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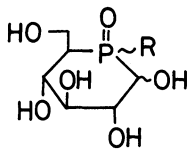
# Synthesis of 1,2,4-Tri-O-acetyl-5-deoxy-5-[(R,S)-ethyl- and phenylphosphino]-3-O-methyl-α,β-D-xylopyranoses and an Efficient Conversion to the Corresponding 5-(Phosphinothioyl)-D-xylopyranoses

Hiroshi YAMAMOTO,* Tadashi HANAYA, Nobuyuki SHIGETOH, Heizan KAWAMOTO, and Saburo INOKAWA

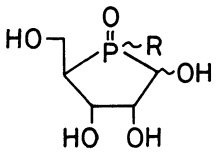
Department of Chemistry, Okayama University, Tsushima, Okayama 700

Reduction of 1,2,4-tri-O-acetyl-5-deoxy-5-[(R,S)-ethyl- and phenylphosphinyl]-α,β-D-xylopyranoses with trichlorosilane in benzene in the presence of triethylamine smoothly afforded the corresponding title 5-phosphino-D-xylopyranoses (**10—13a,b**) without causing epimerization at C-1 and ring-P. Treatment of **10—13** with sulfur efficiently provided the corresponding (phosphinothioyl)-in-ring sugar analogues.

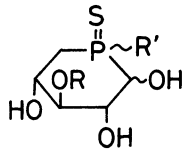
Because of a considerable interest in the physico-chemical properties and potential biological activity, various sugar analogues possessing a phosphorus atom in place of oxygen in the hemiacetal ring have been prepared in recent years:[1-4] e.g., D-glucopyranoses **1**,[5] D-ribofuranoses **2**,[6] and D-xylopyranoses **3**.[2] We now describe a convenient synthesis of the first P-in-ring pyranose analogues having an ethyl- or phenylphosphinediyl group in the hemiacetal ring through such a scheme that can readily be applicable to the preparation of various, similar sugar analogues. Hitherto unreported physico-chemical properties, as well as biological activity, of this type of compounds are anticipated to be highly of interest.




**1 (R=Et,OH)**



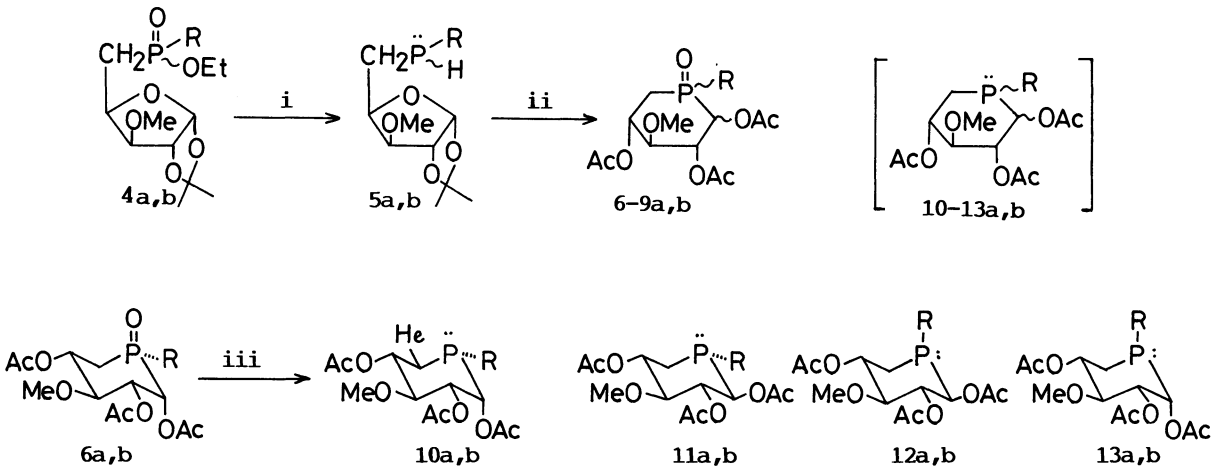

**2 (R=Et,OH)**




**3 (R=Me, R'=Ph)**
**(R=Bn, R'=Et)**

5-Deoxy-5-[ethoxy(ethyl)phosphinyl]-1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranose (**4a**)[7] was first reduced with lithium aluminum hydride (LAH) to give the 5-(ethylphosphino)-D-xylofuranoses **5a**.[8] Attempts to derive the title compounds **10a—13a** from **5a** were then made by the usual method[1] (i.e., hydrolysis with mineral acid and then acetylation, see Scheme 1). However, the main products isolated by silica-gel chromatography turned out to be the four diastereomers (with respect to C-1 and ring-P) of the oxidized 5-(ethylphosphinyl) compounds **6a—9a**.[8] As it was found extremely difficult to obtain **10a—13a** directly from **5a**, reduction of **6a—9a** with an appropriate reducing reagent was sought. After examination of various reagents, trichlorosilane-triethylamine[9] in boiling benzene was found to give the best result. Namely, a pure 5-[(R)-ethylphosphinyl]-α-D-xylo compound **6a** fur-

nished solely 5-[(S)-ethylphosphino] compound **10a** (colorless syrup, 70% isolated yield)[8] with retention of configuration of C-1 and ring-phosphorus atom. Similarly, 5-[(S)-P]-β-anomer **11a** (colorless syrup, 75%), 5-[(R)-P]-β-epimer **12a**, and 5-[(R)-P]-α-anomer **13a** were prepared[8] from the corresponding 5-[(R,S)-ethylphosphinyl]-α,β-D-xylopyranoses **7a**, **8a**, and **9a**, respectively.




Scheme 1. **a**: R=Et, **b**: R=Ph. Reagents: i, $LiAlH_4$/THF, 5 °C; ii, 1 M HCl-EtOH (1:1), 80 °C, 4 h then $Ac_2O$-Pyridine; iii, $HSiCl_3$-$Et_3N$/benzene, 80 °C, 2 h.

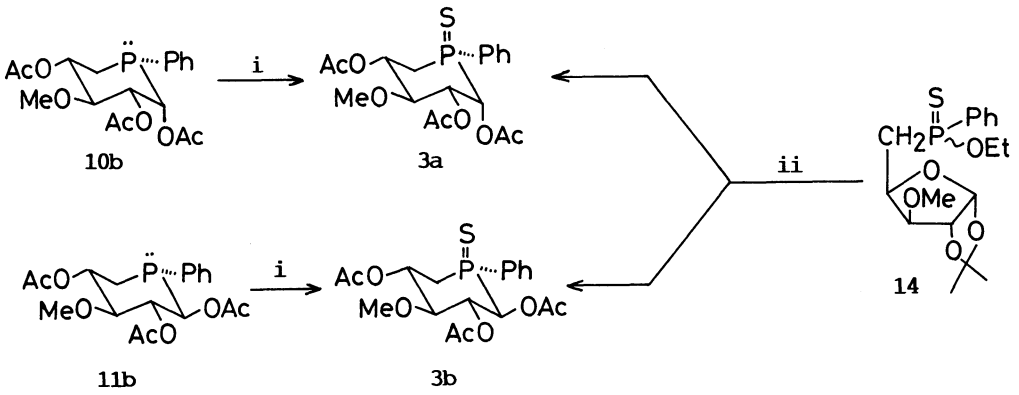
Almost identical results were obtained when the 5-(phenylphosphinyl) compounds **4b**[2] were subjected to the same procedures as those for **4a**. Namely, 5-(phenylphosphino)-α-D-xylofuranoses **5b** prepared from **4b** by the LAH reduction yielded only the oxidized 5-[(R,S)-phenylphosphinyl]-α,β-D-xylopyranoses **6b–9b**.[2] Therefore, **6b–9b** were reduced with trichlorosilane, providing[8] the corresponding 5-[(R)-phenylphosphino]-α-D-xylopyranose **10b** (syrup, 81% yield), 5-[(R)-P]-β-anomer **11b** (colorless prisms, mp 165–166 °C, 80% yield), 5-[(S)-P]-β-epimer **12b**, and 5-[(S)-P]-α-anomer (**13b**), respectively. These 5-phosphino compounds **10–13a,b** are stable at room temperature as long as they are kept as crystals or pure syrups (under nitrogen). In solution, however, they are rather unstable and tend to be slowly oxidized to **6–9a,b** in an open air; care to avoid oxygen should therefore be taken even on recrystallization. This would be the main reason for failure in preparation of these phosphino compounds directly from **5a,b**, whose procedure involves prolonged boiling with ethanolic HCl for deprotection of the 1,2-diol. The configurations of **10–13a,b**, all approximately in the $^4C_1$(D) conformation, were established by analysis of their 500-MHz $^1H$ NMR spectra (see Table 1), by taking into account the known parameters of structurally related compounds obtained before; e.g., **6b–9b**.[2] It is noteworthy that an appreciable upfield shift (ca. 0.2–0.5 ppm) is observed for signals of protons in the vicinity of a lone pair of electrons of ring-phosphorus in **10–13** compared with those close to P=O group in **6–9**. Those precise parameters, obtained for the first time by the present study on **10–13**, are thought to be of high value in determining the structures of other phosphino-in-ring sugar analogues, preparation of which is currently under investigation.

Table 1. $^1$H NMR (500 MHz) Parameters for Selected P-in-Ring Sugars in $CDCl_3$[a)]

| Compd | Chemical shift (δ) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1 | H-2 | H-3 | H-4 | He-5 | Ha-5 | Ac-1,2,4[b)] | | | MeO-3 | PCH | PCH' | $PCCH_3$ |
| | | | | | | | | | | | ($PC_6H_5$(o, m, p)) | | |
| **10a** | 5.73 | 5.12 | 3.53 | 5.05 | 2.04 | 1.88 | 2.18 | 2.09 | 2.03 | 3.46 | 1.46 | 1.35 | 1.01 |
| **10b** | 5.85 | 5.24 | 3.59 | 5.24 | 2.29 | 2.52 | 1.77 | 2.14 | 2.03 | 3.49 | (7.35 | 7.33 | 7.33) |
| **11a** | 5.26 | 5.23 | 3.25 | 5.05 | 2.18 | 1.55 | 2.08 | 2.05 | 2.04 | 3.44 | 1.62 | 1.50 | 1.05 |
| **11b** | 5.58 | 5.34 | 3.39 | 5.17 | 2.34 | 2.03 | 1.92 | 2.08 | 2.05 | 3.48 | (7.52 | 7.38 | 7.39) |
| **12a** | 5.33 | 5.45 | 3.19 | 5.10 | 2.10 | 1.57 | 2.08 | 2.05 | 2.04 | 3.46 | 1.78 | 1.78 | 1.16 |

| | Coupling constant (Hz) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $J_{1,2}$ | $J_{1,P}$ | $J_{1,5e}$ | $J_{2,3}$ | $J_{2,P}$ | $J_{3,4}$ | $J_{4,5e}$ | $J_{4,5a}$ | $J_{4,P}$ | $J_{5a,5e}$ | $J_{5e,P}$ | $J_{5a,P}$ |
| **10a** | 2.5 | 9.6 | 2.0 | 10.0 | 2.5 | 9.6 | 3.5 | 12.2 | 3.5 | 12.3 | c) | 5.9 |
| **10b** | 2.2 | 8.9 | 1.7 | 10.0 | 3.3 | 9.7 | 3.8 | 12.2 | 2.9 | 12.0 | 6.0 | 4.8 |
| **11a** | 10.8 | 5.3 | 0 | 9.1 | 3.6 | 9.4 | 3.7 | 12.4 | 3.3 | 12.4 | 7.1 | 6.9 |
| **11b** | 10.8 | 5.4 | 0 | 9.4 | 4.7 | 9.4 | 3.7 | 12.2 | 3.4 | 12.5 | 6.7 | 4.3 |
| **12a** | 10.7 | 17.8 | 0 | 9.6 | 1.8 | 9.8 | 4.4 | 11.9 | 0.5 | 15.1 | 4.6 | 7.9 |

a) Measured with a Varian VXR-500 instrument (the SC-NMR Lab., Okayama Univ.). The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique as well as by COSY spectra (if necessary), and the parameters were confirmed by a computer-assisted simulation analysis. b) The assignments of acetoxyl groups may have to be interchanged. c) Uncertain because of overlapping with acetoxyl signals.




Scheme 2. Reagents: i, $S_8$/benzene, 80 °C, 1 h; ii, $NaAlH_2(OCH_2CH_2OMe)_2$, $H_3O^+$, and then $Ac_2O$-Pyridine (Ref. 2).

A versatile reactivity of these phosphino-D-xylopyranoses is demonstrated by a facile conversion of these compounds into the corresponding 5-(phosphinothioyl) derivatives, as exemplified by the reactions of **10b** and **11b** to give **3a** and **3b**, respectively (both approximately in 80% isolated yields, see Scheme 2), upon

treatment with powdered sulfur in boiling benzene under argon. Compounds **3a** and **3b** had been obtained[2] only in a few % overall yields from the 5-[(ethoxy)-phenylphosphinothioyl]-D-xylofuranose precursors **14** but the attempted conversion of 5-phosphinyl compounds **6a** and **7b** directly into **3a** and **3b** has remained unsuccessful (e.g., by refluxing with phosphorus pentasulfide in benzene for 30 h under argon). Therefore, the above procedure via intermediates of phosphino-in-ring type is expected to be suitable for an efficient synthesis of a wide variety of (phosphinothioyl)-in-ring sugar analogues that are considered to be of interest in view of potential biological activity.

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