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Dearomatizing Anionic Cyclization of *N*-Alkyl-*N*-benzyl(dinaphthyl)phosphinamides. A Facile Route to γ-(Amino)dihydronaphthalenylphosphinic Acids

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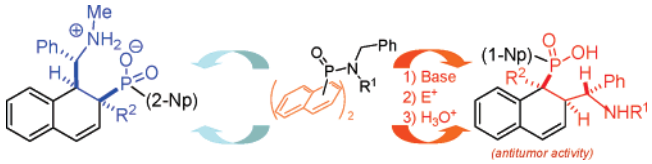
Received August 9, 2007



The dearomatizing anionic cyclization of *N*-alkyl-*N*-benzyldi(*n*-naphthyl)phosphinamides ($n = 1, 2$) and subsequent trapping with a series of electrophiles (MeOH, MeI, CF_3SO_3Me, $Me_3O^+BF_4^-$, AllylBr, and $PhCH_2Br$) have been accomplished. Optimized reaction conditions (base, temperature, reaction time) allow for synthesizing tetrahydro-1*H*-naphtho[1,2-*c*][1,2]-azaphosphole 1-oxides **13** and **18** and tetrahydro-1*H*-naphtho[2,1-*c*][1,2]azaphosphole 3-oxides **16** and **27**−**29** in high yield and diastereoselectivity. Appropriate selection of the base proved to be critical for promoting anionic cyclization of 2-naphthyl derivatives. The dearomatized heterocycles are transformed quantitatively into γ-(*N*-alkylamino)phosphinic acids by acid hydrolysis of the P−N linkage. Bioactivity assays on five human tumor cell lines for one of these amino acids revealed growth inhibition factors (GI_{50}) at a micromolar scale. Additionally, evidence for the feasibility of intermolecular nucleophilic dearomatization and sequential nucleophilic attack to both aromatic rings of dinaphthylphosphinamides have been obtained.

Introduction

Many natural products and compounds of pharmaceutical importance consist of a partially saturated carbocyclic or heterocyclic system which imparts some rigidity to the molecule and acts as a scaffold to which a variety of functional groups are connected. This architecture provides the harmonious combination of conformational preferences and spatial arrangement of substituents appropriated for eliciting a biological response.[1] Nucleophilic dearomatizing reactions (N_DAr),[2] i.e., the conjugate addition of a nucleophile to an aromatic ring, constitute an attractive approach for the regio- and stereocontrolled formation of hydroaromatic compounds incorporating different degrees of functionalization.[3] The nucleophilic attack can occur either inter- or intramolecularly, the latter process being called dearomatizing anionic cyclization (DAC).[2,4] Drozd and co-workers discovered the feasibility of DAC reactions almost 40 years ago when investigating the lithiation of aryl mesityl sulfones.[5] However, the synthetic scope of these transformations was rather limited.[6] The boost of DAC methodology as a useful synthetic tool in organic chemistry started in the late 1990s with the work of Clayden's group on tertiary arylcarboxamides.[7] The anionic cyclization of *N*-benzylic

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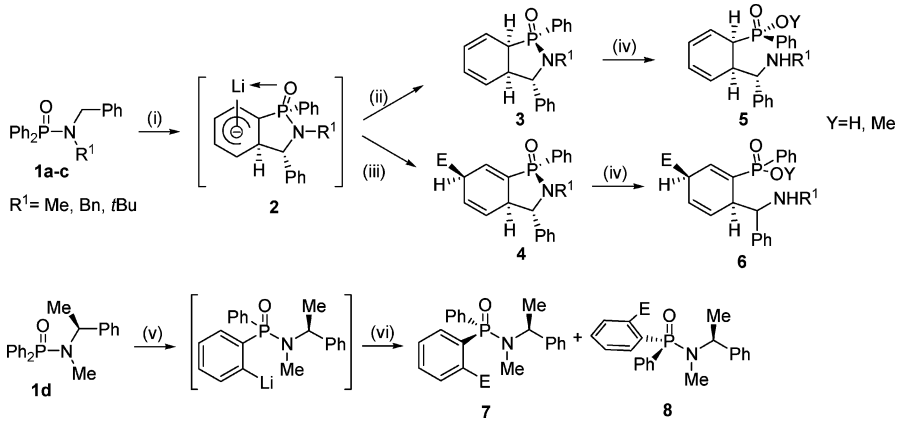
10.1021/jo701607s CCC: $37.00
Published on Web 11/03/2007

SCHEME 1[a]



[a] Conditions: (i) *s*BuLi (1.5−2.5 equiv), HMPA or DMPU (6 equiv), THF, −90 °C, 0.5−12 h; for **1d** *t*BuLi, HMPA or DMPU (6 equiv), THF, −90 °C, 1 min to 12 h; (ii) MeOH (5.0 equiv), −90 °C, 0.5 h; (iii) E^+ = DTBMP, RX, or RCHO, −90 °C, 0.5−2 h; (iv) 2 N HCl (aq), Me_2CO or 0.6 N HCl (g), MeOH, rt; (v) *t*BuLi, THF, −90 °C, 2 h; (vi) E^+ = MeI, PhCHO, Me_3SnCl, $(nBu)_3SnCl$, Ph_3SnCl.

phenyl and naphthyl carboxamides furnished dihydroaromatic products containing a pyrrolid-2-one fragment that proved to be valuable starting materials for the synthesis of natural products of the kainic acid family[8] and some non-natural analogues.[9]

The essentials of DAC methodology are the existence of acidic protons, generally of benzylic type, in the proximity of an electron-withdrawing group linked to an aromatic ring. This group directs the approach of the base to the deprotonation site without suffering nucleophilic addition and, at the same time, activates the aromatic ring toward the subsequent intramolecular attack of the carbanion formed. *N*-Benzylphosphinamides fulfill nicely these criteria. We have shown that *N*-alkyl-*N*-benzyldiphenylphosphinamides **1a**−**c** can be lithiated at the benzylic position upon treatment with *s*BuLi in THF in the presence of HMPA or DMPU. The NC_α anions formed undergo anionic cyclization by Michael addition to the ortho position of the *P*-phenyl ring leading to dearomatized species,[10] which were trapped with a series of electrophiles affording tetrahydro-2,1-benzazaphospholes **3** and **4** with high regio- and stereocontrol (Scheme 1).[11] DAC reactions of chiral phosphinamides (e.g., **1d**) and subsequent alkylation proceed with very high enantioselectivity.[12] The dearomatized products **3** and **4** were readily transformed into the corresponding γ-aminophosphinic acids **6** and **7** by solvolysis of the P−N linkage. This family of compounds showed interesting antitumor properties.[13]

Mechanistic studies[14] have shown that the PO linkage of phosphinamides **1** direct the lithiation in THF at both the *ortho* and benzylic positions. The coordinating cosolvent (HMPA or DMPU) seems to catalyze the conversion of the *ortho* anion into the corresponding benzylic species that cyclize to the phosphorus-stabilized lithium intermediate **2**. Interestingly, in the absence of HMPA or DMPU tertiary diphenylphosphinamides can be deprotonated at the *ortho* position almost quantitatively and trapped very efficiently with a variety of electrophiles to give *ortho* functionalized phosphinamides **7** and **8** with low to moderate regioselectivity (Scheme 1).[15]

Naphthalenes are known to be less reluctant to nucleophilic addition than benzenes.[2] Furthermore, the introduction of a dihydronaphthalene fragment would be very interesting taking into account that dihydronaphthalenes are useful skeletons for the synthesis of biological active molecules.[1,2,16] In a preliminary communication we have reported that the nucleophilic dearomatization of *N*-alkyl-*N*-benzyldi(1-naphthyl)phosphinamides affords new benzo[*e*]-1-phosphisoindoles in high yield and

(4) For reviews, see: (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, The Netherlands, 2002. (b) Mealy, M. J.; Bailey, W. F. J. *Organomet. Chem.* **2002**, *646*, 59. (c) Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721. For some recent examples, see: (d) Monje, P.; Graña, P.; Paleo, M. R.; Sardina, F. J. *Org. Lett.* **2006**, *8*, 951. (e) Wang, Z.; Xi, Z. *Synlett* **2006**, 1275. (f) Nishiwaki, K.; Ogawa, T.; Tagami, K.-I.; Tanabe, G.; Muraoka, O.; Matsuo, K. *Tetrahedron* **2006**, *62*, 10854. (g) Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. *J. Org. Chem.* **2007**, *72*, 3484.

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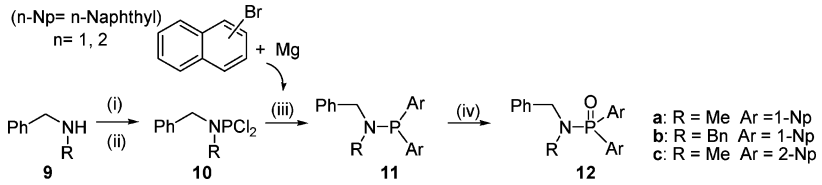
SCHEME 2 [a]



[a] Conditions: (i) *n*BuLi, THF, −30 °C, 30 min; (ii) PCl_3 (2 equiv), THF, −30 °C, 45 min; (iii) ArMgBr (Ar = 1- or 2-naphthyl) (2.15 equiv), THF−Et_2O, rt, 1 h; (iv) *m*CPBA, CH_2Cl_2, 0 °C, 30 min.

diastereoselectivity.[17] In contrast to diphenylphosphinamides, the process can be performed very efficiently in the absence of coordinating additives without observing products derived from *ortho* lithiation. We describe here the detailed study of the dearomatizing anionic cyclization−electrophilic quench sequence of 1-naphthyl- and 2-naphthylphosphinamides. The dearomatized anions generated in the DAC reaction were trapped with methanol as protonating agent and with a series of alkylating agents. The reaction conditions were optimized for each electrophile, and the results are compared with those obtained for diphenylphosphinamides. The elaboration of the new azaphosphol derivatives formed into the corresponding γ-aminophosphinic acids is examined. In addition, preliminary anticancer assays on one of the new dihydronaphthyl γ-aminophosphinic acids obtained are also shown.

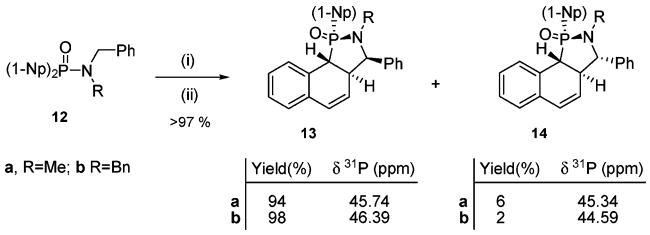
Results and Discussion

The starting phosphinamides **12a**−**c** were synthesized through the three step process shown in Scheme 2:[17] (i) preparation of dichloroaminophosphines **10** through reaction of the appropriate lithiated amine with PCl_3; (ii) condensation of **10** with 1-naphthyl or 2-naphthylmagnesium bromide to give diarylaminophosphines **11**; and (iii) oxidation of **11** by treatment with *meta*-chloroperbenzoic acid (*m*CPBA). Compounds **10a**,**b** have been previously synthesized through reaction of PCl_3 with the corresponding benzylamine. However, neither yields nor the full characterization of these compounds were given.[18] In our hands, the use of this methodology[19] afforded a mixture of mono- and di-addition products after a tedious workup. We found that dichloroaminophosphines **10** can be prepared in almost quantitative yields by allowing the reaction of 2 equiv of phosphorus trichloride with a solution of the lithium benzylamine resulting from the deprotonation of the corresponding benzylamine **9** with *n*BuLi in THF at −30 °C for 30 min. The ^{1}H and ^{31}P NMR spectra of the crude products indicated purities higher than 97%. Therefore, the compounds were used without additional purification. The condensation of dichlorophosphines **10** with an excess of 1-naphthyl- or 2-naphthylmagnesium bromide[20] at room temperature was monitored through ^{31}P NMR. The conversion of **10** into **11** is evidenced by an upfield shift of ca. 100 ppm. The dinaphthylphosphinamines **11** thus formed were isolated as syrups stable to air and were quantitatively transformed into phosphinamides **12** upon oxidation with *m*-chloroperbenzoic acid[21] at 0 °C (Scheme 2). Yields and ^{31}P NMR data of compounds **10**−**12** are given in Table 1.

TABLE 1. Isolated Yields and ^{31}P NMR Data of Compounds 10−12

product	R	Ar	yield (%)	δ^{31}P (ppm)
10a	Me		>97	164.08
10b	Bn		77	161.07
11a	Me	1-Np	94	56.03
11b	Bn	1-Np	88	54.71
11c	Me	2-Np	80	68.55
12a	Me	1-Np	>97	39.66
12b	Bn	1-Np	>97	40.38
12c	Me	2-Np	96	32.97

SCHEME 3 [a]



[a] Conditions: (i) *s*BuLi (2.5 equiv), THF, −90 °C, 30 min; (ii) MeOH (2 mL), −90 °C, 20 min.

Dearomatization−Protonation Studies. First, we investigated the DAC reactions of 1-naphthylphosphinamides. Lithiation of compounds **12a**,**b** by reaction with 2.5 equiv of *s*BuLi in THF at −90 °C for 30 min, followed by quenching with methanol at the same temperature, led to the formation of the phosphorus-containing tricyclic systems **13** showing a *trans* 6,5-ring junction in very high yield, together with small amounts (2 − 6%) of the epimer at the NC_α carbon, **14** (Scheme 3). The diastereoselectivity of the process improves with increasing the bulkiness of the R substituent linked to the nitrogen. Thus, the ratio **13a**:**14a** of 94:6 for R = Me increases to 98:2 for **13b**:**14b**, where R = $PhCH_2$. The dearomatized products **13a**,**b** were purified by precipitation from diethyl ether. Crystals of **13a** suitable for X-ray analysis were grown by recrystallization from a mixture of dichloromethane, acetonitrile, and tetrahydrofurane at room temperature (see Supporting Information for structural data). Compound **14a** could be isolated through column chro-

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(18) (a) For **10a** (bp 165 °C/0.15 Torr), see: Imbery, D.; Friebolin, H. *Z. Naturforsch. B* **1968**, *23*, 759. (b) For **10b** (δ (^{31}P, 30% $CHCl_3$) = 138.1 ppm), see: Gouesnard, J. P.; Dorie, J.; Martin, G. J. *Can. J. Chem.* **1980**, *58*, 1295.

(19) PCl_3 was added to a toluene solution of *N*-methylbenzylamine and triethylamine (2.5 equiv) at −78 °C, and the mixture was stirred for 30 min at this temperature.

(20) For other examples of Grignard addition to aminodichlorophosphines, see: (a) Burg.; A. B.; Slota, P. J., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 1107. (b) Strecker, R. A.; Snead, J. L.; Sollot, G. P. *J. Am. Chem. Soc.* **1973**, *95*, 210.

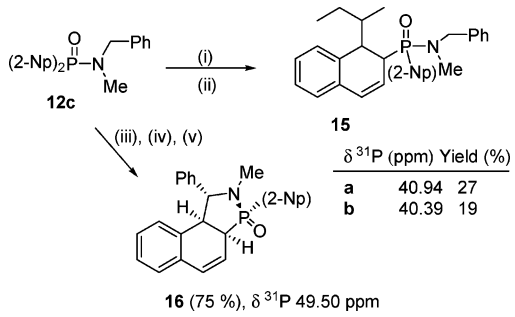
(21) Alternatively, the oxidation can be also performed with H_2O_2.

TABLE 2. Distribution of Products Obtained in the Dearomatization−Alkylation of Dinaphthylphosphinamides 12a,b

	SM	EX	*T* (°C)	*t* (h)	**18**	**19**	**20**	**21**	**22**	**23**
1	**12a**[a]	MeI	−90	2	42 (**a**)	6 (**a**)	1 (**a**)		24	
2	**12a**[b]	MeI	−90	2	43 (**a**)	6 (**a**)	2 (**a**)		6	
3	**12a**[c]	MeI	−90	2	64 (**a**)	9 (**a**)	4 (**a**)			
4	**12a**[d]	MeI	−90	8	76 (**a**)	7 (**a**)	3 (**a**)	−	−	−
5	**12a**	CF_3SO_3Me	−90	8	89 (**a**)	4 (**a**)	−	9 (**a**)[e]	−	−
6	**12a**[f]	Me_3OBF_4	−90	14	51 (**a**)	2 (**a**)	4 (**a**)	−	1	3
7	**12a**[g]	Me_3OBF_4	−30	8	64 (**a**)	13 (**a**)	16 (**a**)	−	−	−
8	**12b**[h]	MeI	−90	8	11 (**b**)	3 (**b**)	−	−	−	−
9	**12b**	MeI	−30	8	78 (**b**)	10 (**b**)	4 (**b**)	−	−	−
10	**12b**[i]	CF_3SO_3Me	−30	8	30 (**b**)	20 (**b**)	−	29 (**b**)[j]	−	−
11	**12b**[k]	Me_3OBF_4	−30	8	41 (**b**)	15 (**b**)	27 (**b**)	−	−	−
12	**12a**	$CH_2{=}CHCH_2Br$	−30	23	41 (**c**)	5 (**c**)	−	11 (**c**)	28	1

[a] HMPA (6 equiv) was used as cosolvent. A total of 6% and 3% of dearomatized compounds **13a** and **13b** were also obtained. [b] A total of 19% of **13a** was isolated. [c] TMEDA (6 equiv) was used as cosolvent. A total of 13% and 1% of dearomatized compounds **13a** and **13b** were also detected. [d] Only 2% of **13a** was formed. [e] Not isolated. [f] A total of 15% of dearomatized protonation products was also formed. [g] Small amounts of **13a** (5%) and **13b** (2%) were isolated. [h] The major product formed was **13b** (73%). [i] The NMR spectra for the reaction crude showed the presence of two other diastereomers in percentages of 8% and 2%. [j] A total of 9% of **13b**. [k] Minor amounts (∼5%) of the products corresponding to the 1,4-conjugated addition of the organolithium to the phosphinamide were also detected.

SCHEME 4[a]



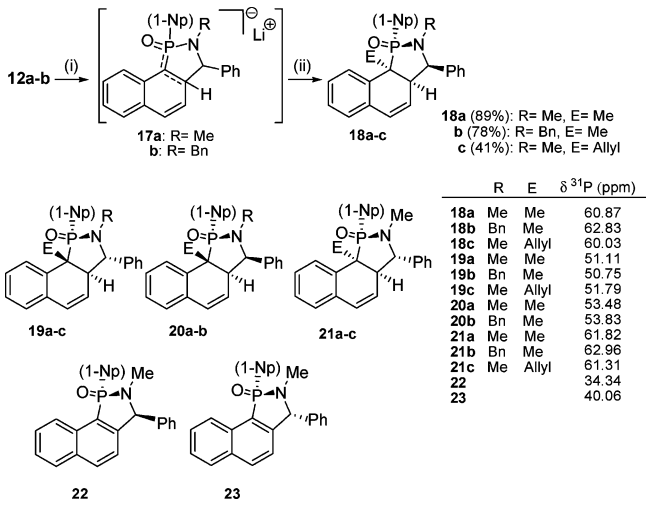
[a] Conditions: (i) *s*BuLi (2.5 equiv), THF, HMPA (6 equiv), −90 °C, 30 min; (ii) MeOH, −90 °C, 20 min; (iii) LDA (2.5 equiv), THF, −85 °C to −30 °C, 1.5 h; (iv) −30 °C, 1 h; (v) MeOH, −30 °C, 20 min.

matography (eluent: ethyl acetate/hexane 1:1). The very small amount of benzo-1-phosphaisoindol **14b** formed did not allow its isolation. It was identified from the crude reaction mixture.[22]

Compared with the DAC reactions of diphenylphosphinamides **1**,[11] and arylcarboxamides,[7a,8a] the nucleophilic dearomatization−protonation of naphthylphosphinamides **12a**,**b** shows two notable differences. First, the anionic cyclization of lithiated **12a**,**b** occurs almost quantitatively without the requirement of a coordinating cosolvent. Moreover, addition of HMPA during the metalation step proved to be detrimental for the process. After protonation with methanol, a mixture of seven products is obtained and the yield of **13a** decreases until 73%. Second, the annelation of the five-membered ring to the desaromatized naphthalene system takes place with a *trans* stereochemistry exclusively. The preference for the *trans* junction may be explained by assuming that the methanol approach to the carbanionic center is under the control of the P−O linkage through hydrogen-bonding formation.

Next, as a logical extension, we decided to apply the DAC-protonation methodology developed for 1-naphthylphosphinamides to the 2-naphthyl derivative **12c**. Unfortunately, under the reaction conditions shown in Scheme 3 for phosphinamides **12a**,**b**, the isomer **12c** furnishes a very complex mixture of

SCHEME 5[a]



[a] Conditions: (i) *s*BuLi (2.5 equiv), THF, *T* (°C), 30 min; (ii) EX (2.5 equiv), *T* (°C), *t* (h).

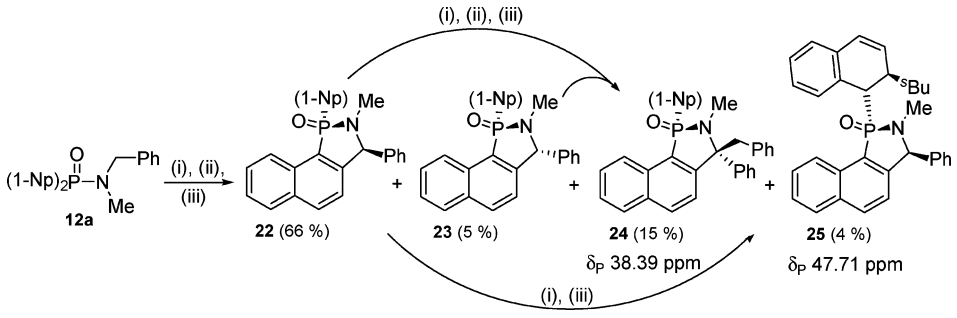
products, as evidenced by the ^1H and ^{31}P NMR spectra of the crude reaction mixture. When the lithiation with *s*BuLi is realized in the presence of HMPA, the conversion reaches 91%. Careful column chromatography of the crude reaction mixture allowed the isolation of dihydronaphthalenes **15** in a yield of 46% as a mixture of diastereoisomers in a ratio of 59:41, coeluting with phosphinamide **12c** (Scheme 4). Compounds **15** are the [1,4] conjugated addition products resulting from the attack of the organolithium base to the α position of phosphinamide **12c**.[22] The relative configuration of the sterogenic centers of **15** could not be established unequivocally. Attempts of promoting the anionic cyclization of **12c** by using alternative protonating agents[23] and increasing the temperature of the reaction to −30 °C, were unsuccessful.

Dihydronaphthalenes **15** represent the first examples of an intermolecular nucleophilic dearomatizing reaction of an arylphosphinamide.[2] However, the performance of this N_DAr reaction is very modest both in terms of yield and degree of structural diversity that may be achieved. To avoid the direct attack of

(22) The structures of all new compounds were assigned based on their spectroscopic data: APCI-MS and 1D (^1H, ^{13}C, ^{31}P, DEPT, selective gTOCSY) and 2D (gCOSY45, gHMQC, gHMBC, and gNOESY) NMR experiments. See Supporting Information for structural characterization.

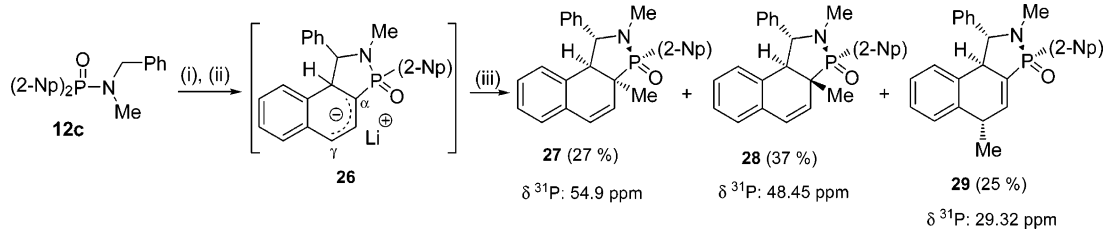
(23) 2,6-di-*tert*-Butil-4-methylphenol, *tert*-butanol, *p*-toluensulphonic acid, and ^{t}BuCONHCHMe$_2$ were also used as the proton source.

SCHEME 6 [a]



[a] Conditions: (i) *s*BuLi (2.5 equiv), THF −90 °C, 30 min; (ii) $PhCH_2Br$ (2.5 equiv), −90 °C, 8 h; (iii) H_2O.

SCHEME 7 [a]



[a] Conditions: (i) LDA (2.5 equiv), THF, −85 °C to −30 °C, 1.5 h; (ii) −30 °C, 1 h; (iii) MeI (2.5 equiv), −30 °C, 12 h.

the alkyl-lithium base to the 2-naphthyl ring of **12c** we explored the feasibility of using the non-nucleophilic and bulky base LDA as deprotonating agent. Clayden and co-workers showed that lithium amides metalate tertiary *N*-benzyl-arylcarboxamides at the NC_α position and that the anions undergo dearomatizing anionic cyclization very efficiently.[24] We were pleased to see that the deprotonation of **12c** with LDA in THF in the temperature range of −85 to −30 °C, followed by quenching with methanol at −30 °C, provided the anticipated dearomatized heterocycle **16** in high yield and selectivity (Scheme 4). Similar to the analogous DAC reaction of naphthylcarboxamides, the product with a *cis* 6,5-ring junction is exclusively formed.[24a] Purification of benzophosphaisoindol **16** was achieved by flash chromatography.[22]

Dearomatization−Alkylation Studies. In order to expand the scope of the dearomatizing anionic cyclization reactions of dinaphthylphosphinamides **12a**−**c**, the electrophilic quenching with several alkylating agents was also investigated. The results obtained in the DAC−alkylation process using MeI, CF_3SO_3Me, $Me_3O^+BF_4^-$, AllylBr, and BnBr are shown in Schemes 5−8 and Table 2.

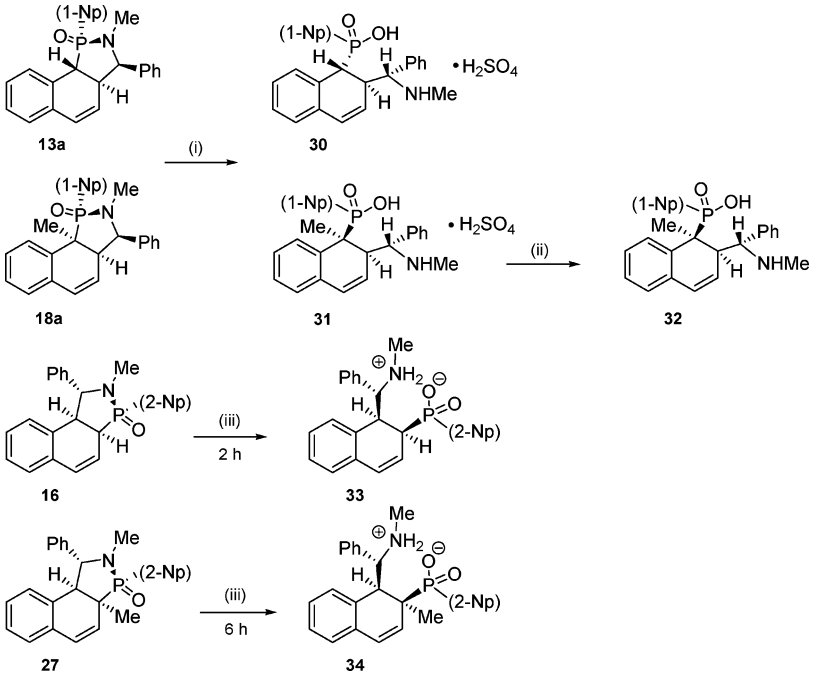
Three reagents, MeI, CF_3SO_3Me, and $Me_3O^+BF_4^-$, were evaluated for installing a methyl group adjacent to the phosphorus atom of the dearomatized anions **17a**,**b** formed in the benzylic deprotonation of **12a** and **12b**. In all cases, heterocycles **18a**,**b** are the major products formed. They were isolated by precipitation from diethyl ether.[22] Compound **18b** could be recrystallized from a mixture of ethanol, dichloromethane, and hexane at room temperature. The crystal structure obtained through X-ray diffraction is given as Supporting Information. After some optimization, we find out that methylation of **17a** (R = Me) with MeI at −90 °C for 8 h affords **18a** in high yield and with high stereoselectivity (Table 2, cf. entries 1−4). However, at this temperature the analogous reaction of dearomatized **17b** (R = Bn) furnishes **18b** in very low yield (11%, entry 8). Fortunately, at −30 °C anions **17b** undergo addition to MeI very efficiently to give **18b** in 78% yield. Methylations with harder electrophiles produced a beneficial effect only for the reaction of **17a** with CF_3SO_3Me. The dearomatization is quantitative, and the amount of **18a** obtained increases to 89% (entry 5). The ^{31}P NMR spectrum of the crude mixture showed the presence of a new stereoisomer in 7% yield, tentatively assigned to product **21** (Scheme 5) based on the magnitude of the ^{31}P chemical shift (δ_P 61.82 ppm, see Chart S1, Supporting Information). Under the reaction conditions optimized for quenching with MeI, the methylations of **17b** with CF_3SO_3Me and of **17a**,**b** with $Me_3O^+BF_4^-$ proceed with low yield and/or stereocontrol. Increasing the temperature or the reaction time (entries 6, 7) does not produce significant improvements. These results indicate that $Me_3O^+BF_4^-$ reacts in a more indiscriminate manner[25] as compared with the other methylating reagents and that bulky R substituents linked to the nitrogen hinder the approach of the electrophile to the carbanionic center.

Alkylation of **17a** by reaction with allylbromide revealed the existence of two competing pathways, electrophilic trapping of the dearomatized anion and oxidation of the anion restoring the aromaticity of the naphtlyl ring. High conversions are observed when the process is accomplished at −30 °C for 23 h. In this way, dearomatized allylheterocycle **18c** is obtained in moderate yield (41%) together with isomers **19** (5%) and **21** (11%) and significant amounts of the rearomatized derivative **22** (28%) (Scheme 5, Table 2, entry 12).[22] Additionally, compound **23** epimer of **22** at the NC_α carbon was barely detectable in the ^{31}P NMR spectrum of the crude mixture. Rearomatization becomes the dominant process when anion **17a** is allowed to react with benzyl bromide. Under the reaction conditions optimized for the methylation with MeI (THF, −90 °C, 8 h),

(24) (a) Clayden, J.; Menet, C. J.; Mansfield, D. *Org. Lett.* **2000**, *2*, 4229. (b) Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett* **2001**, 302. (c) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38. (d) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059.

(25) In the reaction of **17a** with $Me_3O^+BF_4^-$, small amounts of rearomatized byproducts **22** and **23** are also formed (Table 2, entry 6).

SCHEME 8 [a]



[a] Conditions: (i) 4.5 N H_2SO_4, dioxane (1:1), reflux, 8 h; (ii) 1 N NaOH; (iii) 2 N HCl, acetone, rt, then 1 N NaOH.

the treatment of **17a** with BnBr provides a mixture of 2,3-dihydro-1*H*-naphtho[1,2-*c*][1,2]azaphosphole 1-oxides **22** (66%), **23** (5%), **24** (15%), and **25** (4%) (Scheme 6). The benzylation of **17a** at −30 °C affords similar results. Isolation of these compounds was achieved by flash chromatography (ethyl acetate:hexane, 1:1).[22] Compounds **22** and **23** represent the two possible diastereoisomers generated in the rearomatization of **17a**. The stereogenic centers of the major isomer **22** show the same relative configuration observed for the major dearomatized products **13** and **18**.

The formation of heterocycles **24** and **25** can be explained by the action of the excess of reagents used on **22** or **23**. Successive NC_α deprotonation−benzylation of **22** (alkylation with inversion of configuration) or **23** (alkylation with retention of configuration) leads to **24**, whereas compound **25** results from the N_DAr process consisting of the addition of *s*BuLi to the *ortho* position of the naphthyl ring of **22**, activated by the phosphinamide moiety, followed by protonation. As far as we know, heterocycle **25** constitutes the first example of a tandem process on a diaryl system in which one aromatic ring undergoes anionic cyclization while the other is dearomatized by nucleophilic addition.[2] Although only small amounts of heterocycles **24** and **25** are generated, their presence may help to shed light on the rearomatization process. The synthesis of these two compounds implies that rearomatization occurs prior to workup. Aromatization byproducts have been previously detected in the DAC reaction and subsequent alkylation of diphenylphosphinamides.[11a,c] In this case, the presence of HMPA may contribute to accelerate the departure of a hydride anion necessary for rearomatization.[26] However no additives intervene in the formation of **24** and **25**. We suggest that the distribution of alkylated dearomatized products and rearomatized compounds result from a balance between competing *C*- vs *O*-alkylation of the intermediate phosphorus-stabilized anions formed in the DAC step. *C*-Alkylation leads to stable dihydroaromatic systems, whereas the *O*-alkylated derivatives evolve via rearomatization under the reaction conditions used.[11d,27] For brominated electrophiles, oxidation promoted by a small release of bromine could also be operative.

The DAC−alkylation process was extended to *N*-benzyl-*N*-methyl-(2-naphthyl)phosphinamide **12c**. The lithiation with LDA and subsequent addition of MeI at −30 °C provides a mixture of tetrahydro-1*H*-naphtho[2,1-*c*][1,2]azaphosphole 3-oxides **27**, **28**, and **29** in a yield of 89% and in a ratio of 30:42:28 (Scheme 7).[22] Compounds **27** and **28** arise from MeI attack to both faces of anion **26** at the α-position with respect to the phosphorus. The regioisomer **29** represents the product of methylation through the γ-position of the allylic anion **26**. Heterocycles **27**−**29** were purified through flash column chromatography.

Synthesis of Naphthalenyl γ-Aminophosphinic Acids. We have previously shown that intramolecular anionic dearomatizing processes of *N*-alkyl-*N*-benzyldiphenylphosphinamides constitute a useful strategy for synthesizing conformationally constrained functionalized γ-aminophosphinic acids.[11,12] These are compounds of a great interest due to the relevance of their biological properties.[13,28] To ascertain the utility of the present metholodology for the synthesis of γ-(*N*-alkylamino)(dihydronaphthalenyl)phosphinic acids, the dearomatized compounds **13a**, **16**, **18a**, and **27** were submitted to acid hydrolysis. In contrast to benzazaphospholes **3** and **4** (Scheme 1), which are readily hydrolyzed upon treatment with dilute hydrochloric acid

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(28) (a) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Franz, J. E.; Villafranca, J. J.; Dilanni, C. L.; Colanduoni, J. I.; Li, B.; Schineller, J. B. *Biochemistry* **1990**, *29*, 366. (b) Kukhar, V. P.; Hudson, H. R., Eds. *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; John Wiley: New York, 2000. (c) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.−Anti-Cancer Agents* **2001**, *1*, 301.

at ambient temperature,[11a,b,] rupture of the P−N bond of compounds **13a** and **18a** required heating under reflux a solution of the heterocycles in a mixture of dioxane and 4.5 N aqueous H_2SO_4 (1:1) during 8 h.[29] In this way, γ-aminophosphinic acids **30** and **31** (δ_P (DMSO-d_6) 26.25 and 36.60 ppm, respectively) are quantitatively obtained as the corresponding sulfates.[17] Neutralization of **31** by treatment with 1 N NaOH allows the isolation of the free amino acid as zwitterion **32** (Scheme 8). Hydrolysis of **16** and **27**, however, could be smoothly achieved by reaction with 2 N aqueous HCl in acetone at room temperature.[30] After neutralization with 1 N NaOH the respective γ-aminophosphinic acids **33** and **34** are isolated in quantitative yield (Scheme 8).[22]

Preliminary antitumor studies reveled that naphthalenyl γ-aminophosphinic acid **32** showed promising growth cell inhibition levels against five human tumor cell lines. The in vitro GI_{50} (μM) values obtained are as follows: prostate (LNcaP) 0.85, breast (SK-BR3) 8.7, leukemia (K-562) 8.32, pancreas (PANC1) 9.39, and cervix (HELA) 2.76.

Conclusions

Optimized conditions have been found for the dearomatization anionic cyclization of *N*-alkyl-*N*-benzyldinaphthylphosphinamides. DAC reactions of 1-naphthyl derivatives can be achieved expeditiously by metalation with *s*BuLi at low temperatures. 2-Naphthylphosphinamides undergo anionic cyclization when the deprotonation is carried out with LDA. In contrast to diphenylphosphinamides, the cyclization reactions do not require the use of additives such as HMPA or DMPU. Quenching the dearomatized anions with methanol, MeI, or CF_3SO_3Me affords tetrahydronaphthoazaphosphole oxides in high yields and diastereoselectivities. Slight differences in the performance of these transformations are assigned to the influence of the bulkiness of the substituent linked to the nitrogen. Electrophilic trapping with allylBr leads to a mixture of dearomatized allylated products and rearomatized naphthalenyl derivatives. The latter are exclusively obtained when benzyl bromide is used as electrophile. The evolution of the dearomatized anions through these two pathways is explained by the participation of competing *C*- and *O*-alkylation processes. Although naphthylphosphinamides are lithiated in the absence of coordinating cosolvents, products of *ortho* metalation are not detected. This is a significant difference with the DAC reactions of diphenylphosphinamides. Additionaly, the formation of some minor byproducts suggests that intermolecular D_NAr reactions and sequential double dearomatization of both aromatic rings bonded to a phosphinamide moiety may be feasible. The new dearomatized products obtained are quantitatively converted into γ-(*N*-alkylamino)phosphinic acids by hydrolysis of the P−N linkage present in the azaphosphole system. The connection of the amino and phosphinic acid groups to a dihydronaphthalene ring may contribute to reduce the conformational mobility of the system. These motional constraints are important features for applications in peptidomimetic chemistry. The evaluation of γ-aminophosphinic acid **32** as an antitumor agent shows promising results, with GI_{50} values in the range of 0.85−9.39 μM for five human tumor cell lines.

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Experimental Section

For general experimental and X-ray data, see Supporting Information.

Synthesis of Dichlorophosphinamines 10a,b. To a solution of *N*-methyl-*N*-benzylamine (13.5 mmol) or *N*,*N*-dibenzylamine (10.1 mmol) in THF (50 mL) was added a solution of *n*BuLi (8.44 mL/6.30 mL of a 1.6 M solution in hexane, 13.5 mmol/10.1 mmol) at −30 °C. After 30 min of stirring at this temperature, a solution of phosphorus trichloride (2.70 mmol/20.2 mmol) in THF (5 mL) was added. This reaction mixture was stirred at −30 °C for 45 min. Then, the generated LiCl was filtered under inert atmosphere, and the THF and the excess of PCl_3 were distilled under vacuum. The reaction crude thus obtained is dried, and 50−70 mL of dry toluene or diethyl ether was added. Once the amine chlorhidrate was eliminated by filtration, solvent evaporation in vacuum afforded the phosphinamines **10a**,**b** with purity higher than 97% (NMR). This allowed their use in the next synthetic step without further purification.

Dichloro-*N*-benzyl-*N*-methyphosphinamine (10a): isolated yield >97% (3.00 g); ^{1}H NMR δ 2.80 (d, 3H, $^3J_{PH}$ 9.5 Hz), 4.41 (d, 2H, $^3J_{PH}$ 12.5 Hz), 7.32−7.36 (m, 2H), 7.36−7.47 (m, 3H); ^{13}C NMR δ 33.67 (d, $^2J_{PC}$ 10.2 Hz), 55.67 (d, $^2J_{PC}$ 34.2 Hz), 127.97, 128.04, 128.77, 136.04 (d, $^3J_{PC}$ 6.6 Hz); ^{31}P NMR δ 164.08. Anal. Calcd (%) for $C_8H_{10}NPCl_2$ (222.05): C, 43.27; H, 4.54; N, 6.31. Found: C, 43.24; H, 6.30; N, 6.35.

Synthesis of Dinaphthylphosphinamines 11a−c. To a solution of naphthylmagnesium bromide in ether−toluene (1 equiv) was added the dichlorophosphinamines **10a**,**b** (0.48 equiv) in THF (5 mL) at room temperature for 1-naphthylmagnesium bromide or 0 °C for 2-naphthylmagnesium bromide. The reaction mixture was stirred at room temperature for 1 h, and then the magnesium salts were eliminated by filtration. The liquid was then poured into 0.08 M HCl, extracted with ethyl acetate (3 × 15 mL), and washed with 1 N NaOH (1 × 15 mL) and water (1 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuum affording compounds **11a−c** in the presence of small amounts of naphthalene, as syrups stable to air. These mixtures can be used without further purification in the next oxidation step, or in addition, naphthalene in excess can be eliminated by sublimation before the next synthetic step.

***N*-Benzyl-*N*-methyl-*P*,*P*-di-1-naphthylphosphinamine (11a):** isolated yield 94% (5.14 g); ^{1}H NMR δ 2.43 (d, 3H, $^3J_{PH}$ 5.2 Hz), 4.48 (d, 2H, $^3J_{PH}$ 8.5 Hz), 7.28−7.94 (m, 17H), 8.35 (dd, 2H, $^3J_{HH}$ 8.7 Hz,$^4J_{PH}$ 3.4 Hz); ^{31}P NMR δ 56.03. Anal. Calcd (%) for $C_{28}H_{24}NP$ (405.48): C, 82.94; H, 5.97; N, 3.45. Found: C, 83.01; H, 5.95; N, 3.47.

Oxidation of Dinaphthylphosphinamines to 12a−c. To a solution of dinaphthylphosphinamines **11a−c** (8.23−4.05 mmol) in THF or dichloromethane was added 30% v/v (0.63 mL, 6.17 mmol) hydrogen peroxide or 77% *m*-chloroperbenzoic acid (*m*CPBA) (6.17 mmol) at 0 °C. Once the 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 Et_2O afforded **12a**,**b** as solids with a purity higher than 97%. Compound **12c** was obtained as white foam with a purity of 90% (NMR).

***N*-Benzyl-*N*-methyl-*P*,*P*-di-1-naphthylphosphinamide (12a)**: yield after precipitation from Et_2O > 97% (3.47 g); mp 140−142 °C; ^{1}H NMR δ 2.62 (d, 3H, $^3J_{PH}$ 9.6 Hz), 4.47 (d, 2H, $^3J_{PH}$ 7.8 Hz), 7.26−7.46 (m, 7H), 7.52−7.53 (m, 4H), 7.54 (ddd, 2H, $^3J_{HH}$ 6.8 Hz, $^4J_{HH}$ 1.5 Hz, $^3J_{PH}$ 16.4 Hz), 7.91 (m, 2H), 8.03 (d, 2H, $^3J_{HH}$ 8.2 Hz), 8.98 (m, 2H); ^{13}C NMR δ 34.76 (d, $^2J_{PC}$ 4.5 Hz), 53.06 (d, $^2J_{PC}$ 3.5 Hz), 124.60 (d, $^3J_{PC}$ 15.0 Hz), 126.74, 127.61, 127.63, 128.01 (d, $^4J_{PC}$ 4.4 Hz), 128.57, 128.92, 129.24 (d, $^1J_{PC}$ 123.0 Hz), 129.43, 133.22 (d, $^2J_{PC}$ 13.3 Hz), 133.29 (d, $^4J_{PC}$ 3.5 Hz), 134.22 (d, $^3J_{PC}$ 9.7 Hz), 134.31 (d, $^2J_{PC}$ 8.8 Hz,), 137.84 (d, $^3J_{PC}$ 3.5 Hz); ^{31}P NMR δ 39.66; IR (KBr) 1196 cm^{-1}; MS (API-ES) *m*/*z* 422 (M

+ 1). Anal. Calcd (%) for $C_{28}H_{24}NOP$ (421.48): C, 79.79; H, 5.74; N, 3.32. Found: C, 79.73; H, 5.76; N, 3.30.

General Procedure for the Dearomatizing Reactions on Dinaphthylphosphinamides 12a,b. To a solution of the appropriate phosphinamide (4.75×10^{-4} mol) in THF (25 mL) was added a solution of *s*BuLi (0.91 mL of a 1.3 M solution in cyclohexane, 1.19×10^{-3} mol) at −90 or −30 °C. After 30 min of metalation, the corresponding electrophile (2.37×10^{-3} mol for protonation and 1.19×10^{-3} for the other electrophiles) dissolved in THF (4 mL) was added. The reaction mixture was stirred at −90 or −30 °C for *t* min (specified for each reaction in the main text). Then, 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 vacuum. ^1H, $^1H\{^{31}P\}$, and ^{31}P NMR spectra of the crude reaction were measured in order to determine the stereoselectivity of the process. The reaction crude was then purified by precipitation from Et_2O or flash column chromatography using different mixtures of ethyl acetate/hexane as eluent.

General Procedure for the Dearomatizing Reactions on Dinaphthylphosphinamides 12c. To a solution of LDA in THF (1.19×10^{-3} mol) was added a solution of **12c** (4.75×10^{-4} mol) in THF (15 mL) at −85 °C. The mixture reaction was stirred for 1.5 h and allowed to reach −30 °C. After 1 h at −30 °C, MeOH (2.37×10^{-3} mol) for protonation or MeI (1.19×10^{-3}) as electrophiles dissolved in THF (4 mL) was added at the same temperature. The reaction mixture was stirred at −30 °C for *t* min (specified for each reaction in the main text). Then, 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 vacuum. The reaction crude was then purified by flash column chromatography using different mixtures of ethyl acetate/hexane as eluent.

(1*R*$_P$,3*S**,3a*S**,9b*S**)-2-Methyl-1-(1-naphthyl)-3-phenyl-2,3,-3a,9b-tetrahydro-1*H*-naphtho[1,2-*c*][1,2]azaphosphole 1-oxide (13a)**: 88% yield after precipitation from Et_2O (176 mg); mp 201−203 °C; ^1H NMR δ 2.69 (d, 3H, $^3J_{PH}$ 7.8 Hz), 3.78 (dddt, 1H, $^3J_{HH}$ 18.3 Hz, $^3J_{HH}$ 7.1 Hz, $^3J_{HH}$ 2.5 Hz, $^3J_{PH}$ 4.6 Hz), 3.94 (dd, 1H, $^3J_{HH}$ 18.3 Hz, $^2J_{PH}$ 22.1 Hz), 4.77 (dd, 1H $^3J_{HH}$ 7.1 Hz, $^3J_{PH}$ 13.3 Hz), 5.83 (dt, 1H, $^3J_{HH}$ 9.7 Hz, $^3J_{HH}$ 2.5 Hz, $^4J_{PH}$ 2.5 Hz), 6.24 (dd, 1H, $^3J_{HH}$ 9.7 Hz, $^4J_{HH}$ 2.5 Hz), 6.72 (dt, 1H, $^3J_{HH}$ 7.5 Hz, $^4J_{HH}$ 1.7 Hz), 6.89 (dt, 1H, $^3J_{HH}$ 7.5 Hz, $^4J_{HH}$ 1.7 Hz, $^5J_{PH}$ 1.7 Hz), 6.96 (t, 1H, $^3J_{HH}$ 7.5 Hz), 7.35 (d, 1H, $^3J_{HH}$ 7.5 Hz), 7.40 (dt, 1H, $^3J_{HH}$ 7.1 Hz, $^4J_{HH}$ 1.7 Hz), 7.47 (ddd, 1H, $^3J_{HH}$ 7.9 Hz, $^3J_{HH}$ 7.1 Hz, $^4J_{PH}$ 2.7 Hz), 7.50 (t, 2H, $^3J_{HH}$ 7.1 Hz), 7.61 (ddd, 1H, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 6.9 Hz, $^4J_{HH}$ 1.2 Hz), 7.66 (dd, 2H $^3J_{HH}$ 7.1 Hz, $^4J_{HH}$ 1.7 Hz), 7.78 (ddd, 1H, $^3J_{HH}$ 8.6 Hz, $^3J_{HH}$ 6.9 Hz, $^4J_{HH}$ 1.7 Hz), 7.87 (ddd, 1H, $^3J_{HH}$ 7.1 Hz, $^4J_{HH}$ 1.4 Hz, $^3J_{PH}$ 15.7 Hz), 7.91 (dd, 1H, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.7 Hz), 8.01 (d, 1H, $^3J_{HH}$ 7.9 Hz), 9.79 (d, 1H, $^3J_{HH}$ 8.6 Hz); ^{13}C NMR δ 29.54 (d, $^2J_{PC}$ 3.9 Hz), 42.39 (d, $^2J_{PC}$ 4.8 Hz), 43.31 (d, $^1J_{PC}$ 92.8 Hz), 66.60 (d, $^2J_{PC}$ 8.7 Hz), 124.38 (d, $^3J_{PC}$ 14.1 Hz), 126.41, 126.57 (d, $^3J_{PC}$ 21.3 Hz), 126.68, 126.80 (d, $^1J_{PC}$ 99.1 Hz), 126.84 (d, $^3J_{PC}$ 6.0 Hz), 127.04, 127.16, 127.33, 127.56, 127.80, 127.98, 128.13, 128.84, 129.15, 130.22, 133.67 (d, $^4J_{PC}$ 3.3 Hz), 134.01 (d, $^3J_{PC}$ 9.0 Hz), 134.18 (d, $^2J_{PC}$ 10.5 Hz), 135.62 (d, $^2J_{PC}$ 11.1 Hz), 137.54; ^{31}P NMR δ 45.74; IR (KBr) 1151 cm^{-1}; MS (API-ES) *m*/*z* 422 (M + 1). Anal. Calcd (%) for $C_{28}H_{24}NOP$ (421.48): C, 79.79; H, 5.74; N, 3.32. Found: C, 79.75; H, 5.73; N, 3.30.

(1*R,3*R*$_P$**,3a*S**,9b*S**)-2-Methyl-3-(2-naphthyl)-1-phenyl-2,3,-3a,9b-tetrahydro-1*H*-naphtho[2,1-*c*][1,2]azaphosphole 3-oxide (16)**: yield after chromatography (ethyl acetate/hexane 1:1) was 72% (144 mg). Oil. ^1H NMR δ 2.48 (d, 3H, $^3J_{PH}$ 8.8 Hz), 3.39 (ddt, 1H, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.7 Hz, $^2J_{PH}$ 11.3 Hz), 3.56 (ddd, 1H, $^3J_{HH}$ 9.8 Hz, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 1.0 Hz), 4.34 (d, 1H, $^3J_{HH}$ 9.8 Hz), 6.13 (d, 1H, $^3J_{HH}$ 7.4 Hz), 6.35 (dddt, 1H, $^3J_{HH}$ 12.2 Hz, $^3J_{HH}$ 9.8 Hz, $^4J_{HH}$ 2.7 Hz, $^4J_{HH}$ 1.0 Hz, $^3J_{PH}$ 9.8 Hz), 6.77 (ddt, 1H, $^3J_{HH}$ 9.8 Hz, $^4J_{HH}$ 2.7 Hz, $^4J_{PH}$ 2.7 Hz), 6.89 (dt, 1H, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.8 Hz), 7.13−8.04 (m, 13H), 8.67 (d, 1H, $^3J_{PH}$ 14.2 Hz); ^{13}C NMR δ 28.91 (d, $^2J_{PC}$ 2.4 Hz), 38.63 (d, $^1J_{PC}$ 84.1 Hz), 48.41 (d, $^2J_{PC}$ 1.2 Hz), 70.08 (d, $^2J_{PC}$ 17.0 Hz), 120.47 (d, $^2J_{PC}$ 8.0 Hz), 126.28 (d, $^2J_{PC}$ 10.9 Hz), 126.78−128.63, 128.76 (d, $^3J_{PC}$ 4.8 Hz), 128.94, 128.99, 129.14 (d, $^4J_{PC}$ 1.3 Hz), 130.52 (d, $^3J_{PC}$ 11.6 Hz), 130.63 (d, $^1J_{PC}$ 127.5 Hz), 131.90 (d, $^4J_{PC}$ 2.6 Hz), 132.63 (d, $^3J_{PC}$ 13.8 Hz), 133.88 (d, $^2J_{PC}$ 9.4 Hz), 134.83 (d, $^4J_{PC}$ 2.3 Hz), 138.72 (d, $^3J_{PC}$ 10.3 Hz); ^{31}P NMR δ 49.50; IR (KBr) 1259, 1180 cm^{-1}; MS (API-ES) *m*/*z* 422 (M + 1). Anal. Calcd (%) for $C_{28}H_{24}NOP$ (421.47): C, 79.79; H, 5.74; N, 3.32. Found: C, 79.76; H, 5.76; N, 3.27.

General Procedure for the Preparation of *N*-Methyl-γ-aminophosphinic Acids 28−29 (Procedure A) and 30−31 (Procedure B). Procedure A: A solution of the appropriate benzazaphosphole (**13a**, **18a**) (1.64×10^{-4} mol) in a mixture of dioxane (0.60 mL), water (0.53 mL), and concentrated sulfuric acid (0.07 mL) was heated to reflux for 8 h. Then, the solution was cooled and optional pH was set to neutral by adding 1 N NaOH. The resulting solution was extracted with ethyl acetate (3 × 15 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford aminophosphinic acids **30** and **32**. Procedure B: To a solution of the appropriated benzazaphosphole (**16**, **27**) (2.37×10^{-4} mol) in acetone (10 mL), 2 N HCl (1 mL) was added at room temperature. The mixture reaction was stirred 2 h for **16** and 6 h for **27** precursors. Then, the reaction mixture was treated with 1 N NaOH until neutral pH and extracted with ethyl acetate (3 × 15 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford aminophosphinic acids **33** and **34**.

1-Naphthyl-{(1*R,2*R**)-2-[(1*R**)-1-(methylamino)(phenyl)-methyl]-1,2-dihydronaphthalen-1-yl}phosphinic acid sulfate (30)**: yield crude reaction >97% (88 mg). ^1H NMR (DMSO-d_6, 75 °C) δ 2.10 (s, 3H), 3.16 (d, 1H, $^2J_{PH}$ 20.8 Hz), 3.67 (d, 1H, $^3J_{HH}$ 8.8 Hz), 4.15 (m, 1H), 6.04 (bm, 1H, ArH), 6.21(bs, 2H), 6.68−6.76 (m, 2H), 6.91 (m, 1H), 7.16−7.43 (m, 8H), 7.64 (dd, 1H, $^3J_{HH}$ 7.1 Hz, $^3J_{PH}$ 13.2 Hz), 7.83 (d, 1H, $^3J_{HH}$ 8.2 Hz),7.90 (d, 1H $^3J_{HH}$ 8.2 Hz), 8.37 (d, 1H, $^3J_{HH}$ 8.8 Hz); ^{13}C NMR (DMSO-d_6, 75 °C) δ 32.43, 37.33, 44.46 (d, $^1J_{PC}$ 85.3 Hz), 67.59 (d, $^3J_{PC}$ 18.0 Hz), 124.36 (d, $^3J_{PC}$ 13.2 Hz), 125.40, 125.94−126.77, 126.85, 127.81, 128.32, 128.52−129.04, 129.43 (d, $^3J_{PC}$ 7.2 Hz), 131.37, 131.65 (bm), 133.39 (d, J_{PC} 9.6 Hz), 133.90 (d, J_{PC} 9.6 Hz), 134.14 (d, $^2J_{PC}$ 7.2 Hz), 135.60 (d, $^4J_{PC}$ 3.6 Hz), 208.47; ^{31}P NMR (DMSO-d_6, 75 °C) δ 26.80; MS (API-ES) *m*/*z* 440 (M + 1 for γ-amino-phosphinic acid). Anal. Calcd (%) for $C_{28}H_{26}NO_2P{\cdot}H_2SO_4$ (537.56): C, 62.56; H, 5.25; N, 2.61. Found: C, 62.52; H, 5.28; N, 2.67.

1-Naphthyl-{(1*R,2*S**)-1-methyl-2-[(1*S**)-1-(methylamino)-(phenyl)methyl]-1,2-dihydronaphthalen-1-yl}phosphinic acid (32):** yield crude reaction >97% (74 mg). ^1H NMR (65 °C) δ 1.81 (d, 3H, $^3J_{PH}$ 12.8 Hz), 2.66 (s, 3H), 3.23 (ddd, 1H, $^3J_{HH}$ 4.4 Hz, $^3J_{HH}$ 2.8 Hz, $^3J_{PH}$ 33.4 Hz), 4.77 (s, 1H), 6.11 (dd, 1H, $^3J_{HH}$ 7.5 Hz, $^4J_{PH}$ 1.9 Hz), 6.39 (t, 1H, $^3J_{HH}$ 7.5 Hz), 6.80 (dd, 1H, $^3J_{HH}$ 10.6 Hz, $^4J_{HH}$ 1.7 Hz), 6.93−7.16 (m, 7H), 7.35 (t, 1H, $^3J_{HH}$ 7.2 Hz), 7.51 (dt, 1H, $^3J_{HH}$ 8.3 Hz, $^4J_{HH}$ 1.9 Hz), 7.63 (d, 2H, $^3J_{HH}$ 7.8 Hz), 7.79 (d, 1H, $^3J_{HH}$ 8.3 Hz), 7.96 (d, 1H, $^3J_{HH}$ 8.3 Hz), 8.17 (bs, 1H), 7.37 (bs, 1H), 11.56 (bs, 1H, OH), 13.12 (bs, 1H, NH); ^{13}C NMR (60 °C) δ 21.99 (d, $^2J_{PC}$ 1.8 Hz), 32.00, 46.27 (d, $^1J_{PC}$ 82.9 Hz), 53.07 (d, $^2J_{PC}$ 3.0 Hz), 62.31 (d, $^3J_{PC}$ 2.4 Hz), 123.94 (d, $^3J_{PC}$ 12.6 Hz), 124.18−125.26, 126.06 (d, J_{PC} 2.4 Hz), 126.29 (d, J_{PC} 3.0 Hz), 126.46 (d, J_{PC} 3.0 Hz), 126.59 (d, J_{PC} 3.6 Hz), 127.43, 127.73, 128.48, 128.76, 130.51, 131.63 (d, $^4J_{PC}$ 3.0 Hz), 133.04 (d, J_{PC} 10.2 Hz), 135.14−135.58, 133.59 (d, J_{PC} 7.2 Hz), 136.27, 137.91 (d, $^2J_{PC}$ 3.0 Hz); ^{31}P NMR (65 °C) δ 34.34; IR (KBr) 3438, 1261 cm^{-1}; MS (API-ES) *m*/*z* 454 (M+1). Anal. Calcd (%) for $C_{29}H_{28}NO_2P$ (453.51): C, 76.80; H, 6.22; N, 3.09. Found: C, 76.82; H, 6.24; N, 3.08.

2-Naphthyl-{(1*R,2*R**)-1-[(1*S**)-1-(methylamino)(phenyl)-methyl]-1,2-dihydronaphthalen-2-yl}phosphinic acid (33):** yield crude reaction >97% (72 mg); mp 292−294 °C (decomposed); ^1H NMR NMR δ 2.42 (s, 3H), 3.50 (m, 1H, $^2J_{PH}$ 20.3 Hz), 4.35 (s, 2H), 6.00 (dt, 1H, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 2.3 Hz,$^3J_{PH}$ 9.2 Hz), 6.45 (d,

1H, $^3J_{HH}$ 7.3 Hz), 6.57−6.66 (m, 2H), 6.91−8.06 (m, 13H), 8.61 (d, 1H, $^3J_{PH}$ 12.3 Hz), 11.47 (bs, 1H), 12.62 (bs, 1H); ^{13}C NMR δ 31.42, 42.08 (d, $^1J_{PC}$ 95.2 Hz), 43.06 (d, $^2J_{PC}$ 3.5 Hz), 61.47, 125.53−129.49, 132.59, 132.78 (d, $^3J_{PC}$ 3.5 Hz), 133.32 (d, $^2J_{PC}$ 8.5 Hz), 134.42 (d, $^4J_{PC}$ 1.8 Hz), 135.19 (d, $^3J_{PC}$ 14.0 Hz), 135.35; ^{31}P NMR δ 33.77; IR (KBr) 3410, 1182 cm^{-1}; MS (API-ES) *m*/*z* 440 (M + 1). Anal. Calcd (%) for $C_{28}H_{26}NO_2P$ (439.49): C, 76.52; H, 5.96; N, 3.19. Found: C, 76.54; H, 5.94; N, 3.18.

Acknowledgment. Dedicated to Prof. Vicente Gotor on the occasion of his 60th birthday. Financial support through Ministerio de Educación, Cultura y Deporte (project CTQ2005-01792), is gratefully acknowledged. G.R.G. thanks Ministerio de Ciencia y Tecnología for a doctoral fellowship. We thank PharmaMar S.A. for the biological assays carried out.

Supporting Information Available: Structural analysis, experimental procedures, and characterization data for all compounds, 1D ^{1}H, ^{13}C, and DEPT135 of all new compounds, 2D gNOESY spectra of **13a**,**b**, **14a**, **18a**−**c**, **22**−**25**, **27**, **33**, and **34**, 1D experiments of **30** and **32** at different temperatures, and X-ray data of **13a** and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701607S