

Synthesis of Chiral β -Iodo- and Vinylorganophosphorus(V) Compounds by Fragmentation of Carbohydrate Anomeric Alkoxy Radicals

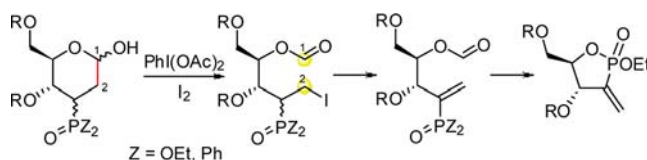
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ABSTRACT



A new general methodology for the synthesis of chiral vinylphosphonate and vinylphosphine oxide carbohydrate derivatives has been developed using the anomeric alkoxy radical fragmentation reaction as the key step. The synthetic sequence proceeded via β -iodophosphonate and β -iodophosphine oxide intermediates, which may be interesting synthons for the introduction of phosphorus into organic molecules. These vinylphosphonates could be easily transformed into 2-methylene-1-phosphapentofuranoses (3-methylene-1,2-oxaphospholanes) and β -aminophosphonates, isosteres of biologically active α -methylene- γ -lactones and β -amino acids, respectively.

Considerable attention has been focused on vinylphosphonates¹ and vinylphosphine oxides² because they are useful synthetic intermediates in organic transformations having in addition a wide range of biochemical applications in many areas. These organophosphorus compounds due to the electrophilic double bond are used as key starting materials in Michael and radical additions, 1,3-cycloadditions,

Diels–Alder, Stetter, and metathesis reactions, among others. In particular, Michael addition of amines to vinylphosphonates has attracted special interest in the preparation of β -aminophosphonic acids as isosteres of β -amino acids.³

Moreover, 1-(iodomethyl)alkylphosphine oxides appear to be practically unknown, with only one of the simplest members of the family, (2-iodoethyl)(diphenyl)phosphine oxide, having been synthesized.⁴ 1-(Iodomethyl)alkylphosphonates are also relatively rare compounds, and the literature examples that we were able to uncover correspond almost exclusively to diethyl 2-iodoethylphosphonate or simple alkyl-branched derivatives. They have been prepared by halogen or OTs/I exchange under Finkelstein conditions⁵ or by metallophosphorylation of zirconocene–alkene complexes

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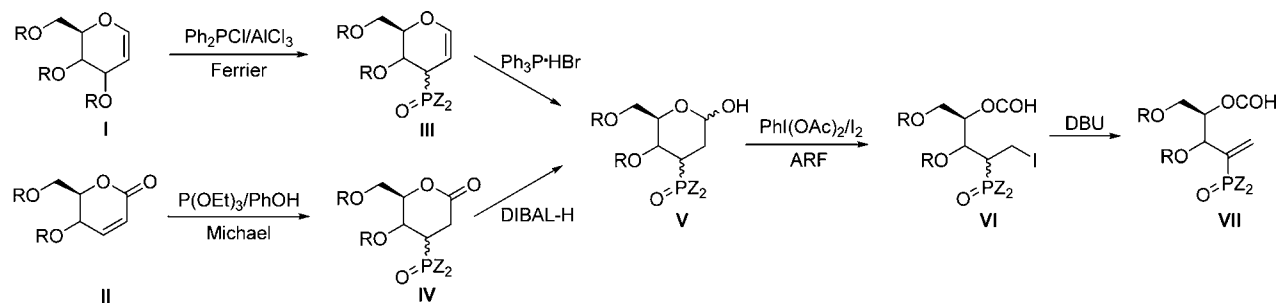
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Scheme 1. Alkoxy Radical β -Fragmentation of 2,3-Dideoxy-3-phosphorylhexopyranoses^a



^a ARF = alkoxy radical β -fragmentation reaction; Z = Ph (phosphine oxides), Z = OEt (phosphonates).

with chlorophosphate using iodine as electrophile.⁶ Studies on the chemical reactivity of these compounds have been largely limited to diethyl 2-iodoethylphosphonate.^{5a,c,7}

Previous work from our laboratory described the carbohydrate anomeric alkoxy radical β -fragmentation reaction (ARF) by treatment of the free anomeric alcohol with hypervalent iodine in the presence of iodine.⁸ Exploiting these sugar transformations, we set out to develop a new methodology for elaboration of chiral vinylphosphine oxide and vinylphosphonate derivatives of generalized structure VII (Scheme 1). Regioselective introduction of the C–P bond into the carbohydrate skeleton was accomplished using two different protocols. 3-Phosphinyl derivatives III (Z = Ph) were prepared from glycals I via an anomalous Ferrier reaction while a Michael addition to the readily available unsaturated lactones II was used for the synthesis of 3-phosphonylated sugars IV (Z = OEt). Subsequently, either the acid-catalyzed hydration of III (Z = Ph) or the reduction of IV (Z = OEt) afforded the required γ -hydroxyphosphorus compounds V which were then submitted to the ARF reaction to give β -iodophosphorus compounds VI. Dehydroiodination of VI provided the desired vinylorganophosphorus VII.

In pursuance of this goal we decided to prepare first 3-phosphinylated-glycals **1**, **5**, and **9** by reaction of the corresponding perbenzylated D-glucal, D-galactal, and D-lactal, respectively, with diphenylphosphenium cation using a previously reported procedure developed by Yamamoto et al. for perbenzylated D-glucal (Table 1).⁹ The extension of this methodology to perbenzylated D-galactal afforded **5** as a sole stereoisomer. The reaction was also expanded to disaccharide D-lactal, but a mixture of the four Ferrier isomers, by *P*-nucleophilic attack at C-1 and C-3, were obtained as described in the Supporting

Information. For the present study, only the major 3 α -isomer **9** (45%) has been used.

Hydration of these glycals by a modification of the procedure of Falck et al.¹⁰ with catalytic amounts of $\text{Ph}_3\text{P}\cdot\text{HBr}$ in refluxing THF/H₂O gave hexopyranose compounds **2**, **6**, and **10** in high yields. The ARF reactions were performed under the conditions stated in Table 1, with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 . The ARF proceeded smoothly and the β -iodo phosphine oxides **3**, **7**, and **11** were obtained in good yields. In the fragmentation of **10**, the major product **11** (67%) was accompanied by a side product identified as lactone **33S** (15%, see the Supporting Information). The dehydroiodination of the β -iodo phosphine oxides was effectively accomplished with DBU in benzene to afford vinylphosphine oxides **4**, **8**, and **12** in high yields.

In the iodide elimination of **11**, partial hydrolysis of the formate group was observed, and besides vinylphosphine oxide **12**, a small amount of the corresponding alcohol **34S** (13%, see the Supporting Information) was obtained, the global yield of the vinylphosphine oxide reaching 96%.

Preliminary attempts to prepare 3-phosphonylated sugar of general structure III (Z = OEt) using a modified Yamamoto protocol by reaction of perbenzylated D-glucal with $(\text{EtO})_2\text{PCl}/\text{AlCl}_3$ proved to be unsuccessful; therefore, an alternative route was sought. The phospho-Michael addition of triethyl phosphite to readily accessible pent-2-enono-1,4-lactones¹¹ and hex-2-enono-1,5-lactones¹² under the conditions described by Kofoed and Pedersen,¹³ using phenol as protonating agent, afforded the 3-phosphonylated γ - and δ -lactones **13**, **17**, and **21**. The reaction proceeded with excellent regio- and diastereoselectivity for **13** and **21**, but as should be expected for a sterically less demanding substrate, the glucose derivative **17** was obtained as an inseparable

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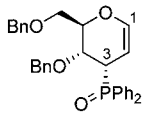
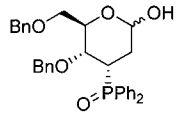
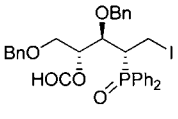
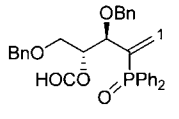
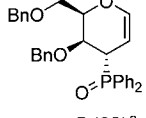
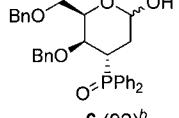
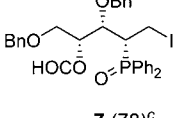
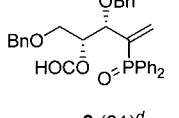
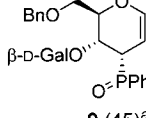
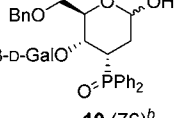
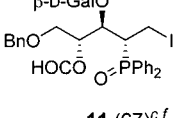
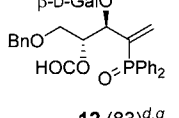
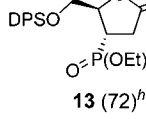
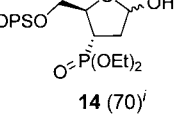
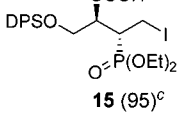
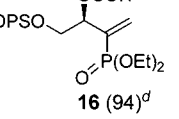
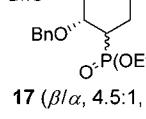
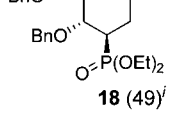
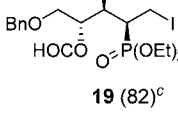
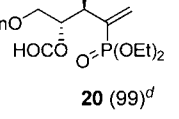
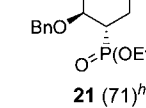
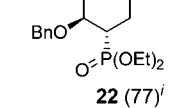
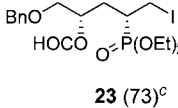
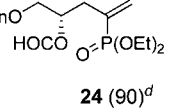
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Table 1. Synthesis of β -Iodo- and Vinylorganophosphorus(V) Compounds

substrate	time (h)	γ -hydroxy phosphorus (%)	time (h)	β -iodo phosphorus (%)	time (h)	vinyl phosphorus (%)	time (h)
 1 (49)^a	3	 2 (90)^b	1.5	 3 (79)^c	2.5	 4 (89)^d	0.5
 5 (62)^a	5	 6 (92)^b	3.75	 7 (78)^c	2	 8 (91)^d	1
 9 (45)^{a,e}	22	 10 (76)^b	6	 11 (67)^{c,f}	0.5	 12 (83)^{d,g}	12
 13 (72)^h	6	 14 (70)ⁱ	1.3	 15 (95)^c	0.75	 16 (94)^d	0.25
 17 (β/α, 4.5:1, 98)^h	4.5	 18 (49)ⁱ	1	 19 (82)^c	1	 20 (99)^d	0.25
 21 (71)^h	1.5	 22 (77)ⁱ	1.5	 23 (73)^c	1.5	 24 (90)^d	1

^a Reagents and conditions per mmol of substrate: $\text{Ph}_2\text{P}(\text{Cl})$ (2 mmol), AlCl_3 (2 mmol), DCM (5 mL), 0 °C \rightarrow reflux. ^b $\text{Ph}_3\text{P} \cdot \text{HBr}$ (0.12–0.46 mmol), THF (21.5 mL), reflux. ^c $\text{PhI}(\text{OAc})_2$ (1.1–1.5 mmol), I_2 (0.6–1.1 mmol), DCM (25 mL). ^d DBU (1.1–2.6 mmol), PhH (25 mL), 9–10 °C. ^e For brevity β -D-Gal refers to the perbenzylated moiety of β -D-galactose. ^f 15% of oxidized lactone (**33S**, see the Supporting Information) is also obtained. ^g 13% of hydrolyzed compound (**34S**, see the Supporting Information) is also obtained. ^h $\text{P}(\text{OEt})_3$ (5 mmol), PhOH (4.2 mL), 100 °C. ⁱ DIBAL-H (4 mmol), PhCH_3 (33 mL), –78 °C.

mixture of isomers (dr $3\beta/3\alpha$, 4.5:1). Separation of the isomers was chromatographically accomplished in the next step after the DIBAL-H reduction of the carboxylate group and the reaction sequence was continued only with the major β -diastereoisomer **18**.

Thus, the other β -hydroxyphosphonates **14** and **22** were also obtained and submitted to the ARF radical reaction. Analogously to the β -iodophosphine oxides prepared before, β -iodophosphonates **15**, **19**, and **23** were obtained in good to excellent yield and when chemically pure are also stable compounds which can be stored at –20 °C for a long time and handled at room temperature without any apparent deterioration. Finally, base-mediated elimination of the iodide compounds afforded vinylphosphonates **16**, **20**, and **24** in high yields. The series **18**–**20** was efficiently conducted on a large scale: starting from 8.3 mmol (3.86 g) of **18**, 7.3 mmol of **19** (88%) and 7.3 mmol of **20** (100%) were obtained.

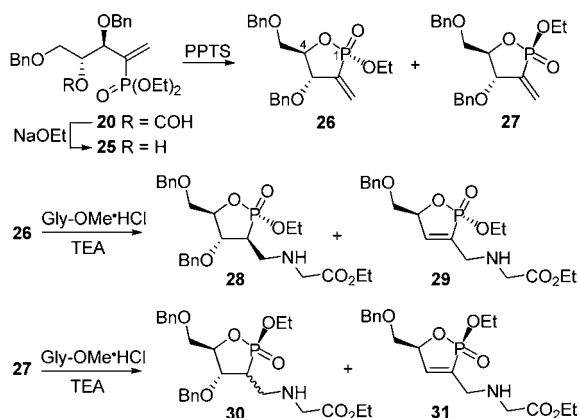
The synthetic usefulness of these compounds has been preliminarily assessed, and the results are summarized in Scheme 2. We were interested in the formation of 2-methylene-1-phosphapentofuranoses (3-methylene-1,2-oxaphospholanes) (e.g., **26** and **27**), which are isosteres of α -methylene- γ -butyrolactones.¹⁴ The α -methylene- γ -butyrolactone is an important structural motif found in a great variety of natural products, many of which exhibit useful significant biological activities.¹⁵ We have found

(14) The *C*-isostere of **26** and **27** (2-deoxy-2-methylene-D-erythro-pentono-1,4-lactone) has been prepared; see: Porto, R. S.; Coelho, F. *Synth. Commun.* **2004**, *34*, 3037–3046 and references cited therein.

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Scheme 2. Synthesis of 2-Methylene-1-phosphapentofuranoses and Their Addition Products with Glycine



scant information on the synthesis of 3-methylene-1,2-oxaphospholanes derivatives.¹⁶

The preparation of 2-methylene-1-phosphapentofuranoses **26** and **27** was achieved starting from the vinylphosphonate **20**. Basic hydrolysis of the formate ester afforded alcohol **25**, which was subsequently subjected to intramolecular transesterification using PPTS. The diastereomeric mixture of **26** and **27** was separated by chromatography. The phosphorus stereochemistry was tentatively assigned by the small but significant deshielding effect of the P=O bond on all syn related protons (e.g., **26/27** $\Delta\delta$ 0.2 ppm for H3 β and –0.15 ppm for H4 α).¹⁷ The value of the NMR ring coupling constants ($^3J_{P,H3}$, $^3J_{P,H4}$, and $^3J_{H3,H4}$) differ markedly in both isomers. Since all of them depend on the dihedral angle in a Karplus-type relationship these differences are attributable to different conformations of the ring.¹⁸ Indeed, molecular mechanics models indicate that in **26** the 1,2-oxaphospholane ring preferentially adopts an E_4 conformation with phase angle $P = 52^\circ$, while **27** shows a preference for an E_3 ($P = 204^\circ$).^{17b,c,19}

Finally, the use of these vinylphosphonates as scaffolds was exemplified by the addition of Gly-OMe·HCl to **26**

and **27** (Scheme 2). The reaction stereochemistry could be ascribed to steric hindrance by the two vicinal ether groups. Exclusive 1,4-conjugate addition on the β -side of the molecule was observed in **28**, whereas the sterically less demanding substrate **27** afforded a separable mixture of α - and β -isomers **30**. The stereochemistry at C-2 was assigned by NOESY experiments, with some of the observed interactions also confirming the phosphorus stereochemistry assigned previously for **26** and **27** (for details, see the Supporting Information).²⁰ In both cases, the conjugate elimination of the vicinal benzyl ether was observed as a side reaction, leading to the formation of **29** and **31**.

In summary, we have developed a simple and effective methodology for the synthesis of chiral 1-alkylvinylphosphonate and -phosphine oxide building blocks with two or three carbon tethers possessing one or two stereogenic centers, respectively. The method utilizes inexpensive carbohydrates as starting materials and is amenable for large-scale synthesis. The fragmentation reaction proceeded under very mild conditions allowing the isolation of the 1-(iodomethyl)alkylphosphonate and -phosphine oxide intermediates. Moreover, the method can be applied to disaccharides such as the perbenzylated D-lactal derivative **9** without great loss of efficiency. Prior structural modifications and protection patterns of the carbohydrate increase the potential of the method, e.g., **16** where selective deprotection and derivatization of the alcohols may be attempted.

The ease with which these relatively complex 1-(iodomethyl)alkylphosphonates can be synthesized on a large scale may prompt further research to gain more insight into their chemical reactivity.

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Supporting Information Available. Experimental procedure and spectral data for all pure compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(20) Due to the expected flexibility conformational of 1,2-oxaphospholane rings, the NOESY studies of **28** and **30** were made on minimized structures.

The authors declare no competing financial interest.

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