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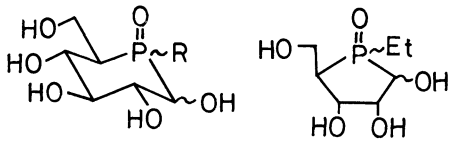
# Synthesis of 2,4-Dideoxy-4-[(S)-methyl- and (R)-cyclohexylphosphinyl]-α,β-D-erythro-pentofuranoses. The First P-in-Ring Sugar Analogues of 2-Deoxy-D-ribofuranose Type

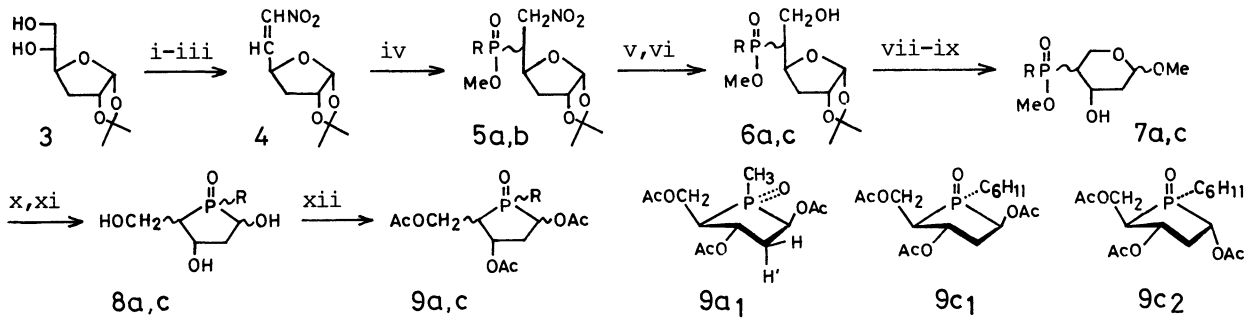
Hiroshi YAMAMOTO,* Ayashi NOGUCHI, Kenji TORII, Keiji OHNO, Tadashi HANAYA, Heizan KAWAMOTO, and Saburo INOKAWA
Department of Chemistry, Okayama University, Tsushima, Okayama 700

Starting with 3-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose, methyl 2,4-dideoxy-4-[(methoxy)methyl- and cyclohexylphosphinyl]-D-glycero-pentopyranosides were prepared in a 9 step sequence (20–25% overall yield). These were converted into the title compounds, which were characterized as the 1,3,5-tri-O-acetates.

Because of a considerable interest in the physicochemical 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] e.g., D-glucopyranoses **1**[2] and D-ribofuranoses **2**.[3] We now describe a convenient synthesis of the first P-in-ring sugar analogues with 2-deoxy-D-ribofuranose structure having an alkylphosphinyl group in the ring through such a scheme that can readily be applicable for the preparation of various other 2,4-dideoxy-4-phosphinyl-D- and L-aldofuranoses.




Thus, 3-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose (**3**)[4] was converted into the key intermediates **7a** (20% overall yield) and **7c** (25%) by sequence of **3** → **4** → **5** → **6** → **7** (9 steps) as illustrated in Scheme 1.[5] Then, **7a** and **7c** were (separately) subjected to the reduction with sodium dihydrobis(2-methoxyethoxy)-aluminate (SDMA), followed by hydrolysis in ethanolic 0.5 M HCl at 80 °C, affording crude 2,4-dideoxy-4-(methyl- and cyclohexylphosphinyl)-D-glycero-pentofuranoses




Scheme 1. **a**: R=Me, **b**: R=Ph, **c**: R=cyclohexyl. Reagents: i, $NaIO_4$; ii, $MeNO_2$-MeONa/MeOH; iii, $Ac_2O$-AcONa; iv, RPH(=O)OMe in benzene, 80 °C; v, $H_2$-$PtO_2$; vi, $NaNO_2$/AcOH; vii, aq AcOH; viii, $NaIO_4$; ix, $H^+$/MeOH; x, SDMA; xi, 0.5 M HCl-EtOH; xii, $Ac_2O$-Pyridine.

(**8a** and **8c**), respectively, which were converted into their tri-O-acetates (**9a** and **9c**) by the usual method (in 15 and 18% overall yields from **7a** and **7c**, respectively). By rechromatography of **9a** in a column of silica gel with 19:1 (v/v) ethyl acetate-ethanol as the eluant, a pure product 1,3,5-tri-O-acetyl-2,4-didexoy-4-[(S)-methylphosphinyl]-β-D-erythro-pentofuranose (**9a**$_1$) was isolated as colorless prisms (mp 135-136 °C, 4% overall yield from **7a**).[6] By the similar chromatographic purification of **9c**, 4-[(R)-cyclohexylphosphinyl]-β- analogue **9c**$_1$ (colorless needles, mp 146–147 °C, 3% yield from **7c**) and its α-anomer **9c**$_2$ (colorless syrup, 5% yield) were separated as pure compounds.[6] The configuration of **9a**$_1$ and **9c**$_{1,2}$, all approximately in the $^3T_2$(D) conformation, was established by analysis of their 500-MHz $^1$H NMR spectra (see Table 1), by taking into account the known parameters of structurally related compounds obtained before; e.g., per-O-acetates[3] of **2**. Those parameters for **9a**$_1$ and **9c**$_{1,2}$ are considered to be highly versatile in determining the structures of other 2,4-dideoxy-4-phosphinyl-D- and L-aldofuranoses, preparation of which is currently under investigation.

Table 1. $^1$H NMR (500 MHz) Parameters for **9a**$_1$ and **9c**$_{1,2}$ in $CDCl_3$[a]

| | Chemical Shifts (δ) and Coupling Constants (Hz) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Compd | H-1 | H-2 | H-2' | H-3 | H-4 | H-5 | H'-5 | Ac-1,3,5[b] | R-P | $J_{1,2}$ | $J_{1,2'}$ |
| **9a**$_1$ | 5.33 | 2.39 | 2.38 | 5.12 | 2.61 | 4.44 | 4.23 | 2.13,2.10,2.10 | 1.63[c] | 3.9 | 5.8 |
| **9c**$_1$ | 5.23 | 2.51 | 2.02 | 5.38 | 2.41 | 4.47 | 4.24 | 2.16,2.07,2.05 | 2.13[d] | 4.4 | 6.9 |
| **9c**$_2$ | 5.49 | 2.67 | 1.82 | 5.48 | 2.58 | 4.45 | 4.27 | 2.13,2.11,2.04 | 2.13[d] | 4.8 | 4.3 |

| | Coupling Constants (Hz) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $J_{1,P}$ | $J_{2,2'}$ | $J_{2,3}$ | $J_{2,P}$ | $J_{2',3}$ | $J_{2',P}$ | $J_{3,4}$ | $J_{3,P}$ | $J_{4,5}$ | $J_{4,5'}$ | $J_{4,P}$ | $J_{5,5'}$ | $J_{5,P}$ | $J_{5',P}$ |
| **9a**$_1$ | 6.4 | 14.6 | 6.7 | 22.5 | 9.5 | 5.5 | 7.7 | 3.3 | 5.9 | 8.0 | 20.6 | 11.7 | 17.4 | 13.3 |
| **9c**$_1$ | 6.1 | 14.4 | 6.3 | 16.6 | 7.9 | e) | 6.3 | 7.0 | 6.8 | 8.4 | 6.3 | 11.7 | 6.8 | 11.3 |
| **9c**$_2$ | 16.2 | 14.3 | 7.1 | 21.0 | 8.7 | 8.4 | 6.3 | 1.5 | 6.1 | 9.0 | 6.3 | 11.6 | 6.1 | 9.3 |

a) Measured with a Varian VXR-500 instrument. b) The assignments of acetoxyl groups may be interchanged. c) For Me-P; $J_{Me,P}$=13.5 Hz. d) For HC-P. For the remaining cyclohexyl protons: δ=1.25-1.95 (10H, m). e) Uncertain because of overlapping with the AcO signals.

References

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5) MS (high-resolution) and $^1$H NMR data (mostly at 500 MHz) were in agreement with the products described in this paper. The complete data for the newly isolated products as well as a result of a more precise conformational study will be presented in a future paper.
6) Besides these pure compounds, though not yet completely separated, other diastereomers of **9a** and **9c** were obtained from the remaining fractions. These were mostly compounds of 2-deoxy-D-ribofuranose type but contained a minor proportion of the L-threo-pentofuranoses (by NMR). Their complete separation and the characterization are in progress. Improvement of the synthetic route to the key intermediates **7** as well as optimization of the conversion of **7** to **9** are also under intensive investigation.

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