Asymmetric synthesis of α-substituted alkylphosphonates based on symmetrical dialkyl phosphites

O. I. Kolodiazhnyi,[a] E. V. Grishkun,[a] S. Sheiko,[a] O. Demchuk,[a] H. Thoennessen,[b] P. Jones,[b] and R. Schmutzler[b]*

[a]*Institute of Bioorganic Chemistry, National Academy of Sciences of Ukraine, 1 ul. Murmanskaya, 253094 Kiev, Ukraine. Fax: 38 (044) 573 2552. E-mail: oik@bpci.kiev.ua*

[b]*Institute für Anorganische und Analytische Chemie der K. Vilgelmin Technischen Universität, Hagenring 30, D-38106 Braunschweig, Germany. Fax: (0) 531 391 5387. E-mail: iaac@mac1.anchem.nat.tu-bs.de*

Chiral C_2-symmetrical dialkyl phosphites and C_3-symmetrical trialkyl phosphites, derived from (−)-borneol, (−)-menthol, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, were studied as the starting reagents for the preparation of chiral organophosphorus compounds. The reactions of C_2-symmetrical dialkyl phosphites and C_3-symmetrical trialkyl phosphites with aldehydes and amines or aldehydes are accompanied by asymmetrical induction at the α-carbon atom to yield optically active α-aminoalkylphosphonates or α-hydroxyalkylphosphonates, respectively. The stereoselectivity of the reaction depends on the structure of the starting compounds and the reaction conditions.

Key words: asymmetric synthesis, optically active α-hydroxyalkylphosphonates, optically active α-aminoalkylphosphonates, the Kabachnik—Fields reaction, the Pudovik reaction, symmetrical chiral dialkyl phosphites, C_3-symmetrical trialkyl phosphites, (+)-(*R*)-α-hydroxybenzylphosphonic acid.

The recent decade was marked by high activity in the field of asymmetric synthesis of organophosphorus compounds. Methods[1,2] for the synthesis of various optically active organophosphorus compounds became available. Nevertheless, further investigations in this field are of theoretical interest and practical importance.

We herein suggest C_2-symmetrical dialkyl and C_3-symmetrical trialkyl phosphites containing chiral secondary alkoxy groups as new chiral, nonracemic starting compounds for asymmetric synthesis of organophosphorus derivatives. The synthetic potentialities of these compounds are demonstrated in the Kabachnik—Fields and the Pudovik reactions.[3,4] An asymmetric version of the Kabachnik—Fields reaction is practically unknown. Asymmetric synthesis using the Pudovik reaction was investigated insufficiently.[5—7] Anions of chiral cyclic phosphorodiamidites were shown to react stereospecifically with aldehydes resulting in the formation of hydroxy phosphonates. Diastereoselectivity of the reaction depended on the structure of the starting phosphorodiamidite and ranged from comparatively low to high.

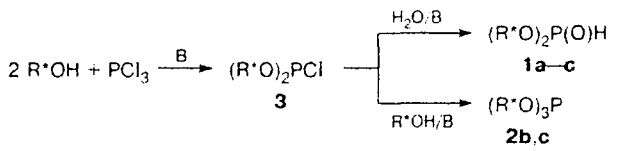
Asymmetric synthesis under the conditions of the Kabachnik—Fields and the Pudovik reactions is of interest, as it results in the formation of optically active α-aminoalkylphosphonic and α-hydroxyalkylphosphonic acids, which possess high biological activities as pharmaceutical preparations, bioregulators, and herbicides.[8—12] Biological activities of these compounds strongly depend on the absolute configuration of the C_α atom.[13—15] Thus, asymmetric synthesis of this class of compounds is of particular interest.

We have developed convenient methods for the synthesis of di- and trialkyl phosphites (**1** and **2**, respectively) from available optically active starting alcohols. Compounds **1** and **2** have the symmetry axis passing through the P atom, which is an important factor that decreases the number of possible diastereomers. Chiral phosphites **1a—c** and **2b,c** were synthesized by the reaction of optically active secondary alcohols, *viz.*, (−)-[(1*R*,2*S*,5*R*)-menthol, (−)-[(1*S*)-*endo*]-borneol, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, with PCl_3 in the presence of Et_3N or Py. The reaction yielded initially phosphorochloridites **3**, which were identified by ^{31}P NMR (δ_P 141) or isolated in individual form. For example, dimenthyl phosphorochloridite **3c** was isolated as a colorless hygroscopic liquid, which can be distilled in high vacuum without decomposition. Then phosphorochloridites **1** were hydrolyzed into dialkyl phosphites **1a—c** or were treated with the corresponding alcohol to give trialkyl phosphites **2b,c** (Scheme 1). Intermediate isolation of phosphorochloridites facilitates preparation of pure compounds **1** and **2**. Synthesis of dimenthyl phosphite was described earlier,[16,17] but the compound was obtained as a crude product. Dimentyl phosphite as such, as well as dialkyl phosphites **1** and trialkyl phosphites **2**, have not been previously considered as asymmetric inductors. A detailed discussion of this problem is presented in a recent review.[2]

Translated from *Izvestiya Akademii Nauk, Seriya Khimicheskaya*, No. 8, pp. 1588—1593, August, 1999.

1066-5285/99/4808-1568 $22.00

Scheme 1



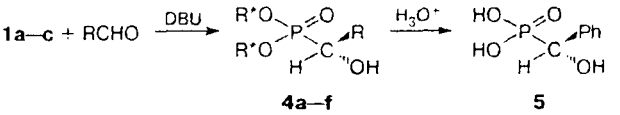
B = Et_3N or Py;
R* = (1*S*)-*endo*-bornyl (**a**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl (**b**), (1*R*,2*S*,5*R*)-menth-2-yl (**c**)

Dimentyl phosphite **1c** was purified by distillation in high vacuum and obtained as the analytically pure product for the first time. Dibornyl phosphite **1a** was recrystallized from hexane or acetonitrile. Diglucofuranosyl phosphite **1b** and triglucofuranosyl phosphite **2b** were isolated by preparative column chromatography on silica gel. Easily oxidizable derivatives of trivalent phosphorus **1b,c** with high molecular mass were purified by column chromatography on oxygen-free silica gel in an inert atmosphere. The structure and purity of compounds **1** and **2** were proved by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, mass spectrometry, TLC, and elemental analysis.

The addition of aldehydes to sterically hindered phosphorous acid diesters **1** (the Pudovik reaction) takes place only in the presence of such a strong base as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzing the reaction. In the presence of weaker bases (Et_3N, 1,4-diazabicyclo[2.2.2]octane) the reaction does not proceed or proceeds very slowly. $^{31}P\{^1H\}$ NMR study showed that the reaction is regio- and stereospecific and results in the formation of α-hydroxyalkylphosphonates in high yields (Scheme 2). However, the stereoselectivity of the reaction depends on the structure of the starting compounds and the reaction conditions. For example, compound **4c** (R = Ph) is obtained with a low diastereomer excess (*de* 33%), whereas in the case of compound **4d** (R = 4-$Me_2NC_6H_4$), *de* is ≈ 50%. If the reaction is carried out at lower temperature, the stereospecificity is increased. For example, the reaction of dimenthyl phosphite with benzaldehyde at room temperature yields α-hydroxyalkylphosphonate **4c** as a mixture of diastereomers in a ratio of 6 : 4 (*de* 20%), whereas at −20 °C the diastereomer ratio is increased to 2 : 1 (*de* 33%). In the case of compound **4d**, *de* is 33% at ~20 °C and 50% at −20 °C. Hydroxyalkylphosphonates are crystalline substances and can easily be obtained with 98—100% stereochemical purity after one or two recrystallizations from acetone or hexane.

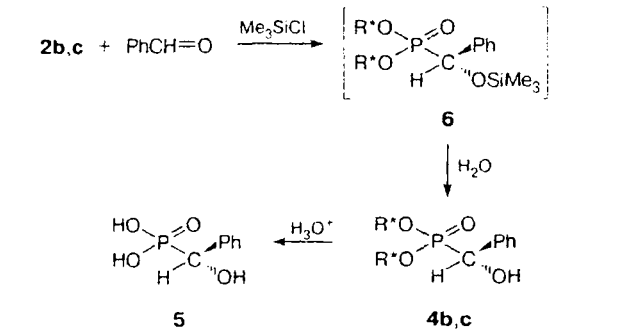
Asymmetric induction was also observed in the reaction of C_3-symmetrical phosphorous acid triesters **2b,c** (R* = (1*R*,2*S*,5*R*)-menth-2-yl or 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) with aldehydes in the presence of trimethylchlorosilane (Scheme 3). The reaction occurs at room temperature without a solvent and results in the formation of silyl ethers **6**, which are easily hydrolyzed in the course of isolation resulting in hydroxyalkylphosphonates in a total yield of 85—90% and with diastereomer ratios in the reaction mixtures of 10 : 1 (**6b**) and 3 : 1 (**6c**). One or two subsequent recrystallizations of the resulting mixtures from hexane or acetonitrile afford α-hydroxyalkylphosphonates with 100% stereochemical purity.

Scheme 2



R* = (1*S*)-*endo*-bornyl, R = Ph (**4a**);
R* = 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl, R = Ph (**4b**);
R* = (1*R*,2*S*,5*R*)-menth-2-yl (**4c—f**), R = Ph (**4c**); $C_6H_4NMe_2$-4 (**4d**); C_6H_4OMe-4 (**4e**); Pr^i (**4f**)

Scheme 3



R* = 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl (**b**); (1*R*,2*S*,5*R*)-menth-2-yl (**c**)

The structures of diesters **4b,c** were confirmed by mass spectrometry and ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The ratio of diastereomers and the stereochemical purity of the compounds obtained were determined by HPLC and $^{31}P\{^1H\}$ NMR spectroscopy (Table 1).

Table 1. Products of C_2-symmetrical addition of phosphites to aldehydes and aldimines

Compound	Yield[a] (%)	*de* (%)	M.p. /°C[b]	$[\alpha]_D^{20}$ [b]	δ_P[c]
4a	85	33	95	−39	21.69 (21.60)
4b	80	84	Oil	—	23.02 (22.86)
4c	90	33	139	−88.9	20.36 (20.08)
4d	80	50	161	−69.2	21.17 (20.60)
4e	95	35	150	−77.1	20.09 (19.98)
4f	90	78	73.5	−91.5	20.36 (20.08)
7a	94	50	144	−47.0	24.00 (23.81)
7b	90	33	86—87	−57.9	21.81 (21.67)
7c	85	83	132.5	−88.9	23.30 (23.03)

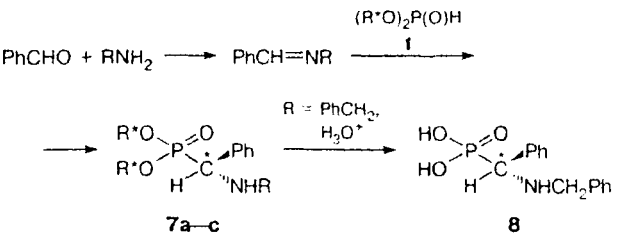
[a] Total yield of two diastereomers.
[b] Melting point and $[\alpha]_D^{20}$ are given for the major diastereomer.
[c] The values of δ_P for the minor diastereomer are given in parentheses.

Diesters **4b,c** were hydrolyzed by refluxing with HCl in aqueous dioxane to give (+)-α-hydroxybenzylphosphonic acid **5**. Its (*R*)-configuration was established by comparison with (−)-(*S*)-α-hydroxybenzylphosphonic acid, described before.[5,18] Acid **5** obtained is characterized by an optical rotation of the opposite sign and hence it has the opposite configuration.

High stereoselectivity was observed in the case of the reaction of C_2-symmetrical phosphites **1** with aldehydes and amines (the Kabachnik—Fields reaction). The reaction was performed directly with benzaldehyde and amines (compound **7a**) or with the corresponding Schiff's bases (compounds **7b,c**) (Scheme 4). The reaction is carried out at room temperature or at 60—80 °C, resulting in α-aminoalkylphosphonic acid diesters in high yields and sufficient stereoselectivity: *de* = 50% (**7a**), 33% (**7b**), and 83% (**7c**).

Recrystallization of α-aminoalkylphosphonic acid diesters from hexane yields stereochemically pure α-aminoalkylphosphonates **7**. Hydrolysis of esters **7a,b** in aqueous dioxane results in the formation of α-aminoalkylphosphonic acid **8**,[19] as reported earlier.[20] The structure of (−)-dibornyl benzylaminobenzylphosphonate **7a** was confirmed by X-ray diffraction analysis (Fig. 1).

Scheme 4



7a—c **8**

R* = (1*S*)-*endo*-bornyl, R = $PhCH_2$ (**7a**);
R* = (1*R*,2*S*,5*R*)-menth-2-yl, R = $PhCH_2$ (**7b**);
R* = (1*R*,2*S*,5*R*)-menth-2-yl, R = (*R*)-Me(Ph)CH (**7c**)

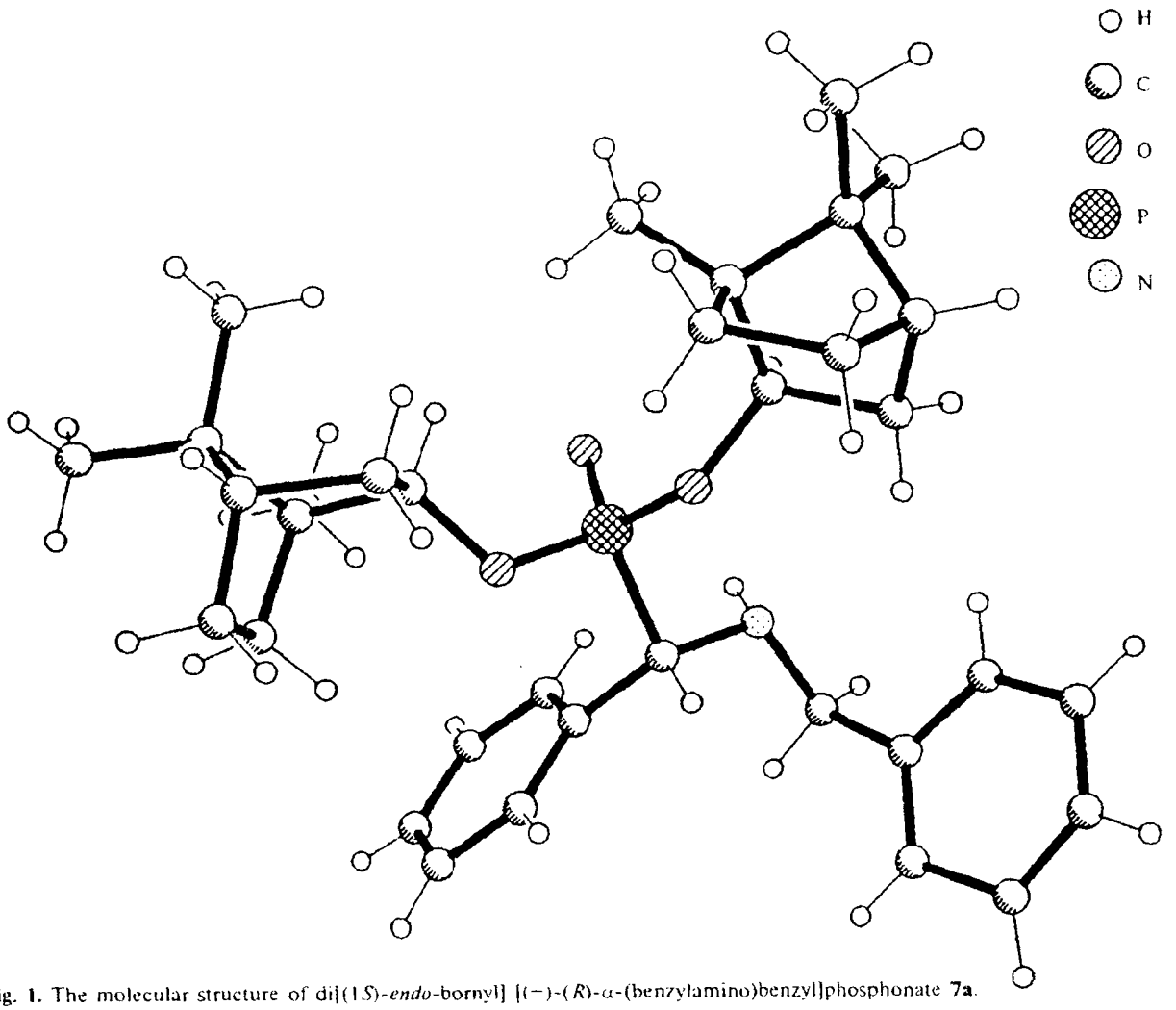


Fig. 1. The molecular structure of di[(1*S*)-*endo*-bornyl] [(−)-(*R*)-α-(benzylamino)benzyl]phosphonate **7a**.

Thus, easily available phosphites **1** and **2** can be successfully used as the starting compounds for asymmetric synthesis of organophosphorus compounds including the preparation of enantiometrically pure derivatives of α-hydroxy- and α-aminoalkylphosphonic acids. Further studies of these compounds under the conditions of the asymmetric version of the Kabachnik—Fields reaction and other relative reactions are in progress.

Experimental

^1H, ^{13}C, and ^{31}P NMR spectra were registered on Varian VXR-300 (300 MHz) and Bruker WP-200 (200 MHz) spectrometers in $CDCl_3$ or C_6D_6 with Me_4Si as the internal standard (^1H and ^{13}C) and 85% H_3PO_4 as the external standard (^{31}P). HPLC was performed on LKB (Sweden) and Milikhrom-1A (Russia) instruments with a Silasorb DEA column. Optical rotations were measured on a Perkin—Elmer 241 polarimeter. Solvents were carefully purified and dehydrated by standard methods. Optically active compounds, *viz.*, (−)-(1*R*,2*S*,5*R*)-menthol, (−)-[(1*S*)-*endo*]-borneol, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and (+)-(*R*)-α-methylbenzylamine were purchased from Fluka and Lancaster.

(−)-Bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) phosphite (1b). A solution of 9.1 g (0.035 mol) 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 7 mL of Py in 25 mL of hexane was added dropwise to a solution of 2.74 g (0.02 mol) of PCl_3 in 15 mL of hexane with stirring and cooling to −20 °C. Then the reaction mixture was stirred for 2 h at −20 °C and cooled again to 0 °C. Water (0.03 mol) was added, and the mixture was kept for ~10 h at −20 °C. Pyridine hydrochloride was filtered off, and the solvent was removed *in vacuo*. The residue (viscous liquid) was dissolved in hexane, 3—4 mL of Et_3N was added, and the mixture was kept in the refrigerator for ~10 h. The precipitate was filtered off, the solvent was evaporated, and the residue was chromatographed on silica gel (eluent ethyl acetate—hexane, 1 : 1) using TLC control (Silufol), R_f 0.38. Yield: 70%, $[\alpha]_D^{20}$ −13.8° (*c* 3.0, toluene). Found (%): P, 5.15. $C_{24}H_{39}O_{13}P$. Calculated (%): P, 5.46. ^{13}C NMR ($CDCl_3$), δ: 22.9 and 23.67 (both s, $\underline{C}(CH_3)_2$); 25.0 (d, CH_3, $J_{C,P}$ = 4 Hz); 26.2, 26.7, and 26.97 (all s, $\underline{C}H_3$); 28.84 and 30.28 (both s, $\underline{C}(CH_3)_2$); 67.46 (s, CH_2O); 72.36 (d, POC, $J_{C,P}$ = 17 Hz); 74.8, 76.4, 81.16, and 85.1 (all s, $\underline{C}HO$). ^{31}P NMR ($CDCl_3$), δ: 8.34 (dt, $^1J_{P,H}$ = 725 Hz, $^3J_{P,H}$ = 10 Hz). MS (chemical ionization, NH_3): *m/z* 567 [M^+ + 1].

(−)-Di[(1*S*)-*endo*-bornyl] phosphite (1a). A solution of 1.35 g (0.01 mol) of PCl_3 in 25 mL of diethyl ether was added dropwise to a solution of 3.1 g (0.02 mol) of (−)-[(1*S*)-*endo*]-borneol and 3.5—4 mL of Et_3N in 25 mL of diethyl ether with stirring and cooling to −10 to −20 °C. Then the reaction mixture was stirred for 2 h at −20 °C and cooled to 0 °C. Water (0.015 mol) was added, and the mixture was kept for ~10 h at −20 °C. Triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was chromatographed on silica gel (eluent hexane—ethyl acetate, 1 : 1). The solvent was removed to give the residue, which soon crystallized. Phosphite **1a** can be recrystallized from hexane or acetonitrile at −10 °C. Yield: 75%, m.p. 182 °C (acetonitrile), $[\alpha]_D^{20}$ −24.5° (*c* 1.5, ethyl acetate). Found (%): P, 8.35. $C_{20}H_{35}O_3P$. Calculated (%): P, 8.74. ^{31}P NMR ($CDCl_3$), δ: 7.6 (dt, $^1J_{H,P}$ = 689 Hz, $^3J_{H,P}$ = 8.1 Hz).

Di-[(−)-(1*R*,2*S*,5*R*)-menth-2-yl] phosphite (1c). ***Method A.*** A solution of 1.35 g (0.01 mol) of PCl_3 in 25 mL of diethyl ether was added dropwise to a solution of 3.1 g (0.02 mol) of (−)-(1*R*,2*S*,5*R*)-menthol and 4 mL of Et_3N in 25 mL of diethyl ether with stirring and cooling to −20 °C. Then the reaction mixture was stirred for 2 h at −20 °C and cooled to 0 °C. Water (0.015 mol) was added, and the mixture was kept for ~10 h at −20 °C. Triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was distilled *in vacuo*. Yield: 80%, m.p. 130—132 °C (0.02 Torr). Dimenthyl phosphite obtained by this procedure can be used for further syntheses without vacuum distillation.

Method B. A solution of 1.35 g (0.01 mol) of PCl_3 in 25 mL of diethyl ether was added dropwise to a solution of 3.1 g (0.02 mol) of (−)-(1*R*,2*S*,5*R*)-menthol and 4 mL of Et_3N in 25 mL of diethyl ether with stirring and cooling to −20 °C, and the reaction mixture was stirred for 2 h at −20 °C. Triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was distilled *in vacuo* to give (1*R*,2*S*,5*R*)-dimenthyl phosphorochloridite **3c**, yield 80%, m.p. 125 °C (0.02 Torr). ^{31}P NMR ($CDCl_3$), δ: 145 (t, $^3J_{P,H}$ = 10 Hz). Found (%): Cl, 7.81. $C_{20}H_{38}ClO_2P$. Calculated (%): Cl, 7.62.

A solution of 0.3 mL (0.017 mol) of water in 2 mL of Et_3N was added dropwise to a solution of 3.7 g (0.01 mol) of (1*R*,2*S*,5*R*)-dimenthyl phosphorochloridite **3c** with stirring and cooling to 0 °C. The mixture was stirred for 2 h at −20 °C and kept for ~10 h. Triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was distilled *in vacuo*. Yield: 80%, m.p. 130—132 °C (0.02 Torr), $[\alpha]_D^{20}$ −73.6° (*c* 2.0, toluene). Found (%): P, 8.29. $C_{20}H_{39}O_3P$. Calculated (%): P, 8.64. ^1H NMR ($CDCl_3$), δ: 0.7 (d, 6 H, 2 CH_3, $J_{H,H}$ = 7.0 Hz); 0.9 (d, 12 H, 4 CH_3, $J_{H,H}$ = 7.0 Hz); 1.1—2.3 (m, 18 H, CH_2 + CH); 4.2 (m, 2 H, 2 OCH); 7.17 (d, 1 H, P—H, $^1J_{H,P}$ = 700 Hz). ^{31}P NMR ($CDCl_3$), δ: 5.12 (dt, $^1J_{P,H}$ = 700 Hz, $^3J_{P,H}$ = 8.1 Hz).

Tris(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) phosphite (2b). A solution of 2.74 g (0.02 mol) of PCl_3 in 30 mL of toluene was added dropwise to a solution of 14.4 g (0.06 mol) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 10 mL of Et_3N in 50 mL of toluene with stirring and cooling to −20 °C. The reaction mixture was stirred for 2 h at −20 °C. Triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was chromatographed on silica gel (eluent ethyl acetate—hexane, 1 : 1) using TLC control (Silufol), R_f 0.61. Yield: 80%. Viscous colorless liquid. Found (%): P, 3.70. $C_{36}H_{57}O_{18}P$. Calculated (%): P, 3.83. ^{31}P NMR ($CDCl_3$), δ: 144.5 (q, $^3J_{P,H}$ = 10 Hz). MS (chemical ionization, NH_3): *m/z* 809 [M^+ + 1].

Tri[(1*R*,2*S*,5*R*)-menth-2-yl] phosphite (2c). A solution of 9.4 g (0.06 mol) of (−)-menthol and 10 mL of Et_3N in 50 mL of toluene was added dropwise to a solution of 2.74 g (0.02 mol) of PCl_3 in 30 mL of toluene with stirring and cooling to −20 °C, and the reaction mixture was stirred for 2 h at −20 °C. Triethylamine hydrochloride was filtered off, and the solvent was evaporated. The residue was spectroscopically pure trimenthyl phosphite, which was used in the synthesis of (−)-dimenthyl (α-hydroxybenzyl)phosphonate (**4c**) without additional purification. ^{31}P NMR ($CDCl_3$), δ: 148.0 (q, $^3J_{P,H}$ = 8.0 Hz). MS (chemical ionization, NH_3): *m/z* 497 [M^+ + 1].

(−)-Di[(1*R*,2*S*,5*R*)-menth-2-yl] (α-hydroxybenzyl)phosphonate (4c). ***Method A.*** Benzaldehyde (1.1 g, 0.10 mol) and DBU (two drops) were added to dimenthyl phosphite **1c** (3.5 g, 0.01 mol) at 0 °C. The mixture was kept for 6 h at 0 °C and for ~10 h at −20 °C. The ^{31}P NMR spectrum showed the presence of only two signals at δ_P 20.36 and 20.08 in a ratio of 2 : 1. Crystallization from acetonitrile or hexane gave the stereochemically pure diastereomer. Yield: 55%, m.p. 139 °C, $[\alpha]_D^{20}$ −88.9° (*c* 1.0, toluene).

Method B. Benzaldehyde (0.55 g, 0.005 mol) and 1.5 mL of trimethylchlorosilane were added to trimenthyl phosphite **2c** (2.5 g, 0.005 mol) at 0 °C. The mixture was kept for 1 h at 0 °C, then the temperature was gradually increased to ~20 °C, and the mixture was kept for 1—2 h. The ^{31}P NMR spectrum showed the presence of only two signals at δ_P 20.36 and 20.08 in a ratio of 3 : 1. The volatile substances were removed *in vacuo*, and the residue was passed through silica gel (eluent ethyl acetate—hexane, 1 : 1). The solvent was removed *in vacuo*, and the residue was crystallized from hexane with cooling. Yield: 60%, m.p. 139 °C, $[\alpha]_D^{20}$ −88.9° (*c* 1.0, toluene). Found (%): P, 6.55. $C_{27}H_{45}O_4P$. Calculated (%): P, 6.67. ^{1}H NMR ($CDCl_3$), δ: 0.7—1.0 (m, 18 H, 6 CH_3); 1.1—1.2 (m, 18 H, CH_2 + CH); 3.7 (br, 1 H, OH); 4.2 (dt, 2 H, 2 OCH, $J_{H,H}$ = 2.3 Hz, $J_{H,H}$ = 4.1 Hz); 4.92 (d, 1 H, CHP, $J_{H,P}$ = 11 Hz); 7.2—7.5 (m, 5 H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 127.99 and 127.8 (both d, $J_{C,P}$ = 2.5 Hz); 127.3 (d, C_6H_5, $J_{C,P}$ = 9.6 Hz); 71.6 (d, PC, $J_{C,P}$ = 160 Hz); 48.6 (d, CHO[a], $J_{C,P}$ = 14 Hz); 48.5 (d, CHO[b], $J_{C,P}$ = 13.2 Hz); 45.66, 42.53, 34, 31.5, 25.31, 22.7, 21.97, 21.13, 21.03, 15.74, 15.60 (all s, diastereomer methyl groups). ^{31}P NMR ($CDCl_3$), δ: 23.71. MS (EI, 70 eV): *m/z* 464 [M$^+$].

1-Hydroxyphosphonates **4a,b,d—f** were synthesized from phosphites **1a—c** in the same way. The yields, diastereomer ratios, melting points, optical rotations, and ^{31}P NMR data for compounds **4a,b,d—f** are given in Table 1.

(R)*-(+)-α-Hydroxybenzylphosphonic acid (5).** ***Method A. Hydrochloric acid (6 *M*, 3 mL) was added to a solution of 1 g of dimenthyl (α-hydroxybenzyl)phosphonate **4c** in 3 mL of dioxane, and the reaction mixture was kept for 3—4 days at 80 °C. Hydrolysis was monitored by ^{31}P NMR. When the reaction was complete, the solvent was evaporated, the residue was dissolved in EtOH, and an excess of cyclohexylamine (~0.8 g) was added. The precipitated crystals of cyclohexylammonium salt of acid **5** were filtered off. Yield: 70%, m.p. 226 °C, $[\alpha]_D^{20}$ +14° (*c* 1.0, 50% aqueous MeOH), which points to the *R*-configuration of acid 5. (*S*)-(−)-α-Hydroxybenzylphosphonic acid cyclohexylammonium salt was described earlier.[18]

Method B. Benzaldehyde (0.55 g, 0.005 mol) and 1.5 mL of trimethylchlorosilane were added to tris(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) phosphite **2b** (2.8 g, 0.005 mol) at 0 °C. The temperature was gradually increased to ~20 °C, and the mixture was kept for 1—2 h. The ^{31}P NMR spectrum shows the presence of only two signals of bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) (α-hydroxybenzyl)phosphonate (**4b**) at δ_P 23.02 and 22.86 in a ratio of 10 : 1. The volatile products were removed *in vacuo*, and the residue was passed through silica gel (eluent ethyl acetate—hexane, 1 : 1). The solvent was removed *in vacuo*, and the residue was hydrolyzed with hydrochloric acid in dioxane as described in the previous experiment. The yield of α-hydroxybenzylphosphonic acid was 60%.

Di[(1*S*)-*endo*]bornyl [(−)-(*R*)-α-(benzylamino)benzyl]phosphonate (7a). *N*-Benzylbenzylideneamine (1.8 g, 0.01 mol) was added to dibornyl phosphite **1a** (3.5 g, 0.01 mol) at 0 °C, and the reaction mixture was kept for 24 h at 80 °C. The ^{31}P NMR spectrum showed the presence of two signals at δ_P 24.0 and 23.81 in a ratio of 3 : 1. Then the reaction mixture was passed through a short column with silica gel (eluent hexane—ethyl acetate, 2 : 1, 300 mL; then 1 : 1). The solvent was removed *in vacuo*, and the crystalline residue was recrystallized from acetonitrile or hexane to give the stereochemically pure diastereomer. Yield: 60%, m.p. 144 °C, $[\alpha]_D^{20}$ −47° (*c* 1.0, toluene). Found (%): P, 5.31. $C_{35}H_{50}NO_3P$. Calculated (%): P, 5.49. ^{1}H NMR ($CDCl_3$), δ: 0.5 (s, 3 H, CH_3); 0.73, 0.75, 0.79, 0.82 (all s, 12 H, 4 CH_3); 1.0—1.8 (m, 16 H, CH_2 + CH); 3.5 (d, 1 H, PhCH[a], $J_{H,H}$ = 13.3 Hz); 3.8 (d, 1 H, PhCH[b], $J_{H,H}$ = 13.3 Hz); 3.95 (d, 1 H, CHP, $J_{H,P}$ = 20.8 Hz); 4.52 (dt, 1 H, NH, $J_{H,P}$ = 26.8 Hz, $J_{H,H}$ = 7 Hz); 7.2—7.4 (m, 10 H, 2 C_6H_5). ^{31}P NMR ($CDCl_3$), δ: 24.0.

Di(1*R*,2*S*,5*R*)-menth-2-yl [(−)-(*S*)-α-(benzylamino)benzyl]phosphonate (7b). *N*-Benzylbenzylideneamine (1.8 g, 0.01 mol) was added to di[(1*R*,2*S*,5*R*)-menth-2-yl] phosphite **1c** (3.5 g, 0.01 mol) at 0 °C, and the reaction mixture was kept for 12 h at 60—80 °C. The ^{31}P NMR spectrum showed the presence of two signals at δ_P 21.91 and 21.67 in a ratio of 2 : 1. Then the reaction mixture was passed through a short column with silica gel (eluent hexane—ethyl acetate 2 : 1 (300 mL) and then 1 : 1). The solvent was removed *in vacuo*, and the crystalline residue was recrystallized from acetonitrile or hexane to give the stereochemically pure diastereomer. Yield: 60%, m.p. 86—87 °C, $[\alpha]_D^{20}$ −57.9° (*c* 1.0, toluene). Found (%): P, 5.32. $C_{34}H_{52}NO_3P$. Calculated (%): P, 5.59. ^{1}H NMR ($CDCl_3$), δ: 0.5 (s, CH_3); 0.6—0.95 (m, 18 H, 6 CH_3); 1.1—2.2 (m, 16 H, CH_2 + CH); 3.55 (d, PhCH[a], $J_{H,H}$ = 13 Hz); 3.75 (d, PhCH[b], $J_{H,H}$ = 13 Hz); 3.98 (d, 1 H, CHP, $J_{H,P}$ = 20.6 Hz); 4.43 (m, 1 H, NH); 7.2—7.4 (m, 10 H, C_6H_5). ^{31}P NMR ($CDCl_3$), δ: 21.95.

Di(1*R*,2*S*,5*R*)-menth-2-yl [1(*R*)-phenyl-(1(*R*)-phenylethylamino)methyl]phosphonate (7c). Benzaldehyde (1.1 g, 0.01 mol) and optically pure (+)-(*R*)-α-methylbenzylamine (1.1 g, 0.01 mol) were added to di[(1*R*,2*S*,5*R*)-menth-2-yl] phosphite **1c** (3.5 g, 0.01 mol) at 0 °C, and the reaction mixture was kept for 24 h at ~20 °C. The ^{31}P NMR spectrum showed the presence of two signals at δ_P 23.30 and 23.03 in a ratio of 10 : 1. The stereochemically pure diastereomer was obtained by crystallization from hexane. Yield: 75%, m.p. 132.5 °C, $[\alpha]_D^{20}$ −88.9° (*c* 1.0, toluene). Found (%): P, 5.34. $C_{35}H_{54}NO_3P$. Calculated (%): P, 5.45. ^{1}H NMR ($CDCl_3$), δ: 0.50 (m, CH_3); 0.75—1.05 (m, 18 H, menthyl CH_3); 1.28 (d, 3 H, C<u>H</u>$_3$CH, $J_{H,H}$ = 6.5 Hz); 1.00—2.00 (m, 16 H, CH_2 + CH); 3.82 (q, 1 H, C<u>H</u>CH$_3$, $J_{H,H}$ = 6.4 Hz); 4.20 (d, 1 H, CHP, $J_{H,H}$ = 16.7 Hz); 4.30 (m, 1 H, NH); 7.25 (m, 10 H, C_6H_5). ^{31}P NMR ($CDCl_3$), δ: 23.30. MS (EI, 70 eV): *m/z* 568 [M$^+$].

O. I. Kolodiazhnyi is grateful to the German Research Council (DFG) and the State Foundation for Basic Research of Ukraine (DFFD) for financial support.

References

1. D. Valentine, Jr., *Asymmetric Synthesis*, Eds. J. D. Morrison and J. W. Scott, Academic Press, Orlando—San Diego—New York, 1984, **4**, p. 267.
2. O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 1998, 1279.
3. M. I. Kabachnik and T. A. Medved', *Dokl. AN SSSR*, 1952, **83**, 689 [*Dokl. Chem.*, 1952 (Engl. Transl.)].
4. K. V. Vatsuro and G. L. Mishchenko, *Imennye reaktsii v organicheskoi khimii* [*Named Reactions in Organic Chemistry*], Khimiya, Moscow, 1976, p. 196 (in Russian).
5. V. J. Blazis, K. J. Koeller, and S. D. Spilling, *Tetrahedron: Asymmetry*, 1994, 499.
6. P. Rath and C. D. Spilling, *Tetrahedron Lett.*, 1994, **35**, 227.
7. V. Sum and T. P. Kee, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1778.
8. D. V. Patel and D. E. Rielly-Gauvin, *Tetrahedron Lett.*, 1990, **31**, 5587.

9. S. E. Denmark, N. Chatani, and S. V. Pansare, *Tetrahedron*, 1992, **48**, 2191.
10. J. A. Sikorski, M. J. Miller, D. S. Braccolino, D. G. Cleary, S. D. Corey, J. L. Font, K. J. Gruis, C. Y. Han, K. C. Lin, P. D. Pansegrau, J. E. Ream, D. Schnur, A. Shah, and M. C. Walker, *Phosphorus, Sulfur, and Silicon*, 1993, **76**, 115.
11. B. Stowasser, K.-H. Budt, L. Jian-Qi, A. Peyman, and D. Ruppert, *Tetrahedron Lett.*, 1992, **33**, 6625.
12. L. Maier, *Phosphorus, Sulfur, and Silicon*, 1993, **76**, 119.
13. F. Hammerschmidt and H. Vollenkle, *Liebigs Ann. Chem.*, 1989, 577.
14. T. Yokomatsu and S. Shibuia, *Tetrahedron Asymmetry*, 1992, **3**, 377.
15. T. Kametani, K. Kigasawa, and M. Hiragi, *Heterocycles*, 1981, **16**, 1205.
16. B. L. Feringa, A. Smaaedijk, and H. Wynberg, *J. Am. Chem. Soc.*, 1985, **107**, 4798.
17. M. Gulea-Purcarescu, E. About-Jaudet, and N. Collignon, *Tetrahedron Lett.*, 1995, **36**, 6635.
18. V. J. Blazis, K. J. Koeller, and S. D. Spilling, *J. Org. Chem.*, 1995, **60**, 931.
19. S. E. Denmark, N. Chatani, and S. V. Pansare, *Tetrahedron*, 1992, **48**, 2191.
20. O. I. Kolodiazhnyi, E. V. Grishkun, S. Sheiko, O. Demchuk, H. Thoennessen, P. Jones, and R. Schmutzler, *Tetrahedron Asymmetry*, 1998, 1645.

Received March 10, 1997;
in revised form March 1, 1993