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AN IMPROVED SYNTHESIS OF 1,2,3,4,6-PENTA-*O*-ACETYL-5-DEOXY-5-*C*-[(*R,S*)-ETHYLPHOSPHINYL]-α,β-D-GLUCOPYRANOSES, AND FORMATION OF 2,3,4,6-TETRA-*O*-ACETYL-1,5-ANHYDRO-5-DEOXY-5-*C*-[(*R*)-ETHYLPHOSPHINYL]-D-GLUCITOL

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ABSTRACT

Treatment of 3-*O*-acetyl-5-deoxy-5-*C*-[ethyl(methoxy)phosphinyl]-1,2-*O*-isopropylidene-6-*O*-(triphenylmethyl)-α-D-*xylo*-hexofuranose, conveniently prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucose in 8 steps, with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by methanolic hydrochloric acid, and then acetic anhydride in pyridine, gave the title D-glucopyranoses in a higher overall yield than by the previous, alternative route. A minor amount of the title D-glucitol was also isolated, and characterized. Accurate ^{1}H-n.m.r. parameters for these ring-phosphorus-containing sugar analogs were obtained by the simulation analysis of their 400-MHz spectra.

INTRODUCTION

We recently reported[1] the first synthesis of unsubstituted 5-deoxy-5-*C*-(ethylphosphinyl)-D-glucopyranoses (**7**), starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) by the sequence **1** → **2** → **3** → **4** → **5** → **7**, and the final products were characterized as the four kinds of peracetates **8a–d**. The overall yield of these transformations, in 15 steps, was 0.9%. Our interest in the further investigation of the physicochemical properties, as well as their potential biological activity, prompted us to explore a more efficient route for preparing such D-glucose analogs having phosphorus in the hemiacetal ring[2]. We now describe an improved synthesis of **7** from **1** by a different route.

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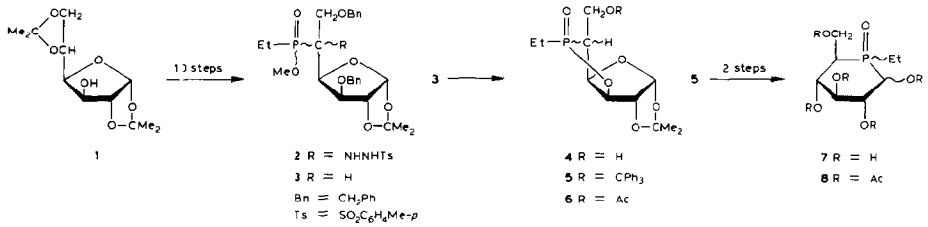


RESULTS AND DISCUSSION

Addition of methyl ethylphosphinate to 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-nitro-α-D-*xylo*-hex-5-enofuranose[3] (**9**), available from **1** in 4 steps (42% overall yield), had been reported[4] to give a mixture (**10**) of the D-*gluco* and L-*ido* compounds in 90% yield. Reduction of this mixture in the presence of hydrochloric acid in methanol, with platinum oxide as the catalyst, afforded[4] the 6-amino-D-gluco- and -L-ido-furanose hydrochlorides (**11**) (80% yield), the deamination of which with nitrous acid gave the D-gluco- and L-ido-furanoses (**12**) in a 59% yield. Although the D-*gluco* component of **12** had been shown[4] to be spontaneously transformed into the 5-deoxy-5-*C*,3-*O*-(*cyclo*-ethylphosphinate)-D-glucofuranose (**6**), we obtained stable compound **12** in 75% overall yield from **10** in the present reinvestigation.

Compound **12** was then converted into the 6-*O*-triphenylmethyl (**13**) and 6-*O*-(tetrahydropyran-2-yl) (**14**) derivatives in 50 and 71% yield, respectively, by the usual methods. Reduction of **13** with sodium dihydrobis(2-methoxyethoxy)-aluminate (SDMA), followed by hydrolysis in methanolic 0.5M hydrogen chloride at 65°, afforded a crude mixture (**7**) of 5-deoxy-5-*C*-(ethylphosphinyl)hexopyranoses which were characterized by conversion into the peracetates with acetic anhydride in pyridine by the method described previously[1]. Purification on a column of silica gel, with 1:19 (v/v) methanol–dichloromethane as the eluant, gave a colorless oil (R_F 0.5–0.3 with the same eluant; 25% overall yield from **13**), which

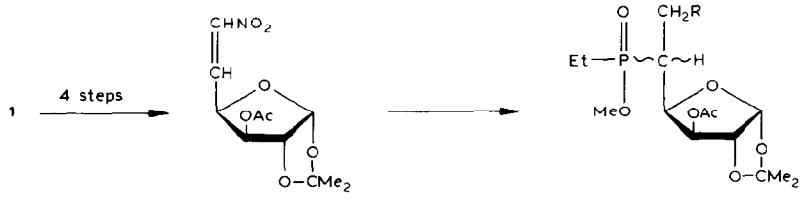


TABLE I

400-MHz, ^{1}H-N M R PARAMETERS FOR **8a–d** AND **15** IN $CDCl_3$[a]

Compounds	*Chemical shifts (δ)*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*AcO-1,2,3,4,6*[b]	*P-CH_2-C*	*P-C-CH_3*
8a	5.38	5.72	5.22	5.58	2.37	4.49	4.44	2.16, 2.07, 2.06, 2.01, 1.99	2.065	1.19
8b	5.84	5.56	5.45	5.59	2.50	4.45	4.41	2.21, 2.09, 2.07, 2.03, 1.98	1.72	1.21
8c[c]	5.65	5.35	5.25	5.25	2.35	4.70	4.30	2.20, 2.09, 2.07, 2.04, 1.98	2.0	1.40
8d[c]	5.93	5.24	5.45	5.28	2.60	4.75	4.30	2.18, 2.09, 2.07, 2.04, 1.98	2.0	1.40
15	2.73[d]	4.87	5.23	5.21	2.53	4.68	4.29	— 2.09, 2.08, 2.06, 2.04	1.82	1.37
	2.10[e]									

	Coupling constants (Hz)[f]															
	$J_{1,2}$	$J_{1,P}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{4,5}$	$J_{4,P}$	$J_{5,6}$	$J_{5,6'}$	$J_{5,P}$	$J_{6,P}$	$J_{6',P}$	$J_{6,6'}$	$^2J_{H,P}$	$^3J_{H,P}$	$^3J_{H,H}$
8a	11.0	3.6	10.0	3.0	10.0	11.5	2.7	7.4	5.0	3.5	11.5	15.5	11.5	15	19.2	7.7
8b	3.2	11.7	10.0	0.3	12.5	15.0	3.0	8.3	6.0	5.0	16.2	19.0	14.5	15	18.3	7.5
8c[c]	10	3														7.5
8d[c]	4.0	12	10		10	12		4	2		24	9	14	15		7.5
15	4.0[g]	15.5[h]	9.5	2.0	10.0	11.0	4.0	3.8	2.5	18.2	23.1	8.7	12.0	15.2	17.6	7.6
	11.5[i]	8[j]	14.5[k]													

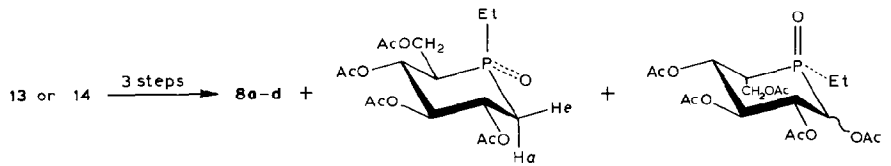
[a]Although some of the parameters for **8a–d** were previously reported[1], these have been re-examined by simulation analysis (see ref. 6), resulting in the correction of a few of the previous values. [b]Acetoxyl assignments are interchangeable. [c]Some values are approximate, because of overlapping with other signals. [d]For H-1e. [e]For H-1a. [f] *J* values confirmed by double resonance. [g]$J_{1e,2}$ [h]$J_{1e,P}$ [i]$J_{1a,2}$ [j]$J_{1a,P}$ [k]$J_{1a,1e}$

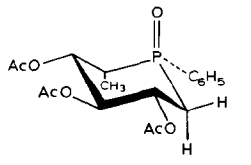
was found to consist mostly of a mixture of the peracetates (**8**). By rechromatography with the same eluant, the crude product was separated into four major fractions, which will be referred to as A, B, C, and D according to their decreasing R_F values (0.50, 0.45, 0.40–0.35, and 0.30) with 5% methanol–dichloromethane).

Fractions A (5% overall yield from **13**) and B (6% yield) were found by 400-MHz, ^{1}H-n.m.r. spectroscopy to be respectively the β (**8a**) and α anomer (**8b**) of penta-*O*-acetyl-5-deoxy-5-*C*-[(*R*)-ethylphosphinyl]-D-glucopyranose[1]. Accurate parameters of the 400-MHz, ^{1}H-n.m.r. signals, obtained by computer-aided simulation analysis, are shown in Table I, and these values are considered to be important in view of ready establishment of the configurations of the ring-carbon atoms, the orientations of the protons thereon, and the stereochemistry of the phosphorus atom in such hexopyranoses.

The slowest-eluting fraction (D) was a colorless oil (1.5% yield), the molecular composition of which was confirmed by high-resolution, e.i.-mass spectrometry to be $C_{16}H_{25}O_9P$ (corresponding to that of **8** less CH_2CO_2). The precise structure, 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-5-deoxy-5-*C*-[(*R*)-ethylphosphinyl]-D-glucitol (**15**), for this product was established on the evidence of the 400-MHz, ^{1}H-n.m.r. spectroscopy. The characteristic splitting-patterns of the three AMX-type, proton signals at δ 2.53, 2.73, and 2.10, due to H-5 and two H-1, as well as the large magnitudes of the $J_{4,5}$ (11.0 Hz) and $J_{5,P}$ (18.2 Hz) values, and an appreciable, upfield shift (~0 4 p.p.m.) for the H-2 and H-4 signals, which differed markedly from those[5] of 2,3,4-tri-*O*-acetyl-1,5-anhydro-5,6-dideoxy-5-*C*-[(*S*)-phenylphosphinyl]-L-iditol (**17**), were compatible with the 5-*C*-[(*R*)-ethylphosphinyl]-D-glucitol structure; the assignments of the signals are recorded in Table I. This over-reduced product was apparently formed, owing to use of an excess of SDMA, *via* a reaction pathway similar to that described[5] for the formation of **17**.

Fraction C was a colorless liquid which was found, by 400-MHz, ^{1}H-n.m.r. spectroscopy, to be mainly a mixture of **8c** (2%) and **8d** (2%). However, besides

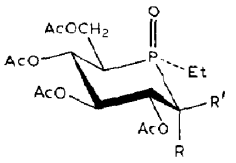




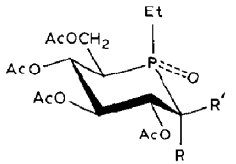
the signals of these compounds, an H-5 signal of low intensity was present at δ 2.91, with a large $J_{5,P}$ (20 Hz) and a small $J_{4,5}$ (5 Hz) value, suggesting that this fraction also contained a small proportion of an L-idopyranoid compound (**16**), taking into account the characteristic splitting patterns of its proton signals that closely resembled those of per-*O*-acetyl-5,6-dideoxy-5-*C*-[(*S*)-phenylphosphinyl]-α,β-L-idopyranoses[5]. Separation of **8c** from **8d** could not be achieved by repeated chromatography.

Reduction of the 6-*C*-(tetrahydropyran-2-yl) compound **14** with SDMA, followed by the same treatment as for **13**, afforded **8a** and **8b**, but in a less satisfactory yield (2% each), probably owing to the instability of the protecting group on O-6 during the reductive reaction.

Thus, compounds **8a–d** have now become available from **1**, in 11 steps in 3.5% overall yield, *via* the key intermediates **10** and **13**.



8a R = H, R′ = OAc
8b R = OAc, R′ = H



8c R = H, R′ = OAc
8d R = OAc, R′ = H

EXPERIMENTAL

General methods. — All reactions were monitored by t.l.c., and the products were detected with sulfuric acid–ethanol, or cobalt(II) chloride–acetone, as the indicator. Column chromatography was performed by using Wako C-200, unless otherwise specified. T.l.c. was conducted on plates precoated with silica gel (0.25 mm, Merck). ^{1}H-N.m.r. spectra were recorded, for solutions in $CDCl_3$, with a Hitachi–Perkin–Elmer R-20A (60 MHz) or Bruker WH-400 cryospectrometer (400-MHz, for **8, 15,** and **16**) at 27°. Chemical shifts are recorded as δ values relative to tetramethylsilane (δ 0.0) as the internal standard. Mass spectra were recorded with a Hitachi RM-50GC low-resolution, or an A.E.I. MS 50 ultra-high-resolution, instrument (for **15**), and are given in terms of *m/z* (relative intensity) compared with base peaks.

Materials. — 3-*O*-Acetyl-5-deoxy-5-*C*-[ethyl(methoxy)phosphinyl]-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**12**) was prepared, by the method described previously[4], from[3] **9**, via **10** and **11**, in a 67% overall yield. When purified by use of a column of silica gel, the colorless syrupy **12** remained unchanged on standing at room temperature.

3-O-Acetyl-5-deoxy-5-C-[ethyl(methoxy)phosphinyl]-1,2-O-isopropylidene-6-O-(triphenylmethyl)-α*-D-xylo-hexofuranoses* (**13**). — A mixture of **12** (0.45 g, 1.28

mmol) and chlorotriphenylmethane (0.75 g, 2.7 mmol) in dry pyridine (5.5 mL) was heated for 5 days at 40–50°, cooled, and evaporated at 15° *in vacuo* (pump). A solution of the residue in CH_2Cl_2 was successively washed with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel with 1:1 ethyl acetate–benzene as the eluant, giving, besides recovered starting-material **12** (11%), **13** as a colorless syrup (0.38 g, 50% yield); R_F 0.2–0.4 (1:19 EtOH–EtOAc); ^{1}H-n.m.r.: δ 1.30, 1.53 (2 s, 6 H, CMe_2), 0.7–2.0 (m, 5 H, P-CH_2CH_3), 2.0–2.5 (m, 1 H, H-5), 2.05 (s, 3 H, AcO-3), 3.8–4.8 (m, 4 H, H-2,4,6,6'), 3.35 (d, 3 H, *J* 10 Hz, POMe), 5.35 (br d, 1 H, *J* 3 Hz, H-3), 5.87 (d, 1 H, *J* 4 Hz, H-1), and 7.1–7.7 (m, 15 H, CPh_3); *m/z* 594 (M^+).

3-O-Acetyl-5-deoxy-5-C-[ethyl(methoxy)phosphinyl]-1,2-O-isopropylidene-6-O-(tetrahydropyran-2-yl)-α-D-xylo-hexofuranoses (**14**). — A mixture of **12** (0.50 g, 1.42 mmol), dihydropyran (0.68 mL, 7.45 mmol), and *p*-toluenesulfonic acid (35 mg) in dry 1,4-dioxane (10 mL) was stirred for 7 days at 20°, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and processed as described for **13**, giving **14** as a colorless syrup (0.44 g, 71%); R_F 0.1–0.2 (EtOAc); ^{1}H-n.m.r.: δ 1.39, 1.50 (2 s, 6 H, CMe_2), 0.8–2.3 [m, 11 H, P-CH_2CH_3, C-$(CH_2)_3$-C-O-6], 2.08 (s, 3 H, AcO-3), 2.4–2.9 (m, 1 H, H-5), 3.76, 3.78 (2 d, 3 H, *J* 10 Hz, P-OMe), 3.5–3.9 (m, 3 H, C-CH_2-O-CH-O-6), 4.0–4.8 (m, 4 H, H-2,4,6,6'), 5.26 (d, 1 H, *J* 3 Hz, H-3), and 5.90 (d, 1 H, *J* 4.0 Hz, H-1); *m/z* 436 (M^+).

1,2,3,4,6-Penta-O-acetyl-5-deoxy-5-C-(ethylphosphinyl)-α,β-D-glucopyranoses (**8a–d**) *and 2,3,4,6-tetra-O-acetyl-1,5-anhydro-5-deoxy-5-C-[(R)-ethylphosphinyl]-D-glucitol* (**15**). *A.* — According to the procedure described[1] for **5**, compound **13** (540 mg, 0.91 mmol) was treated with 0.5 mL (1.5 mmol) of SDMA (70% in toluene) at 0° until the starting material disappeared, then with oxygen-free, methanolic 0.5M HCl under argon at 65°, and finally, with acetic anhydride–pyridine. The crude products were chromatographed on a column of silica gel, with 1:19 MeOH–CH_2Cl_2 as the eluant. The fraction having R_F 0.5–0.3 (with the same eluant) was collected, and evaporated *in vacuo*, giving the peracetates **8** as a mixture of diastereoisomers; colorless oil (101 mg, 25% overall yield from **13**). This product was separated by chromatography (Merck Lobar, prepacked, Size A), with 1:99 MeOH–CH_2Cl_2 as the eluant, into four fractions, A–D.

Fraction A (R_F 0.50) gave **8a** as colorless crystals (20 mg, 5% yield from **13**); m.p. 233° (lit.[1] m.p. 233°); for ^{1}H-n.m.r. data, see Table I.

Fraction B (R_F 0.45) gave **8b** as a colorless oil (24 mg, 6%); for ^{1}H-n.m.r. data, see Table I.

Fraction C (R_F 0.40–0.35) gave a colorless oil, which consisted mainly of **8c** (8 mg, 2%) and **8d** (8 mg, 2%), but contained a small proportion (~0.5%) of the minor product **16**; for ^{1}H-n.m.r. data, see Table I.

Fraction D (R_F 0.30) gave **15** as a colorless oil (6 mg; 1.5% from **13**); for 400-MHz, ^{1}H-n.m.r. data, see Table I; *m/z* 393 (2.99, M + 1), 392 (3.56, M^+), 350 (8.9, M − CH_2CO), 333 (16.2, M − AcO), 306 (42.7, M − 2 CH_3CO − H), 291

(28.0, M − AcO − CH_2CO), 289 (24.2), 264 (13.7), 247 (51.7), 231 (25.3), 205 (46.2), and 163 (100, $C_6H_{12}O_3P$).

Anal. Calc. for $C_{16}H_{25}O_9P$ (M^+): mol. wt., 392.1235. Found: mol. wt., 392.1235.

Besides these separated products, an unseparated mixture (30 mg) of **8a–d** and **15** was recovered from the intermediate fractions.

B. Following the same procedure as before, compound **14** (720 mg, 1.65 mmol) was successively treated with SDMA (1 mL, 3 mmol), methanolic HCl, and acetic anhydride–pyridine. Purification of the crude products by means of a column of silica gel afforded **8a** (8 mg, 2% yield) and **8b** (8 mg, 2%), in addition to a mixture of smaller amounts of **8c, 8d,** and **15**.

REFERENCES

1 H. YAMAMOTO, K. YAMAMOTO, S. INOKAWA, M. YAMASHITA, M.-A. ARMOUR, AND T. T. NAKASHIMA, *J. Org. Chem.*, 48 (1983) 435–440, and references cited therein.
2 For a review, see H. YAMAMOTO AND S. INOKAWA, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 135–191.
3 R. L. WHISTLER AND R. E. PYLER, *Carbohydr. Res.*, 12 (1970) 201–210.
4 H. TAKAYANAGI, K. SEO, M. YAMASHITA, H. YOSHIDA, T. OGATA, AND S. INOKAWA, *Carbohydr. Res.*, 63 (1978) 105–113.
5 H. YAMAMOTO, K. YAMAMOTO, H. KAWAMOTO, S. INOKAWA, M.-A. ARMOUR, AND T. T. NAKASHIMA, *J. Org. Chem.*, 47 (1982) 191–193; S. INOKAWA, K. YAMAMOTO, H. KAWAMOTO, H. YAMAMOTO, M. YAMASHITA, AND P. LUGER, *Carbohydr. Res.*, 106 (1982) 31–42; H. YAMAMOTO, K. YAMAMOTO, S. INOKAWA, AND P. LUGER, *ibid.*, 113 (1983) 31–43.
6 K. SATAKE, Y. HARA, H. MURATA, AND H. YAMAMOTO, *Kagaku*, 39 (1984) (3) A1–A8.