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Synthesis of new 2-phosphono-α-D-glycoside derivatives by stereoselective oxa-Michael addition to a D-galacto derived enone

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Abstract—The synthesis of new 2-phosphono-α-D-glycoside derivatives by stereoselective oxa-Michael addition to an enone derived from D-galactal and containing a phosphonate group is described. Retro-Michael reactions were prevented by tandem acetylation to trap the unstable enolic intermediates. The stereochemistry of the addition products was established by NOESY experiments and explained with molecular mechanics (MM) and density functional theory (DFT) calculations.

Keywords: Oxa-Michael Addition; 3-Oxo-2-phosphono-α-glycosides; Alcohols; O-Glycosylation

1. Introduction

For a long time, carbohydrates have excited the interest of researchers.[1] Being among the most abundant natural products, they are implicated in many cellular processes such as cell–cell recognition, cellular adhesion, and transport. They also play a fundamental role in vital processes, being present, for example, in nucleic acids or as a component of bacterial cellular walls.[2] The importance, complexity, and variety of natural carbohydrates make their synthesis a challenging and worthy task.

In Nature, carbohydrates are found mainly in the form of *O*-glycosyl derivatives, and, therefore, organic chemistry has witnessed a noticeable increase in research addressed to the development of new stereocontrolled O-glycosylation methods.[3]

Furthermore, among unnatural carbohydrates those containing a phosphonate group appear very interesting. The phosphonate group is a useful and versatile tool for the studies of metabolic regulation, enhancement, and inhibition.[4] It is, in fact, a stable analogue of the naturally occurring phosphate, as the C–P bond is inerted to the enzymes involved in phosphate cleavage. At present, the interest of the chemists and biologists is mainly concerned with glycosyl phosphonates, which are the analogues of glycosyl phosphates involved in the biosynthesis of oligo- and polysaccharides and glycoconjugates.[5]

Although there are a number of naturally occurring sugar 2-phosphates,[6] principally in Gram-negative bacteria lipopolysaccharides, to the best of our knowledge, the literature concerning 2-phosphono sugar analogues is rather scarce,[7] and nothing is known about their biological activity. In this respect, we believe that the development of new methodologies for the stereoselective preparation of 2-phosphono sugars might be an appealing target.

Recently, we have reported on the stereocontrolled preparation from 2-(diethoxyphosphoryl)hex-1-en-3-ulose (**1**)[8] of 3-oxo-2-phosphono-α-C-glycosides through a Michael-type addition of organocopper reagents and have shown that the phosphonate group has a remarkable activating effect on the Michael addition. Hereafter,

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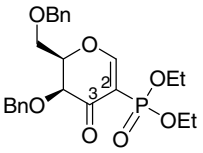
we wish to describe the extension of these studies to the addition of a series of alcohols to **1**. To the best of our knowledge, the literature concerning the O-glycosylation via Michael addition of O-nucleophiles to hex-1-en-3-uloses derived from carbohydrates is scarce[9] and mainly limited to the addition of MeOH.



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2. Results and discussion

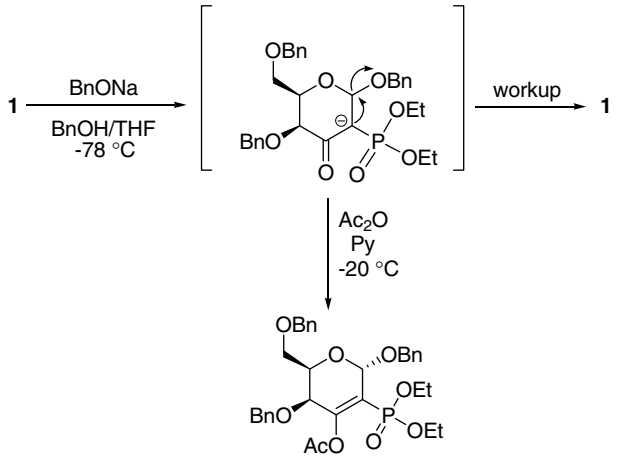
We started this work with the addition at −78 °C of BnONa in BnOH–THF to the Michael acceptor **1**. Nevertheless, though the reaction according to TLC monitoring appeared to proceed,[†] after the workup only the starting material was recovered. After several attempts in which the workup conditions were varied, an ensuing retro-Michael reaction was considered responsible for the results obtained. Thus, quenching the reaction with Ac_2O and pyridine, we were able to obtain the enol acetate **2** as the only product, confirming the above hypothesis (see Scheme 1 and Table 1, entry 1).

Prompted by these findings, the addition to **1** was performed with various alcohols leading to the results presented in Table 1. The yields ranged from moderate to good with an excellent α:β ratio except in the case of propargyl alcohol (entries 8 and 9) in which an α:β ratio of 90:10 was recorded. No change in the diastereoisomeric ratio was observed by varying the reaction time. (Table 1, entries 8 and 9).

Good results were obtained with both primary and secondary alcohols. It is worth noting that yields were shown to depend on reaction temperature. With the exception of the addition of BnOH (Table 1, entries 1 and 2), the best results were obtained at −30 °C. On the other hand, the reaction does not proceed at lower temperature (Table 1, entries 3 and 5), while at 0 °C a rapid decomposition of the starting material occurs.

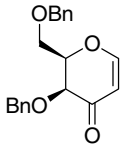
To evaluate the activating effect of the phosphonate group, the reactivity of enones **1** and **8** was compared. BnOH was used as the nucleophile, and the reaction was carried out under the same conditions for both enones: in the case of **1** a total conversion of the starting material was observed, whereas for **8**, which lacked the C-2 phosphonate group, only a 30% conversion was recorded.

[†]TLC (SiO_2, 2:8 hexanes–EtOAc) showed the disappearance of the starting material together with the appearance of a product with a higher R_f.



2 α/β 100/0

Scheme 1. Michael addition of BnONa to 2-(diethoxyphosphoryl)-hex-1-en-3-ulose **1**.



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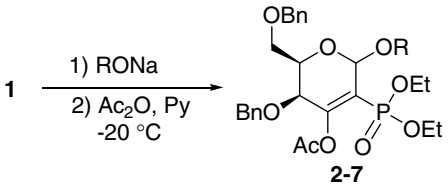
To test the general applicability of the above procedure, the addition of the more sterically hindered D-glucal-derived[10] nucleophile **9a** was performed on enone **1**. Also in this case the reaction showed complete stereoselectivity with the formation of **10** in a 99:1 α:β ratio (Scheme 2).

The diastereoisomeric ratio of the oxa-Michael addition turned out to be unaffected by the reaction time as shown by the results in Table 1 for the addition of BnOH and propargyl alcohol (entries 1, 2 and 8, 9, respectively). Moreover, as stated before, the reaction was completely reversible after workup, and the addition products could not be isolated unless acetylation of the enol intermediate was performed. These results show that the oxa-Michael additions described above are equilibrium processes. To confirm this conclusion, an additional experiment was performed: enone **1** was allowed to react at −30 °C with BnOH for 5 h in order to ensure that all the starting material was consumed (Table 1, entry 2). After this time, MeOH was added, and the reaction was allowed to continue for an additional 5 h at −30 °C. As usual, the addition product was acetylated for 12 h at −20 °C with Ac_2O and pyridine. The ^1H NMR spectrum of the crude reaction mixture showed the presence of a 4:6 mixture of **2** and **3**, confirming thermodynamic control during the Michael addition. As a consequence, the observed α:β stereoselectivity in the Michael addition (Table 1) is simply due to the relative stability of the two anomers

Table 1. Stereoselective addition of various alcohols to 2-(diethoxyphosphoryl)hex-1-en-3-ulose **1**

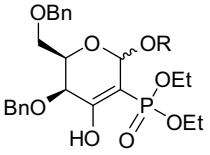


2-7

Entry	R	Solvent	Time (h)	*T* (°C)	Product	α:β[a]	Yield (%)
1	Bn	BnOH–THF	1[b]	−78	**2**	100:0	55
	(3 equiv)	1:1	7[c]				(70)[d]
2	Bn	BnOH–THF	5[b]	−65	**2**	100:0	70
	(5 equiv)	1:0.6	12[c]				(70)[d]
3	Me	MeOH	5[b]	−78	—	—	—
	(4 equiv)		7[c]				
4	Me	MeOH	8[b]	−30	**3**	98:2	60
	(4 equiv)		12[c]				(98)[d]
5	Et	EtOH	8[b]	−78	—	—	—
	(5 equiv)		12[c]				
6	Et	EtOH	8[b]	−30	**4**	98:2	60
	(5 equiv)		12[c]				(70)[d]
7	*n*-Pentyl	*n*-Pentanol	9[b]	−20	**5**	98:2	80
	(5 equiv)		12[c]				(85)[d]
8	Propargyl	Propargyl alcohol	9[b]	−30	**6**	90:10	50
	(5 equiv)		12[c]				(75)[d]
9	Propargyl	Propargyl alcohol	24[b]	−30	**6**	90:10	50
	(5 equiv)		12[c]				(75)[d]
10	2-Pr	2-PrOH	9[b]	−20	**7**	100:0	50
	(5 equiv)		12[c]				(65)[d]

[a] Diastereoisomeric ratios were determined by HPLC analysis of the crude reaction mixtures.
[b] Reaction time of the conjugate addition.
[c] Reaction time of the acetylation.
[d] Yields were calculated on the basis of enone consumption.

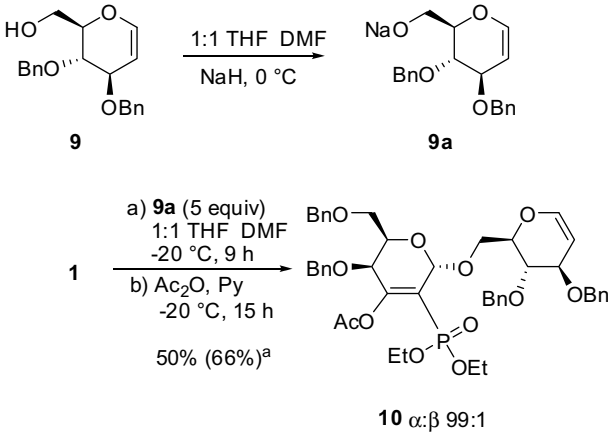
derived from the alcohol addition. Theoretical calculations have been, therefore, carried out on the α and β anomers of **11**–**17** to evaluate such energetic differences.



11 R = Me
12 R = Et
13 R = *n*-pentyl
14 R = propargyl
15 R = *i*-Pr
16 R = Bn
17 R = 3,4-di-*O*-benzyl-D-glucal

Although these calculations could be performed in principle on both the enolic and the ketonic forms, we decided to analyze only the former. In analogy with what we found for the Michael-type addition of organocopper reagents on the *galacto*-derived enone **1**,[8] in this case the addition products are, in fact, also likely to adopt the more stable enolic form.

Given the relatively high number of atoms in these compounds and the excessively large number of local energy minima corresponding to the many conformers,



Scheme 2. Michael addition to enone **1** of compound **9**.[10]

we started our analysis by minimizing a large number of structures generated by sampling the configurational space through a set of classical molecular mechanics (MM) trajectories at different temperatures. In this way, we have determined a global minima geometry for the α and β anomers of each compound. These geometries were then further optimized by calculations

Table 2. Energy differences ($\Delta E = E_\beta - E_\alpha$) between the β and the α anomers of compounds **11**–**17** obtained by both MM and DFT calculations in kcal/mol; β% is the percentage of beta anomer population calculated by the ΔG^0 at the indicated temperature

Entry	Compound	ΔE (MM)	ΔE (DFT)	ΔE + ZPE(DFT)	ΔG^0 (β%)	T (°C)
1	**11**	1.77	1.62[a]	1.55[b]	1.35 (5.6)	−30
2	**12**	1.62	3.05	2.69	2.09 (1.2)	−30
3	**13**	2.26	3.26	2.95	3.68 (<1)	−20
4	**14**	1.61	1.75	1.64	0.06 (46.6)	−30
5	**15**	1.78	3.10	2.83	1.70 (3.2)	−20
6	**16**	1.74	1.29	1.43	2.4 (<1)	−78
7	**17**	1.20	5.30	—	—	−20

[a] Calculation with counterpoise correction gives ΔE (DFT + BSSE) = 1.98.
[b] Calculation in MeOH with PCM model yields ΔE (DFT) = 1.90 and ΔE + ZPE(DFT) = 1.85.

using density functional theory (DFT) methods, followed by a vibrational normal mode analysis and a standard thermochemistry calculation at the experimental temperature. The results from MM and DFT calculations are shown in Table 2 where we have reported the energy differences after minimization for both methods, the energy difference corrected by the ZPE after the normal mode analysis, the value of the ΔG^0 calculated at the given temperature, and the percentage of beta population at the same temperature. The calculations show clearly that the α anomer is always the most stable in each compound. The results are in qualitative agreement with the experimental data, although they are not able to predict exactly the beta anomer population. It is interesting to note, however, that the calculations clearly detect a smaller energy difference in the case of compound **14** where the experiments have also recorded a larger beta population.

The counterpoise correction[11] has been applied to compound **11** to assess the size of basis set superposition errors (BSSEs) and to further check the quality of our calculations. BSSE effects, though present, do not significantly alter our results.

To investigate the possible role of solvent effects in the calculations, we have optimized the structures for compound **11** using a continuum solvent model (PCM) and including zero point energy corrections (ZPE). However, the qualitative behavior turned out to be substantially the same, and the energy differences are even larger. The structure of the solvated molecules turned out to be similar to the ones obtained in vacuum since these were used as the starting geometries in the PCM calculations. We think that an optimization including explicit solvent molecules both during the MM and during the DFT stages might produce results that are in better quantitative agreement with the experiments. Unfortunately, the number of atoms in the compounds examined here, and the relative complexity of their solvent partners, did not allow us to implement such a strategy.

From the analysis of the ab initio optimized structures of the two possible anomeric compounds derived from the alcohol addition to enone **1** (see, for example, Fig. 1), the more stable α anomer has an axial configuration of the glycoside, while the β has an equatorial one. This result is consistent with the prediction based on the anomeric effect[12] according to which, for a stereoelectronic effect, the tendency of heteroatomic substituents bonded at C-1 is to prefer the axial orientation instead of the less hindered equatorial orientation that would be expected from steric considerations.

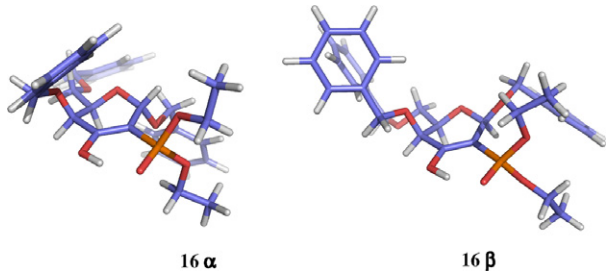


Figure 1. Optimized structures (ab initio calculations) of the two possible anomeric compounds derived from the Michael addition of BnOH on compound **1**.

Although it would be interesting to further explore the nature of the anomeric effect in such compounds, it turns out that these specific molecules are not the ideal candidates for a more thorough analysis of their electronic structure due to their sizes and the prohibitive calculation times that such an analysis would require, especially with the use of more appropriate basis sets. The optimized structures of all the compounds (**11**–**17**) exhibit an intramolecular hydrogen bonding in which the donor is the enolic hydrogen at C-3 and the acceptor is the oxygen of the phosphonate group (O=P) at C-2.

The α anomeric configurations of compounds **2**–**7** were further elucidated by NOESY experiments. The NOESY spectra of compounds **2**, **4**–**7** showed, for example, a correlation between the H-1 and the OCH_2 of the benzyl group on C-4, and that of compound **3** showed a correlation between the OCH_3 and the H-5. The distances between atoms obtained from the integration of the signals in the NOESY spectra are in excellent agreement with those obtained by theoretical calculations.

In conclusion, the Michael addition of O-nucleophiles to the D-galacto derived enone **1** allowed us to prepare

the new glycoside derivatives **2**–**5** and **7** with an excellent α:β ratio. The preparation of propargyl glycoside **6**, even with a slightly minor α:β anomeric ratio, represents a very important result given the recent application of this class of compounds as novel and stable glycoside donors.[3e] The general applicability of the reaction was tested by performing the addition of primary and secondary alcohols and of the more sterically hindered **9a**, resulting in the preparation of the novel disaccharide derivative **10**. The phosphonate group performed, therefore, not only as a good electron-withdrawing group for the oxa-Michael addition, but also as an interesting substituent either for its potential biological activity and/or for the possibility of further functionalizations like, for example, a tandem Horner–Wadsworth–Emmons olefination reaction.

3. Experimental

3.1. General experimental methods

^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Varian Gemini 200 spectrometer with $CDCl_3$ as the solvent and as the internal standard. Chemical shifts are reported in δ units (ppm) and coupling constants (J) are in Hertz. 2D ^{1}H,^{1}H-NOESY experiments were performed on a Bruker AC 300 P spectrometer operating at 300.13 MHz and equipped with a Bruker multinuclear probe head. NOESY experiments were performed in the TPPI phase-sensitive mode with a spectral sweep width of 2.4 kHz in both dimensions, 1024 data points in f_2 and 512 increments in f_1, and a recycle delay of 2 s; a mixing time of 700 ms was used; zero filling in f_1 to 1024 real data points and 90° phase-shifted square-sine bell window functions in both dimensions were applied before Fourier transformation. IR spectra were obtained with a Shimadzu-470 scanning infrared spectrophotometer, with absorptions reported in cm^{-1}. HRESIMS spectra were recorded with Micromass Q-TOF Micro Mass Spectrometer (Waters) in the electrospray-ionization mode. Optical rotations were measured using the sodium D line on a DIP 370 Jasco digital polarimeter. Yields are given for isolated products after column chromatography. All reactions were performed under an inert atmosphere of Ar in flame-dried glassware. All solvents and commercially available reagents were used without purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck F-254 silica glass plates visualized with UV light and a heat-gun after being sprayed with a 2 N H_2SO_4 solution. Column chromatography was performed with E. Merck Silica Gel 60 (230–400 mesh). HPLC analysis was carried out on a Shimadzu LC-10AD; RID detector, 250/4 Nucleosil 100-5 column (Macherey–Nagel), at a flow of 0.8 mL/min; t_R in min.

3.2. Synthesis of compounds 2–7 and 10

3.2.1. Benzyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside (2). To a stirred solution of **1** (35 mg, 0.076 mmol) in anhyd THF (0.6 mL), a 0.5 M BnONa–BnOH[‡] solution (0.23 mmol, 0.46 mL) was added at −78 °C,[§] and the stirring was continued for 1 h under an inert atmosphere of Ar. Pyridine (1 mL) and Ac_2O (0.5 mL) were then added, and the reaction mixture was stirred for 7 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (7 mg, 0.016 mmol) and **2** (26 mg, 0.042 mmol, 55%) as a viscous oil. Data for **2**. $[\alpha]_D^{20}$ −47.5 (*c* 3.4, $CHCl_3$). ^{1}H NMR: δ 7.50–7.21 (m, 15H, 3Ph), 5.53 (d, 1H, $J_{1,P}$ 3.73, H-1), 4.79 (A of AB, 1H, J_{AB} 11.33, H_A of CH_2Ph), 4.67 (B of AB, 1H, J_{BA} 11.33, H_B of CH_2Ph), 4.67 (br s, 2H, CH_2Ph), 4.63–4.50 (m, 3H, CH_2Ph, H-5), 4.22–3.89 (m, 5H, H-4, 2OCH_2CH$_3$), 3.80 (A of ABX, 1H, J_{AB} 9.73, J_{AX} 6.71, 6-H_A), 3.69 (B of ABX, 1H, J_{BA} 9.73, J_{BX} 6.51, 6-H_B), 2.09 (s, 3H, CO(CH$_3$)), 1.29 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.57, OCH$_2$*CH*$_3$), 1.23 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.60, OCH$_2$*CH*$_3$). ^{13}C NMR: δ 168.6 (C=O), 157.7 (d, $J_{C\text{-}3,P}$ 2.98, C-3), 138.0, 137.6, 137.5 (C_{quat}Ph), 128.3, 128.3, 128.2, 128.1, 127.9, 127.63, 127.60 (Ph), 119.3 (d, $J_{C\text{-}2,P}$ 176.62, C-2), 95.3 (d, $J_{C\text{-}1,P}$ 12.30, C-1), 73.4 (2CH_2Ph), 71.0 (CH_2Ph), 70.3 (d, $J_{C\text{-}4,P}$ 9.70, C-4), 69.6 (C-5), 68.3 (C-6), 62.2 (d, $J_{CH_2,P}$ 4.89, 2O*CH*$_2$CH$_3$), 20.8 (CO(*CH*$_3$)), 16.2 (d, $J_{CH_3,P}$ 5.22, OCH$_2$*CH*$_3$), 16.1 (d, $J_{CH_3,P}$ 5.22, OCH$_2$*CH*$_3$). IR ($CHCl_3$): 1760. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 13.4 (100%). HRESIMS: Calcd for $C_{33}H_{39}O_9P$ $[M+Na]^+$: m/z 633.2229; found: m/z 633.2231.

3.2.2. Methyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside (3). To a stirred solution of **1** (30 mg, 0.065 mmol) in anhyd MeOH (0.25 mL), a 1 M MeONa–MeOH solution (0.26 mmol, 0.26 mL) was added at −30 °C, and the stirring was continued for 8 h under an inert atmosphere of Ar. Pyridine (3 mL) and Ac_2O (1.5 mL) were then

[‡] The 0.5 M BnONa–BnOH was prepared by adding anhyd BnOH (2 mL) to NaH (40 mg, 1 mmol, 60% suspension in mineral oil) at 0 °C. The solution was stirred at rt for 30 min.

[§] When the BnOH addition reaction was performed at −65 °C, **2** was obtained in 70% yield.

added, and the reaction mixture was stirred for 12 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (12 mg, 0.026 mmol) and **3** (21 mg, 0.039 mmol, 60%) as a viscous oil and as an inseparable mixture of α:β anomers. Data for **3**. $[\alpha]_D^{20}$ −50.5 (*c* 1.1, $CHCl_3$). ^1H NMR: δ 7.42–7.21 (m, 10H, 2Ph), 5.23 (d, 1H, $J_{1,P}$ 3.69, H-1), 4.62 (br s, 2H, CH_2Ph), 4.61 (A of AB, 1H, J_{AB} 11.87, H_A of CH_2Ph), 4.55 (B of AB, 1H, J_{BA} 11.87, H_B of CH_2Ph), 4.54–4.39 (m, 1H, H-5), 4.24–3.96 (m, 5H, H-4, 2O$CH_2$$CH_3$), 3.79 (A of ABX, 1H, J_{AB} 9.77, J_{AX} 6.68, 6-H_A), 3.73 (B of ABX, 1H, J_{BA} 9.77, J_{BX} 6.68, 6-H_B), 3.46 (s, 3H, OCH_3), 2.06 (s, 3H, CO(CH_3)), 1.31 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.63, OCH_2CH_3), 1.29 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.63, OCH_2CH_3). ^{13}C NMR: δ 168.6 (C=O), 157.5 (d, $J_{C\text{-}3,P}$ 3.05, C-3), 137.9, 137.6 ($C_{quat}Ph$), 128.4, 128.2, 127.9, 127.8, 127.7, 127.6 (Ph), 119.5 (d, $J_{C\text{-}2,P}$ 177.00, C-2), 96.5 (d, $J_{C\text{-}1,P}$ 12.21, C-1), 73.4 ($2CH_2Ph$), 70.1 (d, $J_{C\text{-}4,P}$ 9.92, C-4), 69.4 (C-5), 68.4 (C-6), 62.3 (d, $J_{CH_2,P}$ 3.81, 2 O$CH_2$$CH_3$), 56.2 ($OCH_3$), 20.8 (CO($CH_3$)), 16.3 (d, $J_{CH_3,P}$ 3.05, OCH_2CH_3), 16.1 (d, $J_{CH_3,P}$ 3.43, OCH_2CH_3). IR ($CHCl_3$): 1761. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 21.5 (98%), $t_{R\beta}$ 22.8 (2%). HRESIMS: Calcd for $C_{27}H_{35}O_9P$ $[M+K]^+$: *m*/*z* 573.1656; found: *m*/*z* 573.1680.

3.2.3. Ethyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside (4). To a stirred solution of **1** (36 mg, 0.078 mmol) in anhyd EtOH (0.3 mL), a 1 M EtONa–EtOH solution (0.39 mmol, 0.39 mL) was added at −30 °C, and the stirring was continued for 8 h under an inert atmosphere of Ar. Pyridine (3 mL) and Ac_2O (1.5 mL) were then added, and the reaction mixture was stirred for 12 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 6:4 *n*-hexane–EtOAc) to give the unreacted enone **1** (5 mg, 0.010 mmol) and **4** (26 mg, 0.047 mmol, 60%) as a viscous oil and as an inseparable mixture of α,β anomers. Data for **4**. $[\alpha]_D^{20}$ −51.5 (*c* 1.3, $CHCl_3$). ^1H NMR: δ 7.39–7.21 (m, 10H, 2Ph), 5.35 (d, 1H, $J_{1,P}$ 3.97, H-1), 4.62 (br s, 2H, CH_2Ph), 4.60 (A of AB, 1H, J_{AB} 11.86, H_A of CH_2Ph), 4.55 (B of AB, 1H, J_{BA} 11.86, H_B of CH_2Ph), 4.59–4.41 (m, 1H, H-5), 4.21–3.93 (m, 5H, H-4, 2PO$CH_2$$CH_3$), 3.91–3.53 (m, 4H, CH_2-6, O$CH_2$$CH_3$), 2.06 (s, 3H, CO($CH_3$)), 1.31 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.60, $POCH_2CH_3$), 1.29 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.60, $POCH_2CH_3$), 1.22 (t, 3H, J_{CH_2,CH_3} 7.07, OCH_2CH_3). ^{13}C NMR: δ 168.6 (d, $J_{CO,P}$ 1.66, C=O), 157.3 (d, $J_{C\text{-}3,P}$ 3.15, C-3), 138.0, 137.7 ($C_{quat}Ph$), 128.3, 128.2, 127.8, 127.6, 127.59 (Ph), 119.7 (d, $J_{C\text{-}2,P}$ 176.10, C-2), 95.4 (d, $J_{C\text{-}1,P}$ 12.37, C-1), 73.42, 73.38 ($2CH_2Ph$), 70.3 (d, $J_{C\text{-}4,P}$ 9.73, C-4), 69.3 (C-5), 68.4 (C-6), 64.6 (OCH_2CH_3), 62.2 (d, $J_{CH_2,P}$ 4.84, 2POCH_2CH_3), 20.8 (CO(CH_3)), 16.3 (d, $J_{CH_3,P}$ 3.84, $POCH_2CH_3$), 16.1 (d, $J_{CH_3,P}$ 3.77, $POCH_2CH_3$), 15.1 (OCH_2CH_3). IR ($CHCl_3$): 1761. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 16.3 (98%), $t_{R\beta}$ 17.3 (2%). HRESIMS: Calcd for $C_{28}H_{37}O_9P$ $[M+Na]^+$: *m*/*z* 571.2073; found: *m*/*z* 571.2087.

3.2.4. *n*-Pentyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside (5). To a stirred solution of **1** (56 mg, 0.122 mmol) in anhyd *n*-pentanol (0.2 mL), a 1 M $CH_3(CH_2)_4ONa$–$CH_3(CH_2)_4OH$ solution (0.610 mmol, 0.61 mL) was added at −20 °C, and the stirring was continued for 9 h under an inert atmosphere of Ar. Pyridine (4 mL) and Ac_2O (2 mL) were then added, and the reaction mixture was stirred for 12 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (5 mg, 0.010 mmol) and **5** (56 mg, 0.095 mmol, 80%) as a viscous oil and as an inseparable mixture of α,β anomers. Data for **5**. $[\alpha]_D^{20}$ −65.9 (*c* 3.1, $CHCl_3$). ^1H NMR: δ 7.39–7.21 (m, 10H, 2Ph), 5.33 (d, 1H, $J_{1,P}$ 3.38, H-1), 4.62 (br s, 2H, CH_2Ph), 4.59 (A of AB, 1H, J_{AB} 11.86, H_A of CH_2Ph), 4.53 (B of AB, 1H, J_{BA} 11.86, H_B of CH_2Ph), 4.51 (td, 1H, $J_{5,6}$ 6.5, $J_{5,4}$ 2.6, H-5), 4.22–3.92 (m, 5H, H-4, 2POCH_2CH_3), 3.85–3.65 (m, 3H, 6-H, H_A of OCH_2-$(CH_2)_3CH_3$), 3.61–3.46 (m, 1H, H_B of O$CH_2(CH_2)_3$-CH_3), 2.07 (s, 3H, CO(CH_3)), 1.68–1.48 (m, 2H, $OCH_2CH_2(CH_2)_2CH_3$), 1.39–1.20 (m, 4H, O$(CH_2)_2$-$(CH_2)_2CH_3$), 1.31 (td, 3H, J_{CH_3,CH_2} 7.05, $J_{CH_3,P}$ 0.58, $POCH_2CH_3$), 1.28 (td, 3H, J_{CH_3,CH_2} 7.07, $J_{CH_3,P}$ 0.55, $POCH_2CH_3$), 0.88 (pt, 3H, O$(CH_2)_4CH_3$). ^{13}C NMR: δ 168.6 (d, $J_{CO,P}$ 1.50, C=O), 157.3 (d, $J_{C\text{-}3,P}$ 3.12, C-3), 138.0, 137.7 ($C_{quat}Ph$), 128.3, 128.2, 127.8, 127.6, 127.5 (Ph), 119.7 (d, $J_{C\text{-}2,P}$ 175.93, C-2), 95.4 (d, $J_{C\text{-}1,P}$ 12.37, C-1), 73.4, 73.3 ($2CH_2Ph$), 70.1 (d, $J_{C\text{-}4,P}$ 9.70, C-4), 69.3 (C-5), 69.2, (O$CH_2(CH_2)_3CH_3$), 68.4 (C-6), 62.1 (d, $J_{CH_2,P}$ 4.67, 2POCH_2CH_3), 29.3, 28.2, 22.3 ($OCH_2(CH_2)_3CH_3$), 20.8 (CO(CH_3)), 16.3 (d, $J_{CH_3,P}$ 4.08, $POCH_2CH_3$), 16.1 (d, $J_{CH_3,P}$ 4.03, $POCH_2CH_3$), 13.9 (OCH_2CH_3). IR ($CHCl_3$): 1759. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 11.1 (98%), $t_{R\beta}$ 11.7 (2%). HRESIMS:

Calcd for $C_{31}H_{43}O_9P$ $[M+Na]^+$: m/z 613.2542; found: m/z 613.2570.

3.2.5. Propargyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside 6. To a stirred solution of **1** (50 mg, 0.11 mmol) in anhyd propargyl alcohol (0.3 mL), a 1 M HC≡CCH$_2$ONa–HC≡CCH$_2$OH solution (0.55 mmol, 0.55 mL) was added at −30 °C, and the stirring was continued for 9 h under an inert atmosphere of Ar. Pyridine (4 mL) and Ac_2O (2 mL) were then added, and the reaction mixture was stirred for 12 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (17 mg, 0.037 mmol) and **6** (31 mg, 0.055 mmol, 50%) as a viscous oil and as an inseparable mixture of α,β anomers. Data of **6**. $[\alpha]_D^{20}$ −27.9 (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 7.44–7.22 (m, 10H, 2Ph), 5.52 (d, 1H, $J_{1,P}$ 3.69, H-1), 4.63 (br s, 2H, CH_2Ph), 4.57 (br s, 2H, CH_2Ph), 4.55–4.44 (m, 1H, H-5), 4.35–4.27 (m, 2H, O*CH*$_2$C≡CH), 4.20–4.00 (m, 5H, H-4, 2O*CH*$_2$CH$_3$), 3.84–3.66 (m, 2H, CH$_2$-6), 2.37 (t, 1H, OCH$_2$C≡C*H*), 2.07 (s, 3H, CO(CH$_3$)), 1.32 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.53, OCH$_2$*CH*$_3$), 1.30 (td, 3H, J_{CH_3,CH_2} 7.06, $J_{CH_3,P}$ 0.54, OCH$_2$*CH*$_3$). ^{13}C NMR: δ 168.6 (C=O), 158.1 (d, $J_{C\text{-}3,P}$ 2.86, C-3), 137.9, 137.6 (C_{quat}Ph), 128.4, 128.2, 127.9, 127.71, 127.69 (Ph), 119.1 (d, $J_{C\text{-}2,P}$ 177.67, C-2), 94.3 (d, $J_{C\text{-}1,P}$ 11.83, C-1), 79.0 (*C*≡CH), 74.6, 73.5 (CH_2Ph), 70.2 (d, $J_{C\text{-}4,P}$ 9.66, C-4), 69.8 (C≡*C*H), 69.7 (C-5), 68.1 (C-6), 62.6 (d, $J_{CH_2,P}$ 5.13, O*CH*$_2$CH$_3$), 62.4 (d, $J_{CH_2,P}$ 5.20, O*CH*$_2$CH$_3$), 55.4 (O*CH*$_2$C≡CH), 20.8 (CO(*CH*$_3$)), 16.3 (d, $J_{CH_3,P}$ 6.46, 2OCH$_2$*CH*$_3$). IR ($CHCl_3$): 1761. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 16.9 (90%), $t_{R\beta}$ 17.9 (10%). HRESIMS: Calcd for $C_{29}H_{35}O_9P$ $[M+Na]^+$: m/z 581.1916; found: m/z 581.1901.

3.2.6. 2′-Propyl 3-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranoside (7). To a stirred solution of **1** (50 mg, 0.11 mmol), a 0.3 M 2-PrONa–2-PrOH solution (0.55 mmol, 1.65 mL) was added at −20 °C, and the stirring was continued for 9 h under an inert atmosphere of Ar. Pyridine (4 mL) and Ac_2O (2 mL) were then added, and the reaction mixture was stirred for 12 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (12 mg, 0.026 mmol) and **7** (31 mg, 0.055 mmol, 50%) as a viscous oil and as an inseparable mixture of α,β anomers. Data for **7**. $[\alpha]_D^{20}$ −60.4 (*c* 2.3, $CHCl_3$). ^{1}H NMR: δ 7.36–7.23 (m, 10H, 2Ph), 5.44 (d, 1H, $J_{1,P}$ 3.71, H-1), 4.62 (br s, 2H, CH_2Ph), 4.49–4.60 (m, 3H, CH_2Ph, H-5), 3.91–4.23 (m, 6H, 2O*CH*$_2$CH$_3$, H-4, *CH*(CH$_3$)$_2$), 3.79 (A of ABX, 1H, J_{AB} 9.71, J_{AX} 6.96, 6-H$_A$), 3.71 (B of ABX, 1H, J_{BA} 9.71, J_{BX} 6.39, 6-H$_B$), 2.06 (s, 3H, CO(CH$_3$)), 1.31 (t, 3H, J_{CH_3,CH_2} 6.96, OCH$_2$*CH*$_3$), 1.28 (t, 3H, J_{CH_3,CH_2} 6.96, OCH$_2$*CH*$_3$), 1.21 (d, 3H, *J* 3.98, CH(*CH*$_3$)$_2$), 1.20 (d, 3H, *J* 3.90, CH(*CH*$_3$)$_2$). ^{13}C NMR: δ 168.7 (C=O), 157.3 (d, $J_{C\text{-}3,P}$ 3.08, C-3), 138.0, 137.8 (C_{quat}Ph), 128.3, 128.2, 127.8, 127.6, 127.5 (Ph), 119.9 (d, $J_{C\text{-}2,P}$ 175.74, C-2), 94.1 (d, $J_{C\text{-}1,P}$ 12.30, C-1), 73.4, 73.3, 71.5, 70.3 (d, $J_{C\text{-}4,P}$ 9.63, C-4), 69.1, 68.4, 62.2 (d, $J_{CH_2,P}$ 4.91, O*CH*$_2$CH$_3$), 62.2 (d, $J_{CH_2,P}$ 4.96, O*CH*$_2$CH$_3$), 23.5, 21.7, 20.8, 16.2 (d, $J_{CH_3,P}$ 4.51, OCH$_2$*CH*$_3$), 16.1 (d, $J_{CH_3,P}$ 4.55, OCH$_2$*CH*$_3$). IR ($CHCl_3$): 1764. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 14.6 (100%). HRESIMS: Calcd for $C_{29}H_{39}O_9P$ $[M+Na]^+$: m/z 585.2229; found: m/z 585.2236.

3.2.7. 3-*O*-Acetyl-4,6-di-*O*-benzyl-2-deoxy-2-diethoxyphosphoryl-α-D-*threo*-hex-2-enopyranosyl-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-D-*arabino*-hex-1-enitol (10). To a stirred solution of **1** (50 mg, 0.11 mmol) in anhyd THF (0.15 mL) and DMF (0.15 mL), a 1 M solution of **9a** (0.6 mmol, 0.6 mL) in 1:1 THF–DMF was added at −20 °C, and the stirring was continued for 9 h under an inert atmosphere of Ar. Pyridine (4 mL) and Ac_2O (2 mL) were then added, and the reaction mixture was stirred for 15 h at −20 °C. After this time, the reaction mixture was diluted with Et_2O (5 mL), washed in a separatory funnel with cold satd $NaHCO_3$ (3 × 5 mL), H_2O (until neutral), and brine. The organic extract was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 7:3 *n*-hexane–EtOAc) to give the unreacted enone **1** (12 mg, 0.026 mmol) and **10** (47 mg, 0.055 mmol, 50%) as a viscous oil and as an inseparable mixture of α,β anomers. Data for **10**. $[\alpha]_D^{20}$ −31.8 (*c* 1.9, $CHCl_3$). ^{1}H NMR: δ 7.47–7.16 (m, 20H, 4Ph), 6.32 (dd, 1H, $J_{1',2'}$ 6.20, $J_{1',3'}$ 1.05, H-1′), 5.41 (d, 1H, $J_{1,P}$ 3.72, H-1), 4.84 (dd, 1H, $J_{2',1'}$ 6.20, $J_{2',3'}$ 3.05, H-2′), 4.83 (A of AB, 1H, J_{AB} 11.65, H$_A$ of CH_2Ph), 4.70 (B of AB, 1H, J_{BA} 11.65, H$_B$ of CH_2Ph), 4.62–4.34 (m, 7H, 3CH_2Ph, H-5), 4.23–3.56 (m, 12H, 2O*CH*$_2$CH$_3$, H-4, CH$_2$-6, H-3′, H-4′, H-5′, CH$_2$-6′), 2.06 (s, 3H, CO(CH$_3$)), 1.29 (t, 3H, J_{CH_3,CH_2} 7.05, OCH$_2$*CH*$_3$), 1.27 (td, 3H, J_{CH_3,CH_2} 7.06, OCH$_2$*CH*$_3$). ^{13}C NMR: δ 168.5 (C=O), 157.7 (d, $J_{C\text{-}3,P}$ 3.05, C-3), 144.4 (C-1′), 138.4, 138.3, 137.9, 137.7 (C_{quat}Ph), 128.3, 128.2, 127.9, 127.7, 127.6, 127.5 (Ph), 119.3 (d, $J_{C\text{-}2,P}$ 176.52, C-2), 99.7 (C-2′), 95.6 (d, $J_{C\text{-}1,P}$ 12.04, C-1), 76.4 (C-3′), 75.1 (C-4′), 74.5 (C-5′), 73.5, 73.4,

73.3, 70.3 (4CH_2Ph), 70.2 (d, $J_{C\text{-}4,P}$ 9.68, C-4), 69.4 (C-5), 68.1 (C-6), 67.4 (C-6′), 62.3 (d, $J_{CH_2,P}$ 4.77, 2O$CH_2$$CH_3$), 20.8 (CO($CH_3$)), 16.3 (d, $J_{CH_3,P}$ 3.70, OCH$_2$$CH_3$), 16.2 (d, $J_{CH_3,P}$ 3.70, OCH$_2$$CH_3$). IR ($CHCl_3$): 1762. HPLC: (1:1 *n*-hexane–EtOAc): $t_{R\alpha}$ 12.6 (99%), $t_{R\beta}$ 13.7 (1%). HRESIMS: Calcd for $C_{46}H_{53}O_{12}P$ $[M+Na]^+$: *m*/*z* 851.3172; found: *m*/*z* 851.3214.

3.3. Theoretical calculations

For each compound, we ran a set of classical MM trajectories to sample the configurational space. The trajectories were calculated in vacuum using a Verlet algorithm and the MM3 force field as implemented by the Tinker suite of codes.[13] In general, a first trajectory of 9×10^5 steps of 0.1–0.2 fs was generated using a temperature of 2000 K. Snapshots of this trajectory were saved, each 1×10^3 fs, and optimized using a truncated Newton minimization method. By selecting the lowest energy structures, we obtained a small set of candidates for creating a second set of trajectories at a lower temperature (1000 K). We repeated this cycle once more also for 500 K, and at this point, we were able to easily identify a global minimum structure. The MM energy differences between the β and the α isomers are reported as 'MM' in Table 2.

For each compound, the α and the β MM global minima determined by means of the above procedure were further optimized using density functional theory (DFT) methods: the calculations have been carried out with the GAUSSIAN 03 suite of codes,[14] using a DFT method based on the B3LYP functional. Given the size of the molecules involved in the calculations, we have been forced to use the relatively small 6-31G(d,p) basis set. A larger one would have been certainly desirable, but would have made the calculation times prohibitive.

For all the molecules, we have started by minimizing the structures obtained from MM calculations with the relatively small 6-31G basis set. The resulting structure was then optimized again with a 6-31G(d,p) basis. The energy differences between the optimized structures of the β and the α anomers are those reported as ΔE(DFT) in Table 2. For each structure, we have also performed a normal mode analysis and a thermochemistry calculation at a given temperature in order to have a good estimate of the free-energy difference. The only exception is represented by compound **17** where we were not able to perform the 6-31G(d,p) basis set optimization and the normal mode analysis because of the large number of atoms involved. In this case, the DFT energy shown in Table 2 refers to the 6-31G results.

To account for the solvent effects, we have performed an additional calculation on compound **11**. As a first step, we have optimized the structures obtained in vacuum using the PCM model[15] with the specific MeOH solvent. We have obtained a new ΔE(DFT), which is reported in Table 2. In the second step, we have calculated the vibrational frequencies of the optimized structures in MeOH and we have been able to correct the PCM energies for the ZPE energies.

The 6-31G(d,p) basis may lead to appreciable basis set superposition errors (BSSEs). The counterpoise correction,[11] while not rigorous, can be used to produce corrected energies. We have therefore repeated our calculations on compound **11** using the counterpoise correction implemented in GAUSSIAN 03 to further check the quality of our calculations procedure. We have divided the molecule into two fragments by setting one of them to $^-OCH_3$. The result is reported in Table 2 as ΔE(DFT + BSSE).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.03.009.

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