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Synthesis of enantiomeric diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1,2,3-trihydroxypropylphosphonates

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Abstract

Addition of diethyl phosphite to 2,3-*O*-cyclohexylidene-D-glyceraldehyde catalyzed by triethylamine or fluorides led to *ca.* 35:65 mixtures of diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonates (**4a**) and (**4b**). Application of lithium diethylphosphonate only slightly improved diastereoselectivity. Through chromatographic separation of **4a** and **4b** the protected trihydroxypropylphosphonates became available for the first time as pure enantiomers. The 1*S* configuration in the major diastereoisomer **4b** was assigned on the basis of conformational and configurational analysis of 1,2-*O*-isopropylidene derivatives obtained from the title compounds.

Key words: diastereoselection; phosphonic acids and derivatives; dioxolanes; configuration.

The importance of phosphonic acids in medicinal chemistry is well recognized [1,2]. Numerous examples of inhibitory properties towards several enzymes, as well as antiviral, antibacterial and fungicidal activities have been reported in recent years. The phosphonic and also phosphinic groups can mimic phosphates and carboxylic acids in biologically important compounds, and the corresponding phosphonate (phosphinate) analogs are very useful in studies of metabolic processes. The synthesis of sugar surrogates having phosphorus instead of the ring-oxygen [3] and in the anomeric position of five- [4-6] and six-membered [7-9] rings have also been accomplished. Starting materials for these sugar analogs are easily available from sugar aldehydes and dialkyl phosphite *via* the Abramov reaction [10]. Several years ago one of us described the synthesis of three enantiomeric dimethyl 1,2,3,4-tetrahydroxybutylphosphonates [11] and showed that intramolecular cyclization of these compounds provided analogs of furanosides having phosphorus in the anomeric position [4-6]. Recently, our interest in these area has been focused on 1,2,3-trihydroxypropylphosphonates as possible starting materials for the synthesis of functionalized three-carbon phosphonates. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) [12] could be the best sugar aldehyde for this purpose if the respective diastereoisomeric phosphonates **3a** and **3b** would have been separable. Although several research groups reported the synthesis of various mixtures of **3a** and **3b** (R=CH_2Ph, no ratio given [13]; R=Me,

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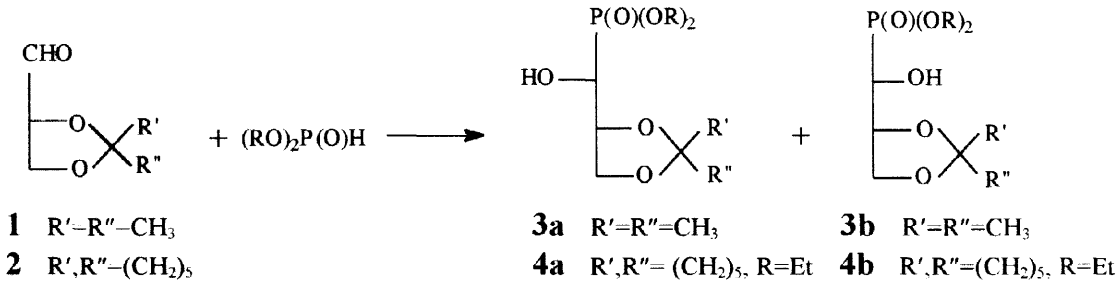
41:59 [14]; R=Me, 35:65 [15,16]) and even the absolute configuration of the major isomer has been established by NMR spectroscopy of Mosher esters [16], no one succeded in separation of **3a** and **3b**. Herein, we wish to describe the synthesis and separation of diastereoisomeric phosphonates **4a** and **4b** obtained from 2,3-*O*-cyclohexylidene-D-glyceraldehyde [17-19] and diethyl phosphite.



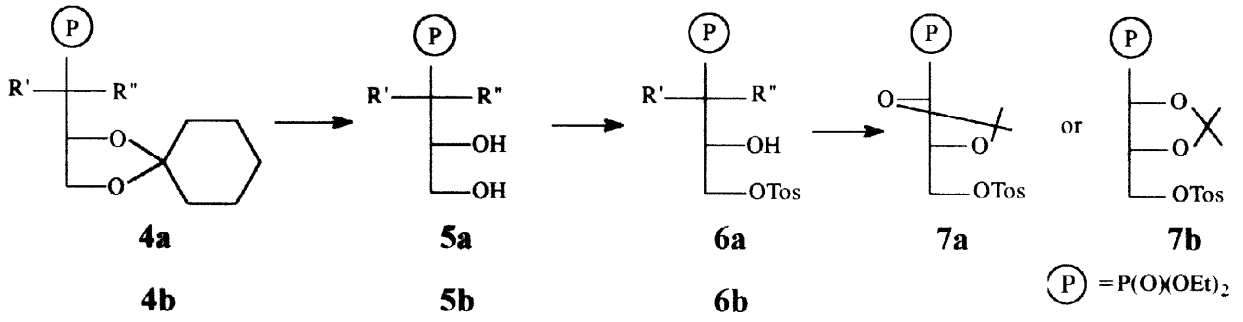
Results and Discussion

Addition of a catalytic amount of triethylamine to a 1:0.95 mixture of **2** and diethyl phosphite gave diastereoisomeric phosphonates **4a** and **4b** in a 35:65 ratio almost quantitatively. They were separated by column chromatography on silica gel to give **4a** (δ ^{31}P 21.55 ppm, 29%), a mixture of **4a** and **4b** (19%) and **4b** (δ ^{31}P 22.25 ppm, 49%). Besides ^{31}P NMR spectroscopy also ^{1}H NMR spectra (100 MHz) were found useful in monitoring the progress of chromatography because *H*-O-C-P resonances for **4a** were always upfield in comparison with those of **4b** and they showed two different coupling patterns. Vicinal *H*-O-C1-*H* coupling constants of 6.8-7.0 Hz and 4.7 Hz, and *P*-C1-O-*H* couplings of 10.6-11.2 Hz and 13.2-14.6 Hz were observed for **4a** and **4b**, respectively. More polar diastereoisomer solidified on standing, and later was recrystallized from hexanes.

Although the diastereoisomeric ratio of **4a** and **4b** obtained in the triethylamine-catalyzed Abramov reaction satisfied our requirement for synthetic availability of both phosphonates we studied the addition of diethyl phosphite and its derivatives to the aldehyde **2** in the presence of other catalysts. No changes in a **4a/4b** ratio were noticed when anhydrous KF (37:63), KF dihydrate (39:61) or CsF (37:63) were used [20]. Addition of lithium diethyl phosphonate to **2** slightly improved stereoselectivity (26:74).

Recently, Yamamoto [15] and Hammerschmidt [16] have assigned the *S* configuration to the major diastereoisomer **3b** obtained from 2,3-*O*-isopropylidene-D-glyceraldehyde and dimethyl phosphite. Based on these findings our major diastereoisomer **4b** also has the *S* configuration because ^{1}H NMR spectral data for the **4a/3a** [15,16] and **4b/3b** [15,16] pairs are almost identical for the comparable parts of the molecules, *i.e.* H-1,2,3a,3b, and the ^{31}P NMR chemical shifts of **3a** [15] and **4a** are upfield in comparison with those of **3b** [15] and **4b**. Furthermore, optical rotation of **4a** is negative, and positive for **4b**, in agreement with Yamamoto's observations for the respective series [15].

Our independent approach to the assignment of the absolute configuration at C-1 in **4a** and **4b** was based on the following sequence of transformations.



a series (R'=OH, R"=H) **b** series (R'=H, R"=OH)

Hydrolysis of the cyclohexylidene groups in **4a** and **4b** provided the title compounds **5a** and **5b** in 94% and 95% yield, respectively. The future introduction of the isopropylidene acetal (**6**→**7**) excluded the selective protection of the primary hydroxy functions in **5a** and **5b** with the acid-labile triphenylmethyl or *t*-butyldimethylsilyl groups. Because of the limited selectivity of *p*-toluenesulfonylation for primary *vs.* secondary hydroxy groups 3-*O*-tosylates **6a** and **6b** were obtained in 51% and 55% yield, respectively. Analyses of the ^{31}P NMR spectra of crude products after tosylation showed the presence of **6a** (86%) contaminated with minute quantities (4-5%) of ditosylates when **5a** was used, while from **5b** a mixture of **6b** (70%), **8b** (16%), **9b** (14%) and a trace of **10b** was formed. Identification of ditosylates **8b** and **9b** was based on ^{1}H NMR spectral data (see Experimental). Isopropylidenation of monotosylates **6a** and **6b** was accomplished with 2,2-dimethoxypropane [21] to give (4*R*,5*R*)-**7a** (77%) and (4*S*,5*R*)-**7b** (66%), respectively.

From the ^{1}H and ^{13}C NMR spectra of **7a** and **7b** the vicinal coupling constants were calculated: H4-C4-C5-H5 (9.2 and 7.3 Hz), P-C4-C5-H5 (11.7 and 16.4 Hz), P-C4-C5-C5′ (4.1 and 3.5 Hz) and P-C4-O-C2 (10.6 and 9.8 Hz), respectively. Although to the best of our knowledge the angular dependence of ^{3}J(PCOC) *vs.* φ(PCOC) is unknown the PCOC coupling of 10.6 Hz in **7a** can be attained for the ^{2}E, $_{3}$E, ^{4}E and $_{5}$E conformations of the 1,3-dioxolane ring. The values of ^{3}J(H4-H5) = 9.2 Hz [22] and ^{3}J(H5-P) = 11.7 Hz [23] are in a good agreement with the ^{4}E conformation of **7a** (Figure 1). However, ^{3}J(PCCC) = 4.1 Hz is surprisingly large for the PCCC dihedral angle of *ca.* 80° [24,25]. In the ^{4}E conformation of **7a** the bulky diethoxyphosphinyl and *p*-toluenesulfonyloxymethyl groups are placed in the energetically favored equatorial positions. In a similar manner the preferred conformation of **7b** was established as ^{1}T$_{2}$ (Figure 1).

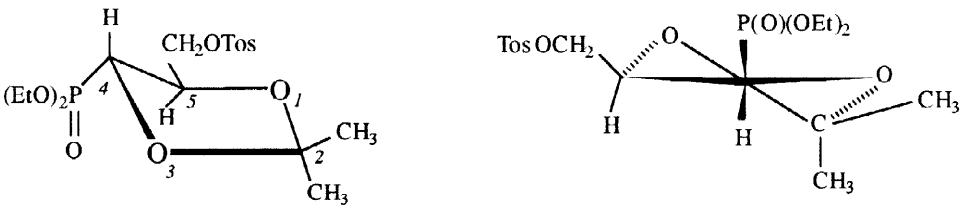


Figure 1. The preferred conformations of **7a** (left) and **7b** (right).

Recently, Shibuya [26] has studied the asymmetric dihydroxylation of diethyl vinylphosphonates and confirmed the relative stereochemistry of the prepared *threo*-α,β-dihydroxyphosphonates only on the basis of ^{3}J(H-P). During these studies he obtained (4*R*,5*R*)-

4-(diethoxyphosphinyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (**11**) and its enantiomer. Although the value of ^3J(H-P) for **11** was not disclosed the rest of the ^{1}H NMR data, especially ^3J(H4-H5) = 9.4 Hz, compares well to those for **7a**, and the ^{31}P NMR chemical shift for **11** (19.7 ppm) is very close to that observed for **7a** (19.2 ppm).

The configurational assignments made by Shibuya [26] were based on a large value of ^3J(P-H) (17.2 Hz) for the *trans*-dioxolane and assumption of a small value of ^3J(P-H) (1.7 Hz) for the *cis*-isomer. Although ^3J(P-H) couplings for the *trans*-dioxolanes (10.1 and 9.8 Hz [26] and 9.2 Hz for **7a**) are close each other, the observed value of ^3J(P-H) for the *cis*-dioxolane **7b** is an order of magnitude larger than expected (16.4 Hz *vs.* 1.7 Hz). For this reason the confirmational analysis of both diastereoisomeric 1,3-dioxolanes **7a** and **7b** was conducted.

In conclusion, we have developed an efficient method for the synthesis of enantiomerically pure 1,2,3-trihydroxypropylphosphonates. Conformational analysis of both diastereoisomeric 1,3-dioxolanes prepared by isopropylidenation of 3-*O*-protected trihydroxypropylphosphonates allowed for unequivocal assignment of the absolute configuration at C-1. Studies on synthetic applications of enantiomeric three-carbon phosphonate chirons, especially in glyco-mimetic chemistry [27], are in progress in this laboratory.

Experimental

^{1}H NMR spectra were taken in $CDCl_3$ on the following spectrometers: Tesla BM 567 (100 MHz), Bruker DPX (250 MHz) and Bruker DRX (500 MHz) with TMS as an internal standard. ^{13}C and ^{31}P NMR spectra were recorded for $CDCl_3$ solutions on a Bruker DPX spectrometer at 62.9 and 101.25 MHz, respectively. IR spectral data were obtained 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 Institute on a Perkin Elmer PE 2400 CHNS analyzer. Optical rotations were measured on a Polamat A polarimeter (Carl Zeiss Jena) in a 1 dm tube.

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}. TLC plates were developed in various $CHCl_3/CH_3OH$ solvent systems. Visualization of spots was effected with iodine vapours.

All solvents were purified by methods described in the literature.

1,2;5,6-*O*-Cyclohexylidene-D-mannitol was obtained in 61% yield according to the literature procedure [18,28]; m.p. 106.5-107°C; lit. [18] m.p. 105-106°C; lit. [28] 104-105°C; lit. [29] 104-106°C.

2,3-O-Cyclohexylidene-D-glyceraldehyde (**2**) [30]. A solution of 1,2;5,6-*O*-cyclohexylidene-D-mannitol (6.84 g, 0.020 mol) in ether (60 ml) was warmed to 30°C and water (40 ml) was added. Sodium metaperiodate (5.20 g, 0.024 mol) was added in one portion followed by $NaHCO_3$ (0.12 g) to bring pH to ~7. After 1 h at 30° the reaction mixture was cooled and saturated with solid NaCl. Ether layer was separated and water phase was extracted with CH_2Cl_2 (6 x 20 ml). Organic extracts were dried ($MgSO_4$), concentrated and the colorless residue was distilled (b.p. 46-50°/0.15 mm Hg) to give **2** (5.213 g, 76%); $[\alpha]^{25}_{578}$ = +62.8 (*c* 3.36, benzene);

lit. [17] $[\alpha]^{23}$ +60.5 (*c* 3.5, benzene); lit. [18] $[\alpha]^{25}$ +61.5° (*c* 3.4, benzene); lit. [29] $[\alpha]_D^{20}$ +60.68 (*c* 3.4, benzene).

Diethyl (1R,2R)- and (1S,2R)-2,3-O-cyclohexylidene-1,2,3-trihydroxypropylphosphonates (**4a**) *and* (**4b**). a) To a mixture of **2** (5.213 g, 30.5 mmol) and diethyl phosphite (3.72 ml, 29.0 mmol) triethylamine (0.424 ml, 3.05 mmol) was added. The reaction mixture soon became warm and viscous. ^{31}P NMR spectrum of the crude product revealed the presence of a 35:65 mixture of **4a** and **4b**.

b) To a suspention of the fluoride (anhydrous KF - 2.48 g, 42.6 mmol; KF dihydrate - 4.01 g, 42.6 mmol, or CsF - 3.30 g, 15.2 mmol) in diethyl phosphite (1.09 g, 7.9 mmol) a solution of **2** (1.45 g, 8.52 mmol) in methylene dichloride (1.0 ml) was added dropwise at room temperature. After stirring for 24 h the fluorides were filtered off, washed with CH_2Cl_2 (10 ml), and the solution was concentrated *in vacuo* to leave mixtures of **4a** and **4b** (see Results) in almost quantitative yields.

c) To a solution of LDA (from 0.78 ml - 5.5 mmol of diisopropylamine and 2.2 ml, 2.5 *M* *n*-BuLi in hexanes) in THF (12 ml) cooled to -60°C diethyl phosphite (0.71 ml, 5.9 mmol) was added and the reaction mixture was stirred for 2 h at this temperature. A solution of **2** (1.00 g, 5.9 mmol) in THF (12 ml) was added dropwise at -60°C and after 30 minutes the reaction mixture was allowed to reach room temperature (1 h). After addition of saturated aqueous NH_4Cl (20 ml) the water phase was extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave a 26:74 mixture of **4a** and **4b** (1.66 g, 92%) as a colorless oil.

Separation of **4a** *and* **4b.** Crude phosphonates **4a** and **4b** (15.09 g) obtained from total of 8.55 g (50.2 mmol) of **2** were collected and subjected to column chromatography on silica gel (300 g) using chloroform-methanol (100:1, v/v). The appropriate fractions were united to give: **4a** (4.50 g, 29%), a mixture of **4a** and **4b** (2.9 g, 19%) and **4b** (7.6 g, 49%).

4a: colorless syrup. $[\alpha]^{25}_{578}$ = -7.0 (*c* = 5.0 in $CHCl_3$). IR (film): ν = 3304, 1234 cm^{-1}. ^{1}H NMR: δ = 4.45 (ddt, $J_{1\text{-}2}$ = 5.0, $J_{2\text{-}3a}$ = 6.6, $J_{2\text{-}3b}$ = 6.4 Hz, $J_{2\text{-}P}$ = 4.0 Hz, 1H, H-2), 4.18 (m, 4H, C*H*$_2$OP), 4.07 (dAB, J_{AB} = 8.5 Hz, 1H, H-3b), 3.92 (dAB, 1H, H-3a), 3.80 (dd, $J_{1\text{-}P}$ = 9.5 Hz, 1H, H-1), 2.73 (brs, 1H, OH), 1.70-1.50 (m, 8H, 4 CH_2), 1.45-1.30 (m, 2H, CH_2), 1.34 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$). ^{13}C NMR: δ = 110.23 (s, OCO), 74.37 (d, ^2J = 3.8 Hz, C-2), 68.22 (d, ^1J = 162.1 Hz, C-1), 65.59 (d, ^3J = 7.7 Hz, C-3), 62.86 and 62.52 (2d, ^2J = 6.8 Hz, *C*OP), 35.97, 34.69, 24.88, 23.78, 23.59 (5s, CH_2), 16.29 and 16.23 (2d, *J* = 5.0 Hz, *C*COP). ^{31}P NMR: δ = 21.55. Anal. calcd. for $C_{13}H_{25}O_6P$ (308.31): C, 50.06; H, 8.17. Found: C, 50.33; H, 8.30%.

4b: m.p. 55-56°C (hexanes). $[\alpha]^{25}_{578}$ +2.3 (*c* = 5.3 in $CHCl_3$). IR (KBr): ν = 3270, 1246 cm^{-1}. ^{1}H NMR: δ = 4.39 (ddt, $J_{1\text{-}2}$ = 4.5, $J_{2\text{-}3a}$ = 6.5, $J_{2\text{-}3b}$ = 6.4, $J_{2\text{-}P}$ = 2.9 Hz, 1H, H-2), 4.19 (m, 4H, C*H*$_2$OP), 4.11 (dd, $J_{1\text{-}P}$ = 8.4 Hz, 1H, H-1), 4.10 (dAB, J_{AB} = 8.7 Hz, 1H, H-3b), 4.06 (dAB, 1H, H-3a), 2.50 (brs, 1H, OH), 1.70-1.50 (m, 8H, 4 CH_2), 1.45-1.30 (m, 2H, CH_2), 1.34 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$). ^{13}C NMR: δ = 109.68 (s, OCO), 74.61 (d, ^2J = 7.0 Hz, C-2), 67.79 (d, ^1J = 161.2 Hz, C-1), 64.87 (d, ^2J = 6.5 Hz, C-3), 62.90 and 62.62 (2d, ^2J = 7.0 Hz, *C*OP), 35.90, 34.73, 25.01, 23.83, 23.67 (5s, CH_2), 16.33 (d, ^3J = 5.5 Hz, *C*COP). ^{31}P NMR: δ = 22.25. Anal. calcd. for $C_{13}H_{25}O_6P$ (308.31): C, 50.06; H, 8.17. Found: C, 50.61; H, 8.29%.

Hydrolysis of the cyclohexylidene group in **4a** *and* **4b** *(general procedure).* A solution of the cyclohexylidene derivative **4a** or **4b** (1.50 mmol) in dioxane (12 ml) containing 0.1 *M* HCl (16 ml) was left at room temperature for 60 h. Volatiles were removed *in vacuo*, the residue was coevaporated with anhydrous dioxane (6 x 10 ml) and dried ($MgSO_4$) as a solution in CH_2Cl_2. Removal of the solvent left crude **5a** or **5b** which were further purified on a silica gel column with chloroform-methanol (20:1, v/v).

Diethyl (1R,2R)-1,2,3-trihydroxypropylphosphonate (**5a**): yield 94%, colorless syrup. $[\alpha]^{25}_{578}$ = -6.8 (*c* = 2.7 in $CHCl_3$). IR (film): ν = 3324, 1217 cm^{-1}. ^1H NMR: δ = 4.35-4.15 (m, 6H, CH_2OP, H-1, H-2), 4.1-3.95 (m, 2H, CH_2), 3.8-3.65 (brs, 2H, OH), 3.45-3.3 (brs, 1H, OH), 1.36 (t, *J* = 7.1 Hz, 6H, CH_3CH_2). ^{13}C NMR: δ = 70.88 (d, ^2J = 3.0 Hz, C-2), 67.93 (d, ^1J = 163.5 Hz, C-1), 63.43 (d, ^2J = 6.9 Hz, COP), 62.93 (d, ^3J = 11.6 Hz, C-3), 62.83 (d, ^2J = 7.2 Hz, COP), 16.42 and 16.37 (2d, ^3J = 5.7 Hz, *C*COP). ^{31}P NMR: δ = 23.25. Anal. calcd. for $C_7H_{17}O_6P$ (228.20): C, 36.84; H, 7.51. Found: C, 36.94; H, 7.98%.

Diethyl (1S,2R)-1,2,3-trihydroxypropylphosphonate (**5b**): yield 95%, waxy solid, m.p. 45-47°C. $[\alpha]^{25}_{578}$ = +3.0 (*c*, 5 in $CHCl_3$). IR (KBr): ν = 3313, 1218 cm^{-1}. ^1H NMR-500 MHz: δ = 4.28-4.16 (m, 4H, CH_2OP), 4.02 (ddd ≈ q, $J_{1\text{-}P} \approx J_{1\text{-}3} \approx J_{1\text{-}OH} \approx 7.5$ Hz, 1H, H-1), 3.99-3.93 (m, 1H, H-2), 3.94-3.88 (ddAB, J_{AB} = 11.6, $J_{3b\text{-}OH}$ = 6.5, $J_{2\text{-}3b}$ = 4.2 Hz, 1H, H-3b), 3.88-3.82 (ddAB, $J_{3a\text{-}OH}$ = 6.5 Hz, $J_{2\text{-}3a}$ = 4.2 Hz, 1H, H-3a), 3.48 (d, $J_{2\text{-}OH}$ = 5.5 Hz, 1H, HO-C-2), 3.09 (t, $J_{3\text{-}OH}$ = 7.5 Hz, 1H, HO-C-3), 2.86 (t, $J_{1\text{-}OH} = J_{PC1OH}$ = 6.5 Hz, 1H, HO-C-1), 1.379 and 1.375 (2t, *J* = 7.0 Hz, 6H, CH_3CH_2). ^{13}C NMR: δ = 72.02 (d, ^2J = 4.8 Hz, C-2), 69.25 (d, ^1J = 161.2 Hz, C-1), 63.36 (d, ^3J = 7.7 Hz, C-3), 63.64 and 63.26 (2d, ^3J = 7.0 Hz, *C*OP), 16.77 and 16.74 (2d, ^3J = 5.7 Hz, *C*COP). ^{31}P NMR: δ = 24.79. Anal. calcd. for $C_7H_{17}O_6P$ (228.20): C, 36.84; H, 7.51. Found: C, 36.60; H, 7.73%.

p-Toluenesulfonylation of **5a** *and* **5b** *(general procedure).* A solution of the triol (1.0 mmol) and *p*-toluenesulfonyl chloride (1.2 mmol) in pyridine (1 ml) was left at 5°C for 60 h. After addition of cold HCl (5%, 10 ml), an aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml). Organic extracts were washed with water, dried ($MgSO_4$) and concentrated. The crude products were purified on silica gel with chloroform-methanol (50:1, v/v).

From **5a** (210 mg, 0.92 mmol) after chromatographic purification of the crude product (270 mg) diethyl (1*R*,2*R*)-1,2-dihydroxy-3-(*p*-toluenesulfonyloxy)propylphosphonate (**6a**) (179 mg, 51%) was obtained as a colorless oil. IR (film): ν = 3300, 1213, 816 cm^{-1}. ^1H NMR: δ = 7.80 and 7.34 (2d, *J* = 8.2 Hz, 2 x 2H, C_6H_4), 4.3-3.8 (m, 10H, CH_2OP, H-1,2,3a,3b, 2 OH), 2.45 (s, 3H, $CH_3C_6H_4$), 1.34 and 1.33 (2t, *J* = 7.0 Hz, 6H, CH_3CH_2). ^{31}P NMR: δ = 23.09. Anal. calcd. for $C_{14}H_{23}O_8PS$: C, 43.97; H, 6.07. Found: C, 44.15; H, 6.27%.

From **5b** (887 mg, 3.89 mmol) after chromatographic purification of the crude product (1.47 g) diethyl (1*S*,2*R*)-1,2-dihydroxy-3-(*p*-toluenesulfonyloxy)propylphosphonate (**6b**) (826 mg, 55%) was obtained as a colorless oil. ^1H NMR: δ = 7.85 and 7.35 (2d, *J* = 8.5 Hz, 2 x 2H, C_6H_4), 4.4-4.0 (m, 8H, CH_2OP, H-1,2,3a,3b), 4.0-3.8 (brs, 2H, OH), 2.44 (s, 3H, $CH_3C_6H_4$), 1.33 and 1.32 (2t, *J* = 7.0 Hz, 6H, CH_3CH_2). ^{31}P NMR: δ = 23.16. Anal. calcd. for $C_{14}H_{23}O_8PS$: C, 43.97; H, 6.07. Found: C, 43.37; H, 6.07%.

From two less polar fractions diethyl (1*S*,2*R*)-1-hydroxy-2,3-bis-(*p*-toluenesulfonyloxy)-propylphosphonate (**8b**) and diethyl (1*S*,2*R*)-2-hydroxy-1,3-bis(*p*-toluenesulfonyloxy)propylphosphonate (**9b**) were obtained after rechromatography.

8b: ^{1}H NMR: δ = 7.9-7.6 and 7.5-7.3 (2m, C_6H_4), 5.0-4.8 (m, H-2), 4.5-4.0 (m, CH_2OP, H-1,3a,3b), 2.44 (s, $CH_3C_6H_4$), 1.33 (t, J = 7.0 Hz, CH_3CH_2). ^{31}P NMR: δ = 19.01.

9b: ^{1}H NMR: δ = 7.9-7.6 and 7.5-7.3 (2m, C_6H_4), 4.90 (dd, J = 4.3, J = 11.8 Hz, H-1), 4.5-4.0 (m, CH_2OP, H-2,3a,3b), 2.47 and 2.45 (2s, $CH_3C_6H_4$), 1.29 (t, J = 7.3 Hz, CH_3CH_2). ^{31}P NMR: δ = 15.79.

Diethyl (1S,2R)-1,2,3-tris(p-toluenesulfonyloxy)propylphosphonate (**10b**). A mixture of di-*O*-tosylates **8b** and **9b** (377 mg, 0.70 mmol) was dissolved in pyridine (0.7 ml) and *p*-toluenesulfonyl chloride (164 mg, 0.84 mmol) was added at room temperature. After 24 h cold 10% HCl (7 ml) was added and the water phase was extracted with CH_2Cl_2 (3 x 10 ml). Organic layer was washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave 335 mg of a brown oil. Purification on a silica gel column gave **10b** (213 mg, 44%) as a colorless oil. ^{1}H NMR: δ = 7.85-7.6 (m, 6H), 7.4 and 7.25 (m, 6H), 5.24 (dd, $J_{1\text{-}2}$ = 1.4 Hz, $J_{1\text{-}P}$ = 15.9 Hz, 1H, H-1), 4.86 (dddd~ddt, $J_{2\text{-}P}$ = 8.2 Hz, $J_{2\text{-}3a}$ = 8.1 Hz, $J_{2\text{-}3b}$ = 3.5 Hz, 1H, H-2), 4.44 (dd, $J_{3a\text{-}3b}$ = 11.8 Hz, 1H, H-3b), 4.3-4.0 (m, 4H, CH_2OP), 3.86 (dd, 1H, H-3a), 2.46 (s, 6H, CH_3-C_6H_4), 2.44 (s, 3H, CH_3-C_6H_4), 1.31 and 1.29 (2d, J = 7.1 Hz, 6H, CH_3COP). ^{31}P NMR: δ = 12.54.

Isopropylidenation of diols **6a** *and* **6b** *(general procedure):* A solution of the diol (1.0 mmol) and 2,2-dimethoxypropane (2.0 mmol) in CH_2Cl_2 (1.5 ml) containing a few crystals of *p*-toluenesulfonic acid was left at room temperature for 24 h. The catalyst was neutralized with NEt_3, and volatiles were removed *in vacuo*. The crude product was purified on a silica gel column using chloroform-methanol-triethylamine (100:1:1, v/v).

From **6a** (278 mg, 0.73 mmol) (4*R*,5*R*)-4-(diethoxyphosphinyl)-2,2-dimethyl-5-(*p*-toluenesulfonyloxymethyl)-1,3-dioxolane (**7a**) (238 mg, 77%) was obtained as a colorless oil. ^{1}H NMR-500 MHz: δ = 7.80 and 7.44 (2d, J = 8.1 Hz, 2 x 2H, C_6H_4), 4.41 (dddd, $J_{4\text{-}5}$ = 9.2, $J_{5\text{-}5'a}$ = 4.7, $J_{5\text{-}5'b}$ = 2.3, $J_{5\text{-}P}$ = 11.7 Hz, 1H, H-5), 4.33 (dd, $J_{5'a\text{-}5'b}$ = 11.0 Hz, 1H, H-5'b), 4.18 (dq, $J_{H\text{-}P}$ = 7.1 Hz, 4H, CH_2OP), 4.10 (dd, 1H, H-5'a), 4.00 (dd, $J_{1\text{-}P}$ = 1.4 Hz, 1H, H-4), 2.45 (s, 3H, $CH_3C_6H_4$), 1.41 and 1.35 (2s, 6H, CH_3CCH_3), 1.327 and 1.321 (2t, J = 7.1 Hz, 6H, CH_3CH_2). ^{13}C NMR: δ = 144.90, 132.60, 129.75 and 127.90 (4s, C_6H_4), 111.89 (d, ^3J = 10.6 Hz, C-2), 75.19 (d, ^2J = 4.4 Hz, C-5), 70.99 (d, ^1J = 174.7 Hz, C-4), 68.08 (d, ^3J = 4.1 Hz, C-5'), 63.08 and 63.00 (2d, ^2J = 6.8 Hz, COP), 26.18 and 26.08 (2s, CH_3CCH_3), 21.50 (s, $CH_3C_6H_4$), 16.31 and 16.25 (2d, ^3J = 5.7 Hz, CCOP). ^{31}P NMR: δ = 19.19. Anal. calcd. for $C_{17}H_{27}O_8PS$ (422.43): C, 48.33; H, 6.44. Found: C, 48.77; H, 6.53%.

From **6b** (191 mg, 0.50 mmol) (4*S*,5*R*)-**7b** (139 mg, 66%) was prepared; colorless oil. ^{1}H NMR-500 MHz: δ = 7.81 and 7.33 (2d, J = 8.2 Hz, 2 x 2H, C_6H_4), 4.56 (dddd, $J_{4\text{-}5}$ = 7.3, $J_{5\text{-}5'a}$ = 8.9, $J_{5\text{-}5'b}$ = 3.0; $J_{5\text{-}P}$ = 16.4 Hz, 1H, H-5), 4.45 (dd, $J_{5'a\text{-}5'b}$ = 10.8 Hz, 1H, H-5'b), 4.32 (dd, $J_{4\text{-}P}$ = 2.3 Hz, 1H, H-4), 4.19 (dd, 1H, H-5'a), 4.20-4.13 (m, 4H, CH_2OP), 2.44 (s, 3H, $CH_3C_6H_4$), 1.57 and 1.43 (2s, 6H, CH_3CCH_3), 1.324 and 1.318 (2t, J = 7.1 Hz, 6H, CH_3CH_2). ^{13}C NMR: δ = 145.20, 132.71, 129.85 and 128.04 (4s, C_6H_4), 111.37 (d, ^3J = 9.8 Hz, C-2), 74.84 (s, C-5), 71.62 (d, ^1J = 172.2 Hz, C-4), 69.28 (d, ^3J = 3.5 Hz, C-5'), 63.29 and 62.96 (2d, ^2J = 6.9 Hz,

COP), 26.83 and 24.71 (2s, CH_3CCH_3), 21.60 (s, C-C_6H_4), 16.38 (d, ^3J = 5.7 Hz, $CCOP$). ^{31}P NMR: δ = 17.84. Anal. calcd. for $C_{17}H_{27}O_8PS$ (422.43): C, 48.33; H, 6.44. Found: C, 48.28; H, 7.02%.

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