Stereoselective Michael-Type Addition of Organocopper Reagents to Enones Derived from Glycals in the Synthesis of 2-Phosphono-α-*C*-Glycosides

Francesca Leonelli,*[a] Marinella Capuzzi,[a] Vincenzo Calcagno,[a] Pietro Passacantilli,[a] and Giovanni Piancatelli*[a]

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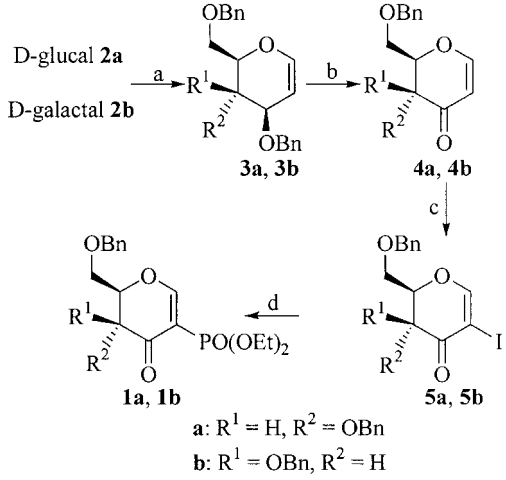
Michael-type additions of various organocopper reagents to the novel carbohydrate-derived 2-(diethoxyphosphoryl)hex-1-en-3-uloses are described. The reactions have proved to be rapid, clean and stereoselective, giving rise to the formation of 3-oxo-2-phosphono-α-*C*-glycosides or the corresponding enol acetates. These compounds are direct precursors of 2-phosphono-α-*C*-glycosides, a very interesting class of molecules never described before.

Introduction

Michael-type addition to activated double bonds of carbohydrate derivatives has recently become a powerful tool for the functionalization of monosaccharides.[1] Among the various examples, one of the most interesting is the preparation of *C*-glycosides,[1a–1c,1g,2] carbohydrate analogues in which the C–O glycosidic linkage is substituted by a C–C bond. During the last three decades, the synthesis of these compounds has attracted the interest of chemists and biochemists thanks to their stability towards enzymes, acids and bases and because the *C*-glycoside moiety is contained in several bioactive natural products.[3]

C-Glycosylphosphonates are known as important enzymatic inhibitors[1h,4] (the C–P bond cannot be hydrolysed by "ordinary" enzymes) and are able to act as stable biomimetics of the corresponding glycosyl phosphates, which have turned out to be the main metabolic precursors and the key glycosylating agents in the biosynthesis of glycoconjugates. We therefore believe that the preparation of new *C*-glycosides containing the phosphonate group is quite valuable.

Here we describe a simple procedure for the preparation of the novel 3-oxo-2-phosphono-α-*C*-glycosides through Michael-type additions of organocopper reagents, starting from 2-(diethoxyphosphoryl)hex-1-en-3-uloses **1a** and **1b**. The presence of the carbonyl function α to the phosphonate group was necessary because of the well documented low reactivity of nonactivated vinyl phosphonates towards 1,4-additions.[5] Compounds **1a** and **1b** were prepared from glycals, such as D-glucal **2a** and the D-galactal **2b**, according to the synthetic procedure reported in Scheme 1.



Scheme 1. Reagents and conditions: a) NaH, BnBr, THF/DMF (4:1), 4 h, 60 °C, 90%. b) CH_3CN, 3-Å molecular sieves, BAIB, TsOH, 2 h, room temp., 40% for **4a**, 60% for **4b**. c) I_2, CCl_4/Py (1:1), 2 h, room temp., 74% for **5a**, 60% for **5b**. d) $P(OEt)_3$, $NiCl_2$, 150 °C, 60%.

The tri-*O*-benzyl-D-glycals **3a** and **3b**, obtained by perbenzylation of the starting D-glucal **2a** and D-galactal **2b** with sodium hydride/benzyl bromide, were selectively oxidized to enones **4a** and **4b** with bis(acetoxy)iodobenzene (BAIB) and TsOH by a well known synthetic procedure.[6] The pyranones **4** were then converted in good yields into the vinyl iodides **5** by treatment with molecular iodine in a CCl_4/Py (1:1) solution.[7] Unexpectedly, initial attempts to perform the cross-coupling reaction for the formation of the C–P bonds in phosphonate compounds **1** with various

[a] Dipartimento di Chimica and Istituto di Chimica Biomolecolare del CNR - Sezione di Roma, Università "La Sapienza", Piazzale Aldo Moro 5, 00185 Roma, Italy
Fax: +39-06-490631
E-mail: francesca.leonelli@uniroma1.it
giovanni.piancatelli@uniroma1.it

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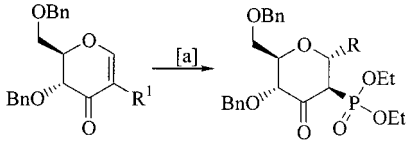
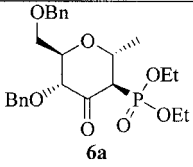
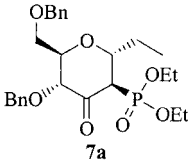
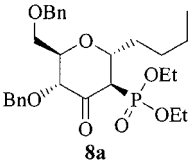
Pd-based catalysts and diethyl hydrogen phosphite failed completely. We therefore considered Kazankova's method[8] for converting vinyl halides into phosphonates by a modified Arbuzov reaction catalysed by triethyl phosphite nickel(0) complex. When this reaction was performed in triethyl phosphite at 150 °C in the presence of $NiCl_2$ as a catalyst the desired products **1** were obtained in fair yields.

Initial experiments involving addition of the organocopper reagents were carried out with the D-glucal-derived enone **1a** as shown in Table 1. The reactions resulted in the formation of the 3-oxo-2-phosphono-α-*C*-glycosides **6a**–**8a**

Table 1. Stereoselective Michael-type addition to 2-(diethoxyphosphoryl)hex-1-en-3-ulose **1a** and enone **4a**.



1a R^1 = $PO(OEt)_2$ **6a-8a** R = Me, Et, *n*Bu
4a R^1 = H

Entry	Enones	R_2CuLi	Solvents	Products	α/β[b]
1	**1a**	R = Me	Et_2O/THF	 **6a**	96/4
2	**1a**	R = Et	Et_2O	 **7a**	74/26[c]
			Et_2O/THF		96/4
3	**1a**	R = *n*Bu	Et_2O	 **8a**	66/34[c]
			Et_2O/THF		96/4
4	**4a**	R = Me	Et_2O/THF	–	–

[a] R_2CuLi (2.5 equiv.), –78 °C, 3 min, 75%. [b] Diastereoisomeric ratios were determined by integration of the corresponding 2-H signal in the 200-MHz ^1H NMR spectra and by HPLC analysis of the crude reaction mixtures. [c] The epimeric mixtures were treated with Ac_2O in Py to give the two corresponding α- and β-enol acetates in unchanged diastereoisomeric ratios.

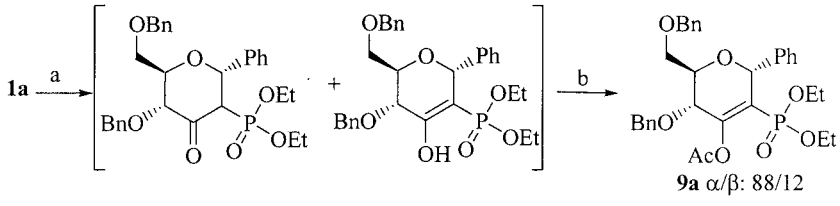
in good yields and with almost complete α diastereoselectivity[9,10] and proved to be extremely rapid (the starting enone had disappeared by TLC in less than 3 minutes). These results show the remarkable accelerating effect of the phosphonate group on the reaction rate. The effect is clearly evident on reference to the conjugate addition on the enone **4a**, for which we observed no product under the same reaction conditions (Table 1, entry 4).[11]

The addition of Ph_2CuLi to **1a** gave a 7:3 mixture of the ketonic and enolic derivatives, which was treated without purification with Ac_2O in Py to give the enol acetate **9a** quantitatively with an α/β diastereoisomeric ratio of 88:12 (Scheme 2). This result was in agreement with previous studies regarding the conjugate addition of phenylcopper reagents to hex-1-enopyran-3-uloses.[1c]

Such behaviour was also noticed with the D-galactal-derived enone **1b** (Table 2): conjugate addition of all the organocopper reagents almost exclusively gave α-*C*-glycosides[12] in enolic form, and these were transformed into the enol acetates **6b**–**9b** as described previously. In this case the C(4)-*galacto* configuration probably forced all the addition compounds to be in enolic form, presumably less crowded than the corresponding ketonic one. As in the case of compound **1a**, the phosphonate group also accelerates the reaction rates for **1b** (Table 2, entry 5).[13]

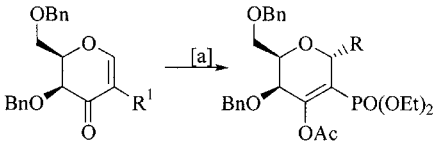
The α-*C*-glycoside configurations in the addition products **6a**–**8a** were established by the presence of clear NOE signals between H-(5) and CH_2R at C(1) (Scheme 3). The assignment of the C(2) configuration was defined by the presence of NOE signals between H-(2) and CH_2R at C(1) (Scheme 3) and by coupling constant analysis ($J_{1,2} \approx 3$ Hz). The presence of a NOE between H-(5) and CH_2R at C(1) also confirmed the α-*C*-glycoside configuration in the galactal-derived addition products **6b**–**8b**. Furthermore we were able to rule out C(4) epimerization[14] in compounds **6**–**9** because the values of $J_{4,5}$ were large (≈ 10 Hz) in products **6a**–**9a**, indicating an axial-axial relationship, and smaller (≈ 3 Hz) in **6b**–**9b** because of an equatorial-axial relationship.

In conclusion, Michael-type organocopper addition to 2-(diethoxyphosphoryl)hex-1-en-3-uloses **1** has been shown here to be stereoselectively α and has allowed us to prepare the novel compounds **6**–**9**, which can in turn be transformed into 2-phosphono-α-*C*-glycosides by means of the well known stereoselective reduction of the carbonyl group[1d,1g,15] (for **6a**–**8a**) or the reduction of the enol acetate function (for **6b**–**9b** and **9a**).[16]



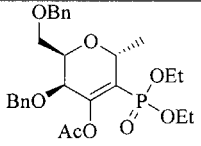
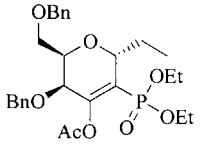
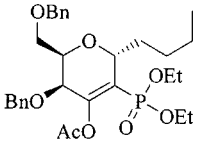
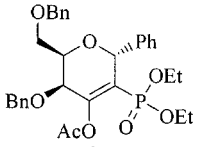
Scheme 2. a) Ph_2CuLi (2.5 equiv.), Et_2O/THF (1:1), –78 °C, 3 min. b) Ac_2O, Py, 40 °C, 12 h, 60% (after two steps)..

Table 2. Stereoselective Michael-type addition to 2-(diethoxyphosphoryl)hex-1-en-3-ulose **1b** and enone **4b**.

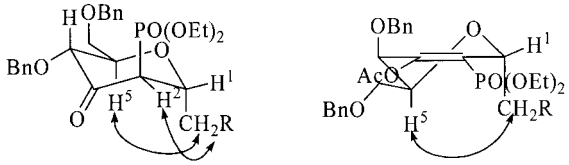


1b R^1 = $PO(OEt)_2$
4b R^1 = H

6b-9b
R = Me, Et, *n*Bu, Ph

Entry	Enones	R_2CuLi	Solvents	Products	α/β[b]
1	**1b**	R = Me	Et_2O	 **6b**	98/2
2	**1b**	R = Et	Et_2O	 **7b**	100/0
3	**1b**	R = *n*Bu	Et_2O	 **8b**	94/6
4	**1b**	R = Ph	Et_2O	 **9b**	70/30
			Et_2O/THF		97/3
5	**4b**	R = Me	Et_2O/THF	-	-

[a] i) R_2CuLi (2.5 equiv.), –78 °C, 3 min. ii) Ac_2O, Py, room temp., 12 h, 70% (after the two steps). [b] Diastereoisomeric ratios were determined by integration of the corresponding 1-H in the 200-MHz ^1H NMR spectra and by HPLC analysis of the crude reaction mixtures.



6a-8a **6b-8b**

Scheme 3. NOE signals in glucal derivatives **6a**–**8a** and in galactal derivatives **6b**–**8b**.

Experimental Section

General: ^1H 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; δ in ppm. IR spectra: Shimadzu-470 scanning infrared spectrophotometer; values given in cm^{-1}. HRMS spectra were recorded with a Micromass Q-TOF *micro* Mass Spectrometer (Waters). Optical rotations were measured at the sodium D line on a DIP 370 Jasco digital polarimeter. Yields are given for isolated products after column chromatography showing a single spot on TLC and no detectable impurities in the ^1H NMR spectrum. All reactions were performed under Ar in flame-dried glassware. All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck F-254 silica glass plates and viewed with the aid of UV light and heat-gun treatment with 2 N H_2SO_4 solution. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). HPLC analysis Shimadzu LC-10AD; RID detector, 250/4 Nucleosil 100-5 column (Macherey–Nagel), at a flow of 0.8 mL min^{-1}; t_R in min.

Tri-*O*-benzyl-D-glucal 3a: Glucal **2a** (Aldrich, 1.00 g, 6.84 mmol) was added slowly at 0 °C to a 4:1 THF/DMF mixture (50 mL) containing NaH (1.09 g, 27.38 mmol, 60% suspension in mineral oil). BnBr (3.2 mL, 27.38 mmol) was then added and the reaction mixture was heated at 60 °C for 4 h. After the reaction mixture had cooled, Et_2O (20 mL) and H_2O (5 mL, slowly) were added and a stream of CO_2 was passed through the solution until neutrality. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 95:5) to give pure **3a**[17] (2.56 g, 6.15 mmol, 90%).

Tri-*O*-benzyl-D-galactal 3b: This compound was prepared from galactal **2b** (Aldrich, 0.50 g, 3.42 mmol) as in the procedure described for **3a**. The crude product was purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 95:5) to give pure **3b**[18] (1.28 g, 3.07 mmol, 90%).

Hex-1-enopyran-3-ulose 4a: Powdered molecular sieves (3 Å, 1.67 g) were added to a solution of **3a** (2.56 g, 6.15 mmol) in anhydrous CH_3CN (120 mL), and the suspension was stirred at 0 °C for 5 min. BAIB (2.38 g, 7.38 mmol) was then added in one portion and the mixture was stirred for 10 min at room temp. TsOH (1.40 g, 7.38 mmol) was added slowly and the stirring was continued for another 75 min. The suspension was then filtered through a pad of Celite, and the residue was washed with CH_2Cl_2. The combined filtrate and washings were washed with s.s. $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then rapidly purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 90:10) to give pure **4a**[6] (0.80 g, 2. 46 mmol, 40%).

Hex-1-enopyran-3-ulose 4b: This compound was prepared from **3b** (1.28 g, 3.07 mmol) as in the procedure described for **4a**. The crude product was purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 90:10) to give pure **4b**[3] (0.60 g, 1.84 mmol, 60%).

Vinyl Iodide 5a: Iodine (1.31 g, 5.18 mmol), dissolved in CCl_4/pyridine (1:1, 10 mL), was added dropwise at 0 °C to a solution of **4a** (0.80 g, 2.46 mmol) in CCl_4/pyridine (1:1, 10 mL). The mixture was stirred for 2 h at room temp., diluted with CH_2Cl_2 (30 mL) and then washed in a separating funnel with H_2O (15 mL), 1 N HCl (2 × 15 mL) and 20% aqueous $Na_2S_2O_3$ (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; hexanes/Et_2O, 80:20) to give pure **5a** (0.82 g, 1.82 mmol, 74%) as a viscous oil. Data for **5a**. $[\alpha]_D$ = +253.6 (*c* = 3.2, $CHCl_3$). ^1H NMR: δ = 7.71 (s, 1 H, 1-H), 7.28–7.44 (m, 10 H, 2 Ph), 5.07 (A of AB, J_{AB} = 10.9 Hz, 1 H, H_A of CH_2Ph), 4.61 (B of AB, J_{BA} = 10.9 Hz, 1 H, H_B of CH_2Ph), 4.59 (A of AB, J_{AB} = 12.0 Hz, 1 H, H_A of CH_2Ph), 4.56 (A of ABX_2, J_{AB} = 11.3, J_{AX} = 3.0 Hz, 1 H, 5-H), 4.53 (B of AB, J_{BA} = 12.0 Hz, 1 H, H_B of CH_2Ph), 4.40 (B of AB, J_{BA} = 11.3 Hz, 1 H, 4-H), 3.82 (d, $J_{6,5}$ = 3.0 Hz, 2 H, 6-H_A, 6-H_B) ppm. ^{13}C NMR: δ = 188.1 (C-3), 164.8 (C-1), 137.3, 136.9 (C_{quat}, Ph), 128.4, 128.0, 127.8, 127.6 (Ph), 81.7 (C-H), 74.5 (CH_2Ph), 73.9 (C-H), 73.5

(CH_2Ph), 67.5 (C-6). IR ($CHCl_3$): $\tilde{\nu}$ = 1693, 1578 cm^{-1}. HRMS: calcd. for $C_{20}H_{19}IO_4$ [M + Na]$^+$: 473.0226; found 473.0229.

Vinyl Iodide 5b: This compound was prepared from **4b** (0.60 g, 1.84 mmol) as in the procedure described for **5a**. The crude product was purified by column chromatography (SiO_2; hexanes/Et_2O, 80:20) to give pure **5b**[1f] (0.52 g, 1.10 mmol, 60%) as a white solid. Data for **5b**. M.p. 126–128 °C (*n*-hexane/Et_2O). $[\alpha]_D$ = +71.0 (c = 1.5, $CHCl_3$). ^1H NMR: δ = 7.78 (s, 1 H, 1-H), 7.21–7.45 (m, 10 H, 2 Ph), 4.70 (A of AB, J_{AB} = 11.8 Hz, 1 H, H_A of CH_2Ph), 4.59–4.67 (m, 1 H, 5-H), 4.58 (A of AB, J_{AB} = 11.9 Hz, 1 H, H_A of CH_2Ph), 4,52 (B of AB, J_{BA} = 11.9 Hz, 1 H, H_B of CH_2Ph), 4.46 (B of AB, J_{BA} = 11.8 Hz, 1 H, H_B of CH_2Ph), 4.00 (d, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 3.91 (A of ABX, J_{AB} = 10.2, J_{AX} = 6.8 Hz, 1 H, 6-H_A), 3.75 (B of ABX, J_{BA} = 10.2, J_{BX} = 5.6 Hz, 1 H, 6-H_B) ppm. ^{13}C NMR: δ = 184.0 (C-3), 165.3 (C-1), 137.2, 136.5 (C_{quat}, Ph), 128.4, 128.3, 128.1, 127.9, 127.7 (Ph), 81.3 (C-H), 74.7 (C-2), 73.6 (CH_2Ph), 73.5 (C-H), 72.2 (CH_2Ph), 67.1 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1679, 1574 cm^{-1}. HRMS: calcd. for $C_{20}H_{19}IO_4$ [M + Na]$^+$: 473.0226; found 473.0223.

Enone 1a: A stirred mixture of $NiCl_2$ (12 mg, 0.09 mmol) in $P(OEt)_3$ (1 mL, 5.83 mmol) was heated at reflux for 1 h. After that time the black solution became clear and **5a** (0.82 g, 1.82 mmol) was added. After 5 h the solution was cooled, diluted with Et_2O, washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) to give pure **1a** (0.50 g, 1.09 mmol, 60%) as a viscous oil. Data for **1a**. $[\alpha]_D$ = +189.4 (c = 7.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1695, 1585 cm^{-1}. ^1H NMR: δ = 8.04 (d, J = 9.1 Hz, 1 H, 1-H), 7.21–7.44 (m, 10 H, 2 Ph), 4.99 (A of AB, J_{AB} = 11.0 Hz, 1 H, H_A of CH_2Ph), 4.41–4.58 (m, 4 H, H_B of CH_2Ph, CH_2Ph, 5-H), 3.96–4.27 (m, 5 H, 4-H, 2 O$CH_2$$CH_3$), 3.73–3.88 (m, 2 H, 6-$H_A$, 6-$H_B$), 1.31 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 1.29 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$) ppm. ^{13}C NMR: δ = 189.6 (C-3), 171.0 (d, J = 18.7 Hz, C-1), 137.1, 136.9 (C_{quat}, Ph), 128.4, 128.3, 128.0, 127.8, 127.6 (Ph), 105.8 (d, J = 191.5 Hz, C-2), 81.8, (C-H), 74.1 (CH_2Ph), 73.6 (d, J = 8.8 Hz, C-H), 73.56 (CH_2Ph), 67.7 (C-6), 62.4, 62.3 (O$CH_2$$CH_3$), 16.2, 16.1 (OCH$_2$$CH_3$) ppm. HRMS: calcd. for $C_{24}H_{29}O_7P$ [M + H]$^+$: 461.1729; found: 461.1721.

Enone 1b: This compound was prepared from **5b** (0.52 g, 1.10 mmol) as in the procedure described for **1a**. The crude product was purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) to give pure **1b** (0.30 g, 1.10 mmol, 60%) as a viscous oil. Data for **1b**. $[\alpha]_D$ = +6.8 (c = 1.3, $CHCl_3$). ^1H NMR: δ = 8.07 (d, J = 9.3 Hz, 1 H, 1-H), 7.18–7.46 (m, 10 H, 2 Ph), 4.41–4.74 (m, 5 H, 2 CH_2Ph, 5-H), 4.00–4.27 (m, 4 H, 2 O$CH_2$$CH_3$), 3.70–3.98 (m, 3 H, 4-H, 6-H_A, 6-H_B), 1.33 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 1.28 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$) ppm. ^{13}C NMR: δ = 186.7 (C-3), 171.1 (d, J = 19.1 Hz, C-1), 137.1, 136.4 (C_{quat}, Ph), 128.3, 128.1, 128.0, 127.8, 127.6 (Ph), 105.5 (d, J = 191.5 Hz, C-2), 81.2 (C-H), 73.5 (CH_2Ph), 73.3 (d, J = 6.5 Hz, C-H), 71.9 (CH_2Ph), 66.9 (C-6), 62.3 (d, J = 6.0 Hz, O$CH_2$$CH_3$), 62.2 (d, J = 6.0 Hz, O$CH_2$$CH_3$), 16.1 (d, J = 3.0 Hz, OCH$_2$$CH_3$), 16.0 (d, J = 3.0 Hz, OCH$_2$$CH_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1684, 1581 cm^{-1}. HRMS: calcd. for $C_{24}H_{29}O_7P$ [M + H]$^+$: 461.1729; found 461.1731.

3-Oxo-2-phosphono-α-*C*-glycoside 6a: A 1.6 M solution of MeLi in Et_2O (Fluka, 0.2 mL, 0.36 mmol of MeLi) was added at 0 °C to a stirred slurry of CuI (34 mg, 0.18 mmol) in dry Et_2O (0.7 mL). After 10 min the mixture was cooled to –78 °C and a solution of **1a** (33 mg, 0.07 mmol) in dry THF (0.7 mL) was added. After only 3 min TLC analysis (AcOEt) showed the complete disappearance of the starting material. Saturated aqueous NH_4Cl (1 mL) and Et_2O (3 mL) were then added to the reaction mixture. The organic layers were washed with saturated aqueous NH_4Cl (3 × 1 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) to give **6a** (26 mg, 0.06 mmol, 75%) as a viscous oil and as a 96:4 inseparable mixture of α/β diastereomers. Data for **6a**. ^1H NMR: δ = 7.20–7.42 (m, 10 H, 2 Ph), 4.81–5.04 (m, 1 H, 1-H), 4.86 (A of AB, J_{AB} = 11.3 Hz, 1 H, H_A of CH_2Ph), 4.61 (d, $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 4.43–4.57 (m, 2 H, CH_2Ph), 4.40 (B of AB, J_{BA} = 11.3 Hz, 1 H, H_B of CH_2Ph), 4.01–4.24 (m, 4 H, 2 O$CH_2$$CH_3$), 3.93 (dt, $J_{5,4}$ = 9.2, $J_{5,6}$ = 3.0 Hz, 1 H, 5-H), 3.70 (d, $J_{6,5}$ = 3.0 Hz, 2 H, 6-H_A, 6-H_B), 3.02 (dd, J = 23.3, $J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 1.33 (pt, J = 7.0 Hz, 6 H, CH_3, OCH$_2$$CH_3$), 1.19 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$) ppm. ^{13}C NMR: δ = 202.0 (C-3), 138.0, 137.3 (C_{quat}, Ph), 128.4, 128.3, 128.0, 127.7, 127.6 (Ph), 78.0 (C-H), 75.3 (C-H), 73.4, 73.3 (CH_2Ph), 70.5 (d, J = 2.7 Hz, C-1), 69.9 (C-6), 63.2 (d, J = 6.9 Hz, O$CH_2$$CH_3$), 62.9 (d, J = 6.9 Hz, O$CH_2$$CH_3$), 58.7 (d, J = 125.1 Hz, C-2), 20.4 (d, J = 10.7 Hz, CH_3), 16.3, 16.2 (OCH$_2$$CH_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1723 cm^{-1}. HPLC (*n*-hexane/AcOEt 1:1): $t_{R\alpha}$ 18.6 (96%), $t_{R\beta}$ 22.8 (4%). HRMS: calcd. for $C_{25}H_{33}O_7P$ [M + H]$^+$: 477.2042; found 477.2029.

3-Oxo-2-phosphono-α-*C*-glycoside 7a: This compound was prepared from **1a** (30 mg, 0.06 mmol) as in the procedure described for **6a**, followed by column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) to give **7a** (24 mg, 0.05 mmol, 75%) as a viscous oil and as a 96:4 inseparable mixture of α/β diastereomers. Data for **7a**. ^1H NMR: δ = 7.20–7.40 (m, 10 H, 2Ph), 4.87 (A of AB, J_{AB} = 11.2 Hz, 1 H, H_A of CH_2Ph), 4.59–4.68 (m, 1 H, 1-H), 4.57 (d, $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 4.41–4.53 (m, 2 H, CH_2Ph), 4.43 (B of AB, J_{BA} = 11.2 Hz, 1 H, H_B of CH_2Ph), 4.03–4.24 (m, 4 H, 2 O$CH_2$$CH_3$), 3.86 (dt, $J_{5,4}$ = 9.5, $J_{5,6}$ = 3.0 Hz, 1 H, 5-H), 3.72 (d, $J_{6,5}$ = 3.0 Hz, 2 H, 6-H_A, 6-H_B), 3.05 (dd, J = 23.4, $J_{2,1}$ = 2.7 Hz, 1 H, 2-H), 1.47–1.81 (m, 2 H, $CH_2$$CH_3$), 1.32 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 1.19 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 0.95 (t, J = 7.3 Hz, 3 H, $CH_2$$CH_3$) ppm. ^{13}C NMR: δ = 201.9 (C-3), 138.1, 137.4 (C_{quat}, Ph), 128.4, 128.34, 128.30, 128.0, 127.7, 127.6 (Ph), 78.1 (C-H), 75.6 (d, J = 3.4 Hz, C-1), 74.7 (C-H), 73.5, 73.4 (CH_2Ph), 69.9 (C-6), 63.2 (d, J = 6.5 Hz, O$CH_2$$CH_3$), 62.7 (d, J = 6.5 Hz, O$CH_2$$CH_3$), 57.4 (d, J = 125.9 Hz, C-2), 26.3 (d, J = 12.2 Hz, $CH_2$$CH_3$), 16.3, 16.2 (OCH$_2$$CH_3$), 9.7 ($CH_2$$CH_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1720 cm^{-1}. HPLC (*n*-hexane/AcOEt 1:1): $t_{R\alpha}$ 13.0 (96%), $t_{R\beta}$ 11.7 (4%). HRMS: calcd. for $C_{26}H_{35}O_7P$ [M + Na]$^+$: 513.2018; found 513.2026.

3-Oxo-2-phosphono-α-*C*-glycoside 8a: This compound was prepared from **1a** (35 mg, 0.08 mmol) as in the procedure described for **6a**, followed by column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) to give **8a** (30 mg, 0.06 mmol, 75%) as a viscous oil and as a 96:4 inseparable mixture of α/β diastereomers. Data for **8a**. ^1H NMR: δ = 7.19–7.41 (m, 10 H, 2Ph), 4.87 (A of AB, J_{AB} = 11.2 Hz, 1 H, H_A of CH_2Ph), 4.59–4.78 (m, 1 H, 1-H), 4.58 (d, $J_{4,5}$ = 9.4 Hz, 1 H, 4-H), 4.54 (A of AB, J_{AB} = 11.8 Hz, 1 H, H_A of CH_2Ph), 4.46 (B of AB, J_{BA} = 11.8 Hz, 1 H, H_B of CH_2Ph), 4.43 (B of AB, J_{BA} = 11.2 Hz, 1 H, H_B of CH_2Ph), 4.03–4.25 (m, 4 H, 2 O$CH_2$$CH_3$), 3.87 (dt, $J_{5,4}$ = 9.4, $J_{5,6}$ = 3.0 Hz, 1 H, 5-H), 3.71 (d, $J_{6,5}$ = 3.0 Hz, 2 H, 6-H_A, 6-H_B), 3.04 (dd, J = 23.4, $J_{2,1}$ = 2.9 Hz, 1 H, 2-H), 1.24–1.84 [m, 6 H, $(CH_2)_3CH_3$], 1.32 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 1.19 (t, J = 7.0 Hz, 3 H, OCH$_2$$CH_3$), 0.87 [t, J = 7.1 Hz, 3 H, $(CH_2)_3$$CH_3$] ppm. ^{13}C NMR: δ = 201.9 (C-3), 138.1, 137.3 (C_{quat}, Ph), 128.4, 128.33, 128.27, 127.9, 127.7, 127.6 (Ph), 78.1, 74.8 (C-H), 74.2 (d, J = 3.4 Hz, C-1), 73.5, 73.4 (CH_2Ph), 69.9 (C-6), 63.0 (d, J = 6.5 Hz, O$CH_2$$CH_3$), 62.7 (d, J = 6.5 Hz, O$CH_2$$CH_3$), 57.6 (d, J = 125.5 Hz, C-2), 32.9 (d, J = 11.4 Hz,),

27.4, 22.1 [$(CH_2)_3CH_3$], 16.3, 16.2 (OCH_2CH_3), 13.9 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1721 cm^{-1}. HPLC (*n*-hexane/AcOEt 1:1): $t_{R\alpha}$ 7.8 (96%), $t_{R\beta}$ 7.1 (4%). HRMS: calcd. for $C_{28}H_{39}O_7P$ $[M + H]^+$: 519.2512; found 519.2526.

2-Phosphono-α-*C*-glycoside 9a: This compound was prepared from **1a** (50 mg, 0.11 mmol) as in the procedure described for **6a**. The crude product, consisting of a mixture of ketonic and enolic compounds, was treated with Ac_2O (0.01 mL, 0.1 mmol) in Py (1 mL) at 40 °C for 12 h. The solution was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) of the crude compound gave **9a** (38 mg, 0.06 mmol) as a viscous oil and as a 88:12 inseparable mixture of α/β diastereomers. Data for **9a**. ^1H NMR: δ = 7.16–7.58 (m, 15 H, 3Ph), 5.58 (d, J = 5.0 Hz, 1 H, 1-H), 4.31–4.62 (m, 5 H, 2 CH_2Ph, 4-H), 3.63–4.06 (m, 5 H, 2 OCH_2CH_3, 5-H), 3.56 (A of ABX, J_{AB} = 10.9, J_{AX} = 3.7 Hz, 1 H, 6-H_A), 3.44 (B of ABX, J_{BA} = 10.9, J_{BX} = 2.7 Hz, 1 H, 6-H_B), 2.18 (s, 3 H, $OCOCH_3$), 1.24 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 0.97 (t, J = 7.0 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR: δ = 168.6 (C=O), 156.8 (d, J = 3.4 Hz, C-3), 137.8, 137.7, 137.6 (C_{quat}, Ph), 129.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.94, 127.89, 127.7 (Ph), 119.2 (d, J = 178.5 Hz, C-2), 75.7 (d, J = 11.8 Hz, C-1), 74.2, 73.3 (CH_2Ph), 71.3 (d, J = 10.7 Hz, C-4), 70.4 (C-5), 68.7 (C-6), 62.2 (d, J = 5.7 Hz, OCH_2CH_3), 62.0 (d, J = 5.7 Hz, OCH_2CH_3), 20.9 (CH_3), 16.1 (d, J = 6.5 Hz, OCH_2CH_3), 15.9 (d, J = 6.5 Hz, OCH_2CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1757 cm^{-1}. HPLC (*n*-hexane/AcOEt 1:1): $t_{R\alpha}$ 17.4 (88%), $t_{R\beta}$ 19.8 (12%). HRMS: calcd. for $C_{32}H_{37}O_8P$ $[M + H]^+$: 581.2304; found 581.2313.

2-Phosphono-α-*C*-glycoside 6b: This compound was prepared from **1b** (35 mg, 0.08 mmol) as in the procedure described for **6a**. The crude product, consisting of a mixture of ketonic and enolic compounds, was treated with Ac_2O (0.01 mL, 0.1 mmol) in Py (1 mL) at room temp. for 12 h. The solution was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (SiO_2; *n*-hexane/AcOEt, 1:1) of the crude compound gave **6b** (29 mg, 0.06 mmol) as a viscous oil and as an 98:2 inseparable mixture of α/β diastereomers. Data for **6b**. ^1H NMR: δ = 7.18–7.44 (m, 10 H, 2Ph), 4.67–4.83 (m, 1 H, 1-H), 4.63 (s, 2 H, CH_2Ph), 4.59 (A of AB, J_{AB} = 11.9 Hz, 1 H, H_A of CH_2Ph), 4.51 (B of AB, J_{BA} = 11.9 Hz, 1 H, H_B of CH_2Ph), 4.22 (td, $J_{5,6}$ = 6.4, $J_{5,4}$ = 2.6 Hz, 1 H, 5-H), 3.93–4.18 (m, 4 H, 2 OCH_2CH_3), 3.99 (d, $J_{4,5}$ = 2.6 Hz, 1 H, 4-H), 3.73 (A of ABX, J_{AB} = 9.7, J_{AX} = 6.4 Hz, 1 H, 6-H_A), 3.69 (B of ABX, J_{BA} = 9.7, J_{BX} = 6.4 Hz, 1 H, 6-H_B), 2.05 (s, 3 H, $OCOCH_3$), 1.50 (d, $J_{Me,1}$ = 6.6 Hz, 1 H, CH_3), 1.32 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR: δ = 169.0 (C=O), 154.2 (d, J = 3.8 Hz, C-3), 138.0, 137.9 (C_{quat}, Ph), 128.4, 128.3, 128.2, 127.83, 127.77, 127.7 (Ph), 123.9 (d, J = 171.3 Hz, C-2), 73.6, 73.4 (CH_2Ph), 70.5 (d, J = 9.9 Hz, C-4), 70.3 (C-5), 70.2 (d, J = 13.7 Hz, C-1), 68.6 (C-6), 62.2 (d, J = 5.3 Hz, OCH_2CH_3), 62.0 (d, J = 5.3 Hz, OCH_2CH_3), 20.8 (CH_3), 18.5 (CH_3), 16.3 (d, J = 3.8 Hz, OCH_2CH_3), 16.1 (d, J = 4.2 Hz, OCH_2CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1758 cm^{-1}. HPLC (*n*-hexane/AcOEt, 1:1): $t_{R\alpha}$ 20.5 (98%), $t_{R\beta}$ 18.2 (2%). HRMS: calcd. for $C_{27}H_{35}O_8P$ $[M + Na]^+$: 541.1967; found 541.1973.

2-Phosphono-α-*C*-glycoside 7b: This compound was prepared from **1b** (45 mg, 0.10 mmol) as in the procedure described for **6b**, followed by column chromatography (SiO_2; *n*-hexane/AcOEt, 60:40) to give **7b** (37 mg, 0.07 mmol, 70%) as a viscous oil. Data for **7b**. $[\alpha]_D^{20}$ = –93.2 (c = 2.3, $CHCl_3$). ^1H NMR: δ = 7.20–7.40 (m, 10 H, 2 Ph), 4.50–4.68 (m, 4 H, 2 CH_2Ph), 4.37–4.50 (m, 1 H, 1-H), 3.91–4.26 (m, 6 H, 2 OCH_2CH_3, 4-H, 5-H), 3.76 (A of ABX, J_{AB} = 9.6, J_{AX} = 6.4 Hz, 1 H, 6-H_A), 3.72 (B of ABX, J_{BA} = 9.6, J_{BX} = 6.4 Hz, 1 H, 6-H_B), 2.05 (s, 3 H, $OCOCH_3$), 1.65–2.04 (m, 2 H, CH_2CH_3), 1.32 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.04 (t, J = 7.3 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 168.9 (C=O), 154.2 (d, J = 4.2 Hz, C-3), 138.0, 137.9 (C_{quat}, Ph), 128.36, 128.33, 128.1, 127.8, 127.6 (Ph), 123.5 (d, J = 171.3 Hz, C-2), 75.2 (d, J = 14.1 Hz, C-1), 73.6, 73.1 (CH_2Ph), 70.5 (d, J = 9.9 Hz, C-4), 70.0 (C-5), 68.8 (C-6), 62.2 (d, J = 5.3 Hz, OCH_2CH_3), 62.0 (d, J = 5.7 Hz, OCH_2CH_3), 24.5 (CH_2CH_3), 20.8 (CH_3), 16.3 (d, J = 4.2 Hz, OCH_2CH_3), 16.1 (d, J = 4.9 Hz, OCH_2CH_3), 10.7 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1756 cm^{-1}. HPLC (*n*-hexane/AcOEt, 1:1): $t_{R\alpha}$ 15.9 (100%). HRMS: calcd. for $C_{28}H_{37}O_8P$ $[M + Na]^+$: 555.2124; found 555.2112.

2-Phosphono-α-*C*-glycoside 8b: This compound was prepared from **1b** (50 mg, 0.11 mmol) as in the procedure described for **6b**, followed by column chromatography (SiO_2; *n*-hexane/AcOEt, 60:40) to give **8b** (43 mg, 0.08 mmol, 70%) as a viscous oil and as an 94:6 inseparable mixture of α/β diastereomers. Data for **8b**. ^1H NMR: δ = 7.21–7.42 (m, 10 H, 2 Ph), 4.49–4.69 (m, 5 H, 2 CH_2Ph, 1-H), 4.18 (td, $J_{5,6}$ = 6.3, $J_{5,4}$ = 2.5 Hz, 1 H, 5-H), 3.96–4.15 (m, 4 H, 2 OCH_2CH_3), 4.02 (d, $J_{4,5}$ = 2.5 Hz, 1 H, 4-H), 3.79 (A of ABX, J_{AB} = 9.8, J_{AX} = 6.3 Hz, 1 H, 6-H_A), 3.69 (B of ABX, J_{BA} = 9.8, J_{BX} = 6.3 Hz, 1 H, 6-H_B), 2.05 (s, 3 H, $OCOCH_3$), 1.37–2.02 [m, 6 H, $(CH_2)_3CH_3$], 1.32 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 0.90 [t, J = 7.0 Hz, 3 H, $(CH_2)_3CH_3$] ppm. ^{13}C NMR: δ = 168.9 (C=O), 154.1 (d, J = 3.8 Hz, C-3), 138.0, 137.9 (C_{quat}, Ph), 128.3, 128.1, 127.7, 127.6 (Ph), 123.5 (d, J = 171.7 Hz, C-2), 73.8 (d, J = 13.7 Hz, C-1), 73.5, 73.1 (CH_2Ph), 70.6 (d, J = 9.9 Hz, C-4), 70.0 (C-5), 68.8 (C-6), 62.1 (d, J = 5.3 Hz, OCH_2CH_3), 61.9 (d, J = 5.7 Hz, OCH_2CH_3), 30.7, 28.3, 22.1 $[(CH_2)_3CH_3]$, 20.8 (CH_3), 16.2 (d, J = 3.8 Hz, OCH_2CH_3), 16.1 (d, J = 4.6 Hz, OCH_2CH_3), 13.9 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1756 cm^{-1}. HPLC (*n*-hexane/AcOEt, 1:1): $t_{R\alpha}$ 12.6 (94%), $t_{R\beta}$ 14.2 (6%). HRMS: calcd. for $C_{30}H_{41}O_8P$ $[M + Na]^+$: 583.2437; found 583.2422.

2-Phosphono-α-*C*-glycoside 9b: This compound was prepared from **1b** (50 mg, 0.11 mmol) as in the procedure described for **6b**, followed by column chromatography (SiO_2; *n*-hexane/AcOEt, 60:40) to give **9b** (44 mg, 0.08 mmol, 70%) as a viscous oil and as an 97:3 inseparable mixture of α/β diastereomers. Data for **9b**. ^1H NMR: δ = 7.10–7.58 (m, 15 H, 3 Ph), 5.61 (d, J = 5.3 Hz, 1 H, 1-H), 4.7 (s, 2 H, CH_2Ph), 4.39 (A of AB, J_{AB} = 11.7 Hz, 1 H, H_A of CH_2Ph), 4.35 (B of AB, J_{BA} = 11.7 Hz, 1 H, H_B of CH_2Ph), 3.97–4.16 (m, 4 H, OCH_2CH_3, 4-H, 5-H), 3.67–3.92 (m, 2 H, H_A of OCH_2CH_3, 6-H_A), 3.42–3.64 (m, 2 H, H_B of OCH_2CH_3, 6-H_B), 2.14 (s, 3 H, $OCOCH_3$), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 0.88 (t, J = 7.0 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR: δ = 169.4 (C=O), 155.8 (d, J = 3.4 Hz, C-3), 137.9, 137.8, 137.1 (C_{quat}, Ph), 129.4, 128.5, 128.35, 128.27, 128.2, 127.8, 127.7, 127.6 (Ph), 121.4 (d, J = 176.6 Hz, C-2), 75.9 (d, J = 12.2 Hz, C-1), 73.6, 73.2 (CH_2Ph), 70.6 (d, J = 9.9 Hz, C-4), 69.8 (C-5), 68.3 (C-6), 62.3 (d, J = 5.7 Hz, OCH_2CH_3), 62.1 (d, J = 5.7 Hz, OCH_2CH_3), 20.8 (CH_3), 16.2 (d, J = 6.5 Hz, OCH_2CH_3), 15.8 (d, J = 6.1 Hz, OCH_2CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1758 cm^{-1}. HPLC (*n*-hexane/AcOEt, 1:1): $t_{R\alpha}$ 15.8 (97%), $t_{R\beta}$ 18.3 (3%). HRMS: calcd. for $C_{32}H_{37}O_8P$ $[M + H]^+$: 581.2304; found 581.2302.

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[9] The α/β diastereoselectivity was improved when the reactions were carried out in a 1:1 Et_2O/THF solution instead of only Et_2O (Table 1, entries 2 and 3).

[10] We obtained a single diastereoisomer at C(2) as demonstrated by the diastereoisomeric ratios of the acetalization reactions performed on **7a** and **8a** (note c, Table 1).

[11] Partial conversion of the starting enone **4a** was achieved only at higher temperatures and longer reaction times.

[12] The presence of THF in the reaction mixture also improved the α/β diastereoselectivity in this case (Table 2, entry 4).

[13] The addition reaction on enone **4b** required higher temperatures and longer times as in the case of **4a**.

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