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Synthesis of stereoisomeric *d,l* and *meso* forms of *O,O′*-bis-(*O,O′*-dialkyl 1-phosphorylbenzyl)phenylphosphonites and -thionophosphonates containing a pseudochiral center and determination of their configurations by NMR spectroscopy

M. N. Dimukhametov, E. V. Bayandina, I. A. Litvinov, and V. A. Al'fonsov*

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center of the Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843 2) 75 5322. E-mail: alfonsov@iopc.kcn.ru

O,O′-Bis-(*O,O′*-dialkyl 1-phosphorylbenzyl)phenylphosphonites (**1a—c**) and -thionophosphonates (**2a—c**) containing a pseudochiral center were synthesized. Based on analysis of the "topic" relations between the chiral fragments of the stereoisomeric *d,l* and *meso* forms of compounds **1a—c** and **2a—c**, the signals in the ^{1}H and ^{31}P {^{1}H} NMR spectra were assigned to particular stereoisomers. All three diastereomers of compound **2a** were isolated in the individual form and characterized.

Key words: configuration, enantiotopism, diastereotopism, pseudochirality, NMR spectroscopy, X-ray diffraction analysis, dichlorophenylphosphine, 1-oxyalkylphosphonates.

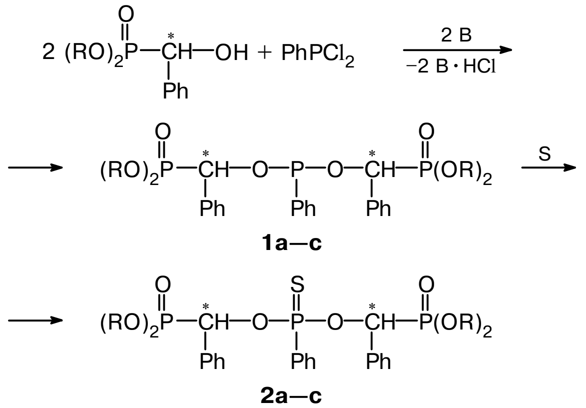
Simple procedures for the determination of the enantiomeric purity of chiral compounds possessing a pseudochiral center (in particular, the P atom) are based on quantitative analysis of the stereoisomeric composition by NMR spectroscopy.[1—4] This approach is based on reactions of two equivalents of a substrate and an appropriate achiral derivatizing reagent to form a compound existing as three diastereomers, *viz*., the *d,l* form (*R,R* and *S,S* configurations of the chiral centers) and two nonequivalent *meso* forms (*R,S* and *S,R* configurations of the chiral centers), which are distinguishable in the NMR spectra. Integration of signals and subsequent calculations by Horeau's formula[5] allows the determination of the enantiomeric excess of the substrate. However, correct analysis requires the precise assignment of the signals observed in NMR spectra to particular stereoisomeric forms. Differences in the "topic" relations between chiral fragments of molecules, which are clearly manifested on comparison of their NMR spectra,[6] can serve as a reliable argument in favor of the assignment of the signals to particular stereoisomers of these compounds. Consequently, these differences can be used for the determination of the relative configurations of the diastereomeric (*d,l* and *meso*) forms. Previously,[7] the differences in the "topic" relations between structurally identical and yet chiral phosphorus-containing fragments have been found for the first time in stereoisomeric compounds containing a pseudochiral center, *viz*., the enantiotopism in the *meso* form and the diastereotopism in the *d,l* form have been revealed.

In the present work, we synthesized stereoisomeric *O,O′*-bis-(*O,O′*-dialkyl 1-phosphorylbenzyl)phenylphosphonites (**1a—c**) and -thionophosphonates (**2a—c**), studied these compounds by ^{31}P {^{1}H} and ^{1}H NMR spectroscopy, and analyzed the spectra based on the "topic" relations between the chiral fragments.

Results and Discussion

Compounds **1** were synthesized from two equivalents of *O,O′*-dialkyl 1-oxobenzylphosphonates and dichlorophenylphosphine in the presence of triethylamine. Compounds **2** were prepared by the subsequent addition of sulfur to compounds **1** (Scheme 1).

Scheme 1



R = Me (**a**), Et (**b**), Pr^i (**c**)
B = Et$_3$N

The ^{31}P {^{1}H} NMR spectra of the reaction mixtures of compounds **1** have signals for the P^{III} nuclei of the

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Table 1. Data of ^{31}P {^{1}H} NMR spectroscopy and the stereoisomer ratios for compounds **1** and **2**

Compound	δ (*J*/Hz)											Ratio of stereoisomers*	
	meso-1			*meso*-2			*d,l*					*meso*-1 : *meso*-2 : *d,l*	(*meso*-1 + + *meso*-2) : *d,l*
	δ_A (δ_C)	δ_B	$^3J_{AB}$ ($^3J_{BC}$)	δ_A (δ_C)	δ_B	$^3J_{AB}$ ($^3J_{BC}$)	δ_A	δ_B	δ_C	$^3J_{AB}$	$^3J_{BC}$		
1a	19.6	178.7	25.6	19.5	174.2	24.3	20.0	169.9	19.3	21.7	22.4	2.10 : 1 : 4.16	1 : 1.34
1b	**	180.4	26.8	**	174.1	24.9	**	170.1	**	21.9	21.9	2.40 : 1 : 4.12	1 : 1.21
1c	**	181.2	28.0	**	173.5	25.4	**	170.8	**	21.8	23.6	1 : 2.01 : 4.34	1 : 1.44
2a	18.1	91.6	32.9	18.6	90.0	34.4	17.9	91.4	18.3	35.2	33.6	2.17 : 1 : 4.25	1 : 1.35
2b	15.5	91.0	33.5	16.0	89.1	35.0	15.3	90.9	15.8	36.2	34.0	2.52 : 1 : 4.26	1 : 1.21
2c	14.1	90.9	35.4	14.5	88.5	37.5	13.8	90.5	14.3	38.9	35.7	2.21 : 1 : 4.60	1 : 1.43

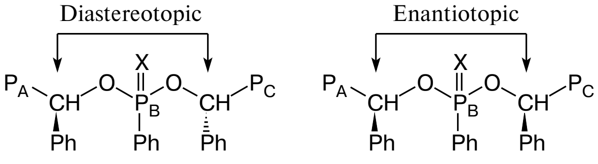
* Determined from the integrated intensities of the signals for the central P_B atom in the spectra of the raw reaction products.
** We failed to unambiguously interpret the signals for the P atoms in the phosphonate fragments.

stereoisomers as a high-field doublet of doublets at δ 170—171 with $^3J_{PP}$ = 22—24 Hz and two triplets at δ 173—181 with $^3J_{PP}$ = 24—28 Hz. The difference between the spin-spin coupling constants for the doublet of doublets is 0.7—1.6 Hz. The phosphorus atoms of two chiral phosphonate fragments are manifested as a complex group of signals at δ 20. Only in the case of compound **1a**, the doublets corresponding to all three stereoisomeric forms were unambiguously identified (Table 1).

In the ^{31}P {^{1}H} NMR spectra of the reaction mixtures of compounds **2**, the signals for the central thionophosphonate P atom are found in the region of δ 88—92 as two triplets with $^3J_{PP}$ = 33—37 Hz and as a doublet of doublets with $^3J_{PP}$ = 34—39 Hz located between the triplets. The difference between the spin-spin coupling constants for the doublet of doublets is 1.6—3.2 Hz. The diastereomer ratios for compounds **1** and **2** differ substantially from the statistical values (see Table 1), which is indicative of stereoselectivity of their formation. The fraction of one of the *meso* forms is ~2 times larger than that of another form. However, the total amount of the *meso* forms is noticeably smaller than the amount of the *d,l* form.

The multiplicities of the signals in the spectra of the reaction mixtures indicate that compounds **1** and **2** are formed as three diastereomers, *viz.*, the *d,l* form and two *meso* forms. Since the chiral fragments in the *d,l* form and in the *meso* forms are diastereotopic and enantiotopic, respectively, the doublet of doublets can be unambiguously assigned to the *d,l* form, whereas the triplets can be assigned to two *meso* forms (Scheme 2).

Scheme 2



d,l form
(*R,R* enantiomer)

meso form
(*RsS* for **1** and *RrS* for **2**)

X is the lone electron pair (**1**) or S (**2**)

We succeeded in isolating all three diastereomers of compound **2a** in the pure form by column chromatography on SiO_2 and analyzed their ^{1}H and ^{31}P NMR spectra.

In the ^{31}P {^{1}H} NMR spectrum of the *d,l* form in CD_3CN, like in the spectrum of the mixture of all three forms, the central P atom gives a doublet of doublets with the center at δ 91.4 and with $^3J_{AB}$ = 35.8 Hz and $^3J_{CB}$ = 34.4 Hz. Two doublets with the centers at δ 17.4 ($^3J_{AB}$ = 35.8 Hz) and 17.9 ($^3J_{CB}$ = 34.4 Hz) correspond to the P atoms of two chiral phosphonate fragments. The difference between the chemical shifts of two non-

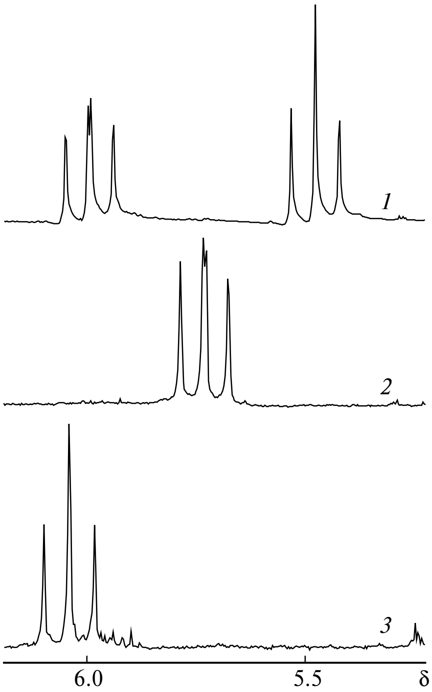


Fig. 1. ^{1}H NMR spectra of the PCH fragments of the diastereomers of compound **2a**: *meso*-1 (*1*), *d,l* (*2*), and *meso*-2 (*3*).

equivalent P atoms is 0.50 ppm. In the ^1H NMR spectrum of the *d,l* form in CD_3CN, the diastereotopism of two phosphonate fragments is most clearly manifested in the signals for two methine protons (Fig. 1, spectrum *1*). These signals are observed as a doublet of doublets (low-field; $^2J_{HP}$ = 14.7 Hz and $^3J_{HP}$ = 12.8 Hz) and a triplet ($^2J_{HP}$ and $^3J_{HP}$ = 14.2 Hz). The difference between the chemical shifts of two diastereotopic protons is 0.53 ppm.

In the ^{31}P {^1H} NMR spectra of the individual *meso* forms in CD_3CN, the central P atoms are manifested as triplets at δ 92.9 (*meso*-1) and 89.9 (*meso*-2), whereas two terminal P atoms are manifested as doublets at δ 18.1 ($^3J_{AB}$ and $^3J_{CB}$ = 34.2 Hz) (*meso*-1) and δ 18.4 ($^3J_{AB}$ and $^3J_{CB}$ = 35.5 Hz) (*meso*-2) due to their magnetic equivalence. Analogously, two enantiotopic methine protons in the ^1H NMR spectrum are observed as one doublet of doublets with $^2J_{HP}$ = 14.9 and $^3J_{HP}$ = 13.4 Hz (*meso*-1) (see Fig. 1, spectrum *2*) and one triplet with $^2J_{HP}$ and $^3J_{HP}$ = 14.4 Hz (*meso*-2) (see Fig. 1, spectrum *3*).

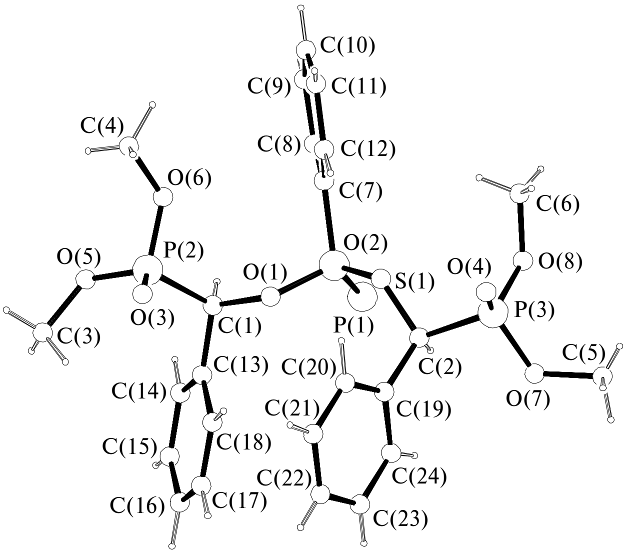


Fig. 2. Molecular geometry of the *meso*-1 diastereomer of compound **2a** in the crystal.

Table 2. Principal bond lengths (*d*) and bond angles (ω) in the structure of the *meso*-1 diastereomer of compound **2a**

Bond	*d*/Å	Bond	*d*/Å
S(1)—P(1)	1.913(1)	C(2)—C(19)	1.497(4)
P(1)—O(1)	1.593(2)	C(7)—C(8)	1.377(5)
P(1)—O(2)	1.590(2)	C(7)—C(12)	1.367(4)
P(1)—C(7)	1.781(3)	C(8)—C(9)	1.360(5)
P(2)—O(3)	1.449(2)	C(9)—C(10)	1.356(5)
P(2)—O(5)	1.565(2)	C(10)—C(11)	1.328(6)
P(2)—O(6)	1.561(2)	C(11)—C(12)	1.390(6)
P(2)—C(1)	1.818(3)	C(13)—C(14)	1.378(3)
P(3)—O(4)	1.453(2)	C(13)—C(18)	1.387(4)
P(3)—O(7)	1.560(2)	C(14)—C(15)	1.380(4)
P(3)—O(8)	1.569(2)	C(15)—C(16)	1.359(5)
P(3)—C(2)	1.811(2)	C(16)—C(17)	1.373(4)
O(1)—C(1)	1.454(3)	C(17)—C(18)	1.372(4)
O(2)—C(2)	1.461(3)	C(19)—C(20)	1.374(4)
O(5)—C(3)	1.440(4)	C(19)—C(24)	1.379(4)
O(6)—C(4)	1.446(4)	C(20)—C(21)	1.382(4)
O(7)—C(5)	1.447(3)	C(21)—C(22)	1.355(5)
O(8)—C(6)	1.428(4)	C(22)—C(23)	1.361(5)
C(1)—C(13)	1.499(4)	C(23)—C(24)	1.379(5)
Angle	**ω/deg**	**Angle**	**ω/deg**
S(1)—P(1)—O(1)	116.14(7)	O(7)—P(3)—O(8)	103.3(1)
S(1)—P(1)—O(2)	116.37(7)	O(7)—P(3)—C(2)	98.7(1)
S(1)—P(1)—C(7)	115.39(9)	O(8)—P(3)—C(2)	104.7(1)
O(1)—P(1)—O(2)	98.81(9)	P(1)—O(1)—C(1)	122.2(2)
O(1)—P(1)—C(7)	106.4(1)	P(1)—O(2)—C(2)	121.7(1)
O(2)—P(1)—C(7)	101.5(1)	P(2)—O(5)—C(3)	120.6(2)
O(3)—P(2)—O(5)	114.7(1)	P(2)—O(6)—C(4)	123.5(2)
O(3)—P(2)—O(6)	117.8(1)	P(3)—O(7)—C(5)	122.0(2)
O(3)—P(2)—C(1)	114.6(1)	P(3)—O(8)—C(6)	121.1(2)
O(5)—P(2)—O(6)	102.6(1)	P(2)—C(1)—O(1)	105.1(1)
O(5)—P(2)—C(1)	105.1(1)	P(2)—C(1)—C(13)	113.3(2)
O(6)—P(2)—C(1)	100.1(1)	O(1)—C(1)—C(13)	111.1(2)
O(4)—P(3)—O(7)	117.6(1)	P(3)—C(2)—O(2)	104.4(1)
O(4)—P(3)—O(8)	114.5(1)	P(3)—C(2)—C(19)	115.2(2)
O(4)—P(3)—C(2)	115.9(1)	O(2)—C(2)—C(19)	113.0(2)

With the aim of confirming the structure and establishing the absolute configuration of the pseudochiral center, the *meso*-1 diastereomer was studied by X-ray diffraction analysis (Table 2). As expected, two chiral centers in the molecule have opposite configurations (*R* and *S* for C(1) and C(2), respectively) (Fig. 2). The pseudochiral P atom has the *r* configuration. In the crystal, the molecule adopts an unsymmetrical conformation. The molecule is characterized by staggered conformations along the P(1)—O(1) and P(1)—O(2) bonds. These conformations differ by the positions of the substituents at the P atom. Thus, the C(1)—O(1) and P(1)—O(2) bonds are in *trans* positions in the case of C(1), whereas the C(2)—O(2) and P(1)—C(7) bonds are in *trans* positions in the case of C(2) (Fig. 3). It should

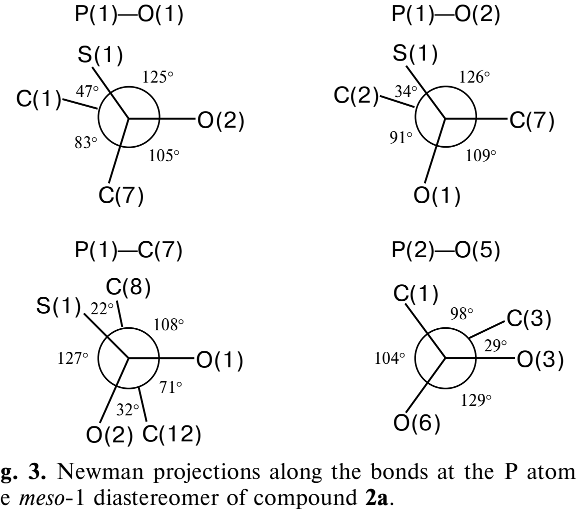


Fig. 3. Newman projections along the bonds at the P atom in the *meso*-1 diastereomer of compound **2a**.

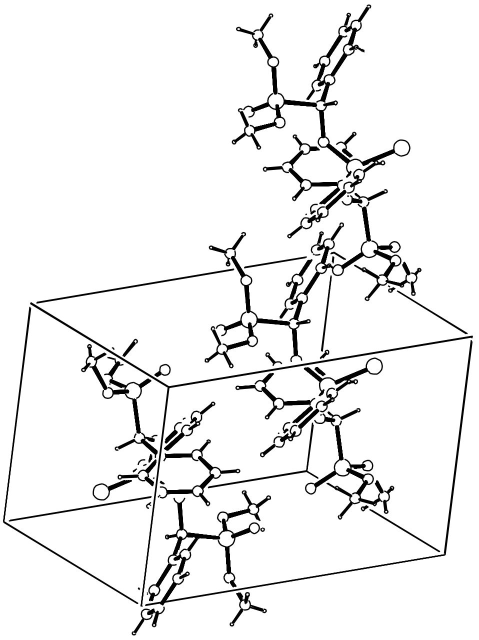


Fig. 4. Molecular packing of the *meso*-1 diastereomer of compound **2a** in the crystal.

be noted that this difference has no effect on the bond lengths at the O(1), O(2), C(1), and C(2) atoms. These bond lengths in the right and left portions of the molecule are equal to within the experimental error. An unsymmetrical conformation is observed about the P(1)—C(7) bond (the S(1)—P(1)—C(7)—C(8) torsion angle is −22.3(3)°) as well. The bond lengths at the P(2) and P(3) atoms are also equal to within the experimental error. Probably, the unsymmetrical conformation of molecule **2a** in the crystal is determined by its unsymmetrical environment (Fig. 4). In the crystal, there is a shortened intermolecular contact between the C atom of the benzene ring and the O(4) atom of the phosphoryl group. This structural fragment is characterized by the following parameters: C(14)—H, 0.92(2) Å; C(14)...O(4′) (*x*, 1 + *y*, *z*), 3.462(3) Å; H...O(4′), 2.56(2) Å; the C(14)—H...O(4′) angle is 166(2)°. The phosphoryl group at the P(2) atom has no short contacts.

The results of our study demonstrated that the unambiguous assignment of the signals in the ^{31}P NMR spectra can be made based on the differences in the "topic" relations between the chiral fragments in the stereoisomeric *d,l* and *meso* forms of compounds **1** and **2**, thus determining their relative configurations. Since these differences are characteristic of all types of compounds containing a pseudochiral center (a pseudochirality element), the signals in the NMR spectra of their mixtures can be easily assigned to particular stereoisomers, which allows one to perform quantitative analysis and to determine the enantiomeric compositions of chiral substrates.

Experimental

The ^{31}P {^{1}H} NMR spectra were recorded on a Bruker MSL 400 spectrometer operating at 162 MHz (85% H_3PO_4 as the external standard) in benzene with the addition of C_6D_6 as the internal lock and in CD_3CN. The ^{1}H NMR spectra were measured on a Bruker WM 250 instrument operating at 250 MHz in CD_3CN. The IR spectra were obtained on a UR-20 instrument.

***O,O′*-Bis-(*O,O′*-dimethyl 1-phosphorylbenzyl)phenylphosphonite (1a) and *O,O′*-bis-(*O,O′*-dimethyl 1-phosphorylbenzyl)phenylthionophosphonate (2a).** A solution of dichlorophenylphosphine (1.18 g, 6.5 mmol) in dry benzene (5 mL) was added with stirring to a solution of *O,O*-dimethyl 1-oxobenzylphosphonate (2.85 g, 13.0 mmol) and triethylamine (1.33 g, 13.0 mmol) in dry benzene (20 mL) under dry argon at ~20 °C. The reaction mixture was stirred at 50 °C for 2 h and the precipitate that formed was filtered off. The filtrate containing compound **1a** was analyzed by ^{31}P {^{1}H} NMR spectroscopy. After the spectrum was recorded, a powder of elemental sulfur (0.31 g, 9.1 mmol) was added to the filtrate and the mixture was heated with stirring at 60 °C for 0.5 h. Excess sulfur was filtered off, the solvent was removed under reduced pressure, and the residue was chromatographed on a column with SiO_2 (100/160 μ) with the use of a 4 : 1 toluene—acetone mixture as the eluent. The contents of the flractions of the eluate were monitored by TLC on Silufol 254 plates (visualization was carried out using an iodine chamber) and by ^{31}P NMR spectroscopy.

The following fractions of compound **2a** were isolated: *meso*-1 (0.31 g, R_f 0.67, toluene—acetone, 1 : 1) as colorless crystals, m.p. 110—111 °C (benzene—hexane, 1 : 1). Found (%): C, 50.50; H, 5.19; P, 16.28; S, 5.51. $C_{24}H_{29}O_8P_3S$. Calculated (%): C, 50.53; H, 5.09; P, 16.32; S, 5.61. IR (Nujol mulls), ν/cm^{-1}: 1260 (P=O); 1040 (P—O—C); 625 (P=S). ^{1}H NMR, δ: 3.46 (d, 6 H, 2 MeO, $^{3}J_{HP}$ = 10.6 Hz); 3.49 (d, 6 H, 2 Me′O, $^{3}J_{HP}$ = 10.6 Hz); 5.76 (dd, 2 H, 2 HCPO, $^{2}J_{HP}$ = 14.9 Hz, $^{3}J_{HP}$ = 13.4 Hz); 7.16—8.20 (m, 15 H arom.).

A mixture of the *meso*-1 diastereomer and the *d,l*-form (1.12 g) in a ratio of 1 : 1.69.

The *d,l* form (0.25 g, R_f 0.63, toluene—acetone, 1 : 1) as a colorless oily liquid with n_D^{20} 1.5570. Found (%): C, 50.70; H, 5.07; P, 16.16; S, 5.77. IR (film), ν/cm^{-1}: 1265 (P=O); 1042 (P—O—C); 635 (P=S). ^{1}H NMR, δ: 3.50, 3.51, 3.53, and 3.57 (all d, 3 H each, 4 MeO, $^{3}J_{HP}$ = 13.1, 13.2, 10.2, and 10.1 Hz); 5.50 (t, 1 H, HCPO, $^{2}J_{HP}$ = $^{3}J_{HP}$ = 14.2 Hz); 6.03 (dd, 2 H, 2 H′CPO, $^{2}J_{HP}$ = 14.7 Hz, $^{3}J_{HP}$ = 12.8 Hz); 7.10—7.95 (m, 15 H arom.).

A mixture of the *d,l* form and the *meso*-2 diastereomer (0.71 g) in a ratio of 2.17 : 1.

The *meso*-2 diastereomer (0.10 g, R_f 0.59, toluene—acetone, 1 : 1) as a colorless oily liquid with n_D^{20} 1.5530. Found (%): P, 16.53; S, 5.23. ^{1}H NMR, δ: 3.71 (d, 6 H, 2 MeO, $^{3}J_{HP}$ = 10.8 Hz); 3.80 (d, 6 H, 2 Me′O, $^{3}J_{HP}$ = 10.6 Hz); 6.04 (t, 2 H, 2 HCPO, $^{2}J_{HP}$ = $^{3}J_{HP}$ = 14.4 Hz); 7.25—8.02 (m, 15 H, arom.).

The total yield of compound **2a** was 67%.

Compounds **1b,c** and **2b,c** were prepared analogously. Compounds **2b,c** were isolated as colorless viscous liquids by column chromatography on SiO_2 using a 3 : 1 benzene—acetone mixture as the eluent.

Thionophosphonate 2b: the yield was 70%; n_D^{20} 1.5430. Found (%): C, 53.62; H, 5.89; P, 14.40; S, 5.10. $C_{28}H_{37}O_8P_3S$. Calculated (%): C, 53.67; H, 5.91; P, 14.86; S, 5.41.

Thionophosphonate 2c: the yield was 79%; n_D^{20} 1.5359. Found (%): C, 56.28; H, 6.58; P, 13.48; S, 4.60. $C_{32}H_{45}O_8P_3S$. Calculated (%): C, 56.30; H, 6.60; P, 13.64; S, 4.69.

X-ray diffraction analysis. Crystals of the *meso*-1 diastereomer of compound **2a**, $C_{24}H_{29}O_8P_3S$, are triclinic. At 20 °C, $a = 9.564(1)$ Å, $b = 9.846(2)$ Å, $c = 15.226(4)$ Å, $\alpha = 80.64(2)°$, $\beta = 82.53(1)°$, $\gamma = 78.97(1)°$, $V = 1381.2(5)$ Å^3, $Z = 2$, $d_{calc} = 1.37$ g cm^{-3}, space group $P\bar{1}$.

The unit cell parameters and the intensities of 3098 reflections of which 2594 reflections were with $I \geq 2\sigma$ were measured on an automated four-circle Enraf-Nonius CAD-4 diffractometer (λMo-Kα radiation, graphite monochromator, $\omega/2\theta$ scanning technique, $\theta \leq 26°$) at 20 °C. The structure was solved by the direct method using the SIR program[8] and refined first isotropically and then anisotropically. Absorption was ignored (μMo was 3.25 cm^{-1}). All H atoms were located from difference electron density syntheses and refined isotropically at the final stage. The final values of the reliability factors were $R = 0.032$ and $R_w = 0.044$ based on 2586 reflections with $F^2 \geq 3\sigma$. All calculations were carried out on an Alpha Station 200 computer using the MolEN program package[9].

The atomic coordinates were deposited with the Cambridge Structural Database or can be obtained from the authors. The molecules were drawn and the intermolecular contacts in the crystals were analyzed using the PLATON 98 program.[10]

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