

S0957-4166(96)00093-6

Simple Route to Chiral Organophosphorus Compounds

Oleg I. Kolodiazhnyi*, Evgen V. Grishkun

Institute of Bioorganic Chemistry, National Academy of Sciences of Ukraine,
Murmanskaya Street, 1, KIEV, 253094, UKRAINE

Abstract: Reaction of chlorides of nonsymmetrically substituted phosphinic and phosphinous acid with (-)-1,2:3,5-disubstituted- α -D-glucofuranose proceeds with very high stereoselectivity to give stereochemically pure phosphinic and phosphinous acid esters, which are starting reagents for preparation of chiral organophosphorus compounds. Stereoselectivity of the reaction depends on the nature of bases, solvent, temperature and excess of chlorophosphine. Copyright © 1996 Elsevier Science Ltd

Chiral phosphinic acid esters are versatile starting compounds for the synthesis of various stereochemically pure organophosphorus compounds, because the ester group at the tervalent phosphorus atom may be easily substituted by alkyl or aryl by reaction with various types of organometallics. However the enantiomerically pure phosphinites are hardly accessible. There are only multistage methods for their synthesis, including chromatographic separations and fractional crystallizations.¹⁻³

In this communication we propose new, simple and efficient routes to optically pure phosphinic acid esters, using derivatives of the naturally occurring *D*-glucofuranose as inducers of chirality. The phosphorylation of various carbohydrates, including *D*-glucofuranose derivatives, is well studied. However literature data show that these reactions proceed with low stereoselectivity.⁴ To our knowledge, our work is the first report proposing *D*-glucofuranose derivatives as chiral auxiliaries for preparation of enantiomerically pure tervalent phosphorus compounds.^{1,2}

We found that the reaction between racemic chlorophosphines **1-3** and (-)-1,2:5,6-diisopropylidene-*D*-glucofuranose **4** or (-)-1,2:5,6-dicyclohexylidene-*D*-glucofuranose **5** in the presence of tertiary bases depends strongly on the reaction conditions: nature of the base, solvent, temperature and excess of chlorophosphine. Under certain conditions this reaction proceeds with very high stereoselectivity to give enantiomerically pure phosphinites **6-8** (Table 1). Thus, the addition of chlorophosphines **1-3** to a solution of (-)-1,2:5,6-diisopropylidene-*D*-glucofuranose **4** in toluene as a solvent at -20^o - +20^o C in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) in good yields furnishes the optically active levorotatory (*S_p*)-phosphinites **6-8** (entries 1-4, Table 1).⁵⁻⁷ HPLC and ³¹P-¹H NMR analyses of the crude reaction mixtures show that the stereochemical purity of the phosphinites **6-8** is 96-100%, the chemical yields ~70%.⁵ Good stereoselectivity of the reaction was also obtained in the presence of triethylamine in toluene (entries 5-7) and in diethyl ether (entries 8,9). On

the contrary, in the presence of the dimethylaniline the d.e. is ~0% (entry 10). Surprisingly, in the presence of pyridine as the base the minor diastereomer of **8** becomes major (entry 11). Consequently, depending the nature of the base the first or the second diastereomer of phosphinites **6-8** may be predominantly obtained

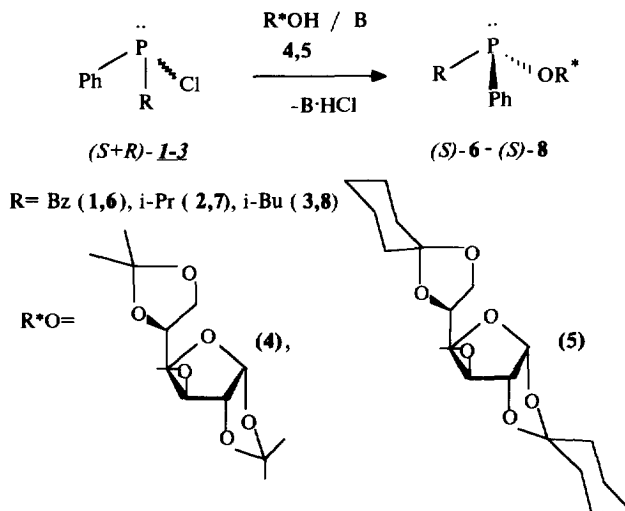
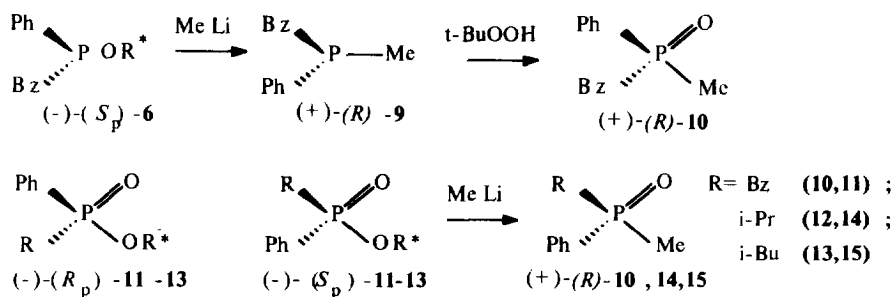


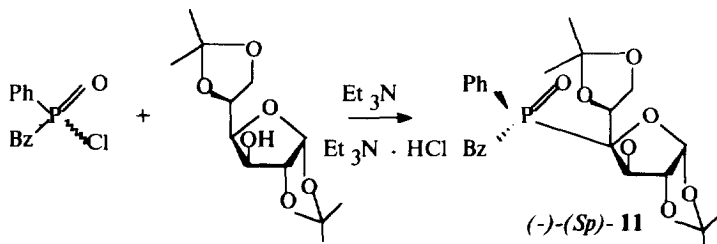
Table 1. Reaction of Chlorophosphines **1-3** with (-)-1,2:5,6-diisopropylidene- α -D-glucofuranose **4**, or (-)-1,2:5,6-dicyclohexylidene-D-glucofuranose **5** in the Presence of tertiary Bases

Entry	R(R')	HOR*	Base	Ratio of Alcohol: Chloro-phosphine	Solvent/Temp., °C	Ratio of (S _p):(R _p) 6-8
1	Bz(Ph)	4	DABCO	1:1	Toluene/-20-+20°	~100:0
2	i-Pr(Ph)	4	DABCO	1:1	Toluene/-20-+20°	~100:0
3	i-Bu(Ph)	4	DABCO	1:1	Toluene/-20-+20°	~96:4
4	i-Bu(Ph)	5	DABCO	1:1	Toluene/-20-+20°	92:8
5	Bz(Ph)	4	Et ₃ N	1:1	Toluene/-20-+20°	~98:2
6	i-Pr(Ph)	4	Et ₃ N	1:1	Toluene/-20-+20°	~100:0
7	i-Bu(Ph)	4	Et ₃ N	1:1	Toluene/-20-+20°	~98:2
8	i-Bu(Ph)	4	Et ₃ N	1:1	Ether/+20°	85:15
9	i-Bu(Ph)	4	Et ₃ N	1:2	Ether/+20°	90:10
10	i-Bu(Ph)	4	PhNMe ₂	1:1	Ether/+20°	50:50
11	i-Bu(Ph)	4	Pyridine	1:1	Ether/+20°	40:60

The phosphinic acid esters **6-8** may be used as starting compounds for the synthesis of enantiomers of organophosphorus compounds, because an alkoxy group at the tervalent phosphorus atom is easily substituted by organometallic nucleophiles. Thus the reaction of phosphinite **6** with methyl lithium proceeds with substitution of the chiral glucufuranosyl group to afford optically active dextrorotatory benzyl-methyl-phenylphosphine **9** for which the (+)-(*R*) absolute configuration is known.⁷ The oxidation of **9** by *tert*-butylhydroperoxide gives (+)-(*R*) benzyl-methyl-phenylphosphine oxide **10** {mp 135°C, $[\alpha]_D^{20} +50$ corresponds to the literature data⁸}. This allows to assign the absolute configuration of the phosphinite **6**. It is well-known that the substitution of alkoxy groups in phosphinites by organolithium compounds occurs with complete inversion of configuration at the tervalent phosphorus atom.^{1,2} Consequently the configuration at the phosphorus atom in the phosphinite **6** is *S*. The oxidation of enantiomerically pure (*S*_p)-phosphinites **6-8** by the *tert*-butylhydroperoxide or by oxygen of the air leads to the formation of the stereochemically pure (*S*_p)-phosphinates **11-13**, which were purified by crystallization in hexane. The (*R*_p) diastereomers of phosphinate **11-13** were obtained by oxidation of the (*R*_p)-phosphinites **6-8** and isolated by column chromatography.^{4,5} The reaction of the (*S*_p) and (*R*_p)-phosphinates **11-13** with the methyl lithium provides (*R*) and (*S*) epimers of tertiary alkyl-methyl-phenylphosphine oxides **10,14,15**⁷



Despite the great difference in the properties of tervalent and pentavalent phosphorus compounds, we found that chloride of benzyl-phenylphosphinous acid reacts stereoselectively with the derivatives of *D*-glucofuranose to provide the enantiomerically pure levorotatory (-)-(*S*_p)-phosphinate **11** in 80% chemical yield and ~100% d.e. The stereochemical purity of **11** was determined by ¹H and ³¹P NMR spectra (the only signal at δ_p 42 ppm is present) and HPLC of the reaction mixture



So, the methodology described in this communication is convenient for the preparation of chiral phosphinites, which are starting reagents for the further transformations into various enantiomerically pure organophosphorus compounds.

Acknowledgements: Financial support for this work from International Science Foundation is gratefully acknowledged (Grant Number U6L000).

References and notes

1. a) Valentine, D., Jr. *Asymmetric Synthesis*. Morrison, J. D. and Scott, J.W. Ed. Academic Press: Orlando, San Diego, New York, 1984: Vol. 4. pp. 267-312;
2. Pietrusiewicz, K.M.; Zablocka, M. *Chem.Rev.* **1994**, *84*, 1375-1411.
3. Farnham, W.B.; Murray, R.K.; Mislow, K. *J.Am.Chem.Soc.* **1970**, *98*, 5809-5810.
4. Nifanti'ev, E.; Gratshev, M.K.; Vasianin, L.K. *Zh.Obshch.Khim.*, **1993**, *63*, 575-580.
5. Kolodiazhnyi, O.I.; Grishkun, E.V.; Golovatyi, O.R.; Ustenko, S.N; *XIIIth International Conference on Phosphorus Chemistry*. Jerusalem. Israel, July 16-21, 1995. Plenary lecture, will be published in *Phosphorus, Sulfur, and Silicon*.
6. -(S_P)-**6**: Yield 75%. δ_P (C₆D₆) 124.2 ppm, [α]_D²⁰ -154 (c=0.1, toluene).^{7,9,10}
-(S_P)-**7**. Yield 75%. δ_P (C₆D₆) 129.1 ppm, [α]_D²⁰ -106 (c=0.05, toluene)
(S_P)-**11**. Yield 80%, mp 175°C (heptane), δ_P (C₆D₆) 42.9 ppm. [α]_D²⁰ -47 (c 0.02, acetone)
(S_P)-**13**. Yield 75%, mp 91°C (hexane), δ_P (C₆D₆) 49.02. [α]_D²⁰ -80 (c 0.02, hexane).
(R_P)-**13**, purified by flash-chromatography (silica gel 60, 230-400 mesh, eluent C₆H₁₄-96:4). Yield 45%, NMR spectra (CDCl₃), δ_P: 47.98 ppm. [α]_D²⁰ -5.2 (c 0.02, hexane).
7. The compounds **6-15** will be in detail described: Kolodiazhnyi, O.I.; Grishkun, E.V. *Phosphorus, Sulfur, and Silicon*, in press.
8. Korpiun, O.; Lewis, R.A.; Chickos, J.; Mislow, K. *J.Am.Chem.Soc.*, **1968**, *90*, 4842-4846.
9. All new compounds were fully characterized by NMR (¹H and ³¹P), and elemental analysis.
10. The NMR spectra were recorded on a "Varian VXR-300" spectrometer at 300 (¹H) and 126.16 MHz (³¹P). HPLC analyses were performed on a "Milichrom-1A" (Russia), Silasorb DEA column 120x2 mm (hexane-isopropanol mixture in 95:5 ratio as eluent).

(Received in UK 1 February 1996)