

Orientation of the Addition of Dimethyl Phosphonate to 5,6-Dideoxy-6-nitro-D-hex-5-enofuranoses

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Synopsis. The addition of dimethyl phosphonate to six 5,6-dideoxy-6-nitro-D-hex-5-enofuranoses at 25 °C in the presence of triethylamine preponderantly gave (5*R*)-adducts, whereas the same reaction at 100 °C without a base yielded (5*S*)-adducts as the main products.

The addition of a phosphorus compound having a P–H bond to nitro olefins constitutes an important method for the formation of a C–P bond.^{1–4} We also utilized the addition of phosphonate (or phosphinate) to (*E*)-5,6-dideoxy-6-nitro-D-hex-5-enofuranoses for the preparation of some P-in-the-ring sugars analogs.^{4–7} The exact orientation of the addition of phosphorus, however, remained virtually unestablished for these reactions. We now report on our systematic investigation of the stereoselectivity of the addition disclosed by employing various types of nitro enoses.

5,6-Dideoxy-6-nitro-D-hex-5-enofuranoses **2a**⁸⁾ (α -D-xylo), **2b**²⁾ (3-deoxy- α -D-erythro), **2c** (α -D-ribo), **2d**⁷⁾ (α -D-lyxo), **2e** (β -D-arabino) and **2f** (β -D-lyxo) were prepared from the corresponding 5,6-diols **1a–f** (Scheme 1). The addition of dimethyl phosphonate to **2a–f** was performed as follows.

Method 1: Treatment of **2a–e** with dimethyl phosphonate at 25 °C in the presence of 0.3 mole equiv of triethylamine (TEA) gave (5*R*)-adducts **3a–e** and (5*S*)-adducts **4a–e** in the ratios shown in Table 1. The same reaction of **2f** resulted in the decomposition of the starting material. The stereoselectivity of the (5*R*)-adducts increased when a β -substituent was present at C₃ of the furanose ring, but was not affected by the presence of an α -substituent.

Method 2: Compounds **2a–f** were heated at 100 °C with dimethyl phosphonate in the absence of a base, yielding mainly (5*S*)-adducts **4a–d**; no adducts were isolated from **2e** and **2f**.

Table 1. Yields and Ratios of the (5*R*)- and (5*S*)-Adducts

Nitro enose	Product	Method 1	Method 2
		Yield/% (ratio) ^{a)}	Yield/% (ratio) ^{a)}
2a	3a : 4a	81 (89 : 11) ^{b)}	83 (35 : 65)
2b	3b : 4b	94 (66 : 34)	91 (48 : 52)
2c	3c : 4c	57 (67 : 33)	55 (38 : 62)
2d	3d : 4d	67 (87 : 13)	65 (22 : 78)
2e	3e : 4e	8 (66 : 34)	0

a) Determined by 500 MHz ¹H NMR. b) Paulsen and Greve (Ref. 1) isolated **3a** (43% yield) from **2a** and HPO(OMe)₂ by Method 1 and the (5*R*)-structure of **3a** was assigned on the basis of the ORD and CD spectra.

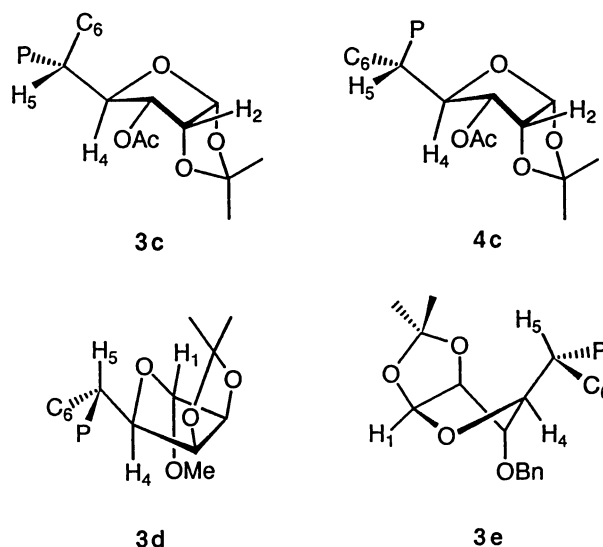
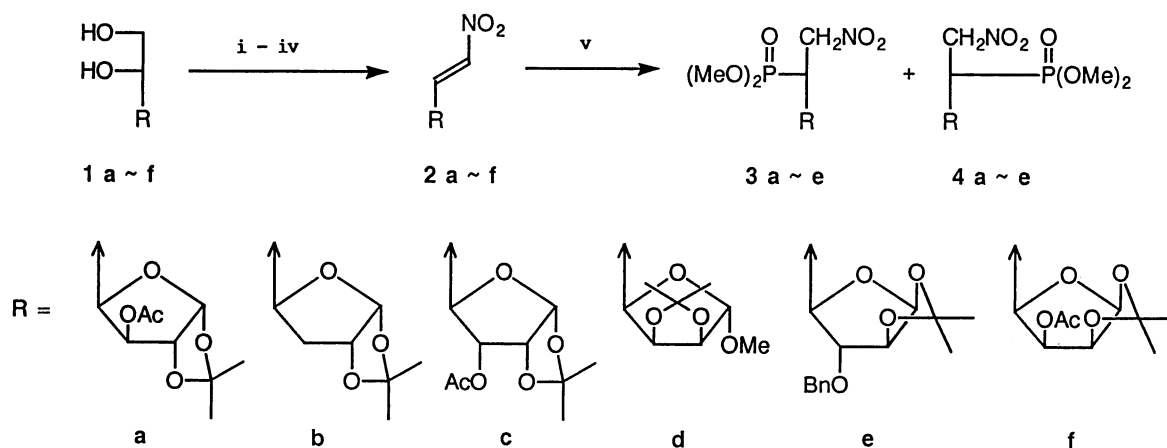


Fig. 1. Most favorable conformations for **3c**, **4c**, **3d**, and **3e**.



Scheme 1. Reagents: i, NaIO₄. ii, CH₃NO₂/CH₃ONa. iii, Ac₂O–AcONa. iv, NaHCO₃. v, HPO(OCH₃)₂.

Table 2. ^1H (500 MHz) and ^{31}P (81 MHz) NMR Parameters for **3** and **4** in CDCl_3

Compd	Chemical shifts (δ)											^{31}P	
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	P(OMe) ₂	Ac-3	CMc ₂			
3a	5.83	4.49	5.26	4.53	3.36	4.83	4.69	3.765, 3.76	2.11	1.51, 1.29	24.7		
4a	5.90	4.46	5.27	4.62	3.57	4.74	4.66	3.77, 3.755	2.12	1.52, 1.30	24.7		
3c	5.78	4.80	4.68	4.54	3.22	4.66	4.64	3.78, 3.77	2.15	1.55, 1.33	25.0		
4c	5.84	4.84	5.33	4.29	3.27	4.68	4.63	3.79, 3.76	2.14	1.52, 1.335	23.6		
3d	4.82	4.55	4.76	4.25	3.59	4.80	4.66	3.81, 3.79	3.29 ^{a)}	1.45, 1.31	25.8		
4d	4.90	4.55	4.76	4.35	3.45	4.84	4.80	3.80, 3.80	3.33 ^{a)}	1.47, 1.29	25.6		
3e	5.93	4.67	4.48	4.41	3.37	4.89	4.70	3.73, 3.73	b)	1.57, 1.31	25.1		
4e	5.79	4.60	4.07	4.11	3.30	4.68	4.45	3.76, 3.73	c)	1.59, 1.36	24.8		
	Coupling constants/Hz												others
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,\text{P}}$	$J_{5,6}$	$J_{5,6'}$	$J_{5,\text{P}}$	$J_{6,6'}$	$J_{6,\text{P}}$	$J_{6'\text{P}}$	J_{POMe}	
3a	3.6	0	2.9	9.3	6.5	5.5	6.0	21.1	15.0	15.5	16.9	10.8, 11.2	d)
4a	3.8	0	2.9	7.5	3.3	4.1	7.5	22.5	14.8	20.2	15.6	10.8, 11.1	
3c	3.7	4.8	9.3	4.2	11.7	5.8	6.1	23.1	14.5	13.2	13.0	11.5, 11.0	
4c	3.5	4.8	9.0	2.7	26.1	4.2	9.2	23.0	14.5	9.2	6.8	11.1, 11.2	
3d	0.5	5.8	3.4	8.5	8.0	6.5	4.7	21.9	14.8	11.8	16.3	10.8, 11.0	e)
4d	0.5	5.8	3.4	7.6	4.4	4.2	6.9	21.5	14.7	20.7	18.3	11.0, 11.0	
3e	3.9	0	0.8	10.7	6.0	3.6	9.1	18.2	14.7	24.1	16.0	10.9, 10.9	f)
4e	4.0	1.4	5.6	7.1	10.9	5.7	6.1	21.5	14.7	g)	13.6	11.1, 11.1	

a) MeO-1. b) BnO-3: $\delta=4.62, 4.65$ (CH_2 , $J=11.6$ Hz), 7.31–7.40 (Ph). c) BnO-3: $\delta=4.54, 4.65$ (CH_2 , $J=11.3$ Hz), 7.31–7.40 (Ph). d) $^5J_{2,P}=1.4$ Hz. e) $^5J_{1,P}=1.0$ Hz. f) $^5J_{1,P}=1.7$ Hz. g) Values uncertain because of overlapping with other signals.

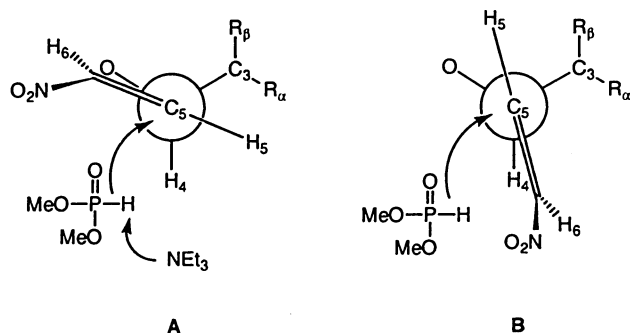


Fig. 2. Conformations of the nitro olefin groups and orientations of the addition.

The α -D-*allo* and β -L-*talo* configurations for the new phosphinyl compounds, **3c** and **4c** (see Fig. 1), were assigned on the basis of their small $J_{4,5}$ values (i.e., the gauche relationship of H-4/H-5), the large $J_{4,P}$ value of **4c** (i.e., the anti relationship of H-4/P-5) and the presence of a long range coupling, $^5J_{2,P}$ in **3c** (see Table 2). Similarly, the α -D-*manno* and β -D-*altro* structures of **3d** and **3e** (Fig. 1) were derived from the large values of $J_{4,5}$ and the presence of $^5J_{1,P}$. Their 5-epimers, **4d** and **4e**, therefore, were assigned to the β -L-*gulo* and α -L-*galacto* derivative, respectively.

The above results suggest that the addition reactions most likely proceed through conformer A in Method 1 and conformer B in Method 2 (Fig. 2) on the following grounds. It was already reported⁹⁾ that in the system of (*E*)- $\text{RCH}(\text{OR}')\text{-CH=CHX}$ (X=an electron withdrawing group) the alkoxy group (OR') exists in such a conformation as to eclipse the double bond. Furthermore, according to the Garbisch equation¹⁰⁾ the $J_{4,5}$ values (2.8–4.3 Hz) of **2a–e** indicate dihedral angles of H-4/

H-5 to be 50–80°, thus suggesting conformer A in Method 1. On the other hand, the preferential formation of the (*5S*)-adduct in Method 2 suggests that the conformation of the transition state is the B-type.¹¹⁾

Experimental

The general methods followed those described earlier,^{6,7)} the TLC solvent system being (A) 1:1 AcOEt–hexane or (B) AcOEt. The NMR parameters¹²⁾ for **3a,c–e** and **4a,c–e** are recorded in Table 2.

The General Procedures for the Preparation of (*E*)-5,6-Dideoxy-6-nitro-hex-5-enofuranoses (2a–f**).** A soln of sodium periodate (580 mg, 2.7 mmol) in water (5 ml) was added dropwise to a soln of **1** (2.3 mmol) in methanol (5 ml) at 0°C. The soln was then stirred at room temp for 1 h and concentrated in vacuo. The residue was extracted with CHCl_3 , dried (Na_2SO_4) and evaporated in vacuo, giving the crude pentodialdo-1,4-furanose derivative. This was dissolved with abs methanol (5 ml) and treated with nitromethane (350 mg, 5.7 mmol) and 25% NaOMe–methanol (1.2 ml, 5.2 mmol) at 0°C. After 2 h, the soln was deionized with methanol-washed Amberlite IR-120 (H^+) ion-exchange resin at 0°C and then evaporated in vacuo, giving the 6-deoxy-6-nitro-hexofuranose derivative.

A suspension of this syrup and NaOAc (1.1 g) in acetic anhydride (2.5 ml) was stirred for 10 h at room temp. The mixture was then poured into cold saturated aq NaHCO_3 (70 ml); the soln was stirred for 2 h at 5°C and twice extracted with CHCl_3 . The combined extracts were washed with water, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography, giving **2**.

3-*o*-Acetyl-1,2-*o*-isopropylidene- α -D-xylo Derivative (2a**):**⁸⁾ 63% yield from **1a**; mp 112–113°C (lit.⁸⁾ 113°C, 53% yield); $R_f=0.68$ (A); ^1H NMR¹²⁾ $\delta=1.34, 1.54$ (3H each, 2s, CMe_2), 2.04 (3H, s, AcO-3), 4.63 (1H, d, $J_{1,2}=3.7, J_{2,3}\approx 0$ Hz, H-2), 5.04 (1H, ddd, $J_{4,5}=3.8, J_{3,4}=3.0, J_{4,6}=2.0$ Hz, H-4), 5.34 (1H, d, H-3), 5.99 (1H, d, H-1), 7.13 (1H, dd, $J_{5,6}=13.2$ Hz, H-5), 7.24 (1H, dd, H-6).

3-Deoxy-1,2-*o*-isopropylidene- α -D-erythro Derivative (2b):²⁾ 74% yield from **1b**; mp 96–97°C (lit.²⁾ 95–97°C, 64% yield); $R_f=0.73$ (A); $^1\text{H NMR}^{12)} \delta=1.34, 1.53$ (3H each, 2s, CMe_2), 1.70 (1H, ddd, $J_{3R,3S}=13.3, J_{3S,4}=11.2, J_{2,3S}=4.5$ Hz, H_{S-3}), 2.37 (1H, dd, $J_{3R,4}=4.5, J_{2,3R}\approx 0$ Hz, H_{R-3}), 4.82 (1H, t, $J_{1,2}=4.0$ Hz, H-2), 4.91 (1H, dtd, $J_{4,5}=3.8, J_{4,6}=1.3$ Hz, H-4), 5.89 (1H, d, H-1), 7.22 (1H, dd, $J_{5,6}=13.3$ Hz, H-6), 7.26 (1H, dd, H-5).

3-*o*-Acetyl-1,2-*o*-isopropylidene- α -D-ribo Derivative (2c): Syrup (46% yield from **1c**); $R_f=0.68$ (A); $^1\text{H NMR} \delta=1.35, 1.57$ (3H each, 2s, CMe_2), 2.18 (3H, s, AcO-3), 4.57 (1H, dd, $J_{3,4}=9.5, J_{2,3}=4.6$ Hz, H-3), 4.79 (1H, dd, $J_{4,5}=2.8$ Hz, H-4), 4.89 (1H, t, $J_{1,2}=3.7$ Hz, H-2), 5.88 (1H, d, H-1), 7.22 (1H, d, $J_{5,6}=13.5$ Hz, H-6), 7.24 (1H, dd, H-5); MS m/z 258 (M-CH_3 ; 100), 149 (18), 129 (89). Found: m/z 258.0616. Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_7$: M-CH_3 , 258.0614.

Methyl 2,3-*o*-Isopropylidene- α -D-lyxo-furanoside Derivative (2d):⁷⁾ 61% yield from **1d**; mp 46–47°C (lit.⁷⁾ colorless syrup, 59% yield); $^1\text{H NMR}$, see Ref. 7.

3-*o*-Benzyl-1,2-*o*-isopropylidene- β -D-arabino Derivative (2e): Syrup (45% yield from **1e**); $R_f=0.66$ (A); $^1\text{H NMR} \delta=1.33, 1.45$ (3H each, 2s, CMe_2), 4.04 (1H, d, $J_{3,4}=2.4, J_{2,3}\approx 0$ Hz, H-3), 4.58, 4.69 (1H each, 2d, $^2J=11.7$ Hz, $\text{CH}_2\text{O-3}$), 4.70 (1H, d, $J_{1,2}=4.0$ Hz, H-2), 4.79 (1H, dt, $J_{4,5}=4.3, J_{4,6}=1.6$ Hz, H-4), 5.99 (1H, d, H-1), 7.19 (1H, dd, $J_{5,6}=13.3$ Hz, H-6), 7.24 (1H, dd, H-5), 7.33–7.41 (5H, m, Ph); MS m/z 306 (M-CH_3 ; 2.8), 129 (59), 91 (100). Found: m/z 306.0976. Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_6$: M-CH_3 , 306.0978.

3-*o*-Acetyl-1,2-*o*-isopropylidene- β -D-lyxo Derivative (2f): Syrup (42% yield from **1f**); $R_f=0.56$ (A); $^1\text{H NMR} \delta=1.32, 1.51$ (3H each, 2s, CMe_2), 2.17 (3H, s, AcO-3), 4.84 (1H, dd, $J_{2,3}=5.2, J_{1,2}=3.9$ Hz, H-2), 5.00 (1H, ddd, $J_{3,4}=7.8, J_{4,5}=5.1, J_{4,6}=1.8$ Hz, H-4), 5.14 (1H, dd, H-3), 5.86 (1H, d, H-1), 7.22 (1H, dd, $J_{5,6}=13.4$ Hz, H-6), 7.37 (1H, dd, H-5); MS m/z 258 (M-CH_3 ; 21), 201 (25), 169 (19), 152 (56), 143 (100). Found: m/z 258.0613. Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_7$: M-CH_3 , 258.0614.

General Procedure for the Preparation of 5,6-Dideoxy-5-dimethoxyphosphinyl-6-nitro-hexofuranoses (3a–e and 4a–e). Method 1. TEA (0.02 ml, 0.14 mmol) was added dropwise at 0°C to a mixture of **2** (0.46 mmol) and dimethyl phosphonate (500 mg, 4.5 mmol), and the mixture was stirred for 2–3 h at 25°C. The excess phosphonate was distilled off at ca. 40°C (0.2 Torr, 1 Torr=133.322 Pa). The residue was chromatographed with AcOEt-hexane , giving an inseparable mixture of **3** and **4** as a syrup.

3-*o*-Acetyl-1,2-*o*-isopropylidene- α -D-glucoside (3a)^{1,5)} and β -L-ido(4a)⁵⁾ Derivatives: 81% yield (89:11) from **2a**; $R_f=0.52$ (B). Recrystallization of this mixture from AcOEt-hexane gave pure **3a** as colorless prisms (70% yield); mp 108–109°C (lit.¹⁾ mp 108–110°C, 43% yield).

3-Deoxy-1,2-*o*-isopropylidene- α -D-ribo-hexoside (3b) and β -L-lyxo-hexoside (4b) Derivatives:⁶⁾ 94% yield (66:34) from **2b**.

3-*o*-Acetyl-1,2-*o*-isopropylidene- α -D-allo (3c) and β -L-talose (4c) Derivatives: 57% yield (67:33) from **2c**; $R_f=0.55$ (B); MS m/z 368 (M-CH_3 ; 3.5), 308 (30), 266 (11), 219 (90), 165 (100). Found: m/z 368.0743. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_{10}\text{P}$: M-CH_3 , 368.0746.

Methyl 2,3-*o*-Isopropylidene- α -D-mannoside (3d) and β -L-gulofuranoside (4d) Derivatives: 67% yield (87:13) from **2d**; $R_f=0.51$ (B); MS m/z 340 (M-CH_3 ; 47), 324 (7.7), 251 (11), 233 (31), 212 (27), 191 (33), 165 (100). Found: m/z 340.0783. Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_9\text{P}$: M-CH_3 , 340.0798.

3-*o*-Benzyl-1,2-*o*-isopropylidene- β -D-altro (3e) and α -L-galactose (4e) Derivatives: 8% yield (66:34) from **2e**; $R_f=0.55$ (B); MS m/z 416 (M-CH_3 ; 1.4), 282 (1.3), 219 (6.5), 91 (100). Found: m/z 416.1116. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_9\text{P}$: M-CH_3 , 416.1111.

Method 2. A mixture of **2** (0.46 mmol) and dimethyl phosphonate (500 mg, 4.5 mmol) was stirred at 100°C for 6–10 h under N_2 . The excess phosphonate was distilled off in vacuo, and the residue was purified by use of column chromatography, giving a mixture of **3** and **4**. These results are summarized in Table 1.

References

- 1) H. Paulsen and W. Greve, *Chem. Ber.*, **106**, 2114 (1973).
- 2) J. M. J. Tronchet, K. D. Pallie, and F. Barbalat-Rey, *J. Carbohydr. Chem.*, **4**, 29 (1985).
- 3) M. Yamashita, M. Sugiura, Y. Tamada, T. Oshikawa, and J. Clardy, *Chem. Lett.*, **1987**, 1407.
- 4) H. Yamamoto and T. Hanaya, "Studies in Natural Products Chemistry," ed by T. I. Atta-ur-Rahman, Elsevier, Amsterdam (1990), Vol. 6, pp. 351–384.
- 5) H. Yamamoto, T. Hanaya, H. Kawamoto, S. Inokawa, M. Yamashita, M.-A. Armour, and T. T. Nakashima, *J. Org. Chem.*, **50**, 3516 (1985).
- 6) T. Hanaya, A. Noguchi, M.-A. Armour, A. M. Hogg, and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, **1992**, in press.
- 7) T. Hanaya, K. Ohmori, H. Yamamoto, M.-A. Armour, and A. M. Hogg, *Bull. Chem. Soc. Jpn.*, **63**, 1174 (1990).
- 8) R. L. Whistler and R. E. Pyler, *Carbohydr. Res.*, **12**, 201 (1970).
- 9) J. M. J. Tronchet and T. N. Xuan, *Carbohydr. Res.*, **67**, 469 (1978).
- 10) E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **86**, 5561 (1964).
- 11) T. Iida, M. Funabashi, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **46**, 3203 (1973).
- 12) Although insufficiently resolved $^1\text{H NMR}$ data at 60 or 90 MHz were reported for these compounds in lit.^{1,2,5,11)} the complete parameters obtained at 500 MHz in the present study are shown here to unambiguously confirm the structural assignments.