Synthesis and steric structure of pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinanes

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Dedicated to Prof. Lutz Tietze on the occasion of his 65th birthday

Abstract
Pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides were prepared by cyclization of the corresponding pyrrolidine- and piperidine-hydrazino alcohols by using phosphorus-containing reagents. Stereochemical and conformational analyses were carried out in order to determine the effect of the ring size on the conformational behavior of the nitrogen-bridged bicyclic system. It was found that the chair conformation in the pyrrolidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides can be shifted toward twisted or distorted conformations.

Keywords: 1,3,4,2-Oxadiazaphosphinanes, conformation

Introduction

1,3,2-O,N,P heterocycles have attracted great interest due to their valuable pharmacological effects and potential for synthetic applications.[1] The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer drugs (cyclophosphamide and ifosfamide), numerous derivatives of which have been prepared to determine their structure–activity relationships.[2] Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory,[3] pesticidal[4] and antimicrobial[5] activities. Phosphorus-stabilized carbanions derived from chiral 1,3,2-oxazaphosphinane 2-oxides have been widely used in the diastereoselective formation of carbon–carbon bonds.[6]

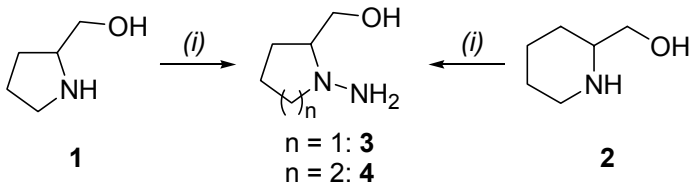
In contrast with the thoroughly investigated 1,3,2-oxazaphosphinane 2-oxide derivatives, less attention has been paid to the preparation and transformations of the corresponding 1,3,4,2-oxadiazaphosphinane 2-oxides, containing an additional nitrogen atom in the heterocyclic ring.[7-10] The first representatives of this ring system were prepared with the aim of identifying potential antitumor agents. However, despite the close structural analogy, cyclophosphamide-

analog 1,3,4,2-oxadiazaphosphinane 2-oxides, and the homologous 1,3,4,2-oxadiazaphosphepine 2-oxides, exhibit negligible anti-leukemic activity.[9,10] There has been only one conformational investigation of this ring system: 4-methyl-2-phenoxy-1,3,4,2-oxadiazaphosphinane 2-oxide attains predominantly the chair conformation, with the P=O group occupying an axial position.[8] As a follow-up of our stereochemical studies on 1,2,3,4-tetrahydroisoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] and on 1,3,4,2-oxadiazaphosphinane 2-oxides attached angularly or linearly to the tetrahydroisoquinoline ring,[12] we set out to prepare 1,3,4,2-oxadiazaphosphinane 2-oxides condensed with pyrrolidine and piperidine rings in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the nitrogen-bridged bicyclic systems.

Results and Discussion

Synthesis

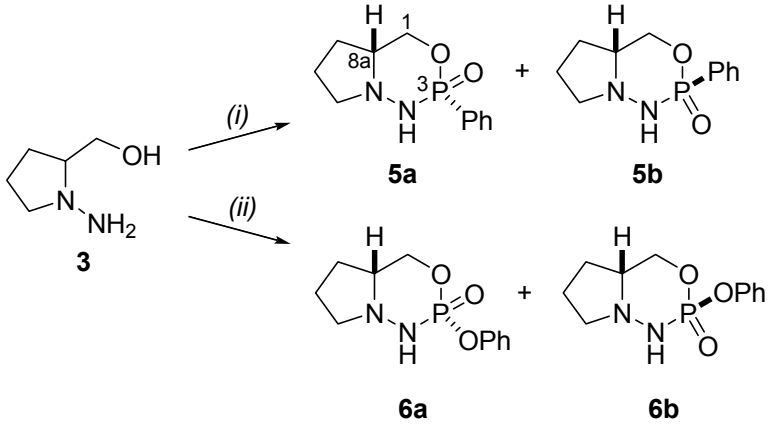
The hydrazino alcohols **3** and **4** required for the synthesis of the 1,3,4,2-oxadiazaphosphinane derivatives were prepared from the corresponding amino alcohols **1** or **2**, the *N*-nitroso derivatives of which were reduced with $LiAlH_4$ according to literature procedures[13,14] (Scheme 1).



Reagents and conditions: *(i)*: see ref. 13.

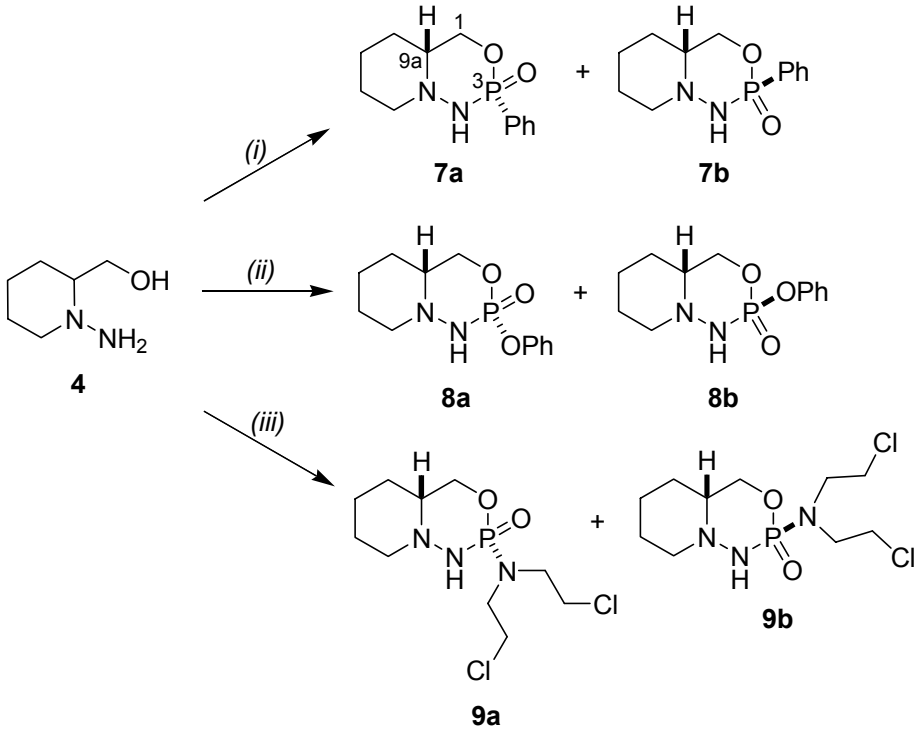
Scheme 1

The cyclizations of compounds **3** and **4** with phenylphosphonic dichloride, phenyl dichlorophosphate and bis-(2-chloroethyl)phosphoramidic dichloride were performed at ambient temperature by using a procedure similar to that described earlier[12] resulting in 1,4,6,7,8,8a-hexahydropyrrolo[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides **5** and **6** and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides **7**, **8** and **9**, respectively (Schemes 2 and 3).



Reagents and conditions: *(i)*: $PhPOCl_2$, Et_3N, THF, R.T., 2 days, then column chromatography, 12% **(5a)**, 10% **(5b)**; *(ii)*: $PhOPOCl_2$, THF, R.T., 2 days, then column chromatography, 17% **(6a)**, 13% **(6b)**.

Scheme 2



Reagents and conditions: *(i)* and *(ii)*, see ref. 12; *(iii)* $(ClCH_2CH_2)_2NPOCl_2$, Et_3N, THF, R.T., 2 days, then column chromatography, 26% **(9a)**, 26% **(9b)**.

Scheme 3

In each case, two diastereomers (**a** and **b**) differing in the configuration of the phosphorus atom were formed; they were separated by column chromatography. No significant differences in the reactivities of the pyrrolidine- and piperidine-hydrazino alcohols or in the stabilities of the ring-closed, homologous products were observed in the reactions.

Structure characterization

The conformational behavior of the nitrogen-bridgehead saturated bicyclic 1,3,4,2-oxadiazaphosphinanes (**5-9**) can be described by an equilibrium of *cis*[1]–*trans*–*cis*[2] type.[15] In the *trans* structure, the A/B hetero rings are *trans*-connected, with a *trans*-diaxial arrangement of the hydrogen at the annelation (H-an) and the nitrogen lone pair. In the two other configurations, the hetero rings are *cis*-connected: for the *cis*[1]-conformation, C-1 is in the inside, while for the *cis*[2] conformation, it is in the outside position (Figure 1). The phosphorus-containing 1,2,3-heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations.[1,16]

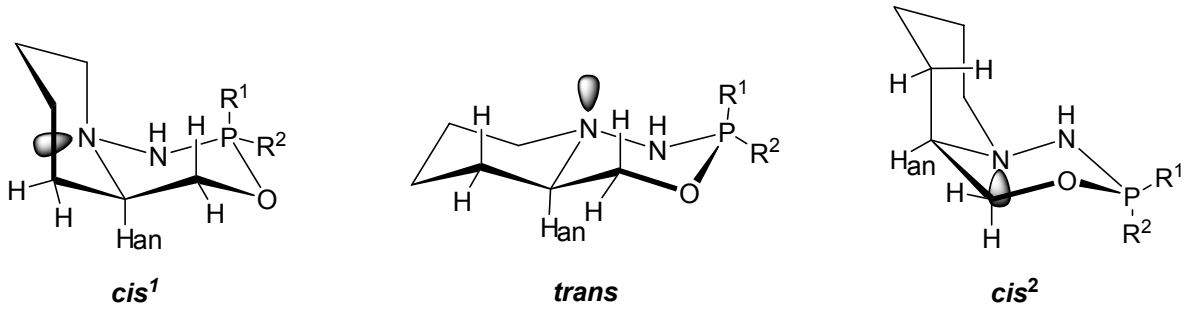


Figure 1. Possible ring connections of 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxa-diazaphosphinanes.

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic ^{3}J couplings and NOE interactions. Second, the relative configuration of the P-phenyl substituent was observed by using the NOEs from the P-phenyl group to H-an (where applicable) and/or the significant differences in the chemical shifts for certain indicator nuclei.

The orientations of H-an (H-9a for **9**; H-8a for **5** and **6**) and the protons connected to the carbons adjacent to the annelation (H-1 and H-X; H-X: H-9 for **9**; H-8 for **5** and **6**) or the protons connected to the carbons adjacent to the nitrogen bridge (H-6) were assigned by using the vicinal coupling constants (Table 1) and the characteristic NOESY cross-peaks.

The data in Table 1 show that H-an has two high vicinal couplings to the axial protons connected to the carbons adjacent to the annelation indicating that H-an is in an axial position and the hetero rings are *trans*-connected. The NOESY cross-peaks detected for H-an and H-$6_{ax.}$ corroborate the *trans*-connection of the hetero rings for all the compounds. The considerably lower ^{3}J(H-$1_{eq.}$–P) values for **5b** and **6b** indicate significant conformational flexibility in the

oxadiazaphosphinane ring attached to the five-membered rings, potentially leading to the presence of twist and/or distorted conformations.

Table 1. Characteristic vicinal coupling constants, in Hz [a]

^3J (Hz)	H-$1_{ax.}$–H-an	H-$1_{eq.}$–H-an	H-$X_{ax.}$–H-an	H-$X_{eq.}$–H-an	H-$1_{ax.}$–P	H-$1_{eq.}$–P
5a	9.8	3.3	10.3	3.0	1.8	18.1
5b	9.3	3.8	10.8	3.8	4.5	17.1
6a	10.1	3.3	10.6	3.5	1.8	19.4
6b	9.8	3.8	11.1	3.8	6.3	13.1
9a	9.6	3.8	10.1	3.5	<1	18.6
9b	10.6	3.3	11.3	3.3	<1	21.7

[a] For the meanings of H-an and H-X, see Figure 1.

As concerns the orientation of the P-substituent, P–R – H-$1_{ax.}$ NOE interactions could readily be detected in **9a**, **6a** and **5a**. It is a trend that H-1_{ax} exhibits a relative downfield shift in compounds containing an axial P=O group (**9b**, **5b** and **6b**), this difference being augmented by the upfield shift of 1-$H_{ax.}$ in **5a** due to the ring current shielding of the axial Ph group (Table 2).

Table 2. Characteristic chemical shifts, in ppm (δ TMS = 0)

	H-$1_{ax.}$	H-$1_{eq.}$
5a	3.93	4.44
5b	4.54	4.42
6a	4.29	4.39
6b	4.36	4.48
9a	3.92	4.16
9b	4.29	4.06

Conclusions

Our results show that pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides can conveniently be prepared by cyclization of the corresponding pyrrolidine- and piperidine-hydrazino alcohols with phosphorus-containing reagents (e.g. $RPOCl_2$). The relative stereochemistry of the ring junction is *trans* for all the compounds studied. The conformation of the oxadiazaphosphinane ring is chair for **9a** and **9b**, while the five-membered ring allows more flexibility for the phosphorus-containing heterocycles.

Experimental Section

General Procedures.

The NMR spectra were recorded in $CDCl_3$ at 300 K on a Bruker AVANCE DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS as internal standard. Melting points were recorded on a Kofler hot plate microscope apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Chemicals were generally of highest purity. For column chromatography, Silica gel 60 (0.063-0.200 mm) was used. Merck Kieselgel $60F_{254}$ plates were used for TLC. The hydrazino alcohols **3** and **4** were prepared according to literature procedures.[13] The syntheses and detailed NMR characterization of 1,3,4,2-oxadiazaphosphinanes **7a**, **7b**, **8a** and **8b** have been published earlier.[12]

General method for ring-closure reactions. To a stirred solution of the appropriate amino alcohol (**3** or **4**, 10 mmol) and triethylamine (2 eq.) in 80 mL of dry THF at RT was added dropwise a solution of the appropriate phosphorus-containing reagent (phenylphosphonic dichloride, phenyl dichlorophosphate or bis-(2-chloroethyl)phosphoramidic dichloride, 1 equiv.) in 30 mL of dry THF. The reaction mixture was stirred for 48 hours at RT and then filtered to remove triethylamine hydrochloride. The filtrate was evaporated to dryness.

3-Phenyl-1,4,6,7,8,8a-hexahydropyrrolo[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides 5a and 5b. The crude product (ratio of the isomers 1:1, based on the ^{1}H NMR spectrum) was purified by column chromatography, with ethyl acetate/methanol (9:1) as eluent. The more mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **5a** (0.29 g, 12%) as white crystals, which were recrystallized from diisopropyl ether–ethyl acetate, m.p. 201-204 ºC. ^{1}H NMR ($CDCl_3$) δ 1.15-1.29 (m, 1H, H-8_{ax}), 1.68-1.88 (m, 3H, H-8_{eq}, H-7), 2.59 (q, 1H, J = 8.6 Hz, H-6_{ax}), 2.74-2.82 (m, 1H, H-8a), 3.24 (dt, 1H, J = 3.3, 8.6 Hz, H-6_{eq}), 3.93 (dt, 1H, J = 1.8, 10.3 Hz, H-1_{ax}), 4.44 (ddd, 1H, J = 3.3, 10.6, 18.1 Hz, H-1_{eq}), 4.63 (s, 1H, NH), 7.46 (dt, 2H, J = 3.8, 7.3 Hz, *m*-Ar), 7.52 (dt, 1H, J = 1.5, 7.3 Hz, *p*-Ar), 7.90 (ddd, 2H, J = 1.5, 8.0, 13.6 Hz, *o*-Ar). ^{13}C NMR ($CDCl_3$) δ 20.6 (C-7), 24.2 (C-8), 55.2 (C-6), 61.9 (C-8a), 72.9 (C-1), 128.3 (Ar), 128.8 (*m*-Ar), 130.5 (*o*-Ar), 131.7 (*p*-Ar). Anal. Calcd for $C_{11}H_{15}N_2O_2P$: C, 55.46; H, 6.35; N, 11.76. Found: C, 55.77; H, 6.18; N, 11.82.

The less mobile diastereomer was crystallized after the evaporation and was filtered from diethyl ether to yield isomer **5b** (0.24 g, 10%, m.p. 142-146 °C) as white crystals, with **5a** as minor impurity (ca 5:100 by ^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ 1.55-1.67 (m, 1H, H-8_{ax}), 1.75-2.02 (m, 3H, H-8_{eq}, H-7), 2.75 (q, 1H, J = 8.3 Hz, H-6_{ax}), 2.87-2.97 (m, 1H, H-8a), 3.49 (dt, 1H, J = 4.0, 8.3 Hz, H-6_{eq}), 4.42 (ddd, 1H, J = 3.8, 10.8, 17.1 Hz, H-1_{eq}), 4.54 (ddd, 1H, J = 4.5, 9.56, 10.8 Hz, H-1_{ax}), 7.49 (dt, 2H, J = 4.0, 7.6 Hz, *m*- Ar), 7.60 (dt, 1H, J = 1.5, 7.6 Hz, *p*- Ar), 7.94 (ddd, 2H, J = 1.5, 8.3, 13.1 Hz, *o*- Ar). ^{13}C NMR ($CDCl_3$) δ 20.5 (C-7), 24.8 (C-8),

56.6 (C-6), 62.5 (C-8a), 69.7 (C-1), 126.8 (Ar), 128.4 (*m*- Ar), 132.1 (*o*- Ar), 132.9 (*p*- Ar). Anal. Calcd for $C_{11}H_{15}N_2O_2P$: C, 55.46; H, 6.35; N, 11.76. Found: C, 65.89; H, 6.74; N, 11.31.

3-Phenoxy-1,4,6,7,8,8a-hexahydropyrrolo[1,2-*d*][1,3,4,2]-oxadiazaphosphinine 3-oxides 6a and 6b. The crude product (ratio of the isomers 1:2, based on the ^{1}H NMR spectrum) was purified by column chromatography with ethyl acetate/*n*-hexane (9:1) as eluent. The more mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **6a** (0.43 g, 17%) as yellow crystals, which were recrystallized from ethyl acetate, m.p. 160-162 ºC. ^{1}H NMR ($CDCl_3$) δ 1.32-1.46 (m, 1H, H-8$_{ax}$), 1.79-1.94 (m, 3H, H-8$_{eq}$, H-7), 2.62 (q, 1H, *J*= 8.6, H-6$_{ax}$), 2.80 (m, 1H, H-8a), 3.30 (dt, 1H, *J* = 3.8, 8.6 Hz, H-6$_{eq}$), 4.29 (dt, 1H, *J* = 1.8, 10.6 Hz, H-1$_{ax}$), 4.39 (ddd, 1H, *J* = 3.3, 10.6, 19.4 Hz, H-1$_{eq}$), 4.57 (d, 1H, *J* = 12.8 Hz, NH), 7.16 (t, 1H, *J* = 7.1 Hz, *p*-Ar), 7.26-7.35 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 20.7 (C-7), 23.7 (C-8), 54.4 (C-6), 60.8 (C-8a), 73.2 (C-1), 120.6 (*m*- Ar), 124.9 (*p*- Ar), 129.5 (*o*- Ar), 150.6 (Ar). Anal. Calcd for $C_{11}H_{15}N_2O_3P$: C, 51.97; H, 5.95; N, 11.02. Found: C, 52.19; H, 5.77; N, 10.89.

The less mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **6b** (0.33 g, 13%) as yellow crystals, which were recrystallized from ethyl acetate, m.p. 119-123 ºC. ^{1}H NMR ($CDCl_3$) δ 1.66-1.85 (m, 2H, H-8$_{ax.}$, H-7), 1.85-2.01 (m, 2H, H-8$_{eq}$, H-7), 2.94 (m, 1H, H-6$_{ax}$), 3.04 (m, 1H, H-8a), 3.32 (m, 1H, H-6$_{eq}$), 4.36 (dt, 1H, *J* = 6.3, 11.1 Hz, H-1$_{ax}$), 4.48 (ddd, 1H, *J* = 3.8, 11.1, 13.1 Hz, H-1$_{eq}$), 7.18 (dt, 1H, *J* = 1.0, 7.6 Hz, *p*-Ar), 7.22-7.25 (m, 2H, *m*-Ar), 7.34 (dt, 2H, *J* = 2.5, 7.6 Hz, *o*-Ar). ^{13}C NMR ($CDCl_3$) δ 21.2 (C-7), 25.1 (C-8), 57.3 (C-6), 61.2 (C-8a), 70.6 (C-1), 120.9 (*m*- Ar), 125.3 (*p*-Ar), 130.1 (*o*- Ar), 150.6 (Ar). Anal. Calcd for $C_{11}H_{15}N_2O_3P$: C, 51.97; H, 5.95; N, 11.02. Found: C, 51.69; H, 6.07; N, 10.79.

3-[Bis-(2-chloroethyl)amino]-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiaza-phosphinine 3-oxides 9a and 9b. The crude product (ratio of the isomers 1:1, based on the ^{1}H NMR spectrum) was purified by column chromatography, with ethyl acetate as eluent. The more mobile diastereomer was crystallized after the evaporation and was filtered from diethyl ether to yield isomer **9a** (0.82 g, 26%) as white crystals, which were recrystallized from diisopropyl ether, m.p. 73-76 ºC. ^{1}H NMR ($CDCl_3$) δ 1.08-1.21 (m, 1H, H-9), 1.21-1.34 (m, 1H, H-8), 1.49-1.65 (m, 2H, H-9$_{eq}$, H-7), 1.68-1.79 (m, 2H, H-8$_{eq}$, H-7), 2.28 (1H, dt, *J* = 2.5, 12.3 Hz, H-6), 2.43 (1H, tt, *J* = 3.5, 10.1 Hz, H-9a), 3.17 (td, 1H, *J* = 3.0, 11.3 Hz, H-6$_{eq}$), 3.34-3.53 (m, 2H, H-1'H-2'), 3.69 (2H, t, *J* = 7.6 Hz, H-3', H-4'), 3.77 (d, 1H, *J* = 7.1 Hz, NH), 3.92 (ddd, 1H, *J* = 4.8, 9.6, 11.1 Hz, H-1), 4.16 (ddd, 1H, *J* = 3.8, 11.1, 18.6 Hz, H-1$_{eq}$). ^{13}C NMR ($CDCl_3$) δ 23.1 (C-8), 24.9 (C-7), 27.1 (C-9), 42.5 (C-3'), 49.5 (C-1',C-2',C-4'), 57.7 (C-6), 62.1 (C-9a), 72.8 (C-1). Anal. Calcd for $C_{10}H_{20}Cl_2N_3O_2P$: C, 37.99; H, 6.38; N, 13.29. Found: C, 38.31; H, 6.19; N, 13.44.

The less mobile diastereomer was crystallized by evaporation and was filtered from *n*- hexane to yield isomer **9b** (0.82 g, 26%) as a white solid, which was recrystallized from diisopropyl ether–ethyl acetate, m.p. 150-152 ºC. ^{1}H NMR ($CDCl_3$) δ 1.18-1.36 (m, 2H, H-9, H-8), 1.54-1.60 (m, 1H, H-9$_{eq}$), 1.64-1.78 (m, 3H, H-8, H-7), 2.30 (td, 1H, *J* = 7.1, 10.1 Hz, H-6$_{ax}$), 2.42 (tt, 1H,

J = 3.3, 10.6 Hz, H-9a), 3.20 (td, 1H, *J* =3.5, 10.1 Hz, H-6_{eq}), 3.35-3.48 (m, 1H, H-1'), 3.48-3.71 (m, 3H, H-2', H-3', H-4'), 4.06 (ddd, 1H, *J* = 3.3, 11.3, 21.7 Hz, H-1_{eq}), 4.29 (dt, 1H, *J* = 1.3, 11.3 Hz, H-1_{ax}). ^{13}C NMR: δ 23.0 (C-8), 24.6 (C-7), 25.9 (C-9), 42.5 (C-3'), 48.9 (C-1',C-2',C-4'), 58.5 (C-6), 62.2 (C-9a), 71.4 (C-1). Anal. Calcd for $C_{10}H_{20}Cl_2N_3O_2P$: C, 37.99; H, 6.38; N, 13.29. Found: C, 37.76; H, 6.52; N, 13.37.

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