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New approach to the enantiomerically pure 1,2,3-trihydroxypropylphosphonates

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Dedicated respectfully to Professor Jan Michalski on the occasion of his 90th birthday

ABSTRACT

The replacement of 2,3-*O*-cyclohexylidene-D-glyceraldehyde with (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde (Ley's aldehyde) has led to significant improvements in the isolation of both diastereoisomers of the respective 2,3-*O*-BDA 1,2,3-trihydroxypropylphosphonates. The triethylamine-catalysed addition of dialkyl phosphites and lithium diethyl phosphonate gave the products in moderate (ca. 1:2) diastereoselectivity while the application of diethyl trimethylsilyl phosphite afforded a 1:9 mixture of diethyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates.

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1. Introduction

Over the decades, numerous applications of phosphonates in medicinal chemistry have been recognised.[1–3] Despite serving as analogues of biologically important phosphates, they also mimic hydroxy- and amino acids in studies on their mode of action in biochemical transformations. For this reason it is necessary for various hydroxy- and aminophosphonates to be synthetically available in an enantiomerically pure form. Recent reviews on the asymmetric syntheses of 1-hydroxyphosphonates[4] and aminophosphonates[5,6] confirmed that this is still an active field of research.

Several years ago, we showed that the enantiomerically pure protected (1*R*,2*R*)- and (1*S*,2*R*)-1,2,3-trihydroxypropylphosphonates could be prepared in good yields when 2,3-*O*-isopropylidene-D-glyceraldehyde **1**[7–10] was replaced with the respective cyclohexylidene acetal **2**.[11,12]

However, in order to achieve the described yields of the enantiomerically pure phosphonates several tedious chromatographic purifications were necessary. For this reason, we looked for the alternative protected glyceraldehydes in order to study the diastereoselectivity of the addition of dialkyl phosphites and, hopefully, to facilitate the chromatographic separation of the respective hydroxyphosphonates. Recently, Ley et al. introduced (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde **3** easily prepared from D-mannitol in two steps (Fig. 1).[13–15]

Since the aldehyde (2*R*,5*R*,6*R*)-**3** contains two additional stereogenic centres when compared to aldehydes (*R*)-**1** and (*R*)-**2,** and the aldehyde functionality is equatorially positioned in a conformationally rigid six-membered ring, one could expect the formation of significantly different ratios of diastereoisomeric hydroxyphosphonates **4a** and **4b**, compared to those produced from D-glyceraldehyde protected as five-membered acetals, that is, **5a** and **5b** (Scheme 1).

The *N*-Boc-aminodiols **8** could be easily transformed into (*R*)- and (*S*)-**6** via oxidative cleavage of the terminal diol moiety followed by immediate $NaBH_4$ reduction of the aldehyde and hydrolysis of the resulting 1-amino-3-hydroxyphosphonates.

Herein, we report the synthesis and separation of diastereoisomeric phosphonates **6a**–**9a** and **6b**–**9b** prepared from the aldehyde **3** and dialkyl phosphites (R = Me, Et, Bn, *i*-Pr), (Scheme 2).

2. Results and discussion

The triethylamine-catalysed addition of dialkyl phosphites (R = Me, Et, Bn, *i*-Pr) to the aldehyde **3** at room temperature was complete in less than 24 h and gave mixtures of phosphonates **6**–**9** (Scheme 1). It was noticed that the diastereoselectivities of the additions were only moderate (Me—30:70; Et—27:73; Bn—35:65; *i*-Pr—25:75) and seem to be only slightly dependent on the size of the alkoxy groups attached to the phosphorus atom. The oily crude products were subjected to chromatographic purification on silica gel columns. From the two diastereoisomeric methyl esters, the minor phosphonate **6a** was separated chromatographically in 7% yield, while the major diastereoisomer was finally purified by crystallisation to give phosphonate **6b** in 59% yield. We succeeded in the isolation of both diastereoisomeric ethyl esters **7a** and **7b**. Compounds **7a** (minor) and **7b** (major) were obtained in 7% and 58% yields, both as crystalline materials. On the other hand, only the major phosphonate **8b** was isolated in 60% yield as colourless oil. Similarly, the major phosphonate **9b** was separated in 55% yield, again, as colourless oil.

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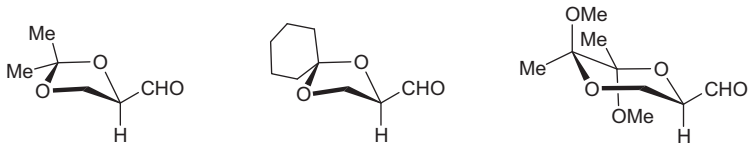
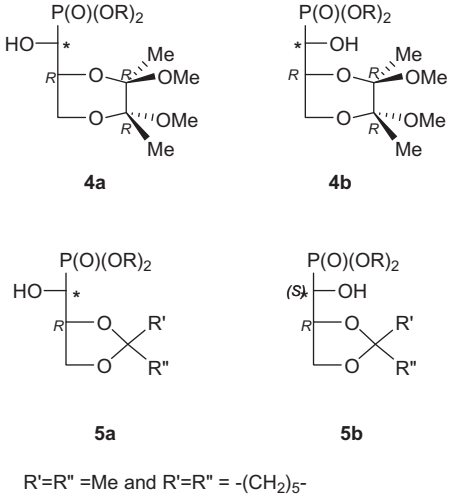


(*R*)-**1** (*R*)-**2** (2*R*,5*R*,6*R*)-**3**

Figure 1. Protected D-glyceraldehydes.

To further study the diastereoselectivity of the addition to the aldehyde **3**, the lithium salt of diethyl phosphite was used. It appeared that a 36:64 mixture of phosphonates **7a** and **7b** was formed. However, due to lack of impurities this mixture was easier to separate and phosphonates **7a** and **7b** were obtained in 18% and 45% yields, respectively, both after column chromatography and crystallisations. We were also interested in the diastereoselectivity of the addition of diethyl trimethylsilyl phosphite. The 1-*O*-silylated phosphonates were deprotected in the presence of fluorides to give a 10:90 mixture of phosphonates **7a** and **7b**. Under these circumstances the major phosphonate **7b** was isolated in 69% yield after crystallisation.

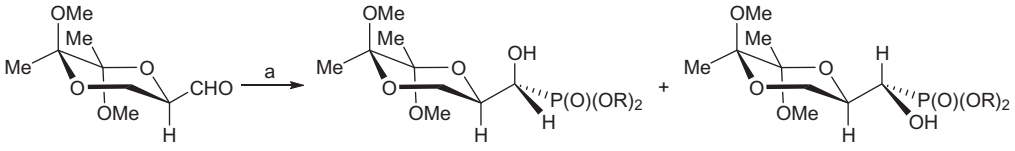
The absolute configurations at C-1 in the diastereoisomeric phosphonates in series **a** and **b** were established in the following way. A 20:80 mixture of phosphonates **7a** and **7b** was subjected to benzylation[16] and then hydrolysed with trifluoroacetic acid[17] to give a 20:80 mixture of the known (1*R*,2*R*)- and (1*S*,2*R*)-1-benzyloxy-2,3-dihydroxypropylphosphonates,[16] (1*R*,2*R*)-**10a** and (1*S*,2*R*)-**10b**, respectively (Scheme 3).



Scheme 1. Stereochemistry of 1-hydroxypropylphosphonates obtained from protected D-glyceraldehydes.

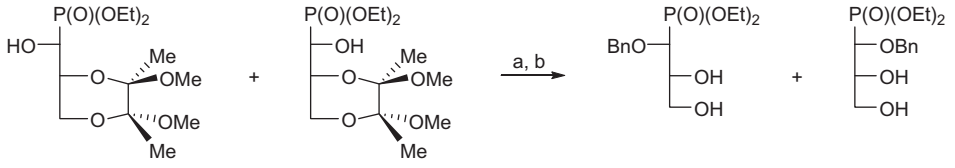
Thus, 1-*O*-benzyl phosphonate (1*R*,2*R*)-**10a** was obtained from minor phosphonates (2*R*,5*R*,6*R*,1′*R*)-**7a** and (1*R*,2*R*)-2,3-*O*-cyclohexylidene-1-hydroxypropylphosphonate (1*R*,2*R*)-**11a**,[11] while both major phosphonates (2*R*,5*R*,6*R*,1′*S*)-**7b** and (1*S*,2*R*)-2,3-*O*-cyclo hexylidene-1-hydroxypropylphosphonate (1*S*,2*R*)-**11b**[11] could be transformed into 1-*O*-benzyl phosphonate (1*S*,2*R*)-**10b**.[16] Based on these observations one may conclude that the stereochemistry of the triethylamine-catalysed addition of diethyl phosphite to the carbonyl group in aldehydes (*R*)-**2** and (2*R*,5*R*,6*R*)-**3** follows the same pattern. Furthermore, since no significant differences in the diastereoselectivities of the addition were observed for the dialkyl phosphites used, we are confident that minor 2,3-BDA-protected phosphonates **6a**, **8a** and **9a** and major 2,3-BDA-protected phosphonates **6b**, **8b** and **9b** have the (2*R*,5*R*,6*R*,1′*R*)- and (2*R*,5*R*,6*R*,1′*S*)-configurations, respectively. Further evidence for our configurational assignments comes from the comparison of the ^{1}H and ^{13}C NMR spectroscopic patterns associated with the substituted propylphosphonate fragment which are almost identical for the minor (series **a**) and major (series **b**) stereoisomers. Finally, all ^{31}P NMR chemical shifts of the minor phosphonates (2*R*,5*R*,6*R*,1′*R*)-**6**–**9a** were observed in a higher field in comparison to those of major phosphonates (2*R*,5*R*,6*R*,1′*S*)-**6**–**9b**. The same relationship was previously noticed for the minor and major phosphonates obtained from 2,3-*O*-isopropylidene-[9,10] and 2,3-*O*-cyclohexylidene-D-glyceraldehyde.[11]

Having established the absolute configurations of the diastereoisomeric 2,3-*O*-BDA-protected phosphonates **6**–**9** conformational studies were performed on the minor **6a**–**8a** and major **6b**–**9b** phosphonates. Based on the vicinal couplings (J_{CCCP} = 12.6–14.3, $J_{H2-H3eq}$ = 3.3–3.4, $J_{H1'-H2}$ = 3.0–3.9 and J_{H2-P} = 4.7–5.1 Hz) observed in the ^{1}H and ^{13}C NMR spectra[18–23] of the minor isomers **6a**–**8a**, one can conclude that in a chloroform solution they exist almost exclusively as single rotamers **12a** (Fig. 2). This conclusion receives additional evidence from the observation of a NOE signal between H1′ and H3eq resonances in the 2D NOESY spectrum of **7a** due to a spatial proximity of these protons in this isomer. Furthermore, the ^{1}H NMR chemical shifts of H1′ and H3eq in the minor isomers: **6a** (3.85 and 3.50 ppm), **7a** (3.77 and 3.55 ppm) and **8a** (3.81 and



(2*R*,5*R*,6*R*)-**3**	R = Me	(2*R*,5*R*,6*R*,1′*R*)-**6a**	(2*R*,5*R*,6*R*,1′*S*)-**6b**
	R = Et	(2*R*,5*R*,6*R*,1′*R*)-**7a**	(2*R*,5*R*,6*R*,1′*S*)-**7b**
	R = Bn	(2*R*,5*R*,6*R*,1′*R*)-**8a**	(2*R*,5*R*,6*R*,1′*S*)-**8b**
	R = *i*-Pr	(2*R*,5*R*,6*R*,1′*R*)-**9a**	(2*R*,5*R*,6*R*,1′*S*)-**9b**

Scheme 2. Addition of dialkyl phosphites to the aldehyde (2*R*,5*R*,6*R*)-**3**. Reagents and conditions: (a) $(RO)_2P(O)H$, 10 mol % NEt_3, rt, 24 h or $(EtO)_2P(O)Li$, −70 °C, 3 h or $(EtO)_2POSiMe_3$, rt, 24 h; Bu_4NF in THF, rt, 1 h.



Scheme 3. Correlation of the absolute configurations of the phosphonates (2*R*,5*R*,6*R*,1′*R*)-**7a** and (2*R*,5*R*,6*R*,1′*S*)-**7b** with (1*R*,2*R*)-**10a** and (1*S*,2*R*)-**10b**. Reagents and conditions: (a) BnBr, Ag_2O, 4 Å MS, CH_2Cl_2, rt, 24 h, 83%; (b) 70% CF_3COOH, rt, 2 h, 92%.

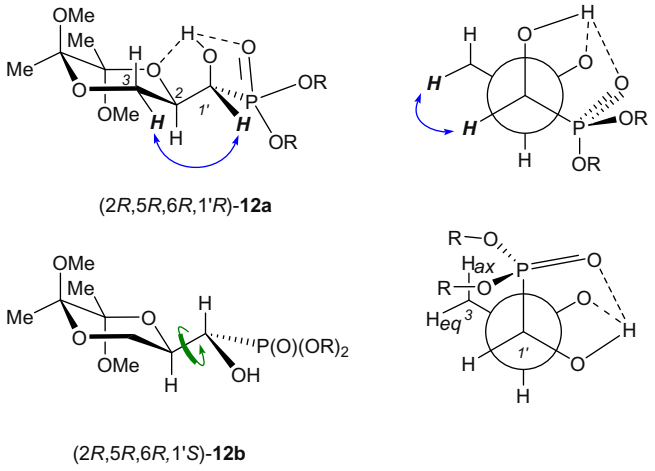


Figure 2. Conformations **12a** and **12b** of the minor and major isomers of phosphonates **7a/8a** and **7b/8b**.

3.46 ppm) are observed at upper field when compared to the shifts of the same protons in the major isomers: **6b** (4.04 and 3.72 ppm), **7b** (3.97 and 3.73 ppm) and **8b** (4.05 and 3.73 ppm). We suggest that the shielding effect of H1′ and H3eq protons in the minor isomers **6a**, **7a** and **8a** originates from the repulsive interactions of the electron densities similar to those in the 1,3-diaxial interactions in six-membered rings.[24]

On the other hand, the 1-hydroxymethylphosphonate fragment freely rotates around the C1′–C2 bond in the major isomers **6b**–**9b**, since the values of diagnostic vicinal couplings $J_{H1'-H2}$ and J_{CCCP} are close to 6 Hz and below 10 Hz, respectively.[18–23]

While looking for the reasons for the conformational stability of minor phosphonates (2*R*,5*R*,6*R*,1′*R*)-**6a**–**8a** we suggest the formation of a strong hydrogen bond as depicted in **12a** (Fig. 2). In this conformation the bulky diethoxyphosphoryl group is located gauche to both the ring oxygen and *H*–C2. On the other hand, in order to observe similar H-bonding in major phosphonates (2*R*,5*R*,6*R*,1′*S*)-**7b/8b** one needs to position the diethoxyphosphoryl group gauche to the ring oxygen and H_{ax}–C3–H_{eq}. However, in this arrangement, serious repulsion of the diethoxyphosphoryl group and hydrogen atoms connected to C3 are expected to make this conformation energetically unfavourable.

3. Conclusions

Ley's aldehyde, (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde **3**, was found to be more effective than 2,3-*O*-cyclohexylidene-D-glyceraldehyde **2** in the syntheses of the respective 1-hydroxyphosphonates greatly facilitating the separation of diastereoisomers. No significant differences in the moderate (ca. 1:2) diastereoselectivities of the triethylamine-catalysed additions of phosphites as well as of lithium diethyl phosphonate were observed for both aldehydes. However, from the aldehyde **3** and diethyl trimethylsilyl phosphate, a 1:9 mixture of diethyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates was obtained.

The absolute configurations of the diastereoisomeric 1-hydroxyphosphonates obtained from Ley's aldehyde were established by chemical correlation with the known diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1-benzyloxy-2,3-dihydoxypropylphosphonates.[16]

The minor 1-hydroxyphosphonates, for example, diethyl (*R*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl] methylphosphonate **7a**, exist as single conformers due to hydrogen bonding, which places the dialkoxyphosphoryl groups in an energetically favoured position, while the (dialkoxyphosphoryl) hydroxymethyl group in the major phosphonates **6b**–**9b** freely rotates around C2–C1′(P) bond.

4. Experimental

The ^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in Hertz. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. 2D NMR (COSY and NOE) measurements were performed on a Bruker Avance III (600 MHz) spectrometer. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin–Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on an Optical Activity PolA-Ar 3001 apparatus. The following absorbents were used: column chromatography, Merck Silica Gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets Silica Gel 60 F_{254}.

4.1. Reaction of dialkyl phosphites 4 with (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxaldehyde (2*R*,5*R*,6*R*)-3 (general procedure)

A mixture of the aldehyde (2*R*,5*R*,6*R*)-**3** (1.10 mmol), dialkyl phosphite (1.00 mmol) and triethylamine (0.10 mmol) was stirred at room temperature for 24 h. After removal of all the volatiles in vacuum (0.1 mm Hg) the oily residue was analysed by ^{1}H and ^{31}P NMR spectroscopy and subjected to chromatographic purification.

4.1.1. Dimethyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates, (2*R*,5*R*,6*R*,1′*R*)-6a and (2*R*,5*R*,6*R*,1′*S*)-6b

After chromatography of the crude product [obtained from the aldehyde (2*R*,5*R*,6*R*)-**3** (0.350 g, 1.71 mmol) and dimethyl phosphite (0.150 mL, 1.62 mmol)] on a silica gel column with chloroform–methanol (gradient: 100:1–50:1, v/v), phosphonate **6a** (0.036 g, 7%) and phosphonate **6b** (0.332 g, 65%) were isolated.

4.1.1.1. Dimethyl phosphonate (2*R*,5*R*,6*R*,1′*R*)-6a. Colourless oil. $[\alpha]_D^{20} = -134.6$ (*c* 0.95, $CHCl_3$). IR (film): ν = 3500, 3223, 2933, 1458, 1374, 1214, 1124, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$):

δ = 4.30 (dddd, J_{2-3ax} = 11.5, J_{2-P} = 4.7, J_{2-1} = 3.4, J_{2-3eq} = 3.4 Hz, 1H, HCCP), 3.91 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.5 Hz, 1H, H_{ax}CCP), 3.85 (d, J = 10.5 Hz, 3H, CH_3OP), 3.84 (dd, J_{1-P} = 11.6, J_{1-2} = 3.4 Hz, 1H, HCP), 3.80 (d, J = 10.7 Hz, 3H, $POCH_3$), 3.50 (dd, $J_{3eq-3ax}$ = 11.5, J_{3eq-2} = 3.4 Hz, 1H, H_{eq}CCP), 3.36 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.50 (br s, 1H, OH), 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$)—spectral data were extracted from the spectrum of a 87:13 mixture of **6a** and **6b**: δ = 99.66 (OCO), 97.98 (OCO), 67.88 (d, J = 161.8 Hz, CP), 66.79 (d, J = 4.5 Hz, *C*CP), 59.87 (d, J = 12.9 Hz, *C*CCP), 53.75 (d, J = 6.3 Hz), 52.97 (d, J = 6.3 Hz), 48.60 and 48.29 (2s, 2 × OCH_3), 17.90 and 17.80 (2s, 2 × CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.65 ppm. Anal. Calcd for $C_{11}H_{23}O_8P$: C, 42.04; H, 7.38. Found: C, 42.10; H, 7.35.

4.1.1.2. Dimethyl phosphonate (2*R*,5*R*,6*R*,1′*S*)-6b. The fractions obtained after chromatography (0.332 g) were recrystallised from ethyl acetate–hexanes to give colourless plates (0.301 g, 59%). Mp 135–137 °C, $[\alpha]_D^{20} = -157.4$ (*c* 1.37, $CHCl_3$). IR (KBr): ν = 3500, 3223, 2933, 1458, 1374, 1214, 1124, 1034 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (dddd, J_{2-3ax} = 11.4, J_{2-P} = 7.5, J_{2-1} = 5.7, J_{2-3eq} = 3.3 Hz, 1H, HCCP), 4.04 (dd, J_{1-P} = 8.4, J_{1-2} = 5.7 Hz, 1H, HCP), 3.91 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.4 Hz, 1H, H_{ax}CCCP), 3.84 (d, J = 10.8 Hz, 3H, CH_3OP), 3.83 (d, J = 10.8 Hz, 3H, $POCH_3$), 3.72 (dd, $J_{3eq-3ax}$ = 11.4, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.32 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 1.65 (br s, 1H, OH), 1.31 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 99.51 (OCO), 98.12 (OCO), 68.56 (d, J = 161.5 Hz, CP), 67.03 (d, J = 4.5 Hz, *C*CP), 60.71 (d, J = 9.8 Hz, *C*CCP), 53.69 (d, J = 6.9 Hz), 53.41 (d, J = 6.9 Hz), 48.38 and 48.20 (2s, 2 × OCH_3), 17.91 and 17.84 (2s, 2 × CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.03 ppm. Anal. Calcd for $C_{11}H_{23}O_8P$: C, 42.04; H, 7.38. Found: C, 42.00; H, 7.23.

4.1.2. Diethyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates, (2*R*,5*R*,6*R*,1′*R*)-7a and (2*R*,5*R*,6*R*,1′*S*)-7b

After chromatography of the crude product [obtained from the aldehyde (2*R*,5*R*,6*R*)-**3** (0.268 g, 1.31 mmol) and diethyl phosphite (0.152 mL, 1.18 mmol)] on a silica gel column with chloroform–methanol (gradient: 100:1–20:1, v/v), phosphonate **7a** (0.055 g, 14%) was obtained. The remaining fractions were chromatographed again on a silica gel column with ethyl acetate–hexane (2:1, v/v) to give phosphonate **7b** (0.280 g, 69%).

4.1.2.1. Diethyl phosphonate (2*R*,5*R*,6*R*,1′*R*)-7a. The fractions obtained after chromatography (0.055 g) were recrystallised from diethyl ether to give colourless plates (0.029 g, 7%). Mp 130–131 °C, $[\alpha]_D^{20} = -143.4$ (*c* 0.90, $CHCl_3$). IR (KBr): ν = 3393, 3273, 2934, 2840, 1234, 1203, 1132, 1025, 968, 879 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30 (dddd, J_{2-3ax} = 11.4, J_{2-P} = 4.8, J_{2-1} = 3.9, J_{2-3eq} = 3.3 Hz, 1H, HCCP), 4.26–4.12 (m, 4H, 2 × CH_2OP), 3.93 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.4 Hz, 1H, H_{ax}CCCP), 3.77 (dd, J_{1-P} = 11.4, J_{1-2} = 3.9 Hz, 1H, HCP), 3.51 (dd, $J_{3ax-3eq}$ = 11.4, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.36 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.0 (br s, 1H, OH), 1.35 (t, J = 7.2 Hz, 6H, 2 × *C*$H_3$$CH_2OP$), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 99.63 (OCO), 97.97 (OCO), 68.15 (d, J = 161.4 Hz, CP), 66.79 (s, *C*CP), 63.09 (d, J = 5.6 Hz), 62.61 (d, J = 6.3 Hz), 60.09 (d, J = 12.6 Hz, *C*CCP), 48.65 and 48.35 (2s, 2 × OCH_3), 17.94 and 17.84 (2s, 2 × CH_3), 16.89 (d, J = 4.5 Hz, *C*$H_3$$CH_2OP$), 16.76 (d, J = 5.1 Hz, *C*$H_3$$CH_2OP$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.06 ppm. Anal. Calcd for $C_{13}H_{27}O_8P$: C, 45.61; H, 7.95. Found: C, 45.90; H, 8.24.

4.1.2.2. Diethyl phosphonate (2*R*,5*R*,6*R*,1′*S*)-7b. The fractions obtained after chromatography (0.280 g) were recrystallised from diethyl ether–hexanes to give colourless plates (0.234 g, 58%). Mp 70–71 °C, $[\alpha]_D^{20} = -142.7$ (*c* 1.1 $CHCl_3$). IR (KBr): ν = 3437, 3254, 2993, 2926, 2836, 1448, 1376, 1212, 1124, 1034, 878 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.23 (dddd, J_{2-3ax} = 11.4, J_{2-P} = 7.8, J_{2-1} = 6.0, J_{2-3eq} = 3.3 Hz, 1H, HCCP), 4.23–4.11 (m, 4H, 2 × CH_2OP), 3.97 (dd, J_{1-P} = 7.5, J_{1-2} = 6.0 Hz, 1H, HCP), 3.86 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.4 Hz, 1H, H_{ax}CCCP), 3.73 (dd, $J_{3ax-3eq}$ = 11.4, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.30 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.0 (br s, 1H, OH), 1.33 (t, J = 7.2 Hz, 6H, 2 × CH_3CH_2OP), 1.28 (s, 6H, 2 × CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 99.56 (OCO), 98.07 (OCO), 68.78 (d, J = 162.0 Hz, CP), 67.09 (d, J = 5.3 Hz, *C*CP), 63.16 (d, J = 6.8 Hz, CH_2OP), 62.88 (d, J = 6.9 Hz, CH_2OP), 60.47 (d, J = 7.9 Hz, *C*CCP), 48.42 and 48.24 (2s, 2 × OCH_3), 17.96 and 17.87 (2s, 2 × CH_3), 16.79 (d, J = 5.9 Hz, *C*H_3CH_2OP), 16.76 (d, J = 6.2 Hz, *C*H_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.63 ppm. Anal. Calcd for $C_{13}H_{27}O_8P$: C, 45.61; H, 7.95. Found: C, 45.83; H, 8.18.

4.1.3. Dibenzyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates, (2*R*,5*R*,6*R*,1′*R*)-8a and (2*R*,5*R*,6*R*,1′*S*)-8b

After chromatography of the crude product [obtained from the aldehyde (2*R*,5*R*,6*R*)-**3** (0.386 g, 1.89 mmol) and dibenzyl phosphite (0.418 mL, 1.89 mmol)] on a silica gel column with ethyl acetate–hexane (2:1, v/v) phosphonate **8b** (0.423 g, 60%) was obtained. The remaining fractions were again chromatographed on a silica gel column with methylene chloride–methanol (100:1, v/v) to give a 9:1 mixture of phosphonates **8a** and **8b** (0.169 g, 24%).

4.1.3.1. Dibenzyl phosphonate (2*R*,5*R*,6*R*,1′*R*)-8a. Colourless oil. (All spectroscopic data of phosphonate **8a** were extracted from spectra of a 9:1 mixture of phosphonates **8a** and **8b**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 10H), 5.12 (d, J = 7.8 Hz, 2H, CH_2Ph), 5.08 (dAB, J_{AB} = 11.7, J = 8.7 Hz, 1H, H_aCH_bPh), 5.02 (dAB, J_{AB} = 11.7, J = 7.8 Hz, 1H, H_aCH_bPh), 4.34 (dddd, J_{2-3ax} = 11.4, J_{2-P} = 5.1, J_{2-3eq} = 3.3, J_{2-1} = 3.0 Hz, 1H, HCCP), 3.91 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.4 Hz, 1H, H_{ax}CCCP), 3.81 (dd, J_{1-P} = 11.4, J_{1-2} = 3.0 Hz, 1H, HCP), 3.46 (dd, $J_{3ax-3eq}$ = 11.4, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.29 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 2.60 (br s, 1H, OH), 1.28 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 136.22 (d, J = 6.0 Hz, $POCH_2C_{ipso}$), 136.06 (d, J = 6.1 Hz, $POCH_2C_{ipso}$), 128.67, 128.64, 128.56, 128.54, 128.14, 128.07, 99.64 (OCO), 97.95 (OCO), 68.43 (d, J = 6.7 Hz, $POCH_2$), 68.34 (d, J = 162.8 Hz, CP), 68.01 (d, J = 6.7 Hz, $POCH_2$), 66.63 (d, J = 2.0 Hz, *C*CP), 59.93 (d, J = 14.3 Hz, *C*CCP), 48.61 and 48.29 (2s, 2 × OCH_3), 17.88 and 17.81 (2s, 2 × CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.95 ppm. Anal. Calcd for $C_{23}H_{31}O_8P$: C, 59.22; H, 6.70. Found: C, 59.00; H, 6.78.

4.1.3.2. Dibenzyl phosphonate (2*R*,5*R*,6*R*,1′*S*)-8b. Colourless oil. $[\alpha]_D^{20} = -84.5$ (*c* 1.40, $CHCl_3$). IR (film): ν = 3270, 2950, 2834, 1456, 1374, 1214, 1144, 1037, 995, 878 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.25 (m, 10H), 5.10 (dAB, J_{AB} = 12.0, J = 8.7 Hz, 1H, H_aCH_bPh), 5.09 (d, J = 7.8 Hz, 2H, CH_2Ph), 5.05 (dAB, J_{AB} = 12.0, J = 8.7 Hz, 1H, H_aCH_bPh), 4.27 (dddd, J_{2-3ax} = 11.7, J_{2-P} = 7.8, J_{2-1} = 5.7, J_{2-3eq} = 3.3 Hz, 1H, HCCP), 4.05 (dd, J_{1-P} = 7.8, J_{1-2} = 5.7 Hz, 1H, HCP), 3.88 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.7 Hz, 1H, H_{ax}CCCP), 3.73 (dd, $J_{3ax-3eq}$ = 11.7, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.26 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.5 (br s, 1H, OH), 1.27 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 136.19 (d, J = 6.3 Hz, $POCH_2C_{ipso}$), 136.15 (d, J = 6.3 Hz, $POCH_2C_{ipso}$), 129.56, 128.54, 128.43, 128.39, 128.10, 127.98, 99.47 (OCO), 98.10 (OCO), 69. 03 (d, J = 161.6 Hz, CP), 68.46 (d, J = 6.8 Hz, $POCH_2$), 68.26 (d, J = 7.5 Hz, $POCH_2$), 67.02 (d, J = 3.9 Hz, *C*CP), 60.34 (d, J = 10.2 Hz, *C*CCP), 48.36 and 48.20 (2s, 2 × OCH_3), 17.88 and 17.84 (2s, 2 × CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.65 ppm. Anal. Calcd for $C_{23}H_{31}O_8P$: C, 59.22; H, 6.70. Found: C, 58.98; H, 6.78.

4.1.4. Diisopropyl (*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates, (2*R*,5*R*,6*R*,1′*R*)-9a and (2*R*,5*R*,6*R*,1′*S*)-9b

After chromatography of the crude product [obtained from the aldehyde (2*R*,5*R*,6*R*)-**3** (0.285 g, 1.40 mmol) and diisopropyl phosphite (0.209 mL, 1.26 mmol)] on a silica gel column with ethyl acetate–hexane (2:1, v/v), phosphonate **9b** (0.256 g, 55%) was obtained as a colourless oil.

4.1.4.1. Diisopropyl phosphonate (2*R*,5*R*,6*R*,1′*S*)-9b. $[\alpha]_D^{20} = -113.2$ (*c* 1.0, $CHCl_3$). IR (film): ν = 3266, 2981, 2948, 1384, 1227, 1144, 1123, 1039, 999, 879 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.90–4.65 (m, 2H, 2 × POC*H*), 4.21 (dddd, J_{2-3ax} = 11.4, J_{2-P} = 6.3, J_{1-2} = 5.4, J_{2-3eq} = 3.3 Hz, 1H, HCCP), 3.93 (dd, J_{1-P} = 7.8, J_{1-2} = 5.4 Hz, 1H, HCP), 3.88 (t, $J_{3ax-3eq} = J_{3ax-2}$ = 11.4 Hz, 1H, H_{ax}CCCP), 3.75 (dd, $J_{3ax-3eq}$ = 11.4, J_{3eq-2} = 3.3 Hz, 1H, H_{eq}CCCP), 3.31 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.80 (br s, 1H, OH), 1.35 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CHOP), 1.34 (d, *J* = 6.0 Hz, 9H, C*H*$_3$CHOP), 1.29 (s, 6H, 2 × CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 99.55 (OCO), 97.95 (OCO), 71.85 (d, *J* = 7.0 Hz, POCH), 71.49 (d, *J* = 7.3 Hz, POCH), 69.06 (d, *J* = 164.3 Hz, CP), 67.31 (d, *J* = 5.5 Hz, *C*CP), 60.37 (d, *J* = 7.7 Hz, *C*CCP), 48.42 and 48.22 (2s, 2 × OCH_3), 24.47 (d, *J* = 5.4 Hz), 24.42 (d, *J* = 5.7 Hz), 24.27 (d, *J* = 5.0 Hz), 24.24 (d, *J* = 5.4 Hz), 17.97 and 17.87 (2s, 2 × CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 21.08 ppm. Anal. Calcd for $C_{15}H_{31}O_8P$: C, 48.64; H, 8.44. Found: C, 48.39; H, 8.72.

4.2. Reaction of the lithium salt of diethyl phosphite with (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxaldehyde (2*R*,5*R*,6*R*)-3

To a solution of lithium diethyl phosphonate [from diethyl phosphite (0.258 mL, 2.00 mmol), diisopropylamine (0.28 mL, 2.0 mmol) and 1.6 M butyl lithium (1.25 mL, 2.0 mmol)] in THF (5 mL) cooled to −70 °C, was added the aldehyde (2*R*,5*R*,6*R*)-**3** (0.448 g, 2.20 mmol) in THF (2 mL). The reaction mixture was stirred at this temperature for 3 h and allowed to reach −10 °C. A saturated aqueous ammonium chloride solution (3 mL) was added followed by methylene chloride (20 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and subjected to column chromatography on silica gel with chloroform–methanol (100:1, v/v) to give phosphonate **7a,** (0.180 g, 29%) which was recrystallised from ether–hexane to provide crystalline **7a,** (0.115 g, 18%) which was in all respects identical to material described above. The remaining fractions were combined and chromatographed on a silica gel column with ethyl acetate–hexane (2:1, v/v) to give phosphonate **7b** (0.350 g, 56%) which was recrystallised from diethyl ether–hexanes to give colourless plates (0.280 g, 45%), and was in all respects identical with the material described earlier.

4.3. Reaction of diethyl trimethylsilyl phosphite with (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxaldehyde (2*R*,5*R*,6*R*)-3

To a solution of the aldehyde (2*R*,5*R*,6*R*)-**3** (0.355 g, 1.65 mmol) in methylene chloride (2 mL), diethyl trimethylsilyl phosphite (0.34 mL, 1.5 mmol) was added dropwise at room temperature. The reaction mixture was left at this temperature overnight, then concentrated and treated with tetrabutylammonium fluoride (1 M, 2.0 mL, 2.0 mmol) for 1 h. After removal of all volatiles the residue was filtered through a pad of silica gel as a chloroform solution. The crude product was subjected to silica gel chromatography with ethyl acetate–hexane (2:1, v/v) to give phosphonate **7b** (0.350 g, 68%), which was identical to the material described earlier.

4.4. Benzylation and hydrolysis of a mixture of diethyl phosphonates (2*R*,5*R*,6*R*,1′*R*)-7a and (2*R*,5*R*,6*R*,1′*S*)-7b

To a solution of a 20:80 mixture of diethyl phosphonates (2*R*,5*R*,6*R*,1′*R*)-**7a** and (2*R*,5*R*,6*R*,1′*S*)-**7b** (0.050 g, 0.15 mmol) in CH_2Cl_2 (4 mL) powdered molecular sieves (0.2 g) were added followed by Ag_2O (0.054 g, 0.23 mmol) and benzyl bromide (0.036 mL, 0.29 mmol). The suspension was stirred at room temperature for 24 h. After standard work-up[16] a 20:80 mixture of crude 1-*O*-benzyl derivatives was obtained (0.052 g, 83%). This mixture was treated at room temperature with 70% CF_3COOH (2.5 mL) for 2 h, concentrated in vacuo and co-evaporated with dioxane (5 × 3 mL). The residue was chromatographed on a silica gel column with chloroform–methanol (50:1, v/v) to give a 20:80 mixture of phosphonates (2*R*,5*R*,6*R*,1′*R*)-**10a** and (2*R*,5*R*,6*R*,1′*S*)-**10b** (0.034 g, 92%), which was identical in all respects to the compounds described earlier.[16]

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