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TETRAHEDRON: *ASYMMETRY*

Chiral symmetric phosphoric acid esters as sources of optically active organophosphorus compounds

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Abstract

Chiral symmetric di- and trialkylphosphites, derivatives of (−)-borneol, (−)-menthol and (−)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, were studied as starting reagents for the preparation of chiral organophosphorus compounds. The reaction occurs by asymmetric induction at the α-carbon atom of substituted α-alkylphosphonates. The stereoselectivity of the reaction depends on the structure of the starting compounds and the reaction conditions. The configuration of the alkylphosphonates was established by NMR spectroscopy, by transformation into α-hydroxyalkylphosphonic acids and by X-ray crystal structure analysis.

The past decade has witnessed high activity in the area of the asymmetric synthesis of organophosphorus compounds.[1] As a result of the intensive studies, methods have been developed for the synthesis of a variety of optically active organophosphorus compounds. Nevertheless, further investigations in this area are desirable.

In this paper we propose chiral C_2-symmetric dialkylphosphites (tricoordinated tautomeric form) and C_3-symmetric trialkylphosphites bearing chiral secondary alkoxy groups, as chiral non-racemic starting compounds for the asymmetric synthesis of organophosphorus compounds. The symmetry reduces the number of possible diastereomers, in particular the center of asymmetry on the phosphorus atom. We studied the chiral symmetric phosphites under the conditions of the Kabachnik–Fields and the Pudovik reactions, which provide optically active α-aminoalkylphosphonic and α-hydroxyalkylphosphonic acids, possessing high biological activity.[1–4] The absolute configuration at the α-position in α-substituted phosphonic acids has been shown to be very important for biological activity,[5] which makes the asymmetric synthesis of these compounds both interesting and of practical significance.

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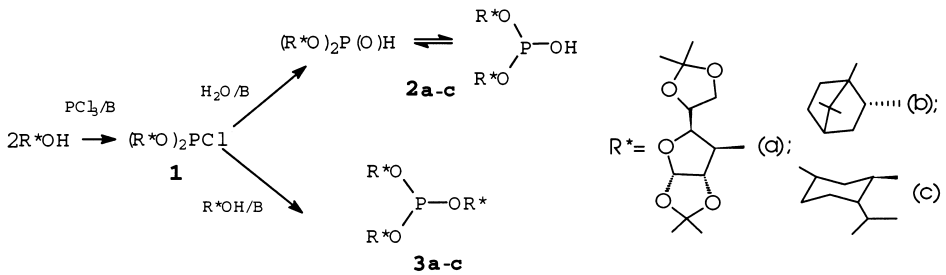
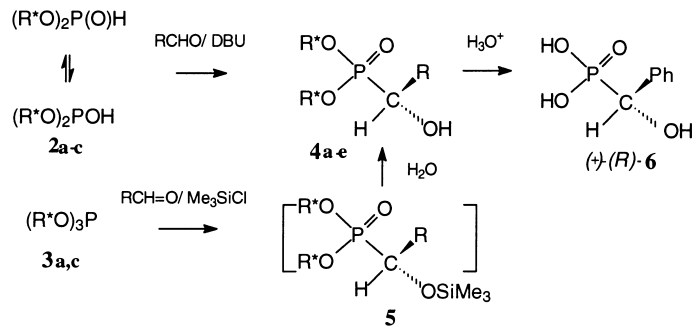
The chiral phosphites **2a**–**c**,**3a**,**c** have been synthesized by the reaction of optically active secondary alcohols **1** [(1*R*,2*S*,5*R*)-(−)-menthol, [(1*S*)-*endo*]-(−)-borneol or (−)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose] with phosphorus trichloride, in the presence of triethylamine as an acceptor of hydrogen chloride, in very good yields (Scheme 1). The phosphites **2** and **3**, obtained in a spectroscopically pure state can be used for further reactions without special purification. Nevertheless we have additionally purified the dibornylphosphite **2a** by recrystallization from hexane, isolated the bis(glucofuranosyl)phosphite **2b** by preparative column chromatography on silica gel, and purified the dimenthylphosphite **2c** by vacuum distillation. The trivalent phosphorus compounds **3a** and **b** were purified by column chromatography under inert gas.[5]



Scheme 1.

The addition of aldehydes to dialkylphosphites **2** (the Pudovik reaction) proceeds only in the presence of strong bases, such as DBU. In the presence of weaker bases (triethylamine, DABCO) the reaction does not proceed or is extremely slow. Studies of the reaction mixtures by $^{31}P–\{^{1}H\}$ NMR showed high regioselectivity and good stereoselectivity of the reaction, resulting in the formation of α-hydroxyphosphonates in high yields (Scheme 2). The stereoselectivity of the reaction depends on the structures of the starting compounds and the reaction conditions. For instance, compound **4b** was obtained in 78% diastereomeric purity (Fig. 1), whereas the diastereomeric excess in the case of compound **4c** was only 55% (Table 1). Crystallization from acetonitrile or hexane allows α-hydroxyalkylphosphonates **4** to be obtained in ~98–100% stereochemical purity.



R*=diisopropyl 1,2:5,6-glucofuranosyl, R=Ph(**4a**), R*=menthyl, R=Pr-i (**4b**), R*=menthyl, R=$C_6H_4NMe_2$ (**4c**); R*=menthyl, R=Ph (**4d**)

Scheme 2.

This high level of asymmetric induction was also observed in the reaction of the C_3-symmetric triesters **3** (R*O=menthyl or 1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl) with aldehydes in the presence of trimethylchlorosilane. The reaction proceded readily at room temperature without solvent to give the silyl derivative ester **5**, which was easily hydrolysed during isolation to yield α-hydroxyalkylphosphonates (85–90%) as a mixture of diastereomers in the ratio of 12:1 (**4a**) and of 3:1

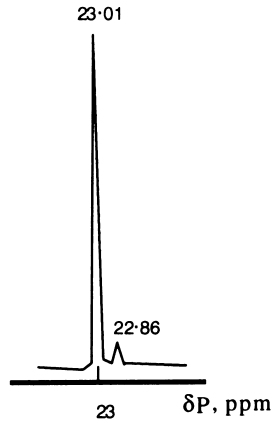


Fig. 1. ^{31}P NMR spectrum of **4b**

Table 1
Addition of symmetric phosphites **2** and **3** to aldehydes and aldimines

Compound[7]	Yield, %	*de*	mp,°C	$[\alpha]_D^{20}$ (0.1, toluene)	δ_P,ppm major/minor
4a	80	84	oil	-	22.86/23.02
4b	85	78	73.5	-91.5	20.36/20.08
4c	90	55	161	-69.2	21.17/20.60
4d	90	33	139	-88.9	20.36/20.08
7a	90	50	86-87	-69.2	21.81/21.67
7b	94	50	144	-47	24.0/23.81
7c	85	84	132.5	-88.9	23.30/23.03

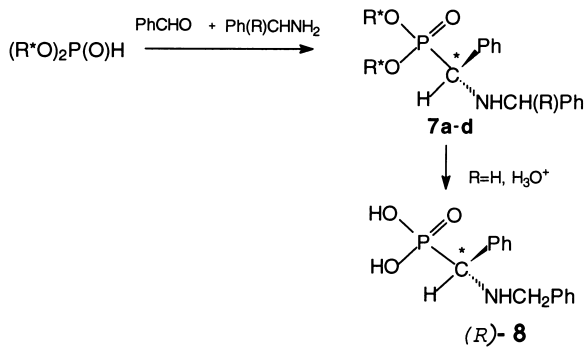
(**4d**). The α-hydroxyphosphonate **4d** was obtained in ~100% stereoisomeric purity as white crystals after one recrystallization of the diastereomeric mixture from hexane.

The diesters **4a** and **4b** are cleanly hydrolysed with aqueous HCl in dioxane to give the (*R*)-α-hydroxybenzylphosphonic acid **6**, the configuration of which has been described.[6a,b] The structure of compounds **4** was confirmed by mass spectroscopy and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy; the diastereoisomeric excesses were determined by HPLC and ^{31}P–{^{1}H} NMR spectra.[7,8]

Good stereoselectivity was also observed in the reaction of phosphites **1**–**3** with aldehydes and amines (the Kabachnik–Fields reaction; Scheme 3). The reaction proceeds at room temperature or upon heating (~60–80°C) to give α-aminophosphonic acid diesters in high yield and good stereoselectivity: de=50 (**7a**), 33 (**7b**) and 90% (**7c**). Crystallization of α-aminophosphonates from hexane furnishes the stereochemically pure species **7**. The hydrolysis of **7a**,**b** with 2 N HCl in aqueous dioxane yields the (*R*)-α-aminobenzylphosphonic acid **8**, whose absolute configuration has been described.[4b]

The absolute (*R*)-configuration of (−)-dibornyl α-(N-benzyl)aminophosphonate **7a** was confirmed by X-ray crystal analysis (Fig. 2).[7]

In conclusion, we have shown that the readily and cheaply available phosphites $(R^*O)_2PHO$ and $(R^*O)_3P$ are efficient starting compounds for the asymmetric synthesis of organophosphorus compounds, including the preparation of enantiomerically pure α-hydroxy- and α-aminoalkylphosphonous acid derivatives on a multigram scale. Detailed studies of this reaction and other reactions of chiral symmetric phosphites are currently underway and will be reported in due course.



R*=(-)-bornyl, R=H (a); R*=(-)-menthyl, R=H (b); R*=(-)-menthyl, R=Me (c)

Scheme 3.

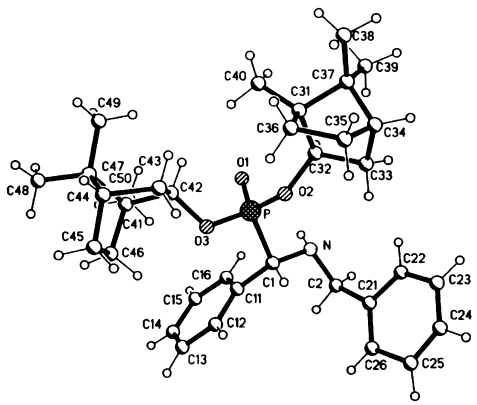


Fig. 2. The molecular structure of **7a**

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7. (a) Data for **2a**: yield 85%; purified by column chromatography (silica gel 60, hexane:ethyl acetate, 1:1); R_f 0.38; ^{31}P NMR (δ, ppm, $CDCl_3$): 8.34, d, *J* 725 Hz; MS m/z 567 (M^+); $[\alpha]_D$ −13.5 (c 0.02, toluene). Data for **2b**: yield 75%; ^{31}P NMR (δ, ppm, $CDCl_3$): 7.6 (dt, $^1J_{HP}$ 689 Hz, $^3J_{HP}$ 81 Hz); $[\alpha]_D$ −24.5 (c 0.15, ethyl acetate). The preparations of compounds **2**–**7** will be described in detail: Kolodiazhnyi O. I., Grishkun E. V., Sheiko S., Demchuk O., Thoennessen H., Jones P., Schmutzler R. *Russ. Chem. Bull.*, in press.
8. The NMR spectra were recorded on a Varian VXR-300MHz spectrometer. HPLC analyses were performed on a Milichrom-1A (Russia) Silasorb DEA column. Commercially available chiral alcohols (1*R*,2*S*,5*R*)-(−)-menthol, [(1*S*)-*endo*]-(−)-borneol and (−)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose of 98% enantiomeric purity were used in this work.