Synthesis and Structure of *O,O*-Diethyl *N*-[(*trans*-4-Aryl-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl)methyl]phosphoramidothioates

by **Zhiwei Miao***, **Jianfeng Zhang**, **Zhanwei Cui**, **Bin Wang**, and **Ruyu Chen***

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China (phone: +86-22-23508857; fax: +86-22-23503627; e-mail: miaozhiwei@nankai.edu.cn)

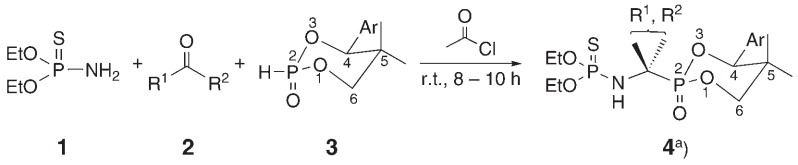
A study on the synthesis of the novel *N*-(cyclic phosphonate)-substituted phosphoramidothioates, *i.e.*, *O*,*O*-diethyl *N*-[(*trans*-4-aryl-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl)methyl]phosphoramidothioates **4a**–**l**, from *O*,*O*-diethyl phosphoramidothioate (**1**), a benzaldehyde or ketone **2**, and a 1,3,2-dioxaphosphorinane 2-oxide **3** was carried out (*Scheme 1* and *Table 1*). Some of their stereoisomers were isolated, and their structure was established. The presence of acetyl chloride was essential for this reaction and accelerated the process of intramolecular dehydration of intermediate **5** forming the corresponding *Schiff* base **7** (*Scheme 2*).

Introduction. – The 1,3,2-dioxaphosphorinane derivatives, an important class of organophosphorus heterocycles, are interesting compounds because of their biological activity, particularly in connection with the design of enzyme inhibitors [1]. It has been found that the configuration of these heterocycles are important for their bioactivities and many biochemical interactions, especially those involving enzymes (for reviews of the biological activity of α-aminophosphonic acides, see [2]). *Zhou* and *Chen* have reported the synthesis and configuration of 1,3,2-dioxaphosphorinane 2-sulfides (selenides), obtained by the tris(diethylamino)phosphine (= *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexaethylphosphorous triamide) method [3]. However, studies on the synthesis and configuration of *N*-(cyclic-phosphonate)-substituted phosphoramidothioate compounds, which are formal α-aminophosphonic acid derivatives, are rare. Phosphoramidothioic acid diesters are reported to have activity in various biological processes. The relative metabolic stability of phosphorothioates is well-documented [4]. Phosphonate and phosphoramidate inhibitors are excellent inhibitors of the zinc metallopeptidases carboxypeptidase A or thermolysin and have also been used to study the mechanisms of enzymes [5]. The phosphoryl group is of fundamental significance in controlling molecular replication, cell biochemistry, and metabolic processes in living species [6]. We describe herein an efficient one-pot synthesis of the novel *N*-(cyclic-phosphonate)-substituted phosphoramidothioates **4a**–**l** exhibiting *trans* configuration of their 1,3,2-dioxaphosphorinane oxide moiety.

Results and Discussion. – The *N*-(cyclic-phosphonate)-substituted phosphoramidothioates, *O*,*O*-diethyl *N*-[(*trans*-4-aryl-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl)methyl]phosphoramidothioates **4a**–**l**, were synthesized by a one-pot

procedure in a *Mannich*-type reaction under mild conditions (*Scheme 1*). *O*,*O*-Diethyl phosphoramidothioate (**1**) [7] was allowed to react with a racemic 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide **3** [8] and various substituted ketones or benzaldehydes **2** in acetyl chloride as solvent [9] to give the target compounds **4a**–**l** in moderate to good yields (52 to 86%; *Table 1*).

Scheme 1



1 **2** **3** **4**[a])

[a]) For Ar, R^1, and R^2, see *Table 1*.

Table 1. *Preparation of* N-*Phosphonate-Substituted Phosphoramidothioates* **4a**–**l** *from Ketones or Benzaldehydes* **2** *and* **3**

	Ar	R^1	R^2	Yield [%][a])		Ar	R^1, R^2	Yield [%][a])
4a	4-ClC_6H_4	H	Ph	52	**4g**	4-ClC_6H_4	$(CH_2)_4$	66
4b	4-ClC_6H_4	Me	Ph	61	**4h**	4-ClC_6H_4	$(CH_2)_5$	62
4c	4-ClC_6H_4	H	4-$MeOC_6H_4$	77	**4i**	4-ClC_6H_4	$(CH_2)_6$	86
4d	Ph	H	4-MeC_6H_4	56	**4j**	Ph	$(CH_2)_4$	81
4e	Ph	H	Ph	67	**4k**	Ph	$(CH_2)_5$	86
4f	Ph	H	4-$MeOC_6H_4$	73	**4l**	Ph	$(CH_2)_6$	76

[a]) After purification by flash column chromatography (2 mmol scale).

The results reveal the scope and versatility of the reaction of various aldehydes or ketones **2** with phosphorothioamidate **1** in the presence of acetyl chloride. It is reasonable to postulate that the addition of **1** to **2** forms the unstable adduct **5** (*Scheme 2*). Acetyl chloride accelerates the dehydration of **5** *via* the intermediate **6** which releases AcOH to give the corresponding *Schiff* base **7**. The reaction of **3** with intermediate **7** directly forms compounds **4**, as a mixture of racemic diastereoisomers in the case of **4a**–**f** (see *Table 2* for some ratios), and the major diastereoisomers were isolated by column chromatography and recrystallization (see *Exper. Part*). The structures of the new compounds **4a**–**l** were unequivocally assigned by ^{31}P-, ^{1}H-, and ^{13}C-NMR, IR, and mass spectroscopic data.

It is interesting to note that in the ^{1}H-NMR spectra of **4a** and **4c**–**f**, a *dd* at δ 4.78–5.18 ($^{2}J(H,P) = 28.0–24.3$, $^{3}J(H,P) = 13.2–11.2$ Hz) appears (*Table 2*), which is assignable to the H-atom (R^1) in α-position with respect to the phosphonate moiety. This signal is diagnostic for an α-aminophosphonate moiety [10]. The ratios of the two diastereoisomers of **4a** and **4c**–**f** (*Table 2*) were determined by integration of the corresponding signals in the ^{31}P-NMR spectra of the crude products. In the ^{1}H-NMR spectra of **4a**–**l**, the chemical shifts of the two Me groups at C(5) of the six-membered ring are different. The ^{31}P-NMR spectra display two *d* (see *Exper. Part*) arising from the $^{31}P,^{31}P$ coupling with a $^{3}J(P(1),P(2))$ of 13.4–33.3 Hz. The IR spectra of **4** show normal stretching absorption bands, indicating

Scheme 2

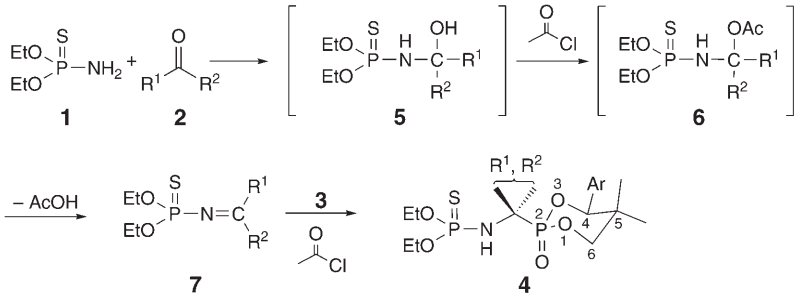


Table 2. *Ratios and* ^{1}*H-NMR Data of the Two Diastereoisomers of* **4a** *and* **4c**–**f**

	Diastereoisomer ratio	Isomer *A*		Isomer *B*	
		δ(H) [ppm] of H–C(α)	δ(P) [ppm]	δ(H) [ppm] of H–C(α)	δ(P) [ppm]
4a	44 : 56	4.78 (*dd*)	70.20, 21.53 (2*d*)	5.03 (*dd*)	68.22, 20.19 (2*d*)
4c	55 : 45	4.98 (*dd*)	72.26, 22.59 (2*d*)	5.18 (*dd*)	69.97, 20.63 (2*d*)
4d	56 : 44	4.82 (*dd*)	72.22, 22.49 (2*d*)	5.00 (*dd*)	70.02, 19.53 (2*d*)
4e	53 : 47	4.81 (*dd*)	69.36, 21.17 (2*d*)	5.39 (*dd*)	68.32, 20.33 (2*d*)
4f	46 : 54	5.18 (*dd*)	70.06, 20.97 (2*d*)	5.32 (*dd*)	69.02, 20.03 (2*d*)

the presence of the NH (*ca.* 3320 cm^{-1}), C–N (*ca.* 1315 cm^{-1}), P=O (1225–1240 cm^{-1}), P–N–C (1110–950 cm^{-1}), and P=S (660–680 cm^{-1}) groups.

As the starting 1,3,2-dioxaphosphorinane oxide **3** possesses two stereogenic centers, namely C(4) and P(2), two diastereoisomers as racemates are possible. Depending on the way of preparation and purification [8], only one diastereoisomer is obtained. In the present case, the ^{31}P-NMR spectrum of **3** (Ar = 4-ClC$_6$H$_4$; *s* at δ(P) 4.82) established the *trans* configuration of the key substrate 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide **3** [8].

Thus, the two racemic diastereoisomers of **4a**–**f** which were formed from **1**–**3** are due to the two different substituents R^1 and R^2 of the carbonyl compound **2**. For example, after column chromatography of **4c**, a mixture of two diastereoisomers was obtained as a white solid exhibiting four *d* in the ^{31}P-NMR (δ(P) 72.26 (*d*, ^3J = 33.3 Hz), 69.97 (*d*, ^3J = 30 Hz), 22.59 (*d*, ^3J = 33.3 Hz), and 20.63 (*d*, ^3J = 30 Hz; *Table 2*)). Due to the P,P splitting, the δ(P) at *ca.* 72 and 22 could be attributed to the P-atom of the phosphoramidothioate and the 1,3,2-dioxaphosphorinane oxide moiety, respectively, of the same diastereoisomer. One isomer was isolated from the mixture obtained by recrystallization at low temperature. The mother liquor was treated by column chromatography, but we did not obtain the other isomer in pure form.

The X-ray crystal-structure analysis of **4j** (*Fig.*) unambiguously established the *trans* configuration of the 1,3,2-dioxaphosphorinane oxide moiety, for which the signal

in the ^{31}P-NMR spectrum appears at a lower field[1]). The unit cell of **4j** contains four molecules. The analysis shows typical bond lengths and bond angles, such as P(1)–S(1) 1.913 Å, P(2)–O(5) 1.574 Å, P(1)–N(1) 1.615 Å, P(2)–C(5) 1.797 Å, N(1)–C(5) 1.490 Å, and P(1)–O(2) 1.551 Å, and O(1)–P(1)–N(1) 106.0° and N(1)–C(5)–P(2) 111.1°. The configuration of the pentane ring in the molecule is a half-chair, and the configuration of the six-membered ring P(2)–O(5)–C(18)–C(17)–C(10)–O(4) is a boat. The angles O(5)–P(2)–O(4) and O(1)–P(1)–O(2) are 102.3° and 98.6°, respectively.

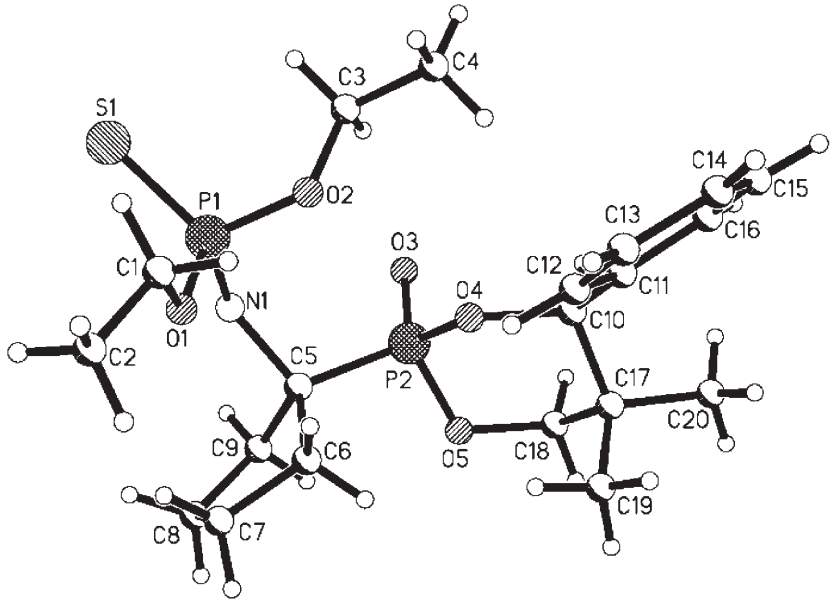


Figure. *ORTEP Plot of the molecular structure of* **4j** (*trans* configuration). Arbitrary atom numbering; 50% probability ellipsoids.

In conclusion, the synthesis and some configurational properties of a series of novel *N*-(cyclic-phosphonate)-substituted phosphoroamidothioates were studied. The syntheses were performed under mild conditions with good yields in the presence of the solvent acetyl chloride, thus allowing to introduce a wide range of substituents at the α-position with respect to the P-atom of the cyclic phosphonate moiety. Acetyl chloride accelerated the process of intramolecular dehydration of **5** forming the corresponding *Schiff* base **7**.

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[1]) Crystallographic data for **4j** (CCDC-603307) were deposited at the *Cambridge Crystallographic Data Center* and can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

Experimental Part

General. The solvent acetyl chloride was redistilled. All the ketones and benzaldehydes **2** were redistilled before use. Column chromatograghy (CC): silica gel *H* (10–40 μm; *Qingdao Marine Chemical Factory*, Qingdao, China). M.p.: *Yanaco* apparatus; uncorrected. IR Spectra: *Equinox55* spectrometer; in cm^{-1}. NMR Spectra: *Varian-AS400* instrument, $CDCl_3$ solns.; chemical shifts δ in ppm, with $SiMe_4$ as an internal standard (^1H) or 85% H_3PO_4 soln. as an external standard (^{31}P), coupling constants *J* in Hz. Mass spectra: *Polaris-Q* instrument of *Thermofinnigan*. Elemental analyses: *Yanaco-CHNCORDER-MT-3* analyzer. X-Ray analysis was carried out on a *Bruker-SMART-1000-CCD* diffractometer with MoK_α radiation (λ 0.71073 Å).

General Procedure. A freshly distilled ketone or benzaldehyde **2** (2 mmol) was added dropwise to a stirred mixture of *O*,*O*-diethyl phosphoramidothioate (**1**; 2 mmol, 0.34 g), racemic 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide **3** [8] (2 mmol), and AcCl (10 ml) at r.t. (TLC (silica gel) monitoring). After 8–12 h stirring at r.t., the mixture was filtered and the filtrate concentrated. The residue was purified by CC (silica gel, AcOEt/petroleum ether (b.p. 60–90°) 1:4): pure **4a**–**l** (diastereoisomer mixtures in the case of **4a**–**f**). One single (major) diastereoisomer (racemic) was isolated from the pure mixtures **4a**–**f** by recrystallization in AcOEt at low temperature; the mother liquor was treated by CC but did not give the other isomer in pure form.

O,O-*Diethyl* N-*{[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ⁵-1,3,2-dioxaphosphorinan-2-yl]-phenylmethyl}phosphoramidothioate* (**4a**; major isomer). White solid. R_f (petroleum ether/AcOEt 4:1) 0.44. M.p. 130–132°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.42–6.90 (*m*, ClC_6H_4, Ph); 5.31 (br. *s*, NH); 4.87–4.80 (*m*, H–C(4)); 4.78 (*dd*, ^2J(P,H) = 28.0, ^3J(P,H) = 13.2, CH); 4.40 (*dd*, ^3J(P,H) = 22.0, ^2J(H,H′) = 11.0, 1 H–C(6)); 3.95 (*d*, ^2J(H,H′) = 11.0, 1 H′–C(6)); 3.93–3.86 (*m*, 1 MeCH_2O); 3.65–3.54 (*m*, 1 MeCH_2O); 1.22 (2*t*, ^3J = 6.8, ^3J = 7.2, 2 *Me*CH_2O); 0.81 (*s*, 1 Me–C(5)); 0.78 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.31, 134.96, 134.31, 133.42, 128.64, 128.33, 127.63, 126.13 (arom. C); 82.35 (*d*, ^2J = 9.0, C(6)); 79.64 (*d*, ^2J = 8.5, C(4)); 63.37 (*d*, ^1J = 134, NH*C*HP); 58.63 (2 MeCH_2O); 23.45 (C(5)); 18.22 (2 *Me*CH_2O); 14.86 (1 Me); 14.67 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 70.20 (*d*, ^3J = 29.4); 21.53 (*d*, ^3J = 29.4). ESI-MS: 518 ($[M+1]^+$).

O,O-*Diethyl* N-*{1-[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ⁵-1,3,2-dioxaphosphorinan-2-yl]-1-phenylethyl}phosphoramidothioate* (**4b**; major isomer). White solid. R_f (petroleum ether/AcOEt 4:1) 0.44. M.p. 107–109°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.58–7.01 (*m*, ClC_6H_4, Ph); 5.62 (br. *s*, NH); 4.45–4.41 (*m*, H–C(4)); 4.28–4.11 (*m*, 2 H–C(6)); 3.95–3.70 (*m*, 2 MeCH_2O); 1.29 (*t*, *J* = 7, 1 *Me*CH_2O); 1.23–1.21 (*m*, 1 Me); 0.93 (*t*, *J* = 7, 1 *Me*CH_2O); 0.77 (*s*, 1 Me–C(5)); 0.46 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 131.21, 130.98, 128.87, 128.56, 127.98, 126.89, 126.30, 125.31 (arom. C); 86.25 (*d*, ^2J = 9.5, C(6)); 80.64 (*d*, ^2J = 8.2, C(4)); 61.72 (*d*, ^1J = 146, NCP); 53.83 (2 MeCH_2O); 24.65 (C(5)); 20.81 (2 *Me*CH_2O); 18.32 (1 Me); 16.36 (1 Me); 15.97 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 70.22 (*d*, ^3J = 31.5); 25.40 (*d*, ^3J = 31.5). ESI-MS: 532 ($[M+1]^+$).

O,O-*Diethyl* N-*{[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ⁵-1,3,2-dioxaphosphorinan-2-yl](4-methoxyphenyl)methyl}phosphoramidothioate* (**4c**; major isomer). Light yellow solid. R_f (petroleum ether/AcOEt 4:1) 0.49. M.p. 138–140°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–6.87 (*m*, ClC_6H_4, $MeOC_6H_4$); 5.42 (br. *s*, NH); 4.98 (*dd*, ^2J(P,H) = 25.0, ^3J(P,H) = 11.6, CH); 4.87–4.83 (*m*, H–C(4)); 4.46–4.41 (*m*, 2 H–C(6)); 4.02–3.98 (*m*, 1 MeCH_2O); 3.79 (*s*, *Me*OC_6H_4); 3.65–3.58 (*m*, 1 MeCH_2O); 1.28 (*t*, *J* = 7, 1 *Me*CH_2O); 0.99 (*t*, *J* = 7, 1 *Me*CH_2O); 0.84 (*s*, 1 Me–C(5)); 0.73 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 134.47, 134.13, 133.88, 132.96, 130.45, 129.66, 128.81, 128.23 (arom. C); 84.25 (*d*, ^2J = 9.0, C(6)); 80.84 (*d*, ^2J = 8.0, C(4)); 75.83 (*Me*OC_6H_4); 63.32 (*d*, ^1J = 121, NHCHP); 55.53 (2 MeCH_2O); 21.75 (C(5)); 17.52 (2 *Me*CH_2O); 15.76 (1 Me); 15.67 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 72.26 (*d*, ^3J = 33.3); 22.59 (*d*, ^3J = 33.3). ESI-MS: 548 ($[M+1]^+$). Anal. calc. for $C_{23}H_{32}ClNO_6P_2S$: C 50.41, H 5.89, N 2.56; found: C 50.31, H 5.91, N 2.61.

O,O-*Diethyl* N-*[(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ⁵-1,3,2-dioxaphosphorinan-2-yl)(4-methylphenyl)methyl]phosphoramidothioate* (**4d**; major isomer). White solid. R_f (petroleum ether/AcOEt 4:1) 0.39. M.p. 102–104°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.36–6.94 (*m*, MeC_6H_4, Ph); 5.44 (br. *s*, NH); 4.82 (*dd*, ^2J(P,H) = 26.2, ^3J(P,H) = 11.2, CH); 4.73–4.63 (*m*, H–C(4)); 4.37 (*dd*, ^3J(P,H) = 21.3, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.87 (*d*, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.72–3.53 (*m*, 2 MeCH_2O); 2.31 (*s*, *Me*C_6H_4);

1.17 (*t*, *J* = 7.2, 1 *Me*CH_2O); 1.06 (*t*, *J* = 7.2, 1 *Me*CH_2O); 1.01 (*s*, 1 Me–C(5)); 0.88 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.37, 134.99, 134.87, 133.78, 132.56, 130.69, 128.70, 127.60 (arom. C); 80.45 (*d*, ^2J = 8.7, C(6)); 78.54 (*d*, ^2J = 8.3, C(4)); 60.87 (*d*, ^1J = 132, NHCHP); 59.73 (2 Me*C*H_2O); 24.35 (*Me*C_6H_4); 22.25 (C(5)); 19.32 (2 *Me*CH_2O); 15.76 (1 Me); 14.87 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 72.22 (*d*, ^3J = 31.4); 22.49 (*d*, ^3J = 31.4). ESI-MS: 498 ([*M* + 1]$^+$).

O,O-*Diethyl* N-*[(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ^5-1,3,2-dioxaphosphorinan-2-yl)phenylmethyl]phosphoramidothioate* (**4e**; major isomer). White solid. R_f (petroleum ether/AcOEt 4:1) 0.42. M.p. 123–125°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–6.84 (*m*, 2 Ph); 5.26 (br. *s*, NH); 4.81 (*dd*, ^2J(P,H) = 26.8, ^3J(P,H) = 11.2, CH); 4.76–4.70 (*m*, H–C(4)); 4.36 (*dd*, ^3J(P,H) = 21.7, ^2J(H,H′) = 11.4, 1 H–C(6)); 3.93 (*d*, ^2J(H,H′) = 11.4, 1 H′–C(6)); 3.88–3.81 (*m*, 1 MeOC*H*$_2$O); 3.63–3.52 (*m*, 1 MeOC*H*$_2$O); 1.21 (*t*, *J* = 7, 1 *Me*CH_2O); 1.08 (*t*, *J* = 7, 1 *Me*CH_2O); 0.79 (*s*, 1 Me–C(5)); 0.70 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.38, 136.51, 132.47, 128.96, 127.64, 126.43, 125.33, 122.32, 121.73, 121.05 (arom. C); 85.45 (*d*, ^2J = 9.7, C(6)); 77.64 (*d*, ^2J = 8.3, C(4)); 66.57 (*d*, ^1J = 138, NHCHP); 57.83 (2 Me*C*H_2O); 24.55 (C(5)); 17.32 (2 *Me*CH_2O); 12.66 (1 Me); 12.47 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.36 (*d*, ^3J = 30.2); 21.17 (*d*, ^3J = 30.2). ESI-MS: 484 ([*M* + 1]$^+$).

O,O-*Diethyl* N-*[(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ^5-1,3,2-dioxaphosphorinan-2-yl)(4-methoxyphenyl)methyl]phosphoramidothioate* (**4f**; major isomer). Light yellow solid. R_f (petroleum ether/AcOEt 4:1) 0.41. M.p. 100–102°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.49–6.76 (*m*, MeOC_6H_4, Ph); 5.44 (br. *s*, NH); 5.18 (*dd*, ^2J(P,H) = 24.3, ^3J(P,H) = 12.1, CH); 4.70–4.66 (*m*, H–C(4)); 4.39 (*dd*, ^3J(P,H) = 22.0, ^2J(H,H′) = 11.4, 1 H–C(6)); 3.95 (*d*, ^2J(H,H′) = 11.4, 1 H′–C(6)); 3.88–3.80 (*m*, 1 MeC*H*$_2$O); 3.72 (*s*, *Me*OC_6H_4); 3.70–3.64 (*m*, 1 MeC*H*$_2$O); 1.17 (*t*, *J* = 7, 1 *Me*CH_2O); 0.83 (*t*, *J* = 7, 1 *Me*CH_2O); 0.79 (*s*, 1 Me–C(5)); 0.70 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 139.43, 136.54, 134.85, 134.62, 133.23, 131.89, 130.11, 128.27, 126.14, 125.63 (arom. C); 82.22 (*d*, ^2J = 9.0, C(6)); 79.74 (*d*, ^2J = 8.0, C(4)); 73.83 (MeO); 65.72 (*d*, ^1J = 125, NHCHP); 53.83 (2 Me*C*H_2O); 22.85 (C(5)); 16.92 (2 *Me*CH_2O); 14.76 (1 Me); 14.37 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 70.06 (*d*, ^3J = 33.0); 20.97 (*d*, ^3J = 33.0). ESI-MS: 514 ([*M* + 1]$^+$).

O,O-*Diethyl* N-*{1-[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl]cyclopentyl}phosphoramidothioate* (**4g**). White solid. R_f (petroleum ether/AcOEt 4:1) 0.50. M.p. 134–136°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.36–7.24 (*m*, ClC_6H_4); 5.53 (br. *s*, NH); 4.48 (*d*, ^3J = 11.2, H–C(4)); 4.22–4.02 (*m*, 2 MeC*H*$_2$O); 3.75 (*dd*, ^3J(P,H) = 22.0, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.33 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.25–1.63 (*m*, $(CH_2)_4$); 1.21 (*t*, *J* = 6.8, 2 *Me*CH_2O); 1.10 (*s*, 1 Me–C(5)); 0.85 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 137.33, 135.62, 126.37, 124.42 (arom. C); 87.90 (*d*, ^2J = 8.5, C(6)); 79.45 (*d*, ^2J = 7.0, C(4)); 61.59 (2 Me*C*H_2O); 58.72 (*dd*, ^1J = 148, ^2J = 7.5, NCP); 38.27 (C(5)); 33.62 (CH_2); 32.70 (CH_2); 24.34 (2 CH_2); 19.82 (1 *Me*CH_2O); 18.86 (1 *Me*CH_2O); 14.64 (1 Me); 13.17 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 70.23 (*d*, ^3J = 14.6); 30.05 (*d*, ^3J = 14.6). ESI-MS: 496 ([*M* + 1]$^+$).

O,O-*Diethyl* N-*{1-[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl]cyclohexyl}phosphoramidothioate* (**4h**). White solid. R_f (petroleum ether/AcOEt 4:1) 0.34. M.p. 128–130°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.32–7.20 (*m*, ClC_6H_4); 5.47 (br. *s*, NH); 4.50 (*d*, ^3J = 11.2, H–C(4)); 4.14–4.07 (*m*, 2 MeC*H*$_2$O); 3.80 (*dd*, ^3J(P,H) = 21.6, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.38 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.08–1.43 (*m*, $(CH_2)_5$); 1.31 (*t*, *J* = 7, 2 *Me*CH_2O); 1.02 (*s*, 1 Me–C(5)); 0.75 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.21, 134.42, 129.17, 128.22 (arom. C); 89.30 (*d*, ^2J = 9.0, C(6)); 80.45 (*d*, ^2J = 8.0, C(4)); 63.69 (2 Me*C*H_2O); 59.92 (*dd*, ^1J = 146, ^2J = 7.7, NCP); 37.37 (C(5)); 32.52 (CH_2); 31.30 (CH_2); 25.24 (2 CH_2); 21.82 (1 *Me*CH_2O); 20.96 (1 *Me*CH_2O); 18.00 (CH_2); 16.14 (1 Me); 15.87 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.62 (*d*, ^3J = 13.4); 29.05 (*d*, ^3J = 13.4). ESI-MS: 510 ([*M* + 1]$^+$).

O,O-*Diethyl* N-*{1-[*trans-*4-(4-Chlorophenyl)-5,5-dimethyl-2-oxido-2λ^5-1,3,2-dioxaphosphorinan-2-yl]cycloheptyl}phosphoramidothioate* (**4i**). Colorless oil. R_f (petroleum ether/AcOEt 4:1) 0.38. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.32–7.19 (*m*, ClC_6H_4); 5.49 (br. *s*, NH); 4.50 (*d*, ^3J = 11.2, H–C(4)); 4.17–4.02 (*m*, 2 MeC*H*$_2$O); 3.80 (*dd*, ^3J(P,H) = 21.8, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.24 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.31–1.67 (*m*, $(CH_2)_6$); 1.30 (*t*, *J* = 7, 2 *Me*CH_2O); 1.04 (*s*, 1 Me–C(5)); 0.73 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 134.71, 134.63, 129.05, 128.29 (arom. C); 83.53 (*d*, ^2J = 6.0, C(6)); 75.29 (*d*, ^2J = 5.0, C(4)); 63.78 (Me*C*H_2O); 63.68 (Me*C*H_2O); 60.51 (*dd*, ^1J = 148, ^2J = 6.8, NCP);

37.06 (C(5)); 34.75 (CH_2); 34.23 (CH_2); 31.18 (2 CH_2); 31.10 (2 CH_2); 22.78 (1 *Me*CH_2O); 21.81 (1 *Me*CH_2O); 17.90 (1 Me); 15.98 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.58 (*d*, $^3J = 14.8$); 30.55 (*d*, $^3J = 14.8$). ESI-MS: 524 ($[M+1]^+$).

*O,O-Diethyl N-[1-(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ⁵-1,3,2-dioxaphosphorinan-2-yl)cyclopentyl]phosphoramidothioate* (**4j**). Light yellow solid. R_f (petroleum ether/AcOEt 4:1) 0.32. M.p. 118–120°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.29–7.20 (*m*, Ph); 5.44 (br. *s*, NH); 4.49 (*d*, $^3J = 10.8$, H–C(4)); 4.09 (*dd*, ^3J(P,H) = 14.0, J(H,H′) = 7.2, 2 MeCH_2O); 3.77 (*dd*, ^3J(P,H) = 21.2, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.57 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.23–1.74 (*m*, 4 CH_2); 1.23 (*t*, $J = 7$, 2 *Me*CH_2O); 1.02 (*s*, 1 Me–C(5)); 0.72 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.17, 134.83, 132.56, 127.30 (arom. C); 84.16 (C(4)); 75.41 (*d*, $^1J = 158$, NCP); 63.57 (C(6)); 63.53 (2 MeCH_2O); 35.50 (1 *Me*CH_2O); 34.86 (1 *Me*CH_2O); 24.85 (C(5)); 21.91 (2 CH_2); 17.99 (2 CH_2); 16.00 (1 Me); 15.92 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.43 (*d*, $^3J = 16.2$); 30.64 (*d*, $^3J = 16.2$). ESI-MS: 462 ($[M+1]^+$). Anal. calc. for $C_{20}H_{33}NO_5P_2S$: C 52.05, H 7.21, N 3.04; found: C 51.92, H 7.09, N 3.04.

*O,O-Diethyl N-[1-(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ⁵-1,3,2-dioxaphosphorinan-2-yl)cyclohexyl]phosphoramidothioate* (**4k**). White solid. R_f (petroleum ether/AcOEt 4:1) 0.62. M.p. 170–172°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34–7.26 (*m*, Ph); 5.49 (*s*, NH); 4.52 (*d*, $^3J = 11.7$, H–C(4)); 4.16–4.06 (*m*, 2 MeCH_2O); 3.81 (*dd*, ^3J(P,H) = 21.4, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.37 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.15–1.44 (*m*, $(CH_2)_5$); 1.27 (*t*, $J = 7$, 2 *Me*CH_2O); 1.01 (*s*, 1 Me–C(5)); 0.77 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.25, 128.58, 128.00, 127.71 (arom. C); 84.03 (*d*, $^2J = 6.0$, C(6)); 75.27 (*d*, $^2J = 6.0$, C(4)); 63.60 (2 MeCH_2O); 58.13 (*dd*, $^1J = 149$, $^2J = 6.1$, NCP); 37.09 (C(5)); 32.35 (CH_2); 31.88 (CH_2); 25.22 (CH_2); 21.97 (CH_2); 21.50 (1 *Me*CH_2O); 18.05 (1 *Me*CH_2O); 18.00 (CH_2); 16.04 (1 Me); 15.99 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.86 (*d*, $^3J = 19.8$); 28.96 (*d*, $^3J = 19.8$). ESI-MS: 476 ($[M+1]^+$).

*O,O-Diethyl N-[1-(*trans-*5,5-Dimethyl-2-oxido-4-phenyl-2λ⁵-1,3,2-dioxaphosphorinan-2-yl)cycloheptyl]phosphoramidothioate* (**4l**). Clear oil. R_f (petroleum ether/AcOEt 4:1) 0.38. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35–7.23 (*m*, Ph); 5.45 (br. *s*, NH); 4.48 (*d*, $^3J = 11.2$, H–C(4)); 4.13–4.07 (*m*, 2 MeCH_2O); 3.79 (*dd*, ^3J(P,H) = 21.2, ^2J(H,H′) = 11.2, 1 H–C(6)); 3.40 (*d*, ^2J(H,H′) = 11.2, 1 H′–C(6)); 2.37–1.55 (*m*, $(CH_2)_6$); 1.29 (*t*, $J = 7$, 2 *Me*CH_2O); 1.04 (*s*, 1 Me–C(5)); 0.74 (*s*, 1 Me–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 128.59, 128.02, 127.68, 126.51 (arom. C); 84.14 (*d*, $^2J = 6.0$, C(6)); 75.36 (*d*, $^2J = 6.1$, C(4)); 63.73 (1 MeCH_2O); 62.18 (1 MeCH_2O); 61.38 (*dd*, $^1J = 147$, $^2J = 6.6$, NCP); 37.11 (C(5)); 34.96 (CH_2); 34.15 (CH_2); 31.23 (2 CH_2); 22.90 (CH_2); 22.78 (CH_2); 21.97 (1 *Me*CH_2O); 18.00 (1 *Me*CH_2O); 16.05 (1 Me); 15.96 (1 Me). ^{31}P-NMR (121 MHz, $CDCl_3$): 69.74 (*d*, $^3J = 15.7$); 30.40 (*d*, $^3J = 15.7$). ESI-MS: 490 ($[M+1]^+$).

REFERENCES

[1] J. Wu, W. Sun, H. G. Xia, X. Y. Sun, *Org. Biomol. Chem.* **2006**, *4*, 1663; A. I. Balabanovich, V. P. Prokopovich, *J. Anal. Appl. Pyrolysis* **2006**, *76*, 169; A. A. Nazarov, M. P. Koroteev, C. G. Hartinger, B. K. Keppler, E. E. Nifant'ev, *Tetrahedron* **2005**, *61*, 10943; M. Chakravarty, B. Srinivas, C. Muthiah, K. C. K. Swamy, *Synthesis* **2003**, *15*, 2368; A. P. Kaplan, P. A. Bartlett, *Biochemistry* **1991**, *30*, 8165; S. Y. Wu, J. E. Casida, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *102*, 177; C. D. Reddy, M. S. Reddy, S. M. Waidu, K. D. Berlin, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *102*, 103; A. Hirashima, *Agric. Biol. Chem.* **1989**, *53*, 175; Y. Nishizuka, *Nature (London, U.K.)* **1984**, *308*, 693; V. L. Boyd, M. F. Summers, S. M. Ludeman, W. Egan, G. Zon, J. B. Regan, *J. Med. Chem.* **1987**, *30*, 366.

[2] J. Hiratake, J. Oda, *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211; P. Kafarski, B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

[3] J. Zhou, R. Y. Chen, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2917.

[4] Z. G. Dikmen, G. C. Gellert, S. Jackson, S. Gryaznov, R. Tressler, P. Dogan, W. E. Wright, J. W. Shay, *Cancer Res.* **2005**, *65*, 7866; M. Nivsarkar, A. K. Gupta, M. P. Kaushik, *Tetrahedron Lett.* **2004**, *45*, 6863; T. K. Venkatachalam, G. Yu, P. Samuel, S. Qazi, S. Pendergrass, F. M. Uckun, *Eur. J. Med. Chem.* **2004**, *39*, 665.

[5] N. Sträter, W. N. Lipscomb, *Biochemistry* **1995**, *34*, 9200; D. W. Christianson, W. N. Lipscomb, *J. Am. Chem. Soc.* **1988**, *110*, 5560; H. Kim, W. N. Lipscomb, *Biochemistry* **1991**, *30*, 8171.
[6] V. Sum, C. A. Baird, T. P. Kee, M. Thornton-Pett, *J. Chem. Soc., Perkin Trans. 1* **1994**, 3183; L. Stryer, 'Biochemistry', Freeman, New York, 3rd edn., 1988; L. Maier, P. J. Diel, *Phosphorus, Sulfur Silicon Relat. Elem*. **1991**, *57*, 57; S. A. Beers, C. F. Schwender, D. A. Loughney, E. Malloy, K. Demarest, J. Jordan, *Bioorg. Med. Chem.* **1996**, *4*, 1693.
[7] Z. G. Li, Q. M. Wang, J. M. Huang, 'Synthesis of Organic Intermediates', Chemical Industry Press, Beijing, 2001, p. 207.
[8] W. Ten Hoeve, H. Wynberg, *J. Org. Chem.* **1985**, *50*, 4508; R. Hulst, R. W. J. Zijlstra, N. K. de Vries, B. L. Feringa, *Tetrahedron Asymmetry* **1994**, *9*, 1701; D. Q. Shi, Z. L. Sheng, X. P. Liu, H. Wu, *Heteroat. Chem.* **2003**, *14*, 266.
[9] C. Y. Yuan, Y. M. Qi, *Synthesis* **1986**, 821; C. Y. Yuan, Y. M. Qi, *Synthesis* **1988**, 472; C. Y. Yuan, S. J. Chen, G. H. Wang, *Synthesis* **1991**, 490.
[10] R. L. Shao, M. H. Yang, C. X. Zhi, *Chin. Chem. Lett.* **1993**, *4*, 767; G. G. Gorenstein, 'Non-Biological Aspects of ^{31}P NMR Spectroscopy', Pergamon Press, Oxford, 1983, Vol. 16; S. E. Denmark, R. L. Dorow, *J. Org. Chem.* **1990**, *55*, 5926.

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