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The First Synthesis of Cyclic α-Amino Phosphonic Acid Amides Bearing the Benzodiazaphosphorinanone System

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ABSTRACT: *For the first time, an approach to cyclic α-amino phosphonate structures bearing a 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxide framework is described. The desired products,* **4** *and* **5**, *were prepared by a modified Pudovik reaction, starting from the benzodiazaphosphorinanone derivative* **1** *and several sulfur-containing five- and six-membered heterocycles,* **2**, *and* **3** *(with a reactive C=N double bond) as imine component (yields up to 81%). Furthermore, the diastereoselectivity of the reaction was investigated (dr up to 62:38).* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 679–686, 1998

INTRODUCTION

Since the class of 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxides was discovered by Coppola et al. in 1978 [1], its nucleophilic character was broadly investigated in a number of substitution and addition reactions [2,3]. Thus, the observed biological activity [4] of alkylated 5,6-benzo[1,3,2]diazaphosphorinan-4-one derivatives mainly influenced the chemistry of these phosphorus structures. In contrast to the well-investigated reaction with carbonyl compounds, information on the addition of compounds of type **1** to the C=N double bond is rare. Until now, to the best of our knowledge, only the thermally induced addition of **1a** to triazine as an imine synthon, in the absence of a solvent, has been described [3], whereas no general synthetic route was known. However, the knowledge of such a reaction might lead to new biologically active α-amino phosphonate structures, bearing an benzodiazaphosphorinan-one component. The importance of the thiazolidine system giving rise to biologically and pharmacologically interesting compounds, e.g., insecticides [5], HIV protease [6], and others is well known, so that the combination of the thiazolidine structure with this kind of phosphoryl group may lead to significant biological activity. Such a combination of two classes of compounds (here, benzodiazaphorinanone ring and amino phosphonic acid structure) of well-known physiological activity is of interest in connection with the "dual-action drugs" strategy [7] for the development of pharmaceuticals.

Pursuing our investigations into the reactivity of the C=N bond toward P(:O)H-derivatives [3,8,9], we now report the addition of 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxides **2** to cyclic imines [10]. We used several 3-thiazolines **2** and the benzothiazine **3** as imine components, forming the corre-

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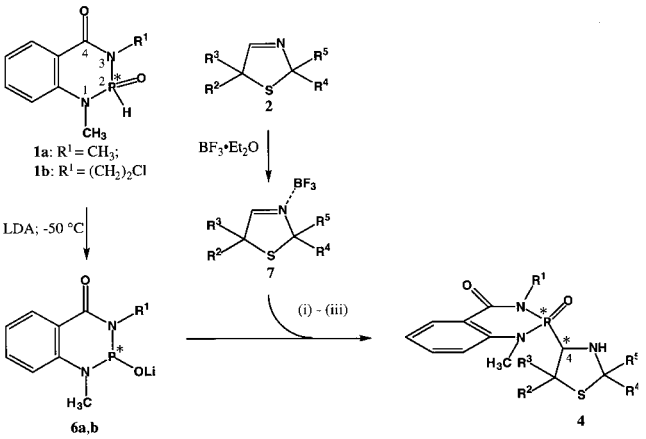
sponding α-amino phosphonic acid derivatives **4** and **5**, respectively. In addition, we were interested in the diastereoselective course of this addition reaction.

RESULTS AND DISCUSSION

In search of a general synthetic method, several published strategies, well known for the addition of $(RO)_2P(:O)H$-derivatives to carbonyl and imine compounds were employed [8a,11,12]. But thermal activation as well as phosphorylation of 3-thiazolines using silylphosphite esters {*N,N'*-anthranilamide}-$POSiMe_3$—generated in situ—are limited in their utility because of incomplete reactions. The same drawback was found using boron trifluoride-activated thiazolines in the addition reaction with 5,6-benzo[1,3,2]diaza-phosphorinan-4-one 2-oxides **1** at room temperature.

Encouraged by the success of Spilling [12] in applying phosphorus acid diamide anions in the asymmetric addition to the C=O-bond, thereupon we used the 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxide anions as a potential phosphorylating agent in the reaction with thiazolines **2**. Recently, we discovered that this strategy of Spilling [12], accompanied by additional Lewis acid activation of the imine, could be successfully employed in the stereoselective addition of chiral cyclic phosphites to thiazolines [8b,13]. Therefore, in the first step, 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxide **1a** was treated with the strong base LDA in THF solution at −50°C to give the corresponding anion **6a**, and, subsequently, the boron trifluoride-activated thiazoline **7** was added to the solution, containing the anion, at the same temperature (Scheme 1). However, stirring the reaction mixture for 3 hours at −50°C and for 12 hours at room temperature, according to a known previous procedure for the addition of cyclic phosphites [8b] only led to a low reaction rate and small amounts of the desired product [14]. To increase the chemical yields, addition of boron trifluoride-activated 3-thiazoline **7** was followed by refluxing the reaction mixture for 4 hours. Increasing the reaction temperature afforded the desired products **4** in satisfactory to good yield, in the range of 37% to 81% (Table 1). To show the generality of this procedure for the addition of benzodiazaphosphorinanones bearing a P(:O)H-group to cyclic imines, the synthetic strategy was applied to a series of thiazolines **2** with different substituents and to the aromatic heterocyclic imine **3** [15]. Concerning the thiazolines, the reactions steps are shown in Scheme 1, and the experimental results are listed in Table 1.



SCHEME 1 Diastereoselective Hydrophosphonylation of the Thiazolines 2 (i) −50°C to rt; (ii) Δ, 4h; (iii) + H_2O/-$LiBF_3OH$

The highest chemical yield was achieved using tetramethyl-3-thiazoline **2a** and the *N*-(2-chloroethyl)-substituted P(:O)H-heterocycle **1b**, resulting in the formation of **4g** in 81% yield. A change of the acyclic *N*-substituent R^1 at the nitrogen atom in the benzodiazaphosphorinanone **1b** from methyl to the bulkier 2-chloroethyl group was not accompanied by a decrease in the yields of the corresponding products **4g–4j**. However, compared with their monocyclic analogues the 3-thiazolines with spiro structure gave the corresponding phosphonic acid derivatives (e.g., **4b** and **4c**) in higher yields. The ^1H, ^{13}C, and ^{31}P NMR spectra of the new compounds **4** are typical for such kind of σ^4-phosphorus compounds. In analogy to similar thiazolidine structures which are P-substituted at the α-amino position [8,9], the carbon NMR spectra show a characteristic coupling $^1J(C,P)$ between 115 and 118 Hz. The phosphorus NMR spectra exhibit the two singulets of the diastereoisomers, with δ ranging from 23.5 to 26.0.

Regarding the stereochemical course of the modified Pudovik addition reaction, the effect of the substituents on the diastereoselectivity can be discussed in detail, based on the different starting materials **1** and **2** that were employed. The diastereomeric ratios (dr) were determined by integration of the phosphorus NMR spectra of the crude products (NMR spectra were recorded in $CDCl_3$). Using **1a** as a phosphorylating component we obtained the products **4a–4f** with diastereomeric ratios dr = 50:50. Thus, the diastereodifferentiation in the resulting addition step to the C=N double bond of the thiazolines **2** (caused by the dissymmetrical benzodiazaphosphorinanone heterocycle) is too low for a diastereoselective induction in the case of the same substituents (CH_3) at the N atoms. Moreover, the results demonstrate that the lack of stereoselectivity of

TABLE 1 Benzodiazaphosphorinanone Adducts **4** Synthesized from the Thiazolines **2**

4	2	R^1	R^2	R^3	R^4	R^5	Yield, %	*dr*[a]
a	**a**	CH_3	CH_3	CH_3	CH_3	CH_3	53	50:50
b	**b**	CH_3	CH_3	CH_3	$-(CH_2)_4-$		69	50:50
c	**c**	CH_3	CH_3	CH_3	$-(CH_2)_5-$		64	50:50
d	**d**	CH_3	C_2H_5	C_2H_5	C_2H_5	C_2H_5	37	50:50
e	**e**	CH_3	C_2H_5	C_2H_5	$-(CH_2)_5-$		60	50:50
f	**g**	CH_3	$-(CH_2)_5-$		$-(CH_2)_4-$		64	50:50
g	**a**	$(CH_2)_2Cl$	CH_3	CH_3	CH_3	CH_3	81	62:38
h	**b**	$(CH_2)_2Cl$	CH_3	CH_3	$-(CH_2)_4-$		60	58:42
i	**e**	$(CH_2)_2Cl$	C_2H_5	C_2H_5	$-(CH_2)_5-$		70	56:44
j	**f**	$(CH_2)_2Cl$	$-(CH_2)_5-$		CH_3	CH_3	39	61:39

[a]dr = diastereomeric ratio; determined by ^{31}P-NMR spectroscopy from the crude products.

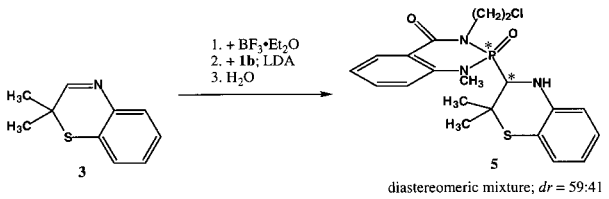
the reaction using **1a** is independent from the nature of the 3-thiazoline substituents. Thus, the substituents of the ring system in **2** have no influence on the course of the stereoselective addition.

However, replacing the methyl group as substituent R^1 by the more sterically demanding (2-chloroethyl)-group, and the use of **1b** makes the reaction diastereoselective. The products **4g**–**4j** were obtained with a diastereomeric ratio, ranging between dr = 56:44 and dr = 62:38, depending on the thiazoline substituents (see Table 1). The highest diastereoselectivity (with dr = 62:38) was observed in the formation of the thiazolidinyl phosphonate derivative **4g**. In conclusion, the diastereoselectivity of the reaction mainly depends on steric (and chemical) properties of the (achiral) substituents at the N atoms of **1**. A further enhancement of the stereodirecting effect might be achieved using sterically more demanding *N*-substituents.

Concerning the reaction mechanism, the diastereoselective addition of **1** should occur, following analogy to a mechanism postulated by Volkmann [16] for the addition of carbanionic nucleophiles to thiazolines in the presence of Lewis acids. The addition of **6** to **7** might lead to a five-membered, cyclic transition state, involving the heteroatoms N, P, O and B, followed by the formation of an anionic intermediate. Subsequent hydrolysis affords the desired product **4**.

To investigate the generality of the modified Pudovik addition, described herein, the reaction was extended to another type of heterocyclic imine, namely the 2H-1,4-benzothiazine **3** (Scheme 2). Chromatographical separation of the resulting diastereomeric mixture gave the two diastereomers **5a,b** (with 15% and 13% yield for the major and minor diastereomer, respectively).

In summary, for the first time an approach to cyclic α-amino phosphonate structures bearing an 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxide



SCHEME 2 Reaction using the 2H-1,4-Benzothiazine 3 as Imine Component

framework was described. The generality of this reaction was shown, conducting the modified Pudovik reaction of **1** with several S-containing five- and six-membered heterocyclic imines to obtain the desired products **4** and **5** in yields up to 81%. The diastereoselectivity of the reaction was demonstrated with diastereomeric ratios up to dr = 62:38. In addition, according to the innovative "dual action drugs" concept for the development of new pharmaceuticals the integration of two kinds of biologically active structural subunits (thiazolidine and benzodiazaphosphorinanone) might be connected with new pharmaceutical properties. We are actively pursuing the extension of this kind of synthesis to further 5,6-benzo[1,3,2]diazaphosphorinan-4-one 2-oxides and heterocyclic imine systems (e.g., oxo-containing heterocyclic imines).

EXPERIMENTAL

The melting points were determined in an open capillary tube on a Dr. Linström instrument and are uncorrected. Elemental analyses were carried out on a Carlo Erba Stumentalione analyzer (MOD 1104). The ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded on a Bruker AM 300 spectrometer, in $CDCl_3$ as a solvent. Mass spectra were recorded on a Finnigan-MAT 212 spectrometer (Datasystem SS 300). The 3-thiazolines **2a,b,c** [18a], **2d,g** [9c], **2e** [9d], and **2f** [17b]

were prepared according to the modified Asinger one pot synthesis method. The 2H-1,4-benzothiazine **3** was prepared as previously reported [18].

General Procedure for the Addition of 5,6-Benzo[1,3,2]diazaphosphorinan-4-one 2-oxides 2 to 3-Thiazolines 1: General Procedure

At −50°C, lithium diisopropylamide (2 mmol; 10%; in hexane) was added to a solution of 5,6-benzo[1,3,2]diazaphosphorinan-4-on-2-oxide in abs. THF (25 mL) via a syringe in an atmosphere of argon. The resulting solution was maintained at −50°C for 30 minutes, and then the boron trifluoride activated 3-thiazoline **2** solution (3 mmol, dissolved in 10 mL abs. THF) was added at this temperature. After having been stirred for 3 hours at −50°C, the reaction mixture was allowed to warm to room temperature. To complete the reaction, the mixture was refluxed for 4 hours, cooled to room temperature, and hydrolysed with water (10 mL). After addition of MTBE (10 mL), the organic layer was separated, washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude product. The crude products are solids or oils that crystallized at room temperature to give pure thiazolidinylphosphorinanes **4a–j**.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(2′,2′,5′,5′-tetramethyl-3′-thiazolidin-4′-yl)-1,3,2λ⁵-diazaphosphorinan-4-one **4a.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 50:50 (pure product). Yield: 0.41 g (53%). mp 144–146°C. IR (KBr): ν = 1660 (C=O), 1250 (P=O). ^{1}H-NMR (diastereomer I) ($CDCl_3$): δ = 1.20, 1.31 [2s, 6H, C5(CH_3)$_2$], 1.48, 1.76 [2s, 6H, C2(CH_3)$_2$], 3.17–3.32 [m, 7H, 2 × NCH_3, C4-H], 6.98–8.19 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer I) ($CDCl_3$): δ = 27.39, 29.05 [C5(CH_3)$_2$], 29.42 [CH_3NP], 31.94 [C(O)NCH_3], 32.12, 32.77 [C2(CH_3)$_2$], 61.34 [C5], 69.00 [d, ^1J = 117.6 Hz, C4], 74.81 [d, ^3J = 23.5 Hz, C2], 115.96 [d, ^3J = 7.7 Hz, 1 × aromat. CH], 119.43, 122.49, 130.77, 134.71, 141.67 [5 × aromat. C], 163.97 [C=O]. ^{31}P-NMR (diastereomer I) ($CDCl_3$): δ = 23.76 [P]. ^{1}H-NMR (diastereomer II) ($CDCl_3$): δ = 1.18, 1.41 [2s, 6H, C5(CH_3)$_2$], 1.48, 1.51 [2s, 6H, C2(CH_3)$_2$], 3.17–3.32 [m, 7H, 2 × NCH_3, C4-H], 6.98–8.19 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer II) ($CDCl_3$): δ = 27.30, 29.05 [C5(CH_3)$_2$], 28.63 [CH_3NP], 31.66 [C(O)NCH_3], 32.03, 32.63 [C2(CH_3)$_2$], 60.96 [C5], 68.55 [d, ^1J = 115.7 Hz, C4], 74.21 [d, ^3J = 23.7 Hz, C2], 114.34 [d, ^3J = 6.8 Hz, 1 × aromat. CH], 118.82, 121.89, 130.64, 134.71, 142.28 [5 × aromat. C], 164.46 [C=O]. ^{31}P-NMR (diastereomer II) ($CDCl_3$): δ = 24.30 [P]. MS (CI-Isobutan): *m/z* (%) = 354 (100) [MH^+]. Calc for $C_{16}H_{24}N_3O_2PS$ (353.4): C, 54.38; H, 6.84; N 11.89. Found: C, 54.24; H, 6.82; N, 11.50.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(2′,2′-dimethyl-1′-thia-4′-aza-spiro[4.4]non-3′-yl)-1,3,2λ⁵-diazaphosphorinan-4-one **4b.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 50:50 (pure product). Yield: 0.52 g (69%). mp 169–172°C. IR (KBr): ν = 1665 (C=O), 1250 (P=O). ^{1}H-NMR (diastereomer I) ($CDCl_3$): δ = 1.23, 1.49 [2s, 6H, C2(CH_3)$_2$], 1.20–2.17 [m, 8H, -(CH_2)$_4$-], 2.52–2.97 [m, 1H, NH], 2.94–3.08 [m, 1H, C4-H], 3.22–3.31 [m, 6H, 2 × NCH_3], 6.95–8.20 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer I) ($CDCl_3$): δ = 23.45, 23.90, 41.26, 43.28 [-(CH_2)$_4$-], 27.46, 29.06 [C2(CH_3)$_2$], 29.36 [CH_3NP], 31.79 [C(O)NCH_3], 59.93 [C2], 69.36 [d, ^1J = 116.6 Hz, C3], 83.50 [d, ^3J = 22.3 Hz, C5], 115.80 [d, ^3J = 6.8 Hz, 1 × aromat. CH], 119.37, 122.41, 130.72, 134.66, 141.72 [5 × aromat. C], 164.48 [C=O]. ^{31}P-NMR (diastereomer I) ($CDCl_3$): δ = 23.83 [P]. ^{1}H-NMR (diastereomer II) ($CDCl_3$): δ = 1.23, 1.49 [2s, 6H, C2(CH_3)$_2$], 1.20–2.17 [m, 8H, -(CH_2)$_4$-], 2.52–2.97 [m, 1H, NH], 2.94–3.08 [m, 1H, C4-H], 3.22–3.31 [m, 6H, 2 × NCH_3], 6.95–8.20 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer II) ($CDCl_3$): δ = 23.53, 23.81, 41.16, 43.28 [-(CH_2)$_4$-], 27.46, 29.06 [C2(CH_3)$_2$], 28.51 [CH_3NP], 31.60 [C(O)NCH_3], 59.58 [C2], 69.01 [d, ^1J = 115.8 Hz, C3], 82.94 [d, ^3J = 22.3 Hz, C5], 114.19 [d, ^3J = 6.3 Hz, 1 × aromat. CH], 118.96, 121.88, 130.56, 134.88, 141.72 [5 × aromat. C], 164.12 [C=O]. ^{31}P-NMR (diastereomer II) ($CDCl_3$): δ = 24.29 [P]. MS (CI-Isobutan): *m/z* (%) = 380 (100) [MH^+]. Calc for $C_{18}H_{26}N_3O_2PS$ (379.4): C, 56.98; H, 6.91; N, 11.07. Found: C, 56.87; H, 6.83; N 10.54.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(2′,2′-dimethyl-1′-thia-4′-aza-spiro[4.5]dec-3′-yl)-1,3,2λ⁵-diazaphosphorinan-4-one **4c.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 50:50 (pure product). Yield: 0.50 g (64%). mp 170–172°C. IR (KBr): ν = 1660 (C=O), 1250 (P=O). ^{1}H-NMR (diastereomer I) ($CDCl_3$): δ = 1.22–2.07 [m, 16H, C2(CH_3)$_2$, -(CH_2)$_5$-], 3.12–3.24 [m, 1H, C3-H], 3.21–3.43 [m, 6H, 2 × NCH_3], 6.98–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer I) ($CDCl_3$): δ = 23.41, 24.98, 25.22, 40.78, 41.55 [-(CH_2)$_5$-], 27.35, 29.21 [C2(CH_3)$_2$], 30.15 [CH_3NP], 31.78 [C(O)NCH_3], 58.86 [C2], 68.13 [d, ^1J = 117.2 Hz, C3], 80.09 [d, ^3J = 22.1 Hz, C5], 115.81 [d, ^3J = 7.6 Hz, 1 × aromat. CH], 119.36, 122.37, 130.70, 134.66, 141.64 [5 × aromat. C], 164.54 [C=O]. ^{31}P-NMR (diastereomer I) ($CDCl_3$): δ = 24.66 [P]. ^{1}H-NMR (diastereomer II) ($CDCl_3$): δ = 1.22–2.07 [m, 16H, C2(CH_3)$_2$, -(CH_2)$_5$-], 3.12–3.24 [m, 1H, C3-H], 3.21–3.43 [m, 6H, 2 × NCH_3], 6.98–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer II)

($CDCl_3$): δ = 23.41, 24.12, 25.22, 40.66, 41.55 [-$(CH_2)_5$-], 27.35, 29.35 [C2$(CH_3)_2$], 28.52 [CH_3NP], 31.61 [C(O)NCH_3], 58.57 [C2], 67.85 [d, ^1J = 116.0 Hz, C3], 79.40 [d, ^3J = 22.1 Hz, C5], 114.26 [d, ^3J = 6.9 Hz, 1 × aromat. CH], 118.96, 121.86, 130.54, 134.84, 142.32 [5 × aromat. C], 164.10 [C=O]. ^{31}P-NMR (diastereomer II) ($CDCl_3$): δ = 24.05 [P]. MS (CI-Isobutan): *m/z* (%) = 394 (100) [MH^+]. Calc for $C_{19}H_{28}N_3O_2PS$ (393.4): C, 58.00; H, 7.17; N, 10.68. Found: C, 57.96; H, 6.83; N, 10.54.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(2′,2′,5′,5′-tetraethyl-3′-thiazolidin-4′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4d.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 54:46 (pure product). Yield: 0.30 g (37%). mp: 118–120°C. IR (KBr): *v* = 1655 (C=O), 1245 (P=O). ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 0.25–1.21 [m, 12H, CH_2CH_3], 1.32–1.85 [m, 8H, CH_2CH_3], 3.22–3.31 [m, 7H, 2 × NCH_3, C4-H], 6.95–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (major diastereomer) ($CDCl_3$): δ = 8.31–10.07 [4 × CH_2CH_3], 28.63 [CH_3NP], 31.77 [C(O)NCH_3], 26.99, 32.33, 33.50, 34.94 [4 × CH_2CH_3], 63.70 [d, ^1J = 116.5 Hz, C4], 69.20 [C5], 81.85 [d, ^3J = 22.2 Hz, C2], 114.26, 119.42, 121.87, 130.42, 134.65, 142.26 [6 × aromat. C], 165.64 [C=O]. ^{31}P-NMR (major diastereomer) ($CDCl_3$): δ = 25.69 [P]. ^{1}H-NMR (minor diastereomer) ($CDCl_3$): δ = 0.25–1.21 [m, 12H, CH_2CH_3], 1.32–1.85 [m, 8H, CH_2CH_3], 3.22–3.31 [m, 7H, 2 × NCH_3, C4-H], 6.95–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (minor diastereomer) ($CDCl_3$): δ = 8.31–10.07 [4 × CH_2CH_3], 29.34 [CH_3NP], 31.95 [C(O)NCH_3], 26.56, 32.51, 33.16, 34.94 [4 × CH_2CH_3], 63.50 [d, ^1J = 115.5 Hz, C4], 69.63 [C5], 82.62 [d, ^3J = 20.4 Hz, C2], 115.82, 119.19, 122.35, 130.71, 134.65, 141.64 [6 × aromat. C], 165.64 [C=O]. ^{31}P-NMR (minor diastereomer) ($CDCl_3$): δ = 25.25 [P]. MS (CI-Isobutan): *m/z* (%) = 410 (100) [MH^+]. Calc for $C_{20}H_{32}N_3O_2PS$ (409.5): C, 58.66; H, 7.88; N, 10.26. Found: C, 58.38; H, 7.76; N, 10.29.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(2′,2′-diethyl-1′-thia-4′-aza-spiro[4.5]dec-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4e.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 50:50 (pure product). Yield: 0.51 g (60%). mp 135–138°C. IR (KBr): *v* = 1660 (C=O), 1250 (P=O). ^{1}H-NMR (diastereomer I) ($CDCl_3$): δ = 0.27 [t, 3H, ^3J = 7.2 Hz, CH_2CH_3], 0.93 [t, 3H, ^3J = 7.3 Hz, CH_2CH_3], 0.91–2.02 [m 14H, 2 × CH_2CH_3, -$(CH_2)_5$-], 3.22–3.31 [m, 7H, C3-H, 2 × NCH_3], 6.93–8.21 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer I) ($CDCl_3$): δ = 8.46, 10.07 [2 × CH_2CH_3], 23.37, 24.11, 25.13, 40.43, 41.56 [-$(CH_2)_5$-], 26.77, 31.71[C2$(CH_2)_2$], 29.43 [CH_3NP], 32.31 [C(O)NCH_3], 63.27 [d, ^1J = 117.0 Hz, C3], 69.03 [C2], 78.37 [d, ^3J = 22.9 Hz, C5], 115.87 [d, ^3J = 7.3 Hz, 1 × aromat. CH], 119.46, 122.34, 130.41, 134.64, 141.65 [5 × aromat. C], 165.59 [C=O]. ^{31}P-NMR (diastereomer I) ($CDCl_3$): δ = 25.75 [P]. ^{1}H-NMR (diastereomer II) ($CDCl_3$): δ = 0.80 [t, 3H, ^3J = 7.2 Hz, CH_2CH_3], 0.93 [t, 3H, ^3J = 7.3 Hz, CH_2CH_3], 0.91–2.02 [m, 14H, 2 × CH_2CH_3, -$(CH_2)_5$-], 3.22–3.31 [m, 7H, C3-H, 2 × NCH_3], 6.93–8.21 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer II) ($CDCl_3$): δ = 9.49, 9.81 [2 × CH_2CH_3], 23.37, 24.85, 25.13, 40.27, 41.40 [-$(CH_2)_5$-], 27.28, 31.95 [C2$(CH_2)_2$], 28.57 [CH_3NP], 33.40 [C(O)NCH_3], 63.51 [d, ^1J = 117.4 Hz, C3], 69.46 [C2], 78.21 [d, ^3J = 22.0 Hz, C5], 114.26 [d, ^3J = 6.7 Hz, 1 × aromat. CH], 119.19, 121.83, 130.69, 134.70, 142.31 [5 × aromat. C], 164.52 [C=O]. ^{31}P-NMR (diastereomer II) ($CDCl_3$): δ = 25.30 [P]. MS (CI-Isobutan): *m/z* (%) = 422 (100) [MH^+]. Calc for $C_{21}H_{32}N_3O_2PS$ (421.5): C, 59.84; H, 7.65; N, 9.97. Found: C, 59.36; H, 7.03; N, 10.24.

5,6-Benzo-1,3-dimethyl-2-oxo-2-(7′-thia-13′-aza-dispiro[5.1.4.2]tetradec-14′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4f.** Diastereomeric ratio: dr = 50:50 (crude product); dr = 50:50 (pure product). Yield: 0.54 g (64%). mp 175–178°C. IR (KBr): *v* = 1660 (C=O), 1250 (P=O). ^{1}H-NMR (diastereomer I) ($CDCl_3$): δ = 1.05–2.14 [m, 18H, -$(CH_2)_5$-, -$(CH_2)_4$-], 2.95 [d, ^2J = 17.1 Hz, 1H, C14-H], 3.22–3.35 [m, 6H, 2 × NCH_3], 6.96–8.15 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer I) ($CDCl_3$): δ = 23.42, 23.61, 23.85, 25.91, 27.30, 36.84, 37.98, 41.09, 43.21 [-$(CH_2)_5$-, -$(CH_2)_4$-], 29.50 [CH_3NP], 32.12 [C(O)NCH_3], 68.12 [C6], 68.97 [d, ^1J = 117.7 Hz, C14], 82.26 [d, ^3J = 23.5 Hz, C12], 115.68 [d, ^3J = 6.9 Hz, 1 × aromat. CH], 119.36, 121.82, 130.68, 134.67, 142.36 [5 × aromat. C], 164.17 [C=O]. ^{31}P-NMR (diastereomer I) ($CDCl_3$): δ = 24.95 [P]. ^{1}H-NMR (diastereomer II) ($CDCl_3$): δ = 1.05–2.14 [m, 18H, -$(CH_2)_5$-, -$(CH_2)_4$-], 3.00 [d, ^2J = 15.6 Hz, 1H, C14-H], 3.22–3.35 [m, 6H, 2 × NCH_3], 6.96–8.15 [m, 4H, aromat. C-H]. ^{13}C-NMR (diastereomer II) ($CDCl_3$): δ = 23.42, 23.61, 23.93, 25.57, 27.30, 36.95, 37.98, 41.25, 43.21 [-$(CH_2)_5$-, -$(CH_2)_4$-], 28.90 [CH_3NP], 31.72 [C(O)NCH_3], 67.71 [C6], 69.31 [d, ^1J = 117.1 Hz, C14], 81.95 [d, ^3J = 23.9 Hz, C12], 114.18 [d, ^3J = 6.8 Hz, 1 × aromat. CH], 118.99, 122.33, 130.52, 134.86, 141.81 [5 × aromat. C], 164.17 [C=O]. ^{31}P-NMR (diastereomer II) ($CDCl_3$): δ = 24.44 [P]. MS (CI-isobutane): *m/z* (%) = 420 (100) [MH^+]. Calc for $C_{21}H_{30}N_3O_2PS$ (419.5): C, 60.12; H, 7.21; N, 10.02. Found: C, 59.98; H, 7.12; N, 9.56.

5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2-(2′,2′,5′,5′-tetramethyl-3′-thiazolidin-4′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4g.** Diastereomeric ratio:

dr = 62:38 (crude product); dr = 63:37 (pure product). Yield: 0.65 g (81%). mp 126–128°C. IR (KBr): ν = 1660 (C=O), 1255 (P=O). ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 0.92–1.52 [m, 9H, C5(CH_3)$_2$, C2(CH_3)], 1.65 [s, 3H, C2(CH_3)], 3.13–3.26 [m, 1H, C4-H], 3.32 [d, ^3J = 7.9 Hz, NCH_3], 3.71–4.36 [m, 4H, (CH_2)$_2$], 6.88–8.17 [m, 4H, aromat. C-H]. ^{13}C-NMR (major diastereomer) ($CDCl_3$): δ = 27.35, 27.61 [C5(CH_3)$_2$], 29.89, 33.68 [C2(CH_3)$_2$], 32.06 [CH_3NP], 40.85, 44.01 [2 × CH_2], 61.26 [C5], 68.65 [d, ^1J = 117.4 Hz, C4], 74.67 [d, ^3J = 23.7 Hz, C2], 116.33 [d, ^3J = 7.7 Hz, 1 × aromat. CH], 119.38, 122.77, 130.95, 135.10, 141.68 [5 × aromat. C], 165.60 [C=O]. ^{31}P-NMR (major diastereomer) ($CDCl_3$): δ = 23.55 [P]. ^{1}H-NMR (minor diastereomer) ($CDCl_3$): δ = 0.92–1.52 [m, 9H, C5(CH_3)$_2$, C2(CH_3)], 1.62 [s, 3H, C2(CH_3)], 3.13–3.26 [m, 1H, C4-H], 3.26 [d, ^3J = 8.1 Hz, NCH_3], 3.71–4.36 [m, 4H, (CH_2)$_2$], 6.88–8.17 [m, 4H, aromat. C-H]. ^{13}C-NMR (minor diastereomer) ($CDCl_3$): δ = 26.66, 28.98 [C5(CH_3)$_2$], 29.17, 33.68 [C2(CH_3)$_2$], 32.52 [CH_3NP], 40.85, 43.25 [2 × CH_2], 60.99 [C5], 68.96 [d, ^1J = 116.6 Hz, C4], 74.08 [d, ^3J = 23.8 Hz, C2], 114.58 [d, ^3J = 7.0 Hz, 1 × aromat. CH], 118.89, 122.11, 130.74, 135.23, 142.41 [5 × aromat. C], 163.59 [C=O]. ^{31}P-NMR (minor diastereomer) ($CDCl_3$): δ = 24.05 [P]. MS (CI-Isobutan): *m/z* (%) = 404 (36) [M(^{37}Cl)H$^+$], 402 (100) [M(^{35}Cl)H$^+$]. Calc for $C_{17}H_{25}N_3O_2PSCl$ (401.8): C, 50.81; H, 6.27; N, 10.46. Found: C, 50.15; H, 6.42; N, 9.94.

5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2-(2′,2′-dimethyl-1′-thia-4′-aza-spiro[4.4]non-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4h.** Diastereomeric ratio: dr = 58:42 (crude product); dr = 59:41 (pure product). Yield: 1.98 g (60%). mp: 126–130°C. IR (KBr): ν = 1660 (C=O), 1250 cm^{-1} (P=O). ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 1.21 [s, 3H, C2-CH_3], 1.36–2.39 [m, 11H, C2-CH_3, -(CH_2)$_4$-], 2.81–2.94 [m, 1H, NH], 2.99–3.09 [m, 1H, C3-H], 3.33 [d, ^3J = 8.0 Hz, 3H, NCH_3], 3.65–4.39 [m, 4H, (CH_2)$_2$], 6.84–8.22 [m, 4H, aromat. C-H]. ^{13}C-NMR (major diastereomer) ($CDCl_3$): δ = 23.72, 23.94 [C2(CH_3)$_2$], 27.41, 28.98, 40.80, 41.47, 43.26, 43.94 [6 × CH_2], 32.02 [CH_3NP], 59.83 [C2], 69.01 [d, ^1J = 117.5 Hz, C3], 83.43 [d, ^3J = 23.1 Hz, C5], 116.26 [d, ^3J = 6.9 Hz, 1 × aromat. CH], 119.42, 122.72, 130.95, 135.05, 141.75 [6 × aromat. C], 163.64 [C=O]. ^{31}P-NMR (major diastereomer) ($CDCl_3$): δ = 24.01 [P]. ^{1}H-NMR (minor diastereomer) ($CDCl_3$): δ = 1.19 [s, 3, C2-CH_3], 1.36–2.39 [m, 11H, C2-CH_3, -(CH_2)$_4$-], 2.81–2.94 [m, 1H, NH], 2.99–3.09 [m, 1H, C3-H], 3.26 [d, ^3J = 7.9 Hz, 3H, NCH_3], 3.65–4.39 [m, 4H, (CH_2)$_2$], 6.84–8.22 [m, 4H, aromat. C-H]. ^{13}C-NMR (minor diastereomer) ($CDCl_3$): δ = 23.39, 23.72 [C2(CH_3)$_2$], 27.75, 29.43, 40.89, 41.22, 43.09, 43.94 [6 × CH_2], 31.71 [CH_3NP], 59.83 [C2], 69.66 [d, ^1J = 117.1 Hz, C3], 82.81 [d, ^3J = 23.6 Hz, C5], 114.37, 119.28, 122.09, 130.63, 135.07, 142.49 [6 × aromat. C], 164.02 [C=O]. ^{31}P-NMR (minor diastereomer) ($CDCl_3$): δ = 24.59 [P]. MS (CI-Isobutan): m/z (%) = 430 (35) [M(^{37}Cl)H$^+$], 428 (100) [M(^{35}Cl)H$^+$]. Calc for $C_{19}H_{27}N_3O_2PSCl$ (427.9): C, 53.33; H, 6.36; N, 9.82. Found: C, 53.07; H, 6.21; N, 9.57.

5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2-(2′,2′-diethyl-1′-thia-4′-aza-spiro[4.5]dec-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4i.** Diastereomeric ratio: dr = 56:44 (crude product); dr = 56:44 (pure product). Yield: 0.66 g (70%). mp 130–132°C. IR (KBr): ν = 1660 (C=O), 1255 (P=O). ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 0.83–1.04 [m, 6H, 2 × CH_2CH_3], 1.17–2.08 [m, 14H, 2 × CH_2CH_3, -(CH_2)$_5$-], 3.20–3.34 [m, 1H, C3-H], 3.31 [d, ^3J = 7.9 Hz, 3H, NCH_3], 3.68–4.35 [m, 4H, (CH_2)$_2$], 6.84–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (major diastereomer) ($CDCl_3$): δ = 9.73, 9.96 [2 × CH_2CH_3], 23.05–44.07 [9 × CH_2], 31.80 [CH_3NP], 62.83 [d, ^1J = 116.1 Hz, C3], 69.14 [C2], 79.34 [d, ^3J = 21.7 Hz, C5], 116.25 [d, ^3J = 6.9 Hz, 1 × aromat. CH], 119.37, 122.63, 130.48, 134.96, 141.66 [5 × aromat. C], 164.47 [C=O]. ^{31}P-NMR (major diastereomer) ($CDCl_3$): δ = 25.50 [P]. ^{1}H-NMR (minor diastereomer) ($CDCl_3$): δ = 0.22 [t, 3H, ^3J = 7.2 Hz, CH_2CH_3], 0.83–1.04 [m, 3H CH_2CH_3], 1.17–2.08 [m, 14H, 2 × CH_2CH_3, -(CH_2)$_5$-], 3.20–3.34 [m, 1H, C3-H], 3.31 [d, ^3J = 7.9 Hz, 3H, NCH_3], 3.68–4.35 [m, 4H, (CH_2)$_2$], 6.84–8.18 [m, 4H, aromat. C-H]. ^{13}C-NMR (minor diastereomer) ($CDCl_3$): δ = 8.34, 10.10 [2 × CH_2CH_3], 23.05–44.07 [9 × CH_2], 32.12 [CH_3NP], 64.37 [d, ^1J = 116.4 Hz, C3], 69.39 [C2], 78.21 [d, ^3J = 22.8 Hz, C5], 114.55 [d, ^3J = 7.1 Hz, 1 × aromat. CH], 119.37, 122.05, 130.88, 135.05, 142.45 [5 × aromat. C], 164.10 [C=O]. ^{31}P-NMR (minor diastereomer) ($CDCl_3$): δ = 25.08 [P]. MS (CI-Isobutan): *m/z* (%) = 472 (38) [M(^{37}Cl)H$^+$], 470 (100) [M(^{35}Cl)H$^+$]. Calc for $C_{22}H_{33}N_3O_2PSCl$ (470.0): C, 56.22; H, 7.08, N, 8.94. Found: C, 55.87; H, 7.14; N 8.51.

5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2-(2′,2′-dimethyl-1′-thia-3′-aza-spiro[4.5]dec-4′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **4j.** Diastereomeric ratio: dr = 61:39 (crude product); dr = 67:33 (pure product). Yield: 0.35 g (39%). mp: 135–139°C. IR (KBr): ν = 1660 (C=O), 1255 (P=O). ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 0.96–1.88 [m, 10H, -(CH_2)$_5$-], 1.32. 1.60 [2s, 6H, C2(CH_3)$_2$], 2.96 [d, ^3J = 6.1 Hz, 1H, NH], 3.16 [d, ^2J = 14.7 Hz, 1H, C4-H], 3.36 [d ^3J = 7.8 Hz, 3H, NCH_3], 3.72–4.38 [m, 4H, (CH_2)$_2$], 7.00–8.15 [m, 4H, aromat. CH]. ^{13}C-NMR (major diastereomer) ($CDCl_3$): δ = 23.36, 23.45

[C2(CH_3)$_2$], 25.94, 27.34, 36.63, 38.01, 40.89, 44.18 [7 × CH_2], 32.52 [CH_3NP], 69.03 [d, ^1J = 117.8 Hz, C4], 69.49 [C5], 73.69 [d, ^3J = 23.7 Hz, C2], 116.21 [d, ^3J = 6.9 Hz, 1 × aromat. CH], 119.40, 122.70, 130.93, 135.06, 141.75 [5 × aromat. C], 163.70 [C=O]. ^{31}P-NMR (major diastereomer) ($CDCl_3$): δ = 24.21 [P]. ^{1}H-NMR (minor diastereomer) ($CDCl_3$): δ = 0.96–1.88 [m, 10H, -(CH_2)$_5$-], 1.17, 1.44 [2s, 6H, C2(CH_3)$_2$], 2.92 [d, ^3J = 6.3 Hz, 1H, NH], 3.16 [d, ^2J = 14.7 Hz, 1H, C4-H], 3.27 [d, ^3J = 8.1 Hz, 3H, NCH_3], 3.72–4.38 [m, 4H, (CH_2)$_2$], 7.00–8.15 [m, 4H, aromat. CH]. ^{13}C-NMR (minor diastereomer) ($CDCl_3$): δ = 23.36, 23.45 [C2(CH_3)$_2$], 25.59, 27.34, 36.97, 38.28, 40.89, 43.48 [7 × CH_2], 32.21 [CH_3NP], 69.17 [C5], 69.44 [d, ^1J = 116.7 Hz, C4], 73.11 [d, ^3J = 24.0 Hz, C2], 114.53 [d, ^3J = 6.8 Hz, 1 × aromat. CH], 118.99, 122.02, 130.69, 135.06, 142.61 [5 × aromat. C], 163.70 [C=O]. ^{31}P-NMR (minor diastereomer) ($CDCl_3$): δ = 24.73 [P]. MS (CI-Isobutan): *m/z* (%) = 444 (35) [M(^{37}Cl)H$^+$], 442 (100) [M(^{35}Cl)H$^+$]. Calc for $C_{20}H_{29}N_3O_2PSCl$ (441.9): C, 54.35; H, 6.61; N, 9.51. Found: C, 54.16; H, 6.49; N, 10.02.

5,6-Benzo-1-methyl-3-(2″-cloroethyl)-2-oxo-2-(2′,2′-dimethyl-3′,4′-dihydro-2H-1,4-benzothiazin-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **5** (crude product; diastereomeric mixture). The synthesis was carried out starting from 0.54 g 2,2-dimethyl-2H-1,4-benzothiazine **3** (3 mmol), 0.39 mL boron trifluoride ethyl etherate (3 mmol), 1.66 mL lithium diisopropylamide solution (2.5 mmol, 1.5 M in cyclohexane) and 0.65 g 5,6-benzo-1-methyl-3-(2′-chloroethyl)-2H-2-oxo-1,3,2λ^4-diazaphosphorinan-4-one **1b** (2.5 mmol). Diastereomeric ratio: dr = 59:41 (crude product); Yield (crude product): 1.03 g. The separation of the diastereomeric mixture was carried out by MPLC chromatography (silica gel 60, eluent: n-hexane/ethylacetate 2:8) of the oily crude product **5**. The major and minor diastereomer were obtained as diastereomerically pure compounds.

rac-5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2-(2′,2′-dimethyl-3′,4′-dihydro-2H-1,4-benzothiazin-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **5a** (major diastereomer; diastereomeric pure). Diastereomeric ratio: dr = 61:39 (crude product); dr ≥ 95:5 (pure product). Yield: 0.16 g (15%). mp 192–193°C. IR (KBr): ν = 1660 (C=0), 1240 cm^{-1} (P=O). R_f-value: 0.78. ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 1.44 [d, ^4J = 2.4 Hz, 3H, C2-CH_3], 1.83 [s, 3H, C2-CH_3], 3.13 [d, ^3J = 7.8 Hz, 3H, CH_3N], 3.74–4.37 [m, 6H, NH, C3-H, (CH_2)$_2$Cl], 5.56–8.00 [m, 8H, aromat. C-H]. ^{13}C-NMR ($CDCl_3$): δ = 26.36 [C2-CH_3], 31.12 [d, ^3J = 10.9 Hz, C2-CH_3], 33.00 [CH_3N], 38.47 [C2], 41.42, 43.36 [(CH_2)$_2$Cl], 61.34 [d, ^1J = 133.6 Hz, C3], 114.75–144.03 [12 × aromat. C], 165.01 [C=0]. ^{31}P-NMR ($CDCl_3$): δ = 22.93 [P]. MS (CI-Isobutan): m/z (%) = 438 (2) [M(^{37}Cl)H$^+$], 436 (5) [M(^{35}Cl)H$^+$], 178 (100) [MH$^+$ − (**1b**)]. Calc for $C_{20}H_{23}N_3O_2PSCl$ (435.9): C, 55.11; H, 5.32; N, 9.64. Found: C, 54.71; H, 5.34; N 9.34.

rac-5,6-Benzo-1-methyl-3-(2″-chloroethyl)-2-oxo-2(2′,2′-dimethyl-3′,4′-dihydro-2H-1,4-benzothiazin-3′-yl)-1,3,2λ^5-diazaphosphorinan-4-one **5b** (minor diastereomer; diastereomeric pure). Diastereomeric ratio: dr = 61:39 (crude product); dr ≤ 5:95 (pure product). Yield: 0.14 g (13%). mp 171–172°C. IR (KBr): ν = 1660 (C=O), 1250 cm^{-1} (P=O). R_f-value: 0.33 ^{1}H-NMR (major diastereomer) ($CDCl_3$): δ = 1.41 [d, ^4J = 1.6 Hz, 3H, C2-CH_3], 1.65 [s, 3H, C2-CH_3], 3.21 [d, ^3J = 7.6 Hz, 3H, CH_3N], 3.64–4.20 [m, 6H, NH, C3-H, (CH_2)$_2$Cl], 5.98–8.03 [m, 8H, aromat. C-H]. ^{13}C-NMR ($CDCl_3$): δ = 26.16 [C2-CH_3], 31.07 [d, ^3J = 8.8 Hz, C2-CH_3], 30.67 [CH_3N], 39.54 [C2], 40.72, 44.56 [(CH_2)$_2$Cl], 63.60 [d, ^1J = 126.2 Hz, C3], 113.38–142.94 [12 × aromat. C], 163.20 [C=O]. ^{31}P-NMR ($CDCl_3$): δ = 23.02 [P]. MS (CI-Isobutan): *m/z* (%) = 438 (1) [M(^{37}Cl)H$^+$], 436 (3) [M(^{35}Cl)H$^+$], 178 (100) [MH$^+$ − (**1b**)]. Calc for $C_{20}H_{23}N_3O_2PSCl$ (435.9): C, 55.11; H, 5.32; N, 9.64. Found: C, 55.03; H, 5.46; N, 9.18.

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