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Synthesis of heterocyclic methylenebisphosphonates by 1,3-dipolar cycloaddition of ethyl diazoacetate to 1,2-benzoxaphosphorin-3-phosphonates

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ABSTRACT

Reaction of salicylaldehydes with tetraethyl ester of methylenebisphosphonic acid, under Knoevenagel reaction conditions, gives the corresponding 1,2-benzoxaphosphorin-3-phosphonates **5** in good yields. The [3+2] regio- and stereoselective cycloaddition of **5a** and **5b** with ethyl diazoacetate gives two P-4 epimers of the corresponding pyrazoline bisphosphonate tetraethyl esters **9** and **10**. Analogously, ethyl diazoacetate reacts with **1** and **2** to give the expected pyrazolines **6**–**8**. The structures of the new compounds are revealed and confirmed by analytical, spectroscopic data and X-ray crystallographic analysis.

1. Introduction

Methylenebisphosphonic acids and their esters are stable analogues of the natural pyrophosphates. They are an important class of pharmacologically active molecules[1,2] and many representatives have found clinical use[1,3] for the treatment of bone diseases such as osteoporosis, hypercalcaemia and Paget's disease, also as antiinflammatory and antiarthritic agents.[1,2] Biological activity of the 1,1-bisphosphonates depends on the substituents bonded with the central carbon atom—halogens, hydroxyl or alkyl groups, amines, etc. Heteroaryl substituted 1,1-bisphosphonates are also very potent substances, especially those containing a nitrogen atom in the ring.[4–9] Furthermore, cyclic 1,1-bisphosphonates, where the geminal substituted carbon is a member of the *N*-heterocyclic ring, have been considered to be useful therapeutics.[4,9–16] Pyrazoline bisphosphonate esters are suitable for the treatment of chronic inflammation and human rheumatoid arthritis.[15,16]

Only a few methods for incorporation of a methylenebisphosphonic moiety in nitrogen-containing heterocycles are reported in the literature.[17] These compounds have been prepared by reactions of lactams with P(III) and P(V) electrophiles,[10–14] and by [3+2]dipolar cycloaddition reactions of diazo species with substituted ethenylidene bisphosphonate esters.[15,16] Additionally, ethenylidene-1,1-bisphosphonates have found good application[9,18–20] in organic synthesis for construction of various methylene-1,1-bisphosphonates with different pharmacological activities. They take part in Michael addition reactions,[9,19,20] cycloaddition reactions with diazo compounds[15,16] and also are used as dienophiles in Diels–Alder reactions.[18]

In a series of papers[21–25] we reported the synthesis and behaviours of new phosphorous containing coumarins prepared via Knoevenagel, Arbuzov and Perkow reactions. Biological activities of some of them have been investigated.[26] It was found[21] that the reactions of some CH-acidic phosphonates with salicylaldehydes under Knoevenagel conditions lead to the preparation of 3-phosphonocoumarins **1** together with 1,2-benzoxaphosphorines **2** (Scheme 1). In our studies on the reactivity of these chemoisomers we found[24] that they possess some differences in their behaviours. During our investigations on the chemistry of phosphonocoumarins and 1,2-benzoxaphosphorines we realized that there are good possibilities for using these compounds for the preparation of new heterocyclic bisphosphonates either by their transformation or by incorporation of two phosphonic groups at the time of construction of heterocycles.

In this article we describe our study on the synthesis of 1,2-benzoxaphosphorine derivatives with phosphonate group in the

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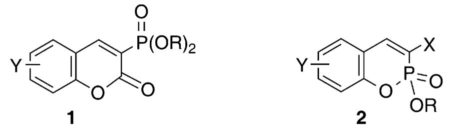
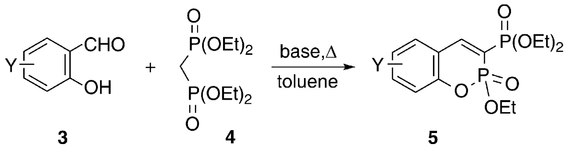


Y = H, 5-Br, 5-Cl, 4-NEt$_2$;
X = COOEt, COOSiMe$_3$, CN ; R = Me, Et

Scheme 1.



Y = H (a), 6-Br (b), 6-Cl (c), 6-OCH$_3$ (d), 7-OCH$_3$ (e), 7-N(C$_2$H$_5$)$_2$ (f)

Scheme 2.

third position of the oxaphosphorine ring. These structures could appear as analogues of vinylidenebisphosphonate esters where one of the phosphonate groups is part of a heterocyclic ring. In order to realize this construction we carried out the reaction of salicylaldehydes with tetraethyl ester of methylenebisphosphonic acid under Knoevenagel reaction conditions. It was interesting to check the chemical behaviours of the new 1,2-benzoxaphosphorin-3-phosphonates in a dipolar [3+2]cycloaddition reaction with diazo compounds. This approach gave us an opportunity to arrange tricyclic system in which methylenebisphosphonic moiety is a part of two heterocycles—oxaphosphorine and pyrazoline.

2. Results and discussions

2.1. Knoevenagel condensation

In connection with our previous investigations it was a good opportunity to use Knoevenagel reaction for the preparation of 1,2-benzoxaphosphorin-3-phosphonate by reacting some salicylaldehydes with a symmetrical CH-acidic phosphonate—tetraethyl ester of methylenebisphosphonic acid. This 1,1-bisphosphonic ester is not often utilized under Knoevenagel reaction conditions. There are only two cases presented[27,28] in the literature where the condensation takes place with aromatic and aliphatic aldehydes in the presence of $TiCl_4$ and *N*-methylmorpholine or pyridine but there are not examples with salicylaldehydes.

The use of the tetraethyl ester of methylenebisphosphonic acid for the synthesis of the desired 3-phosphono-1,2-benzoxaphosphorines required very careful and precise selection of the appropriate and mild conditions. Furthermore, 1,1-bisphosphonate **4**, in contrary to the typically used methylene compounds,[29,30] could give the corresponding carbanion, which is non-enolizable. In accordance with these circumstances in our investigations we chose as bases piperidine, piperidine acetate, β-alanine as well as combination of piperidine with glacial acetic acid. Some reactions were also performed in the presence of molecular sieves (3 Å and 4 Å), zeolite Na13X and basic Al_2O_3, which, however, were unsuccessful.

The results from the reaction between salicylaldehyde **3a** and tetraethyl ester of methylenebisphosphonic acid **4** (Scheme 2) are presented in Table 1. The yields of the reaction product **5a** ranged from 23 to 79% and depend on the quantity of the salicylaldehyde (methods B_2 and B_3) and on the used base (methods A_2, B_3 and D). The reaction proceeds in good yield by using piperidine as catalyst as well as a combination of piperidine and glacial acetic acid. The yields increased by addition of the base (method A_3) or salicylaldehyde (methods B_3) in portions and also when both catalyst and aldehyde were dropped slowly to the reaction mixture. It is necessary to emphasize that in the studied reaction for the first time in our experience in the synthesis of coumarin derivatives[21,31,32] a big excess of the salicylaldehyde was used, which could be related to the unusual CH-acid.

The studied reaction was also performed with a series of substituted 2-hydroxybenzaldehydes in the presence of piperidine and piperidine/glacial acetic acid. As it is shown in Table 2, the yields of 1,2-benzoxaphosphorin-3-phosphononates **5b–f** depend not only on the conditions, as it was mention before, but also on the substituent Y in 2-hydroxybenzaldehydes. The presence of the methoxy group in 5-position in salicylaldehyde leads to the increase in the yield of product **5d** to 92%, but when the substituent in the same position in 2-hydroxybenzaldehyde is a halogen atom (Br, Cl) the yield of the product is only 51% and 45%, respectively (Table 2). A good result for the preparation of **5b** was achieved when 5-bromosalicylaldehyde was added slowly to the reaction mixture. In this case the yield was increased to 69% (Table 2, entry 3). The reactions with 4-methoxy- and 4-diethylaminosalicylaldehyde gave the corresponding oxaphosphorines **5e** and **5f** in 77% and 72% yields, respectively.

The structures of the prepared oxaphosphorin-3-phosphonates **5** were revealed by their analytical and spectroscopic data, whereas the structure of compound **5b** was confirmed by X-ray crystallographic analysis.

Table 1
Reaction conditions and yields of product **5a** obtained from the reaction of methylenebisphosphonate **4** and 2-hydroxybenzaldehyde **3**

Entry	Method	Catalyst	Ratio of reagents (**3a**/**4**/catalyst)	Time (h)	Yield[c] (%) of **5a**
1	A	Piperidine	1:1:1[a]	7	65
2	A_1	Piperidine	2:1:0.1	6	62
3	A_2	Piperidine	1.25:1:0.5	5.5	75
4	A_3	Piperidine	1.25:1:0.5[a]	5.5	79
5	B	Piperidine/AcOH	1.15:1:0.1:0.1	9	58
6	B_1	Piperidine/AcOH	1.5:1:0.1:0.1	7	63
7	B_2	Piperidine/AcOH	2:1:0.1:0.1	6	70
8	B_3	Piperidine/AcOH	2:1:0.1:0.1[b]	6	79
9	C	Piperidine/$ClCH_2COOH$	2:1:0.1:0.1[b]	6	47
10	D	Piperidine acetate/β-alanine	1:1:0.1:0.01	4	23

[a] Piperidine was added in portions.
[b] Base and 2-hydroxybenzaldehyde were added in portions.
[c] Yield of isolated product.

2.2. [3+2]Cycloaddition of ethyl diazoacetate

The second part in our investigations is connected with the synthesis of pyrazoline derivatives of the 1,2-benzoxaphosphorin-3-phosphonates. In this study we used our experience from

Table 2
Reaction conditions and yields of products **5** obtained from the reaction of methylenebisphosphonate **4** and 2-hydroxybenzaldehydes **3**

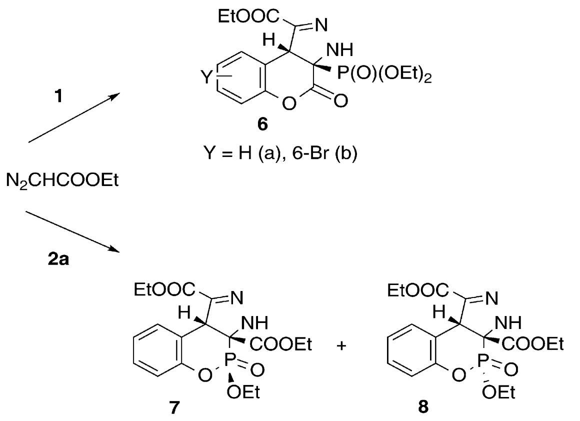
Entry	Method	Y[a]	Ratio of reagents (**3**/**4**/piperidine/AcOH)	Time (h)	Yield[c] (%) of **5**
1	A_2	6-Br	1.25:1:0.5:0	5	33
2	B_3	6-Br	2:1:0.1:0.1[b]	6	51
3	B_4	6-Br	2:1:1:0[b]	6	69
4	B_3	6-Cl	2:1:0.1:0.1[b]	6	45
5	B_3	6-OCH_3	2:1:0.1:0.1[b]	7	92
6	B_3	7-OCH_3	2:1:0.1:0.1[b]	7	77
7	A_2	7-$N(C_2H_5)_2$	1.25:1:0.5:0	6	72

[a] Substituent in 1,2-benzoxaphosphorine-3-phosphononate **5**.
[b] Base and 2-hydroxybenzaldehyde were added in portions.
[c] Yield of isolated product.

previous work on cycloaddition reactions of ethyl diazoacetate to 3-substituted coumarins.[33,34] In most cases the initially formed pyrazoline derivatives were not stable and were transformed to 3,4-pyrazole and 4,4-cyclopropane coumarin derivatives.[33,34] In order to find good conditions for the reaction of 1,2-benzoxaphosphorin-3-phosphonates **5** with ethyl diazoacetate it was necessary firstly to check the reactivity of 3-phosphonocoumarins **1** and 3-ethoxycarbonyl-1,2-benzoxaphosphorine **2a** and the stability of their pyrazoline derivatives.

The reactions of 3-phosphonocoumarins **1a** and **1b** were performed in benzene or chloroform because of their solubility. In all cases an excess of ethyl diazoacetate was used and the reactions were carried out at room temperature. Products **6a** and **6b** were isolated in moderate yields (40 and 47%, respectively) for a 60-day reaction time.

Two diastereoisomeric pyrazolines **7** and **8** were isolated from the reaction of 3-ethoxycarbonyl-1,2-benzoxaphosphorine **2a** with ethyl diazoacetate. They are epimers towards phosphorous-2 atom of the oxaphosphorine ring (Scheme 3). The overall yield and the selectivity of the reaction are due to the solvent used. The yield increases from 70% to 95%, respectively, when the reaction was carried out in methylene chloride/*n*-hexane instead of benzene/*n*-hexane. Moreover, the epimer ratio **7**/**8** changes from 7.0:1 in methylene chloride to 3.6:1 in benzene.



Scheme 3.

As we expected, the 1,3-dipolar cycloaddition of ethyl diazoacetate to 1,2-benzoxaphosphorin-3-phosphonates **5a** and **5b** proceeds with the formation of two epimeric methylenebisphosphonates **9** and **10** (Scheme 4). The results summarized in Table 3 show that the solvent and reaction time were the factors that influenced the yields and ratio of the epimers. When the reaction was carried out in ether/*n*-hexane the overall yield was 76 (Y=H) and 70% (Y=6-Br), respectively, in contrary to benzene where it was 38 and 59%, respectively. The ratio of epimers **9** and **10** depends on the solvent used, similar to the reaction with 1,2-benzoxaphosphorine **2a**. In ether/*n*-hexane for **9a**/**10a** it is 9.9:1 in respect to 3.8:1 observed in the benzene/ether. The ratio of the isomers **9b**/**10b** in the corresponding solvents is 3.7:1 and 2.9:1, respectively.

Table 3
Reaction conditions and yields of pyrazoline bisphosphonates **9** and **10** obtained from the interaction of **5** with ethyl diazoacetate

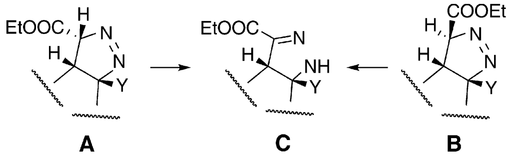
Method	Y	Ratio of reagents (**5**/ethyl diazoacetate)	Solvent	Time (days)	Yield[a] (%)		Overall yield (%)
					9	**10**	
A	H	1:2	C_6H_6/*n*-hexane	30	28	7	35
A_1	H	1:2	C_6H_6/ether	70	30	8	38
B	H	1:2	Ether/*n*-hexane	90	69	7	76
A_1	Br	1:2	C_6H_6/ether	70	44	15	59
B	Br	1:2	Ether/*n*-hexane	70	55	15	70

[a] Yield of isolated product.

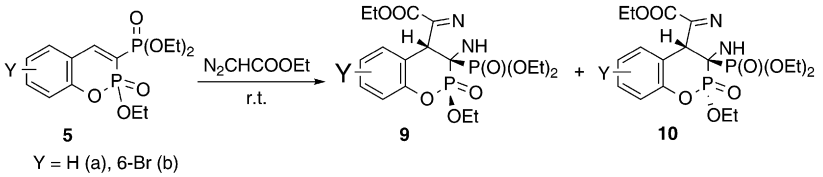
The experimental data given above indicate that there are some differences in the behaviour of compounds **1**, **2a** and **5** in the studied cycloaddition reaction. For example, compound **2a** reacted more rapidly than 3-phosphonocoumarins **1**, which could be explained by a more activated double bond in 1,2-oxaphosphorine **2a**. Additionally, the cycloaddition reaction with 1,2-benzoxaphosphorines **2a** and **5** is accomplished in a short time and with higher yields than 3-phosphonocoumarins **1**. On the other hand, the isolated pyrazoline derivatives are stable compounds in contrary to those prepared earlier from 3-substituted coumarins.[33]

The reaction of 1,3-cycloaddition of diazoacetate is completely regioselective. The terminal nitrogen of the diazo moiety binds to the carbon atom of the C3–C4 double bond bearing the electronegative substituent. This is in agreement with the findings in other analogous reactions with 3-substituted coumarins.[33,35,36] The difference between epimers **7**/**8** and **9**/**10** is the configuration of P-4atom in the oxaphosphorine ring. The favoured epimer, obtained in all cases, has cis disposition of P=O bond of the ring P-4 phosphorus to the pyrazoline ring.

There is no direct evidence for the stereoselectivity; if any, it is in the first stage of the cycloaddition (see structures **A** and **B**). After prototropic shift a pyrazoline with structure **C** was formed due to the acidic character of the proton adjacent to the ethoxycarbonyl group.



The observed site selectivity of the cycloaddition could be attributed to steric factors due to the bulky OEt group of the ring phosphorus, which prevents the approach of the dipole to the oxaphosphorine ring during the cycloaddition from the site of the OEt group. This selectivity could be explained by accepting either one step concerted cycloaddition or a two-step polar reaction. Although we do not have any strong evidence for the reaction mechanism, we incline to accept a two step reaction rather, where the intermediate shows a polar structure, in which, in the case of the favoured epimer, there is an interaction between the terminal nitrogen of the diazo moiety and the oxygen of the P=O bond of the P-2 ring phosphorus atom. This assumption could be supported



Scheme 4.

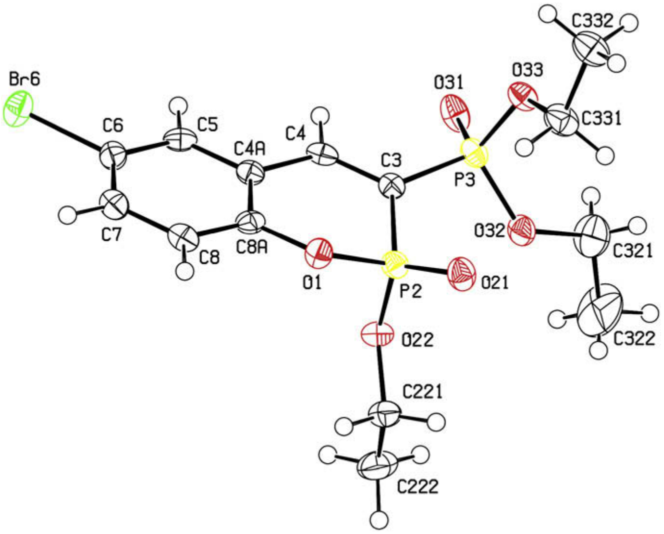


Figure 1. X-ray crystallographic structure of **5b**.

by higher yields of the favoured epimers **7** and **9a**,**b** observed when the reactions were carried out in the more polar solvents.

The structure of compounds **6**–**10** was revealed by their spectroscopic characteristics, whereas the structure of compounds **6a**, **7** and **9a** was confirmed by X-ray analysis (Figs. 2, 3 and 4).

2.3. NMR spectroscopic characteristics of compounds 5–10

Analytical and spectroscopic data of the prepared compounds are in agreement with the given structures, which have been also confirmed by X-ray crystallographic analysis for compounds **5b**, **6a**, **7** and **9a** (Figs. 1–4).

Some ^{1}H and ^{13}C NMR data, especially for the atoms close to phosphorous, are of diagnostic importance for these compounds and can be used for differentiation between the epimeric compounds **7**/**8** and **9**/**10**.

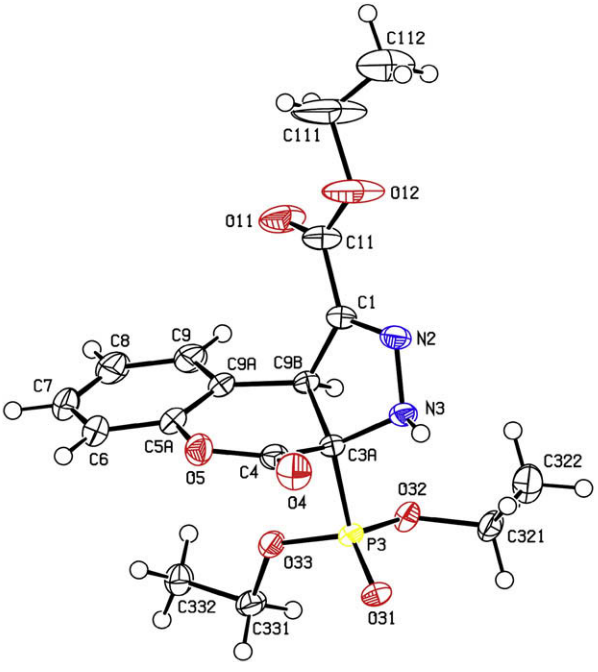


Figure 2. X-ray crystallographic structure of **6a**.

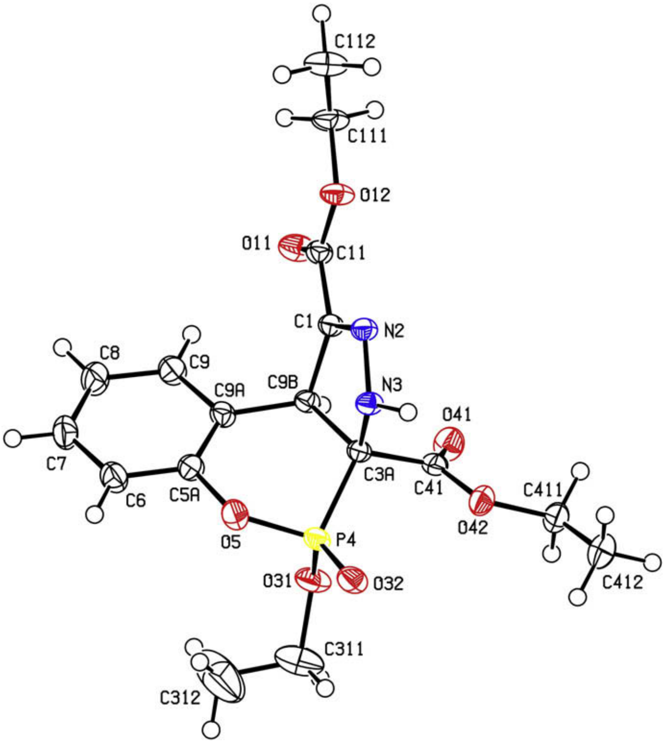


Figure 3. X-ray crystallographic structure of **7**.

Thus, the 4-H proton of **5** in the ^{1}H NMR spectrum appears at $\delta\sim8.0$ coupled with the two phosphorous atoms with $^{3}J_{HCCP}$ values of 40 and 24 Hz. In the ^{13}C NMR spectrum C-3 carbon appears at δ=104–118 with $^{1}J_{CP}$ values of 176–184 Hz and of 156–162 Hz (Scheme 5).

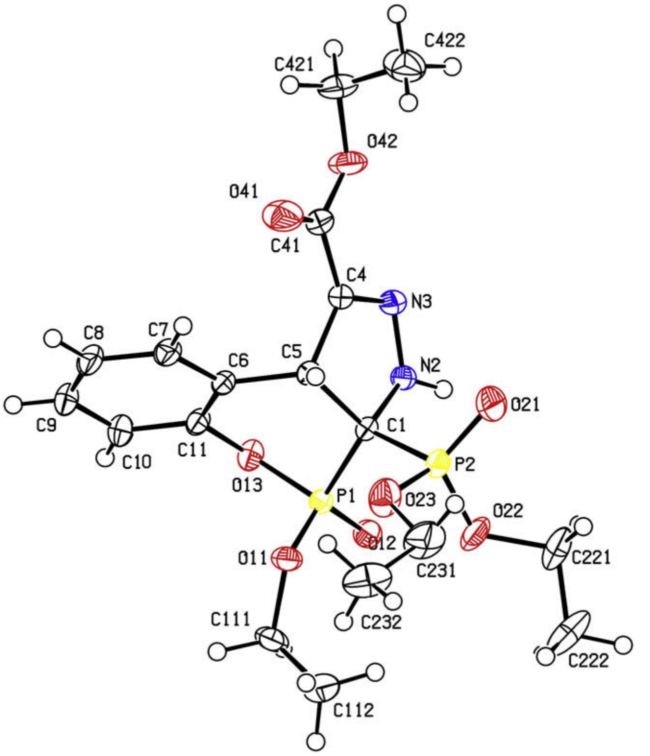
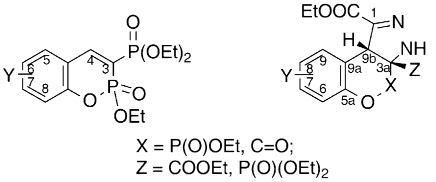


Figure 4. X-ray crystallographic structure of **9a**.



Scheme 5.

From the ^{1}H NMR spectra, it is worth mentioning the appearance of the 9b-H proton at the oxaphosphorine–pyrazoline junction of the molecule in compounds **6**–**10**. In all these compounds 9b-H appears at δ=5.0–5.5. The coupling values, however, depend on the position of the phosphorous atom and on the stereochemistry of the endocyclic 4-P atom. In compounds **6**, the $^3J_{\mathrm{HCCP}}$ equals to $\sim$21 Hz whereas in oxaphosphorines **7** and **8**, $^3J_{\mathrm{HCCP}}$ lowers to 17.4 Hz for the cis disposition between the 9b-H proton and the P4–OEt group in **7** and to 11.3 Hz for the corresponding trans disposition in **8**. For compounds **9** and **10**, 9b-H couples with both 3a-P and P-4 phosphorous atoms with the same $^3J_{\mathrm{HCCP}}$ value of $\sim$26.5 Hz in **9** (cis disposition between the 9b-H proton and the P4–OEt group) and with two different $^3J_{\mathrm{HCCP}}$ values of $\sim$20.0 and 26.5 Hz in **10** (trans disposition between the 9b-H proton and the P4–OEt group). N–H proton of the pyrazoline ring in all these compounds appears as singlet at δ=7.1–7.4.

The C-1 carbon atom shows a $^3J_{\mathrm{CCCP}}$ value of $\sim$14 Hz in compounds **6**, coupling with the 3a-P phosphorous atom, and of 6.8–8.0 Hz in compounds **7**/**8**, coupling with the P-4 ring phosphorous atom. In compounds **9**/**10** the C-1 carbon couples with both 3a-P and P-4 phosphorous atoms with a $^3J_{\mathrm{CCCP}}$ of the same value, giving a triplet of 5.6–6.3 Hz. Analogous differentiation is seen in the $^1J_{\mathrm{CP}}$ values in compounds **6** and **7**/**8**. Thus, C-3a couples with 3a-P and P-4 with $^1J_{\mathrm{CP}}$ values of $\sim$166 Hz in **6** and of 144–145 Hz in **7**/**8**, respectively. In compounds **9**/**10** the C-3a carbon gives a doublet of doublets with $^1J_{\mathrm{CP}}$ values of 133–136 and 152–158 Hz, which, by analogy to compounds **6** and **7**/**8**, are attributed to the couplings with 4-P and 3a-P, respectively. Of interest are also the $^3J_{\mathrm{CCCP}}$ couplings of the C-9a carbon with the two phosphorous atoms in the compounds under consideration. In **7**/**8** the C-9a carbon atom couples with the ring P-4 atom with $^3J_{\mathrm{CCCP}}$ values of 17–18 Hz, whereas in compounds **6** the corresponding $^3J_{\mathrm{CCCP}}$ coupling of C-9a with 3a-P is almost zero. The absence of a detectable $^3J_{\mathrm{CCCP}}$ value in compounds **6** indicates a 90° disposition between the C_{9a}–C_{9b} and C_{3a}–P_3 bonds (in accordance with the X-ray data where the corresponding dihedral angle C_{9a}–C_{9b}–C_{3a}–P_3 has been found to be 84.2° in **6a**, whereas the corresponding C_{9a}–C_{9b}–C_{3a}–P_4 dihedral angle in **7** has been found 24.2°). In compounds **9**/**10** both 3a-P and P-4 phosphorus atoms couple with C-9a, with $^3J_{\mathrm{CCCP}}$ values of 7–10 Hz and 19–22 Hz, respectively. It is also noticed the differentiation of the $^2J_{\mathrm{CCP}}$ coupling values in **9**/**10**, **6** and **7**/**8**. In **9**/**10** this carbon couples with both phosphorous atoms, with $^2J_{\mathrm{CCP}}$ values of 2.8–6.1 Hz, whereas in **6** and **7**/**8** the $^2J_{\mathrm{CCP}}$ is not detectable or very small ($^2J_{\mathrm{CCP}}$=2.2 Hz in **8**). Also, the P-4 phosphorous atom of the oxaphosphorine ring couples with the aromatic C-5a carbon with $^2J_{\mathrm{COP}}$ values of 6.8–8.1 Hz for **9** and **7** epimers and of 5.0–5.4 Hz in **10** and **8** epimers and with the aromatic C-6 carbon with $^3J_{\mathrm{CCOP}}$=5.2–6.8 Hz for **9** and **7** epimers and with $^3J_{\mathrm{CCOP}}$=4.6–5.6 Hz in epimers **10** and **8**.

3. Experimental section

3.1. General remarks

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The IR spectra were recorded with a Specord IR 71, IR 75 spectrophotometer. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker Avance DRX 250 (at 250 MHz for ^{1}H, 62.9 MHz for ^{13}C and 101.3 MHz for ^{31}P, respectively) and on a Bruker AM 300 (at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C, respectively) spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard with deuterochloroform as solvent. ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external standard. The mass spectra were recorded on a 70 eV with VG TS-250 and on an HRMS-MAT8200 spectrometer. Reactions were monitored by TLC on silica gel 60 F_{254}. Column chromatography was carried out on silica gel (Merck 0.063–0.2 mm and 0.043–0.063 mm) using as eluent *n*-hexane/EtOAc and methylene chloride/EtOAc mixtures with increasing polarity. Elemental analyses of C, H and N were carried out in the Laboratory of Elemental Analysis at the Department of Organic Chemistry, University of Sofia.

All chemical reagents were purchased from Merck and Fluka. The starting tetraethyl ester of methylenebisphosphonic acid,[37] 3-phosphono-2-oxo-2*H*-1-benzopyrane **1** and 1,2-benzoxaphosphorine **2**[21] was prepared according to the procedure described.

3.2. Reaction of methylenebisphosphonate 4 with 2-hydroxybenzaldehydes 3. General procedure

Method A. To a solution of the tetraethyl ester of methylenebisphosphonic acid **4** (2 mmol, 0.58 g) and the corresponding 2-hydroxybenzaldehyde **3** in dry toluene (40 mL) piperidine was added dropwise. The solution was refluxed under a Dean–Stark trap until the starting materials were consumed (TLC-monitoring). After evaporation of the solvent under reduced pressure the residue was chromatographed on a silica gel column with *n*-hexane and ethyl acetate (of increasing polarity) as eluent.

Method B. To a solution of the tetraethyl ester of methylenebisphosphonic acid **4** (2 mmol, 0.58 g) and the corresponding 2-hydroxybenzaldehyde **3** in dry toluene (40 mL) piperidine (0.2 mmol, 0.017 g) and glacial acetic acid (0.2 mmol, 0.012 g) were added dropwise. The solution was refluxed under Dean–Stark trap until the starting materials were consumed (TLC-monitoring). After evaporation of the solvent under reduced pressure the residue was chromatographed on a silica gel column with *n*-hexane and ethyl acetate (of increasing polarity) as eluent.

3.2.1. *Diethyl 2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5a***

According to method A the best result was obtained in the presence of 2.5 mmol (0.30 g) 2-hydroxybenzaldehyde **3a** and 1 mmol (0.085 g) piperidine to give a 0.26 g (75%) yield of **5a** (Table 1, entry 3). According to method B the best result was obtained in the presence of 4 mmol (0.48 g) **3a** to give a 0.55 g (79%) yield of **5a** (Table 1, entry 8) as white crystals, mp=60–62 °C (*n*-hexane/ether). IR (CCl_4): ν=1605, 1265, 1225, 1060, 1030 cm^{-1}; ^{1}H NMR (300 MHz) ($CDCl_3$): δ=1.38 (t, $^3J_{\mathrm{HH}}$=6.2 Hz, 3H, $POCH_2CH_3$), 1.39 (t, $^3J_{\mathrm{HH}}$=7.0 Hz, 3H, $POCH_2CH_3$), 1.40 (t, $^3J_{\mathrm{HH}}$=6.2 Hz, 3H, $POCH_2CH_3$), 4.18–4.36 (m, 6H, 3×$POCH_2CH_3$), 7.18–7.52 (m, 4H, aromatics), 8.13 (dd, $^3J_{\mathrm{HCCP}}$=24.0, 40.0 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) ($CDCl_3$): δ=16.2 (d, $^3J_{\mathrm{CCOP}}$=6.8 Hz, 2×CH_3CH_2OP), 16.3 (d, $^3J_{\mathrm{CCOP}}$=6.8 Hz, CH_3CH_2OP), 62.8 (d, $^2J_{\mathrm{COP}}$=4.5 Hz, $POCH_2$), 63.3 (d, $^2J_{\mathrm{COP}}$=6.8 Hz, $POCH_2$), 64.4 (d, $^2J_{\mathrm{COP}}$=6.8 Hz, $POCH_2$), 116.2 (dd, $^1J_{\mathrm{CP}}$=158.2, 176.3 Hz, C-3), 118.9 (d, $^2J_{\mathrm{COP}}$=6.8 Hz, C-8), 120.0 (C-4a), 124.3 (C-6), 131.4 (C-5), 133.5 (C-7), 152.6 (C-4), 154.8 (C-8a); ^{31}P NMR (101.26 MHz) ($CDCl_3$): δ=5.40 (d, *J*=42.6 Hz), 13.80 (d, *J*=42.6 Hz); MS: *m*/*z* (%)=346 (M)$^+$ (55), 245 (76), 238 (88), 209 (81), 194 (57), 182 (100), 118 (64), 89 (61). Anal. Calcd for $C_{14}H_{20}O_6P_2$ (M=346.20): C 48.56; H 5.82. Found: C 48.38; H 5.85.

3.2.2. Diethyl 6-bromo-2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5b**

According to method A the best result was obtained in the presence of 2.5 mmol (0.30 g) 2-hydroxybenzaldehyde **3b** and 1 mmol (0.085 g) piperidine to give a 0.14 g (33%) yield of **5b** (Table 2, entry 1). According to method B the best result was obtained in the presence of 4 mmol (0.48 g) **3b** to give a 0.48 g (69%) yield of **5b** (Table 2, entry 3) as white crystals, mp=96–99 °C (*n*-hexane/ether). IR (CCl$_4$): ν=1600, 1260, 1230, 1050, 1030 cm^{-1}; ^{1}H NMR (300 MHz) (CDCl$_3$): δ=1.39 (t, $^3J_{HH}$=7.0 Hz, 6H, 2×POCH$_2$C*H*$_3$), 1.40 (t, $^3J_{HH}$=7.0 Hz, 3H, POCH$_2$C*H*$_3$), 4.18–4.36 (m, 6H, 3×POC*H*$_2$CH$_3$), 7.07–7.10 (m, 1H, H-7), 7.57–7.58 (m, 2H, H-5, H-8), 8.00 (dd, $^3J_{HCCP}$=24.2, 40.0 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) (CDCl$_3$): δ=16.25 (d, $^2J_{CCP}$=6.1 Hz, 2×*C*H$_3$CH$_2$OP), 16.3 (d, $^2J_{CCP}$=6.1 Hz, *C*H$_3$CH$_2$OP), 62.9 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 63.3 (d, $^2J_{COP}$=4.1 Hz, PO*C*H$_2$), 64.6 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 116.6 (C-6), 118.3 (dd, $^1J_{CP}$=156.5, 176.0 Hz, C-3), 120.6 (d, *J*=8.1 Hz, C-8), 121.5 (t, $^3J_{CCCP}$=17.8 Hz, C-4a), 133.4 (C-5), 135.9 (C-7), 151.5 (d, *J*=8.1 Hz, C-8a), 152.8 (C-4); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=8.69 (d, *J*=42.2 Hz), 16.95 (d, *J*=42.0 Hz); MS: *m*/*z* (%)=425 (M)$^+$ (30), 345 (22), 324 (29), 317 (56), 288 (30), 261 (66), 89 (31), 80 (35), 32 (97), 28 (100). Anal. Calcd for C$_{14}$H$_{19}$O$_6$P$_2$Br (M=425.15): C 39.55; H 4.50. Found: C 39.30; H 4.22.

3.2.3. Diethyl 6-chloro-2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5c**

According to method B the best result was obtained in the presence of 4 mmol (0.48 g) **3c** to give a 0.35 g (45%) yield of **5c** (Table 2, entry 4) as white crystals, mp=93–94 °C (*n*-hexane/ether). IR (CCl$_4$): ν=1600, 1260, 1230, 1050, 1030 cm^{-1}; ^{1}H NMR (300 MHz) (CDCl$_3$): δ=1.39 (t, $^3J_{HH}$=7.2 Hz, 6H, 2×POCH$_2$C*H*$_3$), 1.40 (t, $^3J_{HH}$=7.2 Hz, 3H, POCH$_2$C*H*$_3$), 4.18–4.39 (m, 6H, 3×POC*H*$_2$CH$_3$), 7.13–7.16 (m, 1H, H-7), 7.42–7.46 (m, 2H, H-5, H-8), 8.02 (dd, $^3J_{HCCP}$=24.0, 40.0 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) (CDCl$_3$): δ=16.2 (d, $^2J_{CCP}$=6.1 Hz, 2×*C*H$_3$CH$_2$OP), 16.3 (d, $^2J_{CCP}$=6.1 Hz, *C*H$_3$CH$_2$OP), 62.9 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 63.4 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 64.6 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 118.3 (dd, $^1J_{CP}$=159.0, 176.0 Hz, C-3), 120.3 (d, $^3J_{CCOP}$=8.1 Hz, C-8), 121.0 (t, $^3J_{CCCP}$=18.3 Hz, C-4a), 129.4 (C-6), 130.4 (C-5), 133.1 (C-7), 151.0 (d, $^2J_{CCP}$=8.1 Hz, C-8a), 152.9 (C-4); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=8.70 (d, *J*=42.0 Hz), 16.95 (d, *J*=42.0 Hz); MS: *m*/*z* (%)=380 (M)$^+$ (16), 336 (13), 300 (16), 279 (31), 272 (45), 243 (31), 216 (88), 152 (28), 32 (98), 28 (100). Anal. Calcd for C$_{14}$H$_{19}$O$_6$P$_2$Cl (M=380.70): C 44.17; H 5.03. Found: C 43.94; H 4.88.

3.2.4. Diethyl 6-methoxy-2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5d**

According to method B the best result was obtained in the presence of 4 mmol (0.48 g) **3d** to give 0.69 g (92%) yield of **5d** (Table 2, entry 5) as a colourless oil. IR (CCl$_4$): ν=1600, 1270, 1265, 1040, 1010 cm^{-1}; ^{1}H NMR (300 MHz) (CDCl$_3$): δ=1.38 (t, $^3J_{HH}$=7.4 Hz, 3H, POCH$_2$C*H*$_3$), 1.39 (t, $^3J_{HH}$=7.1 Hz, 3H, POCH$_2$C*H*$_3$), 1.40 (t, $^3J_{HH}$=7.4 Hz, 3H, POCH$_2$C*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 4.19–4.35 (m, 3×6H, POC*H*$_2$CH$_3$), 6.92 (d, $^4J_{HH}$=3.3 Hz, 1H, H-8), 7.04 (qd, $^4J_{HH}$=2.0 Hz, $^3J_{HH}$=9.0 Hz, 1H, H-7), 7.13 (d, $^3J_{HH}$=9.0 Hz, 1H, H-5), 8.05 (dd, $^3J_{HCCP}$=24.4, 39.5 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) (CDCl$_3$): δ=16.3 (d, $^2J_{CCP}$=6.1 Hz, 2×*C*H$_3$CH$_2$OP), 16.4 (d, $^2J_{CCP}$=8.1 Hz, *C*H$_3$CH$_2$OP), 55.9 (s, *C*H$_3$O), 62.8 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 63.2 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 64.2 (d, $^2J_{COP}$=8.1 Hz, PO*C*H$_2$), 114.3 (C-7), 116.7 (dd, $^1J_{CP}$=158.7, 177.0 Hz, C-3), 119.7 (d, $^3J_{CCOP}$=8.1 Hz, C-8), 120.1 (C-5), 120.2 (t, $^3J_{CCCP}$=17.4 Hz, C-4a), 146.7 (d, $^2J_{COP}$=8.1 Hz, C-8a), 154.7 (C-4), 155.8 (C-6); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=9.5 (d, *J*=42.6 Hz), 17.6 (d, *J*=42.3 Hz); MS: *m*/*z* (%)=377 (M+1, 100), 376 (49), 293 (11), 275 (24), 268 (13), 240 (15), 212(25), 197 (11), 148 (7), 65 (12). Anal. Calcd for C$_{15}$H$_{22}$O$_7$P$_2$ (M=376.28): C 47.88; H 5.89. Found: C 48.07; H 5.91.

3.2.5. Diethyl 7-methoxy-2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5e**

According to method B the best result was obtained in the presence of 4 mmol (0.48 g) **3e** to give 0.58 g (77%) yield of **5e** (Table 2, entry 6) as white crystals, mp=55–57 °C (*n*-hexane/ether). IR (CCl$_4$): ν=1620, 1280, 1250, 1050, 1025, 1015 cm^{-1}; ^{1}H NMR (300 MHz) (CDCl$_3$): δ=1.38 (t, $^3J_{HH}$=7.0 Hz, 2×6H, POCH$_2$C*H*$_3$), 1.39 (t, $^3J_{HH}$=6.8 Hz, 3H, POCH$_2$C*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 4.17–4.35 (m, 3×6H, POC*H*$_2$CH$_3$), 6.69 (d, $^4J_{HH}$=2.5 Hz, 1H, H-8), 6.75 (dd, $^4J_{HH}$=2.5 Hz, $^3J_{HH}$=8.6 Hz, 1H, H-6), 7.34 (d, $^3J_{HH}$=8.6 Hz, 1H, H-5), 8.08 (dd, $^3J_{HCCP}$=24.2, 40.1 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) (CDCl$_3$): δ=16.25 (d, $^2J_{CCP}$=8.1 Hz, 2×*C*H$_3$CH$_2$OP), 16.3 (d, $^2J_{CCP}$=4.1 Hz, *C*H$_3$CH$_2$OP), 55.9 (s, *C*H$_3$O), 62.6 (d, $^2J_{COP}$=4.1 Hz, PO*C*H$_2$), 63.1 (d, $^2J_{COP}$=4.0 Hz, PO*C*H$_2$), 64.0 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 103.7 (d, $^3J_{CCOP}$=8.1 Hz, C-8), 111.2 (dd, $^1J_{CP}$=162.0, 181.0 Hz, C-3), 111.3 (C-6), 113.5 (d, $^3J_{CCCP}$=18.3 Hz, C-4a), 132.6 (C-5), 154.6 (d, $^2J_{COP}$=8.1 Hz, C-8a), 154.8 (C-4), 164.1 (C-7); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=6.5 (d, *J*=44.2 Hz), 15.8 (d, *J*=44.2 Hz); MS: *m*/*z* (%)=377 (M+1, 100), 376 (35), 296 (14), 275 (23), 267 (33), 239 (30), 212(40), 196 (8), 158 (7), 133 (6), 65 (7). Anal. Calcd for C$_{15}$H$_{22}$O$_7$P$_2$ (M=376.28): C 47.88; H 5.89. Found: C 47.92; H 6.07.

3.2.6. Diethyl 7-N,N-diethylamino-2-ethoxy-2-oxo-2H-1,2-benzoxaphosphorin-3-phosphonate **5f**

According to method A the best result was obtained in the presence of 2.5 mmol (0.30 g) 2-hydroxybenzaldehyde **3f** and 1 mmol (0.085 g) piperidine to give 0.60 g (72%) yield of **5f** (Table 2, entry 7) as a yellow oil. IR (CCl$_4$): ν=1630, 1580, 1520, 1270, 1240, 1060, 1045 cm^{-1}; ^{1}H NMR (300 MHz) (CDCl$_3$): δ=1.20 (t, $^3J_{HH}$=7.0 Hz, 6H, 2×NCH$_2$C*H*$_3$), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H, POCH$_2$C*H*$_3$), 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H, POCH$_2$C*H*$_3$), 1.38 (t, $^3J_{HH}$=7.0 Hz, 3H, POCH$_2$C*H*$_3$), 3.40 (dd, $^3J_{HH}$=7.0 Hz, $^2J_{HH}$=14.0 Hz, 4H, 2×NC*H*$_2$CH$_3$), 4.16–4.33 (m, 6H, 3×POC*H*$_2$CH$_3$), 6.33 (d, $^4J_{HH}$=2.5 Hz, 1H, H-8), 6.43 (dd, $^4J_{HH}$=2.5 Hz, $^3J_{HH}$=9.0 Hz, 1H, H-6), 7.20 (d, $^3J_{HH}$=9.0 Hz, 1H, H-5), 7.99 (dd, $^3J_{HCCP}$=24.0, 40.0 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz) (CDCl$_3$): δ=12.7 (s, 2×*C*H$_3$CH$_2$N), 16.4 (d, $^2J_{CCP}$=8.1 Hz, 2×*C*H$_3$CH$_2$OP), 16.5 (d, $^2J_{CCP}$=4.1 Hz, *C*H$_3$CH$_2$OP), 45.1 (s, 2×CH$_3$*C*H$_2$N), 62.5 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 63.0 (d, $^2J_{COP}$=4.1 Hz, PO*C*H$_2$), 63.8 (d, $^2J_{COP}$=6.1 Hz, PO*C*H$_2$), 100.0 (d, $^3J_{CCOP}$=6.1 Hz, C-8), 104.6 (dd, $^1J_{CP}$=162.0, 184.0 Hz, C-3), 107.7 (C-6), 108.8 (t, $^3J_{CCCP}$=18.3 Hz, C-4a), 133.1 (C-5), 149.6 (C-7), 152.2 (C-4), 155.6 (C-8a); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=12.5 (d, *J*=46.0 Hz), 20.7 (d, *J*=46.0 Hz); MS: *m*/*z* (%)=418 (M+1, 47), 417 (43), 403 (90), 390 (9), 375 (26), 301 (45), 273 (25), 238 (7), 175 (8), 65 (18), 45 (20), 29 (93), 28 (100), 27 (74). Anal. Calcd for C$_{18}$H$_{29}$NO$_6$P$_2$ (M=417.38): C 51.80; H 7.00. Found: C 51.67; H 6.93.

3.3. Reaction of 3-phosphonocoumarins 1a,b, 1,2-benzoxaphosphorin 2a and 1,2-benzoxaphosphorin-3-phosphonates 5a,b with ethyl diazoacetate

To a solution of the 1,2-benzoxaphosphorin or 3-phosphonocoumarin (1 mmol) in dry solvent ethyl diazoacetate (2 mmol, 0.23 g) was added. The reaction mixture was kept at room temperature for the appropriate time (TLC-monitoring) and *n*-hexane or ether was dropped periodically. The formed crystals were filtered, the solvent was evaporated and the residue was separated by flash chromatography (FC) on silica gel using methylene chloride and ethyl acetate (6:1) as eluent.

3.3.1. Ethyl 3a-diethoxyphosphoryl-4-oxo-3,3a,4,9b-tetrahydrochromeno-[3,4-c]pyrazole-1-carboxylate **6a**

Following a general procedure a sample of 3-phosphonocoumarin **1a** (1 mmol, 0.28 g) in benzene (1 mL) was kept for 60 days and after purification by FC, **6a** was isolated in 40% (0.16 g) yield as white crystals, mp=142–145 °C (benzene/*n*-hexane). IR (CHCl$_3$):

ν=3345, 1750, 1715, 1040, 1015 cm^{-1}; ^{1}H NMR (300 MHz) ($CDCl_3$): δ=1.06 (t, $^{3}J_{HH}$=7.0 Hz, 3H, $COOCH_2CH_3$), 1.29 (t, $^{3}J_{HH}$=7.0 Hz, 6H, 2×$POCH_2CH_3$), 3.86–3.98 (m, 1H, $COOCH_AH_BCH_3$), 4.01–4.09 (m, 1H, $COOCH_AH_BCH_3$), 4.20–4.28 (m, 4H, 2×$POCH_2CH_3$), 5.01 (d, $^{3}J_{HCCP}$=20.9 Hz, 1H, CH-9b), 7.06–7.37 (m, 4H, aromatics), 7.35 (s, 1H, NH), 7.73 (dd, $^{3}J_{HH}$=6.8 Hz, $^{4}J_{HH}$=1.4 Hz, 1H, 9-H); ^{13}C NMR (75.4 MHz) ($CDCl_3$): δ=14.0 (s, $COOCH_2CH_3$), 16.0 (d, $^{3}J_{CCOP}$=6.1 Hz, CH_3CH_2OP), 16.3 (d, $^{3}J_{CCOP}$=6.0 Hz, CH_3CH_2OP), 48.9 (C-9b), 61.8 (s, $COOCH_2CH_3$), 64.5 (d, $^{2}J_{COP}$=6.1 Hz, $POCH_2$), 64.9 (d, $^{2}J_{COP}$=6.1 Hz, $POCH_2$), 68.0 (d, $^{1}J_{CP}$=166.8 Hz, C-3a), 113.9 (C-6), 116.7 (C-9a), 124.8 (C-8), 130.1 (C-7), 132.5 (C-9), 144.2 (d, $^{3}J_{CCCP}$=14.2 Hz, C=N), 150.1 (C-5a), 160.7 ($COOCH_2CH_3$), 165.9 (d, $^{2}J_{CCP}$=6.1 Hz, C-4, C=O); ^{31}P NMR (101.26 MHz) ($CDCl_3$): δ=14.22 (s); MS: m/z (%)=396 (M^+) (12), 368 (26), 323 (13), 283 (14), 266 (16), 259 (47), 213 (42), 186 (79), 158 (27), 138 (72), 131 (27), 111 (100), 82 (43), 65 (18), 29 (80), 28 (80). Anal. Calcd for $C_{17}H_{21}N_2O_7P_1$ (M=396.34): C 51.52; H 5.34; N 7.07. Found: C 51.79; H 5.21; N 6.91.

3.3.2. Ethyl 6-bromo-3a-diethoxyphosphoryl-4-oxo-3,3a,4,9b-tetrahydrochromeno-[3,4-c]pyrazole-1-carboxylate **6b**

Following a general procedure a sample of 6-bromo-3-phosphonocoumarin **1b** (1 mmol, 0.36 g) in chloroform (1.5 mL) was kept for 60 days and after purification by FC, **6b** was isolated in 47% (0.225 g) yield as white crystals, mp=172–175 °C (*n*-hexane/chloroform). IR ($CHCl_3$): ν=3380, 1770, 1725, 1580, 1050, 1025 cm^{-1}; ^{1}H NMR (250 MHz) ($CDCl_3$): δ=1.13 (td, $^{3}J_{HH}$=7.1 Hz, $^{4}J_{HP}$=0.5 Hz, 3H, $POCH_2CH_3$), 1.30 (td, $^{3}J_{HH}$=7.0 Hz, $^{4}J_{HP}$=0.5 Hz, 3H, $POCH_2CH_3$), 1.32 (t, $^{3}J_{HH}$=7.1 Hz, 3H, $COOCH_2CH_3$), 3.98–4.32 (m, 6H, $COOCH_2CH_3$, 2×$POCH_2$), 4.95 (d, $^{3}J_{HCCP}$=20.8 Hz, 1H, CH-9b), 6.95 (d, $^{3}J_{HH}$=8.7 Hz, 1H, H-6), 7.39 (s, 1H, NH), 7.47 (dd, $^{3}J_{HH}$=8.7 Hz, $^{4}J_{HH}$=2.4 Hz, 1H, H-7), 7.87 (d, $^{3}J_{HH}$=2.3 Hz, 1H, H-9); ^{13}C NMR (62.9 MHz) ($CDCl_3$): δ=13.9 (s, $COOCH_2CH_3$), 16.0 (d, $^{3}J_{CCOP}$=5.7 Hz, CH_3CH_2OP), 16.2 (d, $^{3}J_{CCOP}$=5.7 Hz, CH_3CH_2OP), 48.5 (C-9b), 61.9 (s, $COOCH_2$), 64.6 (d, $^{2}J_{COP}$=6.9 Hz, $POCH_2$), 65.0 (d, $^{2}J_{COP}$=6.9 Hz, $POCH_2$), 67.8 (d, $^{1}J_{CP}$=166.0 Hz, C-3a), 115.9 (C-8), 117.2 (C-9a), 118.3 (C-6), 132.9 (C-7), 135.1 (C-9), 144.6 (d, $^{3}J_{CCCP}$=13.7 Hz, C=N), 149.1 (C-5a), 160.3 ($COOCH_2CH_3$), 165.3 (d, $^{2}J_{CCP}$=6.3 Hz, C-4, C=O); ^{31}P NMR (101.26 MHz) ($CDCl_3$): 13.59 (s); HRMS calcd for $C_{17}H_{20}BrN_2O_7PNa$ ($M+Na^+$) 497.00837, found: 497.00802. Anal. Calcd for $C_{17}H_{20}BrN_2O_7P$ (M=475.23): C 42.97; H 4.24; N 5.89. Found: C 42.69; H 4.23; N 5.91.

3.3.3. 1,3a-Diethoxycarbonyl-4-ethoxy-4-oxo-3,9b-dihydro-4,5-benzoxaphosphorino-[3,4-c]-pyrazoles **7** *and* **8**

According to the general procedure a sample of 1,2-benzoxaphosphorin **2a** (1 mmol, 0.28 g) in benzene (0.5 mL) was kept for 30 days. After purification of the reaction mixture by FC, **7** and **8** were isolated in 55% (0.22 g) and 15% (0.06 g) yield, respectively. By changing the solvent to methylene chloride and allowing the reaction mixture for 30 days, after purification of the reaction mixture by FC, **7** and **8** were isolated in 83% (0.33 g) and 12% (0.05 g) yield, respectively.

Epimer **7**: white crystals, mp=173–176 °C (methylene chloride/*n*-hexane). IR ($CHCl_3$): ν=3400, 1750, 1725, 1590, 1035 cm^{-1}; ^{1}H NMR (300 MHz) ($CDCl_3$): δ=1.20 (t, $^{3}J_{HH}$=7.0 Hz, 3H, $COOCH_2CH_3$), 1.31 (t, $^{3}J_{HH}$=7.1 Hz, 3H, $COOCH_2CH_3$), 1.35 (t, $^{3}J_{HH}$=7.1 Hz, 3H, $POCH_2CH_3$), 4.12–4.39 (m, 6H, 2×$COOCH_2CH_3$, $POCH_2CH_3$), 5.38 (d, $^{3}J_{HCCP}$=17.4 Hz, 1H, H-9b), 7.02 (dd, J_{HH}=8.0 and 1.4 Hz, 1H, H-6), 7.19 (dt, J=7.2 and 1.8 Hz, 1H, H-8), 7.29 (dt, J=7.7 and 1.5 Hz, 1H, H-7), 7.46 (s, 1H, NH), 7.75 (dd, J=1.7 Hz, $^{3}J_{HH}$=8.1 Hz, 1H, H-9); ^{13}C NMR (75.4 MHz) ($CDCl_3$): δ=14.1 (s, $COOCH_2CH_3$), 14.1 (s, $COOCH_2CH_3$), 16.1 (d, $^{3}J_{CCOP}$=4.5 Hz, 2×$POCH_2CH_3$), 51.8 (CH-9b), 61.7 (s, $COOCH_2CH_3$), 63.6 (s, $COOCH_2CH_3$), 64.4 (d, $^{2}J_{COP}$=9.0 Hz, $POCH_2$), 70.7 (d, $^{1}J_{CP}$=144.7 Hz, C-3a), 119.8 (d, $^{3}J_{CCOP}$=6.8 Hz, C-6), 121.3 (d, $^{3}J_{CCCP}$=18.1 Hz, C-9a), 125.2 (C-8), 129.7 (C-7) 131.5 (C-9), 143.5 (d, $^{3}J_{CCCP}$=6.8 Hz, C=N), 149.7 (d, $^{2}J_{COP}$=6.8 Hz, C-5a), 161.1 (s, $COOCH_2CH_3$), 166.9 (d, $^{2}J_{CCP}$=4.5 Hz, $COOCH_2CH_3$); ^{31}P NMR (101.26 MHz) ($CDCl_3$): δ=9.39 (s); MS: m/z (%)=396 (M^+) (33), 323 (87), 266 (61), 249 (42), 223 (41), 209 (33), 194 (36), 187 (32), 131 (43), 115 (32), 102 (67), 89 (59), 77 (67), 65 (100), 47 (72), 39 (84). Anal. Calcd for $C_{17}H_{21}N_2O_7P$ (M=396.34): C 51.52; H 5.34; N 7.07. Found: C 51.33; H 5.58; N 7.34.

Epimer **8**: white crystals, mp=172–175 °C (*n*-hexane/ether). IR ($CHCl_3$): ν=3400, 1750, 1725, 1590, 1035 cm^{-1}; ^{1}H NMR (250 MHz) ($CDCl_3$): δ=1.29–1.38 (m, 6H, 2×$COOCH_2CH_3$), 1.47 (td, $^{3}J_{HH}$=7.1 Hz, $^{4}J_{HP}$=0.4 Hz, 3H, $POCH_2CH_3$), 4.26–4.51 (m, 6H, 2×$COOCH_2CH_3$, $POCH_2CH_3$), 5.49 (d, $^{3}J_{HCCP}$=11.3 Hz, 1H, H-9b), 7.03 (dd, J=8.0 and 1.2 Hz, 1H, 6-H), 7.14 (dd as t, J=8.3 Hz, 1H, 8-H), 7.26 (dd as t, J=8.3 Hz, 1H, 7-H), 7.10 (s, 1H, NH), 7.75 (dd, $^{4}J_{HH}$=1.2 Hz, $^{3}J_{HH}$=7.7 Hz, 1H, H-9); ^{13}C NMR (62.5 MHz) ($CDCl_3$): δ=14.0 (s, $COOCH_2CH_3$), 14.1 (s, $COOCH_2CH_3$), 16.5 (d, $^{3}J_{CCOP}$=5.5 Hz, $POCH_2CH_3$), 51.1 (d, $^{2}J_{CCP}$=2.2 Hz, CH-9b), 61.8 (s, $COOCH_2CH_3$), 63.8 (s, $COOCH_2CH_3$), 65.8 (d, $^{2}J_{COP}$=6.2 Hz, $POCH_2$), 70.5 (d, $^{2}J_{CP}$=145.1 Hz, C-3a), 120.3 (d, $^{3}J_{CCOP}$=5.6 Hz, C-6), 120.6 (d, $^{3}J_{CCCP}$=17.6 Hz, C-9a), 125.3 (s, C-8), 129.7 (s, C-7) 131.1 (s, C-9), 144.0 (d, $^{3}J_{CCCP}$=8.0 Hz, C=N), 148.9 (d, $^{2}J_{COP}$=5.4 Hz, C-5a), 161.1 (s, $COOCH_2CH_3$), 167.5 (d, $^{2}J_{CCP}$=4.0 Hz, $COOCH_2CH_3$); ^{31}P NMR (101.26 MHz) ($CDCl_3$): δ=10.66 (s); MS: m/z (%)=396 (M^+) (17), 323 (37), 304 (29), 283 (24), 266 (46), 258 (64), 249 (96), 237 (29), 223 (35), 213 (97), 187 (78), 128 (29), 102 (29), 89 (34), 77 (38), 65 (100), 51 (39), 39 (44). Anal. Calcd for $C_{17}H_{21}N_2O_7P$ (M=396.34): C 51.52; H 5.34; N 7.07. Found: C 51.74; H 5.26; N 7.31.

3.3.4. 1-Ethoxycarbonyl-3a-diethoxyphosphoryl-4-ethoxy-4-oxo-3,9b-dihydro-4,5-benzoxaphosphorino-[3,4-c]-pyrazoles **9a** *and* **10a**

Following a general procedure a sample of 1,2-benzoxaphosphorin **5a** (1 mmol, 0.34 g) in benzene (1 mL) was kept for 30 days. After purification of the reaction mixture by FC, **9a** and **10a** were isolated in 28% (0.13 g) and 7% (0.03 g) yield, respectively (Table 3, method A). By allowing the reaction mixture to react for 70 days (Table 3, method A_1) yields of **9a** and **10a** were almost unchanged (30%, 0.14 g and 8%, 0.04 g, respectively). By changing the solvent to ether (Table 3, method B) and allowing the reaction mixture for 90 days, after purification of the reaction mixture by FC, **9a** in 69% (0.32 g) and **10a** in 7% (0.03 g) yield were isolated.

Epimer **9a**: white crystals, mp=141–143 °C (*n*-hexane/ether). IR (CCl_4): ν=3400, 3340, 1705, 1260, 1055, 1025 cm^{-1}; ^{1}H NMR (300 MHz) ($CDCl_3$): δ=1.22–1.29 (m, $COOCH_2CH_3$, 2×$POCH_2CH_3$), 1.34 (t, $^{3}J_{HH}$=7.0 Hz, 3H, $POCH_2CH_3$), 4.12–4.37 (m, 8H, $COOCH_2CH_3$, 3×$POCH_2CH_3$), 5.11 (t, $^{3}J_{HCCP}$=26.8 Hz, 1H, 9b-H), 7.01–7.31 (m, 4H, aromatics), 7.32 (s, 1H, NH), 7.59 (d, $^{3}J_{HH}$=7.1 Hz, 1H, H-9); ^{13}C NMR (75.4 MHz) ($CDCl_3$): δ=14.0 (s, $COOCH_2CH_3$), 16.3 (d, $^{3}J_{CCOP}$=8.1 Hz, 2×CH_3CH_2OP), 16.5 (d, $^{3}J_{CCOP}$=6.1 Hz, CH_3CH_2OP), 53.1 (d, $^{2}J_{CCP}$=6.1 Hz, C-9b), 61.6 (s, $COOCH_2CH_3$), 63.8 (d, $^{2}J_{COP}$=8.1 Hz, $POCH_2$), 65.0 (d, $^{2}J_{COP}$=6.2 Hz, $POCH_2$), 65.1 (d, $^{2}J_{COP}$=6.1 Hz, $POCH_2$), 66.1 (dd, $^{1}J_{CP}$=133.3, 158.7 Hz, C-3a), 119.9 (d, $^{2}J_{COP}$=5.2 Hz, C-6), 122.2 (dd, $^{3}J_{CCCP}$=7.1, 19.3 Hz, C-9a), 125.1 (C-8), 130.1 (C-7), 131.7 (C-9), 142.2 (t, $^{3}J_{CCCP}$=6.1 Hz, C=N), 150.4 (d, $^{2}J_{COP}$=8.1 Hz, C-5a), 160.9 ($COOCH_2CH_3$); ^{31}P NMR (101.26 MHz) ($CDCl_3$):δ=13.04 (d, J=35.9 Hz), 15.67 (d, J=35.9 Hz); MS: m/z (%)=460 (M^+) (8), 432 (17), 368(13), 323 (100), 324 (61), 295 (21), 249 (42), 223 (27), 182 (35), 114 (35), 69 (43), 65 (33), 41 (31). Anal. Calcd for $C_{18}H_{26}N_2O_8P_2$ (M=460.36): C 46.96; H 5.69; N 6.09. Found: C 46.57; H 5.57; N 6.14.

Epimer **10a**: colourless oil. IR (CCl_4): ν=3360, 1710, 1260, 1060, 1030 cm^{-1}; ^{1}H NMR (250 MHz) ($CDCl_3$): δ=1.23–1.53 (m, 12H, $COOCH_2CH_3$, 3×$POCH_2CH_3$), 4.25–4.48 (m, 6H, $COOCH_2CH_3$, 2×$POCH_2CH_3$), 4.50–4.59 (m, 2H, $POCH_2CH_3$), 5.18 (dd, $^{3}J_{HCCP}$=20.2, 26.7 Hz, 1H, CH-9b), 5.30 (br s, 1H, NH), 7.05–7.34 (m, 4H, aromatic), 7.49 (d, J=7.4 Hz, 1H, H-9); ^{13}C NMR (62.9 MHz) ($CDCl_3$): δ=14.1 (s, $COOCH_2CH_3$), 16.1–16.5 (m, 3×CH_3CH_2OP), 52.2 (t, $^{2}J_{CCP}$=4.4 Hz, C-9b), 61.6 (s, $COOCH_2CH_3$), 64.4 (d, $^{2}J_{COP}$=3.7 Hz, $POCH_2$), 65.4 (d,

$^2J_{COP}$=7.1 Hz, PO*C*H$_2$), 66.2 (d, $^2J_{COP}$=5.8 Hz, PO*C*H$_2$), 66.3 (dd, $^1J_{CP}$=152.8, 135.6 Hz, C-3a), 120.6 (d, $^2J_{COP}$=4.6 Hz, C-6), 125.2 (C-8), 121.5 (dd, $^3J_{CCCP}$=9.5, 19.5 Hz, C-9a), 130.1 (C-7), 131.5 (C-9), 142.6 (t, $^3J_{CCCP}$=5.8 Hz, C=N), 149.7 (d, $^2J_{COP}$=5.2 Hz, C-5a), 161.1 (*C*OOCH$_2$CH$_3$); ^{31}P NMR (101.26 MHz) (CDCl$_3$):δ=11.88 (d, *J*=40.3 Hz), 15.68 (d, *J*=40.3 Hz). Anal. Calcd for $C_{18}H_{26}N_2O_8P_2$ (M=460.36): C 46.96; H 5.69; N 6.09. Found: C 46.66; H 5.81; N 6.40.

*3.3.5. 6-Bromo-1-ethoxycarbonyl-3a-diethoxyphosphoryl-4-ethoxy-4-oxo-3,9b-dihydro-4,5-benzoxaphosphorino-[3,4-c]-pyrazoles **9b** and **10b***

Following a general procedure a sample of 6-bromo-1,2-benzoxaphosphorine **5b** (1 mmol, 0.42 g) in benzene (1 mL) was kept for 70 days and after purification of the reaction mixture by FC, **9b** and **10b** were isolated in 44% (0.24 g) and 15% (0.08 g) yield, respectively (Table 3, method A$_1$). When the reaction took place in ether (1 mL) for 70 days (Table 3, method B), and after purification of the reaction mixture by FC, **9b** and **10b** were isolated in 55% (0.30 g) and 15% (0.08 g) yield, respectively.

*Epimer **9b***: white crystals, mp=159–162 °C (*n*-hexane/ether). IR (CHCl$_3$): ν=3360, 1715, 1580, 1065, 1035 cm^{-1}; ^{1}H NMR (250 MHz) (CDCl$_3$): δ=1.24–1.38 (m, 12H, COOCH$_2$C*H*$_3$, 3×POCH$_2$C*H*$_3$), 4.11–4.40 (m, 8H, COOC*H*$_2$CH$_3$, 3×POC*H*$_2$CH$_3$), 5.04 (t, $^3J_{HCCP}$=26.5 Hz, 1H, CH-9b), 6.91 (d, $^3J_{HH}$=8.6 Hz, 1H, H-6), 7.21 (s, 1H, NH), 7.43 (dd, $^3J_{HH}$=8.6 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-7), 7.74 (d, $^4J_{HH}$=2.3 Hz, 1H, H-9); ^{13}C NMR (62.9 MHz) (CDCl$_3$): δ=14.0 (s, COOCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CCOP}$=5.3 Hz, 2×*C*H$_3$CH$_2$OP), 16.4 (d, $^3J_{CCOP}$=5.3 Hz, *C*H$_3$CH$_2$OP), 52.7 (dd, $^2J_{CCP}$=2.8, 6.0 Hz, C-9b), 61.7 (s, COO*C*H$_2$), 63.8 (d, $^2J_{COP}$=7.3 Hz, PO*C*H$_2$), 65.1 (d, $^2J_{COP}$=7.3 Hz, PO*C*H$_2$), 65.3 (d, $^2J_{COP}$=8.4 Hz, PO*C*H$_2$), 65.9 (dd, $^1J_{CP}$=133.3, 156.6 Hz, C-3a), 117.7 (C-8), 121.6 (d, $^2J_{COP}$=6.3 Hz, C-6), 124.1 (dd, $^3J_{CCCP}$=9.4, 22.0 Hz, C-9a), 132.9 (C-7), 134.4 (C-9) 141.8 (t, $^3J_{CCCP}$=6.3 Hz, C=N), 149.5 (d, $^2J_{COP}$=8.1 Hz, C-5a), 160.6 (*C*OOCH$_2$CH$_3$); ^{31}P NMR (101.26 MHz) (CDCl$_3$): δ=12.51 (d, *J*=35.9 Hz), 15.16 (d, *J*=34.2 Hz); HRMS calcd for $C_{18}H_{25}BrN_2O_8P_2Na$ (M+Na$^+$) 561.01617, found: 561.01658. Anal. Calcd for $C_{18}H_{25}BrN_2O_8P_2$ (M=539.26): C 40.09; H 4.67; N 5.19. Found: C 39.95; H 4.88; N 5.52.

*Epimer **10b***: white crystals, mp=124–127 °C (*n*-hexane/ether). IR (CHCl$_3$): ν=3400, 1720, 1590, 1060, 1030 cm^{-1}; ^{1}H NMR (250 MHz) (CDCl$_3$): δ=1.20–1.42 (m, 9H, COOCH$_2$C*H*$_3$, 2×POCH$_2$C*H*$_3$), 1.47 (t, $^3J_{HH}$=7.0 Hz, 3H, POCH$_2$C*H*$_3$), 4.10–4.40 (m, 6H, COOC*H*$_2$CH$_3$, 2×POC*H*$_2$CH$_3$), 4.45–4.56 (m, 2H, POC*H*$_2$CH$_3$), 5.08 (dd, $^3J_{HCCP}$=19.7, 26.5 Hz, 1H, CH-9b), 5.6 (br s, 1H, NH), 6.92 (d, $^3J_{HH}$=8.7 Hz, 1H, H-6), 7.39 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-7), 7.80 (d, $^4J_{HH}$=2.3 Hz, 1H, H-9); ^{13}C NMR (62.9 MHz) (CDCl$_3$): δ=14.1 (s, COOCH$_2$*C*H$_3$), 16.3 (d, $^3J_{CCOP}$=8.2 Hz, 2×*C*H$_3$CH$_2$OP), 16.4 (d, $^3J_{CCOP}$=5.2 Hz, *C*H$_3$CH$_2$OP), 51.7 (t, $^2J_{CCP}$=4.3 Hz, C-9b), 61.8 (s, COO*C*H$_2$CH$_3$), 64.4 (d, $^2J_{COP}$=7.4 Hz, PO*C*H$_2$), 65.3 (d, $^2J_{COP}$=6.9 Hz, PO*C*H$_2$), 66.4 (d, $^2J_{COP}$=5.7 Hz, PO*C*H$_2$), 66.0 (dd, $^1J_{CP}$=133.2, 152.2 Hz, C-3a), 117.8 (C-8), 122.3 (d, $^2J_{COP}$=4.6 Hz, C-6), 123.5 (dd, $^3J_{CCCP}$=10.3, 20.8 Hz, C-9a), 133.0 (C-7), 133.9 (C-9), 142.1 (t, $^3J_{CCCP}$=5.6 Hz, C=N), 148.8 (d, $^2J_{COP}$=5.0 Hz, C-5a), 160.8 (*C*OOCH$_2$CH$_3$); HRMS calcd for $C_{18}H_{25}BrN_2O_8P_2Na$ (M+Na$^+$) 561.01617, found: 561.01620. Anal. Calcd for $C_{18}H_{25}BrN_2O_8P_2$ (M=539.26): C 40.09; H 4.67; N 5.19. Found: C 39.83; H 4.58; N 5.29.

3.4. X-ray crystallographic analysis

Crystals of the compounds were grown by slow evaporation of their solutions in ethyl acetate/*n*-hexane (**5b**), diethyl ether/benzene (**6a**, **9a**) or benzene/*n*-hexane (**7**). The data were collected on a Bruker APEX SMART CCD diffractometer at 153 K using Mo Kα radiation. Direct methods SHELXS-97[38] and successive interpretation of difference Fourier maps, followed by least-squares refinement SHELXL-97[39] solved the structures. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the refinement in calculated positions. Molecular graphics were prepared using program PLATON.[40]

*Compound **5b***: $C_{14}H_{19}BrO_6P_2$ (*M* 425.14), monoclinic, space group *P*21/*c*, *a*=7.6545(5), *b*=19.3084(13), *c*=23.4677(16) Å, β=91.460(10), *V*=3467.3 Å^3, *Z*=8, ρ=1.629 g cm^{-3}, μ=2.58 mm^{-1}, *F*(000)=1728. Crystal size=0.50×0.40×0.20 mm, $2\theta_{max}$<50°. Goodness-of-fit *F*^{2}=0.958, *wR*2=0.0819.

*Compound **6a***: $C_{17}H_{21}N_2O_7P$ (*M* 396.33), triclinic, space group $P\bar{1}$, *a*=8.7694(5), *b*=9.3721(5), *c*=12.8233(7) Å, α=100.112(2), β=96.150(2), γ=117.153(2), *V*=901.86 Å^3, *Z*=2, ρ=1.459 g cm^{-3}, μ=0.20 mm^{-1}, *F*(000)=416. Crystal size=0.5×0.28×0.25 mm, 2θ<60°. Goodness-of-fit *F*^{2}=1.106, *wR*2=0.1888.

*Compound **7***: $C_{17}H_{21}N_2O_7P$ (*M* 396.33), monoclinic, space group *P*21/*n*, *a*=11.4147(4), *b*=14.5158(5), *c*=11.4822(4) Å, β=93.3390(10), *V*=1899.30 Å^3, *Z*=4, ρ=1.386 g cm^{-3}, μ=0.186 mm^{-1}, *F*(000)=832. Crystal size=0.5×0.52×0.45 mm, 2θ<55°. Goodness-of-fit *F*^{2}=0.985, *wR*2=0.1387.

*Compound **9a***: $C_{18}H_{26}N_2O_8P_2$ (*M* 460.35), triclinic, space group $P\bar{1}$, *a*=9.4071(5), *b*=9.9775(5), *c*=13.1732(7) Å, α=85.6490(10), β=78.6100(10), γ=66.0450(10), *V*=1107.66 Å^3, *Z*=2, ρ=1.380 g cm^{-3}, μ=0.242 mm^{-1}, *F*(000)=484. Crystal size=0.52×0.52×0.38 mm, $2\theta_{max}$<60°. Goodness-of-fit *F*^{2}=0.737, *wR*2=0.1686.

Crystallographic data for the structures in this paper have been deposited in the Cambridge Crystallographic Data Center as a supplementary publication (**5b**, CCDC 694037; **6a**, CCDC 694038; **7**, CCDC 694039; **9a**, CCDC 694040). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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