.6b00220
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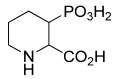
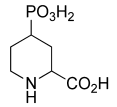
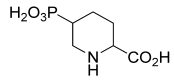
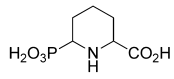
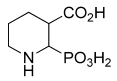
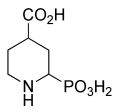
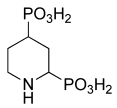
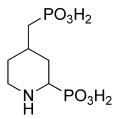
Table 5. Phosphonopiperidinecarboxylic Acids

Entry	Identifier and chemical structure of compound	Yield (^{31}P NMR) (%)	Isolated yield (%)[a]
1.	 **17**	61% major 25% minor	34
2.	 **18**	74% major 19% minor	39
3.	 **19**	74% major 22% minor	72
4.	 **20**	98% major 2% minor	60
5.	 **21**	70% major 15% minor	41
6.	 **22**	78% major Two minor isomers	72
7.	 **23**	96% major 4% minor	50
8.	 **24**	97% major 3% minor	23

[a]Isolated yield of compound after purification.

yldiphosphonic acid (**15**), and 2-phosphono-4-(phosphonomethylene)pyridine (**16**) crystallize as zwitterions with (one of) the phosphonate group deprotonated and pyridinyl N atom protonated (see Figure S2.1). Cell parameters measured for the crystal of 6-phosphonopyrid-2-ylcarboxylic acid monohydrate (**12·H_2O**) are in accordance with the previously published data,[19] and therefore, the structure of **12·H_2O** is not reported here. The crystal structure of monohydrated 2-phosphonopyrid-4-ylcarboxylic acid (**14·H_2O**) was also already described;[20] however, atomic coordinates were not deposited at the Cambridge Structural Database (CSD) (reference code TALSIJ). There are two crystallographically independent zwitterions of **13** and **16** in the asymmetric units (see Figure S2.2). It is also worth mentioning that the carboxylic group of 2,3-substituted compounds **9** and **13** is out of the pyridinyl ring, which is due to steric interaction between neighboring phosphonate and carboxyl moieties.

5-Phosphonopiperid-2-ylcarboxylic acid (**19**) and 2-phosphonopiperid-3-ylcarboxylic acid (in **21·H_2O**) also exist as zwitterions (Figure S2.2) with a phosphonate group in the equatorial position and a carboxyl group in the axial position of the 6-membered ring. This indicates that hydrogen atoms add from one side of the aromatic molecule providing two enantiomers of *cis*-stereoisomer. The centrosymmetric space group $P2_1/n$ indicates that the crystals contain racemic compounds **19** and **21**. The molecular structures of the (*RR*)-enantiomer for **19** and (*RS*)-isomer for **21** are shown in Figure S2.2.

Biological Studies. Preliminary biological studies performed on rat embryo cultures of neurons[21,22] indicated that only one compound, **14**, is toxic to the cells, while the others have a protective effect in the absence of glutamate in the culture medium. Some of the compounds act as antagonists of NMDA receptors (**6**, **14**, and **21**), whereas others act as protectants (**9**) or facilitators (**1**, **2**, **7**, **8**, **18**, and **19**). These studies revealed a very interesting property of these compounds; usually, NMDA agonists are toxic, while the studied compounds intensify the effect of glutamate but at the same time exhibit protective activity toward neurons. This is why they could be called protectants or facilitators. However, further detailed investigation should be performed in order to confirm the obtained biological results.

■ CONCLUSION

A library of novel derivatives of the NMDA antagonist selfotel (CGS 19755) was synthesized. The series of phosphonopyridinecarboxylate esters was obtained via palladium-catalyzed cross-coupling reactions (Hirao coupling) followed by their hydrolysis, and then the series of phosphonopiperidinecarboxylic acids was obtained upon their hydrogenation over PtO_2. The majority of the designed compounds have not been synthesized before, and none of these compounds has been studied as a potential NMDA receptor antagonist.

NMR studies unequivocally identified that hydrogenation of the aromatic ring is a *cis*-process and yields predominantly one diastereomeric mixture of phosphonopiperidinecarboxylic acids.

Preliminary biological studies performed on cultures of neurons indicated that the compounds possess activity toward NMDA receptors. However, further investigation should be performed in order to confirm the obtained biological results.

■ EXPERIMENTAL SECTION

General Information. Reagents and solvents were dried according to standard procedures or freshly distilled if necessary prior to use. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an atmosphere of dry nitrogen in flame-dried glassware. TLC was performed using silica gel 60 F254 plates and heptane/EtOAc as eluents. Visualization was accomplished with UV light and phosphomolybdic acid solution. Flash chromatography was carried out using silica gel AC.C 60 35−70 μm (200−425 mesh) or using CombiFlash Compagnion/TS with a prepacked column (12−120 g) 35−70 μm (200−425 mesh).

Hygrogenation. Hydrogenations were carried out in an autoclave under a pressure of 10 bar.

Spectroscopic Measurements. NMR spectra were recorded with a 400 MHz instrument operating at 400.13 MHz (^{1}H), 100.62 MHz (^{13}C), and 161.97 MHz (^{31}P) and a 600 MHz instrument operating at 600.58 MHz (^{1}H), 151.02 MHz (^{13}C), and 243.12 MHz (^{31}P). Chemical shifts (δ) are given in ppm using internal standards: residual peak of $CDCl_3$ (7.26 ppm), D_2O (4.79 ppm) for ^{1}H NMR, $CDCl_3$ (77.16 ppm) for ^{13}C NMR, H_3PO_4 85% for ^{31}P NMR. Multiplicities are indicated as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dddd (doublet of doublets of doublets of doublets), or m (multiplet). Coupling constants (J) are

DOI: 10.1021/acs.joc.6b00220
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quoted in hertz. The signal assignments were done using 1D and 2D NMR spectra (HMQC, HMBC, HSQC, COSY).

Low- and high-resolution mass spectra were measured using electrospray ionization (ESI) (positive-ion mode). Data are reported in tas m/z (intensity relative to base = 100).

Infrared spectra were taken using solids or neat oils on a diamond surface, and the results are given in cm^{-1}. Peaks are described as w (weak intensity), m (medium intensity), s (strong intensity), vs (very strong intensity), b (broad peak).

Crystallographic Measurements. Measurements were performed on κ-geometry four-circle diffractometers with graphite-monochromatized Mo Kα radiation or Cu Kα radiation. Data were collected at 100(2) or 110(2) K (see Table S2.1 for details).

Data collection, cell refinement, data reduction, and analysis were carried out with the CRYSALIS CCD and CRYSALIS RED.[23] Empirical or analytical absorption correction was applied to the data with the use of CRYSALIS RED. The structures were solved by direct methods with the SHELXS-97 program[24] and refined by a full-matrix least-squares technique based on F^2 using SHELXL-2013[24] with anisotropic thermal parameters for the non-H atoms. All H atoms were found in difference Fourier maps and were refined isotropically. In the final refinement cycles, the non-water H atoms were repositioned in their calculated positions and refined using a riding model with C−H = 0.95−1.00 Å, N−H = 0.88 or 0.99 Å, and O−H = 0.84 Å and with U_{iso}(H) = 1.2U_{eq}(C,N) or 1.5U_{eq}(O). The water H atoms were refined with O−H distances restrained to 0.840(2) Å and with U_{iso}(H) = 1.5U_{eq}(O), and then they were constrained to ride on their parent atoms (AFIX 3 instruction in SHELXL-2013). The phosphonate H atom in **10** was refined in two positions (H1 and H3) with site-occupancy factor of 0.5 each.

The figures presenting the molecular and crystal structures were made using DIAMOND program.[25]

CCDC 1058612−1058620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44(0)1223-336033.

Synthesis. *Preparation of Aromatic Esters: Palladium-Catalyzed Cross-Coupling Reaction (Hirao Coupling). Procedure for the Preparation of a Series of Phosphorylpyridylcarboxylates.* The general procedure is given for the preparation of **1** (methyl 3-diethoxyphosphoryl-pyrid-2-ylcarboxylate). Methyl 3-bromopyridine-2-carboxylate (1.0 equiv, 9.26 mmol, 2.00 g), Pd_2dba_3 (0.05 equiv, 0.463 mmol, 0.424 g), dppf (0.1 equiv, 0.926 mmol, 0.513 g), $(EtO)_2P(O)H$ (1.0 equiv, 9.26 mmol, 1.28 g), and Et_3N (2.0 equiv, 18.5 mmol, 1.87 g) were added to 30 mL of toluene. Mixture was heated at 90 °C for 15 h. After cooling to room temperature, the crude reaction mixture was filtered through filter paper, washed with ethyl acetate, and concentrated in vacuo. The residue was dissolved in dichloromethane and washed three times with saturated solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The compound was purified by column chromatography using heptane/EtOAc as eluent. The same procedure was applied for the preparation of other compounds of this series (compounds **1**−**6**).

*Methyl 3-Diethoxyphosphorylpyrid-2-ylcarboxylate (**1**).* Light brown oil: 0.773 g, yield 31%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 13.35. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.29 (t, $^4J_{HH}$ = 7.1 Hz, 6H, CH_2CH_3), 3.94 (s, 3H, OCH_3), 4.04−4.21 (m, 4H, OCH_2CH_3), 7.45 (2 × AB, $^4J_{PH}$ = 7.8 Hz, $^3J_{HH}$ = 4.9 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, CHCHN), 8.23 (ddd, $^3J_{PH}$ = 13.7 Hz, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, PCCH), 8.71 (ddd, $^5J_{PH}$ = 4.7 Hz, $^3J_{HH}$ = 4.7 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, CHN). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.3 (d, $^3J_{CP}$ = 6.5 Hz, CH_2CH_3), 53.1 (s, OCH_3), 63.0 (d, $^2J_{CP}$ = 5.8 Hz, OCH_2CH_3), 124.0 (d, $^1J_{CP}$ = 187.5 Hz, PC), 124.7 (d, $^3J_{CP}$ = 10.3 Hz, CHCHN), 142.0 (d, $^2J_{CP}$ = 7.1 Hz, PCCH), 151.9 (d, $^4J_{CP}$ = 1.1 Hz, CHN), 153.3 (d, $^2J_{CP}$ = 10.6 Hz, NCC=O), 166.5 (s, C=O). FT-IR (film, cm^{-1}): 2986 ν(w, aromatic CH), 1741 ν(s, C=O) 1298, 1256 ν(s, P=O), 1015 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0853.

*Methyl 4-Diethoxyphosphorylpyrid-2-ylcarboxylate (**2**).* Brown semisolid: 1.771 g, yield 70%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 13.27. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.29 (t, $^4J_{HH}$ = 7.0 Hz, 6H, CH_2CH_3), 3.97 (s, 3H, OCH_3), 4.04−4.20 (m, 4H, OCH_2CH_3), 7.80 (ddd, $^3J_{HP}$ = 13.1 Hz, $^3J_{HH}$ = 4.7 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, CHCHN), 8.39 (ddd, $^3J_{HP}$ = 13.5 Hz, $^4J_{HH}$ = 0.9 Hz, $^5J_{HH}$ = 0.4 Hz, 1H, CHCP), 8.83 (ddd, $^4J_{HP}$ = 5.0 Hz, $^3J_{HH}$ = 4.9 Hz, $^5J_{HH}$ = 0.9 Hz, 1H, CHN). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.3 (d, $^3J_{CP}$ = 6.1 Hz, CH_2CH_3), 53.2 (s, OCH_3), 63.0 (d, $^2J_{CP}$ = 5.8 Hz, OCH_2CH_3), 126.6 (d, $^2J_{CP}$ = 9.2 Hz, CHCP), 128.6 (d, $^2J_{CP}$ = 8.3 Hz, CHCHN), 139.4 (d, $^1J_{CP}$ = 187.3 Hz, CP), 148.3 (d, $^3J_{CP}$ = 12.6 Hz, NCC=O), 150.2 (d, $^3J_{CP}$ = 12.7 Hz, CHN), 164.9 (s, C=O). FT-IR (film, cm^{-1}): 2985 ν(w, aromatic CH), 1722 ν(s, C=O), 1250 ν(s, P=O), 1008 ν(vs, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0846.

*Methyl 5-Diethoxyphosphorylpyrid-2-ylcarboxylate (**3**).* Light brown semisolid: 1.897 g, yield 75%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 14.16. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.28 (t, $^4J_{HH}$ = 7.0 Hz, 6H, CH_2CH_3), 3.97 (s, 3H, OCH_3), 4.05−4.12 (m, 4H, OCH_2CH_3), 8.15 (dd, $^4J_{HP}$ = 11.04 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, NCCH), 8.21 (ddd, $^3J_{HP}$ = 12.8 Hz, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, CHCP), 9.01 (dd, $^3J_{HP}$ = 6.0 Hz, $^4J_{HH}$ = 0.9 Hz, 1H, CHN). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.3 (d, $^3J_{CP}$ = 6.2 Hz, CH_2CH_3), 53.3 (s, OCH_3), 62.9 (d, $^2J_{CP}$ = 5.7 Hz, OCH_2CH_3), 124.5 (d, $^2J_{CP}$ = 11.9 Hz, NCCH), 128.6 (d, $^1J_{CP}$ = 187.7 Hz, PC), 140.9 (d, $^3J_{CP}$ = 8.6 Hz, CHCP), 150.4 (d, $^4J_{CP}$ = 2.1 Hz, NCC=O), 152.1 (d, $^2J_{CP}$ = 12.6 Hz, CHN), 164.9 (d, $^5J_{CP}$ = 1.4 Hz, C=O). FT-IR (film, cm^{-1}): 2971 ν(w, aromatic CH), 1722 ν(s, C=O), 1232 ν(s, P=O), 1015 ν(vs, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0849.

*Methyl 6-Diethoxyphosphorylpyrid-2-ylcarboxylate (**4**).* Dark brown oil: 1.813 g, yield 72%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 9.46. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.31 (t, $^4J_{HH}$ = 7.0 Hz, 6H, CH_2CH_3), 3.93 (s, 3H, OCH_3), 4.16−4.30 (m, 4H, OCH_2CH_3), 7.89 (td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HP}$ = 5.5 Hz, 1H, CHCHCH), 8.05 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HP}$ = 6.8 Hz, 1H, CHCPN), 8.14−8.16 (m, 1H, NCCH). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.4 (d, $^3J_{CP}$ = 5.9 Hz, CH_2CH_3), 53.0 (s, OCH_3), 63.5 (d, $^2J_{CP}$ = 6.1 Hz, OCH_2CH_3), 127.0 (d, $^4J_{CP}$ = 3.7 Hz, NCCH), 130.6 (d, $^2J_{CP}$ = 25.1 Hz, CHCPN), 137.2 (d, $^3J_{CP}$ = 11.7 Hz, CHCHCH), 148.8 (d, $^3J_{CP}$ = 22.7 Hz, NCC=O), 152.7 (d, $^1J_{CP}$ = 227.7 Hz, CN), 165.2 (s, C=O). FT-IR (film, cm^{-1}): 2985 ν(w, aromatic CH), 1725 ν(s, C=O), 1246 ν(s, P=O), 1017 ν(vs, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0841.

*Methyl 2-Diethoxyphosphorylpyrid-3-ylcarboxylate (**5**).* Brown oil: 1.642 g, yield 65%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 9.18. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.3 (t, $^4J_{HH}$ = 7.0 Hz, 6H, CH_2CH_3), 3.91 (s, 3H, OCH_3), 4.12−4.27 (m, 4H, OCH_2CH_3), 7.41−7.44 (m, 1H, NCHCH), 7.91−7.94 (m, 1H, CCHCH), 7.89 (m, 1H, CHN). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 53.1 (s, OCH_3), 63.4 (d, $^2J_{CP}$ = 6.1 Hz, OCH_2CH_3), 125.2 (d, $^4J_{CP}$ = 3.9 Hz, CHCHN), 133.7 (d, $^2J_{CP}$ = 24.4 Hz, CC=O), 136.4 (d, $^3J_{CP}$ = 9.8 Hz, CCHCH), 150.4 (d, $^1J_{CP}$ = 228.5 Hz, CP), 151.1 (d, $^3J_{CP}$ = 21.9 Hz, CHN), 167.2 (s, C=O). FT-IR (film, cm^{-1}): 2971 ν(w, aromatic CH), 1737 ν(s, C=O), 1218 ν(s, P=O), 1017 ν(vs, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0849.

*Methyl 2-Diethoxyphosphorylpyrid-4-ylcarboxylate (**6**).* Brown oil: 1.847 g, yield 73%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 9.88. ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.30 (t, $^4J_{HH}$ = 7.1 Hz, 6H, CH_2CH_3), 3.91 (s, 3H, OCH_2CH_3), 4.11−4.27 (m, 4H, OCH_2CH_3), 7.93 (m, 1H, NCHCH), 8.42 (m, 1H, PCCH), 8.91 (m, 1H, CHN). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.4 (d, $^3J_{CP}$ = 5.8 Hz, CH_2CH_3), 53.0 (s, OCH_3), 63.2 (d, $^2J_{CP}$ = 5.8 Hz, OCH_2CH_3), 125.1 (s, CHCHN), 127.0 (d, $^2J_{CP}$ = 26.6 Hz, PCCH), 137.6 (d, $^3J_{CP}$ = 12.6 Hz, CC=O), 151.4 (d, $^3J_{CP}$ = 22.6 Hz, CHN), 153.4 (d, $^1J_{CP}$ = 228.7 Hz, CP), 164.8 (s, C=O). FT-IR (film, cm^{-1}): 2978 ν(w, aromatic

DOI: 10.1021/acs.joc.6b00220
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CH), 1732 ν(m, C═O), 1248 ν(m, P═O), 1014 ν(vs, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{11}H_{17}NO_5P$ 274.0844, found 274.0847.

*Procedures for the Preparation of Pyridyldiphosphonates. Preparation of tetraethyl pyrid-2,4-yldiphosphonate (**7**).* 2,4-Dibromopyridine (1.0 equiv, 7.94 mmol, 1.88 g), Pd_2dba_3 (0.05 equiv, 0.397 mmol, 0.363 g), dppf (0.1 equiv, 0.794 mmol, 0.440 g), $(EtO)_2P(O)H$ (2.0 equiv,15.8 mmol, 2.19 g), and Et_3N (4.0 equiv, 31.7 mmol, 3.21 g) were added to 30 mL of toluene. The mixture was heated at 90 °C for 15 h. After being cooled to room temperature, the crude reaction mixture was filtered through filter paper, washed with ethyl acetate, and concentrated in vacuo. The residue was dissolved in dichloromethane and washed three times with saturated solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The compound was purified by column chromatography using ethyl acetate/EtOH as eluent.

*Tetraethyl Pyrid-2,4-yldiphosphonate (**7**).* Brown oil: 1.367 g, yield 49%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 9.55 (d, $^4J_{PP}$ = 11.5 Hz, NC*P*), 13.38 (d, $^4J_{PP}$ = 11.5 Hz, C*P*). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.29 (t, $^4J_{HH}$ = 7.1 Hz, 6H, CPOCH$_2$C*H*$_3$), 1.30 (t, $^4J_{HH}$ = 7.1 Hz, 6H, NCPOCH$_2$C*H*$_3$), 4.03−4.28 (m, 8H, OC*H*$_2$CH$_3$), 7.75 (dddd, $^3J_{PH}$ = 13.6 Hz, $^3J_{HH}$ = 4.8 Hz, $^5J_{PH}$ = 2.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, C*H*CHN), 8.19 (dddd, $^3J_{PH}$ = 12.9 Hz, $^3J_{PH}$ = 6.5 Hz, $^4J_{HH}$ = 1.0 Hz, $^5J_{HH}$ = 0.8 Hz, 1H, CPC*H*CP), 8.88 (ddd, $^3J_{HH}$ = 4.8 Hz $^4J_{PH}$ = 4.8 Hz, $^5J_{HH}$ = 0.8 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.3 (d, $^3J_{CP}$ = 2.9 Hz, CPOCH$_2$*C*H$_3$), 16.4 (d, $^3J_{CP}$ = 2.9 Hz, NCPOCH$_2$*C*H$_3$), 63.0 (d, $^2J_{CP}$ = 5.8 Hz, CPO*C*H$_2$CH$_3$), 63.3 (d, $^2J_{CP}$ = 6.1 Hz, NCPOCH$_2$*C*H$_2$CH$_3$), 127.6 (dd, $^2J_{CP}$ = 8.4 Hz, $^4J_{CP}$ = 3.9 Hz, *C*HCHN), 129.0 (dd, $^2J_{CP}$ = 26.1 Hz, $^2J_{CP}$ = 8.6 Hz, CP*C*HCP), 138.2 (dd, $^1J_{CP}$ = 186.5 Hz, $^3J_{CP}$ = 11.6 Hz, *C*P), 150.7 (dd, $^3J_{CP}$ = 22.3 Hz, $^3J_{CP}$ = 12.0 Hz, *C*HN), 152.8 (dd, $^1J_{CP}$ = 227.8 Hz, $^3J_{CP}$ = 11.4 Hz, NC*P*). FT-IR (film, cm^{-1}): 2973 ν(w, aromatic CH), 1249 ν(s, P = O), 1009 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{13}H_{24}NO_6P_2$ 352.1079, found 352.1077.

*Preparation of 2-Diethoxyphosphono-4-(diethoxyphosphonomethylene)pyridine (**8**).* The procedure described earlier for the preparation of **1** was applied. However, this compound was purified by column chromatography using ethyl acetate/EtOH as eluent.

*2-Diethoxyphosphono-4-(diethoxyphosphonomethylene)-pyridine (**8**).* Brown oil: 1.025 g, yield 37%. ^{31}P NMR (161.97 MHz, $CDCl_3$, δ, ppm): 10.79 (s, NC*P*), 23.55 (s, CH$_2$*P*). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.21 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH$_2$POCH$_2$C*H*$_3$), 1.28 (t, $^3J_{HH}$ = 7.0 Hz, 6H, NCPOCH$_2$C*H*$_3$), 3.11 (d, $^1J_{PH}$ = 22.4 Hz, 2H, C*H*$_2$P), 3.97−4.04 (m, 4H, CH$_2$POC*H*$_2$), 4.08−4.24 (m, 4H, NCPOC*H*$_2$), 7.33−7.36 (m, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, C*H*CHN), 7.82 (m, $^3J_{PH}$ = 10.8 Hz, $^4J_{HH}$ = 3.3 Hz, $^4J_{PH}$ = 3.2 Hz, 1H, PCH$_2$CC*H*CP), 8.66 (d, $^3J_{HH}$ = 7.5 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 16.3 (d, $^3J_{CP}$ = 2.1 Hz, CH$_2$POCH$_2$*C*H$_3$), 16.4 (d, $^3J_{CP}$ = 2.2 Hz, NCPOCH$_2$*C*H$_3$), 34.4 (d, $^1J_{CP}$ = 137.4 Hz, *C*H$_2$P) 62.5 (d, $^2J_{CP}$ = 6.8 Hz, CH$_2$PO*C*H$_2$), 63.0 (d, $^2J_{CP}$ = 6.0 Hz, NCPO*C*H$_2$), 127.1 (dd, $^2J_{CP}$ = 5.7 Hz, $^4J_{CP}$ = 3.9 Hz, *C*HCHN), 129.4 (dd, $^2J_{CP}$ = 25.6 Hz, $^3J_{CP}$ = 6.5 Hz, PCH$_2$*C*CHCP), 141.8 (dd, $^2J_{CP}$ = 13.0 Hz, $^3J_{CP}$ = 8.6 Hz, *C*CH$_2$P), 150.6 (dd, $^3J_{CP}$ = 23.7 Hz, $^4J_{CP}$ = 2.6 Hz, *C*HN), 152.0 (d, $^1J_{CP}$ = 229.2 Hz, NC*P*). FT-IR (film, cm^{-1}): 2988 ν(s, aromatic CH), 1249−1242 ν(s, P═O), 1050−1016 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_{14}H_{26}NO_6P_2$ 366.1235, found 366.1232.

Preparation of Aromatic Acids. *General Procedure for Hydrolysis.* A representative procedure for the preparation of **9** (3-phosphonopyrid-2-ylcarboxylic acid) is given. Thus, diethyl pyridyl-2-carboxymethyl-3-phosphonate (1.0 equiv, 1.83 mmol, 0.500 g) was added to 7 mL of 12 M hydrochloric acid. The mixture was heated under reflux for 13 h. After completion of the reaction, hydrochloric acid was removed in vacuo. Water (mQ or distilled) was added, and the hot solution was filtered through filter paper. Purification of the product was carried out by addition of water and its evaporation. This step was repeated three times. The same procedure was applied to the preparation of other compounds of this series compounds: **9**−**15**. Compound **16** was obtained after 15 h of hydrolysis of ester.

*3-Phosphonopyrid-2-ylcarboxylic Acid (**9**).* Beige solid: 0.315 g, yield: 84%. Mp: 208−212 °C. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): 4.76. ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.04 (2 × AB, $^4J_{PH}$ = 7.9 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C*H*CHN), 8.69 (ddd, $^3J_{PH}$ = 5.6 Hz, $^3J_{HH}$ = 4.7 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, PCC*H*), 8.83 (ddd, $^5J_{PH}$ = 12.2 Hz, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 128.2 (d, $^3J_{CP}$ = 10.1 Hz, *C*HCHN), 134.4 (d, $^1J_{CP}$ = 168.2 Hz, *C*P), 142.5 (s, PC*C*H), 145.9 (d, $^2J_{CP}$ = 15.7 Hz, *C*C═O), 150.1 (d, $^4J_{CP}$ = 5.8 Hz, *C*HN), 163.5 (s, *C*═O). FT-IR (film, cm^{-1}): 3676 ν(w, OH), 2988 ν(w, aromatic CH), 1713 ν(m, C═O), 1360 ν(w, P═O), 1075 ν(m, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0073.

*4-Phosphonopyrid-2-ylcarboxylic Acid (**10**).* Beige solid: 0.268 g, yield 72%. Mp: decomposition at 140 °C. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): 3.98. ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.18 (ddd, $^3J_{PH}$ = 11.4 Hz, $^3J_{HH}$ = 5.8 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, C*H*CHN), 8.47 (ddd, $^3J_{HP}$ = 11.2 Hz, $^4J_{HH}$ = 1.2 Hz, $^5J_{HH}$ = 0.6 Hz, 1H, C*H*CP), 8.68 (ddd, $^4J_{HP}$ = 5.7 Hz, $^3J_{HH}$ = 2.9 Hz, $^5J_{HH}$ = 0.6 Hz, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 127.3 (s, *C*HCP), 129.6 (s, *C*HCHN), 141.4 (s, CH−N), 156.8 (d, $^1J_{CP}$ = 163.7 Hz, *C*-P), 159.5 (s, *C*C═O), 163.0 (s, *C*═O). FT-IR (film, cm^{-1}): 3671 ν(w, OH), 2988 ν(w, aromatic CH), 1731 ν(w, C═O), 1268 ν(m, P═O), 1040 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0060.

*5-Phosphonopyrid-2-ylcarboxylic Acid (**11**).* White, amorphous solid: 0.342 g, yield 92%. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): 3.42. ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.36 (ddd, $^3J_{PH}$ = 10.4 Hz, $^3J_{HH}$ = 7.9 Hz, $^5J_{HH}$ = 0.5 Hz, 1H, NCC*H*), 8.72 (ddd, $^3J_{PH}$ = 11.3 Hz, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C*H*CP), 8.76−8.78 (ddd, $^3J_{PH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, $^5J_{HH}$ = 0.6 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 126.7 (d, $^3J_{CP}$ = 11.5 Hz, NC*C*H), 138.1 (d, $^1J_{CP}$ = 174.1 Hz, *C*P), 142.5 (d, $^2J_{CP}$ = 15.6 Hz, *C*HN), 145.0 (s, *C*C═O), 148.8 (d, $^2J_{CP}$ = 7.1 Hz, *C*HCP), 162.6 (s, *C*═O). FT-IR (film, cm^{-1}): 3676 ν(w, OH), 2988 ν(w, aromatic CH), 1732 ν(m, C═O), 1216 ν(m, P═O), 1065−1027 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0062.

*6-Phosphonopyrid-2-ylcarboxylic Acid (**12**).* Cream solid: 0.320 g, yield 86%. Mp: decomposition at 70−80 °C. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): −1.01. ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.19 (ddd, $^3J_{HH}$ = 7.6 Hz, $^3J_{PH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, C*H*CPN), 8.30−8.32 (m, NCC*H*), 8.48 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{PH}$ = 3.0 Hz, 1H, CHC*H*CH). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 127.4 (d, $^4J_{CP}$ = 1.9 Hz, NC*C*H), 131.0 (d, $^2J_{CP}$ = 13.3 Hz, *C*HCPN), 144.4 (d, $^3J_{CP}$ = 9.8 Hz, *C*C═O), 146.1 (d, $^3J_{CP}$ = 9.0 Hz, CHC*H*CH), 152.5 (d, $^1J_{CP}$ = 180.0 Hz, *C*P), 163.1 (s, *C*═O). FT-IR (film, cm^{-1}): 3675 ν(w, OH), 2988 ν(w, aromatic CH), 1723 ν(w, C═O), 1172 ν(w, P═O), 1079 ν(m, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0069.

*2-Phosphonopyrid-3-ylcarboxylic Acid (**13**).* White solid: 0.334 g, yield 90%. Mp: 250 °C dec. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): −2.78. ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 8.13 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, C*H*CHN), 8.81 (d, $^3J_{HH}$ = 5.8 Hz, 1H, CC*H*CH), 8.84−8.86 (m, $^3J_{HH}$ = 8.0 Hz, $^4J_{PH}$ = 3.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 128.3 (s, *C*HCHN), 136.0 (d, $^2J_{CP}$ = 8.4 Hz, *C*C═O), 143.0 (s, *C*CHCH), 146.9 (d, $^3J_{CP}$ = 7.0 Hz, *C*HN), 150.6 (d, $^1J_{CP}$ = 164.4 Hz, *C*P), 172.3 (s, *C*═O). FT-IR (film, cm^{-1}): 3663 ν(w, OH), 2988−2901 ν(w, aromatic CH), 1732 ν(w, C═O), 1260 ν(w, P═O), 1080−1028 ν(m, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0069.

*2-Phosphonopyrid-4-ylcarboxylic Acid (**14**).* White powder: 0.268 g, yield: 72%. Mp: 140 °C dec. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): −2.55. ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.33 (m, 1H, C*H*CHN), 8.48 (dd, $^3J_{PH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, PCC*H*), 8.79 (dd, $^4J_{PH}$ = 6.0 Hz, $^3J_{HH}$ = 1.0 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 127.2 (s, *C*HCHN), 128.4 (d, $^2J_{CP}$ = 11.7 Hz, PCCH), 143.0 (d, $^3J_{CP}$ = 8.1 Hz, *C*HN), 148.6 (d, $^3J_{CP}$ = 8.4 Hz, *C*C═O), 152.7 (d, $^1J_{CP}$ = 175.0 Hz, *C*P), 163.3 (s, *C*═O). FT-IR (film, cm^{-1}): 3414−3306 ν(w, OH), 2368 ν(bw, aromatic CH), 1624 ν(m,

DOI: 10.1021/acs.joc.6b00220
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C═O), 1283 ν(m, P═O), 1043 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_7NO_5P$ 204.0062, found 204.0069.

*Pyrid-2,4-yldiphosphonic Acid (**15**).* White, amorphous solid: 0.259 g, yield: 76%. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): −2.54 (s, NC*P*), 3.95 (d, $^4J_{PP}$ = 3.4 Hz, C*P*). ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 8.09 (m, 1H, C*H*CHN), 8.23 (dd, $^3J_{PH}$ = 11.3 Hz, $^3J_{PH}$ = 7.5 Hz, 1H, CPC*H*CP), 8.65 (m, 1H, C*H*N). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 128.7 (d, $^2J_{CP}$ = 8.8 Hz, *C*HCHN), 129.7 (dd, $^2J_{CP}$ = 11.0 Hz, $^2J_{CP}$ = 8.9 Hz, CP*C*HCP), 141.7 (dd, $^3J_{CP}$ = 11.3 Hz, $^3J_{CP}$ = 7.8 Hz, *C*HN), 151.0 (dd, $^1J_{CP}$ = 174.2 Hz, $^3J_{CP}$ = 9.7 Hz, NCP), 155.6 (d, $^1J_{CP}$ = 164.0 Hz, $^3J_{CP}$ = 7.4 Hz, C*P*). FT-IR (film, cm^{-1}): 2534 ν(w, aromatic CH), 1228−1193 ν(m, P═O), 977.5−911.7 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_5H_8NO_6P_2$ 239.9827, found 239.9826.

*2-Phosphono-4-(phosphonomethylene)pyridine (**16**).* Yellow semisolid: 0.281 g, yield 81%. ^{31}P NMR (161.97 MHz, D_2O, δ, ppm): −2.09 (s, NC*P*), 16.12 (s, CH_2P). ^{1}H NMR (400.13 MHz, D_2O, δ, ppm): 3.33 (d, $^2J_{PH}$ = 22.2 Hz, 2H, CH_2P), 7.84 (d, $^4J_{PH}$ = 5.6 Hz, 1H, C*H*CHN), 8.00 (m, 1H, PCH$_2$CC*H*CP), 8.52 (dd, $^4J_{PH}$ = 6.0 Hz, $^3J_{HH}$ = 1.4 Hz, 1H, C*H*N). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 36.9 (d, $^1J_{CP}$ = 121.1 Hz, *C*H$_2$P), 128.5 (d, $^3J_{CP}$ = 4.8 Hz, *C*HCHN), 130.0 (dd, $^2J_{CP}$ = 11.2 Hz, $^3J_{CP}$ = 4.8 Hz, PCH$_2$*C*CHCP), 140.9 (d, $^3J_{CP}$ = 6.7 Hz, *C*HN), 150.3 (d, $^1J_{CP}$ = 177.7 Hz, NCP), 157.4 (s, *C*CH$_2$P). FT-IR (film, cm^{-1}): 3675 ν(m, OH), 2988−2901 ν(s, aromatic C−H), 1207 ν(s, P═O), 1060 ν(vs, P−O). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{10}NO_6P_2$ 253.9983, found 253.9975.

Reduction. A representative procedure for the preparation of ZD **17** (3-phosphonopiperid-2-ylcarboxylic acid) is given. Pyridyl-2-carboxy-3-phosphonic acid (1.0 equiv, 0.738 mmol, 0.150 g) was hydrogenated over PtO_2 (0.2 equiv, 0.140 mmol, 0.034 g) in 4 mL of H_2O (mQ) at 60 °C and 10 bar for 48 h. The mixture was filtered through filter paper and concentrated in vacuo. The same procedure (sometimes longer hydrogenation time was required) was applied for the preparation of other compounds of this series: **17**−**24**. Only NMR data of the major isomer are described.

*3-Phosphonopiperid-2-ylcarboxylic Acid (**17**).* White powder: 0.0570 g, yield 34%. Mp: 135−137 °C. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 0.04 (13%, phosphates), 19.52 (61%, major isomer), 19.85 (25%, minor isomer), 25.53 (1%). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.72−1.75, 1.95−2.02 (m, 2H, CH_2CH$_2$N) 1.79−1.85, 2.10−2.13 (m, 2H, PCCH_2), 2.48−2.52 (m, 1H, C*H*P), 3.03 (td, $^3J_{HH}$ = 12.3 Hz, $^2J_{HH}$ = 3.8 Hz, 1H, C*H*N), 3.41−3.45 (m, 1H, C*H*N), 4.05 (dd, $^3J_{PH}$ = 28.6 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, C*H*C═O). ^{13}C NMR (100.62 MHz, D_2O, δ, ppm): 19.4 (s, CH$_2$CHN), 24.0 (s, PC*C*H$_2$), 34.1 (d, $^1J_{CP}$ = 129.7 Hz, *C*HP), 44.3 (s, *C*H$_2$N), 58.8 (s, *C*HC═O), 193.5 (d, $^3J_{CP}$ = 2.2 Hz, *C*═O). FT-IR (film, cm^{-1}): 2983 ν(w, aliphatic CH), 1710 ν(m, C═O), 1268 ν(m, P═O), 1039 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0528.

*4-Phosphonopiperid-2-ylcarboxylic acid (**18**).* White powder: 0.0602 g, yield 39%, Mp: decomposition at 150 °C. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 22.42 (74%, major isomer), 22.88 (4%), 23.11 + 23.14 (19%), 23.30 (1.5%), 24.22 (1.5%). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.59−1.68, 2.05 (m, $^2J_{HH}$ = 14.1 Hz, $^3J_{HHcis}$ = 2.9 Hz, 2H, CH_2-CH$_2$−N), 1.59−1.68, 2.43 (m, 2H, CH_2CP), 1.86−1.94 (dtt, $^2J_{PH}$ = 21.6 Hz, $^3J_{HHtrans}$ = 12.7 Hz, $^3J_{HHcis}$ = 3.2 Hz, 1H, C*H*P), 2.98 (ddd, $^3J_{HHtrans}$ = 16.3 Hz, $^2J_{HH}$ = 13.1 Hz, $^3J_{HHcis}$ = 3.1 Hz, 1H, C*H*N), 3.48 (m, $^3J_{HHtrans}$ = $^2J_{HH}$ = 13.1 Hz, $^3J_{HHcis}$ = 2.3 Hz, 1H, C*H*N), 3.68 (dd, $^3J_{HHtrans}$ = 12.7 Hz, $^3J_{HHcis}$ = 3.1 Hz, 1H, C*H*C═O). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 22.4 (d, $^2J_{CP}$ = 2.3 Hz, *C*H$_2$CH$_2$N), 27.0 (d, $^2J_{CP}$ = 2.6 Hz, CH$_2$*C*HP), 33.4 (d, $^1J_{CP}$ = 138.9 Hz, *C*HP), 43.5 (d, $^3J_{CP}$ = 16.8 Hz, *C*H$_2$N), 57.9 (d, $^3J_{CP}$ = 15.4 Hz, *C*HC═O), 172.8 (s, *C*═O). FT-IR (film, cm^{-1}): 3394 ν(w, NH), 2988−2901 ν(w, aliphatic CH), 1710 ν(m, C═O), 1241 ν(w, P═O), 1037 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0536.

*5-Phosphonopiperid-2-ylcarboxylic Acid (**19**).* White powder: 0.111 g, yield 72%. Mp: 165−167 °C. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 19.33 (22%, minor isomer), 19.95 (4%), 20.19 (74%, major isomer). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.53−1.62, 1.90−1.98 (m, 2H, CH_2CHP), 1.90−1.98, 2.28−2.30 (m, 2H, NCHCH_2), 1.98−2.05 (m, 1H, C*H*P), 3.30 (ddd, $^3J_{HH}$ = 13.0 Hz, $^3J_{PH}$ = 12.8 Hz, $^2J_{HH}$ = 10.6 Hz, 1H, C*H*N), 3.37−3.42 (m, 1H, C*H*N), 4.16 (t, $^3J_{HH}$ = 4.9 Hz, 1H, C*H*C═O). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 20.9 (s, CH$_2$CHP), 24.0 (d, $^3J_{CP}$ = 11.2 Hz, NCHCH$_2$), 32.4 (d, $^1J_{CP}$ = 135.5 Hz, CHP), 42.7 (s, CH$_2$N), 55.2 (s, CHC═O), 171.5 (s, C═O). FT-IR (film, cm^{-1}): 2988 ν(w, aliphatic CH), 1716 ν(w, C═O), 1228 ν(w, P═O), 1039 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0529.

*6-Phosphonopiperid-2-ylcarboxylic Acid (**20**).* White powder: 0.0926 g, yield 60%. Mp: 140 °C dec. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 11.00 (98%, major isomer), 11.63 (2%, minor isomer). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.54−1.71 (m, $^3J_{PHtrans}$ = 16.4 Hz, $^3J_{HHtrans}$ = $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, C*H*CHPN), 1.96−1.99 (m, $^3J_{HHtrans}$ = $^2J_{HH}$ = 12.8 Hz, $^3J_{PHtrans}$ = 9.7 Hz, $^3J_{HHcis}$ = 3.1 Hz, 1H, C*H*CHPN), 1.54−1.71, 2.04−2.06 (m, 2H, CH$_2$CH_2CH$_2$), 1.54−1.71, 2.25−2.28 (m, 2H, NCHCH_2), 3.17−3.22 (ddd, $^2J_{PH}$ = 15.8 Hz, $^3J_{HHtrans}$ = 13.1 Hz, $^3J_{HHcis}$ = 2.6 Hz, 1H, C*H*P), 3.83 (dd, $^3J_{HHtrans}$ = 12.7 Hz, $^3J_{HHcis}$ = 3.2 Hz, 1H, C*H*C═O). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 22.1 (d, $^2J_{CP}$ = 12.3 Hz, CH$_2$CHPN), 23.3 (d, $^3J_{CP}$ = 1.9 Hz, CH$_2$CH$_2$CH$_2$), 25.5 (s, NCHCH$_2$), 54.4 (d, $^1J_{CP}$ = 142.2 Hz, CHP), 59.0 (d, $^3J_{CP}$ = 7.7 Hz, CHC═O), 171.9 (s, C═O). FT-IR (film, cm^{-1}): 3671 ν(w, NH), 2972−2901 ν(w, aliphatic CH), 1727 ν(m, C═O), 1228 ν(w, P═O), 1082 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0535.

*2-Phosphonopiperid-3-ylcarboxylic Acid (**21**).* White powder: 0.0633 g, yield 41%. Mp: decomposition at 250 °C. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): −0.04 (3%), 8.30 (3%), 8.60 (70%, major isomer), 9.27 (7%), 10.70 (2%), 11.62 (15%, minor isomers). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.77−1.80, 1.81−1.93 (m, 2H, CH_2CH$_2$N), 1.81−1.93, 2.03−2.08 (m, 2H, CHCH_2CH$_2$), 3.02 (ddd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HHtrans}$ = 12.5 Hz, $^3J_{HHcis}$ = 3.8 Hz, 1H, C*H*N), 3.09 (m, 1H, C*H*C═O), 3.37 (dd, $^2J_{PH}$ = 15.6 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C*H*P), 3.44−3.46 (m, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 18.1 (s, CH$_2$CH$_2$N), 25.0 (d, $^3J_{CP}$ = 9.8 Hz, CHCH$_2$CH$_2$), 38.4 (s, CHC═O), 45.5 (d, $^3J_{CP}$ = 6.2 Hz, CH$_2$N), 55.2 (d, $^1J_{CP}$ = 139.7 Hz, CHP), 177.7 (s, C═O). FT-IR (film, cm^{-1}): 3079 ν(w, NH), 2970 ν(w, aliphatic CH), 1692 ν(m, C═O), 1211−1139 ν(w, P═O), 1067 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0519.

*2-Phosphonopiperid-4-ylcarboxylic Acid (**22**).* White powder: 0.111 g, yield 72%. Mp: 250 °C dec. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 10.42 (78%, major isomer), 10.92 (9%), 11.21 (9%), 11.48 (4%). ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.72−1.80, 2.17 (m, 2H, CH_2CH$_2$N), 1.72−1.80, 2.36 (m, 2H, PCH−CH_2), 2.68 (tt, $^3J_{HHtrans}$ = 12.6 Hz, $^3J_{HHcis}$ = 3.6 Hz, 1H, C*H*C = O), 3.04 (ddd, $^2J_{HH}$ = 16.4 Hz, $^3J_{HHtrans}$ = 13.3 Hz, $^3J_{HHcis}$ = 3.1 Hz, 1H, C*H*N), 3.21 (ddd, $^2J_{PH}$ = 16.2 Hz, $^3J_{HHtrans}$ = 13.3 Hz, $^3J_{HHcis}$ = 2.8 Hz, 1H, C*H*P), 3.45−3.50 (m, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 24.3 (s, CH$_2$CH$_2$N), 26.4 (s, PCHCH_2), 39.0 (d, $^3J_{CP}$ = 12.5 Hz, CHC═O), 44.7 (d, $^3J_{CP}$ = 7.7 Hz, CH$_2$N), 53.4 (d, $^1J_{CP}$ = 141.9 Hz, CHP), 177.8 (s, C═O). FT-IR (film, cm^{-1}): 3456 ν(w, NH), 2988−2901 ν(m, aliphatic CH), 1697 ν(w, C═O), 1242 ν(w, P═O), 1066−1051 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H$^+$] calcd for $C_6H_{13}NO_5P$ 210.0531, found 210.0531.

*Piperid-2,4-yldiphosphonic Acid (**23**).* White powder: 0.0768 g, yield 50%. Mp: 150 °C dec. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 10.71 (d, $^4J_{PP}$ = 8.0 Hz, NCH*P*) (47%), 24.66 (s, CH*P*) (49%), 11.40 (2%), 26.34 (2%), therefore there is 96% of major isomer and 4% of the minor one. ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.65−1.75, 2.08−2.10 (m, 2H, CH_2CH$_2$N), 1.65−1.75, 2.26−2.29 (m, 2H, CHPCH_2CHP), 21.92−1.99 (m, $^2J_{PH}$ = 29.0 Hz, $^3J_{HH}$ = 12.5 Hz, 1H, C*H*P), 3.01 (ddd, $^4J_{PH}$ = 16.1 Hz, $^3J_{HHtrans}$ = 13.1 Hz, $^3J_{HHcis}$ = 3.0 Hz, 1H, C*H*N), 3.19 (ddd, $^2J_{PH}$ = 15.9 Hz, $^3J_{HHtrans}$ = 13.1 Hz, $^3J_{HHcis}$ = 2.8 Hz, 1H, NC*H*P), 3.47 (m, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 22.3 (s, CH$_2$CH$_2$N), 24.5 (s, CHPCH$_2$CHP), 32.6 (dd, $^1J_{CP}$ = 140.1 Hz, $^3J_{CP}$ = 11.2 Hz, CHP), 45.1 (dd, $^3J_{CP}$ = 16.4 Hz, $^3J_{CP}$ = 6.9

DOI: 10.1021/acs.joc.6b00220
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Hz, CH_2N), 53.7 (dd, $^1J_{CP}$ = 141.7 Hz, $^3J_{CP}$ = 15.0 Hz, NCHP). FT-IR (film, cm^{-1}): 3371 ν(w, NH), 2933−2276 ν(m, aliphatic CH), 1126 ν(m, P═O), 911.6 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H^+] calcd for $C_5H_{12}NO_6P_2$ 244.0140, found 244.0152.

*2-Phosphono-4-(phosphonomethylene)piperidine (**24**).* Yellow semisolid: 0.0353 g, yield 23%. ^{31}P NMR (243.12 MHz, D_2O, δ, ppm): 11.01 (s, NCH*P*) (46%), 27.58 (s, CH_2*P*) (51%), 11.80 (1.5%), 28.09 (1.5%); therefore, there is 97% of the major isomer and 3% of the minor isomer. ^{1}H NMR (600.58 MHz, D_2O, δ, ppm): 1.41−1.49, 2.07−2.09 (m, 2H, CH_2CHN), 1.41−1.49, 2.21−2.24 (m, 2H, PCH_2CHCH_2CHP), 1.70−1.82 (m, $^2J_{PH}$ = 18.0 Hz, $^2J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2P), 1.96−2.00 (m, 1H, CHCH$_2$P), 3.02 (ddd, $^4J_{PH}$ = 16.2 Hz, $^3J_{HHtrans}$ = 13.2 Hz, $^3J_{HHcis}$ = 2.9 Hz, 1H, C*H*N), 3.20 (ddd, $^2J_{PH}$ = 15.9 Hz, $^3J_{HHtrans}$ = 13.2 Hz, $^3J_{HHcis}$ = 2.6 Hz, 1H, NC*H*P), 3.40−3.42 (m, $^3J_{HHtrans}$ = 12.8 Hz, $^3J_{HHcis}$ = 2.2 Hz, 1H, C*H*N). ^{13}C NMR (151.02 MHz, D_2O, δ, ppm): 28.9 (d, $^3J_{CP}$ = 9.9 Hz, CH_2CH_2N), 29.4 (dd, $^2J_{CP}$ = 12.9 Hz, $^3J_{CP}$ = 3.7 Hz, CHCH_2P), 31.2 (d, $^2J_{CP}$ = 13.0 Hz, PCH_2CHCH_2CHP), 33.0 (d, $^1J_{CP}$ = 134.3 Hz, CH_2P), 45.3 (d, $^3J_{CP}$ = 7.8 Hz, CH_2N), 54.1 (d, $^1J_{CP}$ = 142.5 Hz, NCHP). FT-IR (film, cm^{-1}): 3675 ν(m, NH), 2988−2901 ν(s, aliphatic CH), 1242 ν(m, P═O), 1057 ν(s, PO). HRMS (TOF MS ES+) (m/z): [M + H^+] calcd for $C_6H_{16}NO_6P_2$ 260.0453, found 260.0457.

Crystallization of Compounds. *Crystals of Phosphonopyridylcarboxylic Acids.* The 0.025 g sample of the product was dissolved in 1 mL of distilled water at 70 °C and allowed to cool very slowly to room temperature. Fine crystals were obtained by room-temperature crystallization after 7 days. They are stable and can be stored at room temperature. This procedure was applied for the crystallization of: **9**−**12**, **13**·H_2O, **14**·H_2O, and **15** (room-temperature crystallization took 10 months).

Crystals of Pyridyldiphosphonic Acid. 2-Phosphono-4-(phosphonomethylene)pyridine (**16**), was dissolved in water and slowly evaporated at 7 °C for one month. Fine crystals are not stable and should be stored at low temperature.

Crystals of Phosphonopiperidylcarboxylic Acids. The 0.040 g sample of compound **19** (5-phosphonopiperid-2-ylcarboxylic acid) was dissolved in 1 mL of distilled water. Fine crystals were obtained by room-temperature crystallization after 4 weeks. They are stable and can be stored at room temperature.

A 0.030 g sample of compound **21** (2-phosphonopiperid-3-ylcarboxylic acid) was dissolved in 1 mL of distilled water at 70 °C and allowed to cool very slowly to room temperature. Fine crystals of **21**·H_2O were obtained by room-temperature crystallization from distilled water (13 months) and recrystallization from the mixture of water and 2-propanol to improve their quality (2 months). They are stable and can be stored at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00220.

NMR, MS, and IR spectra (PDF)

Crystallographic data (PDF)

X-ray data for obtained compounds (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Jan de Weille for expert assistance in the preliminary toxicity studies and for critically reading the manuscript. This work was supported by the French Government Fellowship cotutelle system for joint doctoral studies and by a statutory activity subsidy from the Polish Ministry of Science and Higher Education.

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DOI: 10.1021/acs.joc.6b00220
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