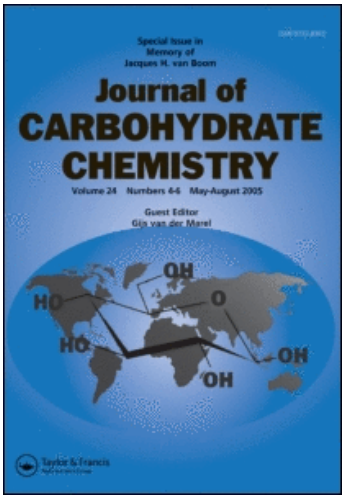


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Concise Synthesis of *P*-Glycosyl Alkenylphosphonates and *P,C*-di and *P,P,C* tri-Glycosyl Phosphonates

Claude Grison[a]; Hicham Chibli[b]
[a] Université Montpellier 2, UMR CNRS, CEFE, France [b] School of Chemical Science and Pharmacy, University of East Anglia Norwich, United Kingdom

To cite this Article Grison, Claude and Chibli, Hicham(2009) 'Concise Synthesis of *P*-Glycosyl Alkenylphosphonates and *P,C*-di and *P,P,C* tri-Glycosyl Phosphonates', Journal of Carbohydrate Chemistry, 28: 1, 12 — 38
To link to this Article: DOI: 10.1080/07328300802638472
URL: http://dx.doi.org/10.1080/07328300802638472

Journal of Carbohydrate Chemistry, 28:12–38, 2009

ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328300802638472

Taylor & Francis
Taylor & Francis Group

Concise Synthesis of *P*-Glycosyl Alkenylphosphonates and *P,C*-di and *P,P,C* tri-Glycosyl Phosphonates

Claude Grison[1] and Hicham Chibli[2]

[1]Université Montpellier 2, UMR CNRS 5175 CEFE, France
[2]School of Chemical Science and Pharmacy, University of East Anglia Norwich, United Kingdom

A direct access to *P*-glycosyl-, *P*, *P*-di-glycosyl alkenylphosphonates and *P*, *C*-glycosyl phosphonates is described. The method involves the Horner reaction of an anion derived from *P*-monoglycosyl and P^1,P'-diglycosyl methylenediphosphonates either on the exocyclic aldehyde group of carbohydrates or on the masked aldehydic form of the furanose hemiacetals. In this last case, the carbonyl olefination, followed by an intramolecular cyclization, leads to *P*, *C*-di and *P*, *P*, *C*-triglycosyl phosphonates.

Keywords *P*-Glycosyl methylenediphosphonates, Horner reaction, Furanose hemiacetals, *P*-Glycosyl alkenylphosphonates, *P*, *C*-diglycosyl phosphonates.

INTRODUCTION

During the last several years there has been considerable interest in the design and synthesis of enzymatically resistant analogs of glycosylphosphates. Among them, glycosylphosphonates have found broad applications as metabolically stable analogs and as potential candidates for therapeutics. In this context, various synthetic approaches to glycosylphosphonates have been described.[1–25] The alkenylphosphonates are useful synthetic intermediates in the preparation of such compounds, because they can act as Michael acceptors; can be employed in Diels-Alder reactions and in free radical coupling; and

Received June 17, 2008; accepted October 21, 2008.
Address correspondence to Claude Grison, CEFE UMR 5175, Campus CNRS, 1919 Route de Mende, 34293 Montoellier Cedex 5, France. E-mail: cgrison@univ-montp2.fr

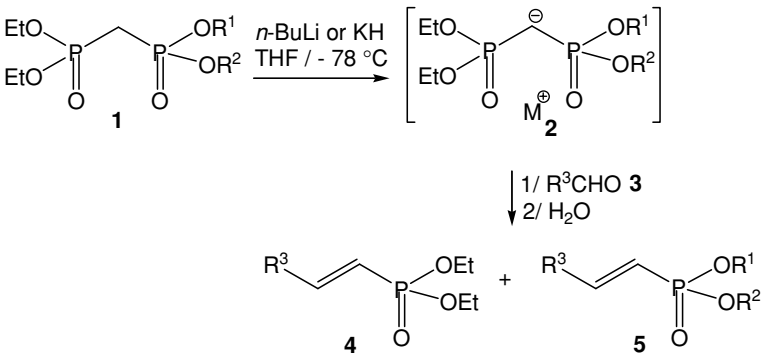
the reduction of the double bond is easy.[26–33] The intramolecular Michael addition is particularly attractive because it is a direct method of *C*-glycosyl phosphonate formation.[34–43]

Although numerous synthetic approaches to dialkyl alkenyl phosphonates are described, the preparation of *P*-monoglycosyl and *P*, *P*-diglycosyl alkenylphosphonates has been largely unexplored due to the difficulties in preparing such unsaturated phosphorus structures. In continuation of our works on the design and synthesis of bioactive glycosylphosphonates,[44–46] we present a rapid and facile access to the title compounds, which is based on a Horner-type reaction.

We previously described a one-pot preparation of *P*-monoglycosyl and *P*, *P*-diglycosyl methylenediphosphonates, which involved the direct generation of methylene diphosphonic anions. It was attractive to explore the reactivity of these compounds with an aldehyde group of carbohydrates in order to build glycosyl alkenylphosphonate systems.

RESULTS AND DISCUSSION

As outlined in Scheme 1, the approach was based on the Horner reaction of carbanions **2**, with a series of carbonyl substrates **3**. To investigate the feasibility of this reaction, the aldehyde group of aliphatic substrates, dialdo sugars, and aldo sugars was successively used as an electrophile for carbonyl olefination. The presence in the same molecule **2** of two different phosphoryl groups on the same carbon can lead to two different olefins. If the leaving group is $(EtO)_2P(O)OLi$, the elimination leads to *P*-glycosyl alkenylphosphonates **5**, and if the leaving group is $(R^1O)(R^2O)P(O)OLi$, **4** was obtained. The unsymmetrical structure of the diphosphorylated reagents presents an interesting problem of regioselectivity.



Scheme 1: Synthesis of *P*-monoglycosyl and *P,P*-diglycosyl alkenylphosphonates **5**.

Because the nature of the counterion of the anions **2** could influence the outcome of the Horner reaction, we performed the deprotonation step using

different bases starting from model compound **1a** and isobutyraldehyde: *n*-BuLi in THF at –78°C and KH in THF at –78°C for 30 min. The addition of the isobutyraldehyde **3a** to the in situ generated anion **2** is run at low temperature and the reaction was stopped after decomposition of the aldol adduct into conjugated olefin **5**; **4** and **5** were characterized by ^{31}P NMR [δ ($CDCl_3$) ppm].

As can be observed from the results in Table 1, the Horner reaction with *n*-BuLi and KH affords a mixture of three isomers, the expected *P*-ribosyl ethyl isopentenylphosphonate **5a**, which was obtained as a mixture of two cpimers, and the diethyl isopentenylphosphonate **4a**.

The diethyl phosphate salt is preponderantly eliminated and the best regioselectivity is obtained with KH (**5a**: 60% after purification).

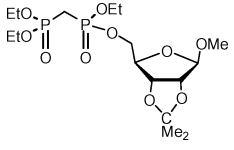
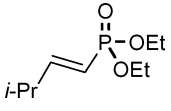
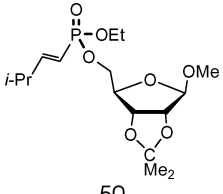
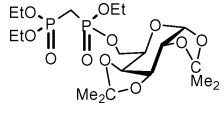
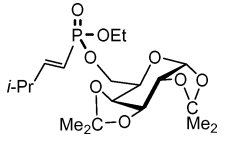
We found that the aldol intermediate exhibits a resistance to decomposition into olefins at – 78°C. Therefore, after addition of the carbonyl compound **3** at – 50°C, the resulting mixture was stirred for 3 h, and then it was allowed to warm to rt. The stirring of the mixture reaction at rt achieved complete olefination after 15 h. As a result, the reaction was generally studied with KH as base under these conditions.

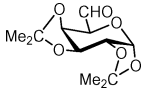
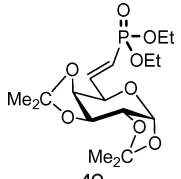
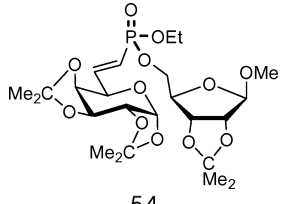
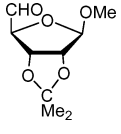
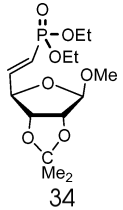
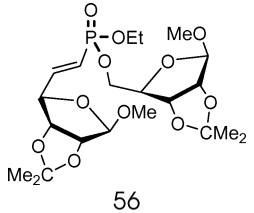
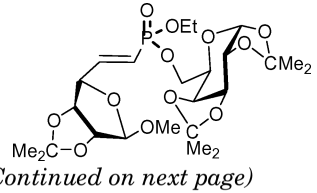
In all cases the addition of an aldehyde **3** to the potassic anions **2** led to the formation of the **4** and **5** regiomers with **5** as major isomer. The regioselectivity of the reaction was shown to be in favor of **5** (50%–60%). However, in complete contrast to our previous studies on the Horner reaction, the regioselectivity was not governed by the steric hindrance of alkoxy groups R^1 and R^2. Curiously, the presence of one or two glucidic moieties induced no modification in the **5/4** ratio of regiomers. The stereoselectivity was excellent and only *E*-isomers were observed. The *P*-glycosylphosphonates **5** was obtained in pure state after chromatography. From a practical point of view, it was noteworthy that the difference of the R_f values between both regiomers **4** and **5** was sufficient for an easy and preparative separation of *P*-glycosylphosphonates **5**. The purity of **5** was evaluated easily by ^{31}P-NMR analysis.

The products **5** were obtained pure in satisfactory yields (46%–60%). The weak sensitivity of the reaction to steric factors is a disadvantage for the regioselectivity, but it is an interesting advantage to incorporate various glycosyl units on the substrates and on the reagents. Thus, the reaction with protected dialdogalactopyranose, dialdoribofuranose, and aldoarabinose occured with comparative ease. Likewise, it was possible to introduce one or two glycoyl units on the same phosphorus atom. These last units can be the same or different, derived from a pyranose or a furanose. In all cases, the efficiency of the carbonyl olefination was conserved. The results described herein demonstrate that this methodology is well suited for forming complex and stable glycosyl phosphonates.

The synthesis of such type of saturated *P*-monoglycosyl and *P*, *P*-diglycosyl alkylphosphonates **6** can also be achieved, in excellent yields, by catalytic hydrogenation of alkenyphosphonates **5** (Sch. 2, Table 2). Because different

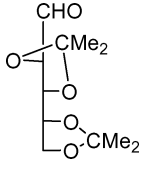
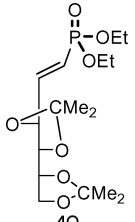
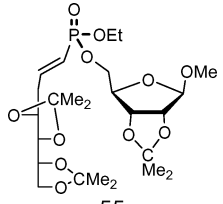
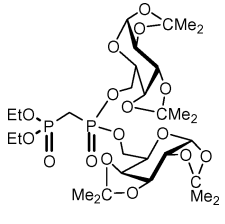
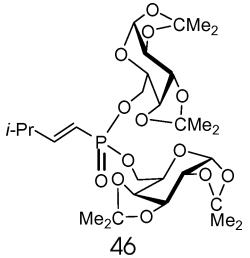
Table 1: Synthesis of *P*-monoglycosyl and *P*, *P*-diglycosyl alkenylphosphonates **5**

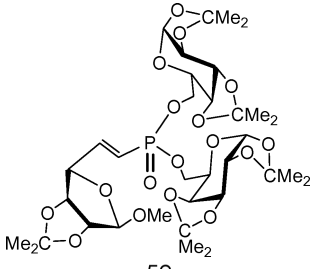
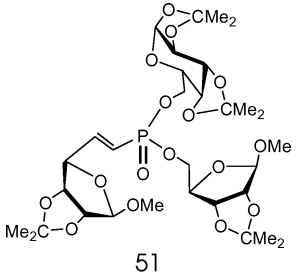
R^3CHO 3	Compounds 1	Regiomeric ratio (5/4) n-BuLi	Regiomeric ratio (5/4) KH	Product yields % Epimeric ratio[c] ^{31}P NMR ($CDCl_3$), δ	
3a	**1a** 			**4a**[d] 	**5a** 
i-PrCHO		66/34[a]			50 43/57 20.29(s,1P)/20.26(s,1P)
3a	**1a**	60/40[b]		**4a** 40	**5a** 43/57
3a	**1a**		66/34[b] 58/42[b]	**4a** 33	**5a** 60 45/55
3a	**1b** 			**4a**	**5b** 
				42	54 52/48 20.63(s,1P)/20.18(s,1P)

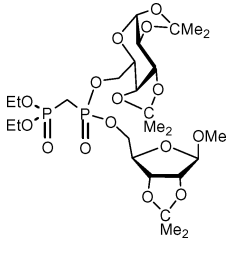
3b 	**1a**	58/42[b]	**4b**[e]  42 18.75(s,1P)	**5c**  54 64/36 19.21(s,1P)/19.01(s,1P)
3c 	**1a**	66/34[b]	**4c**[f]  34 17.98(s,1P)	**5d**  56 52/48 18.55(s,1P)/18.26(s,1P)
3c	**1b**	58/42[b]	**4c** 42	**5e** 

(Continued on next page)

Table 1: Synthesis of *P*-monoglycosyl and *P*, *P*-diglycosyl alkenylphosphonates **5** *(Continued)*

R3CHO 3	Compounds 1	Regiomeric ratio (5/4) n-BuLi	Regiomeric ratio (5/4) KH	Product yields % Epimeric ratio[c] % Epimeric ratio[c] ^{31}P NMR ($CDCl_3$), δ	
					58 60/40 18.66(s,1P)/18.17(s,1P)
3d	**1a**		60/40[b]	**4d**	**5f**
				 40 18.10(s,1P)	 55 50/50 18.65(,1P)/18.61(s,1P)
3a	**1c**		50/50[b]	**4a** 50 19.80(s,1P)	**5g**
					 46 20.99(s,1P)

3c	**1c**	62/38[b]	**4c** 38 18.01(s,1P)	**5h**  52 19.02(s,1P)
3c	**1d**	55/45[b]	**4c** 45	**5i**  51 46/6/28/10 19.02(s,1P)/18.89(s,1P) 18.74(s,1P)/18.06(s,1P)



[a] After addition of the carbonyl compound **3** at–78°C, the resulting mixture was stirred for 1.5 h and hydrolyzed at this temperature.

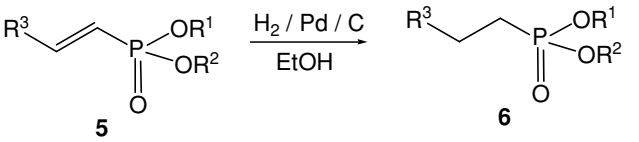
[b] After addition of the carbonyl compound **3** at –50°C, the resulting mixture was stirred for 3 h, then allowed to warm to rt and stirred for 15 h beore hydrolysis.

[c] The presence of a chiral center on the phosphorus atom led to two epimers as observed by ^{31}P NMR analysis, but it was not possible to separate them by chromatography.

[d] For previous syntheses of **4a** see [47,48].

[e] For previous syntheses of **4b** see[49].

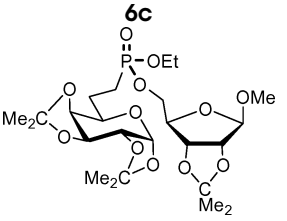
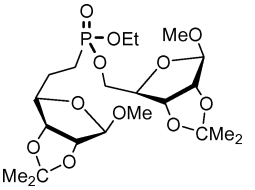
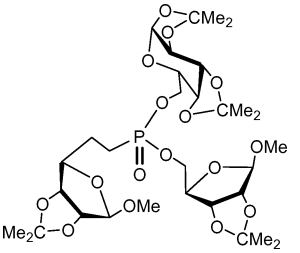
[f] For previous syntheses of **4c** see[50].



Scheme 2: Catalytic hydrogenation of *P*-glycosyl alkenylphosphonates **5**.

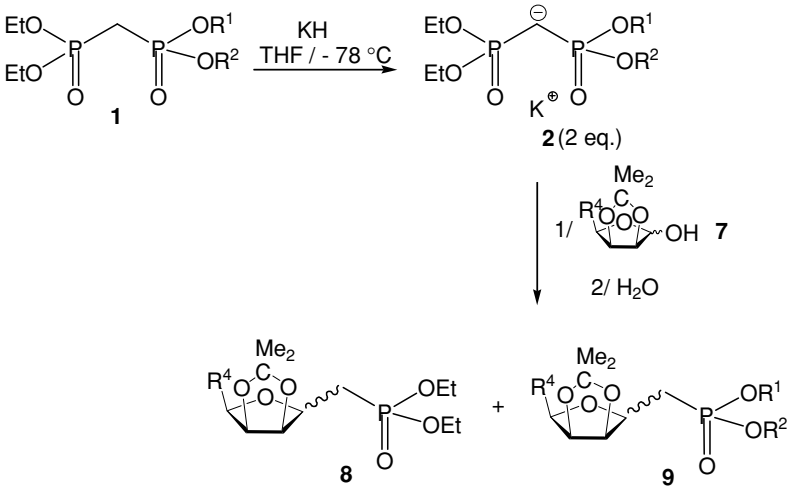
phosphono analogs of natural phosphates are of biological interest, the synthesis of monoglycosyl and diglycosyl alkylphosphono analogs of ribose 5-phosphate and galactose 6-phosphate represents an interesting target. With this aim, we have also studied the catalytic hydrogenation of **5c**, **5d**, and **5i**, a priori the most difficult examples, having steric hindrance on the phosphorus atom. These hydrogenations carried out in the presence of 10% palladium on

Table 2: Catalytic hydrogenation of *P-glycosyl* alkenylphosphonates **5**

Substrates **5**	Product yields % Epimeric ratio
5c	**6c**  98 1/1
5d	**6d**  95 4/3
5i	**6i**  95 10/7

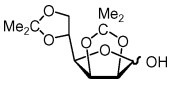
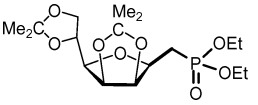
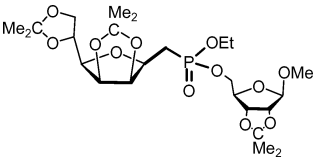
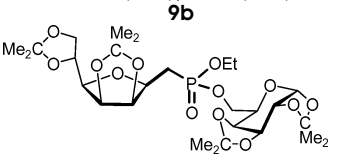
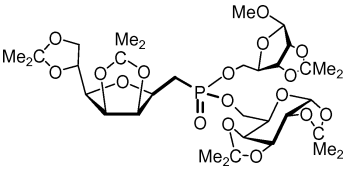
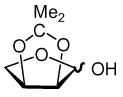
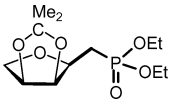
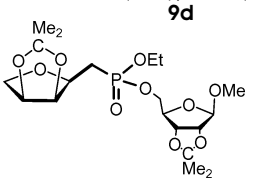
charcoal, in EtOH, at rt were very efficient (95%–98% yield): ^{31}P NMR of the phosphonates **6** indicated the presence of two epimers.

Encouraged by these results, we turned then to the synthesis of *C*-glycosyl phosphonates **9**. These compounds are of particular interest in the research of glycosyl phosphate mimetics, because they represent stable mimetics of the main natural glycosylating agents.[17] The biological potential of *C*-glycosyl phosphonates has been largely unexplored due the difficulties in preparing such structures, which requires a process of *C*-glycosylation. The first synthetic approach reported in 1981 consists of the introduction of a methylenephosphonic group at the anomeric center by nucleophilic substitution on a glycosyl halide using different earbanions derived from the diethyl methylphosphonate. Unsatisfactory results have been obtained and the elimination occurred mainly.[17] More recently, a different strategy has been proposed: it involves the addition of carbanions derived from the diethyl methylphosphonate onto a glyconolactone. However, the reduction of the obtained lactol with triethylsilane failed.[15] In view of these difficulties, indirect methods of glycosyl methylphosphonate synthesis have been developed. They are based on the introduction of functionality (aldehyde, alkyl halide, or methanesulfonate) at the carbon linked to the anomeric center followed by subsequent introduction of a phosphonic group.[17] This approach requires a quite complex starting material. Approaches that involved Wittig-type reactions are applicable to the formation of C-glycosides from lactols. The use of Horner reagents bearing carboxylic or phosphonic ester functionalities seems to be more general.[51–53] If some epimerization of the stereocenter at C-2 was observed, this methodology apperas to have greater synthetic interest in developing an efficient and direct procedure for transformation of readily availabe furanose and pyranose



Scheme 3: Synthesis of *C*-glycosyl phosphonates **9**.

Table 3: Synthesis of *C*-glycosyl phosphonates **9**

Substrates **7**	Compounds **1**	Product yields % Epimeric ratio[a] ^{31}P NMR ($CDCl_3$), δ	
7a 	**1a**	**8a** 	**9a** 
		44[a] 28.12(s,1P) 26.60(s,1P)	45[a]
7a	**1a**	**8a** 40[b]	**9a** 56[b] 21/26/5/4 28.66(s,1P)/28.44(s,1P) 27.23(s,1P)/27.13(s,1P)
7a	**1b**	**8a** 43[b]	**9b**  52[b] 52/48 29.46(s,1P)/28.08(s,1P)
7a	**1c**	**8a** 52[b]	**9c**  45[b] 29/45/18/7 29.94(s,1P)/29.57(s,1P) 28.31(s,1P)/27.47(s,1P)
7b 	**1a**	**8b**  —[c]	**9d**  40°

[a] After addition of the furanose hemiacetal **6** at–50°C, the resulting mixture was stirred for 3 h, then allowed to warm to rt. The solution was stirred for 15 h and was then hydrolyzed.
[b] After addition of the carbonyl compound **3** at–78°C, the resulting mixture was allowed to warm to room temperature. The solution was stirred for 2 h and was hydrolyzed.
[c] It was more difficult to separate and to characterize the regiomers **8b** and **9d**.

hemiacetal into glycosyl phosphonates. This prompated us to study the synthesis of *C*-glycosyl phosphonates bearing one and two *P*-glycosyl units utilizing Horner reaction.

The procedure was based on the reaction of methylene diphosphonic anions **2** with the masked aldehyde function of furanose hemiacetals **7**. The Horner

reaction led to an unsaturated, open-chain intermediate, followed by an intramolecular cyclization to furnish *P*, *C*-diglycosyl phosphonates **9** (Sch. 3).

The choice of the protected sugars **7** as models for testing the Horner reaction of *P*-glycosyl methylenediphosphonate anions **2** with the hemiacetal functionality results from their accessibility and their low tendency to give competitive elimination reactions in basic medium. We describe the reaction of potassium anions **2** of various *P*-glycosyl dimethylenediphosphonates leading to new *C*-glycosyl phosphonates **9**.

As reported in Table 3, the addition of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **7a** onto the in situ generated anions **2** leads, after warming up the reaction to rt, to the mixture of compounds **8** and **9** resulting from the competitive elimination between the two phosphonyl groups during the Horner step. A low-temperature condensation (–78 °C), followed by stirring for 2 h is required to favor the expected *C*-mannosyl phosphonates **9**. In all cases a mixture of α- and β-anomers were obtained. With **9a** and **9c**, both stereomers due to the chirality of the phosphorus atom are observed from the ^{31}P NMR spectrum. The compounds **9a–9c** were purified on silica gel without decomposition and were obtained in satisfactory yields. The separation of the compounds **8** and **9** was easy, and pure derivatives **9a**, **9b**, and **9c** were obtained. The sequence *C*-anomeric olefination/intramolecular Michael reaction was compatible with the protected D-erythrofuranose **7b**, but a small decrease in yield was observed due to a more difficult separation of compounds **8b** and **9d**.

It should be noted that all potassium anions **2** reacted cleanly with furanose hemiacetals **7a** and **7b**. Indeed, a current disadvantage of the Horner-based approach is the competitive retroaldol reaction of substrate **7** before the Horner reaction. This is caused by the strong basicity of the lithium or potassium diphosphonates. Here, no product resulting from the undesirable reaction was detected and the high nucleophilicity of anions **2** only leads to desired reactions. Finally, it is interesting to note that the reactivity of anions **2** was not affected by the steric hindrance of the different glycosyl residues.

CONCLUSION

We have presented in this paper a useful method for the preparation of new *P*-mono and *P*, *P*-diglycosyl alkenyl and alkylphosphonates. This facile and direct reaction starting from the readily available reagents **1** works well with aliphatic substrates, dialdo sugars, and aldo sugars. This methodology can be applied to furanose hemiacetals to afford the complex *P*, *C*-diglycosyl and *P*, *P*, *C*-triglycosyl phosphonates bearing one or two glycosyl units on the phosphorus atom.

EXPERIMENTAL

Carbohydrates and other fine chemicals were obtained from commercial suppliers and used without further purification. Solvents were dried and distilled following standard procedures. All the glassware was dried overnight at 120°C and all the reactions were carried out in inert atmosphere. TLC was carried out on precoated plates (E. Merck Silica Gel 60, F_{254}), and the spots were visualized by charring the plates dipped in 10% H_2SO_4-EtOH. The IR spectra were recorded using a Nicolet 1R-FT spectrophotometer between 3500 and 400 cm^{-1} and are given in cm^{-1}. Column chromatography was performed on silica gel (60–120 mesh). ^1H, ^{13}C, and ^{31}P NMR spectra were recorded with Bruker 400 at 400, 100, and 170 MHz, respectively, in $CDCl_3$. In di- and triglycosyl systems, H of D-galactose derivatives are indicated by "H_g" and H of D-ribose derivatives are indicated by "H_r". The mass spectra were recorded using the FAB or El techniques. **1a**, **1b**, and **1c** were easily prepared according to our previous works.[45]

O′ -(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose)-6-yl *O′* -(methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl [(diethoxyphosphoninyl)methyl] phosphonate 1d

To a vigorously stirred solution of diethyl methylphosphonate (2.9 mL., 20 mmol) in THF (20 mL), *s*-BuLi (20 mmol, of a 1.5 M solution in Hexane) was added dropwise at –78°C. Stirring was maintained for 30 min at −78°C. The *O*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose)-6-yl-phosphorodichloridate[45] (3.77 g, 10 mmol) dissolved in THF (10 mL.) was added dropwise and the mixture was stirred for 30 min at −78°C. Then methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (2.04 g, 10 mmol) dissolved in THF (10 mL) was added dropwise and the mixture was stirred for 10 min at –78°C. After 2 h at rt the reaction was quenched with water (50 mL). The organic layer was extracted with CH_2Cl_2 (3 × 100 mL) and dried over $MgSO_4$. Evaporation of solvents and silica gel chromatography (CH_2Cl_2/EtOH 96:4) provided a diastereomeric mixture **1d** (4.6 g, 70%) as a yellow oil. R_f (1:1 EtO Ae/hexane) 0.39, IR (KBr): v 1245 and 1020; ^1H NMR ($CDCl_3$): δ 5.47 (d, 1H, $J_{1,2} = 4.8$ Hz, H_g-1), 4.89 (s, 1H, H_r-1), 4.65 (dd, 1H, $J_{3,2} = 2.0$, $J_{3,4}$ 6.0 Hz, H_r-3), 4.55–4.47 (m, 2H, H_g-3, H_r-2). 4.31–4.27 (m, 1H, H_r-4) 4.26 (dd, 1H, $J_{2,1} = 4.8$, $J_{2,3} =$ 2.4 Hz, H_g-2), 4.20 (dd, 1H, $J_{4,3} = 8.0$, $J_{4,5} = 2.0$ Hz, H_g-4), 4.16–3.98 (m, 9H, H_r-5, H_g-5, H_g-6, CH_2-CH_3), 3.28 (s, 3 H, O-CH_3), 2.63–2.50 (m, 2H, P-CH_2-P), 1.56 (s, 3H, C(CH_3)$_2$), 1.49 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 1.35 (t, 6H, $J = 7.0$ Hz, CH_2-CH_3), 1.33 (s, 9H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ 112.4, 109.3, 108.6 (*C*(CH$_3$)$_2$), 109.4 (C_r-1), 96.0 (C_g-1), 85.0, 84.9 (C_r-2, C_r-4), 81.7 (C_r-3), 70.5, 70.4, 70.3 (C_g-2, C_g-3, C_g-4), 67.1 (d, $J_{C.P} = 6$ Hz, C_g-5), 65.4–64.7 (m, C_g-6, C_r-5), 62.5 (d, $J_{C.P} = 6$ Hz, CH_2-CH_3), 53.8 (O-*C*H$_3$), 25.9, 24.9, 24.4,

23.9, 23.4 (C(CH_3)$_2$), 24.3 (tl, $J_{C.P}$ = 137 Hz, P-CH_2-P), 15.6 (D, $J_{C.P}$ = 5 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$): δ 20.11 (d, $J_{P.P}$ = 6.4 Hz, 1P), 19.22–19.11 (m, 2P); ESI-MS: *m/z* calcd for $C_{26}H_{46}O_{15}P_2$ 660.58; $[M+Na]^+$; 683.57; found 683.

General Procedure A for the Synthesis of *P*-monoglycosyl and *P,P*-diglycosyl alkenylphosphonate 5a–e

Diphosphonate (4 mmol) **1a** or **1b** dissolved in THF (5 mL) was added to KH (4 mmol washed three times by THF (5 mL) dissolved in THF (12 mL) at −78°C. The mixture is stirred for 30 min and then the aldehyde **3a–c** (2 mmol) dissolved in THF (5 mL) was added dropwise at –78°C while making sure that the temperature did not exceed –70°C. The mixture was maintained for 1 h at – 70°C, 1 h at –50°C and then was allowed to warm up to rt and stirred for 2 h. The reaction was hydrolyzed with water (10 mL). The aqueous solution was washed with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column with EtOAc/Hexane to afford **5a–e**.

O′ -Ethyl *O′* -(methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-y1 isopenten-1-ylphosphonate 5a.

Compound **1a** (1.78 g) was transformed to compound **5a** (colorless oil, 0.22 g, 60%, mixture of two diastereomers 45/55) following the general procedure A. R_f (8:2 EtOAc/hexane) 0.40; ^{1}H NMR ($CDCl_3$); δ 6.88–6.69 (m, 1H, PCH=C*H*), 5.66–5.54 (m, 1H, PC *H*=C), 4.98 (s, 1 H, H-1), 4.60 (dd, 1H, $J_{3,2}$ = 6.0 Hz, $J_{3,4}$ = 12 Hz, H-3), 4.60 (d-d, 1H, H-2), 4.38–4.34 (m, 1H, H-4), 4.14–3.96 (m, 4H, H-5, CH_2-CH_3), 3.24 (s, 3H, O-CH_3), 2.49–2.43 (m, 1H, C*H*(CH_3)$_2$), 1.50 (s, 3H, C(CH_3)$_2$; 1.36 (S, 3H, C(CH_3)$_2$), 1.33 (t, 3H, *J*= 5.0 Hz, CH_2 − CH_3), 0.95 (d, 6H, *J* = 9.0 Hz CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ 160.4 (d, $J_{C.P}$ = 14 Hz, *C* =C-P), 112.9 (d, $J_{C,P}$ = 19 Hz, C=C-P), 109.4 (C-1), 108.8 (*C*(CH_3)$_2$), 85.0–84.9 (m, C-2, C-4), 80.3 (C-3), 65.1 (d, $J_{C.P}$ = 6 Hz, C-5), 62.1 (m, *C*H_2-CH_3), 55.0 (O-*C*H_3), 32.3 (*C*H(CH_3)$_2$), 26.4, 24.8 (C(*C*H_3)$_2$), 20.8 (CH(*C*H_3)$_2$), 16.4–16.2 (m, CH_2-CH_3); ^{31}P NMR ($CDCl_3$): δ 20.29 (s, 1P), 20.26 (s, 1P); FAB-MS: *m/z* calcd for $C_{16}H_{29}O_7P$ 364.37; $[M+H]^+$ 365.38; found 365: for $[M\text{-}MeO]^+$ 333.34: found 333.

O′ -Ethyl *O′* -(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) -6-y1 isopenten-1-ylphosphonate 5b

Compound **1b** (2.00 g) was transformed to compound **5b** (colorless syrup, 0.45 g, 54%, mixture of two diastereomers 52/48) following the general procedure A. R_f (8:2 CH_2Cl_2/EtOH) 0.50; ^{1}H NMR ($CDCl_3$): δ 6.85–6.73 (m, 1H,

PCH-C*H*), 5.66–5.54 (m, 2H, H-1, PCH—C), 4.54 (dd, 1H, $J_{3,2}$=2.5, $J_{3,4}$ =8.0 Hz, H-3), 4.25 (dd, 1H, $J_{2,3}$ =2.5, $J_{2,1}$ =4.8 Hz, H-2), 4.20 (dd, 1H, $J_{4,3}$ =8.0, $J_{4,5}$ =1.6 Hz, H-4), 4.15–4.00 (m, 5H, H-5, H-6, CH_2-CH_3), 2.50–2.44 (m, 1H, CH(CH_3)$_2$), 1.55 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 1.35 (s, 6H, C(CH_3)$_2$), 1.35 (t, 3H, J 7.0 Hz, CH_2-CH_3), 1.10 (d, 6H, J = 7.0 Hz, CH(CH_3)$_2$), ^{13}C NMR ($CDCl_3$): δ 158.2 (d, $J_{C,P}$ = 14 Hz, *C*=C-P), 114.1 (d, $J_{C,P}$ = 190 Hz, C= *C*-P), 110.0, 109.1 (*C*(CH_3)$_2$), 96.2 (C-1), 70.5, 70.4, 70.4 (C-2, C-3, C-4), 67.2 (d, $J_{C,P}$ = 6 Hz, C-5), 64.3 (d, $J_{C,P}$ = 5 Hz, C-6), 61.9 (d, $J_{C,P}$ = 5 Hz, *C*H_2-CH_3), 32.3 (*C*H(CH_3)$_2$), 26.0, 25.9, 25.0, 24.4 (C(*C*H_3)$_2$), 20.8 (CH(*C*H_3)$_2$), 16.4–16.2 (m, CH_2-*C*H_3); ^{31}P NMR ($CDCl_3$); δ 20.63 (s, 1P), 20.18 (s, 1P); FAB-MS: *m/z* calcd for $C_{19}H_{33}O_8P$ 420.43; $[M+H]^+$ 421.44: found 421.

O′ -Ethyl *O′* -(methyl-2,3-O-isopropylidene-β-D-ribofuranose)-5-yl *C*-(6,7-dideoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-hept-6-enopyranose)-7-yl-phosphonate 5c

Compound **1a** (1.80 g) was transformed to compound **5c** (colorless oil, 0.60 g, 54%, mixture of two diastereomers 64/36) following the general procedure A. R_f (1:1 EtOAc/hexane) 0.50, ^{1}H NMR ($CDCl_3$); δ6.77–6.65 (m, 1H, H′-6), 6.02–5.92 (m, 1H, PC*H*=C), 5.53 (d, 1H, $J_{1,2}$ = 5.8 Hz, H′-1), 4.89 (s, 1H, H-1), 4.65 (dd, 1H, $J_{3,2}$ = 5.9, $J_{3,4}$ = 12.0 Hz, H-3), 4.57 (dd, 1H, $J_{3,2}$) = 2.4, $J_{3,4}$ 7.6 Hz, H′-3), 4.51 (tl, 1H, H-2), 4.38–4.35 (m, 1H, H′-5), 4.30–4.27 (m, 1H, H-4), 4.29 (dd, 1H, $J_{2,3}$ = 2.4, $J_{2,1}$ = 5.8 Hz, H′-2), 4.22 (dd, 1H, $J_{4,3}$) = 7.6, $J_{4,5}$ = 2.0 Hz, H′-4), 4.08–3.82 (m, 4H, H-5, CH_2-CH_3), 3.24 (s, 3H, O-CH_3), 1.45 (s, 3H, C(CH_3)$_2$), 1.41 (s. 3H, C(CH_3)$_2$). 1.28–1.24 (m, 15H, C(CH_3)$_2$, CH_2-CH_3); ^{13}C NMR ($CDCl_3$); δ *major*: 148.2 (d, $J_{C,P}$ = 6 Hz, *C* =C-P), 118.0 (d, $J_{C,P}$ = 190 Hz, C= *C*-P), 109.4 (C-1), 109.7, 109.6, 108.8 (*C*(CH_3)$_2$), 96.4 (C′-1), 85.0–84.9 (m, C-2, C-4) 72.3 (C′-4), 70.9 (C′-3), 70.5 (C′-2), 68.1 (d, $J_{C,P}$ = 3 Hz, C′-5), 65.1 (d, $J_{C,P}$ = 6 Hz, C-5), 62.1 (m, *C*H_2-CH_3), 55.0 (O-*C*H_3), 26.4, 26.1, 25.8, 25.0, 24.8, 24.5 (C(*C*H_3)$_2$), 16.4–16.2 (m, CH_2 – *C*H_3); *minor*: 148.0 (d, $J_{C,P}$ = 6 Hz, *C* =C-P), 118.0 (d, $J_{C,P}$ = 190 Hz, C= *C*-P), 109.4 (C-1), 109.7, 109.6, 108.8 (*C*(CH_3)$_2$), 96.4 (C′-1), 85.0–84.9 (m, C-2, C-4), 72.3 (C′-4), 70.9 (C′-3), 70.5 (C′-2), 68.1 (d, $J_{C,P}$ = 3 Hz, C′-5), 65.1 (d, $J_{C,P}$ = 6 Hz, C-5), 62.1 (m, *C*H_2-CH_3), 54.9 (O-*C*H_3), 26.4, 26.1, 25.8, 25.0, 24.8, 24.5 (C(*C*H_3)$_2$), 16.4–16.2 (m, CH_2-CH_3), ^{31}P NMR ($CDCl_3$): δ19.21 (s, 1P), 19.01 (s, 1P); FAB-MS: *m/z* caled for $C_{24}H_{39}O_{12}P$ 550.53; $[M+H]^+$ 551.54; found 551; [M-MeO] 519.50: found 519.

O′, *O′*-Diethyl C-(6,7-dideoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-hept-6-enopyranose)-7-yl-phosphonate 4b

Compound **4b** (colorless syrup, 0.29 g, 46%) was obtained as a co-product of **5c**; ^{1}H NMR ($CDCl_3$): δ6.77–6.65 (m, 1H, H′-6), 6.03–5.94 (m, 1H, PC*H*=C), 5.57 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.62–4.60 (m, 1H, H-3),

4.41–4.39 (m, 1H, H-5), 4.20 (dd, 1H, $J_{2,3}$ = 2.4 and $J_{2,1}$ = 5.0 Hz, H-2), 4.27–4.23 (m, 1H, H-4), 4.10–4.00 (m, 4H, CH_2-CH_3), 1.48 (s, 3H, C(CH_3)$_2$), 1.35 (s, 3H, C(CH_3)$_2$), 1.31–1.28 (m, 12H, C(CH_3)$_2$, CH$_2$-CH_3; ^{13}C NMR ($CDCl_3$): δ147.5 (d, $J_{C,P}$ = 7 Hz, *C* =C-P), 117.0 (d, $J_{C,P}$ = 185 Hz, C= *C*-P), 109.5, 108.7 (*C*(CH$_3$)$_2$), 96.4 (C-1), 85.0–84.9 (m, C-2, C-4), 72.3 (C-4), 70.9 (C-3), 70.5 (C-2), 67.8 (d, $J_{C,P}$ = 3 Hz, C-5), 62.1 (m, *C*H$_2$-CH$_3$), 26.4, 26.1, 24.8, 24.5 (C(*C*H$_3$)$_2$), 16.4–16.2 (m, CH$_2$-CH$_3$); ^{31}P NMR ($CDCl_3$): δ18.75 (s, 1P); FAB-MS: *m/z* caled for $C_{17}H_{29}O_8P$ 392.38: $[M+H]^+$ 393.39: found 393.

O′ -Ethyl *O′* -(Methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranose)-6-yl-phosphonate 5d

Compound **1a** (2.00 g) was transformed to compound **5d** (colorless oil, 0.62 g. 56% mixture of two diastereomers 58/42) following the general procedure A. R_f (7:3 EtOAc/hexane) 0.30; ^{1}H NMR ($CDCl_3$): δ6.80–6.69 (m, 1H, H′-5), 6.02–5.93 (m, 1H, PC*H* =C), 4.89 (s, 1H, H-1), 4.88 (s, 1H, H′-1), 4.70–4.67 (m, 2H, H-3, H′-3), 4.53–4.49 (m, 3H, H-2, H′-2, H′-4), 4.29 (dd, 1H, $J_{4,3}$ = 8.5, $J_{4,5}$ = 6.4 Hz, H-4), 4.09–3.90 (m, 4H, H-5, CH_2-CH$_3$), 3.27 (s, 3H, O-CH_3), 3.24 (s, 3H, O-CH_3), 1.53 (s, 3H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 1.32 (s, 3H, C(CH_3)$_2$), 1.26–1.24 (m, 3H, CH$_2$-CH_3), 1.21 (s, 3H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ *major*: 145.1 (d, $J_{C,P}$ 7 = Hz, C′-5), 116.7 (d, $J_{C,P}$ = 187 Hz, C= *C*-P), 111.6, 111.2 (*C*(CH$_3$)$_2$), 108.0 (C-1), 105.7 (C′-1), 83.7–83.6 (C-2, C-4, C′-2), 80.3 (C-3), 79.3 (C′-3), 78.3 (d, $J_{C,P}$ = 22 Hz, C′-4), 63.8 (d, $J_{C,P}$ = 6 Hz, C-5), 60.8 (d, $J_{C,P}$ = 5 Hz, CH$_2$-CH$_3$), 53.6, 53.5 (O-*C*H$_3$), 25.1, 24.7, 23.7, 23.6 (C(*C*H$_3$)$_2$), 15.0 (d, $J_{C,P}$ = 5 Hz, CH$_2$ – *C*H$_3$); *minor*: 144.9 (d, $J_{C,P}$ 7 = Hz, C′-5), 116.7 (d, $J_{C,P}$ = 188 Hz, C= *C*-P), 111.6, 111.2 (*C*(CH$_3$)$_2$), 108.0 (C-1), 105.7 (C′-1), 83.7–83.6 (C-2, C-4, C′-2), 80.3 (C-3), 79.3 (C′-3), 78.4 (d, $J_{C,P}$ = 22 Hz, C′-4), 63.8 (d, $J_{C,P}$ = 6 Hz, C-5), 60.8 (d, $J_{C,P}$ = 5 Hz, *C*H$_2$-CH$_3$), 53.6, 53.5 (O-CH$_3$), 25.1, 24.7, 23.7, 23.6 (C(*C*H$_3$)$_2$), 15.0 (d, $J_{C,P}$ = 6 Hz, CH$_2$ – *C*H$_3$); ^{31}P NMR ($CDCl_3$); δ18.55 (s, 1P), 18.26 (s, 1P); FAB-MS: *m/z* calcd for $C_{21}H_{35}O_{11}P$ 494.47; $[M+H]^+$ 495.48: found 495. 463; $[M\text{-}MeO^-]^+$ 463.44: found 463.

O′ ,*O′* -Diethyl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranose)-6-yl-phosphonate 4c

Compound **4c** (colorless syrup, 0.33 g, 44%) was obtained as a coproduct of **5d**; ^{1}H NMR ($CDCl_3$); δ6.77–6.66 (m, 1H, H-5), 6.01–5.90 (m, 1H, PC*H* =C), 4.88 (s, 1H, H-1), 4.69 (dd 1H, $J_{3,2}$ = 6.0, $J_{3,4}$ = 3.9 Hz, H-4), 4.51 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.49–4.45 (m, 1H, H-4), 4.07–3.98 (m, 4H, CH_2-CH$_3$), 3.24

(s, 3H, O-CH_3), 1.32 (s, 3H, C(CH_3)$_2$), 1.28–1.24 (m, 3H, CH_2-CH_3), 1.21 (s, 3H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ145.1 (d, $J_{C,P}$ = 7 Hz, *C*-5), 116.7 (d, $J_{C,P}$ = 187 Hz, C= *C*-P), 112.9 (*C*(CH_3)$_2$); 107.0 (C-1), 85.0 (C-2), 80.6 (C-3), 79.7 (d, $J_{C,P}$ = 22 Hz, C-4), 63.8 (d, $J_{C,P}$ = 6 Hz, C-5), 61.8 (d, $J_{C,P}$ = 5 Hz, *C*H_2-CH_3), 54.8 (O-*C*H_3), 26.0, 24.9 (C(*C*H_3)$_2$), 16.3 (d, $J_{C,P}$ = 6 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$); δ17.98 (s, 1P); FAB-MS: *m*/*z* calcd for $C_{14}H_{25}O_7P$ 336.32; $[M+H]^+$ 337.33: found 337.

O′-Ethyl *O′*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) -6-yl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranose)-6-yl-phosphonate 5e

Compound **1b** (2.00 g) was transformed to compound **5e** (colorless syrup, 0.64 g, 58%, mixture of two diastereomers 60/40) following the general procedure A, Rf (7:3 EtOAc/hexane) 0.40; ^{1}H NMR ($CDCl_3$): δ6.78–6.67 (m, 1H, H′-5), 6.04–5.94 (m, 1H, PC*H* =C), 5.46 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 4.87 (s, 1H, H′-1), 4.68 (dd$_2$ 1H$_2$$J_{3,2}$ = 4.0, $J_{3,4}$ = 6.0 Hz, H′-3), 4.54 (dd, 1H, $J_{3,2}$ = 2.4, $J_{3,4}$ = 7.8 Hz, H-3), 4.51 (d, 1H, $J_{2,3}$ = 5.6 Hz, H′-2), 4.49–4.45 (m, 1H, H′-4), 4.25 (dd, 1H, $J_{2,3}$ = 2.4, $J_{2,1}$ = 4.8 Hz, H-2), 4.20 (dd, 1H, $J_{4,3}$ = 7.8, $J_{4,5}$ = 1.6 Hz, H-4), 4.16–3.99 (m, 5H, H-5, H-6, CH_2-CH_3), 3.27 (s, 3H, O-CH_3), 1.46 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.32 (s, 3H, C(CH_3)$_2$), 1.28–1.24 (m, 9H, C(CH_3)$_2$, CH_2-CH_3), 1.21 (s, 3H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 145.8 (d, $J_{C,P}$ = 6 Hz$_2$*C* =C-P), 118.4 (d, $J_{C,P}$ = 187 Hz, C= *C*-P), 112.9, 109.4, 108.7 (*C*(CH_3)$_2$), 107.0 (C′-1), 96.2 (C-1), 85.0 (C′-2), 80.6 (C′3), 79.7 (d, $J_{C,P}$ = 22 Hz, C′-4), 70.6, 70.6, 70.5 (C-2, C-3, C-4), 67.2 (d, $J_{C,P}$ = 6 Hz, C-5), 64.3 (d, $J_{C,P}$ = 5 Hz, C-6), 61.9 (d, $J_{C,P}$ = 5 Hz, *C*H_2-CH_3), 54.7 (O-*C*H_3), 26.0, 25.9, 25.0, 24.9, 24.4 (C(*C*H_3)$_2$), 16.2 (d, $J_{C,P}$ = 7 Hz, CH_2 – *C*H_3); ^{31}P NMR ($CDCl_3$): δ18.66 (s, 1P), 18.17 (s, 1P); FAB-MS: *m*/*z* calcd for $C_{24}H_{39}O_{12}P$ 550.53; $[M+H]^+$ 551.54: found 551.

Synthesis of *O′* -Ethyl *O′* -(methyl-2,3-*O*-isopropylidene-β -D-ribofuranose)-5-yl *C*-(1,2-dideoxy-3,4-5,6-di-*O*-isopropylidene-α-D-arabino-hept-1-enose)-1-yl-phosphonate 5f

Diphosphonate (4 mmol) **1a** dissolved in THF (5 mL) was added to KH (4 mmol, washed three times by THF (5 mL)) dissolved in THF (12 mL) at –78°C. The mixture is stirred for 30 min and then the aldehyde **3d** 2 mmol) dissolved in THF (5 mL) was added dropwise at –78°C, while making sure that the temperature did not exceed –70°C. The mixture was maintained for 1 h at –70°C, 1 h at –40°C and then was allowed to warm up to rt and stirred for 12 h. The reaction was hydrolyzed with water (10 mL). The aqueous solution was washed with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the filtrate was concentrated under

reduced pressure. The crude product was purified over silica gel column with EtOAc/Hexane to afford **5f** (colorless oil, 0.64 g. 55%, mixture of two diastereomers 50/50) R_f (6:4 EtOAc/hexane) 0.50; ^{1}H NMR ($CDCl_3$); δ6.93–6.82 (m, 1H, H′-1), 6.13–6.03 (m, 1H, PC*H*=C), 4.95 (s, 1H, H-1), 4.71 (dd, 1H, $J_{3.2}$ = 5.6 and $J_{3.4}$ = 14.8 Hz, H-3), 4.59–4.57 (m, 1H, H-2), 4.53–4.49 (m, 1H, H′-2), 4.35–4.31 (m, 1H, H-4); 4.13–3.92 (m, 7H, H-5, H′-4, H′-5, *C*H_2-CH_3), 3.65 (tl, 1H, H′-3), 3.31 (s, –3H, O-CH_3), 1.47 (s, 3H, C(CH_3)$_2$), 1.42 (s, 3H, C(CH_3)$_2$), 1.41–1.40 (m, 6H, C(CH_3)$_2$), 1.34–1.31 (m, 9H, C(CH_3)$_2$, CH_2-CH_3); ^{13}C NMR ($CDCl_3$): δ *diastereoisomer* a: 150.0 (d, $J_{C,P}$ = 6 Hz, *C*=C-P), 116.7 (d, $J_{C,P}$ = 189 Hz, C=*C*-P), 109.3 (C-1), 110.3, 109.9, 109.9 (*C*(CH_3)$_2$), 85.0–84.9 (m, C-2, C-4), 81.6 (C-3), 81.1 (C′-4), 79.9 (C′-3), 77.0 (C′-5), 67.6 (C′-6), 65.1 (d, $J_{C,P}$ 6 = Hz, C-5), 62.1 (m, *C*H_2-CH_3), 55.0 (O-*C*H_3), 27.0, 26.7, 26.6, 26.4, 25.1, 24.9 (C(*C*H_3)$_2$), 16.3 (d, $J_{C,P}$ = 6 Hz, CH_2-*C*H_3); *diastereoisomer* b: 149.9 (d, $J_{C,P}$ = 6 Hz, *C*=C-P), 116.6 (d, $J_{C,P}$ = 188 Hz, C=*C*-P), 109.3 (C-1), 110.3, 109.9, 109.9 (*C*(CH_3)$_2$), 85.0–84.9 (m, C-2, C-4), 81.6 (C-3), 81.1 (C′-4), 79.7 (C′-3), 77.0 (C′-5), 67.6 (C′-6), 65.0 (d, $J_{C,P}$ = 6 Hz, C-5), 62.1 (m, *C*H_2-CH_3), 55.0, 54.9 (O-*C*H_3), 27.0, 26.7, 26.6, 26.4, 25.1, 24.9 (C(*C*H_3)$_2$), 16.3 (d, $J_{C,P}$ = 6 Hz, CH_2-*C*H_3); ^{31}P NMR ($CDCl_3$); δ18.65 (s, 1P), 18.61 (s, 1P); FAB-MS: *m*/*z* calcd for $C_{24}H_{39}O_{12}P$ 522.52, $[M+H]^+$ 523.53: found 523; [M-MeO-]$^+$ 491.49: found 491.

O′ ,*O*′ -Diethyl *C*-(1,2-dideoxy-3,4–5,6-di-*O*-isopropylidene-α-D-arabino-hept-1-enose)-1-yl phosphonate 4d

Compound **4d** (colorless syrup, 0.33 g, 45%) was obtained as a coproduct of **5f**; ^{1}H NMR ($CDCl_3$); δ6.89–6.78 (m, 1H, H′-1), 6.12–6.02 (m, 1H, PC*H* =C), 4.52–4.49 (m, 1H, H′-2), 4.13–3.92 (m, 7H, H-4, H′-5, C*H*$_2$-CH_3), 3.65 (tl, 1H, H′-3), 1.42 (s, 3H, C(CH_3)$_2$), 1.41–1.40 (m, 6H, C(CH_3)$_2$), 1.33 (s, 3H, C(CH_3)$_2$), 1.32 (t, $J_{H,H}$ = 6.4 Hz, CH_2-CH_3); ^{13}C NMR ($CDCl_3$); δ 149.2 (d, $J_{C,P}$ = 6 Hz, *C* =C-P), 116.6 (d, $J_{C,P}$ = 187 Hz, C= *C*-P), 110.3, 109.9 (*C*(CH_3)$_2$), 81.1 (C′-4), 79.7 (C′-3), 77.0 (C′-5), 67.6 (C′-6), 61.8 (d, $J_{C,P}$ = 6 Hz, *C*H_2-CH_3), 27.0, 26.7, 26.6, 26.4, 25.1 (C(*C*H_3)$_2$), 16.3 (d, $J_{C,P}$ = 6 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$); δ18.10 (s, 1P), FAB-MS: *m*/*z* calcd for $C_{16}H_{29}O_7P$ 364.37; $[M+H]^+$ 365.38: found 365.

General procedure B for the preparation of 5g–i

Diphosphonate (3 mmol) **1c** dissolved in THF (5 mL) was added to KH (3 mmol, washed three times by THF [5 mL] dissolved in THF (15 mL) at –78°C. The mixture is stirred for 30 min and then the aldehyde **3a–b** (1.5 mmol) dissolved in THF (5 mL.) was added dropwise at –78°C, while making sure that the temperature did not exceed –70°C. The mixture was maintained for 30 min at –70°C, 2 h at –40°C and then was allowed to warm up to rt and stirred for

rt h. The reaction was hydrolyzed with water (10 mL). The aqucous solution was washed with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column with EtOAc/Hexane to afford **5g–i**

Bis-*O*′,*O*′-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose)-6-yl isopenten-l-yl-phosphonate 5g

Compound **5g** (colorless syrup, 0.44 g, 46%) was obtained from **1e** (2.15 g) following the general procedure B. R_f (100% EtOAc) 0.60; ^{1}H NMR ($CDCl_3$); δ 6.80–6.64 (m, 1H, PCH=C*H*), 5.63–5.44 (m, 3H, H-1, PCH=C), 4.61 (dd, 2H, $J_{3,2}$ = 2.4, $J_{3,4}$ = 7.9 Hz. H-3), 4.24 (dd, 2H, $J_{2,3}$ = 2.4, $J_{2,1}$ 5.0 Hz, H-2), 4.22–4.20 (m, 2H, H-4), 4.15–3.98 (m, 6H, H-5, H-6), 2.41–2.34 (m, 1H, C*H*(CH_3)$_2$), 1.47 (s, 6H, C(C*H*$_3$)$_2$), 1.36 (s, 6H, C(C*H*$_3$)$_2$), 1.26 (s, 16H, C(C*H*$_3$)$_2$), 0.98 (d, 6H, *J* = 10.4 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$); δ 160.4 (d, $J_{C,P}$ = 14 Hz, C = C-P), 112.9 (d, $J_{C,P}$ = 190 Hz, C = C-P), 109.4, 108.7 (*C*(CH_3)$_2$), 96.2 (C-1), 70.6, 70.5, 70.4, (C-2, C-3, C-4), 67.0 (d, $J_{C,P}$ = 10 Hz, C-5), 64.2 (d, $J_{C,P}$ = 5 Hz, C-6), 32.3 (*C*H(CH_3)$_2$), 26.0, 25.9, 24.9, 24.4 (C(*C*H$_3$)$_2$), 20.8 (CH(*C*H$_3$)$_2$); ^{31}P NMR ($CDCl_3$); δ 20.99 (s, 1P); FAB-MS; m/z calcd for $C_{29}H_{47}O_{13}P$ 634.46; $[M+H]^+$ 635.4 found 365.

Bis-*O*′ ,*O*′ -(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) -6-yl *C*-(5,6-dideoxy-l-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranose)-6-yl-phosphonate 5h

Compound **5h** (colorless syrup, 0.60 g, 52%) was obtained from **1c** (2.15 g) following the general procedure B. R_f (7:3 EtOAc/hexane) 0.54; ^{1}H NMR ($CDCl_3$); δ 6.81–6.71 (m, 1H, H′-5), 6.07–5.97 (m, 1H, PC*H*=C), 5.45 (d, 2H, $J_{1,2}$ = 4.8 Hz, H-1), 4.80 (s, 1H, H′-1), 4.68 (dd, 1H, $J_{3,2}$ = 4.0, $J_{3,4}$ = 5.6 Hz, H′-3), 4.54 (dd, 2H, $J_{3,2}$ = 2.4, $J_{3,4}$ = 8.4 Hz, H-3), 4.51 (d, 1H, $J_{2,3}$ = 5.6 Hz, H′-2), 4.48–4.44 (m, 1H, H′-4), 4.26–4.18 (m, 4H, H-2, H-4), 4.17–3.98 (m, 6H, H-5, H-6), 3.30 (s, 3H, O-C*H*$_3$), 1.47 (s, 6H, C(C*H*$_3$)$_2$), 1.36 (s, 6H, C(C*H*$_3$)$_2$), 1.32 (s, 3H, C(C*H*$_3$)$_2$), 1.26 (m, 12H, C(C*H*$_3$)$_2$), 1.21 (s, 3H, C(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$); δ 146.8 (d, $J_{C,P}$ = 7 Hz, *C*=C-P), 117.9 (d, $J_{C,P}$ = 180 Hz, C= *C*-P), 109.4, 108.7 (*C*(CH_3)$_2$), 107.3 (C′-1), 96.2 (C-1), 84.8 (C′-2), 80.6 (C′3), 79.0 (d, $J_{C,P}$ = 22 Hz, C′-4), 70.6, 70.5, 70.4 (C-2, C-3, C-4), 67.0 (d, $J_{C,P}$ = 10 Hz, C-5), 64.2 (d, $J_{C,P}$ = 5 Hz, C-6), 54.0 (O-*C*H$_3$), 26.4, 26.0, 25.9, 24.9, 24.4 (C(*C*H$_3$)$_2$); ^{31}P NMR ($CDCl_3$); δ 19.02 (s, 1P); FAB-MS; m/z calcd for $C_{34}H_{53}O_{17}P$ 764.35; 765 [M+H]δ 765.36; found 765.

O′ -(1,2:3,4-di-*O*-isopropylidene-α-D-glactopyranose)-6-yl *O′* -(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranose)-6-yl-phosphonate 5i

Compound **5i** (colorless syrup, 0.55 g, 51%, mixture of four diastereomers 46/9/29/16) was obtained from **1e** (2.00 g) following the general procedure B. R_f (7:3 EtOAc/hexane) 0.54, ^{1}H NMR ($CDCl_3$); δ 6.84–6.71 (m, 1H, H′-5), 6.06–5.94 (m, 1H, PC*H*=C), 5.46 (d, 1H, $J_{1,2} = 4.8$ Hz, Hg-1), 4.89–4.87 (m, 2H, H′-1, H_r-1), 4.71–4.62 (m, 2H, H′-3, H_r-3), 4.55–4.47 (m, 4H, Hg-3, H_r-2, H′-2, H′-4), 4.31–4.27 (m, 1H, H_r-4), 4.26 (dd, 1H, $J_{2,1} = 4.8$, $J_{2,3} = 2.4$ Hz, Hg-2), 4.20 (dd, 1H, $J_{4,3} = 8.0$, $J_{4,5} = 2.0$ Hz, Hg-4), 4.16–3.99 (m, 5H, H_r-5, H_g-5, Hg-6), 3.28 (s, 3 H, O-CH_3), 3.27 (s, 3 H, O-CH_3), 1.48 (s, 3 H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 1.26 (s, 3H, C(CH_3)$_2$), 1.25 (s, 9H, C(CH_3)$_2$), 1.24 (s, 3H, C(CH_3)$_2$), ^{13}C NMR ($CDCl_3$); δ 147.1 (d, $J_{C,P} = 7$ Hz, *C*=C-P), 117.8 (d, $J_{C,P} = 182$ Hz, C=*C*-P), 113.1, 112.4, 109.5, 108.8 (*C*(CH$_3$)$_2$), 109.4 (Cr-1), 107.0 (C′-1), 96.3 (C_g-1), 85.0, 84.9, 84.8 (Cr-2, Cr-4, C′-2), 81.7 (C_r-3), 80.6 (C′-3), 79.7 (d, $J_{C,P} = 22$ Hz, C′-4), 70.7, 70.6, 70.5 (C_g-2, C_g-3, C_g-4), 67.1 (d, $J_{C,P} = 6$ Hz, C_g-5), 65.4–64.7 (m, C_g-6, C_r-5), 55.0 (O-CH$_3$), 26.4, 26.0, 25.9, 25.0, 24.9, 24.4 (C(*C*H$_3$)$_2$); ^{31}P NMR ($CDCl_3$); δ 19.02 (s, 1P), 18.89 (s, 1P), 18.74 (s, 1P), 18.06 (s, 1P); FAB-MS; m/z calcd for $C_{31}H_{49}O_{16}P$ 708.68; $[M+H]^+$ 709.69; found 710; $[M\text{-}MeO^-]^+$ 677.65; found 677.

General procedure C for the preparation of 9a–d

Diphosphonate (3 mmol) **1c** dissolved in THF (5mL) was added to KH (3 mmol, washed three times by THP (5mL) dissolved in THF (15mL) at–78°C. The mixture is stirred for 30 min and then the aldehyde **7a–b** (1.5 mmol) dissolved in THF (5mL) was added dropwise at–78°C, while making sure that the temperature did not exceed–70°C. The mixture was maintained for 30 min at –70°C and then was allowed to warm up to rt and stirred for 2h. The reaction was hydrolyzed with water (10mL). The aqueous solution was washed with CH_2Cl_2 (3 × 3mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column with EtOAc/Hexane to afford **9a–d**.

O′-Ethyl *O′*-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl *C*-(2,5-anhydro-1-deoxy-3,4:6,7-di-O-isopropylidene-D-manno-heptofuranose)-1-yl-phosphonate 9a

Compound **1a** (2.00 g) was transformed to compound **9a** (pink oil, 0.69 g, 56%, mixture of four diastereomers 37/47/9/7) following the general procedure

C. NMR ($CDCl_3$); δ 4.90 (s, 1H, H-1), 4.70–4.60 (m, 3H, H-3, H′2, H′-3), 4.52 (tl, 1H, H-2), 4.33–4.25 (m, 2H, H-4, H′-5), 4.11–3.89 (m, 6H, H-5, H′-6, CH_2-CH_3), 3.82–3.75 (m, 1H, H′-1), 3.46–3.41 (m, 1H, H′-4), 3.25 (s, 3H, O-CH_3), 2.33–2.11 (m, 2H, P-CH_2-C), 1.41 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 1.30 (s, 3H, C(CH_3)$_2$), 1.28–1.26 (m, 6H, C(CH_3)$_2$), CH_2-CH_3), 1.25 (s, 3H, C(CH_3)$_2$), ^{13}C NMR ($CDCl_3$); δ ***diastereoisomer*** a: 109.3 (C-1), 112.5, 109.1, 109.0 (*C*(CH_3)$_2$), 85.2–84.9 (m, C-2 et C-4), 81.6 (C′-4), 81.2 (d, $J_{C,P}$ 7 Hz, C′-2), 80.6 (C′-3), 76.5 (C′-1), 72.9 (C′-5), 66.9 (C′-6), 65.3 (d, $J_{C,P}$ = 6 Hz, C-5), 62.3 (m, *C*H_2-CH_3), 55.0 and 54.9(O-*C*H_3), 26.9, 26.4, 25.7, 25.2, 25.0, 24.9 (C(*C*H_3)$_2$), 25.3 (d, $J_{C,P}$ = 140 Hz, P-CH_2-C′), 16.4 (d, $J_{C,P}$ = 2 Hz, CH_2-CH_3), 109.3 (C-1), 112.5, 109.1, 109.0 (*C*(CH_3)$_2$), 85.2–84.9 (m, C-2 et C-4), 81.6 (C′-4), (C′-4), 81.2 (d, $J_{C,P}$ 7 Hz, C′-2), 80.6 (C′-3), 76.4 (C′-1), 72.9 (C′-5), 66.9 (C′-6), 65.0 (d, $J_{C,P}$ = 6 Hz, C-5), 62.3 (m, *C*H_2-CH_3), 55.0 and 54.9(O-*C*H_3), 26.9, 26.4, 25.7, 25.2, 25.0, 24.9 (C(*C*H_3)$_2$), 25.3 (d, $J_{C,P}$ = 140 Hz, P-CH_2-C′), 16.3 (d, $J_{C,P}$ = 2 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$); δ 28.66 (s, 1P), 28.44 (s, 1P), 27.23 (s, 1P), 27.13 (s, 1P); FAB-MS: m/z calcd for $C_{24}H_{41}O_{12}P$ 552.55, $[M+H]^+$ 553.56; found 553, $[M\text{-}MeO^-]^+$ 521.52; found 521.

O′,O′-Diethyl *C*-(2,5-anhydro-1-deoxy-3,4:6,7-di-*O*-isopropylidene-D-manno-heptofuranose)-1-yl-phosphonte 8a

Compound **8a** (colorless syrup, 0.45 g, 40%) was obtained as a coproduct of **5c.** NMR ($CDCl_3$); δ 4.74–4.70 (m, 1H, H-3), 4.60–4.63 (m, 1H, H-2), 4.38–4.31 (m, 1H, H-5), 4.11–3.96 (m, 6H, H-6, CH_2-CH_3), 3.86–3.79 (m, 1H, H-1), 3.48 (dd, 1H, $J_{H,H}$ = 3.6, $J_{H,H}$ 7.6 Hz, H-4), 2.32–2.09 (m, 2H, P-*CH*$_2$-C), 1.42 (s, 3H, *C*(*CH*$_3$)$_2$), 1.39 (s, 3H, C(C*H*$_3$)$_2$) 1.33 (s, 3H, *C*(*CH*$_3$)$_2$), 1.30–1.26 (m, 6H, C(*CH*$_3$)$_2$, CH_2-*CH*$_3$); ^{13}C NMR ($CDCl_3$); δ 112.4, 109.0 (*C*(CH_3)$_2$), 81.6 (C-4), 81.2 (d, $J_{C,P}$ = 7 Hz, C-2), 80.6 (C-3), 76.5 (C-1), 72.9 (C-5), 66.9 (C-6), 62.0 (d, $J_{C,P}$ = 6 Hz, *C*H_2-CH_3), 61.6 (d, $J_{C,P}$ = 6 Hz, CH_2-CH_3), 26.8, 25.7, 25.1, 25.0, 24.6 (C(*C*H_3)$_2$), 25.3 (d, $J_{C,P}$ = 140 Hz, P-*CH*$_2$-C′), 16.3 (d, $J_{C,P}$ = 2 Hz, CH_2-CH_3), 16.2 (d, $J_{C,P}$ = 2 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$); δ 28.14 (s, 1P); FAB-MS m/z calcd for $C_{17}H_{31}O_8P$ 394.36; $[M+H]^+$ 395.37; found 395.

O′-Ethyl *O′*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) -6-yl *C*-(2,5-anhydro-1-deoxy-3,4:6,7-di-*O*-isopropylidene-D-manno-heptofuranose)-1-yl-phosphonate 9b

Compound **1c** (2.00 g) was transformed to compound **9b** (colorless syrup, 0.60 g, 52%, mixture of α/β) following the general procedure C, R_f (EtOAc) 0.75; NMR ($CDCl_3$); δ 5.51 (d, 2H, $J_{1,2}$ = 5.0 Hz, H-1), 4.74–4.68 (m, 2H, H′2, H′-3), 4.62 (dd, 2H, $J_{3,2}$ = 2,4 $J_{3,4}$ = 8.0 Hz, H-3), 4.38 (m, 1H, H′-5), 4.30 (dd, 2H, $J_{2,1}$ = 5.0, $J_{2,3}$ = 2.4 Hz, H-2), 4.25–4.00 (m, 10H, H-4, H-5, H-6, H′-6), 3.90–3.85 (m, 1H, H′-1), 3.46–3.43 (dd, 1H, J = 3.2, J = 8.0 Hz, H′-4), 2.46–2.23

(m, 2H, P-CH_2-C′), 1.52 (s, 6H, C(CH_3)$_2$), 1.44 (s, 3H, C(CH_3)$_2$), 1.44 (s, 3H, $C(CH_3)_2$), 1.42 (s, 9H, $C(CH_3)_2$), 1.36 (s, 6H, $C(CH_3)_2$), 1.31 (s, 15H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$); δ 112.4, 109.5, 109.1, 108.7, 108.6 ($C(CH_3)_2$), 96.2 (C-1), 81.6 (C′-4), 81.2 (C′-2, C′-3), 76.5 (C′-1), 72.9 (C′-5), 70.7, 70.6, 70.4 (C-2, C-3, C-4), 67.2-67.0 (m, C-5, C′-6), 64.5 (m, C-6), 27.0, 26.1, 26.0, 25.9, 25.2, 24.2, 24.4 (C(CH_3)$_2$), 25.8 (d, $J_{C,P}$ = 141 HZ, P-CH_2-C′); ^{31}P NMR ($CDCl_3$); δ 29.46 (s, 1P), 28.08 (s, 1P); FAB-MS; m/z calcd for $C_{37}H_{59}O_{18}P$ 822.83; $[M+H]_+$ 823.83; found 824.

O′-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose)-6-yl *O′*-(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl *C*-(2,5-anhydro-1-deoxy-3,4:6,7-di-*O*-isopropylidene-D-manno-heptofuranose)-1-yl-phosphonate 9c

Compound **1c** (2.00 g) was transformed to compound **9c** (yellow oil, 0.52 g, 45%, mixture of four diastereomers) following the general procedure C, R_f (7:3 EtOAc/hexane) 0.54; ^{1}H NMR ($CDCl_3$); δ 5,48–5.46 (m, 1H, H_g-1), 4.89 (s, 1H, H_r-1), 4.68–4.61 (m, 3H, H_r-3, H′-2, H′-3), 4.55–4.50 (m, 2H, H_g-3, H_r-2), 4.31–4.25 (m, 3 H, H_g-2, H_r-4, H-5), 4.17–3.95 (m, 8H, H_g-4, H_g-5, H_g-6, H_r-5, H′-6), 3.82–3.80 (m, 1H, H′-1), 3.45–3.38 (m, 1H, H′-4), 3.24 (s, 3 H, O-CH_3), 2.40–2.10 (m, 2H, P-CH_2-C′), 1.47 (s, 3 H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.39 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.30 (s, 9H, C(CH_3)$_2$), 1.25 (s, 3H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ 112.4, 109.9, 108.9, 108.9, 108.6 (C(CH_3)$_2$), 109.3 (C_r-1), 107.0 (C′-1), 96.3 (C_g-1), 85.1, 85.0, 84.8 (C_r-2, C_r-4), 81.6 (C_r-3, C′-4), 81.1, 80.7 (C′-2, C′-3), 76.5 (C′-1), 72.9 (C′-5), 70.7, 70.6, 70.4 (C_g-2, C_g-3, C_g-4), 67.4 (d, $J_{C,P}$ = 7 Hz, C_g-5), 67.0 (C′-6), 65.1–64.9 (m, C_g-6, C_r-5), 55.0 (O-CH_3), 26.4–24.4 (m, P-CH_2-C′, C(CH_3)$_2$); ^{31}P NMR ($CDCl_3$); δ 29.56 (s, 1P), 28.94 (s, 1P), 28.30 (s, 1P), 27.47 (s, 1P); FAB-MS; m/z calcd for $C_{34}H_{55}O_{17}P$ 766.76; $[M+H]^+$ 767.77; found 768; $[M\text{-}MeO]^+$ 734.73; found 735.

O-Ethyl *O′*-(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose)-5-yl *C*-(2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-erythro-pentofuranose)-1-yl-phosphonate 9d

Compound **1a** (2.00 g) was transformed to compound **9a** (yellow oil, 0.41 g, 40%, mixture several diasterecomers) following the general procedure C. α ***anomer***; ^{1}H NMR ($CDCl_3$); δ 4.94 (s, 1 H, H-1), 4.75–4.65 (m, 2H, H-3, H′-3), 4.60–4.55 (m, 1H, H′-2), 4.52 (d, 1H, $J_{2,3}$ = 6 Hz, H-2) 4.35–4.25 (m, 2H, H-4, H′-1), 4.12–3.87 (m, 5H, H-5, H_a-4, CH_2-CH_3), 3.82–3.75 (m, 1H, Hb′-4), 3.25 (s, 3H, O-CH_3), 2.08–1.85 (m, 2H, P-CH_2-C), 1.43 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.29–1.27 (m, 9H, C(CH_3)$_2$), CH_2-CH_3); ^{13}C NMR ($CDCl_3$); δ 109.3 (C-1), 112.9, 112.8 (C(CH_3)$_2$), 85.2, 85.0, 84.9 (C-2, C-4, C′-2), 81.2 (C-3), 80.6

(C′-3), 81.2 (C-3), 80.6 (C′-3), 79.4 (d, $J_{C,P}$ 12Hz, C′-1), 71.8 (C′-4), 65.5 (d, $J_{C,P}$ = 6 Hz, C-5), 61.5 (m, CH_2-CH_3), 54.9 (O-CH_3), 26.5, 26.0, 25.0, 24.8 ($C(CH_3)_2$), 28.1 (d, $J_{C,P}$ - 140 Hz, P-CH_2-C′), 16.3 (d, $J_{C,P}$ = 4 Hz, CH_2-CH_3); *β* ***anomer:*** ^{1}H NMR ($CDCl_3$); *δ* 4.94 (s, 1H, H-1), 4.75–4.65 (m, 2H, H-3, H′-3), 4.60–4.55 (m, 1H, H′-2), 4.52 (d, 1H, $J_{2,3}$ = 6 Hz, H-2), 4.35–4.25 (m, 2H, H-4, H′-1), 4.12–3.87 (m, 5H, H-5, H_a′-4, CH_2-CH_3), 3.72–3.66 (m, 1H, H-1), 3.43–3.38 (m, 1H, H_b′-4), 3.24 (s, 3H, O-CH_3), 2.33–2.12, (m, 2H, P-CH_2-C′), 1.41 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 1.27–1.25 (m, 9H, $C(CH_3)_2$, CH_2-CH_3); ^{13}C NMR ($CDCl_3$); *δ* 109.3 (C-1), 112.4, 112.1 ($C(CH_3)_2$), 85.2, 85.0, 84.9 (C-2, C-4, C′-2) 81.2 (C-3), 81.2 (C-3), 80.6 (C′-3), 80.6 (C′-3), 76.9 (d, $J_{C,P}$ 13 Hz, C′-1), 72.7 (C′-4), 65.5 (d, $J_{C,P}$ = 6 Hz, C-5), 61.5 (m, CH_2-CH_3), 54.9 (O-*C*H_3), 26.4, 26.0, 24.9, 24.8 ($C(CH_3)_2$), 25.4 (d, $J_{C,P}$ = 140 Hz, P-CH_2-C′), 16.3 (d, $J_{C,P}$ = 4 Hz, CH_2-CH_3); ^{31}P NMR ($CDCl_3$); *δ*27.24 (s, 1P), 27.13 (s, 1P), 28.67 (s, 1P), 28.46 (s, 1P); FAB-MS; *m*/*z* calcd for $C_{19}H_{33}O_{10}P$ 452.43; $[M+H]^+$ 453.44; found 453; $[M\text{-}MeO^-]^+$ 422.40; found 422.

General procedure of hydrogenation

Palladium over carbon (0.1 mmol) was added to compound **5c, 5d,** or **5i** (1 mmol) dissolved in ethanol (20 mL). The mixture was stirred in a reactor and the hydrogen pressure was set at 10 bars. After 12 h the solution was filtered through celite and concentrated to give pure compound **6c, 6d**, and **6i**.

O′-Ethyl *O*′-(1-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribofuranose) -5-yl C-(6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-*α*-D-galacto-heptopyranose)-7-yl-phosphonate 6c

Compound **6c** (colorless oil, 0.54 g, 98%. Mixture of two diastereomers) was prepared following the general procedure of hydrogenation. R_f (1:1 EtOAe/hexane) 0.60; ^{1}H NMR ($CDCl_3$); *δ* 5.57 (d, 1H, $J_{1,2}$ = 5.2 Hz, H′-1), 4.95 (s, 1H, H-1), 4.72–4.70 (m, 1H, H-3), 4.58–4.56 (m, 2H, H′-3, H-2), 4.34–4.30 (m, 1H, H-4), 4.28 (dd, 1H, $J_{2,1}$ = 5.2 Hz, $J_{2,3}$ = 2.4, H′-2), 4.13–3.96 (m, 5H, H-5, H′-4, CH_2-CH_3), 3.75–3.72 (m, 1H, H′-5), 3.30 (s, 3H, O-CH_3), 2.10–1.90 (m, 2H, H′-6), 1.84–1.66 (m, 2H, P-CH_2-C), 1.51 (s, 3H, $C(CH_3)_2$), 1.47 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.33–1.30 (m, 12H, $C(CH_3)_2$, CH_2-CH_3); ^{13}C NMR ($CDCl_3$); *δ*109.3 (C-1), 109.2, 108.4 (*C*$(CH_3)_2$), 96.4 (C′-1), 85.0, 84.9 (C-2, C-4), 81.6 (C-3), 72.4 (C′-4), 70.9 (C′-3), 70.2 (C′-2), 67.5 (d, $J_{C,P}$ = 16 Hz, C′-5), 65.0 (d, $J_{C,P}$ = 7 Hz, C-5), 61.9 (m, *C*H_2-CH_3), 55.0 (O-*C*H_3), 26.4, 26.1, 26.0, 25.8, 25.0, 24.5 ($C(CH_3)_2$), 23.3 (d, $J_{C,P}$ = 3 Hz, C′-6), 21.9 (d, $J_{C,P}$ = 141 Hz, PCH_2-C), 16.4 (d, $J_{C,P}$ = 7Hz, CH_2-*C*H_3), ^{31}P NMR ($CDCl_3$); *δ*32.89 (s, 1P), 32.85 (s, 1P); FAB-MS: *m*/*z* calcd for $C_{24}H_{39}O_{12}P$ 552.41; $[M+H]^+$ 553.43; found 553; $[M\text{-}MeO^-]^+$ 521.38; found 521.

O′-Ethyl *O′*-(1-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribofuranose) -5-yl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribo-hexofuranose)-6-yl-phosphonate 6d

Compound **6d** (colorless oil, 0.49 g, 98%, mixture of two diastereomers) was prepared following the general procedure of hydrogenation R_f (7:3 EtOAc/hexane) 0.50; ^{1}H NMR ($CDCl_3$); δ4.89 (s, 1H, H-1), 4.78 (s, 1H, H-1), 4.67–4.65 (m, 1H, H-3), 4.60–4.45 (m, 3H, H′-2, H′-3, H-2), 4.30–4.25 (m, 1H, H-4), 4.10–3.90 (m, 5H, H′-4, H-5, CH_2-CH_3), 3.25 (s, 3H, O-CH_3), 3.24 (s, 3H, O-CH_3), 2.10–2.00 (m, 4H, H′-5, P-CH_2-C), 1.41 (s, 3H, C(CH_3)$_2$), 1.38 (s, 3H, C(CH_3)$_2$), 1.27–1.24 (m, 9H, C(CH_3)$_2$, CH_2-CH_3); ^{13}C NMR ($CDCl_3$); δ 112.4, 112.0 (*C*(CH_3)$_2$), 109.3 (C-1), 106.8 (C′-1), 85.4, 85.0 (C-2, C-4, C′-2), 81.6 (C-3), 79.9 (C′-3), 79.4 (d, $J_{C,P}$ = 18 Hz, C′-4), 65.2 (d, $J_{C,P}$ = 6 Hz, C-5), 61.9 (m, *C*H_2-CH_3), 53.6 (O-*C*H_3), 53.5 (O-*C*H_3), 26.4, 26.0, 25.0, 24.9 (C(*C*H_3)$_2$), 22.2 (d, $J_{C,P}$ = 142 Hz, P-*C*H_2-C), 21.9 (d, $J_{C,P}$ = 5 Hz, C′-5), 16.4 (d, $J_{C,P}$ = 6 Hz, *C*H_2-CH_3); ^{31}P NMR ($CDCl_3$); δ32.29 (s, 1P), 32.26 (s, 1P); FAB-MS; *m*/*z* calcd for $C_{21}H_{37}O_{11}P$ 496.31; $[M+H]^+$ 497.32; found 497; $[M\text{-}MeO^-]^+$ 465.28, found 465.

O′-(1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose)-6-yl *O′* -(1-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribofuranose)-5-yl *C*-(5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribo-hexofuranose)-6-yl-phosphonate 6i

Compound **6i** (colorless syrup, 0.68 g, 95%, mixture of two diastereomers) was prepared following the general procedure of hydrogenation. ^{1}H NMR ($CDCl_3$): δ 5.56 (d, 1H, $J_{1,2}$ = 4.8 Hz, H_g-1), 4.97 (s, 1H, H,-1), 4.80 (s, 1H, H′-1), 4.75–4.73 (m, 1H, H_r-3), 4.64–4.59 (m, 3H, H′-3, H_g-3, H_r-2), 4.56–4.55 (m, 1H, H′-2), 4.38–4.33 (m, 1H, H_g-2, H_r-4), 4.27–4.20 (m, H_g-4, H_g-6), 4.12–4.01 (m, 3H, H_r-5, H_g-5,), 3.97–3.94 (m, 1H, H-4), 3.33–3.32 (m, 3 H, O-CH_3), 2.01–1.97 (m, 4H, H′-5, P-CH_2-C), 1.56 (s, 3 H, C(CH_3)$_2$), 1.49 (s, 3H, C(CH_3)$_2$), 1.46 (s, 6H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$), 1.33 (s, 6H, C(CH_3)$_2$), 1.32 (s, 9H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$); δ112.5, 109.6, 109.3 (C(CH_3)$_2$), 109.4 (C_r-1), 107.0 (C′-1), 96.3 (C_g-1), 85.2, 84.9, 84.8 (C_r-2, C_r-4, C′-2), 81.7 (C_r-3), 79.9 (C′-3), 79.5 (d, $J_{C,P}$ = 17 Hz, C′-4), 70.7, 70.4 (C_g-2, C_g-3, C_g-4), 67.4 (d, $J_{C,P}$ = 6 Hz, C_g-5), 65.1–64.6 (m, C_g-6, C_r-5), 55.0 (O-CH_3), 54.5 (O-CH_3), 26.4, 26.0, 25.9, 25.0, 24.9, 24.4 (C(*C*H_3)$_2$), 22.1 (d, $J_{C,P}$ = 142 Hz, P-*C*H_2-C), 21.7 (d, $J_{C,P}$ = 6 Hz, C′-5,); ^{31}P NMR ($CDCl_3$); δ 33.27 (s, 1P), 32.74 (s, 1P); FAB-MS; m/z calcd for $C_{31}H_{50}O_{16}P$ 710.70; $[M+H]^+$ 711.71; found 712; $[M\text{-}MeO^-]^+$ 679.67; found 679.

REFERENCES

1. Busse, H.; Hakoda, M.; Stanley, M.; Streicher, H.J. Galactose-phosphonates as mimetics of the sialyltransfer by trypanosomal sialdidases. *J. Carbohydr. Chem.* **2007**, 26, 159–164.

2. Torres-Sanchez, M.I.; Zaccaria, C.; Buzzi, B.; Miglio, G.; Lombardi, G., Polito, L., Russo, G.; Lay, L. Synthesis and biological evaluation of phosphono analogues of capsular polysaccharide fragments from Neisseria meningitidis. *A. Chem. Eur. J*. **2007**, 13(23), 6623–6635.

3. Teodorovic, P.; Slaettegard, R.; Oscarson, S. Synthesis of stable C-phosphonate analogs of Neisseria meningitidis group A capsular polysaccharide structures using modified Mitsunobu reaction conditions. *Org. Biomol. Chem*. **2006**, 4(24), 4485–4490.

4. Chang, R.; Vo, T.h.-T.; Finney, Nathaniel S. Synthesis of the C1-phosphonate analog of UDP-GlcNAc. *Carbohydrate Res*. **2006**, 341(12), 1998–2004.

5. Grison, C.; Letondor, C.; Chibili, H.; Coutrot, P. One-pot carbanionic access to methylenebis (phosphonate) analogs of natural P^1,P^2- glycosyl -disubstituted pyrophosphates. *Tetrahedron Lett*. **2005**, 46(38), 6525–6528.

6. Higson, A.P.; Ross, A.J.; Tsvetkov, Y.E.; Routier, F.H.; Sizova, O.V.; Ferguson, M.A.J.; Nikolaev, A.V. Synthetic fragments of antigenic lipophosphoglycans from Leishmania major and Leishmania mexicana and their use for characterisation of the Leishmania elongating α-D-mannopyranosylphosphate transferase. *Chem. Eur. J.* **2005**, 11(7), 2019–2030.

7. Kohyama, N.; Hayashi, T.; Yamamoto, Y. Synthesis of a methylene analog of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide monophosphate (ZMP). *Biosci. Biotechnol. Biochem*. **2005**, 69(4), 836–838.

8. Belakhov, V.; Dovgolevsky, E.; Rabkin, E.; Shulami, S.; Shoham, Y.; Baasov, T. Synthesis and evaluation of a mechanism-based inhibitor of KDO8P synthase. *Carbohydr. Res*. **2004**, 339(2), 385–392.

9. Centrone, C.A.; Lowary, T.L. Sulfone and phosphinic acid analogs of decaprenolphosphoarabinose as potential anti-tuberculosis agents. *Bioorg. Med. Chem*. **2004**, 12(21), 5495–5503.

10. Gaurat, O.; Xie, J.; Valery, J.-M. Synthesis of *C*-glycosyl phosphate and phosphonate, analogues of N-acetyl-α-D-glucosamine 1-phosphate. *J. Carbohydr. Chem*. **2003**, 22(7–8), 645–656.

11. Centrone, C.A.; Lowary, T.L. An efficient route for the synthesis of glycosyl phosphinic acids. *J. Org. Chem.* **2003**, 68(21), 8115–8119.

12. Orsini, F.; Caselli, A. SmI_2-mediated reactions of diethyl iodomethylphosphonate with esters and lactones: a highly stereoselective synthesis of a precursor of the *C*-glycosyl analogue of thymidine 5′-(β-1-rhamnosyl)diphosphate. *Tetrahedron Lett.* **2002**, 43(40), 7259–7261.

13. Compain, P.; Martin, O.R. Carbohydrate mimetics-based glycosyltransferase inhibitors. *Bioorg. Med. Chem*. **2001**, 9, 3077–3092 and reference cited therein.

14. Dondoni, A.; Marra, A.; Pasti, C. Stereoselective synthesis of *C*-glycosylphosphonates from their ketols. Reconsideration of an abandoned route. *Tetrahedron Asymm*. **2000**, 11, 305–317.

15. Kovensky, J.; McNeil, M.; Sinay, P. D-Galactofuranosylphosphonates. First Synthesis of UDP-C-D-galactofuranose. *J. Org. Chem.* **1999**, 64(17), 6202–6205.

16. Nicotra, F. Synthesis of glycosyl phosphate mimies. In *Carbohydrate Mimics. Concepts and Methods*: Chapleur, Y., Wiley-VCH: Weiheim, **1998**, 67–85 and references cited therein.

17. Dondoni, A.; Daninos, S.; Marra, A.; Formaglio, P. Synthesis of ketosyl and ulosonyl phosphonates by Arbuzov-type glycosidation of thiazolylketol acetates. *Tetrahedron* **1998**, 54(33), 9859–9874.

18. Rubira, M.J.; Perez-Perez, M.J.; Balzarini, J.; Camarasa, M.J. Synthesis of phosphonate analogs of 2-deoxyribose 1-phosphate. *Synlett* **1998**, 2, 177–179.

19. Behr, J.-B.; Evina, C.M.; Phung, N.; Guillerm, G. Synthesis of (difluoromethyl) phosphonate azasugars designed as inhibitors for glycosyl transferases. *J. Chem. Soc. Perkin Trans. 1* **1997**, 11, 1597–1599.

20. Herpin, T.F.; Motherwell, W.B.; Roberts, B.P.; Roland, S.; Weibel, J.-M. Free radical chain reactions for the preparation of novel anomeric carbohydrate difluoromethylene-phosphonates and - phosphonothioates. *Tetrahedron* **1997**, 53(44), 15085–15100.

21. Arth, H.-L.; Fessner, W.-D. Enzymes in organic synthesis part 13. Practical synthesis of 4-hydroxy-3-oxobutylphosphonic acid and its evaluation as a bio-isosteric substrate of DHAP aldolase *Carbohydr. Res.* **1998**, 305(3–4), 313–321.

22. Chung, S.K.; Moon, S.-H., Synthesis and biological activities of (4,6-di-*O*-phosphonato-β-D-mannopyranosyl)-methylphosphonate as an analog of IL-myo-inositol 1,4,5-trisphosphate. *Carbohydr. Res.* **1994**, 260(1), 39–50.

23. Chung, S.K.; Moon, S.H. Synthesis of (1-deoxy-4,6-*O*-bisphosphoryl-β-D-mannopyranosyl)methane phosphonate as an analog of L-myo-inositol-1,4,5-trisphosphate. *J. Chem. Soc., Chem. Comm*. **1992**, (1), 77–97.

24. Loeschner, T.; Engels, J. One pot Rp-diastereoselective synthesis of dinucleoside methyl phosphonates using methyldichlorophosphine. *Tetrahedron Lett*. **1989**, 30(41), 5587–5590.

25. Chen, G.-R.; Praly, J.-P. Free-radical and ionic routes towards hydrolytically stable and bioactive C-glycosyl compounds. *C. R. Chimie* **2008**, 11(1–2), 19–28.

26. Vidal, S; Bruyere, I; Malleron, A; Auge, C; Praly, J-P. Non-isosteric C-glycosyl analogues of natural nucleotide diphosphate sugars as glycosyltransferase inhibitors. *Bioorg. Med. Chem*. **2006**, 14(21), 7293–7301.

27. Dembitsky, V.M.; Quntar, A.A.A.; Haj-Yehia, A.; Srebnik, M. Recent synthesis and transformation of vinylphosphonates. *Mini-Reviews in Organic Chemistry* **2005**, 2(1), 91–109 and references cited therein.

28. Praly, J.-P.; Ardakani, A.S.; Bruyere, I.; Marie-Luce, C.; Bing, B.Q. Towards α- or β-D-*C*-glycosyl compounds by tin-catalyzed addition of glycosyl radicals to acrylonitrile and vinylphosphonate, and flexible reduction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with cyanoborohydride *Carbohydr. Res.* **2002**, 337(18), 1623–1632.

29. Junker, H-D.; Fessner, W-D. Diastereoselective synthesis of *C*-glycosyl phosphonates via free-radical glycosylation. *Tetrahedron Lett.* **1998**, 39, 269–272.

30. McClure, C.K.; Hansen, K.B.; Herzog, K.J.; Link, J.S.; Arnold, F.P. Diels - Alder reactivity of a keto vinylphosphonate. Empirical and theoretical observations application to the syntheses of phosphonate analogs of myo-inositol. *Phosphorus Sulfur Silicon* **1996**, 109–110.

31. Julina, R.; Vasella, A., Deoxy-nitrosugars. 10th Communication. Synthesis of isosteric phosphonate analogs of ulose-l-phosphates. *Helv. Chim. Acta* **1985**, 68(4), 819–830.

32. Mirza, S.; Vasella, A. Deoxynitrosugars. 7th Communication. Synthesis of methyl shikimate and of diethyl phosphashikimate from D-ribose. *Helv. Chim. Acta* **1984**, 67(6), 1562–1567.

33. Pachamuthu, K.; Figueroa-Perez, I.K.; Ali, I.A.I.; Schmidt, R.R. Synthesis of glycosyl phosphonates by Michael-type addition to 2-nitroglycals. *Eur. J. Org. Chem.* **2004**, 3959–3961.

34. Wen, X.; Hultin, P.G. Concise and stereo-controlled syntheses of phosphonate *C*-glycoside analogs of β-D-ManNAc and β-D-GlcNAc 1-*O*-phosphates. *Tetrahedron Lett.* **2004**, 45(8), 1773–1775.

35. Borodkin, V.S.; Ferguson, M.; Nikolaev, A.V. Synthesis of β-D-Galp-(1$\rightarrow$4)-α-D-Manp methanephosphonate, a substrate analogue for the elongating α-D-mannosyl phosphate transferase in the Leishmania. *Tetrahedron Lett.* **2001**, 42(31), 5305–5308.

36. Cipolla, L.; La Ferla, B.; Nicotra F. Synthesis of potential inhibitors of carbohydrate processing enzymes. *Carbohydr. Polym.* **1998**, 37(3), 291–298.

37. Nicotra, F. Modified carbohydrates and carbohydrate analogs. In *Carbohydr. Chem.*; Boons G.J. Blackie, Ed. Blackie Academic & Professional: London **1998**, 384–429 and references cited therein.

38. Cipolla, L.; La Ferla, B.; Panza, L.; Nicotra, F. Direct synthesis of the isosteric phosphono analogs of α-L-rhamnose l-phosphate and β-L-fucose l-phosphate *J. Carbohydr. Chem.* **1998**, 17(7), 1003–1013.

39. Lee, Y.J.; Moon, S.-H.; Chung, S.-K. Synthetic studies of hexopyranosylmethylphosphonates by two phase Witti-Horner reaction. *Kor. J. Med. Chem.* **1995**, 5(2), 80–85.

40. Chung, S.-K., Moon, S.-H. Synthesis and biological activities of (4,6-di-*O*-phosphonato-β-D-mannopyranosyl)-methylphosphonate as an analog of IL-myo-inositol 1,4,5-trisphosphate. *Carbohydr. Res.* **1994**, 260(1), 39–50.

41. McClard, R.W.; Witte, J.F. Stable and nonmetabolizable c-glycosylphosphonyl analogs of 5-phosphorylribose 1-α-dipnosphate that act as inihibitors or orotate phosphoribosytransferase. *Bioorg. Chem*. **1990**, 18, 165.

42. McClard, R.W.; Tsimikas, S.; Schriver, K.E. Inhibition of fructose bisphosphatase and stimulation of phosphofructokinase by a stable isosteric phosphonate analog of fructose 2, 6-bisphosphate. *Arch. Biochem Biophys*. **1986**, 245, 282.

43. Grison, C.; Chibli, H.; Barthes, N.; Coutrol, P.J. One-pot carbanionic synthesis of P^1, P^2-diglycosyl, P^1, P^1, P^2-triglycosyl and P^1, P^1, P^2, P^2-tetraribosyl methylenediphosphonates, *J. Org. Chem.* **2006**, 71, 7978–7988.

44. Grison, C.; Joliez, S.; De Clereq E.; Coutrot, P. Monoglycosyl, diglycosyl, and dinucleoside methylenediphosphonates: direct synthesis and antiviral activity *Carbohydr. Res.* **2006**, 341, 1117–1129.

45. Grison, C.; Letondor, C.; Chibli, H.; Coutrot, P. One-pot carbanionie access to methylenebis (phosphonate) analogs of natural P^1, P^2-glycosyl-disubstituted pyrophosphates. *Tetrahedron Left.* **2005**, 46(38), 6525–6528.

46. Ruiz, M.; Fernandez, M.C.; Diaz, A.; Quintela J.M.; Ojea, Vi. Diastereoselective synthesis of 2-amino-4-phosphonobutanoic acids by conjugate addition of lithiated Schoellkopf's bislactim ethers to vinylphosphonates. *J. Org. Chem.* **2003**, 68(20), 7634–7645.

47. Truel, L.; Mohamed-Hachi, A.; About-Jaudet, E.; Collignon, N. A convenient (F.)-stereoselective synthesis of alkenylphosphonates. *Synthetic Comm.* **1997**, 27(2), 297–302.

48. Moffatt, J.G.; Jones, G.H. (Syntex Corp.) Didealkylation of phosphonate esters U.S. Patent **1970**, US 3524846 19700818. *Chem. Abstr.* **1971**, 75, P. 130091g.

49. Blackburn, G.M.; Rashid, A. Enantionspecific syntheses of the methylene- and α-fluoromethylenephosphonate anlogs of 3-phospho-D-glyceric acid. *J. Chem. Soc., Chem. Comm.* **1989**, 1, 40–41.

50. Freeman, F.; Robarge, K.D. Epimerization at C-2 during the Wittig reaction of 2,3,5-tri-*O*-benzyl-D-ribose and methylidenetriphenylphosphorane, *Carbohydr. Res.* **1986**, 154, 270–274.

51. Allevi, P.; Ciuffreda, P.; Colombo, D.; Monti, D.; Speranza, G.; Manitto, P. The Wittig-Horner reaction on 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. *J. Chem. Soc., Perkin Trans. 1* **1989**, (7), 1281–1283.

52. Wen, X.; Hultin, P.G. Concise and stereo-controlled syntheses of phosphonate C-glycoside analogs of β-D-ManNAc and β-D-GlcNAc 1-O-phosphates. *Tetrahedron Lett* **2004**, 45(8), 1773–1775.