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Synthesis of 2H-1,2-oxaphosphorin 2-oxides

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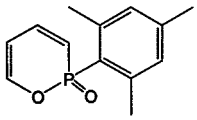
Abstract

Two novel heterocyclic dienes, 2-ethoxy-3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxide (**3**) and 5-bromo-2-ethoxy-3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxide (**4**), are described. They were prepared in four steps starting from 2-ethoxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (**12a**,**b**) (*trans* and *cis*) by a bromination–dehydrobromination sequence. Free radical bromination of **12a**,**b** with NBS/AIBN furnished two isomeric bromides **13a**,**b**. Isomer **13b** gave 2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxide (**14**) on treatment with LiCl/DMF. Isomer **13a** underwent C–OEt bond cleavage followed by HBr elimination to give the phosphonic acid **17**. Treatment of **14** with NBS/AIBN afforded isomeric 5-bromo-2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxides (**15a**,**b**) and 5,5-dibromo-2-ethoxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxide (**18**), separated by chromatography. Dehydrobromination of **15a**,**b**, and **18** with an excess of Et_3N in toluene at 80–95 °C provided the target dienes **3** and **4**, respectively.

Keywords: Phosphorus heterocycles; 2*H*-1,2-Oxaphosphorin 2-oxide; Bromination; Synthesis; Dehydrobromination

1. Introduction

Analogs of α-pyrone have been of considerable interest to synthetic chemists because of their biological properties [1–7]. The activity of α-pyrones as HIV protease inhibitors sparked additional interest in the investigation of these compounds [1,2]. Sulfur and selenium intracyclic analogs of α-pyrone exhibited strong photobiological activity [8]. Furthermore, pyrones are valuable substrates in the Diels–Alder reaction as precusors for more complex systems [6,7,9–13]. By contrast, only two phosphorus analogs of α-pyrone (**1** and **2**) have been previously synthesized [14,15]; important steric or electronic effects accounted for their stability.



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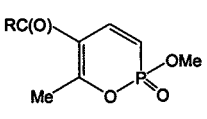

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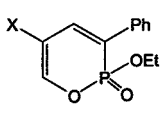

3 X = H
4 X = Br

Due to our interest in the physico-chemical properties of non-stabilized phosphorous α-pyrone analogs, we undertook synthesis of two 3-phenyl-2*H*-oxo-1,2-oxaphosphorin 2-oxides **3** and **4**. The synthetic pathway allowed isolation of several 5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide derivatives which may serve as valuable synthetic intermediates.

2. Results and discussion

2.1. Bromination–dehydrobromination of phostone (5)

Prior work in our laboratory on the synthesis of 2-ethoxy-1,2-dioxaphosphorinane **5** (phostone) and its derivatives [16–18] suggested the use of **5** as a starting material. Bromination–dehydrobromination of **5** was expected to provide the cyclic diene, 2-ethoxy-2H-1,2-oxaphosphorin **9** (Scheme 1).

Free radical bromination of **5** with NBS in the presence of AIBN in CCl_4 was unsuccessful. However, **5** was brominated by treatment with LDA in bromine–THF (Scheme 2) to give a 1:1 mixture of monobro-

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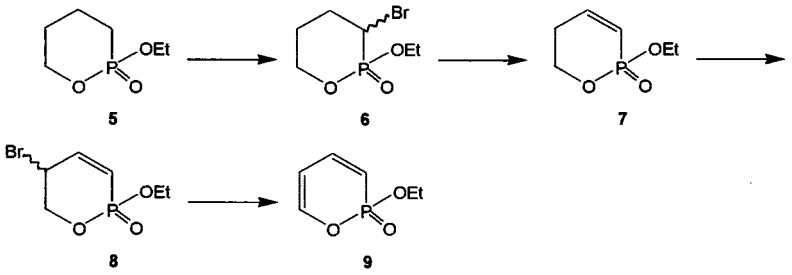


Scheme 1.

mides **6a**,**b** (1:1.7 *cis* and *trans* isomers) and dibromide **10** after purification. The monobromide and dibromide were easily separated by flash-chromatography. Their structures were supported by NMR spectroscopy (^{31}P, ^{1}H, ^{13}C) and GC-MS. Attempted sequential addition of LDA and Br_2 was less successful, resulting in a mixture of **5**, **6** and **10** in a 64:23:10 ratio, respectively.

Attempted dehydrobromination **6** in the presence of KO-*t*-Bu or DBU at room temperature did not yield any product. When DBU–THF was used at 60 °C for 12 h, a complex mixture of five products was obtained (δ ^{31}P-NMR, ppm (content): 16.0 (1), 13.64 (2), 8.0 (7.4), 7.1 (8.7)). Only a small amount of compound **7** was observed by GC-MS. Conditions involving KO-*t*-Bu–DMSO (room temperature, 12 h) also gave a complex mixture containing only a small amount of the desired product by GC-MS. An attempt to use LiCl as a dehydrobromination agent led to exocyclic C–O cleavage to give **11** (Scheme 3). The ^{13}C-NMR spectrum of this phosphonic acid is very similar to that of **6**.

2.2. Bromination–dehydrobromination of phenyl phostone (12)

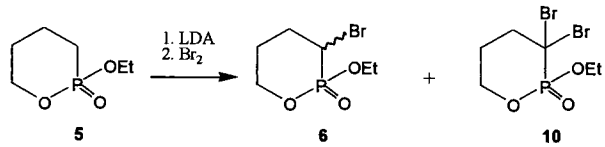
The presence of the phenyl substituent in 3-phenyl-2-oxo-1,2-oxaphosphorinane **12a**,**b** (*trans* and *cis* isomers previously assigned [18] by X-ray and NMR spectroscopy) permitted facile introduction of a bromo substituent via AIBN-initiated bromination with 1.5 equivalents of NBS in refluxing CCl_4 to give **13a**,**b** (Scheme 4).

Although the **12b**(*cis*)/**12a**(*trans*) ratio was varied from 3.2:1 to 0.7:1, a constant 2.1:1 ratio of **13b**:**13a** was observed in the ^{31}P-NMR spectra. The **12b**/**12a** ratio did not change over the course of the reaction (GC, ^{31}P-NMR). The isomers of **13** were separated by flash chromatography to give 25% of **13a** and 65% of **13b** (overall 90% yield). The structure of **13** was supported by elemental combustion analysis, GC-MS and NMR spectral data (Table 1). Comparison of ^{31}P-NMR and ^{13}C-NMR data of **13a**,**b** with that of **12a**,**b** allowed a tentative stereo-assignment of the former pair of isomers. The phosphorus chemical shifts in the *cis* isomers (**12b**, **13b**) were upfield relative to the *trans* isomers (**12a**, **13a**).

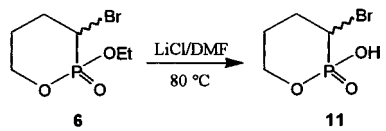
Each of the individual isomers of **13** partially isomerized to give 13% of the other isomer by GC (injector temperature 260 °C). The mechanism for the isomerization is not clear. In addition, the invariant **13a/13b** ratio obtained during the bromination reaction of **12a**,**b** (vide infra) was anticipated since bromination would give the same free radical intermediate. For **13b** (*cis* isomer) the further transformation to 2-ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin **14** (9%) occurred.

Attempts to dehydrobrominate **13** with conventional reagents such as potassium *tert*-butoxide in (THF or DMSO) or DBU in THF were unsuccessful. Elimination was achieved (Scheme 5) by treatment of the major *cis* isomer **13b** with LiCl–Li_2CO_3 in DMF using conditions reported for dehydrohalogenation of α,α-dihalocarboxylates [19] and 1,2-dibromocyclohexane [20]. Heating **13b** with LiCl (twofold excess) and Li_2CO_3 (0.5 equivalents) in DMF at 80 °C for 1.5 h gave **14** in only 28% yield (after water-workup and chromatography).

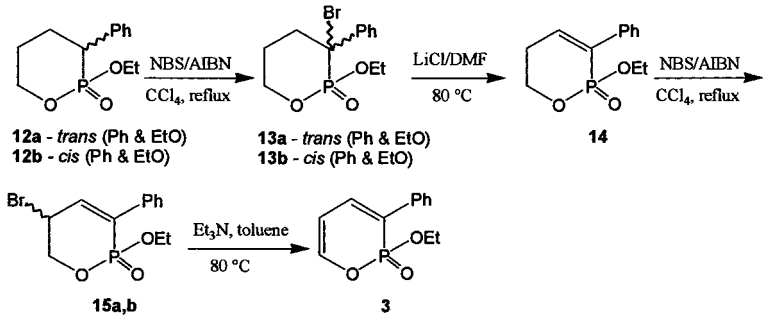
In contrast to the observed low yield for the dehydrohalogenation of α,α-dihalocarboxylates using LiCl in the absence of Li_2CO_3 [18], we were able to increase the yield (57%) of **14**. Similar to the results employing LiCl–Li_2CO_3, two water-soluble byproducts (^{31}P-NMR, δ 11.2, 9.3 ppm) were observed in the reaction mixture. The structure of **14** was confirmed by elemental analysis, GC-MS and ^{1}H- and ^{13}C-NMR data (Table 1).



Scheme 2.



Scheme 3.

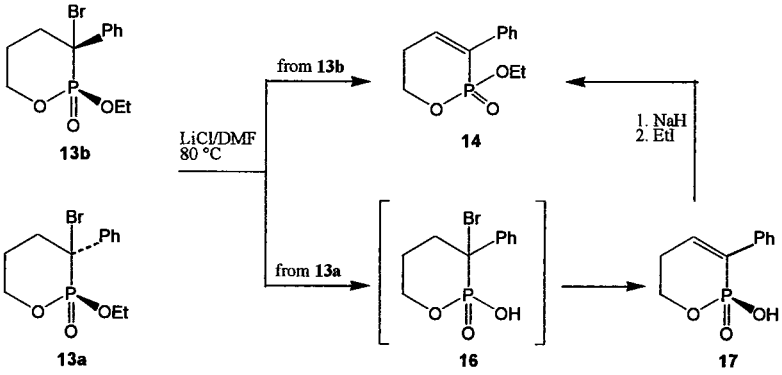


Scheme 4.

Table 1
NMR data for the phostone derivatives **3**, **4**, **12**, **13**, **14**, **15** and **18**

Compound	^{31}P-NMR ($CDCl_3$)	^{13}C-NMR ($CDCl_3$)				
		C-3 ($^1J_{CP}$)	C-4 ($^2J_{CP}$)	C-5 ($^3J_{CP}$)	C-6 ($^2J_{CP}$)	C-7 ($^2J_{CP}$) [a]
3	10.9	125.9 (166)	135.3 (3.6)	105.6 (20.6)	144.5 (13.4)	134.3 (11.3)
4	7.6	127.8 (168)	138.6 (3.4)	101.7 (22.8)	141.8 (15.1)	134.4 (11.3)
12a (*trans*)	26.5	43.1 (126)	30.1 (4.9)	27.1 (3.7)	68.9 (4.9)	136.5 (6.1)
12b (*cis*)	22.4	43.0 (125)	28.9 (6.1)	27.1 (4.9)	70.0 (7.2)	135.6 (8.5)
13a (*trans*)	16.7	58.4 (141)	38.1 (2.2)	24.8 (4.3)	69.6 (5.5)	138.7 (bs)
13b (*cis*)	14.0	58.2 (140)	35.9 (3.9)	23.8 (6.5)	70.2 (7.1)	138.5 (bs)
14	11.6	131.3 (165)	141.7 (5.1)	27.9 (10.5)	65.4 (5.7)	135.7 (10.1)
15a	10.0	132.7 (164)	139.9 (2.9)	41.5 (9.3)	70.8 (6.7)	134.4 (10.5)
15b	9.9	132.6 (160)	140.0 (3.6)	41.9 (9.7)	69.6 (5.5)	134.2 (9.0)
18	8.2	127.8 (163)	143.3 (bs)	52.6 (9.8)	75.6 (7.0)	132.3 (8.6)

[a] C-7 is the *ipso* carbon of the phenyl substituent.

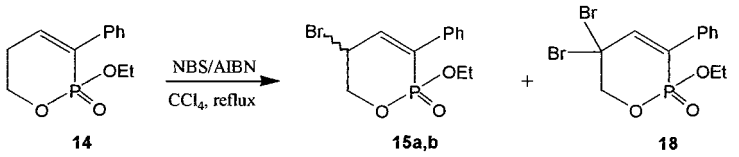


Scheme 5.

Treatment of the minor isomer with LiCl **13a**(*trans*) for 2 h led to 2-hydroxy-5,6-dihydro-3-phenyl-2*H*-1,2-oxaphosphorin 2-oxide **17** (^{31}P-NMR, δ 9.3 ppm) along with a small amount (10%) of **14** and a product of unknown structure (8%, δ 10.7 ppm); the latter was transformed to **17** upon further heating. This suggested that the reaction of **13a** generated the intermediate bromophosphinic acid **16**, which underwent subsequent elimination to give **17** (Scheme 5). The structure of **17** was supported by ^{1}H and ^{13}C-NMR spectral data which were very similar to ester **14**. Compound **17** was converted to **14** upon treatment with NaH followed by EtI. The two water-soluble by-products observed for the reaction **13b**(*cis*) with LiCl were likely compounds **16** and **17**.

*2.3. Bromination–dehydrobromination of 5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**14**)*

Treatment of **14** with NBS (1.05 equivalents)–AIBN in refluxing CCl_4 gave an approximate ratio 1.5:0.7:1 of **15a**:**15b**:**18** with an overall yield (48%) (Scheme 6).



Scheme 6.

Increase of amount of NBS (1.5 equivalents) resulted in only the single isomer **15a** and **18** (crude ratio 1:1.7) with an enhanced yield (73%). Compound **18** and the isomers **15a**,**b** were all separated by chromatography.

Isomers **15a**,**b** were easily equilibrated in the presence of Et_3N or pyridine at room temperature to afford a **15b**:**15a** mixture (1.6:1). Similar to other cases, chromatography altered the **15a**:**15b** ratio to 1:3. The nearly identical NMR data of **15a**,**b** isomers prevented isomer assignments.

Similar to the GC-MS behavior of isomer **13b**, we observed dehydrobromination upon injection of isomers **15a**,**b** to give diene **3**. The ratio of **15**:**3** varied from one injection to another, and the individual isomers of **15** were not separated. Moreover, the dibromide **18** cleanly dehydrobrominated during the injection to give the diene **4** as the only observable peak.

Attempted dehydrobromination of bromide **15a** with potassium *tert*-butoxide, DBU or LiCl–Li_2CO_3, did not produce diene **3** as indicated by ^{31}P- and ^{13}C-NMR spectroscopy. The lack of dehydrobromination in the presence of LiCl was attributed to nucleophilic substitution of Br by Cl; a pair of new compounds (δ 10.0, 9.8 ppm: **19a**,**b**) was observed (Scheme 7). The MS peaks of isomeric chlorides **19a**,**b** (1.5:1; isomer assignment unknown) in the GC-MS along with a peak of the diene **3** (30%, thermal dehydrohalogenation) supported this assumption. The GC-MS data indicated that one isomer of the **19** underwent elimination much faster than the other. The structure of **19** was also supported by its ^{13}C-NMR spectrum which was similar to that of bromide analogs **15**.

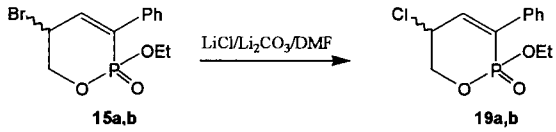
Ultimately, dehydrobromination of **15** was achieved upon heating with an excess of Et_3N in toluene at 95 °C, producing **3** in 71% yield (Scheme 4). Likewise, dehydrobromination of **18** at 80 °C gave **4** in 54% yield (Scheme 8). Similar to **13a**, the treatment of dibromide **18** with LiCl–Li_2CO_3 in DMF led to both elimination and C–O cleavage to render the phosphonic acid **20** which was characterized in the crude mixture. The ^{1}H- and ^{13}C-NMR features of the heterocyclic ring in **20** were close to that of **4**.

The ^{1}H-NMR spectrum of diene **3** is especially interesting as all the coupling constants in this molecule are well resolved and readily assigned (Fig. 1).

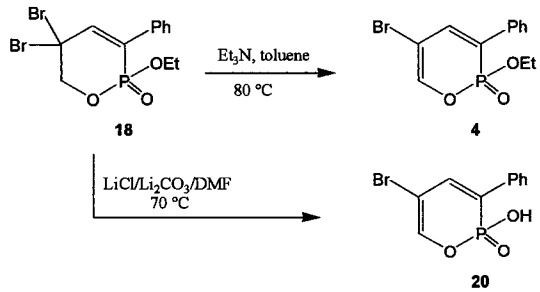
The cyclic dienes were sufficiently stable upon chromatography with silica gel. However, after isolation diene **3** decomposed in a few weeks at room temperature. The bromominated diene **4** was more stable which permitted the longer storage of this material.

2.4. Diels–Alder reactions of 2H-1,2-oxaphosphorin 2-oxides

Acyclic phosphorus-containing dienes are known to be good reactants in the Diels–Alder reaction [21,22]. The cyclic mesityl-2,4-butadienylphostinate underwent Diels–Alder addition with maleic anhydride or dimethyl acetylenedicarboxylate, but only under forcing conditions, which caused decomposition of the postulated adducts [14]. The diene **3** was anticipated to react with tetracyanoethylene dienophile. However, this reaction failed to afford any cycloadduct under the conventional conditions at 75 °C in THF or in the presence of $BF_3{\cdot}OEt_2$ (one equivalent) or $LiClO_4$ (25%) in CH_2Cl_2



Scheme 7.



Scheme 8.

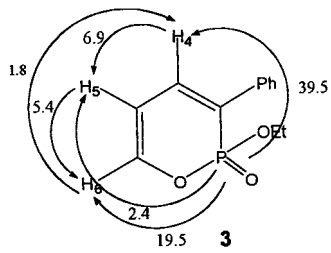


Fig. 1. Coupling constants (in MHz) from ^{1}H-NMR spectrum of diene **3**.

under ultrasound radiation at room temperature. This suggested that the electron withdrawing properties of the phosphorus and phenyl groups decreased the electron donor capability of this fragment.

In conclusion, the first non-stabilized 2-oxo-1,2-oxaphosphorinane-3,5-diene derivatives **3** and **4** were synthesized in four steps from the phenyl phostone **12**. The key intermediates and isomers were isolated and characterized by NMR spectroscopy; GC-MS, and elemental combustion analysis.

3. Experimental

3.1. General

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. NMR spectra were recorded on a GE OMEGA 300 MHz NMR spectrometer. $CDCl_3$ was used as the solvent in all cases unless stated otherwise. Chemical shifts for ^{1}H- and ^{13}C- (75 MHz) NMR were reported in ppm relative to TMS and to 85% H_3PO_4 for ^{31}P-NMR (121 MHz). Coupling constants, J, are given in Hz. Two-dimensional NMR spectra (COSY, HETCOR and DEPT) supported the structural assignments for all new isolated compounds. GC-MS data were obtained on a Hewlett–Packard 5890A gas chromatograph-5970 series mass selective detector: capillary column DB-1, 0.25 mm; id 30 m; injection temperature 260 °C; determinant temperature 265 °C; initial temperature 100 °C for 5 min then 10 °C min^{-1}; final temperature 250 °C. Elemental analyses were performed by Quantitative Technologies Inc., NJ. HR-MS were performed by the Washington University Resource for Biomedical and Bio-Organic Mass Spectrometry, St. Louis, MO. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. TLC (Aldrich) plates were developed by iodine. All chemicals were purchased from the Aldrich Chemical Co. and used without further purification. Preparative flash chromatography was performed with Acros silica gel (0.035–0.075 mm). The preparation of **5** and **12** was previously described [18].

3.2. 3-Bromo-2-ethoxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (mixture **6a**,**b**) and 3,3-dibromo-2-ethoxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (**10**)

An LDA solution (11 mmol) in THF (10 ml) was slowly added over 10 min to a solution of phostone **5** (1.64 g, 10 mmol) and bromine (1.60 g, 10 mmol) at −78 °C. Immediate decoloration was observed. After stirring for 30 min the mixture was quenched with saturated $NaHCO_3$ (5 ml) at −78 °C and then allowed to warm to room temperature (r.t.). The THF was evaporated, the residue was extracted with CH_2Cl_2 (3 × 5 ml), and the organic phase washed with water (5 ml) and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography on SiO_2 (EtOAc–hexanes, 1:1, then EtOAc) to give a 1:1.7 mixture of **6a**/**6b** (0.39 g, 16%) and **10** (0.55 g, 17%) as yellowish oils.

6: $R_f = 0.37$ (EtOAc); $t_R = 18.9$ min; ^{31}P-NMR δ(content): 16.8 (**6a**), 14.5 (**6b**), (**6a**:**6b**, 1:1.7); ^{1}H-NMR δ(**6a**:**6b**, 1:1.7): 4.45–4.18 (m, 4H), 3.95–3.86 (m, 1H), 2.63–2.14 (m, 2H), 2.11–1.68 (m, 2H), 1.47 (dt, 3 H, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.6$), 1.38 (dt, 3 H, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.4$); ^{13}C-NMR (**6a**) δ: 69.52 (d, $^2J_{CP} = 5.7$), 63.26 (d, $^2J_{CP} = 6.2$), 36.64 (d, $^1J_{CP} = 141.5$), 32.46 (d, $^2J_{CP} = 0.9$), 24.50 (d, $^3J_{CP} = 5.4$), 16.21 (d, $^3J_{CP} = 3.8$); ^{13}C-NMR (**6b**) d: 69.65 (d, $^2J_{CP} = 6.6$), 63.99 (d, $^2J_{CP} = 6.6$), 36.20 (d, $^1J_{CP} = 140.4$), 33.55 (d, $^2J_{CP} = 5.0$), 26.97 (d, $^3J_{CP} = 5.6$), 16.21 (d, $^3J_{CP} = 3.8$). MS m/e (relative intensity) 244 ([M$^+$], 7), 242 ([M$^+$], 6), 217 (45), 215 (46), 163 (43), 135 (100), 108 (25), 106 (24), 71 (18), 55 (70), 41 (37).

10: $R_f = 0.20$ (EtOAc–hexanes, 1:1); $t_R = 15.1$ min; ^{31}P-NMR δ: 8.7; ^{1}H-NMR δ: 4.51–4.25 (m, 4H), 3.04–2.77 (m, 2H), 2.22–2.07 (m, 1H), 1.93–1.77 (m, 1H), 1.42 (dt, 3H, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.8$); ^{13}C-NMR δ: 70.02 (d, $^2J_{CP} = 8.3$), 66.22 (d, $^2J_{CP} = 7.1$), 53.03 (d, $^1J_{CP} = 145.9$), 45.92 (bs), 25.86 (d, $^3J_{CP} = 3.2$), 16.38 (d, $^3J_{CP} = 2.9$). MS m/e (relative intensity) 324 ([M$^+$], 1), 322 ([M$^+$], 2), 320 ([M$^+$], 1), 297 (13), 295 (24), 293 (12), 243 (33), 241 (32), 215 (55), 213 (56), 186 (24), 135 (34), 133 (51), 53 (100), 47 (42).

3.3. 3-Bromo-2-hydroxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (**11**)

A mixture of **6** (50 mg, 0.2 mmol), LiCl (17 mg, 0.4 mmol) and DMF (5 ml) was heated at 80 °C for 6 h. ^{31}P-NMR (DMF) δ: 8.2; ^{13}C-NMR (DMF) δ: 66.03 (d, $^2J_{CP} = 4.1$), 43.60 (d, $^1J_{CP} = 136.1$), 33.22 (d, $^2J_{CP} = 2.4$), 24.98 (d, $^3J_{CP} = 2.7$).

3.4. 3-Bromo-2-ethoxy-3-phenyl-1,2-oxaphosphorinane 2-oxide (**13a**,**b**)

A solution of **12a**:**12b** (1:0.7), (1.46 g, 6.08 mmol), NBS (1.62 g, 9.1 mmol, 1.5 equivalents), and AIBN (0.15 g, 0.9 mmol, 0.15 equivalents) in CCl_4 (15 ml) was stirred and refluxed for 3.0 h. The residue was cooled at 0 °C and the succinimide was removed by filtration. The solvent was evaporated in vacuo and the residue **13a**:**13b** (1:2.1 by ^{31}P-NMR) was chromatographed on SiO_2 (EtOAc–hexane, 1:1) to give **13a** (0.49 g, 25%) and **13b**(*cis*) (1.26 g, 65%) as colorless oils (total 90%).

13a: $R_f = 0.36$ (EtOAc–hexanes, 1:1); $t_R = 19.0$ min; ^{31}P-NMR δ: 16.7; ^{1}H-NMR δ: 7.80–7.75 (m, 2H), 7.40–7.27 (m, 3H), 4.53–4.27 (m, 4H), 3.05–2.93 (m,

1H), 2.79–2.64 (m, 1H), 2.37–2.22 (m, 1H), 1.89–1.78 (m, 1H), 1.42 (dt, 3H, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.4$); ^{13}C-NMR δ: 138.69 (bs), 128.47 (two peaks are overlapped), 127.89 (d, $^3J_{CP} = 5.8$), 69.56 (d, $^2J_{CP} = 5.5$), 65.45 (d, $^2J_{CP} = 7.4$), 58.44 (d, $^1J_{CP} = 141.3$), 38.13 (d, $^3J_{CP} = 2.2$), 24.76 (d, $^3J_{CP} = 4.3$), 16.41 (d, $^3J_{CP} = 5.4$); MS *m*/*e* (relative intensity) 320 ([M$^+$], 0.6), 318 (M$^+$, 0.6), 239 (100), 211 (19), 209 (13), 195 (25), 131 (56), 129 (72), 103 (27), 91 (43), 77 (36), 51 (19); Anal. Calc. for $C_{12}H_{16}BrO_3P$: C, 45.16; H, 5.05; Found: 45.68; H, 5.19%.

13b: $R_f = 0.46$ (EtOAc–hexanes, 1:1); $t_R = 19.9$ min; ^{31}P-NMR δ: 14.0; ^{1}H-NMR δ: 7.85–7.80 (m, 2H); d 7.41–7.29 (m, 3H), 4.46–4.23 (m, 2H), 3.98–3.85 (m, 1H), 3.67–3.54 (m, 1H), 2.80–2.55 (m, 3H), 1.86–1.78 (m, 1H), 0.93 (dt, 3H, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.4$); ^{13}C-NMR δ: 138.48 (bs), 128.53, 128.21, 127.55 (d, $^3J_{CP} = 6.6$), 70.24 (d, $^2J_{CP} = 7.1$), 63.84 (d, $^2J_{CP} = 7.6$), 58.18 (d, $^1J_{CP} = 140.0$), 35.91 (d, $^2J_{CP} = 3.9$), 23.84 (d, $^3J_{CP} = 6.5$), 15.75 (d, $^3J_{CP} = 2.5$); MS *m*/*e* (relative intensity) 320 ([M$^+$], 0.3), 318 ([M$^+$], 0.3), 239 (100), 211 (18), 209 (21), 195 (24), 131 (58), 129 (72), 103 (25), 91 (43), 77 (33), 51 (18); Anal. Calc. for $C_{12}H_{16}BrO_3P$: C, 45.16; H, 5.05. Found: C, 45.12; H, 5.04%.

*3.5. 2-Ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**14**) (from **13b**)*

3.5.1. Method A (LiCl–Li_2CO_3)

Bromide **13b** (0.81 g, 2.54 mmol) was dissolved in dry DMF (4 ml). To this solution (in a dry box) was added LiCl (0.215 g, 5.08 mmol) and Li_2CO_3 (0.094 g, 1.27 mmol). The mixture was stirred at 80 °C for 2.0 h. The DMF was evaporated under high vacuo at 40 °C, then water (4 ml) was added, and the water phase was extracted by ether (3 × 4 ml). The organic phase was washed by brine (2 ml) and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography on SiO_2 (EtOAc–hexanes, 1:1, then EtOAc) to give **14** (0.17 g, 28%) as a colorless oil: $R_f = 0.21$ (EtOAc–hexanes, 1:1); $t_R = 17.5$ min; ^{31}P-NMR δ: 11.6; ^{1}H-NMR δ: 7.61–7.56 (m, 2H), 7.39–7.31 (m, 3H), 6.78 (dt, 1H, $^3J_{HP} = 42.3$, $^3J_{HH} = 4.2$), 4.58–4.40 (m, 2H), 4.18–4.00 (m, 2H), 2.78–2.64 (m, 1H), 2.59–2.46 (m, 1H), 1.23 (dt, 3H, $^3J_{HH} = 7.1$, $^4J_{HP} = 1.4$); ^{13}C-NMR δ: 141.73 (d, $^2J_{CP} = 5.1$), 135.68 (d, $^2J_{CP} = 10.1$), 131.29 (d, $^1J_{CP} = 164.6$), 128.32, 127.87, 126.86 (d, $^3J_{CP} = 5.4$), 65.36 (d, $^2J_{CP} = 5.7$), 62.13 (d, $^2J_{CP} = 7.1$), 27.92 (d, $^3J_{CP} = 10.5$), 16.02 (d, $^3J_{CP} = 3.7$); MS *m*/*e* (relative intensity): 238 (M$^+$, 50), 209 (100), 191 (25), 130 (18), 116 (38), 115 (77), 105 (11), 102 (19), 89 (14), 77 (23), 65 (14), 51 (19). Anal. Calc. for $C_{12}H_{15}O_3P$: C, 60.50; H, 6.35. Found: C, 59.91; H, 6.41%.

3.5.2. Method B (LiCl)

Bromide **13b** (4.50 g, 14.1 mmol) was dissolved in dry DMF (20 ml) in a dry-box. To this solution was added LiCl (1.20 g, 28.3 mmol). The mixture was stirred at 80 °C for 2.0 h. The DMF was evaporated under high vacuo at 40 °C, then water (20 ml) was added, and the water phase was extracted by ether (3 × 20 ml). The organic phase was washed by brine (10 ml) and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography on SiO_2 (EtOAc–hexanes, 1:1, then EtOAc) to give **14** (1.90 g, 57%) as a colorless oil identical to the product obtained from method A above.

*3.6. 2-Hydroxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**17**)*

Compound **13b** (0.33 g, 1.03 mmol) was treated with LiCl in DMF for 3 h at 80 °C and worked up as in method B. The compound **17** was characterized by NMR methods without DMF removal and water-workup in a DMF–$CDCl_3$ solution. ^{31}P-NMR ($CDCl_3$–DMF) δ: 9.3. ^{1}H-NMR ($CDCl_3$–DMF) δ: 7.67 (bs, 1H), 7.53–7.50 (m, 2H), 7.21–7.19 (m, 3H), 6.55 (dt, 1H, $^3J_{HP} = 40.7$, $^3J_{HH} = 4.0$), 4.33 (dt, $^3J_{HP} = 13.5$, $^3J_{HH} = 4.5$, 2H), 2.45 (m, 2H); ^{13}C-NMR ($CDCl_3$–DMF) δ: 139.3 (bs), 135.72 (d, $^2J_{CP} = 9.6$), 131.82 (d, $^1J_{CP} = 165.8$), 127.26, 126.51, 126.26 (d, $^3J_{CP} = 6.4$), 64.25 (d, $^2J_{CP} = 5.1$), 27.39 (d, $^3J_{CP} = 9.6$).

*3.7. Conversion of **13b** to **14** by alkylation of **17***

Compound **13b** (0.33 g, 1.03 mmol) was treated with LiCl in DMF for 3 h at 80 °C. The DMF was evaporated in high vacuo at 40 °C and dry THF (3 ml) was added. NaH (0.03 g, 12.5 mmol) was added in dry-box at r.t. The mixture was stirred for 10 min and then cooled to 0 °C. Ethyl iodide (0.195 g, 12.5 mmol) was added and the mixture was allowed to warm up. The THF was evaporated, then water (2 ml) was added and water phase was extracted by ether (3 × 2 ml). The organic phase was washed by brine (1 ml) and dried over Na_2SO_4; yield 28%; spectral and chromatographic characteristics identical with **14**.

*3.8. 5-Bromo-2-ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**15a**,**b**) and 5,5-dibromo-2-ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**18**) using 1.5 equivalents NBS*

A solution of **14** (0.67 g, 2.81 mmol), NBS (0.75 g, 4.2 mmol), and AIBN (0.062 g, 0.42 mmol) in CCl_4 (5 ml) was stirred and refluxed for 2.5 h. The residue was cooled at 0 °C and the succinimide was removed by filtration. The solvent was evaporated in vacuo and the residue (**15a**:**18**, 1.7:1 by ^{31}P-NMR) was chromatographed on SiO_2 (EtOAc–hexane, 1:3) to give **15a** (0.09 g, 10%) and **15b** (0.28 g, 31%) as colorless oils and crystalline **18** (0.35 g, 32%).

15a: $R_f = 0.22$ (EtOAc–hexanes, 1:3); $t_R = 19.4$ min; ^{31}P-NMR δ: 10.0; ^{1}H-NMR δ: 7.65–7.59 (m, 2H), 7.42–7.34 (m, 3H), 6.78 (ddd, $^2J_{HP} = 40.0$, $^3J_{HH} = 4.6$, $^4J_{HH} = 0.7$, 1H), 4.84 (d of parent qn, $^3J_{HH} = 4.0$, $^4J_{HP} = 0.3$, 1H), 4.74 (ddd, $^2J_{HH} = 12.6$, $^3J_{HH} = 3.4$, $^3J_{HP} = 10.2$, 1H), 4.62 (dddd, $^2J_{HH} = 12.6$, $^3J_{HH} = 4.1$, $^3J_{HP} = 16.7$, $^4J_{HH} = 0.7$, 1H), 4.24–4.00 (m, 2H), 1.25 (t, $^3J_{HH} = 7.1$, 3H); ^{13}C-NMR δ: 139.94 (d, $^2J_{CP} = 2.9$), 134.43 (d, $^2J_{CP} = 10.5$), 132.74 (d, $^1J_{CP} = 163.7$), 129.11, 128.77, 127.36 (d, $^3J_{CP} = 6.4$), 70.77 (d, $^2J_{CP} = 6.7$), 62.96 (d, $^2J_{CP} = 6.2$), 41.52 (d, $^3J_{CP} = 9.3$), 16.29 (d, $^3J_{CP} = 2.3$); MS m/e (relative intensity) 318 ([M$^+$], 0.5), 316 ([M$^+$], 1), 314 ([M$^+$], 0.5), 237 (65), 209 (100), 191 (13), 144 (14), 128 (29), 115 (41), 105 (20), 89 (70). Anal. Calc. for $C_{12}H_{14}BrO_3P$ (mixture of isomers): C, 45.45; H 4.45. Found: C, 45.20; H, 4.41%.

15b: $R_f = 0.18$ (EtOAc–hexanes, 1:3); ^{31}P-NMR δ: 9.9; ^{1}H-NMR δ: 7.65–7.59 (m, 2H), 7.39–7.35 (m, 3H), 6.82 (ddd, $^2J_{HP} = 39.9$, $^3J_{HH} = 5.0$, $^4J_{HH} = 0.9$, 1H), 4.94–4.85 (m, 2H), 4.62–4.46 (m, 1H), 4.20–3.96 (m, 2H), 1.20 (t, $^3J_{HH} = 7.1$, 3H); ^{13}C-NMR δ: 140.02 (d, $^2J_{CP} = 3.6$), 134.16 (d, $^2J_{CP} = 9.0$), 132.61 (d, $^1J_{CP} = 159.5$), 129.17, 128.84, 127.18 (d, $^3J_{CP} = 6.3$), 69.62 (d, $^2J_{CP} = 5.5$), 63.85 (d, $^2J_{CP} = 6.4$), 41.85 (d, $^3J_{CP} = 9.7$), 16.07 (d, $^3J_{CP} = 4.1$).

18: m.p. 81–82 °C (EtOAc–hexanes, 1:3); $R_f = 0.30$ (EtOAc–hexanes, 1:3); $t_R = 19.0$ min; ^{31}P-NMR δ: 8.2; ^{1}H-NMR δ: 7.67–7.59 (m, 2H), 7.46–7.35 (m, 3H), 7.08 (d, $^3J_{HP} = 38.7$, 1H), 4.99 (parent t, $^3J_{HP} = 12.6$, $^2J_{HH} = 12.6$, 1H), 4.81 (ddd, $^3J_{HP} = 14.6$, $^2J_{HH}$ 12.6, $^4J_{HH}$ 0.9, 1H), 4.23–4.04 (m, 2H), 1.24 (t, 3H, $^3J_{HH}$ 6.6); ^{13}C-NMR δ: 143.26, 132.31 (d, $^2J_{CP} = 8.6$), 129.35 (bs), 128.62, 127.78 (d, $^1J_{CP} = 162.8$), 127.12 (d, $^3J_{CP} = 6.4$), 75.62 (d, $^2J_{CP} = 7.0$), 63.61 (d, $^2J_{CP} = 6.1$), 52.61 (d, $^3J_{CP} = 9.8$), 15.76 (d, $^3J_{CP} = 6.3$); MS m/e (relative intensity): 316 ([M$^+$ − HBr], 84), 314 ([M$^+$ − HBr], 82), 288 (98), 286 (100), 224 (17), 222 (16), 143 (16), 115 (86), 77 (16), 63 (19). Anal. Calc. for $C_{12}H_{13}Br_2O_3P$: C, 36.40; H 3.31. Found: C, 36.02; H, 3.23%.

3.9. Treatment of **14** with 1.05 equivalents of NBS

A solution of **14** (0.83 g, 3.48 mmol), NBS (0.65 g, 3.66 mmol), and AIBN (0.057g, 0.35 mmol) in CCl_4 (6 ml) was stirred and refluxed for 2.5 h. The residue was cooled at 0 °C and the succinimide was removed by filtration. The solvent was evaporated in vacuo and the residual mixture of **15a**:**15b** (2.3:1) and **18** (the ratio of **15a**,**b**:**18** was 2.2:1 by ^{31}P-NMR) was chromatographed on SiO_2 (EtOAc–hexane, 1:3) to give a mixture of **15a**,**b** (0.31 g, 28%) as a colorless oil and crystalline **18** (0.27 g, 20%).

3.10. Equilibration of 5-Bromo-2-ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**15a**,**b**) by triethylamine

To a solution of pure **15a** (42 mg, 0.13 mmol) in $CDCl_3$ (0.5 ml) was added triethylamine (134 mg, 0.19 ml, ten equivalents) at r.t. After 0.5 h a 1:1.6 ratio of **15a**:**15b** was observed by ^{31}P-NMR spectroscopy.

3.11. 5-Chloro-2-ethoxy-5,6-dihydro-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**19a**,**b**)

In a dry-box, bromide **15a** (30 mg, 0.09 mmol) was dissolved in dry DMF (0.5 ml) and to this solution was added LiCl (15 mg, 0.36 mmol) and Li_2CO_3 (13 mg, 0.18 mmol). The mixture was stirred at 70 °C for 2.0 h to give crude **19a**,**b**. ^{31}P-NMR δ: 10.0; 9.8 (1:1) (DMF); ^{13}C-NMR (DMF) (mixture of isomers) δ: 139.94 (d, $^2J_{CP} = 8.6$), 137.47 (d, $^2J_{CP} = 8.8$), 134.27 (d, $^2J_{CP} = 11.1$), 133.99 (d, $^2J_{CP} = 10.0$), 131.21 (d, $^1J_{CP} = 163.8$), 128.36 (d, $^3J_{CP} = 2.0$), 128.14 (d, $^3J_{CP} = 7.9$), 127.24, 126.77, 126.64 (d, $^4J_{CP} = 6.2$), 126.40 (d, $^4J_{CP} = 5.9$), 70.88 (d, $^2J_{CP} = 7.8$), 69.23 (d, $^2J_{CP} = 5.4$), 62.89 (d, $^2J_{CP} = 6.1$), 61.57 (d, $^2J_{CP} = 7.5$), 52.26 (d, $^3J_{CP} = 12.1$), 51.91 (d, $^3J_{CP} = 9.2$), 15.14 (d, $^3J_{CP} = 6.0$), 14.85 (d, $^3J_{CP} = 4.7$). **19a**: $t_R = 18.4$; MS m/e (relative intensity) 274 ([M$^+$], 6), 272 ([M$^+$], 14), 237 (49), 209 (100), 191 (16), 128 (31), 115 (63), 77 (17), 51 (13). **19b**: $t_R = 18.6$; MS m/e (relative intensity) 274 ([M$^+$], 6), 272 ([M$^+$], 12), 237 (34), 209 (100), 154 (20), 128 (45), 115 (81), 77 (18), 51 (17).

3.12. 2-Ethoxy-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**3**)

A solution of **15a** (0.42 g, 1.3 mmol) and triethylamine (1.34 g, 1.85 ml, ten equivalents) in toluene (5 ml) was stirred at 95 °C for 1.5 h. Then it was filtrated, washed with toluene, and the solvent and excess of triethylamine were removed in vacuo. The residue was chromatographed on silica gel (EtOAc–hexanes, 1:3) to give **3** (0.24 g, 71%). $R_f = 0.21$ (EtOAc–hexanes, 1:3); $t_R = 16.5$ min; ^{31}P-NMR δ: 10.9; ^{1}H-NMR δ: 7.65–7.62 (m, 2H), 7.42–7.31 (m, 3H), 7.98 (ddd, $^3J_{HH} = 6.9$, $^4J_{HH} = 1.8$, $^3J_{HP} = 39.5$, 1H), 6.89 (ddd, $^3J_{HH} = 5.4$, $^4J_{HH} = 1.8$, $^3J_{HP} = 19.5$, 1H), 5.80 (ddd, $^3J_{HH} = 6.9$, $^3J_{HH} = 5.4$, $^4J_{HP} = 2.4$, 1H), 4.13 (dq, $^3J_{HH} = 7.1$, $^3J_{HP} = 0.8$, 1H), 4.10 (dq, $^3J_{HH} = 7.1$, $^3J_{HP} = 1.4$, 1H), 1.24 (dt, $^3J_{HH} = 7.1$, $^4J_{HP} = 0.5$, 3H); ^{13}C-NMR δ: 144.49 (d, $^2J_{CP} = 13.4$), 135.25 (d, $^2J_{CP} = 3.6$), 134.30 (d, $^2J_{CP} = 11.3$), 128.43, 128.13, 126.56 (d, $^3J_{CP} = 7.6$), 125.91 (d, $^1J_{CP} = 166.1$), 105.56 (d, $^3J_{CP} = 20.6$), 63.13 (d, $^2J_{CP} = 7.2$), 15.67 (d, $^3J_{CP} = 6.8$); MS m/e (relative intensity) 236 ([M$^+$], 70), 208 (73), 144 (43), 115 (100), 89 (20), 77 (11), 63 (16), 51 (11). HREI MS Anal. Calc. for $C_{12}H_{13}O_3P$ 236.0613. Found: 236.0602.

3.13. 5-Bromo-2-ethoxy-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**4**)

A solution of **18** (0.30 g, 0.76 mmol) and triethylamine (0.77 g, 7.6 mmol) in toluene (3 ml) was heated

at 80 °C for 2.5 h. The work-up and chromatography was similar to that described for **3**. Compound **4** (0.13 g, 54%) was isolated as a yellowish oil. $R_f = 0.37$ (EtOAc–hexanes, 1:3); $t_R = 19.0$ min; ^{31}P-NMR δ: 7.6; ^{1}H-NMR (benzene-d_6) δ: 7.54–7.00 (m, 2H), d 7.07–6.98 (m, 3H), 6.56 (dd, $^4J_{HH} = 2.3$, $^3J_{HP} = 37.3$, 1H), 6.33 (dd, $^4J_{HH} = 2.3$, $^3J_{HP} = 18.2$, 1H), 3.88–3.69 (m, 2H), 0.78 (t, $^3J_{HH} = 7.1$, 3H); ^{13}C-NMR δ: 141.77 (d, $^2J_{CP} = 15.1$), 138.56 (d, $^2J_{CP} = 3.4$), 133.41 (d, $^2J_{CP} = 11.3$), 129.14, 128.88, 127.80 (d, $^1J_{CP} = 168.1$), 127.55 (d, $^3J_{CP} = 7.6$), 101.74 (d, $^3J_{CP} = 22.8$), 64.08 (d, $^2J_{CP} = 8.2$), 16.00 (d, $^3J_{CP} = 6.9$); MS m/e (relative intensity) 316 ([M$^+$], 74), 314 ([M$^+$], 72), 288 (79), 286 (79), 224 (14), 222 (14), 143 (16), 115 (100), 77 (19), 63 (23), 47 (15). HREI MS Anal. Calc. for $C_{12}H_{12}BrO_3P$ 313.9707. Found. 313.9711.

*3.14. 5-Bromo-2-hydroxy-3-phenyl-2H-1,2-oxaphosphorin 2-oxide (**20**)*

A solution of **18** (70 mg, 0.22 mmol), LiCl (19 mg, 0.45 mmol), Li_2CO_3 (8 mg, 11 mmol) in DMF (0.5 ml) was heated at 70 °C for 2 h. The DMF was removed and isolated, crude compound was characterized: ^{31}P-NMR δ: 3.8; ^{1}H-NMR δ: 7.86–7.75 (m, 2H), d 7.43–7.41 (m, 3H), 7.01 (dd, $^4J_{HH} = 1.7$, $^3J_{HP} = 16.6$, 1H), 6.82 (dd, $^4J_{HH} = 1.7$, $^3J_{HP} = 34.1$, 1H); ^{13}C-NMR δ: 142.15 (d, $^2J_{CP} = 9.5$), 134.89 (d, $^2J_{CP} = 8.8$), 133.51, 131.86 (d, $^1J_{CP} = 169.9$), 128.08, 127.53, 126.54 (d, $^3J_{CP} = 6.7$), 101.74 (d, $^3J_{CP} = 22.7$).

*3.15. Attempted reaction of 3-phenyl-2-ethoxy-2-oxo-1,2-oxaphosphorinane-3,5-diene (**3**) with tetracyanoethylene (thermal and (or) $BF_3{\cdot}OEt_2$ activation)*

To a solution of diene **3** (30 mg, 0.13 mmol) in THF (0.25 ml) was added a solution of tetracyanoethylene (17 mg, 0.13 mmol) in THF (0.25 ml) at r.t. The solution immediately turned to brown–orange. It was kept for 2 h at r.t. The solution was heated at 75 °C over 1 h. After it was cooled, $BF_3{\cdot}OEt_2$ (18 mg, 0.13 mmol) was added at r.t. and kept for 2 h at r.t. The solution was refluxed for 1 h. Only starting material was found by ^{31}P-NMR, GC-MS and TLC after each attempt.

*3.16. Attempted reaction of 3-phenyl-2-ethoxy-2-oxo-1,2-oxaphosphorinane-3,5-diene (**3**) with tetracyanoethylene ($LiClO_4$ activation)*

To diene **3** (30 mg, 0.13 mmol) was added a solution of $LiClO_4$ (25%) and TCE in CH_2Cl_2 (0.5 ml) at r.t. It was subjected with ultrasonic radiation for 1 h. Only starting material was found by ^{31}P-NMR, GC-MS and TLC.

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References

[1] S. Thaisrivongs, D.L. Romero, R.A. Tommasi, M.N. Janakiraman, J.W. Strohbach, J. Med. Chem. 39 (1996) 4630.
[2] H.W. Hamilton, B.D. Tait, C. Gajda, S.E. Hagen, D. Ferguson, Bioorg. Med. Chem. Lett. 6 (1996) 719.
[3] L. Cook, B. Ternai, P. Ghosh, J. Med. Chem. 30 (1987) 1017.
[4] W.C. Groutas, T.L. Huang, M.A. Stanga, M.J. Brubaker, M.K. Moi, J. Heterocycl. Chem. 22 (1985) 433.
[5] G.H. Posner, J.K. Lee, M.C. White, R.H. Hutchings, H. Dai, J. Org. Chem. 62 (1997) 3299.
[6] G.H. Posner, J. Ishihara Tetrahedron Lett. 35 (1994) 7545.
[7] D. Perez, G. Bures, E. Guitian, L. Castedo, J. Org. Chem. 61 (1996) 1650.
[8] D. Vedaldi, S. Caffieri, S. Frank, F. Dall'Acqua, A. Jakobs, J. Piette, Farmaco 50 (1995) 527.
[9] K. Afarinkia, V. Vinader, T.D. Nelson, G.H. Posner, Tetrahedron 48 (1992) 9111.
[10] T. Shimo, K. Kataoka, A. Maeda, K. Somekawa, J. Heterocycl. Chem. 29 (1992) 811.
[11] I.E. Marko, G.R. Evans, J.-P. Declercq, Tetrahedron 50 (1994) 4557.
[12] C. Tanyeli, O. Tarhan, Synth. Commun. 19 (1989) 2453.
[13] K. Afarinkia, G.H. Posner, Tetrahedron 33 (1992) 7839.
[14] L. Sigal, L. Loew, J. Am. Chem. Soc. 100 (1978) 6394.
[15] A.I. Razumov, B.G. Liorber, M.P. Sokolov, T.V. Zykova, R.A. Salakhutdinov, J. Obshch. Khim. 48 (1978) 51.
[16] T.M. Lane, O.P. Rodriguez, S.E. Cremer, D.W. Bennett, Phosphorus, Sulfur, Silicon Relat. Elem. 103 (1995) 63.
[17] S.E. Cremer, A.G. Sommese, O.P. Rodriguez, Phosphorus, Sulfur, Silicon Relat. Elem. 75 (1993) 107.
[18] A.M. Polozov, S.E. Cremer, J. Can. Chem. 77 (1999) 1274.
[19] L. Forti, F. Ghelfi, U.M. Pagnoni, Tetrahedron Lett. 36 (1995) 3023.
[20] A. Weisz, A. Mandelbaum, J. Org. Chem. 49 (1984) 2648.
[21] H.-J. Liu, W.M. Feng, J.B. Kim, E.N.C. Browne, Can. J. Chem. 72 (1994) 2163.
[22] T. Calogeropoulou, D.F. Wiemer, J. Org. Chem. 53 (1988) 2295.