New Chiral Bicyclic Phosphoramides Derived from L-Glutamic Acid

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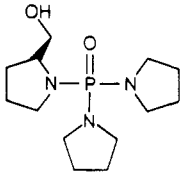
New cyclic chiral phosphoramides derived from (7a*S*)-1,2,5,6,7,7a-hexahydropyrrolo[1,2-*c*]diazaphosphole 3-oxide have been synthesized and isolated in 100% diastereomeric purity from (+)-(*S*)-glutamic acid. The configuration at the phosphorus atom and the diastereomeric purities have been determined for each compound through ^{1}H and ^{31}P NMR examination. The enantiomeric purity for two compounds could be evaluated through the measurement of ^{31}P NMR shifts induced by addition of (−)-(*R*)-*N*-(3,5-dinitrobenzoyl)-1-phenylethylamine as a chiral solvating agent.

Hexamethylphosphoramide (HMPA) is often used to induce variations in the reactivity of transition-metal complexes. As an example, in the alkylation of palladium-complexed olefins, the use of HMPA could extent the scope of reagents from stabilized carbanions to ketone and ester enolates, oxazoline anions, and protected cyanohydrin anions.[1] Moreover, in the alkylation of π-allylpalladium chloride by ester enolates, addition of HMPA led to a cyclopropanation reaction instead of an allylic alkylation.[2]

Few crystalline HMPA-containing transition-metal complexes have been described. Among them, MoO_5HMPA[3] has been used for the epoxidation of olefins[4] or allylic alcohols.[5] MoO_5HMPA,pyridine (MoOPH) is a useful reagent for the oxidation of enolates of ketones, esters, and lactones into α-hydroxy derivatives[6] and of cyanides into cyanohydrins.[7]

Chiral analogues of HMPA are unusual. To the best of our knowledge, 1,[8] **2a**,[9] and **2b**[10] were the only chiral phosphoramides yet to be described. Only one asymmetric synthesis has been reported to involve an optically active phosphoramide as ligand in complexes: the asymmetric epoxidation of *trans*-2-octene by MoO_5–pyridine–**2b** complexes.[10]



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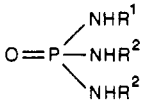
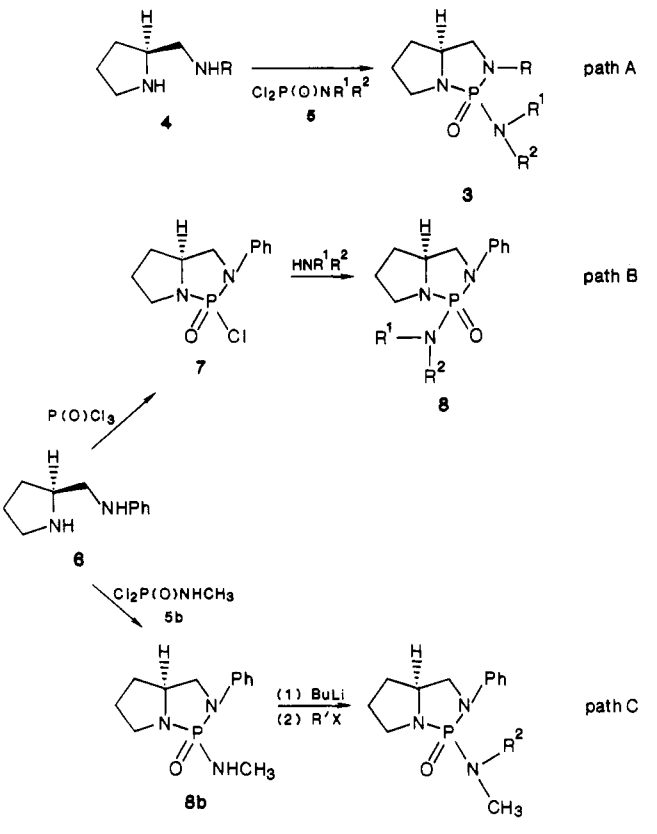


2a: $R^1 = R^2$ = (1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl

b: R^1 = (*R*)-1-phenylethyl; R^2 = Me

We anticipated that structurally rigid chiral cyclic phosphoramides would be promising for ligand-induced asymmetric synthesis. No cyclic chiral phosphoramide has been reported so far. In this paper are presented details of the preparation, separation, and structural assignments of the 3*R* and 3*S* isomers of some (7a*S*)-1,2,5,6,7,7a-hexahydropyrrolo[1,2-*c*]diazaphosphole 3-oxides **3**. We aimed at devising a versatile synthetic scheme to prepare phosphoramides **3** with variations for R^1, R^2, and R^3 and configurations at P-3 and C-7a.

Scheme I



a: $R^1 = R^2 = CH_3$
b: R^1 = H; $R^2 = CH_3$
c: R^1, R^2 =
d: R^1, R^2 =
e: R^1 = H; $R^2 = (CH_2)_2N(CH_3)_2$
f: $R^1 = CH_3$; $R^2 = CH_2C{\equiv}CH$
g: $R^1 = CH_3$; $R^2 = CH_2CO_2Et$
h: $R^1 = CH_3$; $R^2 = C(S)NHCH_3$
i: R^1, R^2 =
j: R = CH_3; R^1 = H; $R^2 = COC_2H_5$
k: R = H; $R^1 = R^2 = C_6H_5$

Synthetic Procedures for the Preparation of 3 and 8. The syntheses were carried out in a one-step procedure (Scheme I, path A) by treatment of chiral diamines **4** with

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Scheme II

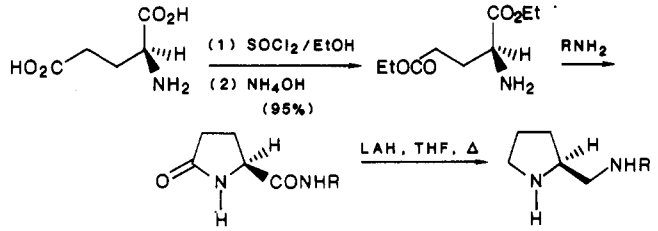

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Table I. Preparation and Physical Data for 3 and 8

compd	config at P[a]	synth route	yield, %[b]	mp, °C	$[\alpha]_D$,[c] deg
8a	*S*	A,B	25	100	−25.5
8a	*R*	A	33	150	+86
8b	*S*	A,B	35	120	−26
8b	*R*	A	24	191	+79.8
8c	*S*	A	27	98	−41
8c	*R*	A	18	152	+84
8d	*S*	A	13	108–110	−38.8
8d	*R*	A	13	164	+85
8e	*S*	B	61	150	−3[d]
8f	*S*	C	55	140	
8f	*R*	C	56	112	+72
8g	*S*	C	40	90	−13
8g	*R*	C	50	92	+80
8h	*S*	C	48	150	−3.8
8i	*S*	C	50		−52.2
3j	*S*	A	16	202	−89
3j	*R,S*	A	36	oil	
3k	*R*	A	9.4	210–211	+34[d]
3k	*R,S*	A	22	190–191	

[a] Attributed on the basis of ^1H and ^{31}P NMR chemical shifts (see text). [b] Isolated yield (not optimized). [c] Acetone, *c* 1. [d] $CHCl_3$, *c* 1.

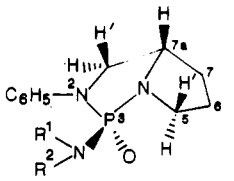
the appropriate phosphoramidic dichlorides **5**. Although derived from proline,[11] diamines **4** were more readily and economically obtained from glutamic acid (commercially available in both enantiomeric forms) as outlined in Scheme II. **6** (**4**, R = Ph) was prepared in a two-step procedure from (*S*)-(+)-glutamic acid according to Iriuchuima.[12]

Through a second procedure (Scheme I, path B), the diamine **6** reacted with phosphoryl chloride ($POCl_3$) to give the diastereomeric 3-chloro-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-oxide (**7**; in a 93:7 ratio after liquid chromatography). Samples of pure diastereomers could be isolated by column chromatography. To the major diastereomer was assigned the 3*S* configuration by ^1H NMR examination (vide infra). It gave with $NH_2(CH_2)_2NMe_2$ a single diastereomer **8e** (isolated as the oxalate salt) to which the 3*S* configuration was assigned (^1H and ^{31}P NMR): the substitution thus proceeded with inversion of configuration at the P atom.

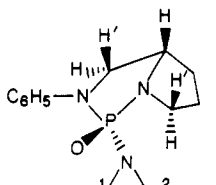
In the third procedure (Scheme I, path C), **8b**, prepared by reaction of **6** with the appropriate *N*-methylphosphoramidic dichloride (**5b**), was N-alkylated after deprotonation (BuLi) to give the phosphoramides **8f,g**. Use of *n*-BuLi as a base for deprotonation proved to be superior to NaH[13] which gave degradation products through the opening of the 1,3,2-diazaphosphole ring.

In most cases, the phosphoramides **3** (epimeric at the phosphorus atom) were obtained in a pure (98%) diastereomeric form either by repeated crystallization or separation through silica gel column chromatography (Table I).

Table II. ^1H NMR Data for Compound 8



(3*S*)-**8** (endo P=O)



(3*R*)-**8** (exo P=O)

compd	config at P	chemical shifts,[a] ppm H′-1	H-1	H′-5	H-5	H-7a
8a	*S*	3.27	3.76	2.81	3.47	3.76
8a	*R*	3.26	3.68	3.13	2.94	3.87
8b	*S*	3.23	3.85	2.80	3.49	3.65
8b	*R*	3.40	3.67	2.93	3.40	3.84
8c	*S*	3.25	3.79	3.01	3.55	3.79
8c	*R*	3.5	3.74	3.15	3.4	3.98
8d	*S*	3.28	3.78	2.83	3.47	3.78
8d	*R*	3.3	3.67	3.1	3.17	3.91
8e	*S*	3.28	3.82	2.78	3.50	3.82
8f	*S*	3.3	3.8	2.83	3.47	3.98
8f	*R*	3.33	3.72	2.95	3.21	3.91
8h	*S*	3.55	4	2.97	3.55	4
8h	*R*	3.54	3.94	2.90	3.15	4.08
8i	*S*	3.5	4.23	3	3.75	4.23

[a] In DMSO, relative to TMS.

Structural and Stereochemical Assignments. Structural and stereochemical assignments were made on rationalization of the ^1H and $^{31}P\{^1H\}$ NMR data, assuming that the bicyclo[3.3.0] ring system with bridgehead nitrogen should show a low-energy cis-fused configuration.[14] For all compounds **8** described in the table, the 3*S* configuration at phosphorus atoms corresponds to an endo P=O configuration. Conversely the compound **7** with endo P=O configuration has a *R* configuration at the P atom, as a consequence of the modification of the order of priority of the substituents.

(1) ^1H NMR Data. The absolute configuration at phosphorus in diastereomeric **7** and **8** was assigned through examination of the ^1H NMR data and comparison of the lanthanide-induced shifts.

In phosphorus-containing heterocycles, protons in a 1,3-cis relation to a P=O group are deshielded.[15] Comparison of the chemical shifts for the H-1 and H-5 protons within the pair of diastereomers **8** showed a through-space deshielding effect $\Delta\delta$ 0.2–0.5 of P=O at the H-5 and H-1 protons for (3*S*)-**8** relative to (3*R*)-**8** (Table II). H-7a protons were deshielded in (3*R*)-**8** ($\Delta\delta$ 0.1–0.2) relative to (3*S*)-**8**, probably owing to the same effect. Moreover, in the 3*R* series, H-7a was generally found as the most deshielded aliphatic proton.

The same trends were observed for compounds **7** (for which the diastereomer with endo P=O has a 3*R* configuration). Absolute configuration at the phosphorus atom for **7** could be confirmed by lanthanide shift experiments. The phosphoryl oxygen in 1,3,2-oxazaphospholidine 2-oxide structure is the most likely to coordinate preferentially with lanthanide shift reagents.[16] Small amounts of

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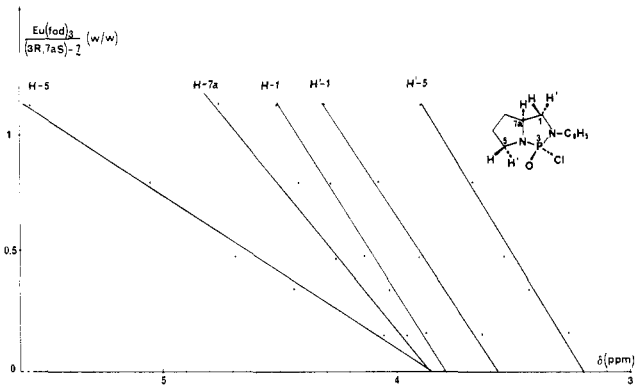


Figure 1. ^{1}H NMR data for LIS experiments on (3*R*,7a*S*)-**7** and (3*S*,7a*S*)-**7**.

Table III. ^{31}P NMR Spectral Data[a] for 8 and 3

compd	endo P=O (3*R* config at P)	exo P=O (3*S* config at P)
8a	18.9	25.3
8b	18.42[b]	24.98[b]
	17.7	24.6
8c	15.2	22.85
8d	16.2	22.5
8e[c]		23.6[d]
8f	17.5	24.1
8g	17.68[b]	23.57[b]
8h	17.0	24.6
3j		23.3[d]
3k	19.7	24.6

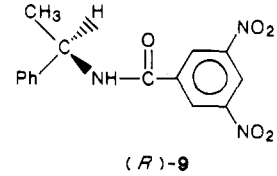
[a] In DMSO-d_6; ppm downfield from 85% H_3PO_4, the external reference. [b] $CDCl_3$ as solvent. [c] With 1.5(CO_2H)$_2$ (as the sesquioxalate). [d] Only one diastereomer was isolated. The 3*S* configuration was assigned on the basis of the ^{31}P value.

$Eu(fod)_3$ were added to $CDCl_3$ solutions of (3*R*)- and (3*S*)-**7**, and the ^{1}H NMR spectra were recorded after each addition. Graphs were plotted for each proton against the proportion (w/w) of shift reagent (Figure 1). Since it is expected that proton in a cis relation to the P=O group coordinating the shift reagent will exhibit a smaller slope than those in a trans relation, the H-5 with δ 3.85 was assigned to the 3*R* isomer (endo P=O), in agreement with the previous attribution (vide supra).

Such a trend was not observed in LIS experiments with the diastereomeric amides **8a**. The most rapidly shifted protons were those of the NMe_2 group in each isomer, indicating a preferential coordination of the europium complex with this group, relative to the P=O group.

(2) ^{31}P NMR Data. Diastereomeric and Enantiomeric Purities. Differences of about 6–7 ppm were recorded for the ^{31}P NMR shift of each diastereomer in **8a–h** (Table III). This constitutes a good criteria for evaluation of the diastereomeric purities of phosphoramides. Diastereomers of the exo P=O series showed higher ^{31}P δ values (23 ppm) than those of the P=O endo series (<19 ppm). So that an empirical correlation could be established between ^{31}P NMR shifts and the absolute configuration at the phosphorus atom.

To estimate the enantiomeric purity of phosphoramides about C-7, we found that the ^{31}P{^{1}H} NMR signals for each enantiomer in racemic **8a** and **8b** could be distinguished through addition of small amounts of (*R*)-(−)-**9**. This latter



(*R*)-**9**

compound has proved to be useful in determining the ee of sulfoxides and phosphine oxides by examination of their ^{1}H NMR spectra.[18] Diastereomeric mixtures of racemic **8a** and **8b** were prepared according to path A (Scheme I) from racemic **6** that was obtained from DL-glutamic acid. It was observed that addition of increasing amounts of **9** to $CDCl_3$ solutions of racemic **8a** and **8b** induced (i) a nonequivalence for the ^{31}P{^{1}H} NMR signals of each enantiomer (Figure 2) and (ii) greater shifts for the enantiomers of the 3*S* series compared to those recorded for enantiomers of the 3*R* series. Examination of the ^{31}P{^{1}H} NMR signals for optically active diastereomers (about C-7) in the presence of appropriate amounts of added **9** allowed the determination of their ee, 88% for (3*R*,7a*S*)-**8a** and 70% for (3*S*,7a*S*)-**8a**, whereas (3*S*,7a*S*)-**8b** and (3*R*,7a*S*)-**8b** were enantiomerically pure (ee >99%).

Structurally rigid, optically active phosphoramides have been synthetized in diastereomerically pure forms from commercially available, cheap (+)-(*S*)-glutamic acid. The configuration at the phosphorus atom, the diastereomeric purities of the compounds were determined through examination of the ^{1}H and ^{31}P{^{1}H} NMR data. For two compounds the enantiomeric purities were measured (^{31}P NMR) with the aid of (−)-(*R*)-**9** as chiral solvating agent.

These phosphoramides are currently being investigated as chiral ligands for metal complexes to be used as reagents or catalysts.

Experimental Section

Melting points were uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Bruker WP 200 SY spectrometer at 200 MHz. Chemical shifts are relative to Me_4Si. Where complex signals were obtained the spectral parameters are given as chemical shifts (multiplicity, *J* (in Hz), relative intensity). ^{31}P chemical shifts are relative to 85% H_3PO_4. Optical rotations were determined on a Perkin Elmer 141 polarimeter, using a 1 dm path length cell. Infrared spectra were recorded on a Perkin Elmer spectrometer Model 983G or 580 B.

Silica gel 60 (230–400 mesh) supplied by Merck was used for flash chromatography.[18] Elemental combustion analyses were performed by Rhone-Poulenc. THF was distilled under nitrogen on benzophenone–ketyl before use. The following chemicals were prepared by the methods reported in the literature: *N*,*N*-dimethylphosphoramidic dichloride (**5a**),[19] *N*-methylphosphoramidic dichloride (**5b**),[19] *N*-phenylphosphoramidic dichloride (**5k**),[19] *N*-(dichlorophosphinyl)morpholine (**5c**),[20] and *N*-benzoylphosphoramidic dichloride (**5j**).[21] (*R*)-(−)-**9**[18] showed mp 158–160 °C, $[\alpha]^{20}_D$ −49° (*c* 1, acetone).

***N*-(Dichlorophosphinyl)-*N'*-methylpiperazine (5d).** A mixture of 40 g (0.4 mol) of *N*-methylpiperazine and 40.4 g (0.4 mol) of triethylamine was added dropwise to a stirred solution of 36.6 mL (0.4 mol) of phosphorus oxychloride in 600 mL of ether at such rate that the temperature did not exceed 5 °C.

The reaction mixture was allowed to warm up to 20 °C within 2 h. Salts were filtered, and the solvent was evaporated under reduced pressure; the resulting oil was distilled in vacuo to yield 65 g of *N*-(dichlorophosphinyl)-*N'*-methylpiperazine contaminated with its hydrochloride as a colorless liquid: bp_1 104–114 °C; IR (neat) 1280, 560, 520 cm^{-1}.

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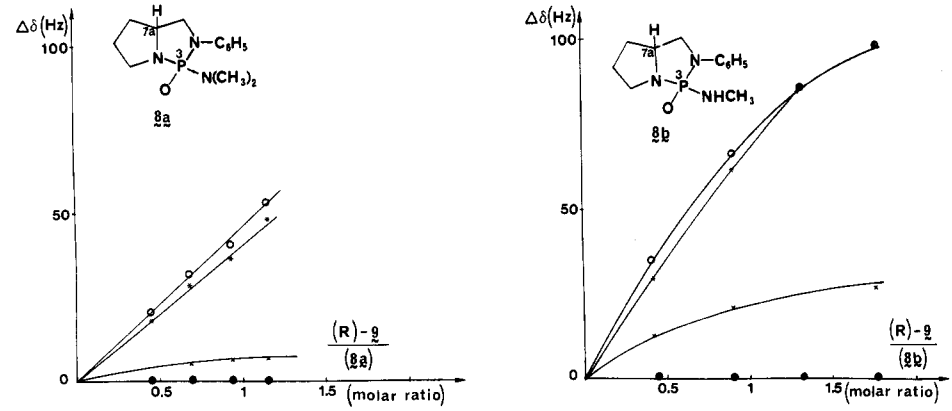

Figure 2. ^{31}P NMR shift induced by addition of (*R*)-**9** in $CDCl_3$ for racemic **8a** and **8b**: (○) 3*S*,7a*R*; (*) 3*S*,7a*S*; (×) 3*R*,7a*R*; (●) 3*R*,7a*S*.

Preparation of Chiral Diamines 4. (*S*)-2-(Anilinomethyl)pyrrolidine (6) (4, R = Ph) was prepared according to Iriuchuima's procedure from L-glutamic acid:[12] bp_1 122–126 °C, $[\alpha]_D$ +18.3° (*c* 1.02, ethanol) [lit. $bp_{0.4}$ 117–120 °C, $[\alpha]^{24}_D$ +18.6 (*c* 1, methanol)].[12]

(*S*)-2-[(Methylamino)methyl]pyrrolidine (4, R = CH_3) was prepared according to a modification of the method described by Schmidt and Scholm,[22] *N*-methyl-5-oxopyrrolidine-2-carboxamide being reduced with lithium aluminum hydride in refluxing THF instead of diborane: *N*-methyl-5-oxopyrrolidine-2-carboxamide (66.5 g, 0.468 mol) was added by portions to a refluxing mixture of 44 g of lithium aluminum hydride and 1410 mL of THF. After addition the mixture was refluxed for 21 h and then cooled in an ice–water bath; excess hydride was destroyed by cautious addition of 100 mL of ethyl acetate followed by 560 mL of 2.5 N sodium hydroxide solution. Anhydrous magnesium sulfate was added and after the mixture stirred for 15 min, the salts were filtered off and washed with THF. The filtrate was concentrated under reduced pressure and the yellow oily residue distilled in vacuo to give 37.7 g (61%) of 2-[(methylamino)-methyl]pyrrolidine (hydrate): $bp_{0.05}$ 35–36 °C; $[\alpha]^{20}_D$ +21.8° (*c* 1, dichloromethane); ^1H NMR ($CDCl_3$) δ 1.34 (1 H, m), 1.8 (3 H, m), 2.46 (3 H, s), 2.55 (2 H, dt, *J* = 5 and 10), 2.91 (2 H, dt, *J* = 1.5 and 7.5); water, 1 mol per mol. Anal. Calcd for $C_6H_{14}N_2 \cdot H_2O$: N, 21.18. Found: N, 21.49.

(*S*)-2-(Aminomethyl)pyrrolidine (4, R = H) was prepared by lithium aluminum hydride reduction of L-prolinamide in THF:[23] bp_{17} 78–80 °C, $[\alpha]_D$ 8.4° (*c* 2.03, water) (lit.[23] bp_{11} 65 °C). The dihydrochloride: mp 121 °C (EtOH), $[\alpha]^{20}_D$ −1.4° (*c* 0.58, water) [lit.[23] mp 124 °C, $[\alpha]^{24}_D$ −1.2° (*c* 0.299, water)].

3-(Dimethylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-Oxide (8a). To a solution of 30.3 g (0.3 mol) of triethylamine and 26.4 g (0.15 mol) of (*S*)-2-(anilinomethyl)pyrrolidine in 450 mL of dry THF previously cooled to 0 °C was added within 25 min a solution of 23.4 g (0.15 mol) of *N*,*N*-dimethylphosphoramidic dichloride in 150 mL of THF. The cooling bath was removed and the reaction mixture stirred for 90 min. The salt was filtered off and the THF evaporated in vacuo. The remaining crystalline solid was chromatographed on silica gel elution with EtOAc.

3*S*,7a*S* diastereomer of 8a: yield, 10 g (25.1%); white needles, mp 100 °C (cyclohexane); $[\alpha]^{20}_D$ −25.5° (*c* 1, acetone); TLC (silica, AcOEt) R_f 0.38; ^1H NMR (Me_2SO-d_6) δ 1.55 (m, 1 H, H′-7), 1.82 (m, 2 H, CH_2-6), 1.99 (m, 1 H, H′-5), 3.27 (m, 1 H, H′-1), 3.47 (m, 1 H, H-5), 3.76 (m, 2 H, H-1 and H-7a), 6.89 (t, *J* = 7.5, 1 H, Ar para), 7.0 (d, *J* = 7.5, 2 H, Ar ortho), 7.25 (t, 2 H, *J* = 7.5, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 25.3; IR 1605, 1505, 1480, 1300, 1070, 1000, 550 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_3O_2P$: C, 58.86; H, 7.60; N, 15.84; P, 11.67. Found: C, 58.79; H, 7.57; N, 15.88; P, 11.67.

3*R*,7a*S* diastereomer of 8a: yield, 13.2 g (33%); white needles, mp 150 °C (cyclohexane/EtOAc, 1/1); $[\alpha]^{20}_D$ +86° (*c* 1, acetone); TLC (silica, AcOEt) R_f 0.13; ^1H NMR (Me_2SO-d_6) δ 1.64 (m, 1 H, H-7), 1.96 (m, 2 H, H-6), 2.06 (m, 1 H, H-7), 2.53 (d, *J* = 10.5, 6 H, $N(CH_3)_2$), 2.94 (m, 1 H, H-1), 3.87 (m, 1 H, H-7a), 6.84 (m, 1 H, H′-1), 3.68 (m, 1 H, H-1), 3.87 (m, 1 H, H-7), 6.84 (t, *J* = 7.5, 1 H, Ar para), 7.02 (d, *J* = 7.5, 2 H, Ar ortho), 7.23 (t, 2 H, *J* = 7.5, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 18.9; IR 1600, 1500, 1480, 1300, 1000, 550 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_3O_2P$: C, 58.86; H, 7.60; N, 15.84; P, 11.67. Found: C, 58.79; H, 7.57; N, 15.88; P, 11.67.

1,2,5,6,7,7a-Hexahydro-3-(methylamino)-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (8b) was prepared by using the same procedure as above, starting from 52.8 g (0.3 mol) of (*S*)-2-(anilinomethyl)pyrrolidine, 60.6 g (0.6 mol) of triethylamine, and 44.4 g (0.3 mol) of *N*-methylphosphoramidic dichloride in 1200 mL of THF, followed by silica gel chromatography elution with EtOAc.

3*S*,7a*S* diastereomer of 8b: yield, 26.4 g (35%); white crystals, mp 121 °C (cyclohexane/EtOAc, 95/5); $[\alpha]^{20}_D$ −25.8° (*c* 1.02, acetone); ^1H NMR (Me_2SO-d_6) δ 1.55 (m, 1 H, H′-7), 1.81 (m, 2 H, CH_2-6), 1.98 (m, 1 H, H-7), 2.24 (dd, *J* = 14 and 6, 3 H, NCH_3), 2.8 (m, 1 H, H′-5), 3.23 (m, 1 H, H′-1), 3.49 (m, 1 H, H-5), 3.65 and 3.85 (2 m, 2 H, H-7a and H-1), 4.59 (dq, *J* = 12.5 and 6, 1 H, NH), 6.87 (t, 1 H, Ar para), 7.12 (d, 2 H, Ar ortho), 7.23 (t, 2 H, Ar ortho); ^{31}P NMR (Me_2SO-d_6) δ 24.6. Anal. Calcd for $C_{12}H_{18}N_3OP$: C, 57.36; H, 7.22; N, 16.72; P, 12.33. Found: C, 57.15; H, 7.09; N, 16.49; P, 11.95.

3*R*,7a*S* diastereomer of 8b: yield, 17.8 g (24%); white crystals, mp 191 °C (CH_3CN/*i*-Pr_2O, 1/1); $[\alpha]^{20}_D$ +79.4° (*c* 1.08, acetone); ^1H NMR (Me_2SO-d_6) δ 1.73 (m, 1 H, H′-7), 2.03 and 2.12 (m, 3 H, CH_2-6 and H-7), 2.85–3.15 (m, 5 H, $PN(CH_2)_2$ and H′-5), 3.20–3.50 (m, 5 H, $(CH_2)_2O$ and H′-1), 3.74 (m, 1 H, H-1), 3.98 (m, 1 H, H-7a), 6.95 (t, *J* = 7.5, 1 H, Ar para), 7.15 (d, *J* = 7.5, 2 H, Ar ortho), 7.33 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 15.2. Anal. Calcd for $C_{15}H_{22}N_3O_2P$: C, 58.62; H, 7.22; N, 13.67; P, 10.08. Found: C, 58.67; H, 7.35; N, 13.63; P, 10.16.

1,2,5,6,7,7a-Hexahydro-3-morpholino-2-phenylpyrrolo-[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (8c) was prepared by using the same procedure as above, starting from 26.4 g (0.15 mol) of (*S*)-2-(anilinomethyl)pyrrolidine, 30.6 g (0.3 mol) of triethylamine, and 30.6 g (0.15 mol) of *N*-(dichlorophosphinyl)morpholine in 600 mL of THF, followed by silica gel chromatography elution with EtOAc/cyclohexane (9/1), to give the following.

3*S*,7a*S* diastereomer of 8c: yield, 12.6 g; white crystals, mp 98 °C (cyclohexane); $[\alpha]^{20}_D$ −40.0° (*c* 1.15, acetone); ^1H NMR (Me_2SO-d_6) δ 1.55 (m, 1 H, H′-7), 1.85 (m, 2 H, CH_2-6), 1.99 (m, 1 H, H-7), 2.82–3.01 (m, 5 H, $PN(CH_2)_2$ and H′-5), 3.25–3.55 (m, 6 H, $(CH_2)_2O$, H′-1 and H-5), 3.79 (m, 2 H, H-1 and H-7a), 6.92 (t, *J* = 7.5, 1 H, Ar para), 7.09 (d, *J* = 7.5, 2 H, Ar ortho), 7.29 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 22.85; IR 1600, 1500, 1480, 1300, 970, 550 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_3O_2P$: C, 58.62; H, 7.22; N, 13.67; P, 10.08. Found: C, 58.85; H, 7.39; N, 13.59; P, 10.11.

3*R*,7a*S* diastereomer of 8c: yield, 8.4 g; white crystals, mp 152 °C (cyclohexane/EtOAc); $[\alpha]^{20}_D$ +83.3° (*c* 1.05, acetone); ^1H NMR (Me_2SO-d_6) δ 1.73 (m, 1 H, H′-7), 2.03 and 2.12 (m, 3 H, CH_2-6 and H-7), 2.85–3.15 (m, 5 H, $PN(CH_2)_2$ and H′-5), 3.20–3.50 (m, 5 H, $(CH_2)_2O$ and H′-1), 3.74 (m, 1 H, H-1), 3.98 (m, 1 H, H-7a), 6.95 (t, *J* = 7.5, 1 H, Ar para), 7.15 (d, *J* = 7.5, 2 H, Ar ortho), 7.33 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 15.2; IR

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1600, 1500, 1480 (m), 1300, 970, 550 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_3O_2P$: C, 58.62; H, 7.22; N, 13.67; P, 10.08. Found: C, 58.67; H, 7.35; N, 13.63; P, 10.16.

1,2,5,6,7,7a-Hexahydro-2-(4-methylpiperazinyl)-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 2-Oxide (8d). To a solution of 40 g (0.227 mol) of (*S*)-2-(anilinomethyl)pyrrolidine and 25.2 g (0.25 mol) of triethylamine in 700 mL of THF, previously cooled to 0 °C, was added within 1 h a solution of 49.3 g (0.227 mol) of 1-(dichlorophosphinyl)-4-methylpiperazine in 225 mL of THF. The cooling bath was removed, and the reaction mixture was stirred during 2 h. The salts were filtered off, and the solvent was evaporated in vacuo. The residue was dissolved in 500 mL of dichloromethane, and the solution was washed with 3 × 250 mL of water, dried, and concentrated to give 19.6 g of an oily mixture of the two isomers. The aqueous phases were made alkaline (pH 9, NaOH) and extracted with 200 mL of EtOAc to give 36.7 g of isomers mixture. The separation of isomers was performed by repetitive fractional crystallizations from EtOAc/cyclohexane (1/1) (3*R* isomer) and cyclohexane (3*S* isomer).

3*S*,7a*S* diastereomer of 8d: yield, 9.2 g (13%); white crystals, mp 108–110 °C (cyclohexane); $[\alpha]^{20}_D$ −38.8° (*c* 1.12, acetone); ^1H NMR (Me_2SO-d_6) δ 1.55 (m, 1 H, H′-7), 1.83 (m, 2 H, CH_2-6), 2.0 (m, 1 H, H-7), 2.05 (s, 3 H, NCH_3), 2.05–2.25 (m, 4 H, $(CH_2)_2NMe$), 2.83 (m, 1 H, H′-5), 2.97 (m, 4 H, $PN(CH_2)_2$), 3.28 (m, 1 H, H′-1), 3.47 (m, 1 H, H-5), 3.78 (m, 2 H, H-1 and H-7a), 6.89 (t, *J* = 7.5, 1 H, Ar para), 7.04 (d, *J* = 7.5, 2 H, Ar ortho), 7.24 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 22.5. Anal. Calcd for $C_{16}H_{25}N_4OP$: C, 59.98; H, 7.87; N, 17.49; P, 9.67. Found: C, 60.3; H, 7.89; N, 17.20; P, 9.50.

3*R*,7a*S* diastereomer of 8d: yield, 10 g (13.4%); white crystals, mp 164 °C (EtOAc/cyclohexane); $[\alpha]^{20}_D$ +85° (*c* 1, acetone); ^1H NMR (Me_2SO-d_6) δ 1.67 (m, 1 H, H′-7), 1.9–2.2 (m, 7 H, $(CH_2)_2NMe$, CH_2-6 and H-7), 2.0 (s, 3 H, NCH_3), 2.8–3.1 (m, 5 H, $PN(CH_2)_2$ and H′-5), 3.17 (m, 1 H, H-5), 3.3 (m, 1 H, H′-1), 3.67 (m, 1 H, H-1), 3.91 (m, 1 H, H-7a), 6.84 (t, *J* = 7.5, 1 H, Ar para), 7.05 (d, *J* = 7.5, 2 H, Ar ortho), 7.24 (t, *J* = 7.5, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 16.2. Anal. Calcd for $C_{16}H_{25}N_4OP$: C, 59.98; H, 7.87; N, 17.49; P, 9.67. Found: C, 59.85; H, 7.91; N, 17.53; P, 9.80.

3-[(2-(Dimethylamino)ethyl)amino]-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (8e). A solution of 20.3 g (79 mmol) of 3-chloro-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-oxide (3*S*,7a*S* isomer) and 13.95 g (158 mmol) of *N*,*N*-dimethylethylenediamine in 300 mL of THF was heated to reflux temperature during 150 min. The reaction mixture was filtered and concentrated in vacuo, and the oily residue was purified by chromatography on silica gel (eluent EtOAc/MeOH) to give 19.9 g (yield 82.9%) of the expected compound as a yellow oil. A solution of 14 g of this base in 100 mL of THF was added to a solution of 4.1 g of oxalic acid in 20 mL of ethanol. The resulting crystals were filtered, washed, and dried in vacuo to give the sesquioxalate of the title compound (3*S*,7a*S* isomer): yield, 11 g (61.1%); white crystals, mp 150 °C; $[\alpha]^{20}_D$ −3° (*c* 1, water); ^1H NMR (Me_2SO-d_6) δ 1.56 (m, 1 H, H′-7), 1.84 (m, 2 H, CH_2-6), 2.0 (m, 1 H, H-7), 2.67 (s, 6 H, $N(CH_3)_2$), 2.78–3.05 (m, 5 H, H′-5 and NCH_2CH_2), 3.28 (m, 1 H, H′-1), 3.50 (m, 1 H, H-5), 3.82 (m, 2 H, H-7a and H-1), 5.05 (m, 1 H, NH), 6.92 (t, *J* = 7.5, 1 H, Ar meta), 7.7–9.2 (br, COOH); ^{31}P NMR (Me_2SO-d_6) δ 23.6. Anal. Calcd for $C_{15}H_{25}N_4OP{\cdot}1.5C_2H_2O_4$: C, 48.76; H, 6.37; N, 12.64; P, 6.99. Found: C, 48.66; H, 6.52; N, 12.67; P, 6.89.

3-(*N*-Methyl-*N*-propargylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-Oxide (8f). A solution of 8.3 g (33 mmol) of (3*R*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-oxide in 350 mL of dry THF was treated dropwise at −70 °C with 22 mL (35 mmol) of a 1.6 M solution of butyllithium in hexane and then with a solution of 3.93 g (33 mmol) of propargyl bromide in dry THF. The reaction mixture was allowed to warm to room temperature, stirred during 5 h, and then diluted with 500 mL of water and 500 mL of EtOAc. The organic phase was washed with a saturated NaCl solution, dried, and concentrated in vacuo. The oily residue was chromatographed (silica gel, EtOAc), and the purified product was crystallized from cyclohexane/EtOAc (9/1): yield, 5.6 g (56.4%); white crystals, mp 112 °C; $[\alpha]^{20}_D$ +71.8° (*c* 1.09, acetone); ^1H NMR (Me_2SO-d_6) δ 1.66 (m, 1 H, H′-7), 1.8–2.2 (m, 3 H, CH_2-6 and H-7), 2.43 (d, *J* = 14, 3 H, NCH_3), 2.95 (m, 1 H, H′-5), 3.1 (t, *J* = 2, acetylenic CH), 3.21 (m, 1 H, H-5), 3.33 (m, 1 H, H′-1), 3.72 (m, 1 H, H-1), 3.78–3.88 (m, 2 H, propargylic CH_2), 3.91 (m, 1 H, H-7a), 6.85 (t, *J* = 7.5, 1 H, Ar para), 7.04 (d, *J* = 7.5, 2 H, Ar ortho), 7.21 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 17.5. Anal. Calcd for $C_{15}H_{20}N_3OP$: C, 62.27; H, 6.97; N, 14.53; P, 10.71. Found: C, 62.69; H, 6.95; N, 14.47; P, 10.71.

3*S*,7a*S* Diastereomer of 8f. To a suspension 0.48 g of sodium hydride (50% dispersion in mineral oil) in 5 mL of dry THF was added a solution of 2.51 g (10 mmol) of (3*R*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-oxide in 25 mL of dry THF. The reaction mixture was heated to reflux temperature for 1 h and then cooled to −20 °C, treated with a solution of 1.63 g of propargyl bromide in 10 mL of THF, and stirred 1 h between 0 and 10 °C. After dilution with 100 mL of EtOAc and 55 mL of water, the organic layer was washed with water, dried, and concentrated in vacuo. The crystalline residue was purified by column chromatography (silica gel, EtOAc): yield, 1.6 g (55.2%); white crystals, mp 140 °C; ^1H NMR (Me_2SO-d_6) δ 1.57 (m, 1 H, H′-7), 1.85 (m, 2 H, CH_2-6), 2.02 (m, 1 H, H-7), 2.52 (d, *J* = 12, 3 H, CH_3), 2.83 (m, 1 H, H′-5), 3.08 (t, *J* = 2, acetylenic CH), 3.30 (m, 1 H, H′-1), 3.47 (m, 1 H, H-5), 3.60–3.98 (m, 4 H, H-1, H-7a, and propargylic CH_2), 6.90 (t, *J* = 7.5, 1 H, Ar para), 7.03 (d, *J* = 7.5, 2 H, Ar ortho), 7.24 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR (Me_2SO-d_6) δ 24.1.

3-[*N*-Methyl-*N*-((ethoxycarbonyl)methyl)amino]-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-Oxide (8g). 3*R*,7a*S* Diastereomer of 8a. A solution of 18.75 g (75 mmol) of (3*R*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-oxide in 375 mL of dry THF was treated dropwise at 70 °C with 46.9 mL (75 mmol) of a 1.6 M solution of butyllithium in hexane and then with a solution of 12.52 g (75 mmol) of ethyl bromoacetate in 150 mL of dry THF. The reaction mixture was allowed to warm, stirred at room temperature during 1.5 h, and then diluted with 250 mL of water and 250 mL of EtOAc. The organic phase was washed with water (3 × 150 mL), dried, and concentrated in vacuo. The oily residue was chromatographed (silica gel; cyclohexane/EtOAc, 7/3), and the purified product was crystallized from diisopropyl ether: yield, 9.85 g (38.9%); white crystals, mp 90 °C; $[\alpha]^{20}_D$ +80.2° (*c* 1.05, acetone); ^1H NMR (Me_2SO-d_6) δ 1.18 (t, *J* = 7.5, 3 H, CH_3 ester), 1.66 (m, 1 H, H′-7), 1.98–2.08 (m, 3 H, CH_2-6 and H-7), 2.39 (d, *J* = 10, 3 H, NCH_3), 2.93 (m, 1 H, H′-5), 3.32 (m, 1 H, H′-1), 3.55 (m, 1 H, H-5), 3.55 (dd, *J* = 11 and 18, 1 H) and 4.14 (dd, *J* = 18 and 7.5, 1 H) (NCH_2CO), 3.72 (m, 1 H, H-1), 3.89 (m, 1 H, H-7a), 4.06 (q, *J* = 7.5, 2 H, CH_2 ester), 6.86 (t, *J* = 7.5, 1 H, Ar para), 7.02 (d, *J* = 8.5, 2 H, Ar ortho), 7.22 (t, *J* = 8.5, 2 H, Ar meta); ^{31}P NMR ($CDCl_3$) δ 17.68. Anal. Calcd for $C_{16}H_{23}N_3O_3P$: C, 56.96; H, 7.17; N, 12.46; P, 9.18. Found: C, 57.31; H, 7.36; N, 12.52; P, 9.10.

3*S*,7a*S* Diastereomer 8g. This compound was obtained by the same procedure from (3*S*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole: yield, 16.8 g (49.8%); white crystals, mp 92 °C; $[\alpha]^{20}_D$ −13.1° (*c* 1, acetone); ^1H NMR (Me_2SO-d_6) δ 1.18 (t, *J* = 7.5, 3 H, CH_3 ester), 1.53 (m, 1 H, H′-7), 1.83 (m, 2 H, CH_2-6), 1.99 (m, 1 H, H-7), 2.51 (d, *J* = 10, 3 H, NCH_3), 2.85 (m, 1 H, H′-5), 3.30 (m, 1 H, H′-1), 3.45 (m, 1 H, H-5), 3.59 (t, *J* = 18, 1 H) and 3.99 (dd, *J* = 18 and 7.5, 1 H) (NCH_2CO), 3.79 (m, 2 H, H-1 and H-7a), 4.07 (q, *J* = 7.5, 2 H, CH_2 ester), 6.90 (t, *J* = 7.5, 1 H, Ar para), 7.5 (d, *J* = 7.5, 2 H, Ar ortho), 7.27 (t, *J* = 7.5, 2 H, Ar meta); ^{31}P NMR ($CDCl_3$) δ 23.57. IR 1600, 1500, 1480, 1300, 1230, 1195, 1070, 1040, 550 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3O_3P$: C, 56.96; H, 7.17; N, 12.46; P, 9.18. Found: C, 56.75; H, 7.03; N, 12.33; P, 9.08.

3-(1,3-Dimethylthioureido)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-Oxide (8h). 3*R*,7a*S* Diastereomer of 8h. A suspension of 15.6 g (60 mmol) of (3*R*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-oxide in 600 mL of dry THF was treated dropwise at −70 °C with 37.2 mL (60 mmol) of a 1.6 M solution of butyllithium in hexane and then with a solution of 4.38 g (60 mmol) of methyl isothiocyanate in 150 mL of THF. The reaction mixture was allowed to warm up, stirred at room temperature during 16 h, and then diluted with 500 mL of water

and 500 mL of EtOAc. The organic phase was washed with water (2 × 300 mL) and with a saturated NaCl solution (250 mL), dried, and concentrated in vacuo. The residue was chromatographed (silica gel; cyclohexane/EtOAc, 8/2), and the purified product was crystallized from cyclohexane/EtOAc (4/6): yield, 8.51 g (43.8%); white crystals, mp 165 °C; $[\alpha]^{20}_D$ −4.5° (*c* 1.2, acetone); ^{1}H NMR (Me_2SO-d_6) δ 1.6–1.8 (m, 1 H, H′-7), 1.9–2.25 (m, 3 H, CH_2-6 and H-7), 2.92 (d, *J* = 7.5, 3 H, $PNCH_3$), 2.90–3.15 (m, 2 H, CH_2-5), 3.03 (d, *J* = 5, 3 H, $CSNCH_3$), 3.54 (t, 1 H, H′-1), 3.94 and 4.08 (m, 2 H, H-1 and H-7a), 6.97 (t, *J* = 7.5, 1 H, Ar para), 7.08 (d, *J* = 7.5, 2 H, Ar ortho), 7.30 (t, *J* = 7.5, 2 H, Ar meta), 10.43 (q, *J* = 5, 1 H, NH); ^{31}P NMR (Me_2SO-d_6) δ 17.0. Anal. Calcd for $C_{14}H_{21}N_4OPS$: C, 51.84; H, 6.53; N, 17.27; P, 9.55. Found: C, 51.54; H, 6.44; N, 17.28; P, 9.25.

3*S*,7a*S* Diastereomer of 8h. This compound was obtained by the same procedure from (3*S*,7a*S*)-3-(methylamino)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,2,3]diazaphosphole 3-oxide: yield, 12.55 g (48.3%); white crystals, mp 150 °C; $[\alpha]^{20}_D$ −3.8° (*c* 0.89, acetone); ^{1}H NMR (Me_2SO-d_6) δ 1.63 (m, 1 H, H′-7), 1.94 (m, 2 H, CH_2-6), 2.11 (m, 1 H, H-7), 2.97 (m, 1 H, H′-5), 3.02 (d, *J* = 8, 3 H, $PNCH_3$), 3.04 (d, *J* = 4, 3 H, $CSNCH_3$), 3.55 (m, 2 H, H′-1 and H-5), 4.0 (m, 2 H, H-1 and H-7a), 6.98 (t, *J* = 7.5, 1 H, Ar para), 7.01 (d, *J* = 7.5, 2 H, Ar ortho), 7.32 (t, *J* = 7.5, 2 H, Ar meta), 10.32 (q, *J* = 4, 1 H, NH); ^{31}P NMR (Me_2SO-d_6) δ 24.6. Anal. Calcd for $C_{14}H_{21}N_4OPS$: C, 51.84; H, 6.53; N, 17.27; P, 9.55. Found: C, 51.53; H, 6.41; N, 17.50; P, 9.31.

3-(4-Imino-1,4-dihydropyridyl)-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (8i). A solution of 4.7 g (50 mmol) of 4-aminopyridine in 250 mL of THF was added dropwise in 45 min to a solution of 12.8 g (50 mmol) of 3-chloro-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]-diazaphosphole 3-oxide (3*S*,7a*S* isomer). The reaction mixture was stirred overnight at room temperature; the crystals were filtered to give 15.8 g of the expected crude hydrochloride. Repetitive recrystallization from THF/EtOH (7/1) gave the pure compound as a THF solvate (9.6 g; white crystals, mp 225 °C); the hygroscopic desolvated salt was freeze-dried to give 8 g of the title compound as the hydrochloride (3*S*,7a*S* isomer; freeze-dried product): yield, 8 g (50%); $[\alpha]^{20}_D$ −52.2° (*c* 1, acetone); ^{1}H NMR (Me_2SO-d_6) δ 1.73 (m, 1 H, H′-7), 2.0 (m, 2 H, CH_2-6), 2.19 (m, 1 H, H-7), 3.0 (m, 1 H, H′-5), 3.5–3.75 (m, 2 H, H′-1 and H-5), 4.23 (m, 2 H, H-7a and H-1), 6.93 (d, *J* = 6, 2 H, H-3′ and H-5′ pyridine), 7.03 (t, *J* = 7.5, Ar para), 7.05 (d, *J* = 7.5, 2 H, Ar ortho), 7.29 (t, *J* = 7.5, 2 H, Ar meta), 8.43 (t, *J* = 6, 2 H, H-2′ and H-6′ pyridine), 9.15 (br s, 2 H, NH_2^+). Anal. Calcd for $C_{16}H_{19}N_4OP$·HCl: C, 54.78; H, 5.75; N, 15.97; P, 8.83. Found: C, 54.98; H, 5.87; N, 15.62; P, 8.72.

2-(Benzoylamino)-1,2,5,6,7,7a-hexahydro-3-methylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 2-Oxide (3j). To a solution of 25 g (0.22 mol) of (*S*)-[(methylamino)methyl]pyrrolidine in 250 mL of dichloromethane, previously cooled to −70 °C, was added within 1 h a solution of 52.2 g (0.22 mol) of *N*-(dichlorophosphinyl)benzamide in 500 mL of dichloromethane. Triethylamine (44.4 g, 0.44 mol) was then added dropwise, the cooling bath was removed, and the reaction mixture was stirred during 3 h, then washed, dried ($MgSO_4$), and concentrated in vacuo; the resulting oil was purified by silica gel chromatography (EtOAc) and crystalline from ethyl acetate.

3*S*,7a*S* diastereomer of 3j: yield, 9.7 g (15.7%); white crystals, mp 202 °C; $[\alpha]^{20}_D$ −88.8° (*c* 1.0, acetone); ^{1}H NMR (Me_2SO-d_6) δ 1.47 (m, 1 H, H′-7), 1.80 (m, 2 H, CH_2-6), 1.98 (m, 1 H, H-7), 2.44 (d, *J* = 10, 3 H, NCH_3), 2.81 (m, 1 H, H′-5), 3.05 (m, 1 H, H′-1), 3.45 (m, 2 H, H-5 and H-1), 3.82 (m, 1 H, H-7a), 7.44 (t, *J* = 7.5, 2 H, Ar meta), 7.55 (t, *J* = 7.5, 1 H, Ar para), 7.97 (d, *J* = 7.5, 2 H, Ar ortho), 9.38 (br s, 1 H, CONH); ^{31}P NMR (Me_2SO-d_6) δ 23.3. Anal. Calcd for $C_{13}H_{18}N_3O_2P$: C, 55.91; H, 6.50; N, 15.05; P, 11.9. Found: C, 56.3; H, 6.57; N, 15.18; P, 10.53.

3-Anilino-1,2,5,6,7,7a-hexahydropyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (3k). To a solution of 27 g (0.27 mol) of (*S*)-2-(aminomethyl)pyrrolidine in 1350 mL of dichloromethane, previously cooled to −65 °C, was added within 10 min a solution of 57 g (0.27 mol) of *N*-phenylphosphoramidic chloride in 350 mL of dichloromethane followed by 60.1 g (0.59 mol) of triethylamine. The cooling bath was removed, and the reaction mixture was stirred during 15 h. The solid was filtered, washed with 2 × 30 mL of dichloromethane and 4 × 50 mL of water, and dried: yield, 15.7 g (24.5%); white crystals, mp 191–192 °C; 1/1 mixture of diastereomers (TLC, NMR). The organic phase of the filtrate was washed with 4 × 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The resulting solid was triturated with water and dried: yield, 40.6 g (63%) of the crude mixture of isomers; white crystalline solid, mp 184–186 °C.

3*R*,7a*S* Diastereomer of 3k. This isomer could be obtained by repetitive crystallizations of 35 g of the crude mixture from EtOAc/DMF (1/5): yield, 6 g (9.4%); white crystals, mp 210–211 °C; $[\alpha]^{20}_D$ +34.3° (*c* 0.96, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6) δ 1.46 (m, 1 H, H′-7), 1.6–1.9 (m, 3 H, H-7 and CH_2-6), 2.76 (m, 1 H, H′-5), 2.9–3.1 (m, 2 H, H′-1 and H-5), 3.4 (m, 1 H, H-1), 3.82 (m, 1 H, H-7a), 4.7 (d, *J* = 10, 1 H, PNH), 6.75–7.3 (m, 6 H, Ar and NHAr); ^{31}P NMR (Me_2SO-d_6) δ 19.2. Anal. Calcd for $C_{11}H_{16}N_3OP$: C, 55.60; H, 6.80; N, 17.71; P, 13.06. Found: C, 55.90; H, 6.60; N, 17.40; P, 13.13.

3-Chloro-1,2,5,6,7,7a-hexahydro-2-phenylpyrrolo[1,2-*c*][1,3,2]diazaphosphole 3-Oxide (7). To a solution of 40 g (0.227 mol) of (*S*)-2-(anilinomethyl)pyrrolidine and 45.85 g (0.454 mol) of triethylamine in 1600 mL of THF, previously cooled to 0 °C, was added within 25 min a solution of 34.84 g (0.227 mol) of phosphorus oxychloride in 681 mL of THF. The cooling bath was removed, and the reaction mixture was stirred during 1.5 h. The salts were filtered off, and solvent was evaporated in vacuo. The crystallization of the residue from 450 mL of a 2/1 mixture of EtOAc and cyclohexane gave 34.5 g (59.2%) of the 3*S*,7a*S* isomer as pale yellow crystals: mp 135 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.6 (m, 1 H, H′-7), 2.03 (m, 3 H, H-7 and $CHCH_2$-6), 3.1 (m, 1 H, H′-5), 3.35 and 3.40 (m, 2 H, H′-1 and H-5), 4.0 and 4.14 (m, 2 H, H-1 and H-7a), 7.08 (t, *J* = 7.5, 1 H, Ar para), 7.29 and 7.36 (d and t, *J* = 7.5, 4 H, Ar ortho and meta); ^{13}C NMR ($CDCl_3$) δ 32.7 (C-7, J_{C-P} = 5 Hz), 36.7 (C-6, J_{C-P} = 3 Hz), 51.2 (C-5, J_{C-P} = 3 Hz), 56.6 (C-1, J_{C-P} = 18 Hz), 64.5 (C-7a, J_{C-P} = 9.5 Hz).

Crystallization of mother liquors gave 10 g (17%) of a 3/1 mixture of the 3*S*,7a*S* and 3*R*,7a*S* isomers. Column chromatography of this mixture on silica gel eluting with a 3/2 mixture of cyclohexane and EtOAc gave 7.6 g of the 3*S*,7a*S* isomer. Only a small amount (0.2 g) of the less polar 3*S*,7a*S* isomer could be obtained: white crystals, mp 130 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.62 (m, 1 H, H′-7), 1.94 (m, 2 H, CH_2-6), 2.11 (m, 1 H, H-7), 3.1 (m, 1 H, H′-5), 3.55–4.0 (m, 4 H, CH_2-1, H-7a and H-5), 7.08 (t, *J* = 7.5, 1 H, Ar para), 7.25 (d, *J* = 7.5, 2 H, Ar ortho), 3.37 (t, *J* = 7.5, 2 H, Ar meta); ^{13}C NMR ($CDCl_3$) δ 33.5 (C-7), 40 (C-6), 5.5 (C-5), 55 (C-1, J_{C-P} = 9 Hz), 64.5 (C-7a, J_{C-P} = 9.5 Hz).

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Registry No. (3*S*,7a*S*)-**3j**, 110638-59-0; (3*R*,7a*S*)-**3j**, 110715-42-9; (3*R*,7a*S*)-**3k**, 110638-60-3; (3*S*,7a*S*)-**3k**, 110715-43-0; **4** (R = CH_3), 110638-61-4; **4** (R = H), 69500-64-7; **5a**, 677-43-0; **5b**, 36598-86-4; **5c**, 1498-57-3; **5d**, 104125-22-6; **5d**·HCl, 110638-62-5; **5j**, 4737-14-8; **5k**, 6955-57-3; **6**, 64030-44-0; (3*S*,7a*S*)-**7**, 110638-63-6; (3*R*,7a*S*)-**7**, 110715-46-3; (3*S*,7a*S*)-**8a**, 110638-50-1; (3*S*,7a*S*)-**8a** (sesquioxalate), 110715-44-1; (3*R*,7a*S*)-**8a**, 110715-36-1; (3*S*,7a*S*)-**8b**, 110638-51-2; (3*R*,7a*S*)-**8b**, 110715-37-2; (3*S*,7a*S*)-**8c**, 110638-52-3; (3*R*,7a*S*)-**8c**, 110715-38-3; (3*S*,7a*S*)-**8d**, 110638-53-4; (3*R*,7a*S*)-**8d**, 110715-39-4; (3*S*,7a*S*)-**8e**, 110638-54-5; (3*S*,7a*S*)-**8f**, 110638-55-6; (3*R*,7a*S*)-**8f**, 110715-40-7; (3*S*,7a*S*)-**8g**, 110638-56-7; (3*R*,7a*S*)-**8g**, 110715-41-8; (3*S*,7a*S*)-**8h**, 110638-57-8; (3*R*,7a*S*)-**8h**, 110715-45-2; (3*S*,7a*S*)-**8i**, 110638-58-9; *N*-methylpiperazine, 109-01-3; *N*-methyl-5-oxopyrrolidine-2-carboxamide, 3770-16-9; L-prolinamide, 7531-52-4; *N*,*N*-dimethylethylenediamine, 108-00-9; propargyl bromide, 106-96-7; ethyl bromoacetate, 105-36-2; methyl isothiocyanate, 556-61-6; 4-aminopyridine, 504-24-5.