Synthesis and Structural Analysis of 5-Deoxy-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinothioyl]-α- and β-D-xylopyranoses

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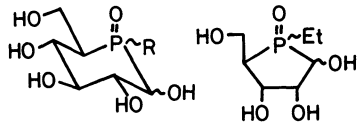
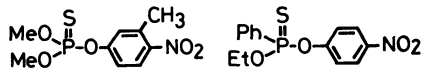
Treatment of 5-deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose with ethyl phenylphosphinothioate in the presence of NaH in DMF gave a 1:1 mixture of the 5-deoxy-5-*C*-[(*R*)- and (*S*)-(ethoxy)phenylphosphinothioyl] derivatives. Reduction of these D-xylofuranoses with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by the acid hydrolysis, provided the title compounds, which are the first sugar analogues having a phosphinothioyl group in the hemiacetal ring. These compounds were converted into four, separable 1,2,4-tri-*O*-acetates, the structures and conformations of which were established by spectroscopy. The corresponding per-*O*-acetyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl] analogues were also prepared and their previously presented structures were revised. Complete ^{1}H NMR (500-MHz) parameters of these two types of compounds are given for a comparative, structural study.

A large number of sugar analogues having a phosphorus atom in place of oxygen in the hemiacetal ring have been prepared in recent years:[1] e.g., D-glucopyranose type **1**[2] and D-ribofuranose type **2**.[3] Such compounds are of interest from the viewpoint of their physicochemical properties and potential biological activity.[1] All of these analogues possess an alkyl-, aryl-, or hydroxyphosphinyl group in the hemiacetal ring, but no derivatives containing a phosphinothioyl group in the ring have been prepared so far. On the other hand, it is well-known that many organophosphorus insecticides of P=S type, such as fenithion[4] (**3**) and EPN[5] (**4**), are in wide use and the P=S functional group of these compounds is effective in the relatively facile permeability through the skin of insects and then the slow oxidative desulfurization to generate the active P=O form by the action of a microsomal oxidase in vivo.[6] In this paper we wish to describe a detailed study on the two synthetic routes to the first sugar analogue having a phosphinothioyl group in the hemiacetal ring, as well as a comparative study with the corresponding 5-*C*-(phenylphosphinyl) derivatives, taking a 3-*O*-methyl-D-xylopyranose analogue as a model compound.[7]





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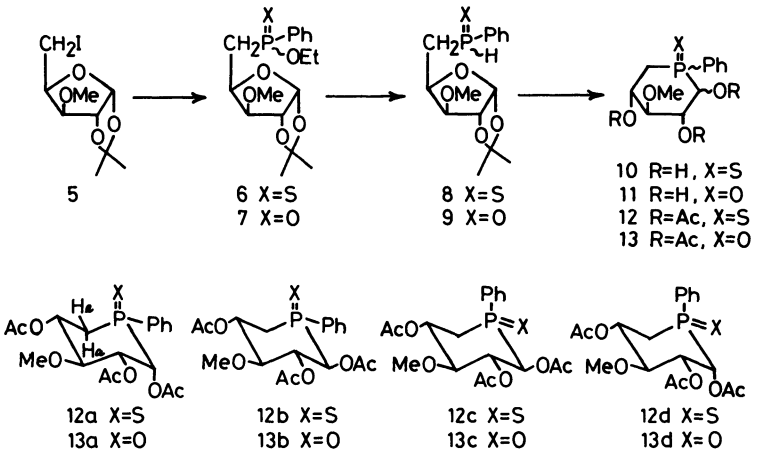
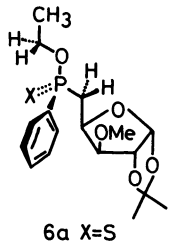
Results and Discussion

After examination of various reaction conditions, introduction of a phosphinothioyl group to the model compound was found to be best achieved by the reaction of 5-deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose[8] (**5**) with ethyl phenylphos-

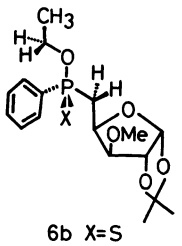


Scheme 1. Synthesis of 5-deoxy-3-*O*-methyl-5-*C*-(phenylphosphinothioyl)-D-xylopyranoses.

phinothioate[9] in dry *N,N*-dimethylformamide (DMF) containing an equivalent of sodium hydride at 0 °C for 3 h under argon (see Scheme 1). Thus the 5-*C*-[(*R*)- and (*S*)-(ethoxy)phenylphosphinothioyl] derivatives **6a,b** were obtained in 84% yield as a 1:1 mixture which were chromatographically inseparable. Compound **6** was obtained in less satisfactory yields when the reaction was carried out at room temp in DMF (3 h, 40% yield) or at elevated temps in benzene or xylene (19 h, ca. 9% yield). Complete ^{1}H NMR spectral parameters of both **6a** and **6b** were obtained at 500-MHz and are summarized in Table 1, by taking into consideration the similar spectral data of the 5-*C*-[(ethoxy)phenylphosphinyl] analogues **7a** and **7b** which were separable by chromatography (see later). On inspecting the molecular models of these *P*-epimers (see formulas **6a** and **6b**), the characteristic upfield shift of the δ value for MeO-3 of **6a** (δ 2.99) from the normal value of **6b** (δ 3.41) strongly suggests the most likely configurations of the P atom of **6a** and **6b** to be (*R*) and (*S*), respectively, because a stronger shielding effect on the MeO-3 group apparently exists in **6a** by the *P*-phenyl group in the vicinity.



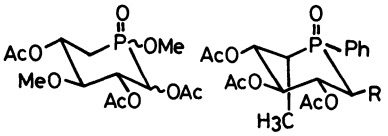
6a X=S
7a X=O

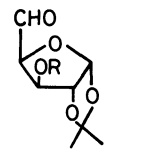


6b X=S
7b X=O

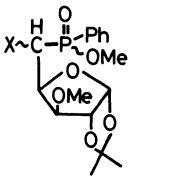
Reduction of **6** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in dry benzene or tetrahydrofuran (THF) was found to proceed much slower than that of the alkoxyphosphinyl analogues which normally completes within 30 min at 0 °C.[1-3] Thus, the reduction was carried out at 20 °C for 17 h to give the unstable 5-*C*-(phenylphosphinothioyl) compound **8**. Other conditions such as with SDMA in benzene (at 50 °C for 30 h or 20 °C for 35—44 h), SDMA in THF (0 °C, 26 h) or $LiAlH_4$ in ether (20 °C, 60 h) have been found so far to result in less satisfactory yields of **8** from **6**; in most cases the starting material **6** remains unchanged. The acid-catalyzed deprotection of 1,2-*O*-isopropylidene group of **8** and the subsequent ring-transposition in oxygen-free 0.5 M HCl–EtOH (1:1 v/v) (1 M=1 mol·dm^{-3}) at 80 °C for 2 h provided 5-deoxy-3-*O*-methyl-5-*C*-(phenylphosphinothioyl)-D-xylopyranoses (**10**).

The structural assignment of **10** was made by converting them into the 1,2,4-tri-*O*-acetates **12** by treatment with acetic anhydride–pyridine at 20 °C for 20 h as in the case of the previous phosphorus-containing sugar analogues.[1-3] Purification of the crude mixture by column chromatography on silica gel using ethyl acetate–hexane as eluant and then recrystallization gave four, crystalline diastereomers: 5-deoxy-3-*O*-methyl-5-*C*-[(*S*)-phenylphosphinothioyl]-α-D-xylopyranose (**12a**, 1.8% overall yield from **6**), the 5-*C*-[(*S*)-P]-β- (**12b**, 1.8% yield), the 5-*C*-[(*R*)-P]-β- (**12c**, 3.4% yield), and the 5-*C*-[(*R*)-P]-α-isomer (**12d**, 2.3% yield). The identical molecular composition ($C_{18}H_{23}O_7PS$) of **12a—d** was confirmed by the high-resolution MS. The precise configurations and the $^4C_1$(D) conformation of **12a—d** were established on the basis of the 500-MHz ^{1}H NMR spectra by taking into account the known parameters of structurally similar compounds obtained before; e.g., the four diastereomers (with respect to the C-1 and ring-P atom) of per-*O*-acetyl-5-deoxy-5-*C*-(methoxyphosphinyl)-3-*O*-methyl-D-xylopyranoses[8,10] (**14**) and other related compounds such as 5-*C*-[(*S*)-(phenylphosphinyl)]-α-L-idopyranoses[11] (**15**) and L-iditol[11] (**16**). The complete NMR assignments of **12a—d** are listed in Table 1 and will be discussed later.





17 R=Me
18 R=Bn



19 X=OH
20 X=O-C-N
S
21 X=H

Meanwhile, the corresponding four 5-*C*-phenylphosphinyl derivatives **13a—d** of the above thioyl compounds have been prepared by Seo,[12] employing 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose[13] (**17**) as the starting material by sequence **17**→**19**→**20**→**21**→**9**→**11**→**13**; structural assignments of the final products were made on the evidence of the insufficiently resolved 60-MHz ^{1}H NMR data and the values of optical rotations.[12] Having found some ambiguity in a part of the reported NMR assignments for **13a—d** and felt necessity of a comparative study of the exact parameters of **12a—d** with those of **13a—d** for further structural proof for the former compounds, we decided to prepare **13a—d**, by using **7** as the starting material. Thus, **7** was readily obtained from **5**[14] by the Michaelis-Arbusov reaction with diethyl phenylphosphonite in 91% yield as a 1:1 mixture of the two

Table 1. ^{1}H NMR (500-MHz) Parameters for **6**, **7**, **12**, and **13** in $CDCl_3$[a]

Compd	H-1	H-2	H-3	H-4	H-5 (H_a-5	H-5′ H_e-5)	Me_2C-O-1,2 (AcO-1,2,4)[b]		
6a	5.80	4.49	3.49	4.62	2.69	2.58	1.50,	1.30	
6b	5.75	4.53	3.73	4.39	2.78	2.49	1.40,	1.28	
7a	5.80	4.50	3.52	4.53	2.47	2.38	1.47,	1.29	
7b	5.78	4.53	3.66	4.32	2.52	2.31	1.39,	1.28	
12a	5.68	5.90	3.67	5.68	(2.91	2.60)	(1.94,	2.14,	2.03)
12b	5.79	5.78	3.57	5.65	(2.44	2.61)	(1.91,	2.09,	2.07)
12c	5.77	5.08	3.53	4.92	(2.37	3.23)	(2.16,	2.14,	2.07)
12d	6.11	4.77	3.65	4.83	(2.56	3.16)	(2.31,	2.14,	2.04)
13a	5.76	5.62	3.69	5.54	(2.49	2.68)	(1.98,	2.12,	2.04)
13b	5.60	5.75	3.58	5.53	(2.05	2.70)	(1.93,	2.09,	2.07)
13c	5.80	5.09	3.57	4.99	(2.33	3.01)	(2.15,	2.08,	2.05)
13d	6.10	4.78	3.70	4.86	(2.55	3.00)	(2.25,	2.15,	2.06)

Compd	MeO-3	HC-O-P	H′C-O-P	Me-C-O-P	Ph(*o*, *m*, *p*)		
6a	2.99	4.12	3.78	1.28	7.92,	7.43,	7.53
6b	3.41	4.12	3.79	1.27	7.93,	7.48,	7.53
7a	3.06	4.09	3.86	1.29	7.81,	7.48,	7.55
7b	3.39	4.11	3.89	1.31	7.81,	7.48,	7.55
12a	3.51				7.83,	7.49,	7.57
12b	3.51				7.89,	7.51,	7.58
12c	3.47				7.95,	7.56,	7.58
12d	3.47				7.86,	7.59,	7.59
13a	3.52				7.72,	7.50,	7.60
13b	3.53				7.75,	7.52,	7.60
13c	3.49				7.95,	7.57,	7.64
13d	3.48				7.89,	7.60,	7.65

Coupling constant

Compd	$J_{1,2}$	$J_{1,P}$	$J_{1,5e}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{4,5a}$ ($J_{4,5}$	$J_{4,5e}$ $J_{4,5'}$	$J_{4,P}$	$J_{5a,5e}$ $J_{5,5'}$	$J_{5a,P}$ $J_{5,P}$	$J_{5e,P}$ $J_{5'P}$)
6a	3.0			0		3.0	(9.1	4.4	8.7	14.5	10.6	17.8)
6b	3.9			0		3.0	(8.7	4.6	9.5	14.2	15.5	14.2)
7a	3.9			0		3.1	(9.5	4.7	6.4	14.8	12.8	17.7)
7b	3.9			0		3.1	(9.0	5.0	7.2	14.9	16.6	14.8)
12a	2.8	7.5	2.3	10.2	0	9.7	11.8	3.9	3.0	13.1	10.4	15.9
12b	11.0	0.3	0	9.4	3.4	9.7	11.8	4.2	3.3	13.8	8.5	16.7
12c	10.9	6.6	0	8.8	5.2	9.4	11.9	4.1	3.9	15.3	13.8	15.3
12d	2.6	7.2	2.2	10.1	0	9.4	12.1	4.2	2.8	15.2	15.1	14.5
13a	2.8	10.8	2.3	10.1	0	9.7	12.0	4.3	2.2	14.0	6.4	18.3
13b	11.0	2.7	0	9.5	2.8	9.6	12.3	4.3	2.9	14.5	4.2	19.5
13c	10.3	11.3	0	8.3	5.8	8.9	11.4	4.3	5.5	15.1	17.5	15.4
13d	2.6	8.9	2.0	9.3	3.6	8.7	11.2	4.3	5.5	15.0	18.5	15.0

Compd	*P*-OEt					*P*-Ph					
	$J_{H,H'}$	$J_{P,H}$	$J_{H,Me}$	$J_{P,H'}$	$J_{H',Me}$	$J_{P,2}$	$J_{P,3}$	$J_{P,4}$	$J_{2,3}$	$J_{3,4}$	J_m[c]
6a	10.2	9.8	7.1	8.5	7.0	13.1	3.3	1.8	7.0	7.5	1.5
6b	10.2	9.8	7.1	8.7	7.0	13.1	3.3	1.8	7.0	7.5	1.5
7a	10.1	7.1	7.1	7.1	7.1	12.1	3.3	1.4	8.3	7.5	1.5
7b	10.1	7.1	7.1	7.1	7.1	11.8	3.3	1.5	7.5	7.5	1.5
12a						13.4	3.5	1.8	7.5	7.7	1.5
12b						13.9	3.3	2.0	7.3	7.5	1.5
12c						12.8	3.3	1.8	8.1	7.8	1.5
12d						12.8	3.2	2.0	8.0	7.5	1.5
13a						11.8	3.3	1.5	7.5	7.5	1.5
13b						12.5	3.3	1.7	7.5	7.5	1.5
13c						11.8	3.3	1.7	7.7	7.7	1.5
13d						12.1	3.2	1.6	7.5	7.7	1.5

a) The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique and the parameters were confirmed by a computer-assisted simulation analysis. Very slight corrections were made on a few of the parameters for **12c, d** that were reported in Ref. 7, because the spectra of pure **12c** and **12d** have now become available. b) The assignments of acetoxyl groups may have to be interchanged. c) Approximate J values for meta-coupling of the *P*-phenyl ring protons: $J_{2,4'}$, $J_{2,6'}$, and $J_{3,5}$.

diastereomers, which were separable by chromatography into pure components **7a** and **7b**. From the analysis of the complete ^{1}H NMR data (see Table 1) the most likely configuration of the phosphorus atom of **7a** and **7b** were assigned to (*R*) and (*S*), respectively, on the same grounds taken into consideration in the case of **6a,b** shown above.

For the preparative purpose, however, the crude mixture **7** (without separation) can be subjected to the reduction with SDMA, because both **7a** and **7b** afford the identical 5-deoxy-5-*C*-phenylphosphinyl compound **9**[12] (see Scheme 1). Thus, after following the usual procedures,[1-3] **9** was led to **11** and then to **13**, from which the four diastereomers, **13a** (colorless needles, mp 202—203 °C, 11% overall yield from **7**), **13b** (colorless needles, mp 296—298 °C, 11% yield), **13c** (colorless syrup, 5% yield), and **13d** (colorless needles, mp 148—149 °C, 6% yield) were separated by silica-gel chromatography. As in the case of **12a—d** shown above, these compounds were characterized by MS and 500-MHz ^{1}H NMR (see Table 1 for the summarized parameters) as 5-deoxy-3-*O*-methyl-5-*C*-[(*S*)-phenylphosphinyl]-α-D-xylopyranose (**13a**), 5-*C*-[(*S*)-P]-β- (**13b**), 5-*C*-[(*R*)-P]-β- (**13c**), and 5-*C*-[(*R*)-P]-α- isomer (**13d**), in contrast to the previously reported assignments[12] of the structures 5-*C*-[(*R*)-P]-β-, 5-*C*-[(*R*)-P]-α-, 5-*C*-[(*S*)-P]-β-, and 5-*C*-[(*S*)-P]-α- isomer, respectively.

The ^{1}H NMR data of **12** and **13** generally follow the characteristic features in the δ and *J* values for 5-deoxy-5-*C*-(alkyl-, aryl-, and methoxyphosphinyl)-D-aldopyranoses approximately in the $^4C_1$(D) conformation.[1-3] Namely, the axial orientations (*S*) of the ring P=S and P=O groups in **12a,b** and **13a,b** are established by the downfield shift (0.7—1.1 ppm) of the H-2 and H-4 signals from those of **12c,d** and **13c,d** having equatorial P=S and P=O groups (see the δ values in Table 1). The α-orientation of C-1 is derived by considering the small magnitudes of $J_{1,2}$ (2.6—2.8 Hz) and $J_{1,5e}$ (2.0—2.3 Hz) values of **12a,d** and **13a,d**, whereas the β-anomers **12b,c** and **13b,c** show large $J_{1,2}$ (10.3—11.0 Hz) and negligible $J_{1,5e}$. It is noteworthy to mention some characteristic features in the spectral data of **12** and **13** more in detail for the purpose of comparison:

1) The proton signals of H-2 and H-4 of **12a** and **12b** appear at a slightly lower field (0.1—0.3 ppm) compared with those of **13a** and **13b**. The axial P=S group in the $^4C_1$(D) conformation therefore seems to excert a larger down-field shift on the signals of protons at the 1,3-diaxial positions in comparison with the same effect by the axial P=O group.

2) Appreciable differences in the magnitudes of the $J_{1,P}$, $J_{5a,P}$, and $J_{5e,P}$ are observed between the corresponding diastereomers of **12a—d** and **13a—d** (e.g., compare the $J_{1,P}$ values of **12a** and **13a**).

3) All of the AcO-1 signals of **12a,b** and **13a,b** appear at a rather high field (δ 1.91—1.99), indicating that these acetoxyl groups are most likely to be situated at the positions above the plane of the vicinal, equatorial *P*-phenyl ring. Significant down-field shifts (ca. 0.4 ppm) are observed for the δ values of H_a-5 of **12a,b** from those of the corresponding **13a,b** which seem to have normal values. Taking into consideration of the known values of the torsion angles (determined by X-ray crystallography[1,11]) between the P=O bond and the plane of the *P*-phenyl ring of compounds **15** and **16** (see Fig. 1), the most probable torsion angle between P=S and the plane of the *P*-phenyl ring of **12a** and **12b** in $CDCl_3$ solution is illustrated in Fig. 1, which would account for the above unusual δ values of H_a-5 and AcO-1 of these compounds.

However, exact reasons for these interesting features of the NMR parameters of the P=S compounds compared with those of the P=O analogues have remained to be further clarified employing a larger number of similar sugar analogues; particularly, the relation to their $^4C_1$(D) conformational deviations as well as intrinsic characters of P=S bonding affecting

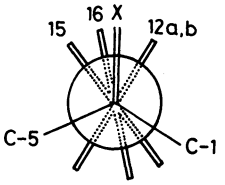
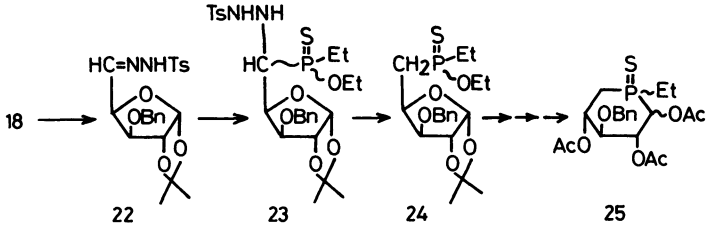


Fig. 1. "Newman" projection down the P–C(phenyl) bond illustrating the phenyl ring. [The digits mark the phenyl rings for compounds **15** (15, X=O),[11] **16** (16, X=O),[11] **12a**, and **12b** (12a, b, X=S)].



Scheme 2. Synthesis of 5-deoxy-3-*O*-benzyl-5-*C*-(ethylphosphinothioyl)-D-xylopyranoses.

the δ and J values of the neighboring groups would be of interest. Nevertheless, these exact parameters for **12a—d** are certainly of value in determining other 5-deoxy-5-*C*-phosphinothioyl-D-aldopyranoses that are still unknown.

Another approach for the synthesis of the sugar analogues having a P=S group in the ring was also made (see Scheme 2) utilizing a similar scheme employed for the synthesis of D-ribofuranose analogues[3] **2**. Namely, condensation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[15] (**18**) with tosylhydrazine in methanol at 20 °C for 2 h gave the hydrazone **22** (85% yield), which was treated with ethyl ethylphosphinothioate[9] in the presence of trifluoromethanesulfonic acid at 0—20 °C for 7 h, thus affording the 5-*C*-[(ethoxy)ethylphosphinothioyl] derivative **23** (73%). Although reduction of **23** with sodium borohydride in THF was repeatedly examined at 25—50 °C for 7—48 h, the desired compound **24** was obtained in fluctuating yields (10—55%) besides a large amount of unidentified by-products. The same treatment of **24** (as in the case of **6** and **7**) with SDMA, followed by the 0.5 M HCl–EtOH and then acetic anhydride–pyridine afforded a diastereomeric mixture of 1,2,4-tri-*O*-acetyl-3-*O*-benzyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-ethylphosphinyl]-α,β-D-xylopyranoses (**25**, colorless syrup) in only 1.6% overall yield from **24**. Compounds **25** were not separable into each diastereomers by chromatography. Therefore the synthetic approach shown in Scheme 2 seems to be less satisfactory than that described in Scheme 1.

Although improvement of the yields of some steps particularly of the reduction and the subsequent ring-enlargement reactions of the D-xylofuranoses **6** and **24** remains to be done, present work demonstrates an effective way for the preparation of 5-deoxy-5-*C*-(phenylphosphinothioyl)-D-xylopyranoses from an appropriate precursor. This scheme is therefore expected to be applicable to the preparation of various other 5-deoxy-5-*C*-phosphinothioyl-D- and L-aldofuranoses and pyranoses, which is currently under investigation.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and were uncorrected. All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent. Column chromatography was performed with Wako C-200 silica gel [or Merck Lobar prepacked silica gel (Size A) for rechromatography of **12** and **13**]. The ^{1}H NMR spectra were measured in $CDCl_3$ with a Hitachi R-600 (60-MHz, FT) or Varian VXR-500 instrument (500-MHz, the CS-NMR Lab., Okayama Univ.) at 27 °C. Chemical shifts (at 60-MHz unless otherwise specified) were recorded as δ values relative to tetramethylsilane as internal standard. The mass spectra were taken on a Shimadzu LKB-9000 low-resolution or a JEOL JMX-HX100 high-resolution instrument and were given in terms of m/z (rel intensity) compared with the base peak.

5-Deoxy-5-*C*-[(*R*)- and (*S*)-(ethoxy)phenylphosphinothioyl]-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranoses (6a, b). In a 100 cm^3 two-necked flask was placed sodium hydride (60% in oil, 688 mg, 1.2 equiv), which was then washed twice with dry hexane under argon and diluted with dry DMF (10 cm^3). To this suspension was dropwise added a solution of ethyl phenylphosphinothioate[9] (4.00 g, 1.5 equiv) in dry DMF (10 cm^3) at room temp under argon. After the consumption of sodium hydride to form the sodium salt of the thioate, a solution of **5**[8] (4.50 g) in dry DMF (10 cm^3) was dropwise added at 0 °C, followed by stirring at this temp for 3 h. The solvent was evaporated in vacuo (pump). The residue was dissolved in chloroform and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography with 1:3 AcOEt–hexane, giving an inseparable, 1:1 (by ^{1}H NMR) mixture of **6a** and **6b** (presumably 5-*C*-[(*R*)-P] and (*S*)-P diastereomer, respectively): A colorless syrup (4.50 g, 84%); R_f=0.65 (1:2 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS m/z 373 (M+1; 27.5), 372 (=0), 340 (42), 312 (12), 311 (15), 287 (17), 282 (25), 186 (100), 185 (18), 157 (39), 153 (41), and 142 (21).

Found: m/z 373.1190. Calcd for $C_{17}H_{26}O_5PS$: M+1, 373.1239.

1,2,4-Tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinothioyl]-α,β-D-xylopyranoses (12a—d). A solution of SDMA (490 mg, 70% in toluene, 3.0 equiv) in dry benzene (3 cm^3) was dropwise added into a solution of **6** (300 mg) in dry benzene (5 cm^3) at 5 °C under argon, followed by stirring at 20 °C for 18 h. Cold water (ca. 0.5 cm^3) was slowly added at 0 °C under stirring to decompose excess SDMA. The resulting white ppt was centrifuged and washed with benzene. Combined benzene solutions were concentrated in vacuo to give crude 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinothioyl]-α-D-xylofuranoses (**8**) as a colorless syrup.

This was immediately dissolved in oxygen-free ethanol (5 cm^3) and 0.5 M hydrochloric acid (5 cm^3). The mixture (pH ca. 1) was degassed with argon and then refluxed for 2 h. The cooled mixture was neutralized by adding enough Amberlite IRA-45. The resin was filtered off and washed with aq ethanol. The filtrate was evaporated in vacuo to give crude 5-deoxy-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinothioyl]-α,β-D-xylopyranoses (**10**) as a colorless syrup.

This was dissolved in pyridine (2 cm^3) and acetic anhydride (1 cm^3) at 5 °C. The mixture was stirred at 20 °C overnight, diluted with a small amount of cold water, and concentrated in vacuo. The residue was dissolved in chloroform and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed with 1:2 AcOEt–hexane to give **12a—d**; **12d** was separated from **12c** by recrystallization (three times).

12a (5-*C*-[(*S*)-Phosphinothioyl]-α-isomer): Colorless needles (6.0 mg, 1.8% overall yield from **6**); mp 177—178 °C (from 1:1 AcOEt–hexane); R_f=0.24 (1:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS m/z 414 (M$^+$; 12.5), 382 (12), 356 (16), 355 (38), 324 (29), 323 (56), 322 (57), 313 (20), 294 (19), 281 (52), 280 (100), 265 (27), 264 (28), 239 (43), 238 (28), 222 (31), 171 (22), 87 (23), 71 (31), and 43 (68).

Found: m/z 414.0930. Calcd for $C_{18}H_{23}O_7PS$: M, 414.0902.

12b (5-*C*-[(*S*)-Phosphinothioyl]-β-isomer): Colorless needles (6.0 mg, 1.8% yield from **6**); mp 166.5—167 °C (from 1:1 AcOEt–hexane); R_f=0.31 (1:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 414 (M^+; 8.3), 355 (14), 323 (14), 322 (56), 281 (35), 280 (100), 239 (29), 238 (29), and 43 (51).

Found: *m/z* 414.0825. Calcd for $C_{18}H_{23}O_7PS$: M, 414.0902.

12c (5-*C*-[(*R*)-Phosphinothioyl]-β-isomer): Colorless needles (7.7 mg, 2.3% yield from **6**); mp 231—232 °C (from 1:1 AcOEt–hexane); R_f=0.44 (1:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 414 (M^+; 2.5), 355 (13), 354 (38), 295 (72), 294 (45), 254 (19), 253 (100), 252 (66), 157 (20), 155 (66), 113 (68), and 43 (72).

Found: *m/z* 414.0914. Calcd for $C_{18}H_{23}O_7PS$: M, 414.0902.

12d (5-*C*-[(*R*)-Phosphinothioyl]-α-isomer): Colorless needles (11.3 mg, 3.4% yield from **6**); mp 181—182 °C (from 1:1 AcOEt–hexane); R_f=0.44 (1:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 414 (M^+; 30.7), 354 (16), 296 (24), 295 (54), 294 (49), 281 (23), 253 (94), 252 (79), 237 (53), 128 (40), 127 (45), 113 (96), 71 (84), and 43 (100).

Found: *m/z* 414.0902. Calcd for $C_{18}H_{23}O_7PS$: M, 414.0902.

5-Deoxy-5-*C*-[(*R*)- and (*S*)-(ethoxy)phenylphosphinyl]-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranoses (7a,b). A mixture of **5** (500 mg) and diethyl phenylphosphonite (1.58 g, 5.0 equiv) was heated at 160 °C for 4 h under nitrogen and then concentrated below ca. 80 °C in vacuo. The residue was dissolved in ether and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed with 1:1 AcOEt–hexane to give a 1:1 (by ^{1}H NMR) mixture of **7a** and **7b** as a colorless syrup (516 mg, 91% yield). The mixture was separated by careful rechromatography into the pure diastereomers.

7a (5-*C*-[(*R*)-P] isomer): Colorless syrup (170 mg, 30%); R_f=0.28 (2:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 356 (M^+).

7b (5-*C*-[(*S*)-P] isomer): Colorless syrup (190 mg, 34%); R_f=0.23 (2:1 AcOEt–hexane); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 356 (M^+).

1,2,4-Tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α,β-D-xylopyranoses[12] (13a—d). Similar procedures to those for **12** from **6** were employed. Thus, **7** (320 mg) was treated with SDMA (218 mg, 1.2 equiv) at 5 °C for 30 min, giving **9** as a colorless syrup. This was refluxed with 1:1 ethanol–0.5 M HCl (10 cm^3, oxygen-free) to afford **11** as colorless syrup. This was acetylated with Ac_2O–pyridine to give a mixture of **13**, which was separated by column chromatography with a gradient solution of 2:1 AcOEt–hexane→AcOEt→19:1 AcOEt–EtOH.

13a (5-*C*-[(*S*)-Phenylphosphinyl]-α-isomer): Colorless needles (39 mg, 11% yield from **7**); mp 202—203 °C (from 1:1 AcOEt–hexane, Ref. 12, mp 295—296 °C); R_f=0.44 (AcOEt); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 398 (M^+).

13b (5-*C*-[(*S*)-P]-β-isomer): Colorless needles (40 mg, 11% yield from **7**); mp 296—298 °C (from 1:1 AcOEt–hexane, Ref. 12, mp 200—200.5 °C); R_f=0.44 (AcOEt); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 398 (M^+).

13c (5-*C*-[(*R*)-P]-β-isomer): Colorless syrup (17 mg, 5% yield from **7**); R_f=0.33 (AcOEt); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 398 (M^+).

13d (5-*C*-[(*R*)-P]-α-isomer): Colorless needles (20 mg, 6% yield from **7**); mp 148—149 °C (from AcOEt–hexane, Ref. 12, syrup); R_f=0.22 (AcOEt); ^{1}H NMR (500-MHz), see Table 1; MS *m/z* 398 (M^+).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose 5-Tosylhydrazone (22). To a solution of **18**[15] (300 mg) in dry methanol (15 cm^3) was added tosylhydrazine (200 mg, 1.07 equiv) at 0 °C. The mixture was stirred at room temp for 2 h and then evaporated in vacuo. The residue was dissolved in chloroform, dried (Na_2SO_4), concentrated in vacuo, and then purified by column chromatography, giving **22** as colorless needles (406 mg, 85% yield): mp 129—132 °C (from AcOEt–hexane); R_f=0.68 (1:1 AcOEt–hexane); ^{1}H NMR δ=1.31, 1.48 (6H, 2s, Me_2C), 2.42 (3H, s, Me-C_6-S), 4.02—4.80 (5H, m, H-2,3,4, CH_2-O-3), 5.94 (1H, d, $J_{1,2}$=3.4 Hz, H-1), 7.15, 7.82 (2H, each, 2brd, *J*=8 Hz, C_6H_4-S), 7.25 (6H, brs, C_6H_5-C-O-3, NH), and 8.13 (1H, s, H-5); MS *m/z* 446 (M^+).

(*R*)- and (*S*)-3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[(*R*)- and (*S*)-(ethoxy)ethylphosphinothioyl]-5-*C*-[(2-tosyl)-hydrazino]-α-D-*xylo*-pentofuranose (23). A mixture of **22** (200 mg) and ethyl ethylphosphinothioate[9] (320 mg, 5 equiv) was degassed with argon. Trifluoromethanesulfonic acid (25 mg, 0.4 equiv) was dropwise added to the above mixture at 0 °C with stirring under argon, followed by stirring at 20 °C for 7 h. The mixture was diluted with chloroform (ca. 30 cm^3) and neutralized by washing with cold, saturated aq $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt–hexane, giving **23** as a yellow syrup (192 mg, 73%): R_f=0.68 (1:1 AcOEt–hexane); ^{1}H NMR δ=0.65—1.65 (6H, m, MeC-P, MeC-O-P), 1.28, 1.48 (6H, 2s, Me_2C), 1.7—2.4 (2H, m, C-CH_2-P), 2.39 (3H, s, MeC_6-S), 3.4—5.0 (7H, m, H-2,3,4, CH_2-O-P, NH), 4.64 (2H, s, CH_2-O-3), 5.93 (1H, d, $J_{1,2}$=3.5 Hz, H-5), and 6.8—7.9 (10H, m, H-5, C_6H_5-C-O-3, C_6H_4-S); MS *m/z* 584 (M^+).

3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[(*R*)- and (*S*)-(ethoxy)ethylphosphiothioyl]-α-D-xylofuranose (24). To a solution of **23** (100 mg) in dry THF (10 cm^3) was slowly added sodium borohydride (32 mg) at 5 °C. The mixture was degassed with argon, stirred at 50 °C for 13 h, and then refluxed for 9 h (under argon). It was diluted with ether and an aq saturated solution of Na_2SO_4 was added. After separation, the aq layer was extracted with ether. The combined ethereal layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography to give **24** as a yellow syrup (38 mg, 55% yield): R_f=0.6 (1:2 AcOEt–hexane); ^{1}H NMR δ=0.8—1.6 (6H, m, MeC-P, MeC-O-P), 1.34, 1.49 (6H, 2s, Me_2C), 1.6—2.4 (4H, m, 2H-5, CH_2-P), 3.5—4.9 (5H, m, H-2,3,4, CH_2-O-P), 4.58, 4.66 (2H, 2s, CH_2-O-3), 5.91 (1H, d, $J_{1,2}$=3.8 Hz, H-1), and 7.34 (5H, s, C_6H_5-C-O-3); MS *m/z* 400 (M^+).

1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-ethylphosphinothioyl]-α,β-D-xylopyranoses (25). The same procedures as those for **12** and **13** were employed. Thus, **24** (66 mg) was treated with SDMA (0.05 cm^3) at 5 °C for 5.5 h, followed by the usual procedures, giving an inseparable mixture of **25** as a pale yellow syrup (1.2 mg, 1.6% yield from **24**): R_f=0.5—0.7 (1:1 AcOEt–hexane); ^{1}H NMR δ=0.8—1.6 (3H, m, MeC-P), 1.6—2.1 (2H, m, $MeCH_2$-P), 1.88, 2.02, 2.09 (9H, 3brs, 3AcO), 2.2—3.5 (2H, m, 2H-5), 3.5—4.0 (1H, m, H-3), 4.60 (2H, brs, CH_2O-3), and 4.8—6.0 (3H, m, H-1,2,4); MS *m/z* 442 (M^+; 28.1), 383 (9), 336 (14), 332 (19), 305

(13), 292 (14), 262 (30), 245 (59), 203 (29), 185 (100), 157 (20), 138 (23), 137 (21), 109 (38), 91 (81), and 43 (33).

Found: *m/z* 442.1243. Calcd for $C_{20}H_{27}O_7PS$: M, 442.1208.

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