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Double Dearomatization of Bis(diphenylphosphinamides) through Anionic Cyclization. A Facile Route of Accessing Multifunctional Systems with Antitumor Properties

Gloria Ruiz-Gómez,[†] María José Iglesias,[†] Manuel Serrano-Ruiz,[‡] Santiago García-Granda,[§] Andrés Francesch,[||] Fernando López-Ortiz,*[,†] and Carmen Cuevas[||]

Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento, 04120 Almería, Spain, Área de Química Inorgánica, Universidad de Almería, Carretera de Sacramento, 04120 Almería, Spain, Departamento de Química Física y Analítica, Universidad de Oviedo, Avda. Julián Clavería 8, 33006 Oviedo, Spain, and PharmaMar S.A. Av. de los Reyes, 1, P.I. La Mina, 28770 Colmenar Viejo, Madrid, Spain

flortiz@ual.es

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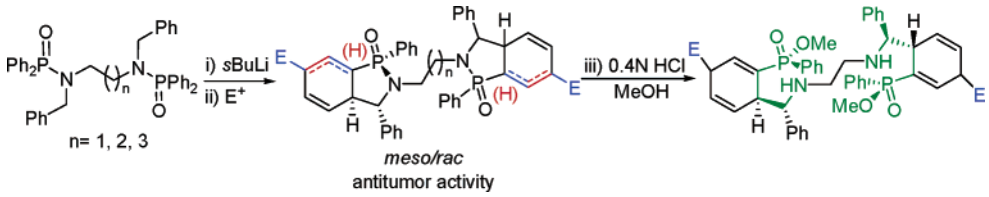

The sequential one-pot double dearomatization of bis(*N*-benzyl-*P*,*P*-diphenylphosphinamides) via anionic cyclization is described for the first time. Protonation and alkylation of the dearomatized dianions provide bis(tetrahydro-2,1-benzazaphospholes) in good yield and with very high regio- and stereocontrol. Acid-catalyzed methanolysis of the bisheterocycles affords bis(methyl γ-aminophosphinates) stereospecifically. The doubly phosphorylated systems proved to be active against a series of cancer cell lines.

Introduction

The tetrahedral phosphinic acid moiety plays a central role in the biological activity of a wide range of natural products and synthetic compounds.[1] The properties of this structural motif as a pharmacophore arise mainly from the capability of mimicking the transition state of enzymatic amide formation or hydrolysis[2] and of interacting with the metal present in the active site of some metalloenzymes.[1e,3] It has been shown that acyclic and cyclic phosphinamides bearing a hydroxamic acid functional group are potent antitumor agents acting as inhibitors of matrix metalloproteinases.[3a,d] Among the family of compounds containing the P(O)OH fragment, γ-aminophosphinic acids and their derivatives represent an important subclass of therapeutic agents.[4] They are phosphorus analogues of γ-aminobutyric acid, GABA, the major inhibitory neurotransmitter in the mammalian central nervous system. This structural

* Corresponding author. Telephone: +34 950 015478. Fax: +34 950 015481.
[†] Área de Química Orgánica, Universidad de Almería.
[‡] Área de Química Inorgánica, Universidad de Almería.
[§] Universidad de Oviedo.
[||] PharmaMar S.A.

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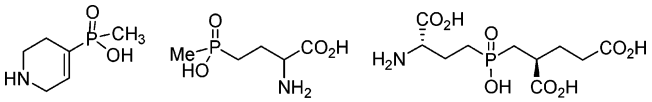
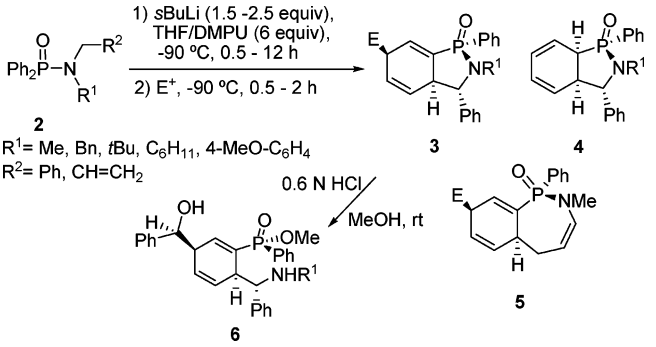
CHART 1



similarity led to the identification of TPMPA (Chart 1) as the most potent $GABA_C$ receptor antagonist known to date.[5] The γ-aminophosphinic acid substructure is also present in phosphinothricin, a phosphoglutamic acid analogue in which the CO_2H group distal to the amino moiety has been replaced by a $P(O)(OH)CH_3$ fragment. Phosphinothricin is a component of the natural tripeptide bialaphos and is being currently used as a nonselective herbicide.[6] Some phosphinothricin analogues have been found to be inhibitors of glutamine synthase[7] and showed herbicidal activity as well.[8] The pseudopeptide **1** is a key component of a potent inhibitor of human folylpoly-γ-glutamate synthetase, FPGS.[9]

We have shown that γ-aminophosphinic acid and esters are accessible via a methodology based on nucleophilic dearomatizing reactions (N_DAr) of tertiary diphenylphosphinamides.[10] N_DAr reactions followed by electrophilic trapping allow for exploitation of the latent functionalization represented by the conjugated π system of benzenoid rings to prepare more elaborate molecules.[11] In the case of dearomatizing anionic cyclization (DAC) processes, the loss of aromaticity is concomitant with the formation of a carbo- or heterocyclic ring. The first examples of DAC reactions were reported 40 years ago.[12] However, the utility of this strategy for constructing complex molecules has been demonstrated only recently. Clayden et al. showed that DAC reactions of lithiated tertiary benzamides provide the key intermediates for the synthesis of a series of natural products and non-natural derivatives.[13] Phenyl

SCHEME 1. Anionic Cyclization-Electrophilic Trapping of Diphenylphosphinamides



triazenes[14] and tosylaziridines[15] were also dearomatized via anionic cyclization after treatment with an organolithium base.

We have previously reported that the lithiation of diphenylphosphinamides **2** with an excess of ^{s}BuLi in THF at −90 °C in the presence of HMPA or DMPU leads to the formation of N−C_α anions[16] that undergo anionic cyclization by attack at the *ortho* position of a *P*-phenyl ring. Electrophilic trapping of the dearomatized species afforded tetrahydro-2,1-benzazaphospholes **3** and **4** and 2,1-benzazaphosphepine **5** with high regio- and stereocontrol (Scheme 1).[16b,17] These heterocycles may be converted into γ-aminophosphinic acids and esters (e.g., **6**) through acid solvolysis of the phosphinamide linkage.[10,17a,18]

In these transformations, the N−R^1 substituent generally acts as a passive spectator. Only the bulkiest group exerted some influence on the reaction course due to steric effects.[18] Preliminary antitumor assays on some of the dearomatized compounds synthesized showed promising growth cell inhibition parameters. We thought that the utility of this methodology could be further extended by connecting two *N*-benzyldiphenylphosphinamide moieties through a methylene chain and performing the double dearomatization on the resulting bisphosphinamides via the one-pot sequential anionic cyclization-electrophilic quench. The bis(azaphosphaheterocyclic) system thus formed may exhibit enhanced biological activity as compared to the monoheterocycles.[18a] The results of this study together with the evaluation of the cytotoxicity of some selected products are presented in this paper.

Results and Discussion

The required bisphosphinamides **8a**−**c** have been prepared in high yield by treating the corresponding *N*,*N*′-dibenzylamine **7** with chlorodiphenylphosphine (2.1 equiv) in toluene in the

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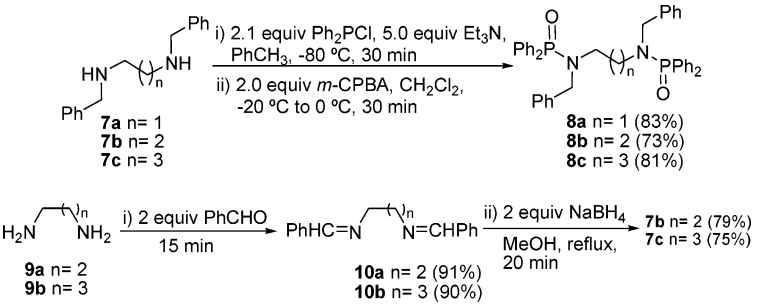
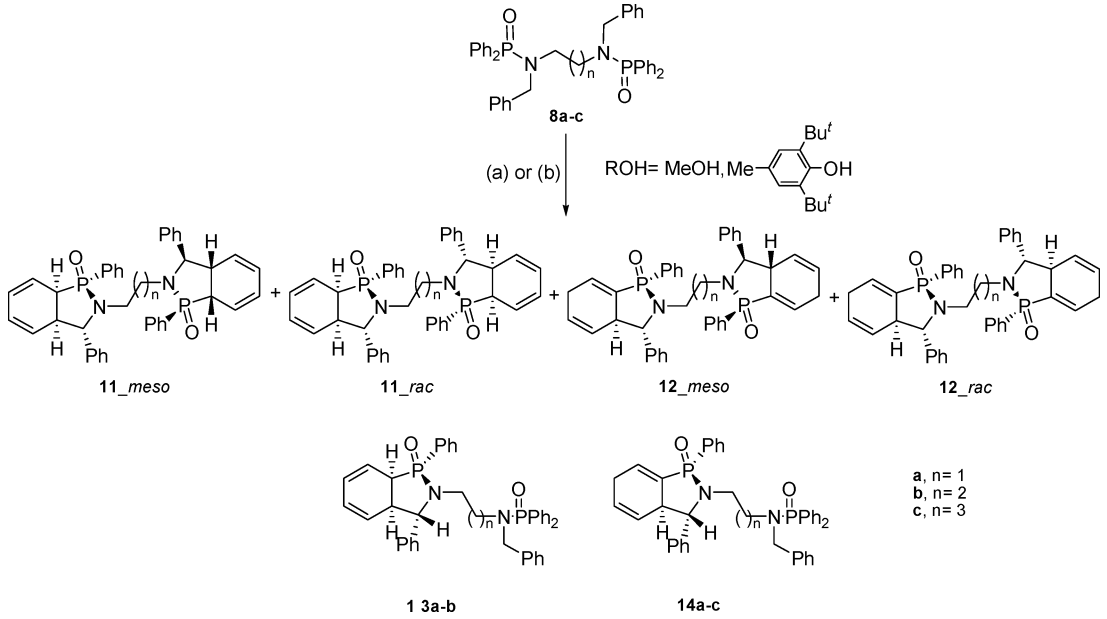
SCHEME 2. Synthesis of Bisphosphinamides 8



SCHEME 3. Synthesis of Bis(tetrahydro-2,1-benzazaphospholes) 11 and 12[a]



[a] Reaction conditions: (a) (i) ^{s}BuLi (5 equiv), THF, −90 °C, HMPA (10 equiv), t_1 (min); (ii) ROH (8 equiv), −90 °C, 30 min; (b) (i) ^{s}BuLi (5 equiv), THF, −90 °C, HMPA (10 equiv), t_1 (min); (ii) TBDMSCl (5 equiv), −90 °C, 30 min; (iii) MeOH, −90 °C, 30 min.

presence of triethylamine (5 equiv) at −80 °C for 30 min,[19] followed by in situ oxidation with *m*-CPBA (Scheme 2). *N*,*N*′-Dibenzylethylenediamine **7a** is commercially available. Diamines **7b**,**c** were synthesized according to the methods described in the literature as shown in Scheme 2.[20]

The double anionic cyclization of bisphosphinamides **8** might lead to a complex mixture of products: *meso* and chiral (racemic) compounds in which the dearomatized heterocyclic system may contain three or four stereogenic centers and the carbon−carbon double bonds can be distributed in a variety of positions. Using the DAC-protonation sequence of reactions of phosphinamides **2** as reference,[18] the dearomatization of **8a**−**c** was performed by lithiating the bisphosphinamides with 5 equiv of ^{s}BuLi at −90 °C in THF in the presence of an excess of HMPA. The dearomatized species were neutralized by adding methanol or 2,6-di(*tert*-butyl)-4-methylphenol (DTBMP) and stirring the reaction mixture for 30 min (Scheme 3). By analogy with the reactions of monophosphinamides,[18a] it was expected that the use of MeOH would favor the formation of heterocycles containing a [1,3]-cyclohexadiene system with a *cis* fusion (i.e., compounds **11**), whereas [1,4]-cyclohexadiene derivatives would be the major products of the trapping reaction with the bulky phenol (compounds **12**). The metalation time was optimized for each substrate and protonating agent, and the results are shown in Table 1. As a rule, longer times were needed for achieving the metalation of **8c**. Gratifyingly, the double DAC−MeOH reaction afforded the bis(tetrahydro-2,1-benzazaphospholes) **11** in good yields as a mixture of *meso*:*rac* stereoisomers. Small amounts (18−24%) of doubly dearomatized products protonated at the γ position with respect to the phosphorus (i.e., compounds **12** as mixtures of *meso*:*rac* stereoisomers), as well as monodearomatized products protonated at the α (**13**, 6%) and γ (**14**, 6−28%) positions, were also formed. Compounds **13a** and **14a** (n = 1) were synthesized in high yield (≥85%) and with excellent regio- and stereoselectivities by treatment of **8a** with ^{s}BuLi (1.2 equiv) at −90 °C in THF in the absence of HMPA for 30 min and subsequent addition of an excess of MeOH or DTBMP at the same temperature. For compounds **11**, the diastereoselectivity increased in the series **11a** < **11c** <

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TABLE 1. Optimized Reaction Conditions for the Synthesis of 2,1-Bisazaphospholes 11 and 12 and Distribution of Products

entry	reaction conditions	t_1 (min)	ROH	**11** yield (%) (*meso*:*rac*)	**12** yield (%) (*meso*:*rac*)	ratio **11**:**12**
1	a	30	MeOH	**a**, 59 (63:37)[a,b]	**a**, 19 (68:32)[a]	3.1:1
2	b	30	MeOH	**a**, 75 (64:36)[a]	**a**, 14 (87:13)[a]	5.4:1
3	a	30	MeOH	**b**, 58 (86:14)[a]	**b**, 18 (67:33)[a]	3.2:1
4	b	30	MeOH	**b**, 65 (57:43)[a]	**b**, 5 (73:27)[a]	13:1
5	a	120	MeOH	**c**, 54 (73:27)	**c**, 24 (80:20)[a]	2.2:1
6	b	120	MeOH	**c**, 94 (100:0)		99:<1
7	a	60	DTMBP		**a**, 75 (61:39)	<1:99
8	a[c]	60	DTMBP		**a**, 75 (70:30)	<1:99
9	a[d]	60	DTMBP		**a**, 97 (67:33)	<1:99
10	a	60	DTMBP		**b**, 73 (67:33)	<1:99
11	a	120	DTMBP		**c**, 83 (83:17)	<1:99

[a] Concentration of the reaction 7−10 mM. [b] Also formed 4% of $Ph_2P(O)Bu^s$. [c] Concentration of the reaction 1 mM. [d] Solvent anhydrous and deoxygenated.

11b (entries 1, 3, 5), while for derivatives **12** the ratio of *meso*:*rac* stereoisomers is almost identical for **12a**,**b** and increases slightly for the bisazaphosphole with the longest methylene chain, **12c** (entries 7−11).

We have previously shown that quenching the dearomatized anions formed in the DAC reactions of phosphinamides **2** with methanol can be achieved in high yield and with total α regioselectivity, provided that the anion is allowed to react with *tert*-butyldimethylchlorosilane (TBDMSCl) prior to the addition of the protonating agent.[17a] To our delight, the application of this modified method to the dearomatization-methanol trapping of bisphosphinamides **8** [Scheme 3, reaction conditions (b)] resulted in a significant improvement of both the yield of **11** and the ratio **11**:**12** (cf., entries 1, 3, 5 with the corresponding 2, 4, 6). The preference for the protonation at the α position increased with the increment of the methylene groups of the linker (entries 2, 4, 6). In this sense, the reaction of **8c** is singular for it affords **11c** exclusively and in almost quantitative yield. This fact suggests that in the reaction mediated by TBDMSCl, the system behaves as two isolated mono-phosphinamides when the doubly dearomatized species are separated by four methylenic groups.

The DAC-protonation reaction with the bulky phenol was remarkable. The process furnished bisazaphospholes **12** almost exclusively. This means that starting on achiral substrates, products containing six chiral centers are formed in good yield. The heterocycles were obtained as mixtures of *meso*:*rac* isomers. The diastereoselectivity increased steadily with increasing the length of the methylene bridge.

Products formally involving double N_DAr reactions have been reported. The anions resulting either through borohydride reduction or enolate addition to nitroarenes have been trapped via Mannich reaction with formaldehyde and primary diamines to give bis(3-azabicyclo[3.3.1]nonanes) linked through a methylene bridge, generally in low yields.[21] Genuine examples of double N_DAr reactions are the coupling of 9-anthracenediazonium salts with the amine precursors[22] and the bis-adduct formed in the reaction of the Grignard reagent of 1,8-bis(chloromethyl)-naphthalene with 9-trimethylsilylanthracene.[23] However, to the best of our knowledge, this is the first time that a double DAC reaction has been described.

We next extended the potential of the double DAC reaction of bisphosphinamides **8** by introducing a functionalization into the dearomatized systems. Previous studies on *N*-alkyl-*N*-benzyldiphenylphosphinamides **2** indicated that an arylhydroxymethyl fragment could be installed very efficiently at the position γ to the phosphorus by trapping the dearomatized anions formed in the anionic cyclization with aldehydes.[17b,18b] Thus, we explored the reactivity of dilithiated bisphosphinamide **8c** toward benzaldehyde. After some experimentation, we found the optimized reaction conditions shown in Scheme 4. The reaction affords quantitatively the expected γ-functionalized bis-(tetrahydro-2,1-benzazaphospholes) **15** as a mixture of **15**_*meso* and **15**_*rac* stereoisomers in a ratio 89:11, which in turn are obtained as mixtures of epimers at the hydroxylic carbon (ratio of **15a**_*meso*:**15b**_*meso* of 85:15; ratio of **15a**_*rac*:**15b**_*rac* of 64:36). Bisazaphosphole **15a**_*meso* could be isolated through flash-column chromatography (eluent AcOEt:MeOH 25:1). The isomers **15b**_*meso*, **15a**_*rac*, and **15b**_*rac* could not be separated and were identified from a mixture of the compounds in a relative ratio of 37:40:23. As observed for the analogous reaction of phosphinamides **2**, the major product obtained arose from the addition of the prochiral electrophile with *like* topicity (see below for structural assignment).

DAC reactions of diarylphosphinamides provide an entry to conformationally restricted γ-aminophosphinic acids and esters by solvolysis of the P−N bond of the azaphosphole ring.[17,18,24] The bisheterocycles prepared here also successfully undergo this solvolysis. For instance, the treatment of **12a**_*meso* with a diluted methanolic solution of HCl at room temperature for ca. 1 h produced quantitatively the methanolysis of the phosphinamide linkage affording the bis(methyl γ-aminophosphinate) **16** stereospecifically (Scheme 5). As in the monocyclic series,[17a] inversion of the configuration at the phosphorus center is assumed.[25]

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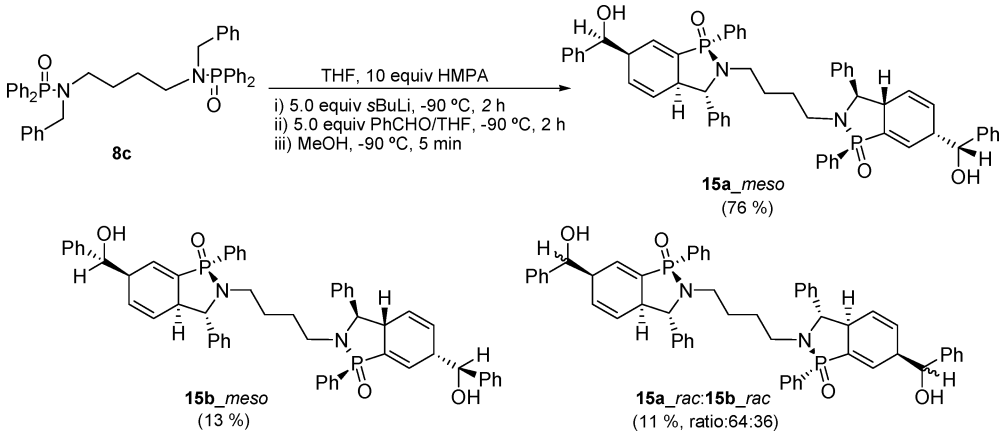
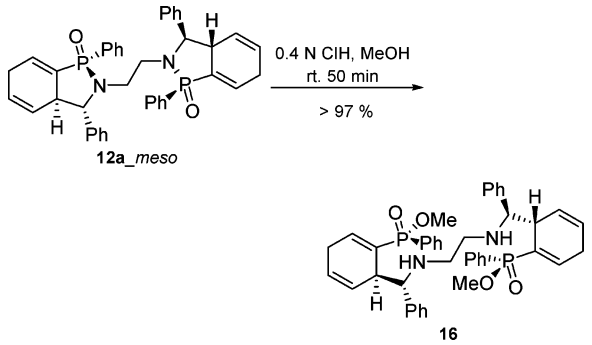
SCHEME 4. Synthesis of Functionalized Bis(tetrahydro-2,1-benzazaphospholes) 15



SCHEME 5. Synthesis of Bis(methyl γ-aminophosphinate) 16



Structural Characterization. Pure compounds **11**, **12**, and **15a**_*meso* could be readily isolated.[26] The structural assignment was based on the analysis of the APCI-MS, 1D (^{1}H, ^{13}C, ^{31}P, and DEPT), and 2D (gCOSY45, gHMQC, gHMBC, and gNOESY) spectra. The [1,3]- and [1,4]-cyclohexadiene systems can be easily distinguished on the basis of their NMR data (e.g., the sp^3/sp^2-hybridized carbon α to the phosphorus, see Supporting Information), the most characteristic being the specific region of the ^{31}P NMR spectrum in which each regioisomer appears (Table 2, Figure S1). Products of protonation at the α position, **11**, appear at $\delta(^{31}P) \approx 48$ ppm, whereas compounds **12** and **15** are identified by $\delta(^{31}P)$ values of about 28 ppm. The presence of the phenylhydroxymethyl fragment in compounds **15a**_*meso* is evidenced in the $^{13}C\{^1H\}$ spectrum by a singlet signal at δ 74.31 ppm for the methine carbon. The CH−OH group shows two signals in the ^{1}H NMR spectrum at δ 5.25 and 6.34 ppm for the methine and hydroxy protons, respectively. The relative configuration of the benzazaphosphole fragments was deduced from the magnitude of the $^3J(^nX^1H)$ (X = ^{1}H, ^{31}P)[18] and was confirmed through the respective NOESY spectra (Supporting Information). Thus, the *cis* fusion of the rings in compounds **11** is deduced from the large magnitude of the vicinal coupling between the bridgehead methine protons [$^3J(^1H^1H) > 10$ Hz]. The *syn* arrangement of the phenyl rings in the azaphosphole fragment is consistent with the absence of ^{31}P,^{1}H coupling between the phosphorus nucleus and the proton of the methine carbon bonded to the nitrogen atom. Selected NOEs observed for compounds **11**, **12**, and **15a** are shown in Figure 1 (see also Supporting Information). The NOE correlations detected for the PhCHOH moiety in the diastereoisomers **15a**_*meso* and **15b**_*meso* indicate that attack *like* of the dearomatized carbanion to the carbonyl group leading to **15a**_*meso* takes place preferentially, in agreement with the analogous reaction of the corresponding monophosphinamide **2**.[10]

The *meso*/*rac* pairs of stereoisomers could be unequivocally identified for **11a**, **12a**, and **11c** by means of X-ray diffraction analysis. Single crystals of **11a**_*meso* and **11c**_*meso* were obtained by slow evaporation of their dichloromethane−chloroform solutions,[27] whereas **12a**_*meso* crystallized from a dichloromethane solution. All crystal structures showed the existence of an inversion center. The spacer connecting the heterocycles adopts a staggered conformation in which the bisbenzazaphosphole fragments are arranged antiperiplanar, thus minimizing the steric interactions between the bulkiest groups (see Supporting Information). The P═O bonds are oriented in opposite directions, which contributes to minimize dipole interactions.

In all other cases, the assignment of the *meso*/*rac* isomers was realized through chiral HPLC.[28] The chromatogram of *rac* derivatives showed two well-separated peaks corresponding to the two enantiomers present in the racemate. Under the same experimental conditions, the chromatogram of the *meso* isomers exhibited a single peak with a retention time clearly different from that of the *rac* stereoisomers (Figure S22). The results of the stereochemical analysis indicate that the *meso* compounds were preferentially formed in all cases.

In Vitro Cytotoxicity Studies. Representative dearomatized compounds were submitted to in vitro cytotoxicity assays to evaluate their properties as possible antitumor agents. For completeness, the bisphosphinamides **8a** and **8c** were included in the bioactivity study as well. A preliminary screening was carried out for the activity of bisphosphinamides **8a** and **8c** and benzazaphospholes **11a**−**c**_*meso*, **14a**, and **15a**_*meso* on HT29 (colon), LoVo-Dox (colon), and A549 (NSCL) cells at concen-

(26) Compound **11a**_*meso* was recrystallized from a mixture of dicholoromethane−chloroform. The bisazaphospholes **12a**_*meso* and **12c**_*meso* precipitated from diethyl ether. All other compounds were purified through column chromatography on silica gel or silica gel containing a 5% of triethyl amine or neutral Al_2O_3 using mixtures of AcOEt:MeOH as eluent. Heterocycles **12a**−**c**_*rac* were obtained as mixtures of **12a-c**_*rac*:**12a-c**_*meso* in ratios of 70:30, 21:79, and 52:48, respectively.

(27) Although the analysis of the X-ray data of **11a**_*meso* provided a clear identification of the structure (Supporting Information), the poor quality of the crystal did not allow a complete structural analysis.

(28) The stationary phase consisted of a Chiralcel OD-H column, and eluent mixtures of hexane:isopropanol were used at a constant flux of 0.5 mL/min operating in isocratic mode.

TABLE 2. ^{31}P NMR Data (δ, ppm) of 2,1-Bisazaphospholes 11, 12, and 15[a]

$\delta(^{31}P)$	11a	11b	11c	12a	12b	12c	15a	15b
meso	47.63	48.83	49.48	28.07	28.67	28.76	28.67	29.01
rac	49.17	49.22[b]	49.30[b]	29.21[c]	28.45[c]	28.84[c]	28.92[d]	29.19[d]

[a] For comparison, the $\delta(^{31}P)$ values of **3a** (E = H, R^2 = Me) and **4** are 30.81 and 52.01 ppm, respectively.[17a] [b] Chemical shift measured from the crude reaction. [c] Chemical shift measured from a mixture of *rac* and *meso* structures.[26] [d] The relative configuration of the carbon bearing the OH group could not be unequivocally established.

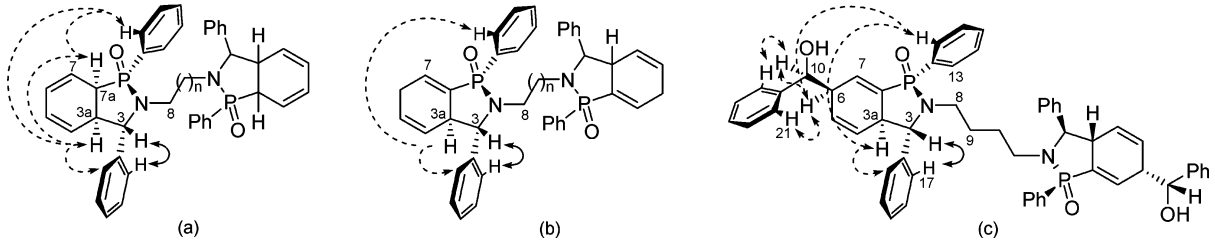


FIGURE 1. Selected NOEs measured in the 2D NOESY spectra of (a) **11**, (b) **12**, and (c) **15a**_*meso*.

TABLE 3. In Vitro GI_{50} (μM) Results for Phosphinamide 8c and a Series of Benzazaphosphole Compounds

	prostate	ovary	breast	melanoma	NSCL	leukemia	pancreas	colon			cervix
compound	LN-caP	IGROV	SK-BR3	SKMEL28	A549	K562	PANC1	HT29	LOVO	LOVO-DOX	HELA
8c	1.53	2.71	0.37	2.00	2.54	3.92	3.10	2.90	2.75	0.82	3.10
11b_*meso*	1.89	3.39	1.29	2.52	3.04	4.43	3.73	3.96	3.07	1.92	2.92
11c_*meso*	6.56	7.97	>15.0	>15.0	>15.0	9.58	13.8	>15.0	>15.0	15.0	>15.0
15a_*meso*	3.98	>11.4	>11.4	>11.4	>11.4	5.90	11.4	>11.4	>11.4	>11.4	>11.4
14a	1.16	2.79	0.43	1.53	2.45	2.23	2.56	3.39	2.83	0.68	3.14

trations of 50, 15, and 5 μg/mL. Gratifyingly, good tumor growth inhibition, less than 0% of viability for concentrations of 50 and 15 μg/mL, was observed for **8c** and bisbenzazaphospholes **11b**,**c**_*meso*, and **15a**_*meso* (see Supporting Information). By contrast, compounds **8a** and **11a**_*meso* proved to be inactive. Interestingly, monodearomatized compound **14a** showed also a remarkable biological activity (see Supporting Information). These results indicate that bis-benzazaphosphole derivatives, as well as non-dearomatized bisphosphinamides, show relevant in vitro cytotoxicity activity provided that the phosphinamide moieties are separated by an aliphatic chain of three or four carbon atoms. For mono-benzazaphosphole systems, remarkable activity is observed even for phosphinamide moieties separated by a methylene chain of two carbons.

A panel of 11 human tumor cell lines was subsequently used to evaluate the cytotoxic potential of compounds **8c**, **11b**_*meso*, **11c**_*meso*, **14a**, and **15a**_*meso*: prostate carcinoma tumor cells (LN-caP), ovarian cells sensitive (IGROV), SK-BR3 breast adenocarcinoma, MEL28 malignant melanoma, A-49 lung carcinoma NSCL, K562 chronic myelogenous leukemia, PANC1 pancreatic epitheloid carcinoma, HT29 colon carcinoma cells, LoVo lymph node metastasis cells and the corresponding LoVo-Dox cells resistant to Doxorubicin, and cervix epitheloid carcinoma (HeLa). A conventional colorimetric assay[29] was set up to estimate GI_{50} values, that is, the drug concentration that causes 50% cell growth inhibition after 72 h continuous exposure to the test molecules. The results are summarized in Table 3.[30]

Although the number of compounds tested is small, some trends in structure−activity relationships (SAR) can be deduced from the data collected in Table 3. The comparison between **11b**_*meso* and **11c**_*meso* indicates that antitumor efficacy diminishes on increasing from three to four methylene groups the chain length of the linker connecting the two dearomatized moieties. For most cell lines, the installation of a polar group at the γ-position with respect to the phosphorus, cf., **11c**_*meso* and **15a**_*meso*, produces a slight improvement of the tumor growth inhibition. Curiously, the doubly dearomatized compounds proved to be less efficient than bisphosphinamide **8c** for inhibiting the tumor growth. Nevertheless, the best results were obtained for **14a** containing a mono-dearomatized fragment linked to an intact diphenylphosphinamide moiety. Overall, the in vitro data suggest that the dearomatization of a single Ph_2P-(O) unit of bisphosphinamides **8** is beneficial for the antitumor activity and that the effect of the second phosphinamide group may contribute to improve the hydrophobicity of the molecule. The bioassays performed do not provide information about the mode of action of the new phosphinamide derivatives. Phosphinamides bearing a hydroxamic acid substituent linked at the nitrogen atom act as potent matrix metalloproteinase inhibitors.[3a,d,31] On the basis of structural similarities of these inhibitors with the compounds here described, one may expect that the later most probably interact with the same targets.

In summary, we have demonstrated the feasibility of in situ double anionic cyclization dearomatization-electrophilic trapping reactions of bisdiphenylphosphinamides. The methodology developed allows the conversion of easily available achiral starting materials into multifunctional compounds containing 6−10 stereocenters in a single reaction step in moderate to good yield and with very high regio- and stereocontrol. Antitumor assays on some benzazaphospholes synthesized showed promising results that may be useful for further SAR work. The P−N

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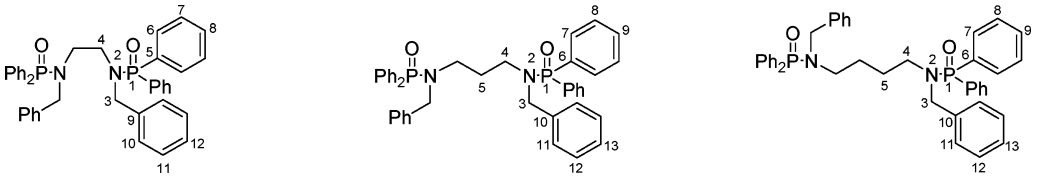
CHART 2. Scheme Numbering Used for the NMR Assignments of (*N*-Benzyl-*P*,*P*-diphenylphosphinamides) 8a−c



linkage of the dearomatized bisheterocycles obtained can be smoothly solvolyzed to give bis(γ-aminophosphinic esters). This simple transformation makes it possible to conceive further applications of bisbenzazaphospholes **11** and **12** as building blocks for the construction of macromolecules containing unusual functionalizations. This chemistry is being currently explored.

Experimental Section

For general experimental details, see the Supporting Information.

General Procedure for the Preparation of Bis(*N*-benzyl-*P*,*P*-diphenylphosphinamides) 8a−c. To a solution of the appropriate *N*,*N*′-dibenzylalkylendiamine (8.6 mmol) and triethylamine (6.0 mL, 43.0 mmol) in toluene (120 mL) was added chlorodiphenylphosphine (3.24 mL, 18.06 mmol) at −80 °C. After 30 min of stirring, the solvent was distilled. Next, a solution of *m*-CPBA (77%) (3.85 g, 17.2 mmol) in CH_2Cl_2 (30 mL) was added at −40 °C. Once oxidation was complete (30 min), the reaction was poured into ice water and extracted with ethyl acetate (3 × 15 mL) and washed with 1 N NaOH (2 × 15 mL) and water (1 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Precipitation from AcOEt and Et_2O afforded **8a** and **8b**,**c**, respectively, as white solids with a purity higher than 97% (NMR) (Chart 2).

***N*,*N*′-Ethane-1,2-diylbis[*N*-benzyl-*P*,*P*-diphenyl(phosphinic amide)] (8a).** Isolated yield 83% (4.57 g). Mp 171 °C. ^{1}H NMR δ 3.10 (m, 4H, $^3J_{PH}$ 10.6 Hz, H-4), 3.83 (d, 4H, $^3J_{PH}$ 9.9 Hz, H-3), 7.02 (m, 4H, ArH), 7.18−7.60 (m, 18H, ArH), 7.74 (m, 8H, $^3J_{PH}$ 12.1 Hz, H-6). ^{13}C NMR δ 44.02 (C-4), 49.73 (d, $^2J_{PC}$ 3.7 Hz, C-3), 127.12 (C-12), 127.75 (C-10), 128.41 (d, $^2J_{PC}$ 6.0 Hz, C-6), 128.62 (C-11), 130.31 (d, $^1J_{PC}$ 128.6 Hz, C-5), 131.85 (d, $^4J_{PC}$ 1.8 Hz, C-8), 132.20 (d, $^3J_{PC}$ 9.6 Hz, C-7), 137.27 (d, $^3J_{PC}$ 4.0 Hz, C-9). ^{31}P NMR δ 31.00. MS (*m*/*z*) 641 (M + 1, 100). Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 75.08; H, 6.03; N, 4.36.

***N*,*N*′-Propane-1,3-diylbis[*N*-benzyl-*P*,*P*-diphenyl(phosphinic amide)] (8b).** Isolated yield 73% (4.11 g). Mp 118 °C. ^{1}H NMR δ 1.72 (m, 2H, H-5), 2.53 (m, 4H, $^3J_{HH}$ 7.9 Hz, $^3J_{PH}$ 10.4 Hz, H-4), 4.03 (d, 4H, $^3J_{PH}$ 9.7 Hz, H-3), 7.28 (m, 10H, H-11, H-12, H-13), 7.39−7.52 (m, 6H, H-8, H-9), 7.83 (m, 4H, $^3J_{PH}$ 11.5 Hz, H-7). ^{13}C NMR δ 25.67 (t, $^3J_{PC}$ 3.3 Hz, C-5), 42.45 (d, $^2J_{PC}$ 3.0 Hz, C-4), 49.05 (d, $^2J_{PC}$ 3.0 Hz, C-3), 127.31 (C-13), 128. 43 (C-12, C-13), 128.51 (d, $^3J_{PC}$ 13.2 Hz, C-8), 131.75 (d, $^1J_{PC}$ 129.2 Hz, C-6), 131.75 (d, $^4J_{PC}$ 3.0 Hz, C-9), 132.31 (d, $^2J_{PC}$ 9.0 Hz, C-7), 136.98 (d, $^3J_{PC}$ 4.2 Hz, C-10). ^{31}P NMR δ 30.83. MS (*m*/*z*) 655 (M + 1, 100). Anal. Calcd (%) for $C_{41}H_{40}N_2O_2P_2$: C, 75.21; H, 6.16; N, 4.28. Found: C, 75.26; H, 6.17; N, 4.31.

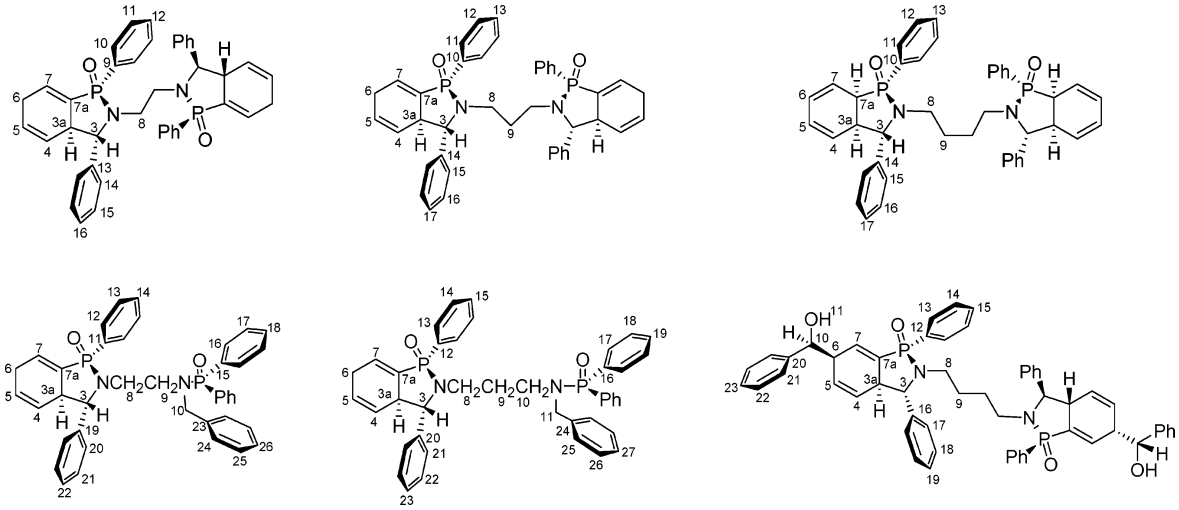
***N*,*N*′-Butane-1,4-diylbis[*N*-benzyl-*P*,*P*-diphenyl(phosphinic amide)] (8c).** Isolated yield 81% (4.65 g). Mp 158 °C. ^{1}H NMR δ 1.16 (m, 4H, H-5), 2.61 (m, 4H, $^3J_{HH}$ 7.0 Hz, $^3J_{PH}$ 10.5 Hz, H-4), 4.08 (d, 4H, $^3J_{PH}$ 9.8 Hz, H-3), 7.28 (m, 10H, H-11, H-12, H-13), 7.39−7.52 (m, 12H, H-8, H-9), 7.84 (m, 8H, $^3J_{PH}$ 11.7 Hz, H-7). ^{13}C NMR δ 25.14 (d, $^3J_{PC}$ 3.3 Hz, C-5), 42.90 (d, $^2J_{PC}$ 3.0 Hz, C-4), 49.24 (d, $^2J_{PC}$ 3.6 Hz, C-3), 127.23 (C-13), 128.24 (C-11), 128. 36 (C-12), 128.44 (d, $^3J_{PC}$ 12.9 Hz, C-8), 131.70 (d, $^4J_{PC}$ 2.7 Hz, C-9), 131.91 (d, $^1J_{PC}$ 128.9 Hz, C-6), 132.30 (d, $^2J_{PC}$ 9.3 Hz, C-7), 137.37 (d, $^3J_{PC}$ 4.8 Hz, C-10). ^{31}P NMR δ 30.92. MS (*m*/*z*) 669 (M + 1, 100). Anal. Calcd (%) for $C_{42}H_{42}N_2O_2P_2$: C, 75.43; H, 6.33; N, 4.19. Found: C, 75.42; H, 6.22; N, 4.36.

General Procedure for the Dearomatizing Anionic Cyclization of Bis(*N*-benzyl-*P*,*P*-diphenylphosphinamides) 8a−c. To a solution of **8a−c** (2.99×10^{-4} mol) and HMPA (0.52 mL, 2.99×10^{-3} mol) in THF (30 mL) was added a solution of ^{s}BuLi (1.15 mL, of a 1.3 M solution in cyclohexane, 1.50×10^{-3} mol) at −90 °C. After 30 min of metalation was added MeOH (2 mL) or 2,6-di-*tert*-butyl-4-methylphenol (DTBMP) (532.4 mg, 2.39×10^{-3} mol). The reaction mixture was stirred at −90 °C for 30−120 min (see Table 1). Next, the reaction mixture was poured into ice water and extracted with ethyl acetate (3 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. ^{1}H, ^{1}H{^{31}P}, and ^{31}P{^{1}H} NMR spectra of the crude reaction were measured to determine the regio- and stereoselectivity of the process. The reaction mixture was then purified by recrystallization from a mixture of dicholoromethane−chloroform, precipitation from diethyl ether, or by flash column chromatography (silica gel, silica gel containing a 5% of triethyl amine, or neutral alumina) using different mixtures of ethyl acetate:methanol as eluent.

(1*R*$_P$*,3*R,3a*S**,7a*S**)-2-{2-[(1*S*$_P$*,3*S**,3a*R**,7a*R**)-1,3-Diphenyl-1-oxide-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol-2-yl]-ethyl]}-1,3-diphenyl-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (11a_*meso*).** Yield after recrystallization from $CH_2Cl_2/CHCl_3$ 35% (67 mg) (Chart 3). Mp 230−1 °C. ^{1}H NMR δ 2.58 (m, 2H, H-8), 2.81 (m, 2H, H-8′), 2.89 (m, 2H, H-3a), 3.06 (tt, 2H, $^3J_{HH}$ 11.4 Hz, $^3J_{HH}$ 3.0 Hz, $^2J_{PH}$ 11.4 Hz, H-7a), 4.12 (d, 2H, $^3J_{HH}$ 9.3 Hz, H-3), 5.29 (ddt, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.5 Hz, $^4J_{HH}$ 0.8 Hz, H-4), 5.85 (dddt, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 3.0 Hz, $^4J_{HH}$ 0.8 Hz, $^3J_{PH}$ 9.5 Hz, H-7), 5.92 (ddc, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.5 Hz, $^4J_{HH}$ 0.8 Hz, $^5J_{PH}$ 0.8 Hz, H-5), 6.04 (m, 2H, $^4J_{PH}$ 2.4 Hz, H-6), 7.09 (m, 4H, H-14), 7.31−7.55 (m, 12H, ArH), 7.62 (m, 4H, $^3J_{PH}$ 12.2 Hz, H-10). ^{13}C{^{1}H} NMR δ 37.49 (d, $^1J_{PC}$ 84.1 Hz, C-7a), 40.77 (d, $^2J_{PC}$ 2.4 Hz, C-8), 43.44 (C-3a), 68.35 (d, $^2J_{PC}$ 21.6 Hz, C-3), 119.40 (d, $^2J_{PC}$ 8.4 Hz, C-7), 123.38 (d, $^3J_{PC}$ 11.4, C-4), 124.27 (d, $^3J_{PC}$ 5.4 Hz, C-6), 124.36 (d, $^4J_{PC}$ 1.2 Hz, C-5), 127.54 (C-14), 128.23 (C-16), 128.42 (d, $^3J_{PC}$ 12.7 Hz, C-11), 128.71 (C-15), 131.49 (d, $^2J_{PC}$ 9.9 Hz, C-10), 131.61 (d, $^4J_{PC}$ 2.9 Hz, C-12), 133.33 (d, $^1J_{PC}$ 12.5 Hz, C-9), 138.91 (d, $^3J_{PC}$ 9.6 Hz, C-13). ^{31}P{^{1}H} NMR δ 47.63. MS (*m*/*z*) 641 (M + 1, 100). Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 75.10; H, 6.05; N, 4.33.

(1*R*$_P$*,3*R,3a*S**,7a*S**)-2,2′-Ethane-1,2-diylbis(1,3-diphenyl-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol)1,1′-Dioxide(11a_*rac*).** Yield after chromatography (AcOEt/MeOH, 25:1) 20% (38 mg). Oil. ^{1}H NMR δ 2.67−2.94 (m, 6H, H-3a, H-8), 3.06 (m, 2H, $^2J_{PH}$ 11.7 Hz, H-7a), 4.07 (d, 2H, $^3J_{HH}$ 9.2 Hz, H-3), 5.29 (ddc, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.4 Hz, H-4), 5.87 (m, 2H, $^3J_{PH}$ 9.5 Hz, H-7), 5.94 (ddc, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.4 Hz, $^5J_{HH}$ 0.8 Hz, H-5), 6.06 (m, 2H, H-6), 7.00 (m, 4H, H-14), 7.19−7.40 (m, 6H, H-15, H-16), 7.40−7.59 (m, 6H, H-11, H-12), 7.72 (m, 4H, $^3J_{PH}$ 12.4 Hz, H-10). ^{13}C{^{1}H} NMR δ 37.26 (d, $^1J_{PC}$ 84.1 Hz, C-7a), 40.33 (C-8), 43.39 (C-3a), 67.85 (d, $^2J_{PC}$ 21.0 Hz, C-3), 119.43 (d, $^2J_{PC}$ 8.4 Hz, C-7), 123.31 (d, $^3J_{PC}$ 11.4 Hz, C-4), 124.36 (C-5), 124.44 (d, $^3J_{PC}$ 5.4 Hz, C-6), 127.70 (C-14), 128.36 (C-16), 128.44 (d, $^3J_{PC}$ 13.2 Hz, C-11), 128.61 (C-15), 131.39 (d, $^2J_{PC}$ 10.2 Hz, C-10), 131.61 (d, $^4J_{PC}$ 2.5 Hz, C-12), 133.25 (d, $^1J_{PC}$ 126.2 Hz, C-9), 139.24 (d, $^3J_{PC}$ 9.6 Hz, C-13). ^{31}P{^{1}H} NMR δ 49.17. MS (*m*/*z*) 641 (M + 1, 100).

CHART 3. Scheme Numbering Used for the NMR Assignments of Bis(benzazaphospholes) 11−15



Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 74.78; H, 5.84; N, 4.27.

(1*R*$_P$*,3*R,3a*S**,7a*S**)-2-{3-[(1*S*$_P$*,3*S**,3a*R**,7a*R**)-1,3-Diphenyl-1-oxide-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol-2-yl]-propyl}-1,3-diphenyl-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (11b_*meso*).** Yield after chromatography on silica gel (AcOEt/MeOH, 60:1 to 30:1) 47% (92 mg). Oil. ^{1}H NMR δ 1.50 (m, 2H, H-9), 2.59−2.86 (m, 6H, H-3a, H-8), 3.01 (m, 2H, $^2J_{PH}$ 11.4 Hz, H-7a), 4.10 (d, 2H, $^3J_{HH}$ 9.2 Hz, H-3), 5.32 (m, 2H, H-4), 5.91 (m, 2H, $^3J_{HH}$ 9.5 Hz, $^4J_{HH}$ 2.6 Hz, $^3J_{PH}$ 9.5 Hz, H-7), 5.99 (dd, 2H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.3 Hz, H-5), 6.09 (m, 2H, H-6), H-5), 6.09 (m, 2H, H-6), 7.23 (dd, 4H, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 2.8 Hz, H-15), 7.33−7.56 (m, 12H, ArH), 7.84 (ddd, 4H, $^3J_{HH}$ 7.3 Hz, $^4J_{HH}$ 1.8 Hz, $^3J_{PH}$ 12.7 Hz, H-10). ^{13}C{^{1}H} NMR δ 25.99 (C-9), 37.52 (d, $^1J_{PC}$ 84.7 Hz, C-7a), 39.63 (d, $^2J_{PC}$ 3.0 Hz, C-8), 43.26 (C-3a), 66.58 (d, $^2J_{PC}$ 21.6 Hz, C-3), 119.36 (d, $^2J_{PC}$ 8.1 Hz, C-7), 123.39 (d, $^3J_{PC}$ 11.4 Hz, C-4), 124.46 (d, $^4J_{PC}$ 3.0 Hz, C-5), 124.54 (d, $^3J_{PC}$ 9.6 Hz, C-6), 127.59 (C-15), 128.06 (C-17), 128.46 (d, $^3J_{PC}$ 12.3 Hz, C-12), 128.65 (C-16), 131.58 (d, $^2J_{PC}$ 9.9 Hz, C-11), 131.66 (d, $^4J_{PC}$ 2.4 Hz, C-13), 133.90 (d, $^1J_{PC}$ 126.1 Hz, C-10), 139.32 (d, $^3J_{PC}$ 9.6 Hz, C-14). ^{31}P{^{1}H} NMR δ 48.83. MS (*m*/*z*) 655 (M + 1, 100). Anal. Calcd (%) for $C_{41}H_{40}N_2O_2P_2$: C, 75.21; H, 6.16; N, 4.28. Found: C, 75.28; H, 6.07; N, 4.32.

(1*R*$_P$*,3*R,3a*S**,7a*S**)-2-{4-[(1*S*$_P$*3*S**,3a*R**,7a*R**)-1,3-Diphenyl-1-oxide-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol-2yl]-butyl}-1,3-diphenyl-2,3,3a,7a-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (11c_*meso*).** Yield after chromatography (AcOEt/MeOH, 49:1) 37% (74 mg). Oil. ^{1}H NMR δ 1.03−1.18 (m, 4H, H-9), 2.45−2.64 (m, 4H, H-8), 2.84 (dddd, 1H, $^3J_{HH}$ 10.7 Hz, $^3J_{HH}$ 9.7 Hz, $^3J_{HH}$ 5.9 Hz, $^3J_{PH}$ 2.9 Hz, H-3a), 3.04 (m, 1H, $^3J_{HH}$ 10.7 Hz, $^3J_{HH}$ 3.7 Hz, $^4J_{HH}$ 2.9 Hz, $^2J_{PH}$ 10.7 Hz, H-7a), 4.26 (d, 1H, $^3J_{HH}$ 9.7 Hz, H-3), 5.34 (ddddd, 1H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.9 Hz, $^4J_{HH}$ 2.9 Hz, $^4J_{HH}$ 0.9 Hz, $^4J_{PH}$ 2.3 Hz, H-4), 5.92−6.01 (m, 2H, H-5, H-7), 6.11 (ddddd, 1H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.3 Hz, $^4J_{HH}$ 2.9 Hz, $^4J_{HH}$ 0.9 Hz, $^4J_{PH}$ 0.9 Hz, H-6), 7.21−7.55 (m, 16H, ArH), 7.88 (ddd, 4H, $^3J_{HH}$ 7.7 Hz, $^4J_{HH}$ 1.7 Hz, $^3J_{PH}$ 12.3 Hz, H-11). ^{13}C{^{1}H} NMR δ 25.84 (C-9), 33.77 (d, $^1J_{PC}$ 84.7 Hz, C-7a), 41.85 (d, $^2J_{PC}$ 2.4 Hz, C-8), 43.06 (C-3a), 67.32 (d, $^2J_{PC}$ 20.1 Hz, C-3), 119.51 (d, $^2J_{PC}$ 8.3 Hz, C-7), 123.50 (d, $^3J_{PC}$ 11.4 Hz, C-4), 124.40 (d, $^4J_{PC}$ 3.0 Hz, C-5), 124.51 (d, $^3J_{PC}$ 10.2 Hz, C-6), 127.55 (C-15), 128.11−128.66 (3CHAr), 131.62, (d, $^2J_{PC}$ 9.6 Hz, C-11), 131.74 (d, $^4J_{PC}$ 2.4 Hz, C-13), 134.01 (d, $^1J_{PC}$ 126.2 Hz, C-10), 139.37 (d, $^3J_{PC}$ 10.2 Hz, C-14). ^{31}P{^{1}H} NMR δ 49.48. MS (*m*/*z*) 669 (M + 1, 100). Anal. Calcd (%) for $C_{42}H_{42}N_2O_2P_2$: C, 75.43; H, 6.33; N, 4.19. Found: C, 75.51; H, 6.42; N, 4.23.

(1*R*$_P$*,3*S,3a*R**)-2-{2-[(1*S*$_P$*,3*R**,3a*S**)-(1′,3′-Diphenyl-1-oxide-2′,3′,3a′,6′-tetrahydro-1′*H*-2′,1′-benzazaphosphol-2-yl]ethyl}-1,3-diphenyl-2,3,3a,6-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (12a_*meso*).** Yield after precipitation from Et_2O 50% (96 mg). Mp 219−20 °C. ^{1}H NMR δ 2.64−2.87 (m, 8H, H-6, H-8), 3.12 (m, 2H, H-3a), 3.96 (d, 2H, $^3J_{HH}$ 9.3 Hz, H-3), 5.43 (m, 2H, H-4), 5.69 (m, 2H, H-5), 6.59 (m, 2H, $^3J_{PH}$ 16.6 Hz, H-7), 7.19 (m, 4H, H-14), 7.36−7.51 (m, 12H, ArH), 7.68 (m, 4H, $^3J_{PH}$ 11.6 Hz, H-10). ^{13}C-{^{1}H} NMR δ 27.63 (d, $^3J_{PC}$ 12.6 Hz, C-6), 40.64 (d, $^2J_{PC}$ 2.4 Hz, C-8), 46.62 (d, $^2J_{PC}$ 13.8 Hz, C-3a), 67.19 (d, $^2J_{PC}$ 12.0 Hz, C-3), 122.82 (d, $^3J_{PC}$ 6.6 Hz, C-4), 124.98 (d, $^4J_{PC}$ 1.2 Hz, C-5), 127.90 (C-14), 128.28 (d, $^3J_{PC}$ 13.2 Hz, C-11), 128.49 (C-16), 128.85 (C-15), 131.39 (d, $^4J_{PC}$ 3.0 Hz, C-12), 131.53 (d, $^2J_{PC}$ 10.8 Hz, C-10), 133.04 (d, $^1J_{PC}$ 120.7 Hz, C-7a), 133.53 (d, $^1J_{PC}$ 132.8 Hz, C-9), 135.36 (d, $^2J_{PC}$ 9.6 Hz, C-7), 138.19 (d, $^3J_{PC}$ 8.4 Hz, C-13). ^{31}P-{^{1}H} NMR δ 28.07. MS (*m*/*z*) 641 (M + 1, 100). Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 74.82; H, 6.04; N, 4.38.

(1*R*$_P$*,3*S,3a*R**)-2-{3-[(1*S*$_P$*,3*R**,3a*S**)-1′,3′-Diphenyl-1′-oxide-2′,3′,3a′,6′-tetrahydro-1′*H*-2′,1′-benzazaphosphol-2-yl]propyl}-1,3-diphenyl-2,3,3a,6-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (12b_*meso*).** Yield after chromatography on silica gel-Et_3N (5%) (AcOEt/MeOH, 40:1) 46% (90 mg). Oil. ^{1}H NMR δ 1.40−1.74 (m, 2H, H-9), 2.43 (m, 2H, H-8), 2.71−2.95 (m, 6H, H-6, H-8′), 3.15 (m, 2H, H-3a), 4.18 (d, 2H, $^3J_{HH}$ 9.4 Hz, H-3), 5.57 (m, 2H, H-4), 5.79 (m, 2H, H-5), 6.65 (m, 2H, $^3J_{PH}$ 16.0 Hz, H-7), 7.30−7.55 (m, 16H, ArH), 7.86 (m, 4H, $^3J_{PH}$ 13.1 Hz, H-10). ^{13}C{^{1}H} NMR δ 26.23 (C-9), 27.66 (d, $^3J_{PC}$ 12.6 Hz, C-6), 39.01 (d, $^2J_{PC}$ 3.0 Hz, C-8), 46.34 (d, $^2J_{PC}$ 14.4 Hz, C-3a), 66.00 (d, $^2J_{PC}$ 12.0 Hz, C-3), 123.08 (d, $^3J_{PC}$ 6.6 Hz, C-4), 124.90 (d, $^4J_{PC}$ 1.2 Hz, C-5), 127.97 (C-15), 128.12 (C-17), 128.39 (d, $^3J_{PC}$ 13.1 Hz, C-12), 128.80 (C-16), 131.46 (d, $^4J_{PC}$ 3.0 Hz, C-13), 131.60 (d, $^2J_{PC}$ 10.2 Hz, C-11), 133.04 (d, $^1J_{PC}$ 121.3 Hz, C-7a), 133.91 (d, $^1J_{PC}$ 133.3 Hz, C-10), 134.94 (d, $^2J_{PC}$ 9.6 Hz, C-7), 138.75 (d, $^3J_{PC}$ 8.4 Hz, C-14). ^{31}P{^{1}H} NMR δ 28.67. MS (*m*/*z*) 655 (M + 1, 100). Anal. Calcd (%) for $C_{41}H_{40}N_2O_2P_2$: C, 75.21; H, 6.16; N, 4.28. Found: C, 75.34; H, 6.24; N, 4.30.

(1*R*$_P$*,3*S,3a*R**)-2-{4-[(1*S*$_P$*,3*R**,3a*S**)-1′,3′-Diphenyl-1′-oxide-2′,3′,3a′,6′-tetrahydro-1′*H*-2′,1′-benzazaphospholyl]butyl}-1,3-diphenyl-2,3,3a,6-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (12c_*meso*).** Yield after precipitation from Et_2O 65% (130 mg). ^{1}H NMR δ 1.12 (m, 4H, H-9), 2.38−2.58 (m, 4H, H-8), 2.72−2.94 (m, 4H, H-6), 3.14 (m, 2H, H-3a), 4.05 (d, 2H, $^3J_{HH}$ 9.5 Hz, H-3), 5.50 (m, 2H, H-4), 5.74 (m, 2H, H-5), 6.66 (m, 2H, $^3J_{PH}$ 16.2 Hz, H-7), 7.26−7.39 (m, 10H, ArH), 7.46−7.53 (m, 6H, H-12, H-13), 7.91 (m, 4H, $^3J_{PH}$ 12.8 Hz, H-10). ^{13}C{^{1}H} NMR δ 25.76 (C-9), 27.65 (d, $^3J_{PC}$ 12.6 Hz, C-6), 41.70 (d, $^2J_{PC}$ 2.4 Hz, C-8), 46.25 (d, $^2J_{PC}$ 13.8 Hz, C-3a), 66.72 (d, $^2J_{PC}$ 12.0 Hz, C-3), 122.86 (d, $^3J_{PC}$ 6.0 Hz, C-4), 125.03 (C-5), 127.83 (C-15), 128.26 (C-17),

128.46 (d, $^3J_{PC}$ 13.2 Hz, C-12), 128.80 (C-16), 131.57 (d, $^4J_{PC}$ 2.4 Hz, C-13), 131.75 (d, $^2J_{PC}$ 10.8 Hz, C-11), 133.32 (d, $^1J_{PC}$ 120.7 Hz, C-7a), 133.85 (d, $^1J_{PC}$ 133.4 Hz, C-10), 134.88 (d, $^2J_{PC}$ 9.6 Hz, C-7), 138.65 (d, $^3J_{PC}$ 9.0 Hz, C-14). $^{31}P\{^1H\}$ NMR δ 28.76. MS (*m*/*z*) 669 (M + 1, 100). Anal. Calcd (%) for $C_{42}H_{42}N_2O_2P_2$: C, 75.43; H, 6.33; N, 4.19. Found: C, 75.02; H, 6.42; N, 3.94.

(1*R,3*S**,3a*R**)-2,2′-Butene-1,4-diylbis(1,3-diphenyl-2,3,3a,6-tetrahydro-1*H*-2,1-benzazaphosphol) 1,1′-Dioxide (12c_*rac*).** Yield after chromatography on neutral alumina (AcOEt/MeOH, 30:1) 14% (28 mg). Identified from a mixture of **9c**_*rac*:**9c**_*meso* (52:48). ^1H NMR δ 1.14 (m, 4H, H-9), 2.37−2.57 (m, 4H, H-8), 2.73−2.95 (m, 4H, H-6), 3.15 (m, 2H, H-3a), 4.05 (d, 2H, $^3J_{HH}$ 9.3 Hz, H-3), 5.50 (m, 2H, H-4), 5.75 (m, 2H, H-5), 6.66 (m, 2H, $^3J_{PH}$ 16.5 Hz, H-7), 7.25−7.40 (m, 10H, ArH), 7.47−7.52 (m, 6H, H-12, H-13), 7.88 (m, 4H, $^3J_{PH}$ 12.8 Hz, H-10). $^{13}C\{^1H\}$ NMR δ 25.68 (C-9), 27.64 (d, $^3J_{PC}$ 12.0 Hz, C-6), 41.91 (d, $^2J_{PC}$ 2.4 Hz, C-8), 46.16 (d, $^2J_{PC}$ 13.8 Hz, C-3a), 67.11 (d, $^2J_{PC}$ 12.0 Hz, C-3), 122.83 (d, $^3J_{PC}$ 6.6 Hz, C-4), 125.07 (d, $^4J_{PC}$ 1.2 Hz, C-5), 127.84 (C-15), 128.26 (C-17), 128.44 (d, $^3J_{PC}$ 13.2 Hz, C-12), 128.77 (C-16), 131.54 (d, $^4J_{PC}$ 3.0 Hz, C-13), 131.65 (d, $^2J_{PC}$ 10.2 Hz, C-11), 133.33 (d, $^1J_{PC}$ 120.7 Hz, C-7a), 133.99 (d, $^1J_{PC}$ 134.0 Hz, C-10), 134.88 (d, $^2J_{PC}$ 9.6 Hz, C-7), 138.75 (d, $^3J_{PC}$ 9.0 Hz, C-14). $^{31}P\{^1H\}$ NMR δ 28.84. MS (*m*/*z*) 669 (M + 1, 100). Anal. Calcd (%) for $C_{42}H_{42}N_2O_2P_2$: C, 75.43; H, 6.33; N, 4.19. Found: C, 75.32; H, 6.12; N, 4.34.

(1*R*$_P$*,3*S,3a*R**,6*R**,10*S**))-2-{4-[(1*S*$_P$*,3*R**,3a*S**)-1′,3′-Diphenyl-6′-hydroxyphenylmethyl-1′-oxide-2′,3′,3a′,6′-tetrahydro-1′*H*-2′,1′-benzazaphospholyl]butyl}-1,3-diphenyl-6-hydroxyphenylmethyl-2,3,3a,6-tetrahydro-1*H*-2,1-benzazaphosphol 1-Oxide (15a_*meso*).** Yield after chromatography (AcOEt/MeOH, 15:1) 70% (184 mg). Oil. ^1H NMR δ 1.14 (m, 4H, H-9), 2.49 (m, 2H, $^3J_{PH}$ 14.1 Hz, H-8), 3.00 (m, 2H, H-8′), 3.17−3.28 (m, 4H, H-3a, H-6), 3.15 (m, 2H, H-3a), 4.30 (d, 2H, $^3J_{HH}$ 8.5 Hz, H-3), 5.25 (sa, H-10), 5.53 (m, 2H, $^3J_{HH}$ 10.6 Hz, H-5), 5.72 (dd, 2H, $^3J_{HH}$ 10.6 Hz, $^4J_{PH}$ 4.0 Hz, H-4), 6.34 (sa, 1H, H-11, OH), 6.85 (m, 2H, $^3J_{PH}$ 17.3 Hz, H-7), 7.19−7.58 (m, 26H, ArH), 7.99 (ddd, 4H, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.8 Hz, $^3J_{PH}$ 12.9 Hz, H-13). $^{13}C\{^1H\}$ NMR δ 24.50 (C-9), 40.74 (C-8), 45.74 (d, $^3J_{PC}$ 12.0 Hz, C-6), 46.99 (d, $^2J_{PC}$ 14.4 Hz, C-3a), 65.82 (d, $^2J_{PC}$ 12.0 Hz, C-3), 74.31 (C-10), 124.37 (d, $^3J_{PC}$ 7.2 Hz, C-4), 124.68 (C-5), 125.87 (C-21), 126.59 (C-23), 127.92 (C-22), 128.11−128.78 (CHAr), 131.88 (d, $^4J_{PC}$ 3.6 Hz, C-15), 131.92 (d, $^2J_{PC}$ 10.2 Hz, C-13), 133.02 (d, $^1J_{PC}$ 116.7 Hz, C-12), 133.78 (d, $^1J_{PC}$ 119.5 Hz, C-7a), 138.44 (d, $^3J_{PC}$ 8.4 Hz, C-16), 139.64 (d, $^2J_{PC}$ 8.4 Hz, C-7), 142.83 (C-20). $^{31}P\{^1H\}$ NMR δ 28.67. MS (*m*/*z*) 881 (M + 1, 100). Anal. Calcd (%) for $C_{56}H_{54}N_2O_4P_2$: C, 76.35; H, 6.18; N, 3.18. Found: C, 76.28; H, 6.14; N, 3.25.

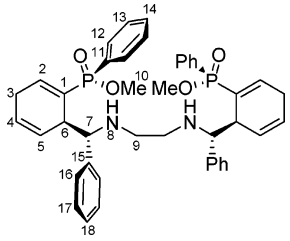
General Procedure for the Optimized Conditions for Monodearomatizing Anionic Cyclization of Bis(*N*-benzyl-*P*,*P*-diphenylphosphinamides) 8a. To a solution of **8a** (2.99×10^{-4} mol) in THF (30 mL) was added a solution of ^{s}BuLi (0.28 mL, of a 1.3 M solution in cyclohexane, 3.56×10^{-4} mol) at −90 °C. After 30 min of metalation was added MeOH (1 mL) or 2,6-di-*tert*-butyl-4-methylphenol (DTBMP) (199.6 mg, 8.97×10^{-4} mol). The reaction mixture was stirred at −90 °C for 30 min. Next, the reaction mixture was poured into ice water and extracted with ethyl acetate (3×15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. ^1H, $^1H\{^{31}P\}$, and $^{31}P\{^1H\}$ NMR spectra of the crude reaction were measured to determine the regio- and stereoselectivity of the process. The reaction mixture was then purified via flash column chromatography using a mixture of ethyl acetate:methanol, 15:1, as eluent.

***N*-{2-[-(1*R*$_P$*,3*R**,3a*S**,7a*S**)-1,3-Diphenyl-1-oxido-1,3,3a,7a-tetrahydro-2*H*-2,1-benzazaphosphol-2-yl]ethyl}-*N*-benzyl-*P*,*P*-diphenylphosphinic Amide (13a).** Yield after chromatography (AcOEt/MeOH, 15:1) 60% (115 mg). Oil. ^1H NMR δ 2.72−2.97 (m, 5H, H-3a, H-8, H-9), 3.04 (m, 1H, $^3J_{HH}$ 11.0 Hz, $^4J_{HH}$ 2.9 Hz, $^2J_{PH}$ 11.0 Hz, H-7a), 3.86 (dd, 1H, $^2J_{HH}$ 15.4 Hz, $^3J_{PH}$ 9.8 Hz, H-10), 4.07 (dd, 1H, $^2J_{HH}$ 15.4 Hz, $^3J_{PH}$ 10.3 Hz, H-10′), 4.10 (d, 1H, $^3J_{HH}$ 10.3 Hz, H-3), 5.27 (dddt, 1H, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 5.5 Hz, $^4J_{HH}$ 1.1 Hz, $^4J_{PH}$ 2.5 Hz, H-4), 5.88−5.98 (m, 2H, H-5, H-7), 6.09 (ddddt, 1H, $^3J_{HH}$ 9.4 Hz, $^3J_{HH}$ 5.3 Hz, $^4J_{HH}$ 2.9 Hz, $^4J_{HH}$ 0.9 Hz, $^4J_{PH}$ 0.9 Hz, H-6), 6.99 (ddd, 2H, $^3J_{HH}$ 7.7 Hz, $^4J_{HH}$ 1.3 Hz, $^4J_{HH}$ 1.3 Hz, H-20), 7.09−7.19 (m, 5H, ArH), 7.23−7.55 (m, 12H, ArH), 7.65 (ddd, 2H, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.1 Hz, $^3J_{PH}$ 12.5 Hz, H-12), 7.70 (ddd, 2H, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.5 Hz, $^3J_{PH}$ 12.8 Hz, H-16), 7.75 (ddd, 2H, $^3J_{HH}$ 6.8 Hz, $^4J_{HH}$ 1.3 Hz, $^3J_{PH}$ 11.9 Hz, H-16′). $^{13}C\{^1H\}$ NMR δ 37.60 (d, $^1J_{PC}$ 84.1 Hz, C-7a), 40.14 (dd, $^2J_{PC}$ 2.4 Hz, $^3J_{PC}$ 4.2 Hz, C-8), 43.46 (C-3a), 44.49 (d, $^2J_{PC}$ 3.0 Hz, C-9), 49.82 (d, $^2J_{PC}$ 3.0 Hz, C-10), 68.25 (d, $^2J_{PC}$ 21.0 Hz, C-3), 119.32 (d, $^2J_{PC}$ 8.4 Hz, C-7), 123.24 (d, $^3J_{PC}$ 11.4 Hz, C-4), 124.42 (d, $^4J_{PC}$ 3.6 Hz, C-5), 124.51 (d, $^3J_{PC}$ 10.2 Hz, C-6), 127.01 (C-24), 127.40 (C-20), 128.30 (d, $^3J_{PC}$ 11.4 Hz, CHAr), 128.37 (d, $^3J_{PC}$ 9.6 Hz, CHAr), 128.25−128.61 (5CHAr), 131.43 (d, $^2J_{PC}$ 10.2 Hz, C-12), 131.48 (d, $^1J_{PC}$ 135.8 Hz, C-15), 131.55 (d, $^1J_{PC}$ 131.6 Hz, C-15′), 131.61 (d, $^4J_{PC}$ 2.4 Hz, CHAr), 131.65 (d, $^4J_{PC}$ 3.0 Hz, CHAr), 131.80 (d, $^4J_{PC}$ 3.0 Hz, CHAr), 132.23 (d, $^2J_{PC}$ 9.0 Hz, C-16), 132.25 (d, $^2J_{PC}$ 9.0 Hz, C-16′), 133.25 (d, $^1J_{PC}$ 125.5 Hz, C-11), 137.50 (d, $^3J_{PC}$ 4.2 Hz, C-23), 139.05 (d, $^3J_{PC}$ 10.2 Hz, C-19). $^{31}P\{^1H\}$ NMR δ 30.92, 49.19. MS (*m*/*z*) 641 (M + 1, 100). Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 74.82; H, 6.10; N, 4.38.

***N*-{2-[(1*R*$_P$*,3*S**,3a*R**)-1,3-Diphenyl-1-oxido-1,3,3a,6-tetrahydro-2*H*-2,1-benzazaphosphol-2-yl]ethyl}-*N*-benzyl-*P*,*P*-diphenylphosphinic Amide (14a).** Yield after chromatography (AcOEt/MeOH, 15:1) 85% (163 mg). Oil. ^1H NMR δ 2.63−3.14 (m, 7H, H-3a, H-6, H-8, H-9), 3.88 (dd, 1H, $^2J_{HH}$ 15.3 Hz, $^3J_{PH}$ 7.4 Hz, H-10), 3.88 (d, 1H, $^3J_{HH}$ 9.3 Hz, H-3), 4.09 (dd, 1H, $^2J_{HH}$ 15.3 Hz, $^3J_{PH}$ 10.0 Hz, H-10′), 5.41 (m, 1H, H-4), 5.72 (m, 1H, H-5), 6.64 (m, 1H, H-7), 7.05 (m, 2H, H-20), 7.13 (m, 2H, H-24), 7.20 (m, 3H, ArH), 7.27−7.55 (m, 12H, ArH), 7.65−7.81 (m, 6H, H-12, H-16, H-16′). $^{13}C\{^1H\}$ NMR δ 27.65 (d, $^3J_{PC}$ 12.8 Hz, C-6), 39.92 (dd, $^2J_{PC}$ 2.8 Hz, $^3J_{PC}$ 4.0 Hz, C-8), 44.52 (d, $^2J_{PC}$ 3.0 Hz, C-9), 46.60 (C-3a), 49.68 (d, $^2J_{PC}$ 3.3 Hz, C-10), 67.26 (d, $^2J_{PC}$ 12.0 Hz, C-3), 122.60 (d, $^3J_{PC}$ 6.6 Hz, C-4), 125.10 (d, $^4J_{PC}$ 1.5 Hz, C-5), 127.03 (C-24), 127.67 (CHAr), 128.34 (CHAr), 128.35 (CHAr), 128.45 (d, $^3J_{PC}$ 9.3 Hz, CHAr), 128.48 (d, $^3J_{PC}$ 11.9 Hz, CHAr), 128.92 (CHAr), 131.46 (CHAr), 131.53 (d, $^1J_{PC}$ 127.7 Hz, CAr), 131.61 (d, $^4J_{PC}$ 1.7 Hz, CHAr), 131.65 (d, $^4J_{PC}$ 2.0 Hz, CHAr), 131.63 (d, $^1J_{PC}$ 128.4 Hz, CAr), 132.26 (d, $^2J_{PC}$ 9.0 Hz, CHAr), 132.29 (d, $^2J_{PC}$ 9.3 Hz, CHAr), 132.87 (d, $^1J_{PC}$ 120.6 Hz, CAr), 133.23 (d, $^1J_{PC}$ 132.6 Hz, CAr), 135.42 (d, $^2J_{PC}$ 9.6 Hz, C-7), 137.63 (d, $^3J_{PC}$ 4.4 Hz, C-23), 138.34 (d, $^3J_{PC}$ 8.4 Hz, C-19). $^{31}P\{^1H\}$ NMR δ 28.52, 30.89. MS (*m*/*z*) 641 (M + 1, 100). Anal. Calcd (%) for $C_{40}H_{38}N_2O_2P_2$: C, 74.99; H, 5.98; N, 4.37. Found: C, 74.92; H, 6.08; N, 4.32.

***N*-{3-[(1*R*$_P$*,3*S**,3a*R**)-1,3-Diphenyl-1-oxido-1,3,3a,6-tetrahydro-2*H*-2,1-benzazaphosphol-2-yl]propyl}-*N*-benzyl-*P*,*P*-diphenylphosphinic Amide (14b).** Yield after chromatography on silica gel-Et_3N (5%) (AcOEt/MeOH, 40:1) 22% (43 mg). Oil. ^1H NMR δ 2.33−2.98 (m, 8H, H-6, H-8, H-9, H-10), 3.18 (m, 1H, H-3a), 3.97 (dd, 1H, $^2J_{HH}$ 15.3 Hz, $^3J_{PH}$ 11.3 Hz, H-11), 4.04 (dd, 1H, $^2J_{HH}$ 15.3 Hz, $^3J_{PH}$ 10.9 Hz, H-10′), 4.06 (d, 1H, $^3J_{HH}$ 9.3 Hz, H-3), 5.53 (m, 1H, H-4), 5.79 (m, 1H, H-5), 6.70 (m, 1H, H-7), 7.15−7.62 (m, 19H, ArH), 7.71−7.95 (m, 6H, H-13, H-17, H-17′). $^{13}C\{^1H\}$ NMR δ 26.25 (d, $^3J_{PC}$ 3.6 Hz, C-9), 27.71 (d, $^3J_{PC}$ 12.6 Hz, C-6), 39.48 (d, $^2J_{PC}$ 3.0 Hz, C-8), 42.26 (d, $^2J_{PC}$ 3.6 Hz, C-10), 46.43 (d, $^2J_{PC}$ 13.2 Hz, C-3a), 48.82 (d, $^2J_{PC}$ 3.0 Hz, C-11), 66.55 (d, $^2J_{PC}$ 12.0 Hz, C-3), 122.78 (d, $^3J_{PC}$ 6.0 Hz, C-4), 125.16 (d, $^4J_{PC}$ 1.2 Hz, C-5), 127.11 (CHAr), 127.94 (CHAr), 128.33 (CHAr), 128. 39 (CHAr), 128.49 (CHAr), 128.51 (d, $^3J_{PC}$ 10.8 Hz, CHAr), 128.55, (d, $^3J_{PC}$ 9.0 Hz, CHAr), 128.58 (CHAr), 128.91 (CHAr), 131.56 (d, $^4J_{PC}$ 2.4 Hz, CHAr), 131.58 (d, $^4J_{PC}$ 1.8 Hz, CAr), 131.65 (d, $^2J_{PC}$ 10.8 Hz, CHAr), 131.75 (d, $^2J_{PC}$ 10.2 Hz, CHAr), 131.93 (d, $^1J_{PC}$ 129.2 Hz, CAr), 131.99 (d, $^1J_{PC}$ 129.2 Hz, CAr), 132.30 (d, $^2J_{PC}$ 9.0 Hz, CHAr), 132.40 (d, $^2J_{PC}$ 9.0 Hz, CHAr), 132.91 (d, $^1J_{PC}$ 120.2 Hz, CAr), 133.68 (d, $^1J_{PC}$ 133.4 Hz, CAr), 135.24 (d, $^2J_{PC}$ 9.6 Hz, C-7), 137.04 (d, $^3J_{PC}$ 3.6 Hz, C-23), 138.50 (d, $^3J_{PC}$ 8.4 Hz, C-19). $^{31}P\{^1H\}$ NMR δ 28.66, 31.27. MS (*m*/*z*) 655 (M +

CHART 4. Scheme Numbering Used for the NMR Assignments of Phenylphosphinate 16



1, 100). Anal. Calcd (%) for $C_{41}H_{40}N_2O_2P_2$: C, 75.21; H, 6.16; N, 4.28. Found: C, 75.24; H, 6.14; N, 4.30.

Synthesis of (R_P*) Methyl {(6*S)-6-[(*R**)-({2-[(*S**)-({(1*R**)-2-[(S_P*)-Methoxy(phenyl)phosphoryl]cyclohexa-2,5-dien-1-yl}-benzyl)amino]ethyl}amino)benzyl]cyclohexane-1,4-dien-1-yl}-Phenylphosphinate (16).** To a solution of **12a**_*meso* (0.16×10^{-3} mol, 0.100 g) in 6 mL of dry methanol was added 4 mL of a solution of 1 M HCl(g) in diethyl ether at room temperature, and the mixture was stirred for 50 min. Next, the pH was set to neutral by adding 1 N NaOH, and the reaction was extracted with ethyl acetate (3×15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording an oil 0.113 g (>97%) (Chart 4).

^{1}H NMR δ 1.38 (m, 2H, H-3), 2.32 (ddd, $^3J_{HH}$ 5.5 Hz, $^3J_{HH}$ 8.6 Hz, $^2J_{HH}$ 23.4 Hz, 2H, H-3′), 2.48 (m, 4H, H-9), 3.51 (m, 2H, H-6), 3.72 (d, $^3J_{PH}$ 11.0 Hz, 6H, H-10), 4.11 (d, 2H, $^3J_{HH}$ 4.2 Hz, H-7), 5.69 (dd, 2H, $^3J_{HH}$ 3.6 Hz, $^3J_{HH}$ 8.6 Hz, H-4), 5.90 (m, 2H, H-5), 6.54 (dd, 2H, $^3J_{HH}$ 4.9 Hz, $^3J_{PH}$ 19.8 Hz, H-2), 7.17 (s, 10H, H-16, H-17, H-18), 7.46−7.58 (m, 6H, H-13, H-14), 7.84 (m, 4H, H-12). ^{13}C{^{1}H} NMR δ 27.23 (d, $^3J_{PC}$ 13.8 Hz, C-3), 41.58 (d, $^2J_{PC}$ 12.0 Hz, C-6), 47.42 (C-9), 51.29 (d, $^2J_{PC}$ 6.0 Hz, C-10), 65.55 (C-7), 125.30 (d, $^3J_{PC}$ 9.6 Hz, C-5), 126.43 (C-18), 126.81 (C-17), 127.00 (d, $^4J_{PC}$ 1.2 Hz, C-4), 128.59 (d, $^3J_{PC}$ 13.2 Hz, C-12), 129.15 (C-16), 130.21 (d, $^1J_{PC}$ 131.6 Hz, C-1), 132.06 (d, $^2J_{PC}$ 9.6 Hz, C-12), 132.22 (d, $^4J_{PC}$ 3.0 Hz, C-14), 139.65 (C-15), 143.49 (d, $^2J_{PC}$ 8.4 Hz, C-2). ^{31}P{^{1}H} NMR δ 34.89. MS (*m*/*z*) 705 (M + 1, 100). Anal. Calcd (%) for $C_{42}H_{46}N_2O_4P_2$: C, 71.58; H, 6.58; N, 3.97. Found: C, 72.23; H, 7.05; N, 4.32.

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Supporting Information Available: ^{13}C, DEPT135, and 2D gNOESY spectra of **11a-c**_*meso*, **11a**_*rac*, **12a-c**_*meso*, **12c**_*rac*, **13a**, **14a**, and **15a**_*meso*, molecular view of **11a**_*meso*, and X-ray data of **11c**_*meso* and **12a**_*meso*. This material is available free of charge via the Internet at http://pubs.acs.org.

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