chromatography (75-mm × 40-mm column of SiO_2, eluted with 5/95% CH_3OH/CH_2Cl_2) afforded a yellow glass foam. Purification by flash chromatography (178-mm × 50-mm column of SiO_2, eluted with 2.5/97.5% CH_3OH/CH_2Cl_2) afforded 2.76 g (51%) of the dimethyl ester of the host dibenzodiazocine (purity ≈ 90%) as a yellow glass foam which was then crystallized from 95% ethanol (≈40 mL) to afford a first crop of 1.5 g as florets of fine yellow needles; a second crop (≈20 mL) of 430.0 mg was also obtained: mp 158.0–162.0 °C; R_f = 0.07 (SiO_2, 2.5/97.5%, CH_3OH/CH_2Cl_2); IR ($CHCl_3$) 3010, 2853, 1724, 1613, 1578, 1497, 1406, 1296, 1195, 1142, 1097, 1013, 840 cm^{-1}; 300 MHz ^1H NMR (DMF-d_7, +90 °C) δ 7.50 (*d*, 2 H, *J* = 8 Hz), 7.41 (d, 2 H, *J* = 8 Hz), 7.30 (t, 2 H, *J* = 8 Hz), 7.16 (d, 2 H, *J* = 8 Hz), 6.95 (d, 2 H, *J* = 8 Hz), 6.77 (s, 2 H), 4.73 (d, 2 H, *J* = 17 Hz), 4.36 (s, 2 H), 4.25 (d, 2 H, *J* = 17 Hz), 3.32 (br s, 6 H), 2.05 (s, 6 H); 300 MHz ^1H NMR ($CDCl_3$, −20 °C) δ 7.62 (m, 2 H), 7.36 (m, 4 H), 7.19 (m, 2 H), 7.04 (m, 2 H), 6.75 (m, 2 H), 4.79 (m, 2 H), 4.47 (m, 2 H), 4.26 (m, 2 H), 3.66 (s), 3.65 (s), 3.31 (s), 2.98 (s), 2.19 (s), 2.15 (s), 1.92 (s), 1.91 (s); 75 MHz ^{13}C NMR ($CDCl_3$, −20 °C) δ 169.5, 168.8, 168.7, 146.4, 141.1, 140.9, 140.8, 140.5, 137.2, 137.1, 136.8, 135.8, 135.5, 132.9, 132.1, 131.6, 131.4, 131.1, 127.8, 127.6, 127.2, 126.8, 126.5, 126.4, 124.4, 124.3, 66.7, 58.8, 58.6, 58.4, 51.9, 51.7, 51.0, 20.8, 20.7, 20.4; MS, *m/e* calcd for $C_{33}H_{30}N_2O_4$ (M^+) 518.2206, measured 518.2208. Anal. Calcd for $C_{33}H_{30}N_2O_4$: C, 76.43; H, 5.83; N, 5.40. Found: C, 76.17; H, 5.87; N, 5.42.

To a stirred heterogeneous mixture of 842.0 mg (35.1 mmol) of anhydrous lithium hydroxide in 6.0 mL of 4:1 (v:v) CH_3OH/water at room temperature was added a hot (50 °C) solution of 523.0 mg (1.0 mmol) of the above diester in 8.0 mL of 4:1 (v:v) CH_3OH/water and 2.0 mL of CH_2Cl_2. The flask was sealed with a wired septum, and the stirred mixture was heated at 50 °C. After 24 h, the excess solid LiOH was removed by filtration and the filtrate was concentrated in vacuo. The concentrate was diluted with 5 mL of water to afford a basic yellow homogeneous solution (pH ≥ 13.0). The basic solution was then acidified by the careful addition of 14.5 mL of 2 N HCl (final pH ≈ 2.0). The white precipitate was extracted with 3 × 20-mL portions of $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 560.0 mg of host as fine white needles. Recrystallization from ≈20 mL of $CHCl_3$ afforded 350.0 mg (first crop) followed by a second (≈10 mL) of 110.0 mg (total 92%) as fine colorless needles which become white and opaque on drying: mp 294–296 °C dec; IR ($CHCl_3$) 3250 (b), 2856, 1700, 1479, 1465, 1294, 1202, 750, 730, 662 cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$, 23 °C) δ 7.44 (d, 2 H, *J* = 8 Hz), 7.38 (d, 2 H, *J* = 8 Hz), 7.27 (t, 2 H, *J* = 8 Hz), 7.11 (d, 2 H, *J* = 8 Hz), 6.98 (dd, 2 H, *J* = 8, 2 Hz), 6.63 (d, 2 H, *J* = 2 Hz), 4.68 (d, 2 H, *J* = 16 Hz), 4.59 (s, 2 H), 4.17 (d, 2 H, *J* = 16 Hz), 2.18 (s, 6 H); 125 MHz ^{13}C NMR ($CDCl_3$, 23 °C) δ 174.3, 146.3, 141.1, 137.0, 135.3, 132.7, 132.4, 128.8, 127.7, 127.4, 127.1, 125.5, 123.8, 67.9, 60.2, 20.5; MS, *m/e* calcd for $C_{31}H_{26}N_2O_4$ (M^+) 490.1893, measured 490.1894. Anal. Calcd for $C_{31}H_{26}N_2O_4 \cdot 1.0CHCl_3$: C, 63.08; H, 4.45; N, 4.58; Cl, 17.41. Found: C, 62.96; H, 4.59; N, 4.78; Cl, 17.04.

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Supplementary Material Available: All NMR data required for the determination of the four dimerization constants and seven association constants discussed in this paper; NMR data for the solute chase experiment (Figure 5) (8 pages). Ordering information is given on any current masthead page.

Stereochemistry of Base-Catalyzed Ring Opening of 1,3,2-Oxathiaphospholanes. Absolute Configuration of 2-{*N*-[(R_c)-1-(α-Naphthyl)ethyl]amino}-2-thiono-1,3,2-oxathiaphospholanes and *O,S*-Dimethyl *N*-[(R_c)-1-(α-Naphthyl)ethyl]phosphoramidothioates†

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Contribution from the Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Department of Bioorganic Chemistry, 90-363 Lodz, Sienkiewicza 112, Poland, and Technical University of Lodz, Institute of Technical Biochemistry, 90-924 Lodz, Stefanowskiego 4/10, Poland. *Received May 8, 1992*

Abstract: Pure diastereoisomers of 2-{[(R_c)-1-(α-naphthyl)ethyl]amino}-2-thiono-1,3,2-oxathiaphospholane (**1**) and *O,S*-dimethyl *N*-[(R_c)-1-(α-naphthyl)ethyl]phosphoramidothioate (**2**) were obtained, and both "slow"-migrating isomers of **1** and **2** were studied by X-ray crystallography which demonstrated their (R_p,R_c) absolute configuration. Therefore, the absolute configuration of both "fast"-migrating isomers of **1** and **2** must be (S_p,R_c). In (R_p,R_c)-**1** oxathiaphospholane, the ring adopts the open-envelope conformation with the C2 atom in the flap position; the S1–P–O1 angle is 97°. DBU-assisted methanolysis of (R_p,R_c)-**1** ("slow") followed by S-methylation, gave (S_p,R_c)-**2** ("fast"). This result is interpreted in terms of an "adjacent" type mechanism of the regio- and stereoselective 1,3,2-oxathiaphospholane ring-opening process. Suggestions are presented regarding the absolute configuration at the phosphorus atom in diastereoisomers of 5′-O-protected nucleoside 3′-*O*-(2-thiono-1,3,2-oxathiaphospholanes), which are synthons for stereocontrolled synthesis of oligo(nucleoside phosphorothioate)s.

In spite of numerous reports concerning the stereochemistry of P–S bond cleavage in acyclic alkyl thioloesters of phosphorus acids, the stereochemistry of the 1,3,2-oxathiaphospholane ring opening is rather obscure.[1] One can consider that the nucleophile may approach the phosphorus atom according to an "in-line" type mechanism via collinear attack from the side opposite to the endocyclic P–S bond and that the resulting intermediate collapses with the ring opening and the cleavage of the P–S bond (a, net inversion). Alternatively the ring opening may result from attack of the nucleophile from the side opposite to the most apicophilic endocyclic oxygen atom, resulting in a trigonal bipyramidal in-

† This paper is dedicated to Prof. F. H. Westheimer on the occasion of his 80th birthday.

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(1) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059.

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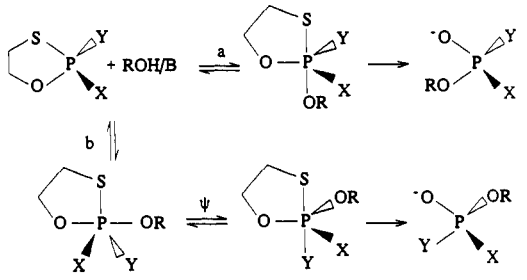
Scheme I. Two Possible Modes of Attack of a Nucleophile at Phosphorus Incorporated into the 1,3,2-Oxathiaphospholane Ring System



termediate which before collapse must undergo pseudorotation, placing the cleavable P–S bond in the apical position (b, "adjacent" type mechanism, net retention).[2]

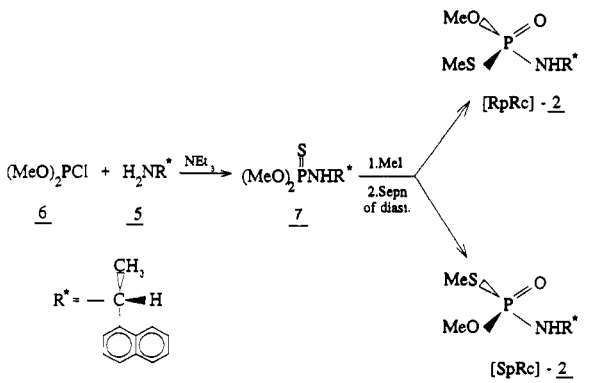
Recently we have found that the base-catalyzed reaction of diastereoisomerically pure 5′-*O*-DMT-nucleoside 3′-*O*-[2-thiono-1,3,2-oxathiaphospholane] with a 5′-OH nucleoside is regio- and stereospecific and results in formation of diastereoisomerically pure dinucleoside 3′,5′-phosphorothioate.[3] Because the absolute P-configuration of the nucleoside 3′-*O*-[2-thiono-1,3,2-oxathiaphospholane] could not be correlated with any known P-chiral phosphates and since attempts at growing crystals suitable for X-ray analysis had failed, we have designed a set of stereochemically informative model compounds, namely 2-[((R_c)-1-(α-naphthyl)ethyl)amino]-2-thiono-1,3,2-oxathiaphospholane (**1**) and *O,S*-dimethyl *N*-[(R_c)-1-(α-naphthyl)ethyl]phosphoramidothioate (**2**). Diastereoisomers of **1** and **2** were separated as pure specimens: "fast"-eluted-**1**, ^{31}P NMR δ = 95.1 ppm; "slow"-eluted-**1**, δ = 94.3 ppm; "fast"-eluted-**2**, δ = 34.6 ppm; and "slow"-eluted-**2**, δ = 35.1 ppm. After several attempts at crystallization, two compounds, namely "slow"-eluted-**1** and "slow"-eluted-**2**, were obtained in the crystalline forms suitable for X-ray examination.

Independently, the "slow"-migrating (TLC assay) isomer of **1** was subjected to 1,8-diazabicyclo[5.4.0]undec-7-ene- (DBU) catalyzed methanolysis, and the resulting *O*-methyl *N*-[(R_c)-1-(α-naphthyl)ethyl]phosphoramidothioate (**3**, ^{31}P NMR δ = 59.8 ppm), without isolation, was alkylated with methyl iodide to give the "fast"-migrating (TLC assay) diastereoisomer of **2**. Since X-ray analyses have shown that both "slow"-**1** and "slow"-**2** possess the (R_p,R_c)-configuration, "fast"-eluted-**2** must be of the (S_p,R_c)-configuration. Thus, after analysis of the available data, the conclusion has been drawn that 1,3,2-oxathiaphospholane ring opening in compound **1** occurs according to the "adjacent" type (b) mechanism.

Results

Preparation of Diastereoisomers of 1 and 2. Reaction of 2-chloro-1,3,2-oxathiaphospholane (**4**) with (*R*)-(+)-1-(α-naphthyl)ethylamine (**5**) was performed in benzene solution in the presence of an equimolar amount of triethylamine. Condensation was followed by addition of elemental sulfur. A diastereoisomeric mixture of **1** (ratio of diastereoisomers ≈ 1:1) was isolated by means of column chromatography on silica gel and subjected to crystallization first from ethyl ether and then from benzene–petroleum ether (5:1, v/v), giving diastereoisomerically pure "slow"-**1**, R_F 0.33, ^{31}P NMR δ = 94.3 ppm ($CDCl_3$), mp 148–149 °C, $[\alpha]^{20}_D$ = −40.0° (*c* 0.65, benzene), yield 22.4%.

Preparative TLC of the mother liquor allowed the separation in low yield (≈5%) of "fast"-**1**, R_F 0.35, ^{31}P NMR δ = 95.6 ppm ($CDCl_3$), mp 128–129 °C, $[\alpha]^{20}_D$ = −133.8° (*c* 0.4, benzene). Both diastereoisomers of **1** were analyzed by means of ^{1}H and ^{13}C NMR and mass spectrometry, and the results fully confirmed their molecular structure. The synthesis of both diastereoisomers of **2** is outlined below.



Condensation of *O,O*-dimethyl phosphorochloridite (**6**) with (*R*)-(+)-1-(α-naphthyl)ethylamine (**5**), performed in the presence of triethylamine and elemental sulfur, led to the formation of *O,O*-dimethyl *N*-((R_c)-1-(α-naphthyl)ethyl)phosphoramidothioate (**7**), which, after chromatography on silica gel and crystallization from ethyl ether–pentane, appeared to be pure; yield 49%, mp 58–59 °C, ^{31}P NMR δ = 74.7 ppm ($CDCl_3$) $[\alpha]^{20}_D$ = −3.5 (*c* 1.0, $CHCl_3$).

A solution of this compound in acetonitrile was treated with a 2-fold molar excess of methyl iodide and left at 60 °C for 16 h. TLC assay showed the disappearance of **7**, and after standard workup, the mixture of diastereoisomers of **2** was subjected to column chromatography.

Further crystallization from benzene yielded "fast"-**2**, TLC assay, R_F = 0.38 in methylene chloride–ethyl acetate (1:1), mp 146–147 °C, $[\alpha]^{20}_D$ = −29.4° (*c* = 1.1, $CHCl_3$), ^{31}P NMR δ = 34.6 ppm (yield 26%), and "slow"-**2**, R_F = 0.31, mp 138–139 °C, $[\alpha]^{20}_D$ = +37.4° (*c* 1.9, $CHCl_3$), ^{31}P NMR δ = 35.14 ppm (yield 13%). Mass spectrometry and ^{1}H NMR analysis fully confirmed the molecular structure of both diastereoisomers of **2**.

DBU-Catalyzed Methanolysis of "Slow"-1. Reaction of "slow"-**1** (δ 94.3 ppm) with DBU–methanol (in the ratio 15:35, v/v) in the solvent benzene-d_6–acetonitrile (1:1, v/v) was followed by means of ^{31}P NMR. After 10 min, the spectrum contained only two signals at 59.8 and 94.6 ppm (ratio 91:9). To this mixture was added MeI, and the ^{31}P NMR spectrum, recorded after 10 min, indicated the disappearance of the signal at 59.8 ppm and the formation of "fast"-eluted-**2**, δ 34.6 ppm. The signal at 94.6 ppm, characteristic for the unchanged substrate "slow"-**1**, was still present, and the ratio of intensities of signals at 34.6 and 94.65 ppm, respectively, was 93:7.

Product "fast"-**2** was isolated by short-column chromatography and, after crystallization from benzene–hexane (3:1), appeared to be identical with an authentic sample of "fast"-**2** prepared by an independent method (vide supra). Independently, the mixture of "fast"- and "slow"-**1**, δ 95.06 and 94.26 ppm (ratio 79:21), in benzene–acetonitrile, was treated with DBU–MeOH and the ^{31}P NMR spectrum, recorded 10 min after mixing of the reagents, indicated the presence of three signals at 95.2, 59.8, and 59.2 ppm, in the ratio 1:24:75, respectively. This mixture, after treatment with MeI, showed the presence of two signals at 35.14 and 34.65 ppm in the ^{31}P NMR spectrum, in the ratio 76:24, which are characteristic for "slow"- and "fast"-**2**, respectively. TLC analysis and intensities of the spots confirmed the above identification.

Single-Crystal X-ray Analysis of Structures of "Slow"-1 and "Slow"-2. Compounds "slow"-**1** and "slow"-**2** were recrystallized from benzene and benzene–hexane (3:1), respectively, and their crystal data are presented in Table I. The molecular structure of "slow"-**1** is presented in Figure 1, while Figure 2 presents two molecules of "slow"-**1** in the unit cell. According to Cahn–Ingold–Prelog rules,[4] the absolute configuration at P is *R* and that at C3 is *R*. The molecule assumes in the solid state an almost ideal envelope conformation of the 1,3,2-oxathiaphospholane ring with the C2 atom in the flap position. Torsional angles for the oxathiaphospholane ring ("slow"-**1**) are shown in Figure 3. The

(2) Richards, F. M.; Wyckoff, H. W. In *The Enzymes*, 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1971; Vol. 4, p 647–806.
(3) Stec, W. J.; Grajkowski, A.; Koziolkiewicz, M.; Uznanski, B. *Nucleic Acids Res.* **1991**, *19*, 5883.
(4) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem.* **1966**, *78*, 413.

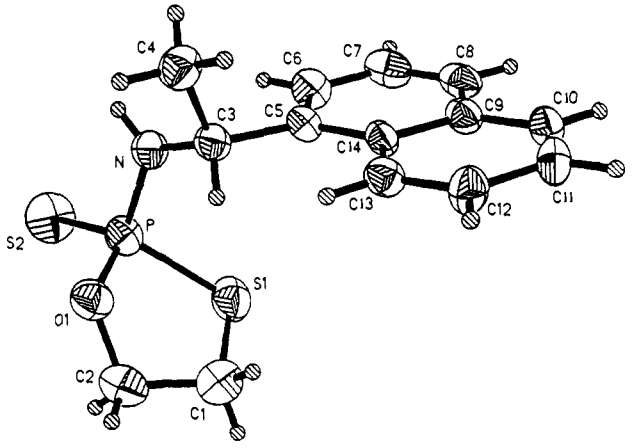


Figure 1. Molecular structure of "slow"-**1**.

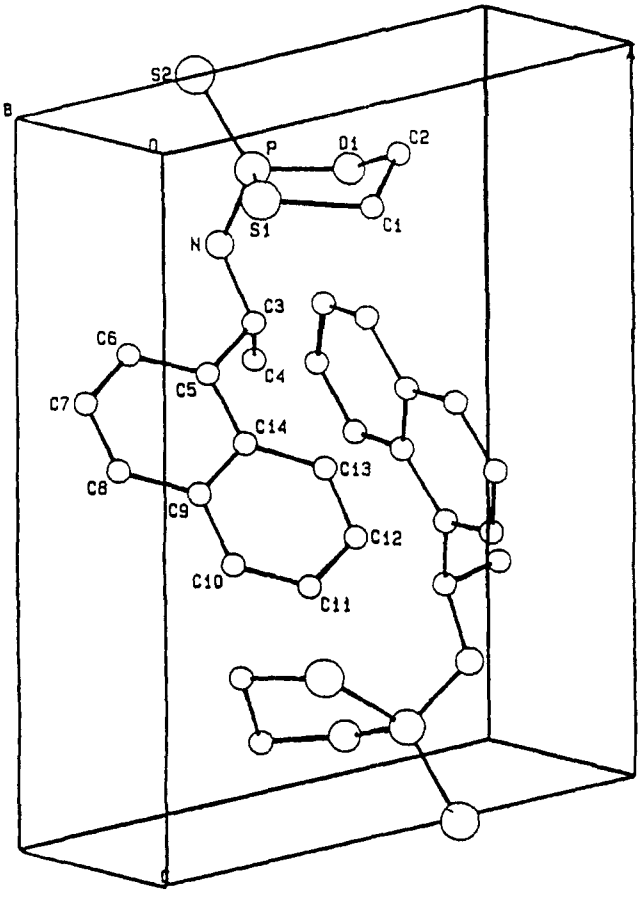


Figure 2. Molecular arrangement of "slow"-**1** in the unit cell.

asymmetry parameters for this ring are $C_S^{(C2)}$ = 1.6 (5) and $C_2^{(P)}$ = 23.3 (5).[5,6] Selected bond distances and bond angles for "slow"-**1** and "slow"-**2** are presented in Tables 2 and 3, submitted as supplementary material. The exocyclic P=S bond is a little shorter [1.924 (2) Å] than that in compounds containing the 1,3,2-dioxaphospholane ring [1.940 (3) Å].[7] The bond lengths between atoms in the five-membered ring ("slow"-**1**) correspond well with the accepted values;[8] they are longer than the corresponding bonds in open-chain compound "slow"-**2** by 3σ–22σ (1.0%–3.3%). However, the presence of three heteroatoms in the oxathiaphospholane ring system is responsible for the deviation

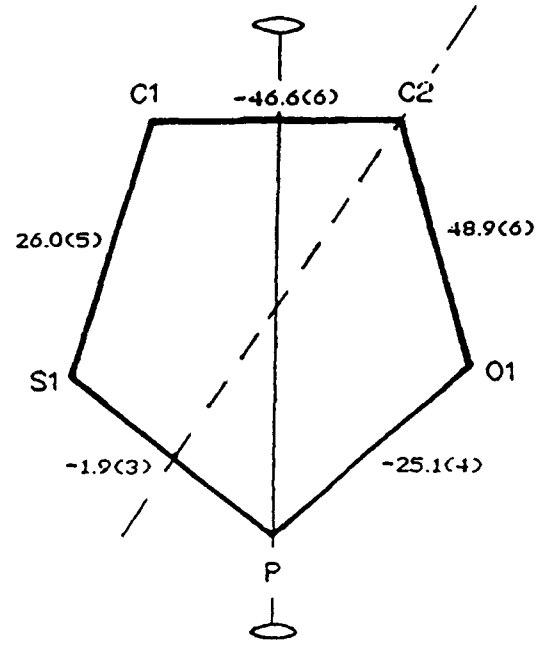


Figure 3. Torsional angles of 1,3,2-oxathiaphospholane ring in "slow"-**1**.

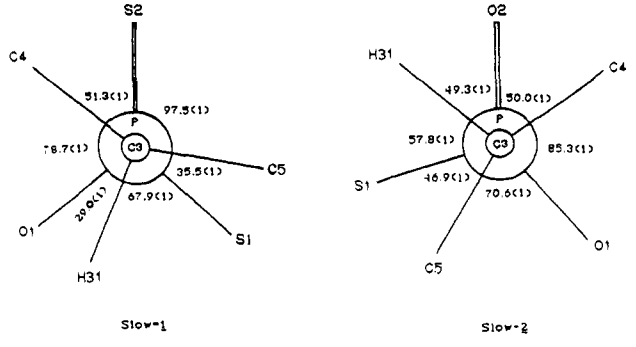


Figure 4. Projection of substituents at C3 and P atoms on the plane perpendicular to the line connecting C3 and P atoms in "slow"-**1** and "slow"-**2**.

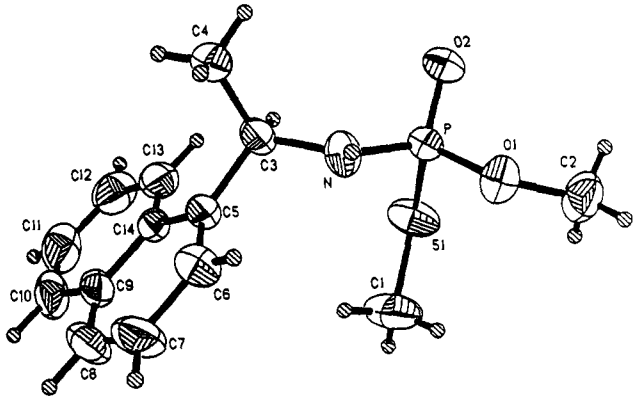


Figure 5. Molecular structure of "slow"-**2**.

of particular bond angles from the average value of 103.8 (4)°. For the stereochemical analysis in "slow"-**1** and "slow"-**2**, it is interesting to show a projection of substituents at C3 and P atoms on a plane perpendicular to the line connecting these atoms (Figure 4). The near antiperiplanar [159.1 (1)°] arrangement of H31 and exocyclic P=S2 bonds in "slow"-**1** when compared to the synclinal arrangement of these substituents in "slow"-**2** is a striking difference between the relative spatial arrangements of substituents in the crystal unit cells of **1** and **2**, respectively. Figure 5 shows a molecule of "slow"-**2** with the atom numbering while Figure 6 presents the molecule arrangement in the unit cell. Atom coor-

(5) Duax, W. L.; Norton, D. A. *Atlas of Steroid Structure*; Plenum: New York, 1975.
(6) Altona, C.; Geise, H. J.; Romers, C. *Tetrahedron* **1968**, *24*, 13.
(7) Wieczorek, M. W. *Phosphorus Sulfur Relat. Elem.* **1980**, *9*, 137.
(8) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974.

Table I. Crystal Data for Molecules "Slow"-**1** and "Slow"-**2** and Experimental Details

	"slow"-**1**	"slow"-**2**
mol form	$C_{14}H_{16}NOS_2P$	$C_{14}H_{18}NO_2SP$
space group	$P2_1$	$P2_12_12_1$
a (Å)	8.497 (2)	7.447 (1)
b (Å)	7.153 (1)	8.551 (2)
c (Å)	12.599 (2)	23.297 (2)
β (deg)	102.13 (2)	
V (Å^3)	749.0 (2)	1483.4 (5)
Z	2	4
μ (cm^{-1})	41.3	4.4
D_c (g/cm^3)	1.373 (2)	1.385 (2)
cryst dimen (mm)	0.15 × 0.2 × 0.6	0.25 × 0.2 × 0.5
max 2θ (deg)	150	56
radiation, λ (Å)	Cu K_α, 1.54178	Mo K_α, 0.70930
scan mode	$\omega/2\theta$	$\omega/2\theta$
scan width	1.06 ± 0.14 tanθ	0.77 ± 0.35 tanθ
hkl ranges	h = 0–10	h = 0–9
	k = 0–8	k = 0–11
	l = −15 to 15	l = 0–30
No. of refl measured		
total	1777	2087
with $I \geq 3\sigma(I)$	1731	1857
EAC correction		no correction
corr factors		
min	0.7153	
max	0.9971	
av	0.9118	
transmission (%)		
min	51.17	
max	99.42	
av	83.14	
R	0.046	0.047

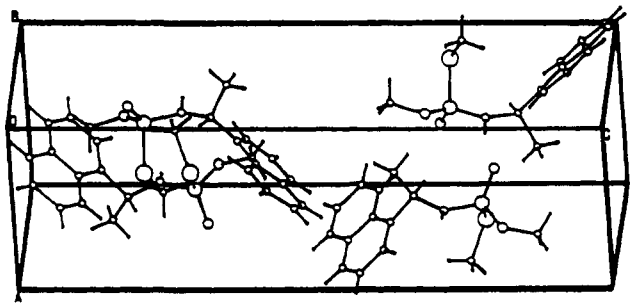
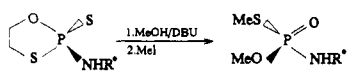


Figure 6. Molecular arrangement of "slow"-**2** in the unit cell.

dinates, bond lengths, bond and torsional angles, and temperature factors of all atoms and values of F_{obs}/F_{calc} (for "slow"-**1** and "slow"-**2**) are deposited at the Cambridge Crystallographic Data Centre.[9]

Discussion

The choice of model compounds **1** and **2** was based on their relatively easy accessibility in diastereoisomerically pure forms, the possibility of their identification by means of ^{31}P NMR spectroscopy and TLC assay, and the accessibility of crystals suitable for X-ray analysis. The unambiguous assignment of absolute configuration in compounds "slow"-**1** and "slow"-**2** as (R_p,R_c) was crucial, since that of their counterparts, "fast"-**1** and "fast"-**2**, had to be (S_p,R_c). Therefore, DBU-catalyzed methanolysis of (R_p,R_c)-**1**, followed by S-methylation of intermediate **3**, gives (S_p,R_c)-**2**.



[RpRc] - 1 [SpRc] - 2

Because the conversion **1** → **2** is nearly quantitative, indicating full regio- and stereospecificity of the 1,3,2-oxathiaphospholane

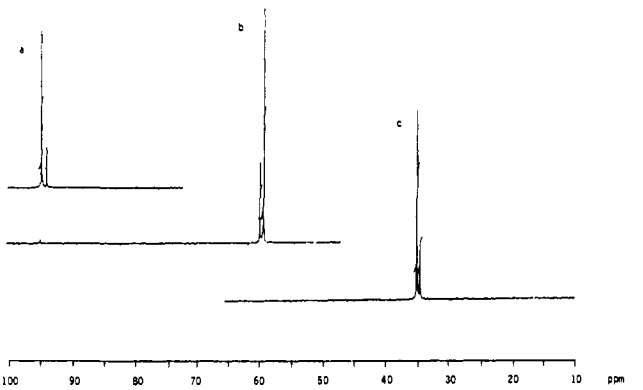
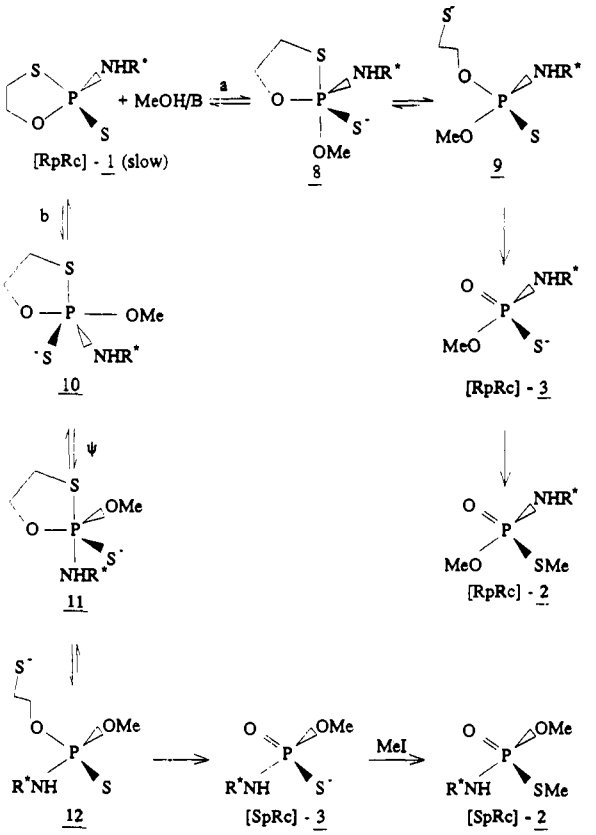


Figure 7. ^{31}P NMR spectra of the products of the reaction between "fast"-**1** (dp 79%) (a) and MeOH–DBU (b), followed by addition of MeI (c).

Scheme II. Stereochemical Analysis of Conversion of "Slow"-**1** into "Fast"-**2** Indicating "Adjacent" Type Mechanism in 1,3,2-Oxathiaphospholane Ring-Opening Process



ring-opening process (see also Figure 7), conclusions can be drawn regarding the mechanism of the reaction under investigation. The direct "in-line" attack of MeOH on (R_p,R_c)-**1** collinear with the endocyclic P–S bond should give the TBP intermediate **8**, which, after cleavage of the apical P–S bond and elimination of ethylene episulfide from **9**, should result in formation of (R_p,R_c)-**3**, the precursor of (R_p,R_c)-**2** (Scheme II, path a). Therefore the most reasonable explanation of our experimental results concerning the mode of 1,3,2-oxathiaphospholane ring opening involves an "adjacent" type mechanism. It is reasonable to consider that MeOH approaches (R_p,R_c)-**1** from the side opposite to the endocyclic P–O bond, resulting in the formation of intermediate TBP-**10**, which has the two most electronegative elements in apical positions. Because the principle of microreversibility requires that the leaving group is located in the apical position,[10] a single

(9) CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

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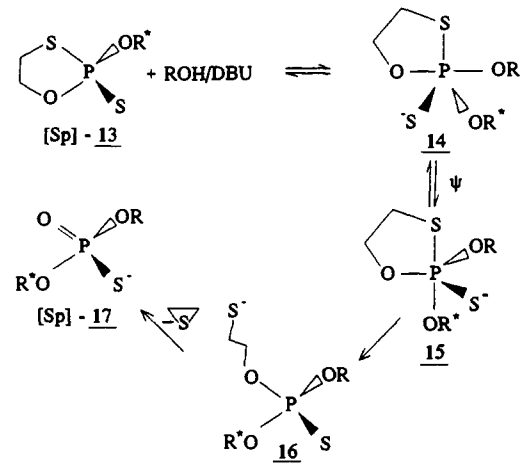
Scheme III. Postulated Course of DBU-Catalyzed Reaction Between "Fast"-Eluted 5′-*O*-DMT-Nucleoside 3′-*O*-[2-Thiono-1,3,2-oxathiaphospholane (**13**) and 3′-*O*-Protected Nucleoside (ROH) and Assignment of Absolute Configuration at Phosphorus in **13**



pseudorotation process (with the S^- ligand as "pivot") leads to intermediate TBP-**11**; its collapse via cleavage of the apical P–S bond and elimination of ethylene episulfide from **12** gives (S_p,R_c)-**3**, which after S-methylation gives (S_p,R_c)-**2** (Scheme II, path b).

One can argue that the function of the catalyst, in this case DBU, has been neglected in this discussion, and such criticism has a rational background, as DBU has been shown to be an active participant in the process of nucleophilic substitution at the phosphorus atom involved in nucleoside 3′-*O*-[*O*-(4-nitrophenyl) *S*-(2-nitrobenzyl) phosphorothioate].[11] However, reaction **1** → **3** is relatively fast compared to the aforementioned process of DBU-catalyzed epimerization of nucleoside 3′-*O*-[*O*-(4-nitrophenyl) *S*-(2-nitrobenzyl) phosphorothioate], and nucleophilic substitution occurs here at the phosphorothioyl but not the phosphoryl center. Secondly, the process under investigation is also fully stereoselective if the reaction of **1** → **3** is catalyzed by a much weaker amine, e.g. triethylamine. Largely on the basis of this last argument, we neglect the function of DBU as the component directly participating via covalent-bond formation in the process of nucleophilic substitution at phosphorus. The driving force for the overall process seems to be *ring-strain relief arising from the opening of the oxathiaphospholane ring, followed by fast elimination of episulfide.*

Analysis of the X-ray data indicates that the side of molecule **1** opposite to the endocyclic P–O bond is easily approachable and the compression of the O1–P–S1 bond angle from 96.9°, as assinged for "slow"-**1**, to ca. 90°, as required for **10** and **11**, is tolerable for such molecules.[12] It is particularly interesting to compare the length of the endocyclic P–S bond in "slow"-**1** (2.094 Å) with that of the P–S bond in "slow"-**2** (2.049 Å) and the S1–P–O1 bond angles in both molecules (96.9° vs 109.0°) in order to explain the observed regioselectivity of the 1,3,2-oxathiaphospholane ring-opening process (exclusive P–S bond cleavage). Retention of configuration, the net stereochemical outcome of the conversion of **1** → **2**, is in full agreement with results of our earlier studies on the mechanism of reaction of ribonucleoside cyclic 3′,5′-phosphorothioates with styrene [^{18}O]-oxide.[13] Therefore, we consider the elucidation of the mechanism of 2-thiono-1,3,2-oxathiaphospholane ring opening of **1** as the rational basis for the tentative assignment of absolute configuration at phosphorus in 5′-*O*-DMT-nucleoside 3′-*O*-(2-thiono-1,3,2-oxathiaphospholanes) **13**.[3]

As mentioned above, "fast"-eluted-**13** in the DBU-catalyzed reaction with 5′-OH-nucleosides leads to (S_p)-dinucleoside 3′,5′-phosphorothioates **17**. According to considerations presented above, the 5′-OH-nucleoside approaches molecule **13** collinearly to the endocyclic P–O bond. Thus, intermediate TBP-**14** must undergo pseudorotation resulting in **15**, which, after cleavage of the endocyclic P–S bond and elimination of ethylene episulphide from **16**, gives (S_p)-**17**. Therefore, the absolute configuration of "fast"-eluted-**13** must be (S_p), and respectively that of "slow"-eluted-**13** must be (R_p). However, this tentative assignment has to be confirmed in independent studies—attempts to prepare crystals of **13** suitable for X-ray analysis are underway.

Experimental Section

(*R*)-(+)-1-(α-naphthyl)ethylamine was purchased from Norse Laboratories Inc. and was distilled before use over CaH_2; bp 80 °C/1 mmHg; $[\alpha]^{20}_D$ = +60° (*c* 5, EtOH) [lit.[14] $[\alpha]^{19}_D$ = 61.6° (*c* 2.0, EtOH)]. Solvents and commercial reagents were dried and distilled before use. Triethylamine, pyridine, and DBU were from commercial sources and were distilled freshly over CaH_2 before use. Elemental sulfur was dried under high vacuum for 3 h. 2-Chloro-1,3,2-oxathiaphospholane (**4**) was obtained according to the literature,[15] bp 78 °C/1 mmHg. *O*,*O*-dimethyl phosphorochloridite (**6**) was obtained by fractional distillation of the product of disproportionation between PCl_3 (1 mol) and trimethyl phosphite (2 mol) in benzene at 60 °C. ^{31}P NMR spectra were run on a Bruker MSL 300 spectrometer using C_6D_6 or $CDCl_3$ as solvent. Chemical shift values were assigned relative to H_3PO_4 as an external standard. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AC 200 or Bruker MSL 300 spectrometer. Mass and high-resolution mass spectra were recorded with a LKB 2091 GCMS spectrometer and a Finnigan MAT 95 instrument. Optical rotation measurements were performed on a Perkin-Elmer 241 MC photopolarimeter. Melting points were assigned in open capillaries and are uncorrected.

2-{*N*-[(R_c)-1-(α-naphthyl)ethyl]amino}-2-thiono-1,3,2-oxathiaphospholanes [(R_p,R_c)- and (S_p,R_c)-1]. Into a solution of 2-chloro-1,3,2-oxathiaphospholane (**4**) (0.621 mL, 0.0064 mol) in benzene (50 mL) was added dropwise a mixture of (*R*)-(+)-1-(α-naphthyl)ethylamine (1.12 g, 0.0064 mol) and triethylamine (0.65 g, 0.0064 mol) in benzene (10 mL) with stirring and external cooling below +5 °C. Stirring at low temperature (5–10 °C) was continued for 1 h. Then sulfur (0.26 g, 0.0081 mol) was added in one portion, and stirring with cooling was continued for 3 h. Solid particles (Et_3NHCl, unreacted sulfur) were filtered off, and the benzene filtrate was concentrated to dryness. The oily residue (ca. 3.0 g) was dissolved in benzene and chromatographed on a silica gel (70–230 mesh) column with benzene as eluent. The fractions containing compound **1** were collected and concentrated to give 1.7 g of the oily mixture of both diastereoisomers [^{31}P NMR δ = 94.6 and 95.6 ppm ($CDCl_3$) ratio ca. 1:1]. The mixture was treated with a small volume of ethyl ether, which caused the precipitation of the solid fraction (1.2 g) slightly enriched in the upfield isomer [^{31}P NMR δ = 94.6 ppm ($CDCl_3$)]. After several recrystallizations from benzene and petroleum ether (5:1 v/v), 0.27 g (22.4%) of the pure diastereoisomer "slow"-**1** {R_F = 0.33 in benzene–ethyl acetate–heptane (7:1:5), TLC [F_{254} plates (Merck)]} was obtained.

The fraction enriched in diastereoisomer "fast"-**1** (R_F = 0.35 in benzene–ethyl acetate–heptane) was several times chromatographed on TLC F_{254} plates (Merck) in the developing system benzene–ethyl acetate–heptane (7:1:5), and 0.1 g (5%) of pure diastereoisomer "fast"-**1** was obtained.

Data for "Fast"-1: mp 128–129 °C; $[\alpha]^{20}_D$ = −133.8° (*c* 0.4, benzene); ^{31}P NMR δ = 95.06 ppm ($CDCl_3$); ^{1}H NMR δ = 1.66 (d, *J* = 6.8 Hz, CH_3), 3.1–3.4 (m, 2 H, CH_2S), 3.8–4.2 (m, 3 H, CH_2O, CH), 5.33–5.46 (m, 1 H, NH), 7.5–8.2 (m, 7 H_{arom}); ^{13}C NMR δ = 24.7 (d, J_{P-C} = 7.8 Hz, CH_3), 36.9 (CH_2S), 49.6 (CH), 68.3 (CH_2O), 122.4, 123.1, 125.5, 125.6, 126.3, 127.9, 128.3, 128.98, 133.7, 139.0 (C_{arom}); MS (70 eV, *m*/*z*) 309 ($M^{\bullet+}$, 14.6%), 276 (69.3%), 170 (100.0%), 168 (21.2%), 155 (48.1%), 154 (28.4%), 153 (52.3%), 127 (21.4%), 115 (11.5%), 107 (59.6%), 77 (6.1%), 42 (6.9%); HRMS for $C_{14}H_{16}NOPS_2$, calcd 309.0411, found 309.0396, error 4.8 ppm. Anal. Calcd for $C_{14}H_{16}NOPS_2$: C, 54.35; H, 5.21; N, 4.53; P, 10.01; s, 20.73. Found: C, 54.36; H, 5.29; N, 3.59; P, 10.69; S, 20.74.

Data for "Slow"-1: mp 148–149 °C; $[\alpha]^{20}_D$ = −40.0° (*c* 0.65, benzene); ^{31}P NMR δ = 94.26 ppm ($CDCl_3$); ^{1}H NMR δ = 1.68 (d, *J* = 6.7 Hz; CH_3), 3.10–3.38 (m, 2 H, CH_2S), 3.86–3.96 (m, 1 H, CH), 4.35–4.50 (m, 2 H, CH_2O), 5.3–5.4 (m, 1 H), 7.2–8.2 (m, 7 H_{arom}); ^{13}C NMR δ = 24.5 (d, J_{P-C} = 5.8 Hz, CH_3), 36.8 (CH_2S), 49.2 (CH), 68.5

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(CH_2O), 122.67, 122.73, 125.45, 125.70, 126.39, 128.15, 129.05 (C_{arom}); MS (70 eV, m/z) 309 ($M^{\cdot+}$, 27.8%), 276 (98.5%), 170 (98.3%), 168 (49.7%), 155 (97.5%), 154 (69.5%), 153 (52.3%), 127 (46.3%), 115 (25.9%), 107 (100.0%), 77 (11.4%), 42 (11.7%); HRMS for $C_{14}H_{16}NOPS_2$, calcd 309.0411, found 309.0416, error 1.6 ppm. Anal. Calcd for $C_{14}H_{16}NOPS_2$: C, 54.35; H, 5.21; N, 4.53; P, 10.01; S, 20.73. Found: C, 54.43; H, 5.30; N, 3.95; P, 10.65; S, 20.60.

Synthesis of *O,S*-Dimethyl *N*-[(R_c)-1-(α-Naphthyl)ethyl]phosphoramidothioate [(R_p,R_c)- and (S_p,R_c)-2]. (a). Into a stirred suspension of sulfur (0.5 g, 0.016 mol) in dichloromethane (20 mL) were added (*R*)-(+)-1-(α-naphthyl)ethylamine (2.45 mL, 0.015 mol) and triethylamine (2.1 mL, 0.015 mol). Then *O,O*-dimethyl phosphorochloridite (1.93 g, 0.015 mol) was added dropwise at a temperature below 10 °C. A slightly exothermic effect accompanied by precipitation of Et_3NHCl was observed. After the reaction mixture was stirred for 0.5 h at ambient temperature, the white precipitate was filtered off and the filter cake was washed with benzene (5 mL). The filtrate was concentrated under reduced pressure, and the oily residue was chromatographed over silica gel (column: φ 2.5 cm × 15 cm, 230–400 mesh) with a gradient of solvents, benzene up to benzene–chloroform (1:1). The fractions containing the product **7** were collected and evaporated to give 3.75 g (84.8%) of this product as a thick oil that solidified upon storage. Crystallization of **7** from diethyl ether by a slow diffusion of pentane yielded 2.2 g (49.7%) of crystalline material, mp 58–59 °C, $[\alpha]^{20}_D = -3.5°$ (*c* 1.0, $CHCl_3$); ^{31}P NMR δ = 74.7 ppm (C_6D_6); ^1H NMR δ = 1.64 (d, 3 H, *J* = 6.8 Hz, CH_3), 3.45 (d, 3 H, $^3J_{P-H}$ = 13.8 Hz, CH_3O), 3.72 (d, 3 H, $^3J_{P-H}$ = 13.8 Hz, CH_3O), 5.31 (s, 1 H, *J* = 7.2 Hz, C*H*), 7.4–8.3 (m, 7 H_{arom}).

(b). A mixture of *O,O*-dimethyl *N*-[(R_c)-1-(α-naphthyl)ethyl]-phosphoramidothioate (**7**) (2 g, 0.0068 mol), methyl iodide (0.71 mL, 0.0136 mol), and acetonitrile (2 mL) was kept at 60 °C in a tightly closed vial for 15 h. The reaction mixture was evaporated to dryness, taken up in chloroform, and passed through a short silica gel (230–400 mesh) column using a gradient of solvents, chloroform up to chloroform–methanol (100:2), to give 1.8 g of a mixture of diastereoisomers. Fractional crystallization from benzene gave 0.52 g (51.8%) of a pure diastereoisomer "fast"-**2** [R_F = 0.38 in methylene chloride–ethyl acetate (1:1)].

The fractions enriched in the second isomer were collected and chromatographed on a silica gel column (column φ 1.5 cm × 20 cm, 230–400 mesh) using dichloromethane–ethyl acetate (1:1) as an eluting system to give 0.130 g (13.0%) of a pure diastereoisomer "slow"-**2** [R_F = 0.31 in dichloromethane–ethyl acetate (1:1)].

Data for "Fast"-2: mp 146–147 °C; $[\alpha]^{20}_D = -29.4°$ (*c* 1.1, $CHCl_3$); ^{31}P NMR δ = 34.65 (C_6D_6–CH_3CN); ^1H NMR δ = 1.70 (d, 3 H, *J* = 6.8 Hz, CH_3), 2.13 (d, 3 H, $^3J_{P-H}$ = 14.7 Hz, CH_3S), 3.76 (d, 3 H, $^3J_{P-H}$ = 12.5 Hz, CH_3O), 5.33 (m, 1 H, C*H*), 7.26–8.25 (7 H_{arom}); ^{13}C NMR δ = 12.2 (d, J_{P-C} = 3.1 Hz, CH_3), 24.6 (d, J_{P-C} = 3.5 Hz, CH_3S), 47.4 (CH_3O), 52.8 (d, J_{P-C} = 10.1 Hz, *C*H), 121.5, 122.2, 123.1, 125.3, 125.7, 126.3, 127.98, 128.9 (C_{arom}); MS (70 eV, m/z) 295 ($M^{\cdot+}$, 14.1%), 280 (31.4%), 248 (31.8%), 170 (100.0%), 125 (20.4%); HRMS for $C_{14}H_{18}NO_2PS$, calcd 295.0796, found 295.0796. Anal. Calcd for $C_{14}H_{18}NO_2PS$: C, 56.93; H, 6.14; N, 4.74; P, 10.49; S, 10.86. Found: C, 56.93; H, 6.20; N, 4.44; P, 10.96; S, 10.96.

Data for "Slow"-2: mp 138–139 °C; $[\alpha]^{20}_D = 37.4°$ (*c* 1.9, $CHCl_3$); ^{31}P NMR δ = 35.14 ppm (C_6D_6–CH_3CN); ^1H NMR δ = 1.68 (d, 3 H, *J* = 6.8 Hz, CH_3), 2.16 (d, 3 H, *J* = 14.7 Hz, CH_3S), 3.60 (d, 3 H, $^3J_{P-H}$ = 12.5 Hz, CH_3O), 5.31 (m, 1 H, C*H*), 7.30–8.20 (7 H_{arom}); ^{13}C NMR δ = 12.2 (d, J_{P-C} = 6.3 Hz, CH_3), 24.7 (d, J_{P-C} = 5.0 Hz, CH_3S), 47.5 (CH_3O), 52.8 (d, J_{P-C} = 8.2 Hz, *C*H), 122.3, 122.4, 122.96, 123.1, 125.4, 125.7, 126.3, 127.9, 127.98, 128.9 (C_{arom}); MS (70 eV, m/z) 295 ($M^{\cdot+}$, 14.1%), 280 (33.6%), 248 (31.5%), 170 (100.0%), 125 (21.7%); HRMS for $C_{14}H_{18}NO_2PS$, calcd 295.0796, found 295.0796. Anal. Calcd for $C_{14}H_{18}NO_2PS$: C, 56.93; H, 6.14; N, 4.74; P, 10.49; S, 10.86. Found: C, 57.47; H, 6.29; N, 4.22; P, 10.74; S, 10.85.

DBU-Catalyzed Methanolysis of Diastereoisomers of 1. (a). Into a solution of "slow"-**1** (30 mg, 0.097 mmol) in a mixture of acetonitrile and benzene (500 μL, 1:1 v/v), placed in a 5-mm NMR tube, were added DBU (15 μL, 0.1 mmol) and MeOH (35 μL, 0.9 mmol). Ten minutes after the reagents were mixed, the ^{31}P NMR spectrum was recorded showing two signals at 59.77 and 94.58 ppm in the ratio 91:9. Methyl iodide (15 μL, 0.2 mmol) was then added, and after 10 min, completion of methylation was confirmed by ^{31}P NMR. Two signals at 34.61 and 94.66 ppm in the ratio 93:7, characteristic for "fast"-**2** and unchanged substrate "slow"-**2**, respectively, were present in the spectrum. The predominant compound of this mixture, "fast"-**2**, was isolated by means of short-column chromatography and, after crystallization from benzene–hexane (3:1), proved to be identical with an authentic sample of "fast"-**2** prepared by an independent method (TLC, ^{31}P NMR assays).

(b). The mixture of diastereoisomers "fast"-**1** and "slow"-**1** in the ratio 79:21 (30 mg, 0.097 mmol) was dissolved in the mixture of acetonitrile and benzene (500 μL, v/v 1:1). The resulting solution was placed in 5-mm NMR tube, and DBU (15 μL, 0.1 mmol) and MeOH (35 μL, 0.9 mmol) were added. Ten minutes after the reagents were mixed, the ^{31}P NMR spectrum was recorded showing three signals at 95.25, 59.78, and 59.16 ppm in the ratio 1:24:75, respectively. Methyl iodide (15 μL, 0.2 mmol) was then added, and completion of methylation was confirmed by ^{31}P NMR. Two signals at 35.14 and 34.65 ppm in the ratio 76:24, characteristic for "slow"-**2** and "fast"-**2**, respectively, were present in the spectrum.

Collection of X-ray Data and Solution of the Structure (for "Slow"-1 and "Slow"-2). The crystal and molecular structures of "slow"-**1** and "slow"-**2** were determined using data collected on a CAD4 diffractometer. Compound "slow"-**1** crystallized in a monoclinic system, space group $P2_1$; "slow"-**2** crystallized in an orthorhombic system, space group $P2_12_12_1$. Crystal data and experimental details are shown in Table I. Intensity data for both compounds were collected at room temperature using a diffractometer with graphite monochromatized radiation. Lattice constants were refined by least-squares fit of 25 reflections in Θ range 21.7–24.6° for "slow"-**1** and 11.3–12.7° for "slow"-**2**. The decline in intensities of three standard reflections for "slow"-**1** (3,2,-4; 4,1,-4; 3,1,-5) was 0.7% during 36.3 h of exposure, and for "slow"-**2** (1,2,-13; 333; 2,1,-11), the decline was 1.0% during 25.4 h. For "slow"-**1** an absorption correction was applied[16] (see Table I). For "slow"-**2**, no corrections were applied. A total of 1731 observed reflections for "slow"-**1** and 1857 for "slow"-**2** [with $I \geq 3\sigma(I)$] was used to solve the structures by direct methods.[17] Structures were refined on the SDP computing package[16] by full matrix least squares using *F*'s. For both compounds, hydrogen atoms connected to carbon were placed at geometrically idealized positions with fixed isotropic thermal parameters equal to 1.3 of the isotropic thermal parameter of the carbon atom and for "slow"-**1** refined as riding with fixed thermal parameters and for "slow"-**2** refined as riding isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms in both structures. The final refinement converged to $R = 0.046$ with unit weight for 175 refined parameters for "slow"-**1** and to $R = 0.047$ with unit weight for 244 refined parameters for "slow"-**2**. The largest shift/error parameter in the last cycle and the largest residual peak in the final difference Fourier map were 0.02 and 0.727 e/Å^3 for "slow"-**1** and 0.01 and 0.388 e/Å^3 for "slow"-**2**, respectively. All calculations were carried out with the Enraf-Nonius SDP crystallographic computing package[16] (except direct methods which were applied with the SHELXS program[17]). Scattering factors were taken from ref 8.

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Supplementary Material Available: Tables of selected bond distances and angles for "slow"-**1** and "slow"-**2** and ^1H NMR spectrum of **7** (3 pages). Ordering information is given on any current masthead page.

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