HETEROCYCLES, Vol. 69, 2006, pp. 283 - 294. © The Japan Institute of Heterocyclic Chemistry
Received, 28th June, 2006, Accepted, 27th July, 2006, Published online, 28th July, 2006. COM-06-S(O)28

SYNTHESIS OF FUNCTIONALIZED PHOSPHOLANE OXIDES AND PHOSPHORINANE OXIDES FROM 1,4- AND 1,5-DI-*O*-MESYLOXY COMPOUNDS

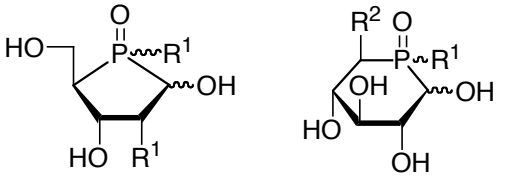
Tadashi Hanaya,* Karsten Schürrle, and Hiroshi Yamamoto

Department of Chemistry, Faculty of Science, Okayama University, Tsushima-naka, Okayama 700-8530, Japan

Abstract – Treatment of 1,4-di-*O*-mesyl-2,3-di-*O*-methyl-L-threitol (**8b**) with phenylphosphine in the presence of sodium hydride in DMSO, followed by the action of hydrogen peroxide, afforded 3,4-dimethoxy-1-phenylphospholane 1-oxide (**7**), while the same treatment of 1,5-di-*O*-mesyl-2,3,4-tri-*O*-methyl-*meso*-xylitol (**11b**) provided 2,3,4-trimethoxy-1-phenylphosphorinane 1-oxide (**14**).

INTRODUCTION

In view of the wide interest in their chemical and potential biological properties,[1] various sugar analogs having a heteroatom (instead of oxygen) in the ring have been prepared. Among such a chemical modification by heteroatoms, we have prepared various sugar analogs (phospha sugars) containing a phosphorus atom in the ring[2]: *e.g.* D-ribose (**1**)[3] and 2-deoxy-D-ribose analogs (**2**)[4] of furanose-type (phospholane oxide), D-xylose (**3**)[5] and D-glucose analogs (**4**)[6] of pyranose-type (phosphorinane oxide). Although some procedures available for introduction of a phosphinoyl group into sugar moiety were developed,[7] synthesis of such sugar analogs often requires rather long reaction steps. Attempts are thus needed to explore a simpler preparative method for the phospholane oxide and the phosphorinane oxide having oxygen functional groups on the ring carbons, since these compounds are potentially useful precursors for various types of phospha furanoses and pyranoses by introducing substituents on the α-carbon of the ring phosphorus.[8]



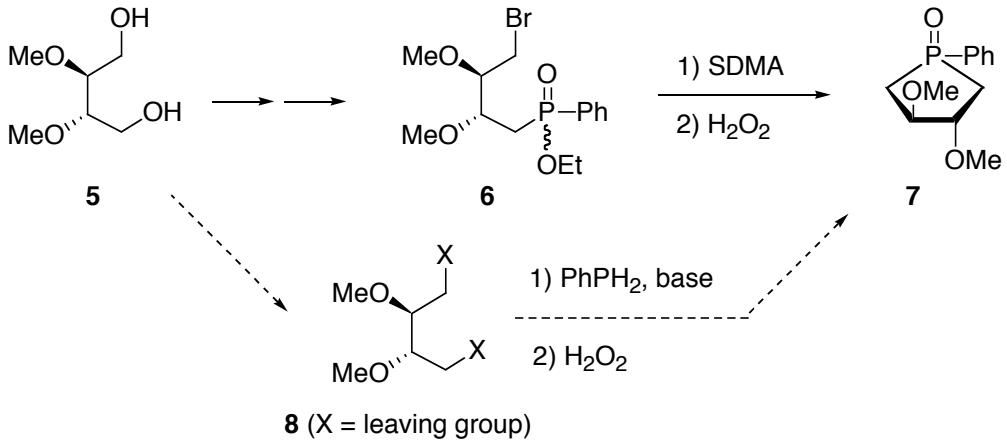
R^1 = OH, Et, Ph

1 R^2 = OH **3** R^2 = H

2 R^2 = H **4** R^2 = CH_2OH

In a previous paper,[9] we reported synthesis of phospholane 1-oxide having oxygen functional groups from a 4-bromobutylphosphinate derivative (Scheme 1): 3,4-dimethoxy-1-phenylphospholane 1-oxide (**7**) was obtained in 48% yield by the reductive cyclization of ethyl 4-bromo-2,3-dimethoxybutyl(phenyl)phosphinate (**6**) [prepared from 2,3-di-*O*-methyl-L-threitol (**5**) in five steps (29% total yield)] with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), followed by the action of hydrogen peroxide. In this procedure, the formation of phospholane ring is based on a two-step approach for C-P bond introduction and an improvement is desirable to prepare the 4-substituted butylphosphinate precursor.

Meanwhile, the ring formation of α,ω-dihaloalkanes with metallic phosphide has also been reported as a procedure for synthesis of phospholanes and phosphorinanes: 1-phenylphospholane was obtained in 30% yield from 1,4-dichlorobutane and dilithium phenylphosphide.[10] As such an approach appeared more suitable for our purposes, we have examined a modification of the leaving groups of substrate (**8**) as well as the reaction conditions to provide **7** in a satisfactory yield (Scheme 1). We describe herein our synthetic studies on the phospholane oxides and phosphorinane oxides having oxygen functional groups on the ring-carbons via the ring formation of α,ω-disubstituted compounds with phenylphosphide.



Scheme 1

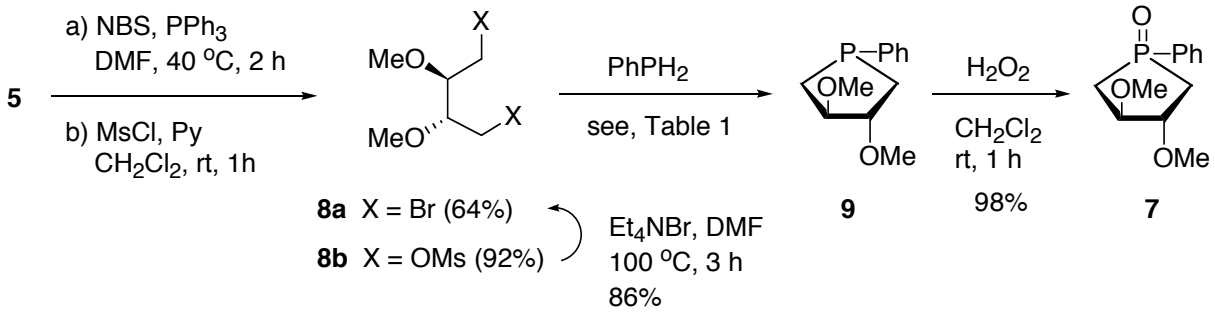
RESULTS AND DISCUSSION

For the precursors of phospholane-ring formation we chose the 1,4-dibromide and 1,4-di-*O*-mesylate of **5** (Scheme 2). Bromination of **5** with NBS in the presence of triphenylphosphine in DMF afforded the 1,4-dibromo-1,4-dideoxy-L-threitol derivative (**8a**)[11] in 64% yield, while mesylation of **5** with mesyl chloride in the presence of pyridine in dichloromethane provided the 1,4-di-*O*-mesyl derivative (**8b**)[12] in 93%. The dibromide (**8a**) was also obtained from **8b** by the reaction with tetraethylammonium bromide in DMF in 86%.

Conversion of **8a,b** to 3,4-dimethoxy-1-phenylphospholane (**9**) was then examined and the results are summarized in Table 1. Treatment of 1,4-dibromo compound (**8a**) with dilithium phenylphosphide,[10] prepared from phenylphosphine[13] and n-butyllithium in THF, afforded **9** in 52% yield (Entry 1), while application of the Kabachnik's procedures[14] for alkylation of phenylphosphine (use of aqueous KOH in

DMSO at 60 °C) improved the yield of **9** (Entry 2). In order to enhance the concentration of phenylphosphide anion, the Kabachnik's conditions were modified by use of stronger base in anhydrous solvent. Thus, treatment of **8a** with phenylphosphine in the presence of sodium hydride in dry DMSO at 60 °C afforded **9** in a satisfactory yield (86%) (Entry 3). By employing the same conditions, the 1,4-di-*O*-mesyl derivative (**8b**) also gave **9** in a similar yield (Entry 4). Therefore the di-*O*-mesylate (**8b**) is apparently a more suitable precursor for our purposes in comparison with the dibromide (**8a**). The phenylphospholane (**9**) was converted into the desired phenylphospholane oxide (**7**) in a quantitative yield by oxidation with hydrogen peroxide.

Preparation of the functionalized phosphorinane oxide was then examined by applying the optimized procedures described above for the ring formation with phenylphosphide (Scheme 3). As the starting material for 3,4,5-trimethoxyphosphorinane 1-oxide (**14**), 2,3,4-tri-*O*-methyl-*meso*-xylitol (**10**) was made from D-xylose in four steps according to the reported method.[15] Bromination of **10** with triphenylphosphine and NBS resulted in a predominant formation of 1,4-anhydro-5-bromo-5-deoxy-2,3-di-*O*-methyl-DL-xylitol (**12**) in 38% yield; the desired 1,5-dibromo compound (**11a**)[16] was obtained in a minor portion (22% yield). Production of **12** can be perceived as the result of the intramolecular substitution of **11a** caused by a methoxy oxygen locating in δ-position of a leaving group.[17] However, when **10** was subjected to mesylation at 0 °C with mesyl chloride in dichloromethane in the presence of pyridine, the 1,5-di-*O*-mesyl-*meso*-xylitol derivative (**11b**)[15,16] was obtained in 89% yield. We therefore employed **11b** as a preferable precursor for the following steps.

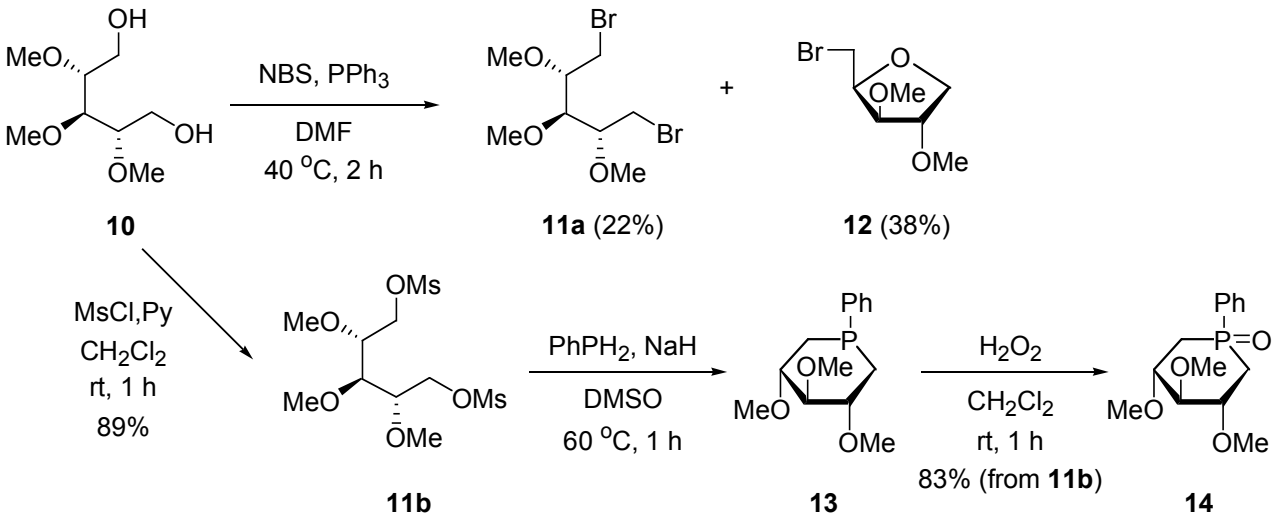


Scheme 2

Table 1. Preparation of 3,4-dimethoxy-1-phenylphospholane (**9**) [a]

Entry	Substrate	Base	Solvent	Temperature, Time	Yield of **9** [b]
1	**8a**	n-BuLi	THF	20 °C, 2 h	52%
2	**8a**	KOH	DMSO-H_2O	60 °C, 2 h	72%
3	**8a**	NaH	DMSO	60 °C, 1 h	86%
4	**8b**	NaH	DMSO	60 °C, 1 h	88%

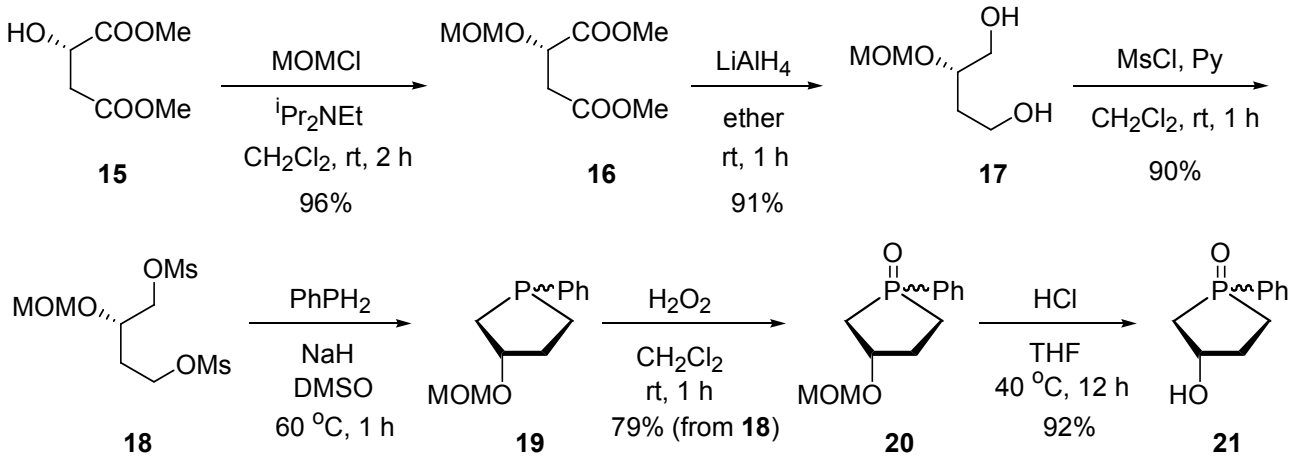
[a] All reactions were carried out by use of 1.3 mol equiv of phenylphosphine and 3 mol equiv of base. [b] Isolated yield by column chromatography. In all cases, a minor amount (ca. 5%) of phospholane oxide (**7**) was also isolated.



Scheme 3

Treatment of compound (**11b**) with phenylphosphine in the presence of sodium hydride in DMSO at 60 °C afforded a crude mixture of the phenylphosphorinane (**13**) and a minor portion of its oxidized product. The mixture was oxidized with hydrogen peroxide and then purified on a silica gel column. The product thus obtained was a sole isomer, whose structure was assigned to be the (1*S*)-1-phenylphosphorinane 1-oxide derivative (**14**) on the basis of ^{1}H NMR spectra (see below).

An application of these procedures to the ring formation of an asymmetric 1,4-dimesyloxy compound was exemplified by the synthesis of (3*S*)-3-hydroxy-1-phenylphospholane 1-oxide (**21**) (Scheme 4). Taking into consideration de-*O*-protection of the oxygen functional group on the ring, we employed acid-labile methoxymethyl (MOM) group. Thus, dimethyl L-malate (**15**) was treated with chloromethyl methyl ether in the presence of *N*-ethyldiisopropylamine to give the 2-*O*-MOM-L-malate (**16**). Compound (**16**) was reduced with lithium aluminum hydride to afford the diol (**17**),[18] which was then mesylated with mesyl chloride to provide the 1,4-di-*O*-mesyl-2-*O*-MOM derivative (**18**).[19]



Scheme 4

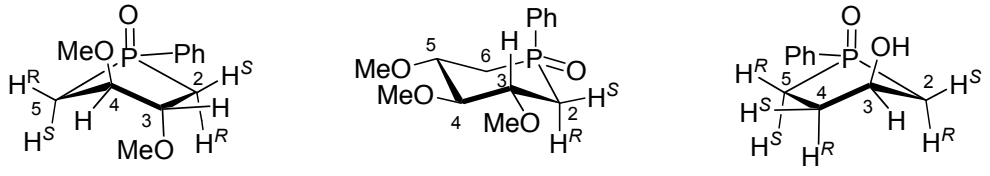
According to the synthetic procedures for **7** and **14**, the treatment of **18** with phenylphosphine and sodium hydride (to give **19**) and the subsequent oxidation with hydrogen peroxide afforded (1*RS,3S*)-3-*O*-MOM-1-phenylphospholane 1-oxides (**20**) as an inseparable diastereomeric mixture (9:1) with regard to phosphorus atom. Cleavage of MOM group of **20** was achieved by acid hydrolysis, affording **21** in 92%. The major isomer of **21** was isolated by crystallization and assigned to be the (1*R*)-epimer (**21a**) by ^{1}H NMR spectra (see below).

The structural and conformational assignments of **7, 14, 21a** were made on basis of their ^{1}H NMR data by referring to characteristic tendency of coupling constants and chemical shifts of phospha sugars (**1–4**) having similar ring structures.[2–6] The favored conformations of **7, 14, 21a** in $CDCl_3$ are shown in Figure 1.

(1) Compound (**7**) has large values of $J_{3,P}$ and $J_{4,P}$ (ca. 23 Hz) and thus is considered to exist predominantly in the $^4T_3$ conformation (or readily variable $^4E \rightleftarrows {}^4T_3 \rightleftarrows E_3$).[3,4,20] Although the phosphorus atom is not asymmetric, orientation of P=O can be derived from the magnitude of two $^2J_{2,P}$ values. Namely, the small $J_{2R,P}$ and $J_{5S,P}$ values (4.4 and 8.3 Hz) indicate a *trans* (or *anti*) relationship of the H^R-2 (H^S-5) and P=O, whereas the large $J_{2S,P}$ and $J_{5R,P}$ values (18.6 and 13.4 Hz) points out a *cis* (or *gauche*) relationship of the H^S-2 (H^R-5) and P=O.[21] All ring protons being in the *cis* connection with P=O (H^S-2, H-3, H^R-5) appear at lower field compared with the corresponding *trans* protons (H^R-2, H-4, H^S-5). This can be explained in terms of a deshielding effect of P=O bond oriented to the same side of the ring and thus supports the structural assignments described above for **7**.

(2) The large coupling constant (10.5 Hz) between H^R-2 and H-3 of **14** indicates the axial orientation of these two protons and thus a predominant existence in the $^5C_2$ conformation having three equatorial methoxy groups. As for the orientation of P=O bond, the large $J_{2R,P}$ value (17.6 Hz) suggests the *gauche* connection of H^R-2–C-2–P=O, namely an equatorial P=O bond having the (*S*)-configuration.

(3) The assignments for H^R-2 (δ 2.20) and H^R-4 (δ 1.99) of **21a** were confirmed by observation of NOE between these signals and H-3 signal (δ 4.68). The large value of $J_{3,P}$ (23.2 Hz) and the small value of $J_{4R,P}$ (8.6 Hz)[22] indicate **21a** exists preponderantly in the $^3T_4$ conformation (or readily variable $^3E \rightleftarrows {}^3T_4 \rightleftarrows E_4$).[3,4,20] The (*R*)-configuration of the phosphorus is derived from relatively small $J_{2R,P}$ and $J_{5S,P}$ values (6.2 and 8.6 Hz)[22] which suggest the *anti* relationship of H^R-2 (H^S-5) and P=O. This configuration is supported by the existence of weak NOE between H^R-2, H^S-5 signals and *ortho* protons of the phenyl group.



7 **14** **21a**

Figure 1. Structures and favored conformations for phospholane oxides (**7, 21a**) and phosphorinane oxide (**14**)

The present work demonstrates a convenient way for preparation of phospholane oxides and phosphorinane oxides having oxygen functional groups, which are potencially useful precursors for phospha sugars; *e.g.*, phospholane oxide (**20**) for 2-deoxy-D-ribofuranose analog (**2**). Application of these findings in further synthesizing other functionalized phospholane oxides and phosphorinane oxides, as well as their derivation into various phospha sugar derivatives, is in progress.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:2, (*B*) 2:1 AcOEt–hexane, and (*C*) 1:9 EtOH–AcOEt]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or spraying them with 20% sulfuric acid–ethanol (with subsequent heating). Optical rotations were measured with a JASCO P-1020 polarimeter. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^1H, 151 MHz for ^{13}C) and Mercury 300 (121 MHz for ^{31}P) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm as an internal standard for ^1H), $CDCl_3$ (77.0 ppm as internal standard for ^{13}C), and 85% phosphoric acid (0 ppm as an external standard for ^{31}P). The assignments of ^{13}C signals were made with the aid of 2D C-H COSY measurements.

1,4-Dibromo-1,4-dideoxy-2,3-di-*O*-methyl-L-threitol (8a).[11]

A. From 5. To a solution of **5** (160 mg, 1.07 mmol) and triphenylphosphine[13] (840 mg, 3.20 mmol) in dry DMF (4 mL) was added NBS (570 mg, 3.20 mmol) at 0 °C. The mixture was stirred at 40 °C for 2 h and then methanol (1 mL) was added at 0 °C. The mixture was concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:4 AcOEt-hexane to give **8a** (189 mg, 64%) as a colorless oil: Rf = 0.73 (*A*).

B. From 8b. A solution of **8b** (185 mg, 0.604 mmol) and tetrabutylammonium bromide (400 mg, 1.90 mmol) in DMF (5 mL) was stirred at 100 °C for 3 h and then concentrated in vacuo. After addition of water, the solution was extracted with $CHCl_3$ three times. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed to give **8a** (143 mg, 86%) (lit.,[11] 82% yield from the 1,4-di-*O*-tosyl derivative).

1,4-Di-*O*-mesyl-2,3-di-*O*-methyl-L-threitol (8b).[12]

To a solution of **5** (2.00 g, 13.3 mmol) and pyridine (2.40 ml, 29.7 mmol) in dry CH_2Cl_2 (20 mL) was added mesyl chloride (2.25 mL, 29.1 mmol) at 0 °C. The mixture was stirred at rt for 1 h and then diluted with $CHCl_3$ (30 mL). The mixture was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:4 AcOEt-hexane to give **8b** (3.75 g, 92%) as colorless needles: mp 53–54 °C (from AcOEt-hexane) (lit.,[12] 92% yield using pyridine as a

solvent, mp 53.8–54.5 °C).

(3*R*,4*R*)-3,4-Dimethoxy-1-phenylphospholane (9).[9]

To a suspension of sodium hydride (60% in mineral oil, 460 mg, 11.5 mmol) in dry DMSO (4 mL) was added, with stirring, phenylphosphine (0.550 mL, 5.00 mol) at 0 °C under argon. After stirring at rt for 15 min, a solution of **8b** (1.17 g, 3.82 mol) in dry DMSO (3 mL) was added. Then the mixture was stirred at 60 °C for 1 h, diluted with water (40 mL), and extracted with $CHCl_3$ three times. The combined extracts were dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:3 AcOEt-hexane to give **9** (753 mg, 88%) as a colorless syrup: R_f = 0.56 (*A*); ^{1}H NMR δ = 1.96 (1H, ddd, $J_{2R,2S}$ = 14.4, $J_{2R,P}$ = 5.7, $J_{2R,3}$ = 4.8 Hz, H^R-2), 2.04 (1H, ddd, $J_{5R,P}$ = 22.4, $J_{5R,5S}$ = 14.2, $J_{4,5R}$ = 6.8 Hz, H^R-5), 2.22 (1H, ddd, $J_{5S,P}$ = 5.4, $J_{4,5S}$ = 3.5 Hz, H^S-5), 2.46 (1H, ddd, $J_{2S,P}$ = 23.9, $J_{2S,3}$ = 6.5 Hz, H^S-2), 3.36, 3.37 (3H each, 2s, MeO-3,4), 3.87 (1H, dddd, $J_{4,P}$ = 17.0, $J_{3,4}$ = 5.7 Hz, H-4), 3.88 (1H, dddd, $J_{3,P}$ = 17.0 Hz, H-3), 7.28 [1H, tq, $J_{m,p}$ = 7.2, $J_{o,p}$ = $J_{p,P}$ = 1.4 Hz, Ph(*p*)], 7.33 [2H, ddd, $J_{o,P}$ = 7.6, $J_{o,m}$ = 7.2 Hz, Ph(*o*)], 7.51 [2H, td, $J_{m,P}$ = 1.8 Hz, Ph(*m*)]; ^{31}P NMR δ = –29.3.

(3*R*,4*R*)-3,4-Dimethoxy-1-phenylphospholane 1-oxide (7).[9,23]

Compound (**9**) (200 mg, 0.892 mmol) was dissolved in $CHCl_3$ (4 mL) and treated with 30% H_2O_2 (1.0 mL, 10 mmol) at rt for 1 h. The mixture was diluted with $CHCl_3$ (20 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give **7** (210 mg, 98%) as colorless prisms: mp 76–77 °C (from AcOEt-hexane) (lit.,[9] mp 76–77 °C); R_f = 0.24 (*C*); $[\alpha]_D^{27}$ +63.6° (*c* = 1.23, $CHCl_3$); ^{1}H NMR δ = 2.19 (1H, ddd, $J_{2R,2S}$ = 15.9, $J_{2R,P}$ = 4.4, $J_{2R,3}$ = 3.4 Hz, H^R-2), 2.23 (1H, ddd, $J_{5R,5S}$ = 15.6, $J_{5S,P}$ = 8.3, $J_{4,5S}$ = 5.1 Hz, H^S-5), 2.27 (1H, dddt, $J_{5R,P}$ = 13.4, $J_{4,5R}$ = 3.7, $J_{3,5R}$ = $J_{2S,5R}$ = 1.0 Hz, H^R-5), 2.46 (1H, dddd, $J_{2S,P}$ = 18.6, $J_{2S,3}$ = 5.9 Hz, H^S-2), 3.41, 3.45 (3H each, 2s, MeO-3,4), 4.06 (1H, dddd, $J_{4,P}$ = 23.0, $J_{3,4}$ = 3.7 Hz, H-4), 4.17 (1H, ddtd, $J_{3,P}$ = 23.2 Hz, H-3), 7.48 [2H, tdd, $J_{o,m}$ = $J_{m,p}$ = 7.3, $J_{m,P}$ = 2.9, $J_{o',m}$ = 1.5 Hz, Ph(*m*)], 7.52 [1H, tq, $J_{o,p}$ = $J_{p,P}$ = 1.6 Hz, Ph(*p*)], 7.83 [2H, ddt, $J_{o,P}$ = 12.2 Hz, Ph(*o*)]; ^{13}C NMR δ = 32.54 (d, $^1J_{5,P}$ = 65.1 Hz, C-5), 33.02 (d, $^1J_{2,P}$ = 64.5 Hz, C-2), 56.99 (MeO), 57.08 (MeO), 82.17 (d, $^2J_{3,P}$ = 8.6 Hz, C-3), 82.42 (d, $^2J_{4,P}$ = 6.9 Hz, C-4), 128.55 [d, $^3J_{m,P}$ = 12.7 Hz, Ph(*m*)], 130.54 [d, $^2J_{o,P}$ = 10.9 Hz, Ph(*o*)], 131.67 [d, $^4J_{p,P}$ = 2.9 Hz, Ph(*p*)], 133.55 [d, $^1J_{ipso,P}$ = 94.4 Hz, Ph(*ipso*)]; ^{31}P NMR δ = 53.6.

1,5-Dibromo-1,5-dideoxy-2,3,4-tri-*O*-methyl-*meso*-xylitol (11a) and 1,4-anhydro-5-bromo-5-deoxy-2,3-di-*O*-methyl-DL-xylitol (12).

Similar procedures to those for **8a** from **5** were employed. Compound (**10**) (80.0 mg, 0.412 mmol) was treated with triphenylphosphine (324 mg, 1.24 mmol) and NBS (220 mg, 1.24 mmol) in dry DMF (2 mL) at 40 °C for 1 h. Purification of the resulting mixture by column chromatography with 1:3 AcOEt-hexane gave **11a** (29.1 mg, 22%) and **12** (35.4 mg, 38%).

11a: Colorless oil: R_f = 0.63 (*A*); ^{1}H NMR δ = 3.44 (2H, dd, $J_{1,1'}$ = 10.5, $J_{1',2}$ = 5.1 Hz, H'-1,5), 3.47 (6H, s, MeO-2,4), 3.59 (3H, s, MeO-3), 3.62 (2H, dd, $J_{1,2}$ = 6.1 Hz, H-1,5), 3.67 (2H, ddd, $J_{2,3}$ = 4.3 Hz, H-2,4), 3.76 (1H, t, H-3). *Anal.* Calcd for $C_8H_{16}Br_2O_3$: C, 30.03; H, 5.04. Found: C, 29.93; H, 4.92.

12: Colorless oil: R_f = 0.55 (*A*); ^{1}H NMR δ = 3.38, 3.45 (3H each, 2s, MeO-2,3), 3.43 (1H, dd, $J_{5,5'}$ = 9.8, $J_{4,5'}$ = 6.1 Hz, H'-5), 3.52 (1H, dd, $J_{4,5}$ = 8.3 Hz, H-5), 3.78 (1H, dd, $J_{3,4}$ = 3.7, $J_{2,3}$ = 0.8 Hz, H-3), 3.83 (1H, dd, $J_{1,1'}$ = 10.0 Hz, $J_{1',2}$ = 1.7 Hz, H'-1), 3.88 (1H, ddd, $J_{1,2}$ = 4.6 Hz, H-2), 4.09 (1H, dd, H-1), 4.21 (1H, ddd, H-4). *Anal*. Calcd for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.19; H, 5.71.

1,5-Di-*O*-mesyl-2,3,4-tri-*O*-methyl-*meso*-xylitol (11b).[15]

By use of same procedures described for **8b** from **5**, compound (**10**) (2.80 g, 14.4 mmol) was treated with mesyl chloride (2.45 mL, 31.7 mmol) and pyridine (2.60 mL, 32.2 mmol) in dry CH_2Cl_2 (20 mL) to give **11b** (4.51 g, 89%) (lit.,[15] 78% yield using triethylamine as a base) as a colorless syrup: R_f = 0.30 (*B*); ^{1}H NMR[24] δ = 3.05 (6H, s, MsO-1,5), 3.49 (6H, s, MeO-2,4), 3.51 (1H, t, $J_{2,3}$ = 4.4 Hz, H-3), 3.52 (3H, s, MeO-3), 3.76 (2H, dt, $J_{1',2}$ = 6.1, $J_{1,2}$ = 4.3 Hz, H-2,4), 4.29 (2H, dd, $J_{1,1'}$ = 11.0 Hz, H'-1,5), 4.46 (2H, dd, H-1,5).

(1*S*,3*R*,4*S*,5*S*)-3,4,5-Trimethoxy-1-phenylphosphorinane 1-oxide (14).[23]

By use of same procedures described for **9** from **8b**, compound (**11b**) (2.00g, 5.71 mmol) was treated with phenylphosphine (0.820 mL, 7.45 mmol) and sodium hydride (60% in mineral oil, 685 mg, 17.1 mmol) in dry DMSO (15 mL). The resulting crude syrup which mainly consisted of (1*R*,3*R*,4*S*,5*S*)-3,4,5-trimethoxy-1-phenylphosphorinane (**13**) was used for the next step without further purification.

A pure sample of **13** was obtained by column chromatography: colorless syrup; R_f = 0.45 (*A*); ^{1}H NMR δ = 1.70 (2H, ddd, $J_{2R,2S}$ = 15.2, $J_{2R,3}$ = 11.3, $J_{2R,P}$ = 9.5 Hz, H_R-2,6), 2.51 (1H, ddd, $J_{2S,3}$ = 3.8, $J_{2S,P}$ = 3.5 Hz, H_S-2), 2.95 (1H, t, $J_{3,4}$ = 9.0 Hz, H-4), 3.23 (2H, ddd, $J_{3,P}$ = 0 Hz, H-3,5), 3.42 (6H, s, MeO-3,5), 3.54 (3H, s, MeO-4), 7.22 [1H, tq, $J_{m,p}$ = 7.2, $J_{o,p}$ = $J_{p,P}$ = 1.5 Hz, Ph(*p*)], 7.32–7.36 [4H, m, Ph(*o*,*m*)]; ^{31}P NMR δ = –41.2.

The above crude syrup was dissolved in $CHCl_3$ (10 mL), treated with 30% H_2O_2 (2.0 mL, 20 mmol) at rt for 1 h. The mixture was diluted with $CHCl_3$ (20 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give **14** (1.32 g, 81%) as colorless needles: mp 76–77 °C (from AcOEt-hexane); R_f = 0.27 (*C*); ^{1}H NMR δ = 2.25 (2H, ddd, $J_{2R,P}$ = 17.6, $J_{2R,2S}$ = 15.1, $J_{2R,3}$ = 10.5 Hz, H_R-2,6), 2.71 (1H, ddd, $J_{2S,P}$ = 14.2, $J_{2S,3}$ = 2.9 Hz, H_S-2,6), 3.27-3.32 (3H, m, H-3,4,5), 3.43 (6H, s, MeO-3,5), 3.56 (3H, s, MeO-4), 7.54 [2H, tdd, $J_{o,m}$ = $J_{m,p}$ = 7.4, $J_{m,P}$ = 3.2, $J_{o',m}$ = 1.4 Hz, Ph(*m*)], 7.57 [1H, tq, $J_{o,p}$ = $J_{p,P}$ = 1.5 Hz, Ph(*p*)], 7.75 [2H, ddt, $J_{o,P}$ = 11.5 Hz, Ph(*o*)]; ^{13}C NMR δ = 30.20 (d, $^1J_{2,P}$ = 61.6 Hz, C-2,6), 57.64 (MeO-3,5), 60.29 (MeO-4), 77.73 (d, $^2J_{3,P}$ = 4.0 Hz, C-3,5), 86.72 (C-4), 129.21 [d, $^3J_{m,P}$ = 11.5 Hz, Ph(*m*)], 129.49 [d, $^2J_{o,P}$ = 9.8 Hz, Ph(*o*)], 132.27 [d, $^1J_{ipso,P}$ = 96.7 Hz, Ph(*ipso*)], 132.36 [d, $^4J_{p,P}$ = 2.3 Hz, Ph(*p*)]; ^{31}P NMR δ = 29.7. *Anal*. Calcd for $C_{14}H_{21}O_4P$: C, 59.15; H, 7.45. Found: C, 59.29; H, 7.61.

Dimethyl 2-*O*-(methoxymethyl)-L-malate (16).

To a solution of **15** (1.32 g, 8.14 mmol) and *N*-ethyldiisopropylamine (2.10 mL, 12.1 mmol) in dry CH_2Cl_2 (10 mL) was added chloromethyl methyl ether (0.92 mL, 12.1 mmol) at 0 °C. The mixture was stirred at rt for 2 h and then diluted with $CHCl_3$ (20 mL). The mixture was washed with water, dried

(Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **16** (1.61 g, 96%) as a colorless oil: R_f = 0.40 (*A*); $[\alpha]_D^{27}$ = –67.1° (*c* = 2.34, $CHCl_3$); ^{1}H NMR δ = 2.81 (1H, dd, $J_{3,3'}$ = 10.5, $J_{2,3'}$ = 6.8 Hz, H'-3), 2.815 (1H, dd, $J_{2,3}$ = 5.6 Hz, H-3), 3.38 (3H, s, MeO-C-O-2), 3.71, 3.76 (3H each, 2s, COOMe), 4.70, 4.74 (1H each, 2d, $^2J_{CH2}$ = 7.1 Hz, CH_2O-2); ^{13}C NMR δ = 37.66 (C-3), 51.98 and 52.30 (COO*Me*), 56.12 (*Me*OCH_2), 71.75 (C-2), 96.44 (CH_2O), 170.39 (C-4), 171.65 (C-1). *Anal*. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.72; H, 6.63.

(*S*)-2-*O*-(Methoxymethyl)-1,2,4-butanetriol (17).[18]

To a solution of **16** (1.65 g, 8.00 mmol) in dry diethyl ether (20 mL) was added a suspension of lithium aluminum hydride (610 mg, 16.0 mmol) in dry diethyl ether (20 mL) at 0 °C under argon. The mixture was stirred at rt for 1 h and then water (2 mL) was added. The mixture was diluted with ethyl acetate (30 mL) and filtered through Celite. The filtrate was evaporated in vacuo and the residue was purified by short-path column chromatography with AcOEt to give **17** (1.09 g, 91%) [lit.,[18] 69% yield by reduction of bis(methoxymethyl) 2-*O*-(methoxymethyl)-L-malate with borane-dimethyl sulfide]: colorless oil; R_f = 0.09 (*B*).

(*S*)-1,4-Di-*O*-mesyl-2-*O*-(methoxymethyl)-1,2,4-butanetriol (18).[19]

By use of same procedures described for **8b** from **5**, compound (**17**) (1.74 g, 11.6 mmol) was treated with mesyl chloride (2.00 mL, 25.8 mmol) and pyridine (2.10 mL, 26.0 mmol) in dry CH_2Cl_2 (20 mL) to give **18** (3.21 g, 90%) [lit.,[19] 100% yield by methoxymethylation of 1,4-di-*O*-mesyl-1,2,4-butanetriol with dimethoxymethane]: colorless syrup; R_f = 0.26 (*B*).

(1*RS*,3*S*)-3-Methoxymethoxy-1-phenylphospholane 1-oxide (20).

By use of same procedures described for **9** from **8b**, compound (**11b**) (2.98 g, 9.72 mmol) was treated with phenylphosphine (1.35 mL, 12.3 mmol) and sodium hydride (60% in mineral oil, 1.16 g, 29.0 mmol) in dry DMSO (20 mL). The resulting crude syrup which mainly consisted of (3*S*)-3-methoxymethyl-1-phenylphospholane (**19**) was used for the following step without further purification.

A pure sample of **19** was obtained by column chromatography: pale yellow syrup; R_f = 0.67 (*A*); ^{31}P NMR δ = –19.7, –20.1* (89:11* diastereomeric mixture with regard to the phosphorus atom); ^{1}H NMR for the major isomer δ = 1.88–2.08 (3H, m, H'-2,4,5), 2.11–2.25 (3H, m, H-2,4,5), 3.37 (3H, s, MeO), 4.36 (1H, sext, $J_{2,3}$ = $J_{2',3}$ = $J_{3,4}$ = $J_{3,4'}$ = $J_{3,P}$ = 5.3–5.5 Hz, H-3), 4.625, 4.66 (1H each, 2d, $^2J_{CH2}$ = 6.9 Hz, CH_2O-3), 7.25 [1H, tq, $J_{m,p}$ = 7.2, $J_{o,p}$ = $J_{p,P}$ = 1.4 Hz, Ph(*p*)], 7.32 [2H, ddd, $J_{o,P}$ = 7.6, $J_{o,m}$ = 7.3 Hz, Ph(*o*)], 7.38 [2H, td, $J_{m,P}$ = 1.5 Hz, Ph(*m*)].

The above crude syrup was dissolved in $CHCl_3$ (15 mL), treated with 30% H_2O_2 (2.0 mL, 20 mmol) at rt for 1 h. The mixture was diluted with $CHCl_3$ (30 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give an inseparable diastereomeric mixture of **20** (18.4 g, 79% from **11b**) as a colorless syrup; R_f = 0.40 (*C*); ^{31}P NMR δ = 55.6, 58.5* (90:10*); ^{1}H NMR for the major isomer δ = 2.03–2.15 (2H, m, H'-4,5),

2.25–2.39 (3H, m, H,H'-2,H-4,5), 3.41 (3H, s, MeO), 4.37 (1H, dquint, $J_{3,P}$ = 15.9, $J_{2,3} = J_{2',3} = J_{3,4} = J_{3,4'}$ = 5.4–5.6 Hz, H-3), 4.73 (2H, s, CH_2O-3), 7.49 [2H, tdd, $J_{o,m} = J_{m,p}$ = 7.4, $J_{m,P}$ = 2.9, $J_{o',m}$ = 1.4 Hz, Ph(*m*)], 7.53 [1H, tq, $J_{o,p} = J_{p,P}$ = 1.5 Hz, Ph(*p*)], 7.70 [2H, ddt, $J_{o,P}$ = 11.7 Hz, Ph(*o*)]. *Anal*. Calcd for $C_{12}H_{17}O_3P$: C, 60.00; H, 7.13. Found: C, 59.91; H, 7.28.

(1*RS*,3*S*)-3-Hydroxy-1-phenylphospholane 1-oxide (21).[23]

Compound (**20**) (500 mg, 2.08 mmol) was dissolved in THF (5.0 mL) and 2M HCl (1.0 mL) was added. The mixture was stirred at 40 °C for 12 h, neutralized with aqueous ammonia and evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by short-path column chromatography with 1:9 EtOH-AcOEt to give a diastereomeric mixture of **21** (375 mg, 92%): R_f = 0.15 (*C*).

The major (1*R*)-epimer (**21a**) was crystallized from 1:9 EtOH-AcOEt as colorless needles: mp 107–108 °C: $[\alpha]_D^{27}$ = +6.41° (*c* = 1.54, $CHCl_3$); ^{1}H NMR δ = 1.99 (1H, dqd, $J_{4R,4S}$ = 13.8, $J_{4R,5S} = J_{4R,5R} = J_{4,P}$ = 8.6, $J_{3,4R}$ = 3.9 Hz, H^R-4), 2.11 (1H, ddd, $J_{5R,5S}$ = 14.2, $J_{5S,P}$ = 5.3, $J_{4S,5S}$ = 3.5 Hz, H^S-5), 2.20 (1H, ddd, $J_{2R,2S}$ = 15.6, $J_{2R,P}$ = 6.2, $J_{2R,3}$ = 5.0 Hz, H^R-2), 2.46 (2H, m, H^S-2, H^S-4), 2.48 (1H, m, H^R-5), 4.39 (1H, br s, HO-3), 4.68 (1H, ddq, $J_{3,P}$ = 23.2, $J_{2S,3} = J_{3,4S}$ = 3.9 Hz, H-3), 7.49 [2H, tdd, $J_{o,m} = J_{m,p}$ = 7.3, $J_{m,P}$ = 2.9, $J_{o',m}$ = 1.4 Hz, Ph(*m*)], 7.54 [1H, tq, $J_{o,p} = J_{p,P}$ = 1.5 Hz, Ph(*p*)], 7.69 [2H, ddt, $J_{o,P}$ = 12.0 Hz, Ph(*o*)]; ^{13}C NMR δ = 27.00 (d, $^1J_{5,P}$ = 65.1 Hz, C-5), 33.75 (d, $^2J_{4,P}$ = 6.9 Hz, C-4), 38.65 (d, $^1J_{2,P}$ = 66.8 Hz, C-2), 70.75 (d, $^2J_{3,P}$ = 8.6 Hz, C-3), 128.83 [d, $^3J_{m,P}$ = 11.5 Hz, Ph(*m*)], 129.71 [d, $^2J_{o,P}$ = 10.4 Hz, Ph(*o*)], 131.97 [Ph(*p*)], 133.37 [d, $^1J_{ipso,P}$ = 88.1 Hz, Ph(*ipso*)]; ^{31}P NMR δ = 61.4. *Anal*. Calcd for $C_{10}H_{13}O_2P$: C, 61.22; H, 6.68. Found: C, 61.08; H, 6.79.

ACKNOWLEDGEMENTS

We are grateful to the SC-NMR Laboratory of Okayama University for the NMR measurements. One of us (K.S.) thanks the EC Commission's program for a fellowship.

REFERENCES AND NOTES

1. H. Paulsen, *Angew. Chem., Int. Ed. Engl.* 1966, **5**, 495; B. Hellman, A. Lernmark, J. Sehlin, I.-B. Taljedal, and R. L.Whistler, *Biochem. Pharmacol*., 1973, **22**, 29; M. Chen and R. L. Whistler, *Arch. Biochem. Biophys*., 1975, **169**, 392; H. Yuasa, M. Izumi, and H. Hashimoto, *Yuki Gosei Kagaku Kyokai Shi*, 2002, **60**, 774.
2. T. Hanaya and H. Yamamoto, *Trends in Heterocyclic Chemistry*, 2003, **9**, 1; T. Hanaya and H. Yamamoto, *Yuki Gosei Kagaku Kyokai Shi*, 1993, **51**, 377; H. Yamamoto and T. Hanaya, 'Studies in Natural Products Chemistry', ed. by T. I. Atta-ur-Rahman, Elsevier, Amsterdam, 1990, Vol. 6, pp. 351–384.
3. T. Hanaya and H. Yamamoto, *Bull. Chem. Soc. Jpn*., 1989, **62**, 2320; H. Yamamoto, Y. Nakamura, S. Inokawa, M. Yamashita, M.-A. Armour, and T. T. Nakashima, *J. Org. Chem*., 1984, **49**, 1364.

4. T. Hanaya, A. Noguchi, M.-A. Armour, A. M. Hogg, and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1992, 295; H. Yamamoto, A. Noguchi, K. Torii, K. Ohno, T. Hanaya, H. Kawamoto, and S. Inokawa, *Chem. Lett.*, 1988, 1575.
5. H. Yamamoto, T. Hanaya, S. Inokawa, K. Seo, M.-A. Armour, and T. T. Nakashima, *Carbohydr. Res.*, 1983, **114**, 83; H. Yamamoto, T. Hanaya, S. Inokawa, M. Yamashita, M.-A. Armour, and T. T. Nakashima, *Carbohydr. Res*., 1984, **128**, C5; T. Hanaya, N. Shigetoh, and H. Yamamoto, *Bull. Chem. Soc. Jpn*., 1988, **61**, 2499; T. Hanaya, N. Shigetoh, H. Yamamoto, M.-A. Armour, and A. M. Hogg, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 421.
6. H. Yamamoto, T. Hanaya, H. Kawamoto, S. Inokawa, M. Yamashita, M.-A. Armour, and T. T. Nakashima, *J. Org. Chem.,* 1985, **50**, 3516; T. Richter, P. Luger, T. Hanaya, and H. Yamamoto, *Carbohydr. Res.*, 1989, **193**, 9; T. Hanaya, A. Akamatsu, H. Kawamoto, M.-A. Armour, A. M. Hogg, and H. Yamamoto, *Bull. Chem. Soc. Jpn*., 1991, **64**, 2398.
7. T. Hanaya, H. Yamamoto, and H. Yamamoto, *Bull. Chem. Soc. Jpn*., 1992, **65**, 1154; T. Hanaya, K. Yasuda, H. Yamamoto, and H. Yamamoto, *Bull. Chem. Soc. Jpn*., 1993, **66**, 2315; T. Hanaya, K. Sugiyama, H. Kawamoto, and H. Yamamoto, *Carbohydr. Res*., 2003, **338**, 1641.
8. R. P. Polniaszek and A. L. Foster, *J. Org. Chem*., 1991, **56**, 3137; A. Yabui, M. Yamashita, T. Oshikawa, T. Hanaya, and H. Yamamoto, *Chem. Lett*., 1993, 93.
9. T. Hanaya, S. Kawase, and H. Yamamoto, *Heterocycles*, 2005, **66**, 251.
10. K. Issleib and S. Häusler, *Chem. Ber*., 1961, **94**, 113.
11. T. Hanaya, A. Akamatsu, S. Kawase, and H. Yamamoto, *J. Chem. Res. (S)*, 1995, 194.
12. I. Takahashi, Y. Hirano, H. Arakawa, H. Kitajima, M. Hatanaka, K. Isa, K. Odashima, and K. Koga, *Heterocycles*, 1997, **46**, 589.
13. Phenylphosphine was prepared from phenylphosphonic dichloride and lithium aluminum hydride according to lit.: L.D. Freeman and G. O. Doak, *J. Am. Chem. Soc*., 1952, **74**, 3414.
14. E. N. Tsvetkov, N. A. Bondarrenko, I. G. Malakhova, and M. I. Kabachnik, *Synthesis*, 1986, 198.
15. M. G. García-Martin, R. R. Pérez, E. B. Hernández, and J. A. Galbis, *Carbohydr. Res*., 2001, **333**, 95.
16. Compounds (**11a,b**) are unstable and gradually change into the corresponding 1,4-anhydro-DL-xylitol derivatives when set aside at room temperature.
17. G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem*., 1965, **30**, 2020; H. Dehmlow, J. Mulzer, C. Seilz, A. R. Strecker, and A. Kohlmann, *Tetrahedron Lett*., 1992, **33**, 3607.
18. S. Bailey, M. R. Harndern, R. L. Jarvest, A. Parkin, and M. R. Boyd, *J. Med. Chem*., 1991, **34**, 57.
19. P. Marino, T. Tejero, J. Revuelta, P. Romero, S. Cicchi, V. Mannucci, A. Brandi, and A. Goti, *Tetrahedron: Asymmetry*, 2003, **14**, 367.
20. L. D. Hall, P. R. Steiner, and C. Pedersen, *Can. J. Chem*., 1970, **48**, 1155.
21. The assignments of H^R-5 and H^S-2 signals were confirmed by the presence of a long-range W-coupling ($J_{3,5R} = J_{2S,5R} = 1.0$ Hz).
22. The potentially informative $J_{2S,P}$, $J_{4S,P}$, and $J_{5R,P}$ values are uncertain because H^S-2, H^S-4, and H^R-5 signals overlap with each other.

23. The carbohydrate nomenclature for **7**: 1,4-dideoxy-2,3-di-*O*-methyl-1,4-phenylphosphonoyl-L-threitol. For **14**: 1,5-dideoxy-2,3,4-tri-*O*-methyl-1,5-[(*S*)-phenylphosphonoyl]-*meso*-xylitol. For **21a**: 1,2,4-trideoxy-1,4-[(*R*)-phenylphosphonoyl]-D-*glycero*-tetritol.
24. The complete parameters for **11b** obtained in the present study are shown here, because NMR data for this compound including insufficient assignments were reported in Ref.15.