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Synthetic Route to 2-Deoxyaldoses by Fluoride-Catalyzed Solvolysis of Enol-Phosphate Esters[1]

Naoki Mitsuo,[2a] Yoshihiro Abe, Takeo Takizawa[2b] and Takehisa Kunieda[2]

Faculty of Pharmaceutical Sciences, University of Tokyo[2]

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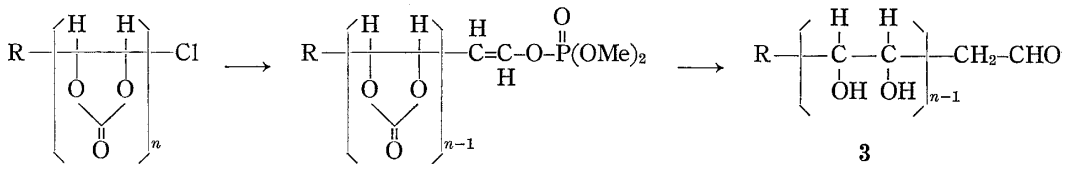
1-Alkenyl and phenyl phosphate esters undergo smooth cleavage of the phosphorus-oxygen linkage by fluoride-catalyzed alcoholysis to give aldehydes (ketones) and phenols, respectively. Application of this method provides a new route to 2-deoxyaldosugars from the enol-phosphates derived from vinylene carbonate telomers.

Keywords——vinylene carbonate telomer; 2-deoxyaldose; enol phosphate; cesium fluoride; aryl phosphate

The study of enol-phosphates[3] has been of long-standing interest in virtue of their synthetic utility as well as their biological significance. In the previous paper[4] we reported that vinylene carbonate telomers **1** ($n=2,3$), which serve as versatile intermediates for the stereoselective preparation of monosaccharides of aldopentoses to aldooctoses,[5] could undergo a smooth Perkow-type reaction with trialkyl phosphites to afford a series of *trans* enol-phosphates **2**. The phosphates thus formed have potential as synthetic intermediates for 2-deoxyaldoses, since hydrolytic conversion of such enol phosphates to aldehydic compounds seems generally to present no difficulty. If generality of the reaction could be established, it would provide a new route to 2-deoxyaldoses from telomers arising from the radical reaction of vinylene carbonate and polyhalomethanes. The present study was undertaken to examine hydrolytic phosphate ester cleavage under conditions mild enough to avoid serious side reactions of the resulting deoxyaldoses, such as epimerization, dehydration and degradation.



1 ($n=2, 3\cdots$) **2** **3**

Chart 1

Contrary to our expectation, the type **2** enol-phosphate linkage was resistant to acidic hydrolysis with 0.1 N hydrochloric acid at 85° (for 24 hr), undergoing preferential cleavage of the carbonate rings to yield polyhydroxy compounds such as the diol **5**. Treatment of the

1) Presented at the 98 th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April, 1978. This paper constitutes Part XIV in the series "Telomers and Oligomers of Vinylene Carbonate." Part XIII: T. Kunieda, Y. Ito and T. Takizawa, *Chem. Pharm. Bull.*, **26**, 3591 (1978).

2) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan*; Present address: *a) School of Pharmacy, Tokushima University of Arts and Science, Yamashiro-cho, Tokushima, 770, Japan*; *b) Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaragi, 300-31, Japan.*

3) F.W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); T.C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 2, Chapter 5, W.A. Benjamin, Inc.

4) N. Mitsuo, T. Kunieda and T. Takizawa, *Chem. Pharm. Bull.*, **25**, 231 (1977).

5) T. Kunieda and T. Takizawa, *Heterocycles*, **8**, 661 (1977).

enol phosphates under more drastic conditions (in 1 N hydrochloric acid at 80°) led to the exclusive formation of α,β-unsaturated aldehydes and not 2-deoxyaldoses. Thus, the phosphates **4** and **5** derived from the $n=2$ telomer **1** gave the 2,3-dideoxypent-2-enose **6** (characterized as the 2,4-dinitrophenylhydrazone), which was also obtainable by similar acid treatment of the *cis* enol acetate **7**[4] arising from the palladium-catalyzed exchange reaction of **4a**. Alkali treatment gave a complicated mixture, and this failure to obtain 2-deoxyaldoses prompted a search for a milder cleavage method.

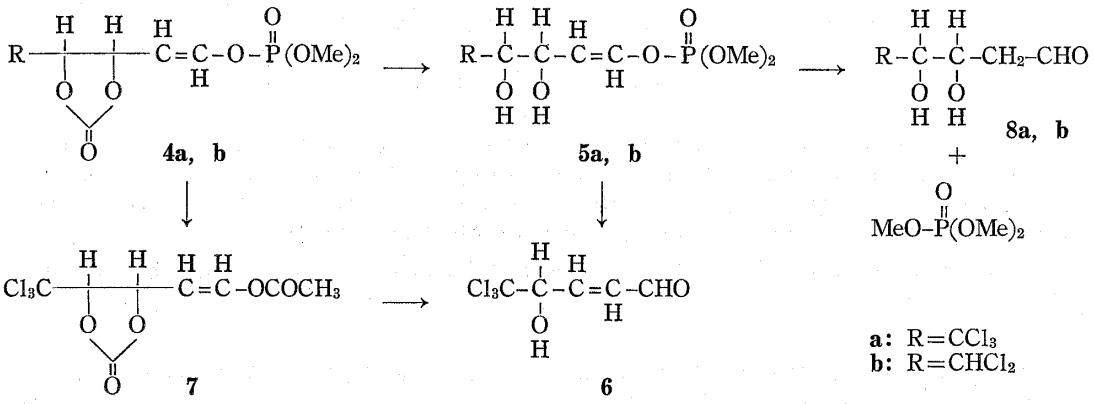


Chart 2

In 1977 a method was reported for the synthesis of mixed trialkyl phosphates by fluoride-catalyzed transesterification.[6] This may be a suitable reaction for the present purpose, since it proceeds under neutral conditions by way of nucleophilic attack of a fluoride ion on the phosphorus atom, followed by smooth cleavage of the phosphorus-oxygen linkage to leave the hydroxyl compounds. This reaction gave satisfactory results when applied to model phosphate compounds under reasonable conditions (with excess cesium fluoride in boiling methanol), as shown in Table I. Phosphate esters examined included 1-decenyl, vinyl, 1-cyclohexenyl, phenyl, *p*-nitrophenyl and *p*-methoxyphenyl dimethyl esters, which are easily obtainable.

Table I. Fluoride-Catalyzed Methanolysis of $(MeO)_2\overset{O}{\overset{\|}{P}}-OR$ to Give ROH and $(MeO)_3P=O$[a]

Compound (R)	Temperature (°C)	Time (hr)	R–OH (R′–C=O)[b] (%)	$(MeO)_3PO$[b] (%)
1-Decenyl[c]	65	22	88	67
Vinyl[d]	78	5.5	20[e]	65[d]
1-Cyclohexenyl	65	72	4 (96)[f]	1
p-Nitrophenyl	65	0.5	76	63
Phenyl	65	4	65	80
p-Methoxyphenyl	65	22	88	79
5a′	50	5.5	39[g]	25
5b′	50	4	64[g]	

a) With 10 eq. of cesium fluoride.
b) Determined by GLC (see the text).
c) A *cis* and *trans* mixture (5 : 9) was used.
d) Diethyl vinyl phosphate was used.
e) Yield isolated as 2,4-dinitrophenylhydrazone.
f) Recovery of the starting material.
g) Isolation yields.
5a′ : 5,5,5-trichloro-3,4-dihydroxy-1-pentenyl.
5b′ : 5,5-dichloro-3,4-dihydroxy-1-pentenyl.

6) K.K. Ogilvie, S.L. Beaucage, N. Theriault and D.W. Entwistle, *J. Am. Chem. Soc.*, **99**, 1277 (1977).

This methanolysis reaction has now been found to be of practical significance in the conversion of enol phosphates to aldehydes, and the ease of aldehyde formation is comparable to that of phenol generation from phenyl esters,[7] though this may not be practically applicable to the generation of ketones, since this reaction proceeds much more slowly.

Based on these promising findings, the enol-phosphate **5** was subjected to fluoride-catalyzed methanolysis in the presence of a 10-fold molar excess of cesium fluoride at 50° to afford 2,5-dideoxy-5,5,5-trichloro-DL-*threo*-pentose (**8a**) in 39% yield as a syrup (characterized as the dinitrophenylhydrazone) in addition to trimethyl phosphate (25%), while the phosphate **4** underwent rapid decomposition (at 30°) to unidentified tarry compounds. The dichloro-2-deoxypentose **8b** was similarly obtained from the corresponding ester **5b** in 64% yield. Thus, the route in Chart 1 may be considered as a general method for 2-deoxyaldosugars starting from vinylene carbonate telomers, as well as a synthetic route to aldoses, as described previously.[5]

Experimental

Melting points were determined on a Yanaco hot stage apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL PS-100 spectrometer and chemical shifts are in ppm downfield from TMS. Infrared (IR) spectra were recorded on a JASCO DS-402G spectrophotometer. Gas liquid chromatography (GLC) analysis was performed with a Hitachi 163 gas chromatograph.

Dimethyl-2-(5-trichloromethyl-2-oxo-1,3-dioxolan-4-yl)vinyl phosphate (**4a**), dimethyl 5,5,5-trichloro-3,4-dihydroxy-1-penten-1-yl phosphate (**5a**) and 2-(5-trichloromethyl-2-oxo-1,3-dioxolan-4-yl)vinyl acetate (**7**) were prepared from 5-chloro-5′-trichloromethyl[4,4′-bi-1,3-dioxolan]-2,2′dione (**1**, R=CCl_3, n=2)[8] according to the procedure described previously.[4,9]

Dimethyl 2-(5-Trichloromethyl-2-oxo-1,3-dioxolan-4-yl)vinyl Phosphate (4b)——A solution of the trichloromethyl derivative (**4a**) (5.0 g) in THF (140 ml) was irradiated with a high-pressure Hg lamp for 6 hr. After removal of the solvent, the residue was chromatographed on silica gel (MeOH/CH_2Cl_2: 9/1) to give colorless crystals (4.1 g). Recrystallization from CCl_4 gave an analytical sample, mp 73—74°, IR (KBr) 3060, 1818, 1675 and 1272 cm^{-1}; NMR ($CDCl_3$) δ 3.85 (6H, d, J=11.0 Hz), 4.70 (1H, d,d, J=5.0 Hz, J'=3.5 Hz), 5.20 (1H, d,d, J=8.5 Hz, J'=5.0 Hz), 5.60 (1H, d,d, J=11.5 Hz, J=8.5 Hz), 5.95 (1H, d, J=3.5 Hz), 6.85 (1H, d,d, J=11.5 Hz, J'=8.0 Hz). *Anal.* Calcd for $C_8H_{11}Cl_2O_7P$: C, 29.93; H, 3.45. Found: C, 30.11; H, 3.41.

Dimethyl 5,5-Dichloro-3,4-dihydroxy-1-penten-1-yl Phosphate (5b)——This was obtained as an oil in 77% yield by treatment of 4b (3.0 g) in 90% aqueous methanol (85 ml) with sodium borohydride (1.4 g) in the manner described for **5a**.[8] It gave the following spectral data, IR (neat) 3360, 1670, 1260 and 1040 cm^{-1}, NMR ($CDCl_3$+D_2O) δ 3.80 (5H, d, J=11.0 Hz), 4.05 (1H, m), 4.40 (1H, d,d, J=8.0 Hz, J'=4.0 Hz), 5.55 (1H, d,d,d, J=12.0 Hz, J'=8.0 Hz, J''=1.0 Hz), 5.75 (1H, d, J=6.0 Hz), 6.70 (1H, d,d, J=12.0 Hz, J'=7.0 Hz).

4-Hydroxy-5,5,5-trichloro-2-pentenal (6)——A solution of the enol phosphate **4a** (0.1 g) in methanol and 1 N hydrochloric acid (1: 1) was gently refluxed for 2 hr. After removal of the methanol, the aqueous solution was extracted with methylene chloride and the extracts were concentrated *in vacuo*. The resulting oil was chromatographed on silica gel (CH_2Cl_2) to afford the enose **6** (9 mg, 15%) as a syrup, IR (neat) 3400, 1690 and 1645 cm^{-1}. NMR ($CDCl_3$) δ 4.40 (1H, d, J=5.50 Hz, disappeared when D_2O was added), 4.95 (1H, t, J=4.5 Hz, doublet peak on addition of D_2O), 6.60 (1H, d,d, J=15.0 Hz, J'=7.0 Hz). 7.00 (1H, d,d, J=15.0 Hz, J'=4.0 Hz), 9.65 (1H, d, J=7.0 Hz). The 2,4-dinitrophenylhydrazone was prepared in ethanol and recrystallized from CCl_4 to give orange needles, mp 193—194°. *Anal.* Calcd for $C_{11}H_9Cl_3N_4O_5$: C, 34.44; H, 2.37; N, 14.61. Found: C, 34.55; H, 2.52; N, 14.49.

This compound was also obtained in *ca.* 10% yield as a major isolable product by similar treatment of the diol **5** and the enol acetate **7**.

2,5-Dideoxy-5,5,5-trichloro-DL-pentose (8a)——The enol phosphate **5a** (0.08 g) and thoroughly dried cesium fluoride (0.37 g) were dissolved in absolute methanol (5 ml) and the solution was heated at 50° for 5.5 hr. GLC (SE-30 column at 110°) analysis showed the formation of trimethyl phosphate (25%). The reaction mixture was concentrated *in vacuo* and the product was purified by chromatography on silica gel (ethyl acetate/CH_2Cl_2) to afford the deoxypentose (0.02 g, 39%) as a colorless powder. IR (KBr) 3400,

7) Selective removal of the *p*-nitrophenyl group from a mixed triaryl phosphate may be feasible due to the considerable difference in reactivity.
8) T. Tamura, T. Kunieda and T. Takizawa, *J. Org. Chem.*, **39**, 38 (1974).
9) N. Mitsuo, T. Kunieda and T. Takizawa, *Chem. Pharm. Bull.*, **26**, 1493 (1978).

1720, 1095 and 965 cm^{-1}, NMR ($CDCl_3$) δ 2.25 (2H, m), 3.65 (2H, m, disappeared when D_2O was added), 4.55 (2H, m), 5.50 (1H, m). In addition to the above peaks, a small doublet signal (J=2.0 Hz) at δ 9.65, attributable to an aldehydic proton ,was observed in the NMR spectrum, indicating the presence of a small proportion of the straight chain form. The 2,4-dinitrophenylhydrazone prepared in ethanol was recrystallized from CCl_4–CH_2Cl_2 as yellow crystals, mp 167—168°. *Anal.* Calcd for $C_{11}H_{11}Cl_3N_4O_6$: C, 32.90; H, 2.76; N, 13.95. Found: C, 33.09; H, 2.80; N, 13.68.

2,5-Dideoxy-5,5-dichloro-DL-*threo*-pentose (8b)——In the manner described above, the dichloromethyl compound **5b** gave the deoxysugar **8b** (0.86 g, 64%) as a syrup. IR (neat) 3350, 1110 and 1040 cm^{-1}, NMR ($CDCl_3+D_2O$) δ 2.25 (2H, m), 4.15 (1H, d,d, J=9.0 Hz, J'=3.0 Hz), 4.50 (1H, m), 5.55 (1H, m), 5.85 (1H, d, J=9.0 Hz).

Fluoride-Catalyzed Methanolysis of Model Phosphate Esters (Table I)——The following phosphates were prepared by slight modification of the reported methods and spectrometically characterized: vinyl diethyl phosphate[10] (bp 88—91°/12 mm), 1-cyclohexenyl dimethyl phosphate[11] (bp 122—124°/5 mm), *p*-nitrophenyl dimethyl phosphate[12] (bp 121—123°/0.13 mm), phenyl dimethyl phosphate[12] (bp 120—123°/3 mm) and *p*-methoxyphenyl dimethyl phosphate[12] (bp 113—116°/0.16 mm). 1-Decenyl dimethyl phosphate was prepared by the Perkow reaction of 2-bromodecanal[13] (2.56 g, bp 74°/0.4 mm, NMR ($CDCl_3$): δ 0.86—2.20 (17 H, m), 4.23 (1H, d, quart, J=3.0 Hz, J'=6.0 Hz, J''=8.0 Hz), 9.40 (1H, d, J=3.0 Hz)) with trimethyl phosphite (1.61 g) in boiling ether (5 ml) for 2 hr. Distillation of the product gave the enol phosphate (bp 120—123°/0.01 mm) in 60% yield as a *cis* and trans mixture (5: 9) as determined by GLC (3 m× SE-30 column at 180°; retention times, 3.8 min and 4.5 min for the *cis* and *trans*, respectively). In the nmr, peaks at δ 5.0 and 5.80 were assignable to the *cis* and *trans* olefinic protons, respectively. *Anal.* Calcd for $C_{11}H_{25}O_4P$: C, 54.55; H, 9.47. Found: C, 54.40; H, 9.12. Calcd: *m/e* 264.1504 (M^+). Obsd: *m/e* 264.1506.

A solution of phenyl or enol phosphate (0.05 M) thus prepared and cesium fluoride (0.5 M) in methanol (5 ml) was gently refluxed with stirring until the phosphate was completely consumed. The reaction mixture was quantitatively analyzed by GLC (SE-30 column) using an internal standard, and the products were identified by gas chromatographic comparison with authentic specimens. The results are summarized in Table I.

10) H. Gross, G. Engelhardt, J. Freiberg, W. Burger and B. Costisella, *Ann.*, **707**, 35 (1967); R.C. DeSelms and T-W. Lin, *J. Org. Chem.*, **32**, 2023 (1967).
11) *cf.* A.N. Pudovik, *Zhur. Obshchei Khim.*, **25**, 2173 (1955); *C.A.*, **50**, 8486*i* (1956).
12) *cf.* V.V. Katyshkina and M. Ya. Kraft, *Zhur. Obshchei Khim.*, **26**, 3060 (1956); *C.A.*, **51**, 8028*a* (1957).
13) R.H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).