Tetrahedron 68 (2012) 126–132

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective synthesis of both enantiomers of *P*-chirogenic 2-oxo-2-thio-1,3,2-oxazaphosphorinane tetramethylammonium salt as key precursors to structurally diverse chiral derivatives

Marian Mikołajczyk [a,*], Jerzy Łuczak [a], Lesław Sieroń [b], Michał W. Wieczorek [b]

[a] Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Heteroorganic Chemistry, Sienkiewicza 112 str., 90-363 Łódź, Poland
[b] Institute of General and Ecological Chemistry, Technical University of Łódź, Żeromskiego 116 str., 90-924 Łodź, Poland

ARTICLE INFO

Article history:
Received 27 July 2011
Received in revised form 7 October 2011
Accepted 24 October 2011
Available online 29 October 2011

Dedicated to the late Professor Anatoly E. Shipov in recognition of his contribution to the oxazaphosphorinane chemistry

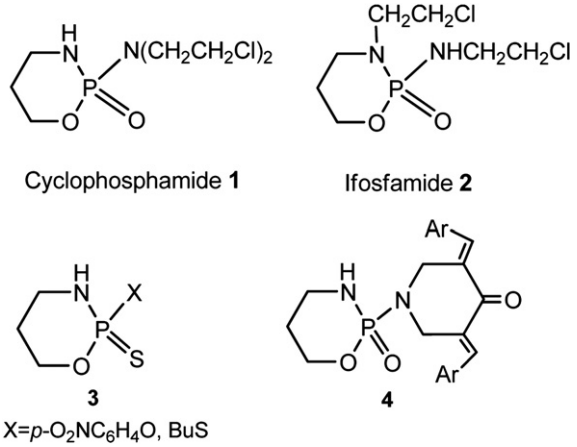
ABSTRACT

A fully stereoselective synthesis of both enantiomers of 2-oxo-2-thio-1,3,2-oxazaphosphorinanyl salt has been accomplished in five steps with an overall 40–45% yield starting from the diastereoisomeric *N*-methylstrychninium salts of methyl *p*-nitrophenyl phosphorothioic acid. Their conversion to the enantiomeric forms of methyl *p*-nitrophenyl phosphorochloridothionate as a two-step phosphorylating agent allowed the formation of the 1,3,2-oxazaphosphorinane ring in this reaction sequence. An alternative four-step approach to the enantiopure title salt was developed which involves in the first and crucial step cyclocondensation between thiophosphoryl chloride and *N*-α-naphthylethyl containing a 1,3-aminopropanol group, occurring with almost complete diastereoselectivity.

1. Introduction

Oxazaphosphorinanes, cyclic six-membered phosphorus compounds derived from 1,3-aminopropanol, have attracted interest from synthetic organic chemists, pharmacologists and biochemists. The early discovery of the anticancer properties of oxazaphosphorinanes stimulated the synthesis of a great number of structurally diverse oxazaphosphorinanes from which two, cyclophosphamide **1** and ifosfamide **2**, were manufactured as chemotherapeutical drugs[1] and are still used in clinical practice. The extensive studies on biological activity and metabolism of cyclophosphamide **1** revealed that it is not cytotoxic as such. However, when transported into a cancer cell it undergoes oxidative degradation to the active, toxic diamidophosphate metabolite. Interestingly, as the phosphorus atom in **1** is stereogenic, the enantiomeric forms of **1** exhibit different activity, the laevorotatory enantiomer being more active.

In a search for selectively active pesticides the group of Kabachnik and Shipov[2–4] has synthesized dozens of racemic 1,3,2-oxazaphosphorinan-2-thiones and found that some of them, especially 1,3,2-oxazaphosphorinan-2-thiones **3** with *p*-nitrophenoxy and butylthio groups bonded to phosphorus, exhibit high nematocide activity with low mammalian toxicity. They also show the strong synergistic effect for pyrethroid insecticides (permethrin and sumithrin). It has been demonstrated that the mechanism of this effect involves in the first step oxidation of the thiophosphoryl group in **3** upon action of monooxygenases to afford the corresponding phosphoryl compounds (oxons) that are further biodegraded by the same metabolic pathway as that determined for cyclophosphamide **1**.



Cyclophosphamide **1** Ifosfamide **2**

3
X=*p*-$O_2NC_6H_4O$, BuS

4

Recently, much attention has been paid to the synthesis of structural analogues of known biologically active compounds like

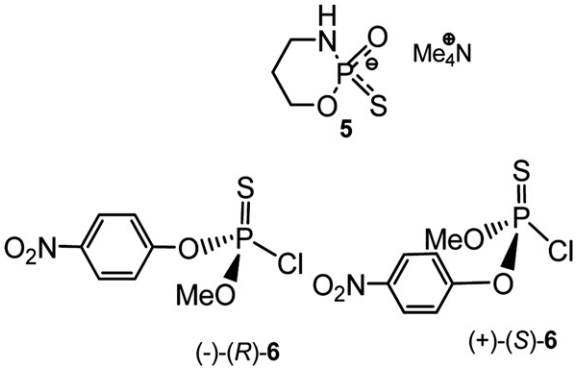
* Corresponding author. E-mail addresses: marmikol@cbmm.lodz.pl, marmikol@bilbo.cbmm.lodz.pl (M. Mikołajczyk).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.085

N-phosphonoacetyl-L-aspartic acid (PALA)[5–7] and 3,5-bis(arylidene)-piperidin-4-ones,[8] which contain the 1,3,2-oxazaphosphorinane moiety. The presence of this heterocyclic ring in structures of these potential drugs should increase or modify their bioactivity and facilitate their penetration through cellular membranes. In fact, it turned out that the cytotoxicity of the piperidinone **4** bearing the 1,3,2-oxazaphosphorinane group at nitrogen is significantly higher than that of the parent piperidinone.[8,9]

In all of these well-motivated and promising studies, a variety of the *P*-chiral but racemic 1,3,2-oxazaphosphorinane structures have been synthesized and tested. As it is well known that pure enantiomers of chiral drugs[10] and insecticides[11] differ in bioactivity, it would be desirable to prepare single enantiomers of a given 1,3,2-oxazaphosphorinane and test different levels of the desired bioactivity and toxicity as well as the rate of metabolism. An additional reason to synthesize enantiomeric 1,3,2-oxazaphosphorinanes came from our recent work on enzymatic oxidation of an insecticidal dithiophosphate to the corresponding oxon catalyzed by chloroperoxidase from *Caldariomyces fumago*.[12] It was found that this oxidation reaction, which generally constitutes the first step of the main biodegradation pathway of thionophosphates both in mammals and insects, occurs with almost complete enantioselectivity converting only one enantiomer of a racemic substrate to the corresponding oxon and leaving the enantiomer with opposite configuration at phosphorus unconsumed.

Taking into account that phosphorus monothioacids are convenient starting materials for the synthesis of a variety of phosphoryl and thiophosphoryl compounds[13] and the fact that the racemic tetramethylammonium salt of 2-oxo-2-thio-1,3,2-oxazaphosphorinane **5** has been obtained, characterized and used in our earlier studies,[14] we decided to elaborate the synthesis of enantiomeric forms of this salt as precursors to other optically active oxazaphosphorinane derivatives.



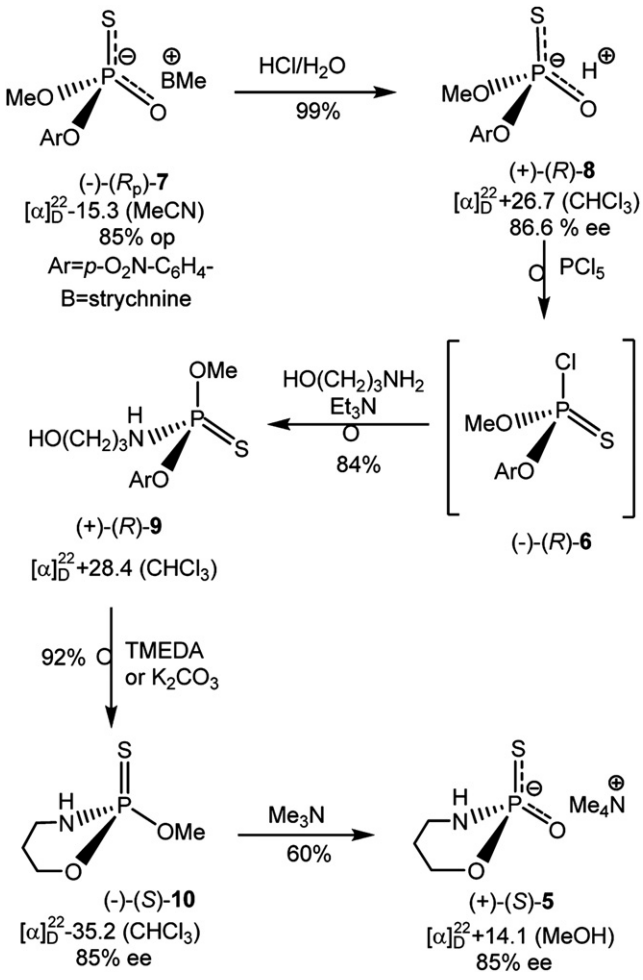
In the first stereoselective approach to **5** devised by us and reported herein a two-step phosphorylating agent, methyl *p*-nitrophenyl phosphorochloridothionate **6**,[15,16] the enantiomeric forms of which can be obtained from the resolved diastereoisomeric *N*-methylstrychninium salts **7** of methyl *p*-nitrophenyl phosphorothioic acid **8**,[17] plays a key role. Due to distinct difference in the leaving group ability between chloride and *p*-nitrophenoxy anions it is possible to achieve selectively nucleophilic mono-substitution at phosphorus in **6** with the chloride anion as a leaving group and then to perform the second nucleophilic substitution reaction, which in our case consists in a ring closure to form the cyclic 1,3,2-oxazaphosphorinane structure. In addition, we also report a highly efficient asymmetric synthesis of **5**, which was unexpectedly discovered in the course of our work on determination of the absolute configuration at phosphorus in some of the intermediate products.

2. Results and discussion

2.1. Stereoselective synthesis of (+)-(*S*)- and (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane 5

The starting diastereoisomeric salts **7** of methyl *p*-nitrophenyl phosphorothioic acid **8** were prepared according to the procedure of Hilgetag and Lehmann[17] and partially resolved by fractional crystallization. The samples of **7** with the values of optical rotation −15.3, +14.2 and +15.3 and the corresponding optical purity values of 85%, 75% and 85% were used for further intended transformations.

The details of our first synthesis of (+)-(*S*)-**5** are outlined in Scheme 1. This commenced with the acidification of the salt (−)-(R_P)-**7** affording the free thioacid (+)-(*R*)-**8**, which was obtained in 99% yield. Its ^{1}H NMR spectrum recorded in the presence of (−)-*tert*-butylphenylphosphinothioic acid as a chiral solvating agent showed two doublets for the *P*-methoxy protons at 3.80 and 3.95 ppm with a relative intensity 93.3:6.7. This ratio corresponds to 86.6% ee. A small difference between the value of optical purity (op) of the salt (−)-**7** and the ee value of the generated thioacid (+)-**8** may be attributed to an inaccuracy of both the optical rotation measurements and resonance signal integrations.



Scheme 1. Synthesis of (+)-(*S*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane **5**.

The reaction of the thioacid (+)-**8** with phosphorus pentachloride gave the corresponding phosphorochloridothionate (−)-**6**, which, after standard isolation from the reaction mixture, was

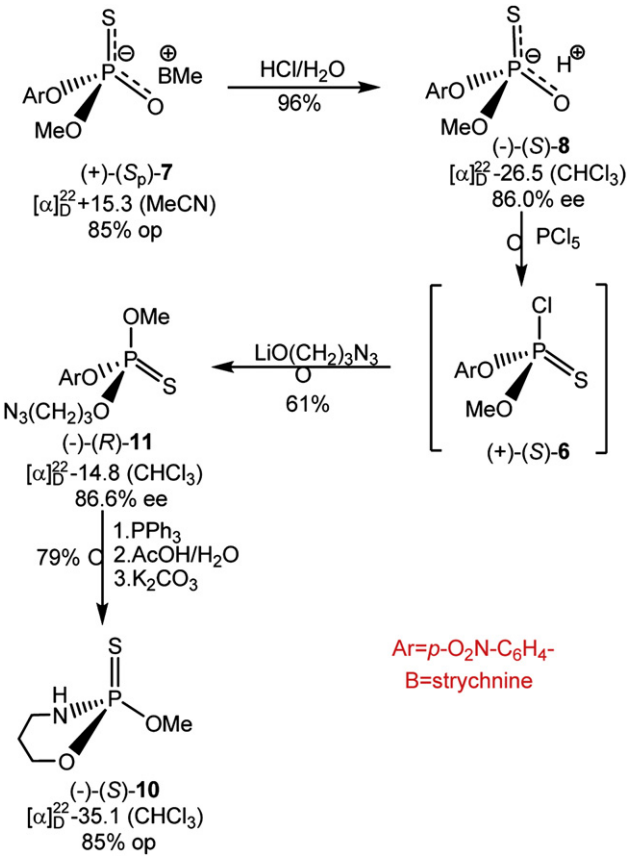
immediately used as a crude product for the condensation reaction with 1,3-aminopropanol in the presence of triethylamine. A single product (+)-**9** obtained in this reaction results from the exclusive N-phosphorylation of 1,3-aminopropanol. The amidodiester structure of **9** and not triester framework (O-phosphorylation) was confirmed by NMR spectroscopy with ^{13}C NMR spectra proving to be most informative and conclusive. In the next step, the amidodiester (+)-**9** in the presence of potassium carbonate or tetramethylenediamine was converted very efficiently (92% yield) into (−)-2-methoxy-1,3,2-oxazaphosphorinan-2-thione **10**. In this case, the intramolecular substitution reaction at phosphorus took place with the participation of the oxypropyl moiety as a nucleophile and *p*-nitrophenoxy anion as a leaving group. It occurred, however, much more slowly than the nucleophilic substitution of the chloride anion in (−)-(*R*)-**6**. Based on the ^{1}H NMR spectrum of the cyclic amidodiester (−)-**10** recorded in the presence of (−)-*tert*-butylphenylphosphinothioic acid, which showed two doublets for the methoxy protons at 3.704 and 3.699 ppm with a relative intensity 7.5:92.5, the ee value for this cyclic product was determined to be 85%. As the optical purity of the starting salt (−)-(R_P)-**7** was the same, its conversion into (−)-**10** via three reactions occurring at the stereogenic phosphorus was found with satisfaction to be stereospecific. Finally, the amidodiester (−)-**10** was treated with trimethylamine to give the desired tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane (+)-**5** in 45% overall yield. Since demethylation of (−)-**10** occurs at the methoxy carbon and the stereogenic phosphorus atom is not involved in this reaction, the salt (+)-**5** obtained has the same ee value and the absolute configuration at phosphorus as that of the precursor phosphonothionoester (−)-**10**.

With regard to the absolute configuration of the ester (−)-**10** and the salt (+)-**5**, at this stage of our work we tentatively ascribed the (*S*)-configuration to them assuming that the reaction of the phosphorochloridothionate (−)-(*R*)-**6** with 1,3-aminopropanol and the conversion of the amidodiester (+)-**9** into (−)-**10** as typical nucleophilic substitution reactions at the chiral thiophosphoryl centre[18] occurred with inversion of configuration at phosphorus. Hence, the (*R*)-configuration was ascribed to the amidodiester (+)-**9**.

The same reaction sequence as shown in Scheme 1 with *N*-methylstrychninium salt (+)-(S_P)-**7**, $[\alpha]_D^{22}$ +14.2 (MeOH), as starting material allowed to synthesize stereoselectively the cyclic amidodiester (+)-(*R*)-**10**, $[\alpha]_D^{22}$ +32.4 ($CHCl_3$), and then (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane **5**, $[\alpha]_D^{22}$ −13.0 (MeOH), in comparable overall yield (42%) (for details of the synthesis of (+)-**10** and (−)-**5** see Experimental section).

We were also able to convert the *N*-methylstrychninium salt (+)-(S_P)-**7** into the ester (−)-(*S*)-**10** in a very simple way by reversing the order of nucleophilic substitution at phosphorus in the phosphorochloridothionate (+)-(*S*)-**6**, i.e., we performed first O-phosphorylation of 3-azidopropanol[19] with the chloride (+)-(*S*)-**6** and then intramolecular N-phosphorylation of (−)-(*R*)-**11** formed in the first reaction. Thus, treatment of lithium 3-azidopropoxide with the phosphorochloridothionate (+)-(*S*)-**6** gave the corresponding triester (−)-(*R*)-**11** in 61% yield. Chiral column chromatography indicated that its ee value was 86.6% providing evidence for a complete stereoselectivity of this step. The free amino group in the latter intermediate was generated in situ from the azido moiety via Staudinger reaction followed by hydrolysis. In the presence of potassium carbonate the intramolecular cyclization took place to give the oxazaphosphorinane (−)-(*S*)-**10** in 79% yield. The optical purity value of the latter confirmed again complete stereoselectivity of the second substitution reaction.

As in the previous reaction sequence shown in Scheme 1, it was assumed that both nucleophilic substitution steps occur with inversion of configuration. The reaction sequence is shown in Scheme 2, which contains some selected experimental details and tentative assignments of the absolute configuration (*R*) and (*S*) to (−)-**11** and (−)-**10,** respectively.

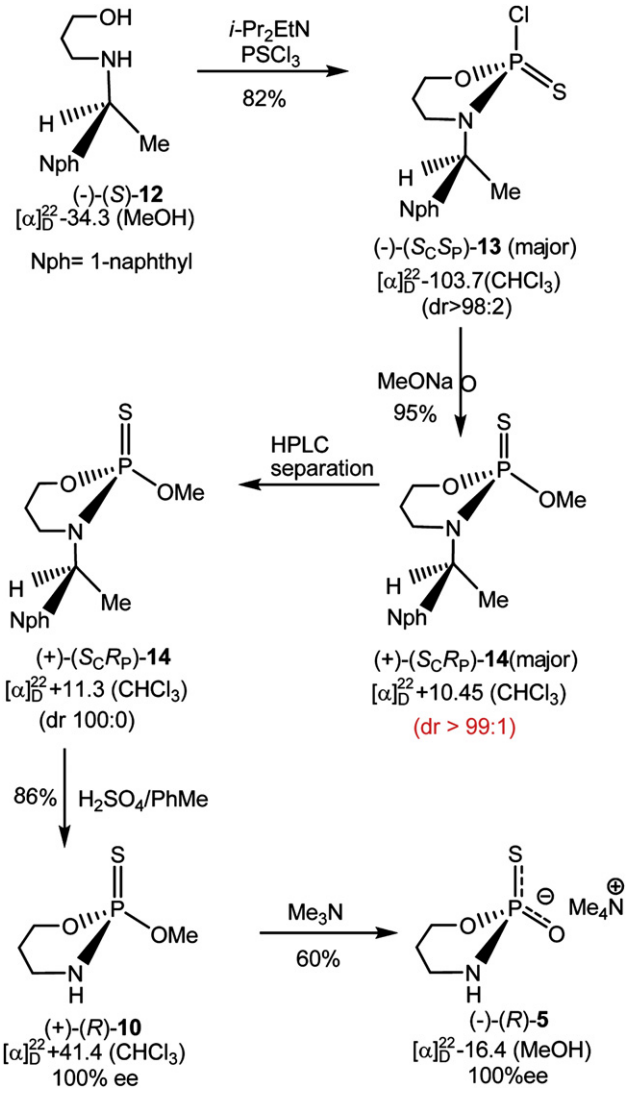


Scheme 2. Synthesis of (−)-(*S*)-2-methoxy-1,3,2-oxazaphosphorinan-2-thione **10**.

2.2. Asymmetric synthesis of enantiopure (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane 5

In an extension of the present work on the stereoselective synthesis of the salts (+)-(*S*)- and (−)-(*R*)-**5** we turned our attention to the diastereoselective synthesis with the hope that a tedious resolution of the starting *N*-methylstrychninium salts (+)-(S_P)- and (−)-(R_P)-**7** may be avoided and a more simple and practical synthetic approach to our targets may be developed. Encouraged by the use of chiral α-phenylethylamine in the early syntheses of the enantiomeric forms of cyclophosphamide **1**[20,21] we prepared (−)-(*S*)-3-hydroxypropyl-1-(1-naphthyl)ethylamine **12** from 3-chloropropanol and (−)-(*S*)-(1-naphthyl)ethylamine. The reaction of (−)-(*S*)-**12** with thiophosphoryl chloride in the presence of triethylamine produced 2-chloro-2-thio-3-[1-(1-naphthyl)ethyl]-1,3,2-oxazaphosphorinane **13**, $[\alpha]_D^{22}$ −122 ($CHCl_3$), as a mixture of two diastereoisomers as revealed by the ^{31}P NMR resonance signals at 69.88 and 69.82 ppm with a relative intensity 87:13. When diisopropylethylamine was used as condensing agent we were very happy to find that the oxazaphosphorinane (−)-**13**, $[\alpha]_D^{22}$ −103.7 ($CHCl_3$), obtained showed only one resonance signal at 69.88 ppm in the ^{31}P NMR spectrum. The investigations on the origin of this unexpectedly very high diastereoselectivity are in progress. In the next step, the chloride (−)-**13** was reacted with sodium methoxide to give the ester (+)-**14**, $[\alpha]_D^{22}$ +10.45 ($CHCl_3$). HPLC revealed that it consisted of the two separable

diastereoisomers of **14**. The major diastereoisomer exhibited optical rotation $[\alpha]_D^{22}$ +11.3 ($CHCl_3$), while the minor one had $[\alpha]_D^{22}$ −189.0 ($CHCl_3$). Interestingly, the major and minor diastereoisomers of **14** showed clearly different ^{31}P NMR signals at 73.11 and 73.82 ppm, respectively. As the ^{31}P NMR spectrum of (+)-**14** with $[\alpha]_D^{22}$ +10.45 ($CHCl_3$) showed only one resonance signal at 73.11 ppm it may be concluded that dr of this sample is >99:1. Based on the optical rotation values of the pure diastereoisomers of (+)-**14** dr of this ester was calculated to be 99.5:0.5 (Scheme 3).



Scheme 3. Synthesis of (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane **5**.

Having the diastereoisomerically pure and crystalline major isomer of (+)-**14** in hand, we determined its crystal and molecular structure by X-ray diffraction (see below) and found that the absolute configuration at phosphorus is (*R*). By making the very reasonable assumption that the chloride–methoxy exchange at phosphorus occurs with inversion of configuration, one may assign the absolute configuration (S_P) to the major diastereoisomer of **13**. Then, the diastereoisomerically pure (+)-(S_C,R_P)-**14** was easily converted into the already known amidodiester (+)-**10** in the reaction with concentrated sulfuric acid in toluene carried out under the modified conditions reported by Sato.[22] Since the removal of the chiral α-naphthylethyl auxiliary involved the cleavage of the benzylic carbon–nitrogen bond in (+)-**14** and any bond around the chiral phosphorus was broken, the amidodiester (+)-**10** formed must be enantiomerically pure and have the same absolute configuration (*R*) at phosphorus. In this way, the correctness of our tentative configurational assignment to (+)-**10** as well as to other intermediate products has been unequivocally confirmed. Finally, the amidodiester (+)-(*R*)-**10** was demethylated by trimethylamine to give the enantiopure tetramethylammonium salt (−)-(*R*)-**5** in 40% overall yield.

2.3. Crystal and molecular structure and absolute configuration of (+)-2-methoxy-3-[1-(1-naphthyl)ethyl]-1,3,2-oxazaphosphorinan-2-thione 14

One of our aims to obtain the diastereoisomerically pure esters **14** bearing the chiral α-naphthylethyl group at nitrogen was to determine unequivocally the absolute configuration at the phosphorus stereocentre. Therefore, it was gratifying to find that the major diastereoisomer (+)-**14** was crystalline and crystals of quality suitable for X-ray diffraction could be obtained by slow crystallization from a hexane–chloroform solution.

A three-dimensional view of the molecule of (+)-**14** and the atom numbering are shown in Fig. 1. It clearly reveals that the absolute configuration at phosphorus P1 and carbon C5 is (*R*) and (*S*), respectively. The six-membered 1,3,2-oxazaphosphorinane ring adopts a slightly twisted chair conformation what is evident from the puckering parameters [Q=0.525(4) Å, θ=5.8(3)° and φ=174(4)°].[23] The thiophosphoryl sulfur atom occupies an equatorial position with the P–S distance of 1.9176(9) Å. The nitrogen atom deviates from planarity. The sum of the bond angles around N1 atom is 353.5(2)° indicating a distinctly distorted sp^2 hybridization. The crystal structure is stabilized by weak intermolecular C–H···π and C–H···S hydrogen-bond type interactions (see Supplementary data).

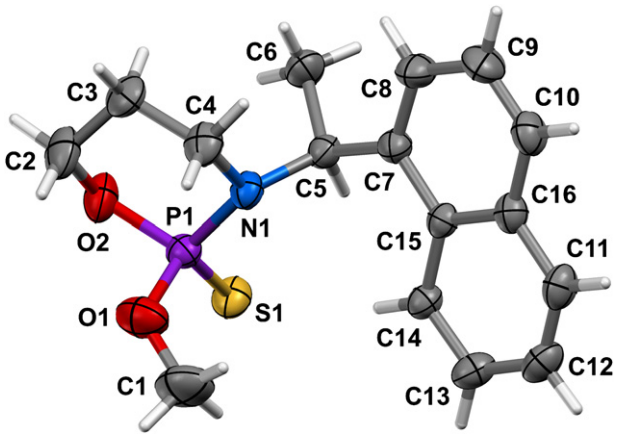


Fig. 1. The molecular structure of (+)-**14** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

3. Conclusion

In conclusion, we have been able to develop a five-step sequence for the stereoselective synthesis of (+)-(*S*)- and (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane. Two crucial steps include nucleophilic substitution at phosphorus in optically active phosphorochloridothionate and intramolecular nucleophilic substitution at phosphorus leading to the formation of the oxazaphosphorinane ring. Both reactions occurred with complete inversion of configuration. An alternative approach to our targets was also developed which is based on the almost fully diastereoselective cyclocondensation reaction between thiophosphoryl chloride and 1,3-aminopropanol bearing an N-α-

naphthylethyl auxiliary. The stereoselective and asymmetric synthesis of the title salts paves the way for the synthesis of other enantiomeric oxazaphosphorinanes and studies on the relationship between chirality at phosphorus and bioactivity.

4. Experimental

4.1. General information

All solvents and chemicals were used as provided by the supplier. Melting and boiling points are uncorrected. NMR spectra were recorded on Bruker AC 200 and Bruker MSL spectrometers. Chemical shifts are quoted in parts per million (ppm). ^{1}H and ^{13}C chemical shifts are reported relative to TMS as an external standard. ^{31}P NMR downfield chemical shifts are expressed with a positive sign relative to an external standard of 85% H_3PO_4. Optical rotations were measured at 22 °C using Perkin–Elmer MC 241 photopolarimeter. Optical purity (op) values were calculated based on specific rotations. Enantiomeric excesses (ee) were determined by HPLC on a Varian Pro-Star instrument using Cyclobond 2000 DMP, or by NMR via diastereoisomeric solvates. Diastereoisomeric ratios (dr) were determined by integration of the resonance signals in ^{1}H and ^{31}P NMR spectra. Mass spectra were recorded on a Finnigan MAT 95 apparatus. Thin layer chromatography (TLC) was conducted on Silica Gel F_{254} TLC purchased from Merck. Column chromatography was performed using Merck silica gel (70–230 mesh).

4.2. Stereoselective synthesis of (+)-(*S*)- and (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane 5

*4.2.1. (+)-(R)-Methyl p-nitrophenyl phosphorothioic acid (**8**).* To a stirred suspension of (−)-(R_P)-methostrychninium salt **7** (3.58 g, 0.6 mmol), $[\alpha]_D^{22}$ −15.3 (*c* 1.2, MeCN) in 50% methanol (25 mL), 2 N hydrochloric acid (60 mL) was added slowly at room temperature. After the salt was completely dissolved, the content was transferred into separating funnel and extracted with dichloromethane (3×60 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude phosphorothioic acid **8** was obtained (1.47 g, 99% yield) as a pale yellow viscous oil and used without additional purification for further reactions. $[\alpha]_D^{22}$ +26.7 (*c*.1.9, $CHCl_3$, 86.6% ee); δ_H (200 MHz, $CDCl_3$) 8.18 (2H, d, *J* 8.9 Hz, ArH), 7.37 (2H, d, *J* 8.9 Hz, ArH), 3.81 (3H, d, J_{H-P} 13.8 Hz, OC*H*$_3$), δ_P (81 MHz, $CDCl_3$) 59.35.

*4.2.2. (−)-(S)-Methyl p-nitrophenyl phosphorothioic acid (**8**).* According to the procedure described above from the salt (+)-(S_P)-**7** (1.79 g, 3 mmol), $[\alpha]_D^{22}$ +14.2 (*c* 1.2, MeOH), the thioacid (−)-**8** was obtained (0.71 g, 96%); $[\alpha]_D^{22}$ −23.4 (*c* 1.8, $CHCl_3$, 77% ee).

*4.2.3. (+)-(R)-Methyl p-nitrophenyl N-(3-hydroxypropyl)phosphoroamidothionate (**9**).* To a stirred phosphorus pentachloride (1.25 g, 6 mmol) in chloroform (50 mL) thioacid (+)-(*R*)-**8** (1.46 g, 5.86 mmol), $[\alpha]_D^{22}$ +26.7, (c 1.9, $CHCl_3$) in chloroform (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h and cooling bath was removed. When room temperature was reached, the reaction mixture was filtered. To the filtrate was added dry toluene (10 mL) and the mixture evaporated to small volume under reduced pressure. Addition of toluene and evaporation was repeated to remove the traces of phosphoryl chloride. A pale yellow oil obtained after evaporation was pre-purified by flash column chromatography (5 g of silica gel, chloroform-*n*-hexane, 1:1) to give phosphorochloridothionate (−)-(*R*)-**6** (1.4 g, 90%); δ_P (81 MHz, $CDCl_3$) 60.37. Without further purification it was dissolved in chloroform (40 mL) and a mixture of 3-aminopropanol (0.395 g, 5.24 mmol) and triethylamine (0.53 g, 5.24 mmol) in chloroform (30 mL) was added dropwise. After 2 h the solution was filtered through silica gel (5 g), concentrated under reduced pressure and purified by flash column chromatography (silica gel, chloroform–ethyl acetate, 98:2) to give the *title compound* **9** (1.49 g, 93%) as a pale yellow oil; [Found: C, 39.1; H, 5.0; N, 9.0; S, 10.2. $C_{10}H_{15}N_2O_5PS$ requires C, 39.21; H, 4.90; N, 9.15; S, 10.45%]; $[\alpha]_D^{22}$ +28.4 (*c* 2.4, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 8.22 (2H, d, *J* 9.2 Hz, ArH), 7.35 (2H, d, *J* 9.2 Hz, ArH), 3.80 (3H, d, J_{H-P} 14.1 Hz, OC*H*$_3$), 3.77 (2H, t, *J* 6.2 Hz, OC*H*$_2$), 3.25 (2H, dt, J_{H-H} 6.4 Hz, J_{H-P} 11.3 Hz, NC*H*$_2$), 1.77 (2H, m, OCH$_2$C*H*$_2$CH$_2$N); δ_C (50 MHz, $CDCl_3$) 155.9 (s, ArC), 141.3 (s, ArC), 125.2 (s, ArC), 121.4 (s, ArC), 60.2 (s, *C*H$_2$OH), 53.8 (d, J_{C-P} 5.2 Hz, *C*H$_3$O), 39.5 (d, J_{C-P} 3.2 Hz, C*C*H$_2$C), 33.1 (d, J_{C-P} 5.9 Hz, NCH$_2$); δ_P (81 MHz, $CDCl_3$) 70.1.

*4.2.4. (−)-(S)-Methyl p-nitrophenyl N-(3-hydroxypropyl)phosphoroamidothionate (**9**).* When the thioacid (−)-(*S*)-**8** (0.7 g, 2.81 mmol), $[\alpha]_D^{22}$ −23.4 (*c* 1.8, $CHCl_3$), was used, the same procedure produced the amidodiester (−)-(*S*)-**9** (0.553 g, 87%) as a pale yellow oil, $[\alpha]_D^{22}$ −25.2 (*c* 1.97, $CHCl_3$).

*4.2.5. (−)-(S)-2-Methoxy-1,3,2-oxazaphosphorinan-2-thione (**10**).* To a stirred solution of the phosphoroamidothionate (+)-(*R*)-**9** (c 2.4, $CHCl_3$), (1.224 g, 4 mmol) in chloroform (40 mL) was added tetramethylenediamine (TMEDA) (0.465 g, 4 mmol) at room temperature. After 48 h the reaction solution was transferred into a separatory funnel, washed with water (4×5 mL), dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel 230–400 mesh, chloroform-*n*-heptane, 9:1) to give the oxazaphosphorinane **10** (0.615 g, 92%) as a pale yellow oil; [Found: C, 29.1; H, 6.3; N, 8.4; P, 18.9. $C_4H_{10}NO_2PS$ requires C, 28.74; H, 6.02; N, 8.38; P, 18.54%]; $[\alpha]_D^{22}$ −35.2 (*c* 3.3, $CHCl_3$, 85% ee); ν_{max} (liquid fil) 3363–3291 (br), 2958–2843 (br), 1723, 1462, 1377, 1325, 1276, 1217, 1079, 1031, 969, 938, 873, 802, 663 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.38–4.24 (2H, m), 3.69 (3H, d, J_{H-P} 13.6 Hz, OC*H*$_3$), 3.41–3.14 (3H, m), 2.16–1.93 (1H, m), 1.64–1.53 (1H, m); δ_C (50 MHz, $CDCl_3$) 68.6 (d, J_{C-P} 8.8 Hz, OC*H*$_2$), 52.9 (d, J_{C-P} 5.0 Hz, OC*H*$_3$), 41.05 (d, J_{C-P} 5.5 Hz, C*C*H$_2$C), 26.0 (d, J_{C-P} 6.9 Hz, *C*H$_2$N); δ_P (81 MHz, $CDCl_3$) 69.22.

*4.2.6. (+)-(R)-2-Methoxy-1,3,2-oxazaphosphorinan-2-thione (**10**).* In a similar way phosphoroamidothionate (−)-**9** (0.5 g, 1.63 mmol), $[\alpha]_D^{22}$ −25.2 (*c* 1.97, $CHCl_3$), gave the oxazaphosphorinane (+)-**10** (0.254 g, 90%), $[\alpha]_D^{22}$ +32.4 (*c* 2.5, $CHCl_3$, 78% ee).

*4.2.7. (+)-(S)-Tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane (**5**).* A mixture of (−)-**10** (0.167 g, 1 mmol), $[\alpha]_D^{22}$ −35.2 (*c* 1, $CHCl_3$) and trimethylamine (0.5 mL) in benzene (3 mL) was kept at room temperature for 2 weeks. The white crystalline salt (+)-**5** produced (0.137 g, 60%) was filtered off, washed with benzene and dried over P_2O_5, mp 218–221 °C; $[\alpha]_D^{22}$ +14.1 (*c* 1.26, MeOH, 85% ee); ν_{max} (KBr) 3513–3340 (br), 3273, 3013, 2952, 1650, 1608, 1487, 1199, 1163, 1075, 1040, 947, 856, 816, 759, 661, 591 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.05–4.35 (3H, m, OC*H*$_2$, N*H*), 3.52 (12H, s, N(C*H*$_3$)$_4$), 3.28–2.85 (2H, m), 2.22–1.87 (1H, m, C*C*H$_2$C), 1.80–1.70 (1H, m, C–C*H*$_2$–C); δ_P (81 MHz, D_2O) 56.6.; LSIMS, Cs^+, 13 keV (NBA): ion (+): *m*/*z* 74 (Me_4N^+), ion (−): *m*/*z* 152 (2-oxo-2-thio-1,3,2-oxazaphosphorinane$^-$).

*4.2.8. (−)-(R)-Tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane (**5**).* Demethylation of (+)-**10** (0.245 g, 1.46 mmol), $[\alpha]_D^{22}$ +32.4 (*c* 2.5, $CHCl_3$), carried out as described above afforded the *title salt* (−)-**5** (0.183 g, 56%), $[\alpha]_D^{22}$ −13.0 (*c* 1.24, MeOH, 78% ee).

*4.2.9. (−)-(R)-Methyl p-nitrophenyl 3-azidopropyl phosphorothionate (**11**).* To an ethereal solution (5 mL) of phosphorochloridothionate

(+)-**6** (0.36 g, 1.35 mmol), obtained from thioacid (−)-**8**, $[\alpha]_D^{22}$ −26.5 ($CHCl_3$) and phosphorus pentachloride as described in Section 4.2.3, was added under stirring lithium 3-azidopropoxide freshly prepared from 3-azidopropanol (0.136 g, 1.35 mmol) and *n*-butyllithium in ether (5 mL). The reaction mixture was stirred overnight, then filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using chloroform–hexane (70:30) as solvent affording the title compound **11** (0.273 g, 61%) as a yellow oil; [Found: C, 36.2; N, 16.7; S, 9.6. $C_{10}H_{13}N_4O_5PS$ requires C, 36.14; N, 16.86; S, 9.64%]; $[\alpha]_D^{22}$ −14.8 (*c* 1.9, $CHCl_3$, 86.6% ee); δ_H (200 MHz, $CDCl_3$) 8.25 (2H, d, *J* 9.2 Hz, ArH), 7.32 (2H, d, *J* 9.2 Hz, ArH), 4.29 (2H, dt, J_{H-P} 9.0 Hz, J_{H-H} 6.2 Hz, OCH_2), 3.88 (3H, d, J_{H-P} 14.0 Hz, OCH_3), 3.46 (2H, t, J_{H-H} 6.4 Hz, CH_2N_3), 1.98 (2H, tt, J_{H-H} 6.4, 6.2 Hz, CCH_2C); δ_P (81 MHz, $CDCl_3$) 64.2; *m*/*z* (CI) 333 (100 MH^+), 305 (35), 166 (20%).

*4.2.10. (−)-(S)-2-Methoxy-1,3,2-oxazaphosphorinan-2-thione (**10**) from (−)-**11**.* To a stirred solution of the triester (−)-**11** (0.2 g, 0.6 mmol) prepared as above in dry toluene (5 mL) was added triphenylphosphine (0.16 g, 0.6 mmol). After 18 h two drops of 50% acetic acid in tetrahydrofuran (2 mL) were added. The stirring was continued for additional 2 h and then potassium carbonate (1 g) added. After stirring overnight, the reaction solution was filtered and concentrated. The residue was purified by column chromatography (Lichroprep, chloroform–methanol, 97:3). The fraction containing the product was collected and solvent evaporated under reduced pressure to afford (−)-**10** (0.132 g, 79%) as a pale yellow oil. [Found: C, 28.5; N, 8.2; S, 18.9. $C_4H_{10}NO_2PS$ requires C, 28.74; N, 8.38; S, 19.14%]; $[\alpha]_D^{22}$ −35.1 (*c* 2.4, $CHCl_3$, 85% op); δ_H (200 MHz, $CDCl_3$) 4.40–4.29 (2H, m), 3.71 (3H, d, J_{H-P} 13.6 Hz, OCH_3), 3.34–3.02 (3H, m), 2.20–1.97 (1H, m), 1.69–1.57 (1H, m); δ_P (81 MHz, $CDCl_3$) 68.7.

4.3. Asymmetric synthesis of (−)-(*R*)-tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane 5

*4.3.1. (−)-2-Chloro-3-[1-(1-naphthyl)ethyl]-1,3,2-oxazaphosphorinan-2-thione (**13**).* To a solution of thiophosphoryl chloride (4.9 g, 28.9 mmol) in chloroform (50 mL) a mixture of *N*-(3-hydroxypropyl)-1-(1-naphthyl)ethylamine **12** (6.58 g, 28.7 mmol), $[\alpha]_D^{22}$ −34.3 (*c* 2, MeOH) in chloroform (40 mL) was added dropwise at 20 °C. After 1 h stirring a second equivalent of diisopropylethylamine (3.70 g, 28.7 mmol) in chloroform (10 mL) was added and stirring was continued for next 20 h. The reaction solution was transferred into separatory funnel, washed with water (4×20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The remaining white solid was purified by column chromatography (silica gel, chloroform) to give the condensation product **13** (7.69 g, 82%); mp 131–132 °C; [Found: C, 55.3; H, 5.3; Cl, 10.6; P, 9.5; S, 9.9. $C_{15}H_{17}ClNOPS$ requires C, 55.30; H, 5.26; Cl, 10.88; P, 9.51; S, 9.84%]; $[\alpha]_D^{22}$ −103.7 (*c* 1.17, $CHCl_3$, dr >98:2); δ_H (200 MHz, $CDCl_3$) 7.88–7.40 (7H, m, ArH), 6.23–6.14 (1H, m, C*H*), 4.44–4.20 (2H, m), 3.13–2.74 (2H, m), 1.72 (3H, d, *J* 6.9 Hz, CH_3), 1.48–1.42 (2H, m); δ_C (50 MHz, $CDCl_3$) 129.3–124.4 (ArC), 70.2 (d, J_{C-P}11.6 Hz, OCH_2), 53.5 (d, J_{C-P} 4.0 Hz, *C*H), 40.1 (d, J_{C-P} 2.6 Hz, CCH_2C), 26.4 (d, J_{C-P} 3.8 Hz, NCH_2), 15.4 (s, CH_3); δ_P (81 MHz, $CDCl_3$), 69.88.

*4.3.2. (+)-2-Methoxy-3-[1-(1-naphthyl)ethyl]-1,3,2-oxazaphosphorinan-2-thione (**14**).* To (−)-**13** (3.25 g, 10 mmol) obtained as above dissolved in a mixture (1:2) of methanol and toluene (30 mL) sodium methoxide generated from sodium (0.23 g) and methanol (20 mL) was added in one portion. Stirring was continued for 7 days at 40 °C. The content was transferred into separatory funnel and washed with water (3×10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated to afford **14** (3.05 g, 95%) as a white solid, mp 158–161 °C; [Found: C, 60.1; H, 6.5; N, 4.3; P, 9.6; S, 9.9. $C_{16}H_{20}NO_2PS$ requires C, 59.81; H, 6.23; N, 4.36; P, 9.65; S, 9.96.%]; $[\alpha]_D^{22}$ +10.45 (*c* 2.1, $CHCl_3$, dr >99:1); δ_H (200 MHz, $CDCl_3$) 8.51–7.40 (7H, m, ArH), 6.14–6.04 (1H, m, C*H*), 4.32–4.16 (2H, m), 3.59 (3H, d, J_{H-P} 13.6 Hz, OCH_3), 3.22–3.04 (1H, m), 2.75–2.60 (1H, m), 2.10–1.56 (m, 2H), 1.73 (3H, d, J_{H-H} 6.9 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 129.2–125.2 (ArC), 68.6 (d, J_{C-P} 8.6 Hz, OCH_2), 53.8 (d, J_{C-P} 4 Hz, *C*H), 52.5 (d, J_{C-P} 6.6 Hz, OCH_3), 40.6 (s, CCH_2C), 28.1 (d, J_{C-P} 3.5 Hz, NCH_2), 19.5 (s, CH_3); δ_P (81 Hz, $CDCl_3$) 73.1.

The two diastereoisomers of **14** were separated by preparative high pressure liquid chromatography: (+)-(S_C,R_P)-**14** (major), mp 161–162 °C; $[\alpha]_D^{22}$ +11.3 (*c* 1.1, $CHCl_3$); δ_P (81 MHz, $CDCl_3$) 73.11; (−) (S_C, S_P)-**14** (minor), $[\alpha]_D^{22}$ −189 (*c* 1.29, $CHCl_3$); δ_P (81 MHz, $CDCl_3$) 73.82.

*4.3.3. (+)-(R)-2-Methoxy-1,3,2-oxazaphosphorinan-2-thione (**10**) from (+)-**14**.* To a stirred cooled (−20 °C) solution of (+)-**14** (0.321 g, 1 mmol), $[\alpha]_D^{22}$ +11.3 ($CHCl_3$, ee 100%) in dry toluene (10 mL) was added concentrated sulfuric acid (0.3 g). After 10 min a cooling bath was removed and stirring was continued for 25 min. Then, the reaction solution was poured into cooled (0 °C) water (40 mL) containing potassium carbonate (0.4 g). The organic layer was separated and the product was extracted from water layer with chloroform (4×40 mL). The combined organic solutions were dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure. The remaining pale yellow oil was purified by column chromatography (silica gel, chloroform–*n*-heptane, 9:1) to afford **10** (0.146 g, 86%); $[\alpha]_D^{22}$ +41.4 (*c* 1, $CHCl_3$, 100% ee); δ_P (81 MHz, $CDCl_3$) 69.26.

*4.3.4. (−)-(R)-Tetramethylammonium 2-oxo-2-thio-1,3,2-oxazaphosphorinane **5** from (+)-**10**.* According to the procedure described in Section 4.2.7 the ester (+)-**10** (0.12 g, 0.72 mmol) prepared above and trimethylamine gave the salt **5** (0.097 g, 60%); $[\alpha]_D^{22}$ −16.4 (*c* 1.2, MeOH, 100% ee); δ_P (81 MHz, $CDCl_3$) 56.7.

4.4. Crystal structure determination

Intensity data for the crystal of (+)-**14** were collected on a Bruker AXS Smart APEX2 CCD 3-circle diffractometer equipped with an IμS microsource Cu Kα radiation (λ=1.54178 Å, 45 kV, 0.65 μA) at room temperature. In experiment 6888 frames were measured at ω and φ-scans with 0.5° intervals with a counting time of 8 s per frame exposure. Data collection and data reduction were done with the SMART and SAINT-PLUS programs.[24] An absorption correction was applied using SADABS program.[25] The structures were solved by direct methods using the SHELXS-97 program.[26] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 using the SHELXL-97 program[26] and the complete set of reflections. All hydrogen atoms were located from Fourier difference maps and refined within the riding model with fixed displacement parameters (U_{iso}(H)=1.5 U_{eq}(C) for the methyl groups and U_{iso}(H)=1.2 U_{eq}(C) for the other groups). The absolute structure was objectively determined by the refinement of Flack parameter to 0.04(3).[27] Figures were drawn using the Mercury program.[28]

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary data no. CCDC 830470. Copy of the data can be obtained free of charge by applying to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.10.085. This data includes MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For an excellent review on cyclophosphamide and its congeners see: Stec, W. J. *Organophosphorus Chem.* **1982**, *13*, 145–174.
2. Shipov, A. E.; Genkina, G. K.; Artyushin, O. I.; Mndzhoyan, Z. O.; Gushchin, B. E.; Chumakova, E. I.; Roslavtseva, S. A.; Eremina, O. Yu.; Bakanova, E. I.; Kagan, Yu. S.; Ershova, E. A.; Mastryukova, T. A.; Kabachnik, M. I. *Russ. Chem. Bull.* **1995**, *44*, 2147–2155.
3. Shipov, A. E.; Genkina, G. K.; Makhaeva, G. F.; Malygin, V. V.; Volkova, R. I.; Roslavsteva, S. A.; Eremina, O. Yu.; Bakanova, E. I.; Mastryukova, T. A.; Kabachnik, M. I. *Russ. J. Biol. Chem.* **1999**, *25*, 14–19.
4. Shipov, A. E.; Artyushin, O. I.; Genkina, G. K.; Khrunin, A. V.; Eremina, O. Yu; Bakanova, E. I.; Roslavtseva, S. A.; Mastryukova, T. A. *Russ. Chem. Bull.* **2000**, *49*, 1593–1597.
5. Shipov, A. E.; Genkina, G. K.; Petrovskii, P. V.; Mastryukova, T. A. *Russ. Chem. Bull.* **2005**, *54*, 2629–2634.
6. Shipov, A. E.; Genkina, G. K.; Petrovskii, P. V. *Russ. Chem. Bull.* **2009**, *58*, 2512–2516.
7. Shipov, A. E.; Genkina, G. K.; Goryunov, E. I.; Goryunova, I. B.; Petrovskii, P. V. *Russ. Chem. Bull.* **2010**, *59*, 122–126.
8. Shipov, A. E.; Genkina, G. K.; Petrovskii, P. V.; Goryunov, E. I.; Makarov, M. V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 945–951.
9. For bioactivity of other *N*-phosphorylated piperidinones see: (a) Makarov, M. V.; Rybalkina, E. Yu.; Röschenthaler, G. V.; Short, K. W.; Timofeeva, T. V.; Odinets, I. L. *Eur. J. Med. Chem.* **2009**, *44*, 2135–2144; (b) Makarov, M. V.; Leonova, E. S.; Rybalkina, E. Yu.; Tongwa, P.; Khrustalev, V. N.; Timofeeva, T. V.; Odinets, I. R. *Eur. J. Med. Chem.* **2010**, *45*, 992–1000.
10. *Drug Stereochemistry*; Wainer, I. W., Drayer, D. E., Eds.; Marcel Dekker,: New York, NY, 1993.
11. Kurihara, N.; Miyamoto, J.; Paulson, G. D.; Zeeh, B.; Skidmore, M. W.; Hollingworth, R. M.; Kuiper, H. A. *Pure Appl. Chem.* **1997**, *69*, 1335–1348.
12. Mikołajczyk, M.; Łuczak, J.; Kiełbasiński, P.; Colonna, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1948–1951.
13. See for example: Mikołajczyk, M.; Leitloff, M. *Usp. Khim.* **1975**, *44*, 1419–1453; *Russ. Chem. Rev. (Engl. Transl.)* **1975**, *44*, 670–702.
14. Mikołajczyk, M.; Omelańczuk, J.; Abdukakharov, W. S. *Tetrahedron* **1982**, *38*, 2183–2188.
15. Gerrard, A. F.; Hamer, N. K. *J. Chem. Soc. B* **1967**, 1122–1125.
16. Hirashima, A.; Eto, M. *Agric. Biol. Chem.* **1983**, *47*, 2831–2839.
17. Hilgetag, V. G.; Lehmann, G. *J. Prakt. Chem* **1959**, *9*, 3–6.
18. Michalski, J.; Mikołajczyk, M. *Tetrahedron* **1966**, *22*, 3055–3059; Mikołajczyk, M. *Tetrahedron* **1967**, *23*, 1543–1549.
19. Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–953.
20. Kinas, R.; Pankiewicz, K.; Stec, W. *J. Bull. Acad. Pol. Sci.* **1975**, *23*, 981–984.
21. Zon, G. *Tetrahedron Lett.* **1975**, *36*, 3139–3142.
22. Sato, T.; Ueda, H.; Nagakawa, K.; Bodor, N. *J. Org. Chem.* **1983**, *48*, 98–101.
23. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
24. SMART and SAINT-PLUS. *Area Detector Control and Integration Software. Versions 5. 629 and 6. 45*; Bruker Analytical X-ray Instruments: Madison, Wisconsin, USA, 2003.
25. Sheldrick, G. M. *SADABS, v. 2. 03, Bruker/Siemens Area Detector Absorption Correction Program*; Bruker AXS: Madison, Wisconsin, 2003.
26. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A39*, 112–122.
27. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.
28. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453–457.