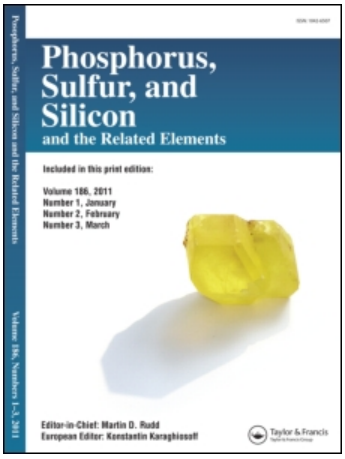

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ASYMMETRIC INDUCTION IN THE REACTION OF NONSYMMETRICAL PHOSPHINIC AND PHOSPHINOUS ACID CLORIDES WITH DERIVATIVES OF D-GLUCOFURANOSE

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ASYMMETRIC INDUCTION IN THE REACTION OF NONSYMMETRICAL PHOSPHINIC AND PHOSPHINOUS ACID CLORIDES WITH DERIVATIVES OF D-GLUCOFURANOSE

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Dedicated to Professor John G. Verkade's 60th birthday

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Reaction of nonsymmetrically substituted chlorophosphines (**1–3**) with (−)-1,2:3,5-di-O-isopropylidene-α-D-glucofuranose (**1**) or (−)-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (**5**) proceeds with high stereoselectivity to give stereochemically pure phosphinic acid esters (**6–8**), which are starting compounds for the preparation of chiral organophosphorus compounds. Reaction of benzyl-phenylphosphinous acid chloride with (**1**) leads to optically pure phosphinous acid ester (**9**). The stereochemistry of the reaction is studied in dependence on the nature of the base, solvent, temperature and excess of chlorophosphine.

Key words: Stereoselectivity, 1,2:3,5-di-O-isopropylidene-α-D-glucofuranose. (−)-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose, nonsymmetrical alkylarylchlorophosphines, chiral phosphinic acid esters, chiral phosphinous acid esters, P-chiral compounds, asymmetric synthesis.

INTRODUCTION

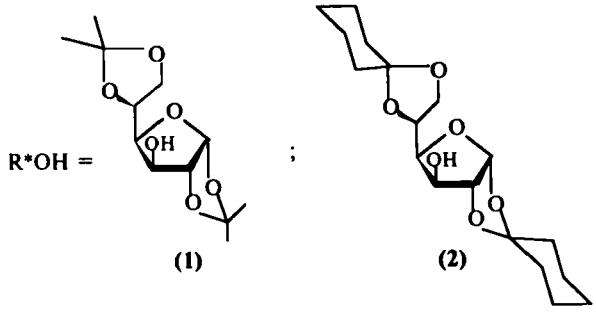
Enantiomers of chiral phosphorus compounds are of interest for several reasons.[1] Many P-chiral organophosphorus compounds exhibit interesting biological activities that may be specific to one enantiomer.[2,3] P-Chiral compounds are of practical value as ligands in catalysts for asymmetric organic syntheses.[4,5] And finally there is intrinsic interest in their preparation and in the study of their many stereoselective transformations. Nowadays, most types of optically pure organophosphorus compounds can be prepared by combining the different methods described in the literature.[1,6] Nevertheless, a simple and general protocol that permits quick access to the desired enantiomers of chiral phosphorus compounds is still greatly needed.

In this work we propose a new, simple and efficient method for the preparation of optically pure phosphorus compounds. We found that the reaction between 1,2:5,6-substituted derivatives of α-D-glucofuranose and nonsymmetrical racemic chlorides of tervalent or pentavalent phosphorus acids in the presence of tertiary bases proceeds independent of reaction conditions with high stereoselectivity to give enantiomerically pure phosphinic and phosphorous acid esters.

RESULTS AND DISCUSSION

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 can be easily substituted on the alkyl or aryl by reaction with various types of organometallics.[1,6,7] However the enantiomerically pure phosphinites are inaccessible. There are only multistage methods for their synthesis, including chromatographic separations and fractional crystallizations.[6,7] The potential route to chiral phosphinites is the reaction of nonsymmetrically substituted chlorophosphines with chiral alcohols. Unfortunately this reaction proceeds, as a rule, with low stereoselectivity to provide a mixture of diastereoisomers, which has to be separated. As an inducer of chirality in this reaction menthol was most often used.[6,7]

We propose to use derivatives of the naturally occurring D-glucofuranose (**1**, **2**) as very effective and accessible chiral auxiliaries for the chiral phosphinite preparation.

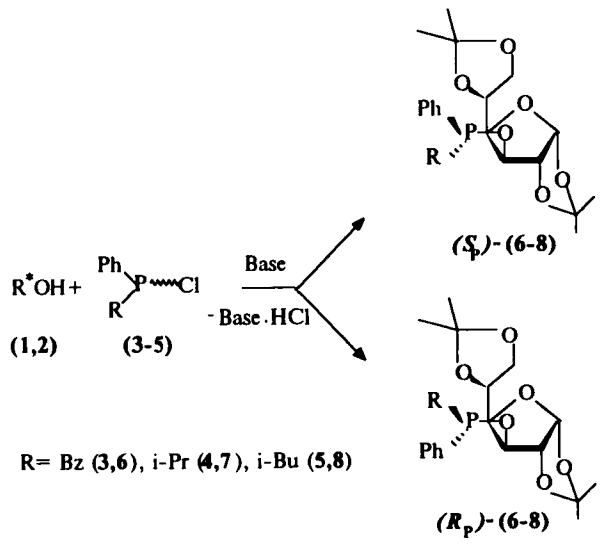


(1) (2)

These carbohydrates are very effective inducers of chirality because of extremely high asymmetry of the molecule, in which the secondary hydroxilic function is flanked by two functionalities that are very different from both a steric and a stereoelectronic point of view: OH group at C-3 is surrounded by a hydrogen at C-2 and by the D-glyceraldehyde chiral backbone at C-4.[8]

The phosphorylation of various carbohydrates, including D-glucofuranose derivatives, is studied. However literature data shows that these reactions proceed with low stereoselectivity.[9] We found that nucleophilic substitution at the tervalent phosphorus atom of nonsymmetrical alkylarylchlorophosphines (**3**–**5**) with (−)-1,2:5,6-diisopropylidene- or (−)-1,2:5,6-dicyclohexylidene-α-D-glucofuranoses (**1**, **2**) in the presence of strong tertiary bases proceeds with high asymmetric induction and may be successfully used in the preparation of chiral, optically pure phosphinic acid esters (Scheme I).

The stereoselectivity of the reaction is dependent to a great degree on the reaction conditions and in the first turn on the nature of the base and the solvent.[8,11] Thus, the addition of racemic chlorophosphines (**1**–**3**) to a solution of (−)-1,2:5,6-diisopropylidene-D-glucofuranose (**1**) in toluene at 20°C in the presence of such strong tertiary bases as 1,4-diazabicyclo[2,2,2]octane (DABCO, entries 1–4, Table I) or triethylamine (entries 6–8) in good yields furnishes the enantiomerically pure phosphinite (**6**–**8**). The stereochemical purity of (**6**–**8**) estimated by means of the $\{^{31}P-^{1}H\}$ NMR spectroscopy and HPLC is ≥98%, the chemical yield >70%. In the pres-



SCHEME I

ence of dimethylaniline in ether the ratio of diastereomers is only 50:50 (de ~ 0%, entry 12). The reaction of the chlorophosphines (**1**–**3**) with the alcohol (**1**) in dimethoxyethane in the presence of sodium hydride evidently via the formation of alcoholate, leads as well to the formation of diastereomers (**6**–**8**) in the ratio 50:50 (de ~ 0%, entry 13). Surprisingly, that in the presence of pyridine instead of DABCO as the base the minor diastereomer (**8**) becomes major (entry 14). Consequently, independent of the nature of the base, the first or the second diastereomer of phosphinites (**4**, **5**) may be predominantly obtained. To our knowledge, this is the first report, that the stereo course of formation of phosphinites depends not only on the chiral alcohol, but also on the nature of the base.

The entries 4 and 5, 8 and 10 show clearly that the stereoselectivity of the reaction depends on the solvent nature. The highest de values were obtained, when toluene was used as a solvent. Thus, the reaction of the isobutylphenylchlorophosphine (**3**) with glucofuranose (**1**) in the presence of triethylamine or DABCO provides (Sp)-phosphinite (**8**) in more than 90% de, while in ether mixtures of diastereomers (Sp)-(**8**) and (Rp)-(**8**) in the ratio 90:10 (de 80%, entry 5) and 86:14 (de 72%, entry 10) were obtained.

The stereoselectivity of the reaction depends as well on the ratio of chlorophosphine/alcohol: twofold excess of chlorophosphine (**3**) increases the diastereomeric purity of phosphinite (**8**) from de 72% up to 78% (entries 9, 10), whereas twofold excess of alcohol (**1**) decreases de to 55% (entry 11).[12]

The phosphinites (**6**–**8**) prepared are stable and can be stored for several days in the refrigerator without any decomposition or racemization. The differences in chemical shifts allow the determination of the purity of phosphinite (**6**–**8**) and the ratio of diastereomers by ^{31}P NMR analysis of the reaction mixtures (Figure 1). Large values of the optical rotation of chiral tervalent phosphorus compounds (**6**–**8**) attract attention. In the case of phosphinite (**6**) the specific optical rotation is $[\alpha]_D$ −154 (toluene).

TABLE I

Reaction of chlorophosphines (**3**–**5**) with (−)-1,2:5,6-diisopropylidene-α-D-glucofuranose (**1**), (−)-1,2:5,6-dicyclohexylidene-α-D-glucofuranose (**2**), (−)-1-diethylamino-2-propanol (**18**), (−)-L-menthol (**19**) and (−)-1-carboethoxy-2-propanol (**20**) in the presence of bases

Entry	R(R')	HOR*	Base	Ratio of Alcohol: Chloro-phosphine	Solvent/Temp.,°C	de*)
1	Bz(Ph)	**(1)**	DABCO	1:1	Toluene/-20-+20°	>98
2	i-Pr(Ph)	**(1)**	DABCO	1:1	Toluene/-20-+20°	>98
3	i-Bu(Ph)	**(1)**	DABCO	1:1	Toluene/-20-+20°	92
4	i-Bu(Ph)	**(2)**	DABCO	1:1	Toluene/-20-+20°	90
5	i-Bu(Ph)	**(1)**	DABCO	1:1	Ether/-20-+20°	80
6	Bz(Ph)	**(1)**	Et_3N	1:1	Toluene/-20-+20°	>98
7	i-Pr(Ph)	**(1)**	Et_3N	1:1	Toluene/-20-+20°	96
8	i-Bu(Ph)	**(1)**	Et_3N	1:1	Toluene/-20-+20°	90
9	i-Bu(Ph)	**(1)**	Et_3N	1:2	Ether/-20-+20°	78
10	i-Bu(Ph)	**(1)**	Et_3N	1:1	Ether/-20-+20°	72
11	i-Bu(Ph)	**(1)**	Et_3N	2:1	Ether/-20-+20°	55
12	i-Bu(Ph)	**(1)**	$PhNMe_2$	1:1	Ether/+20°	0
13	i-Bu(Ph)	**(1)**	NaH	1:1	DME/-20°	0
14	i-Bu(Ph)	**(1)**	Pyridine	1:1	Ether/+20°	-20
15	i-Bu(t-Bu)	**(18)**	Et_3N	1:2	Benzene/+20°	60
16	i-Bu(t-Bu)	**(18)**	Et_3N	1:1	Benzene/+20°	40
17	i-Bu(t-Bu)	**(18)**	Et_3N	2:1	Benzene/+20°	30
18	i-Bu(t-Bu)	**(19)**	Et_3N	1:1	Ether/+20°	40
19	i-Bu(t-Bu)	**(20)**	Et_3N	1:1	Ether/+20°	10

*) Diastereomeric excess [de=(*Sp*)-(*Rp*)] was obtained as average value of 2-4 measurements

The phosphinites (**6**–**8**) may be used as chiral starting reagents for the preparation of enantiomerically pure organophosphorus compounds. Thus, the oxidation of enantiomerically pure (Sp)—phosphinites (**6**–**8**) by *tert*-butylhydroperoxide or by oxygen of the air leads to the formation of enantiomerically pure (Sp)-phosphinates (**10**–**12**) with retention of optical purity and in high yields. The phosphinates (**10**–**12**) were purified by crystallization in hexane. The (Rp)-diastereomer of phosphinates were prepared by oxidation of the (Rp)-diastereomer of phosphinites (**6**–**8**) and isolated by column chromatography. The phosphinites (**6**–**8**) add the sulfur to result in optically active thiophosphinates (**12**–**14**). The reaction of the phosphinites (**6**–**8**) with organolithium compounds proceeds with abstraction of the chiral glucofuranosyl group to afford optically active tertiary phosphines. In the case of the reaction of phosphinite (**6**) with methyllithium dextrorotatory phenyl-benzyl-methylphosphine (**15**) was obtained, (+)-(R) configuration of which is described.[10] This allows the

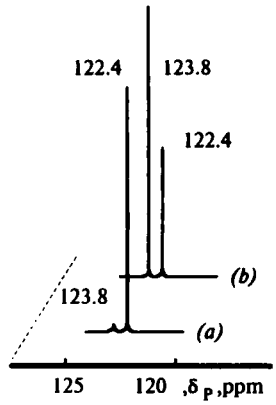
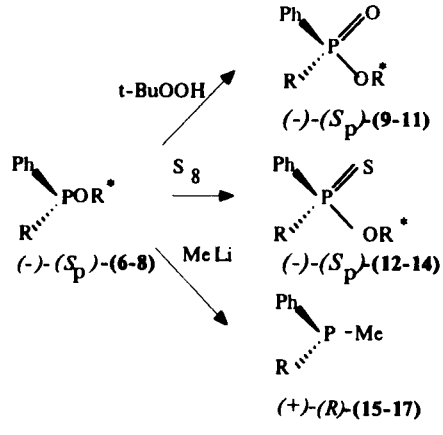


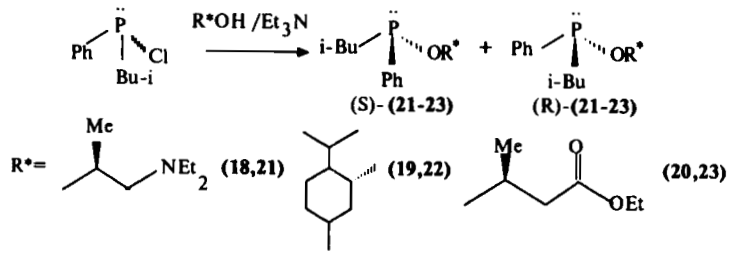
FIGURE 1 The reaction of chlorophosphine (3) with the alcohol (1) in the presence of DABCO (entry 4, Table I) (a) or pyridine (entry 14) (b).



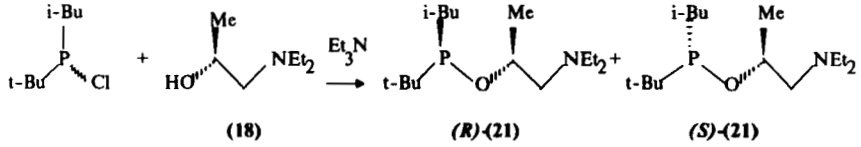
SCHEME II

definition of the configuration at the phosphorus atom of the phosphinite (**6**). It is well-known that the substitution of ester groups in phosphinites by organolithium compounds occurs with inversion of configuration at the tervalent phosphorus atom. Consequently the configuration at the phosphorus atom in the phosphinite (**6**) is (S).[12]

We compared also the behaviour of some other secondary chiral alcohols [(−)-1-diethylamino-2-propanol (**18**), (−)-L-menthol (**19**) and (−)-1-carboethoxy-2-propanol (**20**)] with that of D-glucofuranose derivatives (**1**, **2**) under the same conditions.[13] The results summarized in Table I (entries 15–19) show that the stereoselectivity of the reaction in these cases is far lower, than in case of D-glucofuranose derivatives, though the influence of reaction conditions is the same. Evidently, D-glucofuranose derivatives (**1**, **2**) are the most effective chiral auxiliaries in the secondary alcohols range for the preparation of stereochemically pure phosphinites.

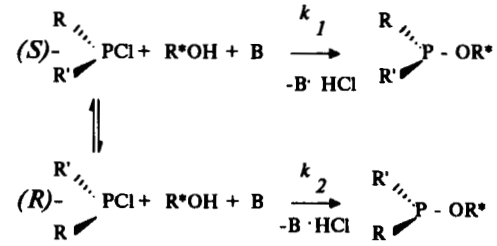


In the case of 1-diethylamino-2-propanol (**18**) we had additional opportunity to study more detailed the influence of chlorophosphine excess on the reaction. This secondary alcohol is more convenient for this purpose, than the D-glucofuranose derivatives, reacting with chlorophosphines in too high stereochemical yields (Table I).



The reaction of *tert*-butyl-isobutylchlorophosphine (**3**) with the alcohol (**18**) at 2:1 ratio of chlorophosphine-alcohol in benzene furnishes 6.5:1.5 (de 60%) mixture of two diastereomers (R)-(**21**) and (S)-(**21**) (δ_P 138 and 135.8 ppm). At that time the diastereomeric excess decreases until 40 and 30%, when the 1:1 and 1:2 ratios of initial reagents are used. The stereocourse of the reaction was monitored by ^{31}P NMR spectroscopy and high-resolution gas-liquid chromatography, the values of de were determined from 2–4 measurements. The phosphinite (**21**) was isolated by vacuum distillation and its (S)- and (R)-diastereomers were separated by flash-chromatography. These compounds are configurationally stable at room temperature, colorless liquids. However they are easily oxidized by oxygen of the air.

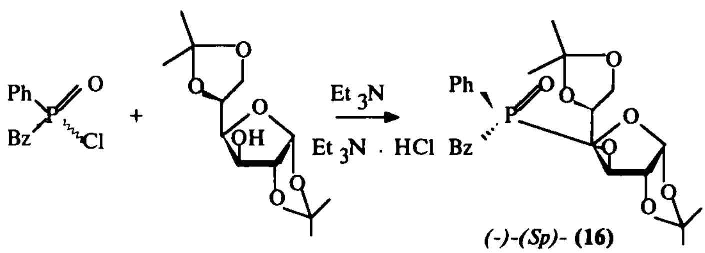
The dependence of the stereocourse of the reaction on the starting chlorophosphine excess show evidently that the reaction is kinetically controlled. We suppose that secondary alcohols react with (S)- and (R)-chlorophosphine epimers in the presence of bases with different rates ($k_1 > k_2$) to convert into phosphinites. It is well-known that chlorophosphines are configurationally unstable and exist as an equilibrium mixture of the (R)- and (S)-forms, because of low pyramidal inversion barrier.[1,14] The reported attempts at synthesizing stable optically active halogenophosphines were



SCHEME III

unsuccessful.[14,15] For example, (+)-(S)-*t*-Bu(Ph)PCl easily lost its optical activity in the polarimeter cell even at −70°C.[15] In our case the excess of chlorophosphine contains more of the enantiomer, which the most easily reacts with 1,2:3,5-diisopropylidene-D-glucofuranose, that provides the most highest yields of one of the two possible phosphinite's epimers. Owing to the (S) ⇌ (R)-chlorophosphine equilibrium the chemical yields of enantiopure phosphinites are more than 50% (usually 70–80%) and the reaction comes to an end.

We found that not only chlorides of phosphinic acids, but also chlorides of phosphonous acids, in particular chloride of benzyl-phenylchlorophosphonous acid, react stereoselectively with the derivatives of D-glucofuranose. The reaction proceeds in the ratio 1:1 to give the enantiomerically pure levorotatory (−)-(Sp)-phosphinate (**16**) in 80% chemical yield. The stereochemical purity of (**16**) was determined by ^{1}H and ^{31}P NMR spectra, where only one signal at δ_P 42 ppm is present, and HPLC of the reaction mixture. Compound (**16**) was obtained as colorless, stable at room temperature solid after crystallization from heptane.



(-)-(Sp)- (**16**)

Upon first inspection one could imagine that in this case also the D-glucofuranose, under the influence of the base, reacts with only one of the enantiomeric chlorides of phosphinous acid, similar to chlorophosphines. However in contrast to chlorophosphines, the chlorides of four-coordinate phosphorus acid are conformationally stable and the equilibrium between (S)- and (R)-epimers does not exist.[1] Besides, the same yield and optical purity of (**16**) are obtained, when 1:1 and 1:2 ratio of starting reagents are used. In order to explain the stereoselectivity observed in this reaction, we assume that the reaction proceeds under thermodynamically controlled conditions via the formation of an intermediate phosphorane that can undergo pseudorotation to convert into the most energetically advantageous epimer. In our recent works we have already described examples of such highly stereoselective reactions proceeding under the thermodynamic control conditions via pentacoordinate phosphorus intermediates.[16,17] For instance, in the case of enantioselective oxidation of phosphinic acid amides by couple CCl_4/ROH, the phosphorane intermediates have been registered and studied by NMR spectroscopy.[17] However further investigations are necessary for more definitive conclusions.

So, the methodology described in this communication is cheap and convenient for the preparation of chiral phosphinites which are starting reagents for the further transformations into various stereochemically pure organophosphorus compounds. Generalization of the methodology is currently being pursued in our laboratory and the result will be reported very soon. Besides working on determining the exact mechanism of the reaction we are now applying this method for the synthesis of

organophosphorus biologically active compounds and chiral organophosphorus synthons.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are not corrected. NMR spectra were recorded on a "Varian VXR-300" spectrometer at 300 (^{1}H) and 126.16 MHz (^{31}P). All chemical shifts are expressed in δ (ppm). ^{1}H chemical shifts are expressed relative to Me_4Si as internal standard. ^{31}P NMR spectra are referenced to external 85% H_3PO_4. GC analyses were performed on a "Chrom-5" with 3.5 m SE-30 column and 50 m open capillary column filled with OV-101. HPLC analyses were performed on a "Milichrom-1A" (Russia) instruments with Silasorb DEA column 120 × 2 mm (hexane-isopropanol mixture in 95:5 ratio as eluent) and Silasorb C-18 120 × 2 mm column (50–60% aqueous acetonitrile as eluent); UV detector, λ_{max} 260 nm. Flash-column chromatography was performed by using Silicagel 60 (230–400 mesh ASTM, E. Merck). 1,2:3,5-diisopropylidene-α-D-glucofuranose $[\alpha]_D$ −11.0 (C = 5, in ethanol), and 1,2:3,5-dicyclohexylidene-α-D-glucofuranose have been prepared by the method reported in the literature.[18,19]

(Sp)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl benzylphenylphosphinite (**6**): To a solution of 0.02 mol of benzyl-phenylchlorophosphine and 3.5 ml of triethylamine in 10 ml of toluene cooled an ice-bath was added dropwise a solution of 0.02 mol of 1,2:3,5-diisopropylidene-D-glucofuranose in 5 ml of toluene. The solution was stirred at first for 3 hours at 0°C, then allowed to stand at room temperature for 12 hours under a nitrogen atmosphere. The precipitate of triethylamine hydrochloride was filtered off (yield − 100%) and washed with 10 ml of ether. The filtrate was evaporated under reduced pressure. The residue is spectroscopically pure phosphinite (**6**), which may be purified by flash-chromatography.

Yield 85%. $[\alpha]_D$ −154 (c 0.1, toluene).[12]
NMR spectra (δ, ppm, $CDCl_3$): δ_P: 124 ppm.

(Sp)-1,2:5,6-Di-isopropylidene-α-D-glucofuranosyl isopropylphenylphosphinite (**7**) was prepared as described above from isopropyl-phenylchlorophosphine of triethylamine and 1,2:3,5-diisopropylidene-D-glucofuranose in toluene.

Yield 90%. $[\alpha]_D$ −105 (c 0.1, toluene).[12]
NMR spectra (δ, ppm, $CDCl_3$): δ_P: 129.1 ppm.

(Sp)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl isobutyl-phenylphosphinite (**8**): To a solution of 0.02 mol of phenyl-isobutylchlorophosphine and 3.5 ml of triethylamine in 10 ml of toluene cooled an ice-bath was added dropwise with stirring 0.02 mol of 1,2:3,5-diisopropylidene-D-glucofuranose in 5 ml of toluene. After being stirred for 3 hours at −20°C. The reaction mixture was allowed to stand at room temperature for 6 hours under a nitrogen atmosphere. The precipitate of triethylamine hydrochloride was filtered off and washed with 10 ml of ether. The filtrate was evaporated under reduced pressure. After the removal of the solvent under reduced pressure the pure phosphinite was obtained. The phosphinite may be additionally purified by distillation in vacuum.

Yield 70%, b.p. 138°C (0.008 mmHg).[11]
NMR spectra (C_6D_6): δ_P 122.12 ppm.
Calcd. for the $C_{22}H_{33}O_6P$: P 7.30. Found: P 7.01.

(Rp)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl isobutylphenylphosphinite (**8**): To a solution of 0.02 mol of phenyl-isobutylchlorophosphine and 3.5 ml of pyridine in 10 ml of ether cooled an ice-bath was added dropwise 0.02 mol of 1,2:3,5-diisopropylidene-D-glucofuranose in 5 ml of ether. After being stirred for 3 hours at 0°C the reaction mixture was allowed to stand at room temperature for 5 hours under a nitrogen atmosphere. The precipitate of pyridine hydrochloride was filtered off and washed with 10 ml of ether. The filtrate was evaporated under reduced pressure and the residue was distilled under vacuum.

Yield 45%, b.p. 138°C (0.008 mmHg).
NMR spectra (δ, ppm, $CDCl_3$): δ_P: 124 ppm.

2-Diethylamino-1-methylethyl tert-butyl-isobutylphosphinite (**21**): a) To a solution of (−) 1-diethyl-amino-2-propanol (0.05 mol, 6.56 g, 7.4 ml) in 10 ml of dimethoxyethane cooled in an ice-bath was added 0.1 mol of sodium hydride. The mixture was stirred for 30 min at room temperature and then cooled to −20°C. The solution of *tert*-butyl-isobutylchlorophosphine (0.05 mol, 9 g, 10 ml) was added

dropwise to the mixture at −20°C. The reaction mixture was warmed to room temperature and stirred during 2 hours under a nitrogen atmosphere. Then the precipitate of sodium chloride was filtered off and washed with 10 ml of ether. The filtrate was evaporated under reduced pressure and the residue was distilled under vacuum. The mixture of (Rp) and (Sp)-diastereomers of (**21**) in the ratio 1:1 was obtained.

Colorless liquid, Yield 85%, b.p. 80°C (0.06 mmHg).
NMR spectra (δ, ppm, C_6D_6): δ_H 1.004 t [J_{HH} 7.0, CH_3CH_2]; 0.937 d [J_{HH} 6.0, $(CH_3)_2C$]; 0.971 d [J_{HH} 6.0, $(CH_3)_2C$]; 1.2 dd [J_{HH} 6.0, J_{HP} 3.0 $\underline{CH_3}CHO$]; 2.501 m (CH_2N); 3.718 m (OCH). δ_P: 136.29 and 138.45.

b) To a solution of (−) 1-diethylamino-2-propanol (0.05 mol, 6.56 g, 7.4 ml) in 10 ml of triethylamine cooled an ice-bath was added 0.1 mol of *tert*-butyl-isobutylchlorophosphine (0.1 mol, 18 g, 19.9 ml). The reaction mixture was allowed to stand at room temperature for 36 hours under a nitrogen atmosphere. The reaction course was monitored by 31P NMR and GC. Then the mixture was diluted by 20 ml of ether, the precipitate of triethylamine hydrochloride was filtered off and washed with 10 ml of ether. The filtrate was evaporated under reduced pressure and the residue was distilled under vacuum. The first fraction was tert-butyl-isobutylchlorophosphine, 9 g, bp 70–80°C (15 mmHg), δ_P 124.3 ppm. The second fraction was the mixture of (Rp) and (Sp)-diastereomers of (**21**) in the ratio 5:1.

Yield 55%, b.p. 80°C (0.06 mmHg), colorless liquid.
(Rp) and (Sp)-diastereomers of (**21**) were separated by flash chromatography:
(+)-(Rp): NMR spectra (δ, ppm, C_6D_6): δ_P 138.45, $[\alpha]_D$ +41.5 (c 0.1, hexane).
(−)-(Sp): NMR spectra (δ, ppm, C_6D_6): δ_P 136.29, $[\alpha]_D$ −54.5 (c 0.1, hexane).
Calcd. for the $C_{15}H_{34}NOP$: P 17.25. Found: P 16.95.

(Sp)-1,2:5,6-Di-isopropylidene-α-D-glucofuranosyl isobutyl-phenylphosphinate (**11**): To a solution of 0.005 mol of the phosphinite (**8**), prepared as described in the previous experiment in 5 ml of toluene cooled an ice-bath was added dropwise 0.0055 mol of *tert*-butylhydroperoxide in 5 ml of the same solvent. The solution was stirred for 0.5 hour at 0°C, then the solvent was removed under reduced pressure and a residue was purified by crystallization in hexane. Colorless prisms.

Yield 68%, m.p. 90°C (hexane), $[\alpha]_D$ −80 (c 0.1, hexane).
NMR spectra (δ, ppm; *J* Hz, $CDCl_3$):
δ_H: 0.914 d [J_{HH} 6.0, 3H, $(CH_3)_2C$]; 1.03 d [J_{HH} 6.0, 3H $(CH_3)_2C'$]; 1.26 s; 1.28 s; 1.34 s; 1.40 s [6H, $(CH_3)_2CO_2$]; 1.8–2.14 m (3H, $CHCH_2$); 4–4.2 m (4H, H-4, H-5, H-6); 4.33 dd (*J* 3.0, *J* 7.0, 1H, H-3); 5.1 d (*J* 3.60, 1H, H-1); 5.92 (*J* 3.60, 1H, H-2); 7.45 m; 7.85 m (5H, C_6H_5). δ_P: 49.02.
Calcd. for the $C_{22}H_{33}O_7P$: P 7.12. Found: P 7.03.

(Rp)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl isobutyl-phenylphosphinate (**11**): To a solution of 0.005 mol of the phosphinite (**8**), prepared as described in the previous experiment, in 5 ml of diethyl ether cooled an ice-bath was added dropwise 0.0055 mol of tert-butylhydroperoxide in 5 ml of the same solvent. The solution was stirred for 0.5 hour at 0°C, then the solvent was removed under reduced pressure and a residue was purified by flash-chromatography (silica gel 60, 230–400 mesh, eluent hexane-isopropanol 96:4).

Yield 45%, $[\alpha]_D$ −6.0 (c 0.05, hexane).
NMR spectra (δ, ppm, $CDCl_3$): δ_P: 47.98 ppm.
Calcd. for the $C_{22}H_{33}O_7P$: P 7.12. Found: P 7.03.

(Sp)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl benzyl-phenylphosphinate (**9**): a) To a solution of 0.02 mol of chloride of benzyl-phenylphosphinous acid and 3.5 ml of triethylamine in 10 ml of toluene cooled an ice-bath was added dropwise a solution of 0.02 mol of 1,2:3,5-diisopropylidene-D-glucofuranose in 5 ml of toluene. The solution was stirred at first for 1 hour at 0°C, then allowed to stand at room temperature for a night under a nitrogen atmosphere. The precipitate of triethylamine hydrochloride was filtered off (yield ~ 100%) and washed with 5 ml of ether. After the solvent was evaporated under reduced pressure and a residue was purified by crystallization in heptane.

Yield 75%, m.p. 175°C, colorless prisms. $[\alpha]_D$ −47.5 (c 0.05, acetone).

b) To a solution of 0.005 mol of the phosphinite, prepared as described in the previous experiment, in 5 ml of diethyl ether cooled an ice-bath was added dropwise 0.0055 mol of *tert*-butylhydroperoxide in 5 ml of the same solvent. The solution was stirred for 0.5 hours at 0°C, then the solvent was removed under reduced pressure and an residue was purified by crystallization in heptane. Colorless prisms.

Yield 80%, m.p. 175°C, $[\alpha]_D$ −47 (c 0.05, acetone).
NMR spectra (δ, ppm; *J* Hz, $CDCl_3$):

δ_H: 1.22 s; 1.25 s; 1.29 s; 1.41 s [6H, $(CH_3)_2CO_2$]; 2.15 m (3H, $CHCH_2$); 3.33 d (2H, PCH_2); 3.9–4.2 m (4H, H-4, H-5, H-6); 4.33 dd (*J* 3.0, *J* 7.0, 1H, H-3); 4.83 d (*J* 3.60, 1H, H-1); 5.81 (*J* 3.60, 1H, H-2); 7.1–7.8 m (9H, C_6H_5 + C_6H_4). δ_P: 42.9.
Calcd. for the $C_{25}H_{31}O_7P$: P 6.53. Found: P 6.45.

(Sp)-1,2:5,6-Di-isopropylidene-α-D-glucofuranosyl isobutylphenylthiophosphinate (**14**): To a solution of 0.005 mol of the phosphinite (**8**) in 5 ml of benzene was added the solution of 0.0055 mol of sulfur in benzene. The solution was then allowed to stand at room temperature for 5 hours, the solvent was removed under reduced pressure and a residue was purified by flash chromatography (silica gel 60, 230–400 mesh, eluent hexane).

Yield 68%, b.p. 91°C (hexane), $[\alpha]_D$ 92 (c 0.1, hexane).
NMR spectra (δ, ppm; *J* Hz, $CDCl_3$):
δ_H: 0.82 d [*J* 3.5, 3H, $(CH_3)_2C$]; 1.05 d [*J* 3.5, 3H, $(CH_3)_2C'$]; 1.24 s; 1.29 s; 1.43 s [6H, $(CH_3)_2CO_2$]; 2.16 m (3H, $CHCH_2$); 3.99 m (3H, H-4, H-5, H-6); 4.13 (1H) 4.50 dd (*J* 2.5, *J* 10.0, 1H, H-3); 5.28 d (*J* 3.0, 1H, H-1); 5.89 (*J* 3.0, 1H, H-2); 7.48 m; 8.05 m (5H,C_6H_5). δ_P: 94.77 ppm.
Calcd. for the $C_{22}H_{33}O_6PS$: P 6.78, S 7.02. Found: P 6.75, S 6.92.

(R)-Methyl-benzyl-phenylphosphine oxide (**15**): To a solution of 0.005 mol of the phosphinite 5 in 5 ml of diethyl ether cooled an ice-bath was added dropwise 0.0055 mol of methyllithium in 2.5 ml of the same solvent. The solution was stirred for 0.5 hours at 0°C, then the precipitate was filtered off the solvent was removed under reduced pressure, a residue was oxidized by *tert*-butylhypochlorite and then purified by crystallization in hexane. Colorless prisms.

Yield 70%. The obtained product was compared with m.p., HPLC and ^{31}P NMR spectra of the authentic sample: m.p. 135°C, $[\alpha]_D$ +50 (c 0.1, C_2H_5OH), δ_P 41.22 ppm {lit.[10] m.p. 134–135°C $[\alpha]_D$ 51}.

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