Carbohydrate Research, 127 (1984) 35–42
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF 1,2,3,4-TETRA-*O*-ACETYL-5-DEOXY-5-*C*-[(*R*) AND (*S*)-METHOXYPHOSPHINYL]-α- AND -β-D-RIBOPYRANOSES

HIROSHI YAMAMOTO, MASAHIKO HARADA, SABURO INOKAWA*,
Department of Chemistry, Faculty of Science, Okayama University, Okayama 700 (Japan)

KUNIAKI SEO,
Department of Industrial Chemistry, Numazu Technical College, Numazu 410 (Japan)

MARGARET-ANN ARMOUR, AND THOMAS T. NAKASHIMA
Department of Chemistry, The University of Alberta, Edmonton, Alberta T6G 2G2 (Canada)
(Received October 5th, 1983; accepted for publication, October 26th, 1983)

ABSTRACT

Treatment of methyl 5-deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by hydrogen peroxide, mineral acid, and hydrogen peroxide, gave 5-deoxy-5-*C*-(hydroxyphosphinyl)-α,β-D-ribopyranoses in 40–45% overall yield. The structures of these sugar analogs were effectively established on the basis of the mass and 400-MHz, ^{1}H-n.m.r. spectra of the title compounds, derived by treatment with diazomethane and then acetic anhydride in pyridine.

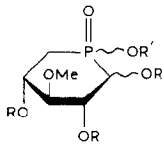
INTRODUCTION

In our initial effort to prepare sugar analogs having a hydroxyphosphinyl group, instead of a more abundantly prepared alkyl- or aryl-phosphinyl group[1], in the hemiacetal ring, we recently reported[2,3] an efficient synthesis of 5-deoxy-5-*C*-(hydroxyphosphinyl)-3-*O*-methyl-D-xylopyranoses (**1**) from 5-deoxy-5-*C*-(diethoxyphosphinyl)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose in four steps in 65% overall yield. The structures of **1** were unequivocally established by conversion into their 1,2,4-tri-*O*-acetyl-5-deoxy-5-*C*-[(*R*,*S*)-methoxyphosphinyl]-D-xylopyranose derivatives (**2**), which were separated into four diastereoisomers (such as **2a** and **2b**) with regard to C-1 and the ring-phosphorus atom.

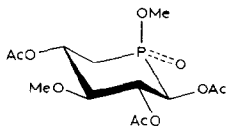
Preparation of such sugar analogs was carried out in order to study their physicochemical properties and also to explore the utility of their potential, biological activity. Among these pentopyranoses, 5-deoxy-5-*C*-(ethyl- and butyl-phosphinyl)-D-xylopyranoses[4] and 5-deoxy-5-*C*-(ethylphosphinyl)-D-ribopyranoses[5] (**3**) had been prepared from the corresponding 5-deoxy-5-*C*-(phosphinyl)pen-

*To whom correspondence should be addressed.

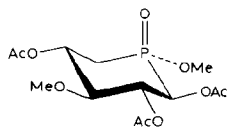
0008-6215/84/$ 03.00



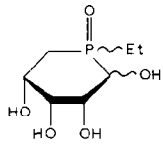
1 R = R′ = H
2 R = Ac, R′ = Me



2a



2b



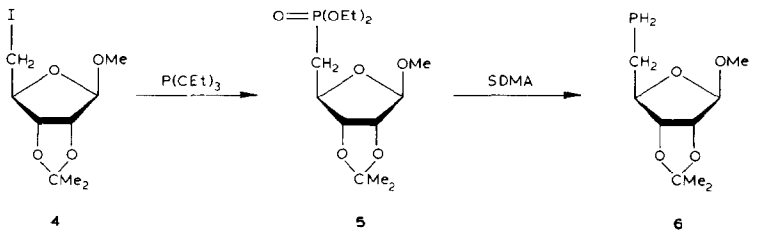
3

tofuranose precursors at an earlier stage of our investigation. We now report the synthesis of 5-deoxy-5-*C*-(hydroxyphosphinyl)-D-ribopyranoses (**10**) and an effective way of achieving their structural assignment by ^{1}H-n.m.r. spectroscopy and high-resolution mass spectrometry.

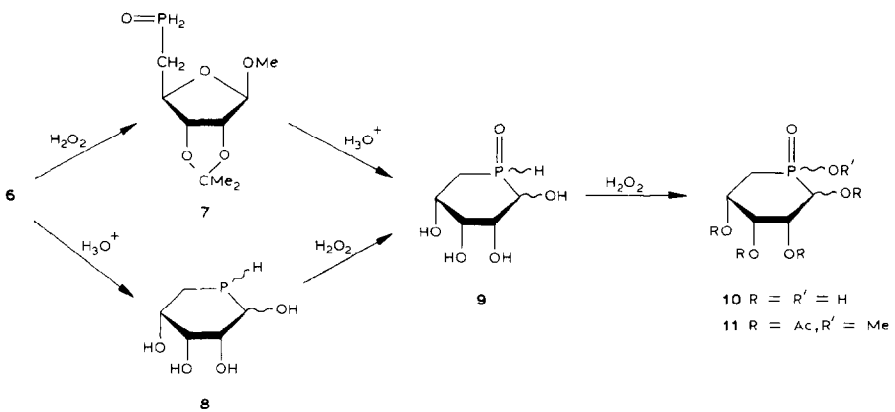
RESULTS AND DISCUSSION

Methyl 5-deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**), which had been prepared[6] by a Michaelis–Arbuzov reaction of its 5-*C*-iodo precursor[5,7] with triethyl phosphite in 31% yield, but was now readily available in 82% yield by our modified method, served as the starting material.

Following a scheme similar to that[2] employed for the preparation of **1**, the phosphonate **5** was reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), to afford the phosphine **6**, which was immediately oxidized with one equivalent of hydrogen peroxide in 2-propanol, to give the phosphine oxide **7**. Hy-



4 5 6



7 8 9

10 R = R′ = H
11 R = Ac, R′ = Me

drolysis of **7** by refluxing with ethanolic 0.25M sulfuric acid under nitrogen afforded the 5-deoxy-5-*C*-(phosphinyl)-D-ribopyranoses **9**, which were further oxidized with an excess of hydrogen peroxide, to give the 5-deoxy-5-*C*-(hydroxyphosphinyl)-D-ribopyranoses **10** in 40% overall yield (from **5**). Alternatively, the products **10** were prepared from **5**, in 45% overall yield, by first subjecting **6** to an acid-catalyzed, ring-enlargement reaction, and then oxidizing the resultant 5-deoxy-5-*C*-(phosphino)-D-ribopyranoses (**8**) with hydrogen peroxide.

As **10** could not be separated into single components either by recrystallization or by column chromatography, an unambiguous structural assignment was made by conversion into their 5-*C*-(methoxyphosphinyl) peracetates **11** by treatment with diazomethane and then acetic anhydride in pyridine. The crude products **11** were separated (by column chromatography on silica gel, using ethyl acetate–hexane as the eluant) into three major fractions, which will be referred to as A, B, and C according to their decreasing R_F values.

Fraction B afforded the main product as a colorless syrup, whose mass spectrum clearly exhibited the molecular-ion peak at *m/z* 381, corresponding to $C_{14}H_{22}O_{10}P$ (M + 1; 1.40%), and also showed the characteristic fragmentation-pattern[3,8] of pentopyranoses having a phosphorus atom in the hemiacetal ring (see later). The precise structure of this compound was derived by comparing its 400-MHz, ^{1}H-n.m.r. spectrum with that[2] of a structurally related analog **2a** (see the n.m.r. parameters of **2a** shown in Table I). That is, the splitting patterns of the H-1

TABLE I

400-MHz, ^{1}H-N M R PARAMETERS FOR 5-DEOXY-5-*C*-(PHOSPHINYL)RIBOPYRANOSES IN $CDCl_3$

Compounds	*Chemical shifts (δ)*							
	H-1	*H-2*	*H-3*	*H-4*	*H-5*e	*H-5*a	*AcO-1,2,3,4*[a]	*MeO–P*
2a[b]	5.44	5.22	3.36	4.98	2.52	1.92	2.14, 2.12, 2.09, 3.51[c]	3.94
11a	5.77	5.21	5.62	5.16	2.33	2.42	2.20, 2.14, 2.03, 2.00	3.95
2b[b]	5.27	5.45	3.42	5.24	2.55	1.91	2.16, 2.10, 2.08, 3.48[c]	3.77
11b	5.55	5.43	5.69	5.40	2.37	2.08	2.20, 2.17, 2.02, 2.00	3.80
11c[d]	5.6	5.4	5.6	5.3	2.3	2.1	2.18, 2.16, 2.05, 2.03	3.77
11d[d]								3.90

	Coupling constants (Hz)[e]												
	$J_{1,2}$	$J_{1,P}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{3,5e}$	$J_{4,5e}$	$J_{4,5a}$	$J_{4,P}$	$J_{5a,5e}$	$J_{5e,P}$	$J_{5a,P}$	J_{POMe}
2a[b]	10.8	3.6	9.6	2.1	9.6	0	4.5	12.0	2.0	14.8	23.6	10.0	10.5
11a	11.2	4.0	2.5	2.0	2.3	1.0	5.0	12.2	2.1	14.0	23.0	11.2	10.5
2b[b]	10.5	5.5	8.7	3.9	8.6	0	4.5	12.5	0.8	14.8	22.5	11.0	11.2
11b	11.2	4.8	2.7	2.2	2.3	1.0	4.6	10.3	2.2	14.0	22.0	11.0	11.0
11c[d]												11.0	
11d[d]												10.0	

[a]Acetoxyl assignments are interconvertible. [b]Ref. 2. [c]MeO-3. [d]Parameters of other signals were not available, because of overlapping (at 60 MHz). [e]*J* values confirmed by double resonance.

signal (doublet of doublets with $J_{1,2}$ 11.2 and $J_{1,P}$ 4.0 Hz) and the appearance of the H-2 and H-4 signals at a slightly higher field (compared with those of **11b**; see later) led to the 5-deoxy-5-*C*-[(*S*)-methoxyphosphinyl]-β-D-ribopyranose structure **11a**, in the $^4C_1$(D) conformation, for this product. The assignments of all signals were readily made as before[1–3,9], and the results are summarized in Table I.

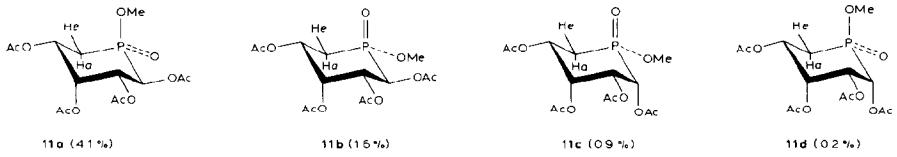
The small magnitude of $J_{2,3}$ and $J_{3,4}$ (compared with those of the xylose analogs **2a** and **2b**), as well as the presence of the 1,5-W coupling ($J_{3,5e}$ 1.0 Hz) would be compatible with the D-ribopyranose structure. It may be noted that the H-5*a* signal appears at a lower field than that of H-5*e* in the spectrum of compound **11a**, probably due to a deshielding effect by the neighboring, axial acetoxyl group on C-3; the H-5*a* signals usually appear at a higher field (0.3–0.7 p.p.m.) than those of H-5*e* for 5-deoxy-5-*C*-(phosphinyl)pyranoses in the $^4C_1$(D) conformation (such as **2a**,**b**)[1–3,9].

The fastest-eluting fraction (A) afforded a minor product as a colorless syrup. Although the splitting patterns in the 400-MHz, ^{1}H-n.m.r. spectrum of this product, on the whole, resembled those of **11a**, the downfield shift (0.2–0.25 p.p.m.) of the H-2 and H-4 signals and the upfield shift (0.15–0.35 p.p.m.) of the H-1 and P–OMe signals accounted for the 5-*C*-[(*R*)-methoxyphosphinyl]-β-D-ribopyranose structure **11b**, presumably in the $^4C_1$(D) conformation; analogous shielding and deshielding by phosphinyl oxygen had been observed among a large number of 5-*C*-[(*R*)- and (*S*)-phosphinyl] epimers[1–3,9]. Assignments for the n.m.r. signals of **11b**, together with the parameters of **2b** for comparison, are recorded in Table I.

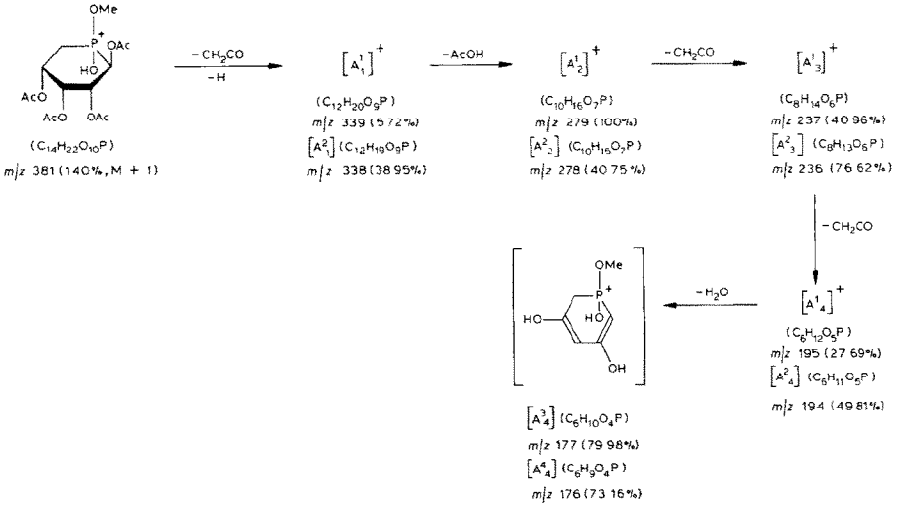
The slowest-moving fraction (C) gave a small amount of a colorless syrup, which, on the evidence of the n.m.r. spectrum, mainly consisted of an inseparable mixture of the α anomers (**11c** and **11d**) of compounds **11b** and **11a**, respectively; their characteristic n.m.r. signals are listed in Table I.

The yields of the four diastereoisomers of the 5-*C*-(methoxyphosphinyl)ribopyranoses **11a–d** are given in Scheme 1. It should be noted that the relatively low yield of each product from **5** can mainly be attributed to inefficient methylation of **10** (dissolved in dimethyl sulfoxide) with ethereal diazomethane.

The β anomers (**11a** and **11b**) preponderate in the formation of the D-ribopyranoses, most probably owing to the thermodynamic stabilities of the anomers of the precursor **10**. The ratio of the (*R*) to (*S*) isomers of the ring-phosphorus atom (**11b**,**c** to **11a**,**d**) is ~1:2. A possible explanation for this result is that the *O*-



Scheme 1. Structure of 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*,*S*)-methoxyphosphinyl]-α,β-D-ribopyranoses and their probable conformation (and yields from **5**).



Scheme 2. Major fragmentation-pathway of compound **11a**.

methylation of **10** with diazomethane would be slightly more favorable for the axial P–OH group compared with that for the equatorial P–OH.

Mass spectrum of compound **11a**. — There has been reported[3,8] a systematic analysis of the mass spectra of the per-*O*-acetylated derivatives of 5-deoxy-5-*C*-(ethylphosphinyl)-D-glucopyranoses and 5-deoxy-5-*C*-(methoxy- and alkyl-phosphinyl)-3-*O*-methyl-D-xylopyranoses. The detailed analysis of the mass spectrum of **11a** is presented here as the first example of that of the peracetylated derivatives of the 5-deoxy-5-*C*-(phosphinyl)-D-ribopyranoses.

The molecular ion of **11a** is clearly detected at *m/z* 381 [$(M + 1)^+$, most probably as the resonance-stabilized, hydroxyphosphonium form]. Compound **11a** then gives rise to the major fragmentations of the first series A (according to the nomenclature used by Kochetkov and Chizhov[10]), as illustrated in Scheme 2. It is noteworthy that species A^1_2, which is formed from the molecular ion by the successive losses of one ketene and one acetic acid group, consisted of the base peak, suggesting the high stability of the phosphorus-containing ring-system. This is in contrast to the spectra[11] of per-*O*-acetylated monosaccharides of oxygen-containing rings, where the intensities of the fragments retaining the hemiacetal ring are generally much lower than those of ring-ruptured fragment-ions.

Further elimination of two molecules of ketene and water from species A^1_2 and A^2_2 leads to the species A^3_4 and A^4_4, having the 1,2-dihydro-λ^5-phosphorin ring system, with an appreciable intensity; the positions of the hydroxyl groups were tentatively assigned at C-2 and -4, where the phosphorin ring-system was considered to be most stable owing to a favorable conjugation.

The intensities of the fragment-ions due to the subsequent ring-opening fragmentations were considerably weaker than those of A_1–A_5, whereas the 3-*O*-methylxyloses **2a** and **2b** gave rise to such phosphorus-free ions as the base peak[8].

Although improvement in the yield of some steps remains to be achieved, the present work demonstrates an efficient preparation of 5-deoxy-5-*C*-(hydroxyphosphinyl)-D-ribopyranoses, and also the effective use of 400-MHz, ^{1}H-n.m.r. spectroscopy for determining the configuration and conformation of 5-deoxy-5-*C*-(methoxyphosphinyl)ribopyranoses.

EXPERIMENTAL

General methods. — Column chromatography was performed by using Merck Lobar silica gel. T.l.c. was conducted on plates precoated with silica gel (0.25 mm, Merck). 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. ^{1}H-N.m.r. spectra were recorded, for solutions in $CDCl_3$ (unless otherwise stated) at 27°, with a Hitachi R-20A (60-MHz) spectrometer or Bruker WH-400 cryospectrometer (400-MHz, for **11a** and **11b**). Chemical shifts are reported as δ values relative to tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) as the internal standard. Mass spectra were recorded with an A.E.I. MS 50 ultra-high resolution instrument, and the results are given in terms of *m/z* (relative intensity compared with the base peak). All molecular formulas shown in Scheme 2 were supported by the accurate mass of the fragment ions, deviation of which from the calculated value was normally within a rage of ±3 p.p.m.

Methyl 5-deoxy-5-C-(diethoxyphosphinyl)-2,3-O-isopropylidene-β-D-ribofuranoside (**5**). — A solution of **4** (10.0 g) in triethyl phosphite (20 mL) was heated under nitrogen for 2 days at 150–160°; an additional amount (5 mL) of $P(OEt)_3$ was added three times during this period. The excess of the phosphite and the diethyl ethylphosphonate produced were distilled off *in vacuo*. The residue was then distilled, to give **5** (8.5 g, 82%) as a colorless syrup; b.p. 133–135°/2.66 Pa (0.02 torr) (lit.[6] 31% yield, b.p. 128°/0.05 torr); R_F 0.55 (3:1 EtOAc–hexane; ^{1}H-n.m.r.: δ 1.30 (t, 6 H, *J* 7.0 Hz, 2 P–C–CH_3), 1.33, 1.44 (2 s, 6 H, CMe_2), 2.10 (dd, 2 H, $J_{H,P}$ 17.5, $J_{4,5}$ 7.0 Hz, 2 H-5), 3.29 (s, 3 H, MeO-1), 4.06 (dq, 4 H, $^3J_{H,P}$ 8.5, $^3J_{H,H}$ 7.0 Hz, 2 P–CH_2–Me), and 4.0–4.9 (m, 4 H, H-1,2,3,4).

5-Deoxy-5-C-(hydroxyphosphinyl)-D-ribopyranoses (**10**). — A solution of **5** (1.06 g) in dry benzene (10 mL) was degassed, and then bubbled with nitrogen. SDMA (70% in toluene; 1.65 mL, 2.0 equiv.) was slowly added at 0° under nitrogen, followed by stirring for 2 h at 5°. A small amount of cold water was added at 0°, to decompose the excess of SDMA, and the mixture was stirred for 30 min, and centrifuged to remove aluminum hydroxide; the precipitate was extracted with several portions of oxygen-free benzene. The organic layers were combined, washed twice with water (free from oxygen gas), dried (Na_2SO_4), and evaporated *in vacuo*, to give *methyl 5-deoxy-2,3-O-isopropylidene-5-C-phosphino-D-ribofuranoside* (**6**) as a colorless liquid; R_F 0.85 (3:1 EtOAc–hexane), 0.90 (5:3:1 *i*PrOH–EtOAc–H_2O).

A. Product **6** was immediately dissolved in 2-propanol (4 mL), and 10% hy-

drogen peroxide (0.8 mL, 0.85 equiv.) was slowly added, with stirring under nitrogen, at 5°, until most of the **6** had disappeared (t.l.c.), thus affording mostly *the 5-phosphinyl derivative* (**7**), which was contaminated with a small proportion of its *5-(hydroxyphosphinyl) derivative*; R_F 0.60 and 0.25, respectively (5:3:1 *i*PrOH–EtOAc–H_2O).

To this solution was added oxygen-free, 0.25M sulfuric acid (5 mL). The mixture was refluxed under nitrogen for 5 h, cooled, and the acid neutralized by adding $Ba(OH)_2$ and $BaCO_3$. The precipitate was filtered off through an active-carbon bed, and the filtrate was passed through a column of (weakly acidic) Amberlite IR-C50 ion-exchange resin, which was then eluted with water (200 mL). The eluate was filtered, and the filtrate evaporated *in vacuo*, to give *5-deoxy-5-C-phosphinyl-*D-*ribopyranoses* (**9**) as a white, amorphous solid; R_F 0.54 and 0.27 (5:3:1 *i*PrOH–EtOAc–H_2O).

A solution of **9** in water (10 mL) was stirred with a large excess (~5–6 equiv.) of 30% hydrogen peroxide for 18 h at 20°, and the mixture was diluted with *i*PrOH and evaporated *in vacuo*, to give crude **10** (0.24 g, 40% overall yield from **5**) as a colorless solid; R_F 0.05–0.1 (5:3:1 *i*PrOH–EtOAc–H_2O); ^{1}H-n.m.r. (D_2O–DSS): δ 1.1–1.6, 1.75–2.35 (2 m, 2 H, H-5,5'), 3.5–4.2 (m, 4 H, H-1,2,3,4), and 4.70 (s, 5 H, 5 OH).

B. Compound **6** was treated with oxygen-free, 0.5M ethanolic sulfuric acid, and then the resulting *5-deoxy-5-C-phosphino-*D-*ribopyranoses* (**8**) was oxidized with 30% hydrogen peroxide as already described, affording **10** (*via* **9**) in 45% overall yield from **5**.

*1,2,3,4-Tetra-*O*-acetyl-5-deoxy-5-C-[(R,S)-methoxyphosphinyl]-*D*-ribopyranoses* (**11a–d**). — To a solution of **10** (0.25 g) in dry Me_2SO (10 mL) was added an excess of ethereal diazomethane at 15°. After being stirred for 3 h, the mixture was evaporated *in vacuo*, and the residue was treated with acetic anhydride (4 mL) in dry pyridine (8 mL) in the usual way[1–3], to give crude mixture **11** as an amber syrup. This was chromatographed in a column of silica gel with 1:1 EtOAc–hexane, which was gradually changed to EtOAc, and the major fractions, namely, A, B, and C [according to their decreasing R_F values (EtOAc)], were collected.

Fraction A (R_F 0.55) gave *5-C-[(R)-methoxyphosphinyl]-β-*D*-ribopyranose* (**11b**) as a colorless syrup (20 mg; 1.6% from **5**); for 400-MHz, ^{1}H-n.m.r. data, see Table I.

Fraction B (R_F 0.47) gave *5-C-[(S)-methoxyphosphinyl]-β-*D*-ribopyranose* (**11a**) as a colorless syrup (50 mg; 4.1% from **5**); for 400-MHz, ^{1}H-n.m.r. data, see Table I; for the high-resolution, e.i.-mass spectrum, see Scheme 2.

Anal. Calc. for $C_{14}H_{22}O_{10}P$: mol. wt., 381.0950. Found: mol. wt., 381.0951.

Fraction C (R_F 0.40) gave an inseparable mixture of the *5-deoxy-5-C-[(R)* and *(S)-methoxyphosphinyl]-α-*D*-ribopyranoses*, **11c** (10 mg, 0.9%) and **11d** (2 mg, 0.2%); for characteristic signals in their ^{1}H-n.m.r. spectra, see Table I.

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 H. YAMAMOTO, T. HANAYA, S. INOKAWA, K. SEO, M.-A. ARMOUR, AND T. T. NAKASHIMA, *Carbohydr. Res.*, 114 (1983) 83–93.
3 H. YAMAMOTO, T HANAYA, S. INOKAWA, AND M.-A. ARMOUR, *Carbohydr. Res.*, 124 (1983) 195–200.
4 S. INOKAWA, Y. TSUCHIYA, K. SEO, H. YOSHIDA, AND T. OGATA, *Bull. Chem. Soc. Jpn.*, 44 (1971) 2279; K. SEO AND S. INOKAWA, *ibid.*, 46 (1973) 3301–3302; 48 (1975) 1237–1239.
5 S. INOKAWA, H. KITAGAWA, K. SEO, H. YOSHIDA, AND T. OGATA, *Carbohydr. Res.*, 30 (1973) 127–132.
6 J. R. PARIKH, M. E. WOLFF, AND A. BURGER, *J. Am. Chem. Soc.*, 79 (1957) 2778–2781.
7 P. A. LEVENE AND E. T. STILLER, *J. Biol. Chem.*, 106 (1934) 421–429.
8 H. YAMAMOTO AND S. INOKAWA, *Phosphorus Sulfur*, 16 (1983) 135–141.
9 H. YAMAMOTO K. YAMAMOTO, K. KAWAMOTO, S. INOKAWA, M.-A. ARMOUR, AND T. T. NAKASHIMA, *J. Org. Chem.*, 47 (1982) 191–193.
10 N. K. KOCHETKOV AND O. S. CHIZHOV, *Adv. Carbohydr. Chem.*, 21 (1966) 29–93.
11 K. BIEMANN, D. C. DEJONGH, AND H. K. SCHNOES, *J. Am. Chem. Soc.*, 85 (1963) 1763–1771; D. C. DEJONGH AND K. BIEMANN, *ibid.*, 85 (1963) 2289–2294.