# (α-L-Rhamnopyranosyl)methylphosphonic Acids: Experimental Evidence of the Analogy with α-L-Rhamnopyranosyl Phosphate

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(α-L-Rhamnopyranosyl)methylphosphonic acid and methyl (2-*O*-methyl-α-L-rhamnopyranosyl)methylphosphonate have been synthesized starting from allyl 3,4-di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-L-rhamnopyranoside. The complete NMR spectroscopic characterization of these two compounds and the comparison of the theoretical and experimental vicinal coupling constants indicates a marked preference for the $^1C_4$ conformation for both compounds, in analogy with the natural phosphate.



## Introduction

The replacement of the anomeric oxygen atom with a methylene group has been proposed as a strategy for obtaining stabilized analogues of glycosides[1] and, in particular, glycosyl phosphates.[2] This approach may be used in various areas, e.g. in the synthesis of analogues which interfere in the glycosylation process as competitive inhibitors of glycosyl transferases or for the preparation of carbohydrate analogues stable to hydrolysis. In this case, the search for analogues is stimulated by the poor stability in water of many types of polysaccharides, e.g. capsular polysaccharides.[3] For example, the capsular polysaccharide of *Streptococcus pneumoniae* type 19F consists of a trisaccharide repeating unit, (→4)-β-D-Man*p*NAc-(1→4)-α-D-Glc*p*-(1→2)-α-L-Rha*p*-(1-$PO_4^-$→), with a phosphodiester bridge which connects a residue of rhamnose at the reducing end of one unit to the nonreducing end of the following unit. A phosphate group at the anomeric position of rhamnose is a reason for its limited stability in water, due to the high propensity of hydrolysis of this group at an acetalic position. In such cases, the replacement of the anomeric oxygen atom with a methylene group transforms an acetyl phosphate into a more stable phosphonate. However, though a methylene group is isosteric with oxygen, its stereoelectronic properties are quite different, so that replacement of the oxygen atom could, in principle, produce major changes in the conformational behavior. Natural α-L-rhamnosyl phosphate **1** in the $^1C_4$ conformation (Figure 1) has substituents at positions 1 and 2 in an axial orientation and those at positions 3, 4, and 5 in equatorial orientations. Even in the presence of a bulky aglycon group the ring does not revert to this normally preferred conformation;[4] the anomeric effect is one of the factors that contribute to this preference. Its phosphono analogue **2** does not utilise the anomeric effect such that the $^4C_1$ conformation can be more easily attained and therefore produce a significant contribution to the overall conformational population.

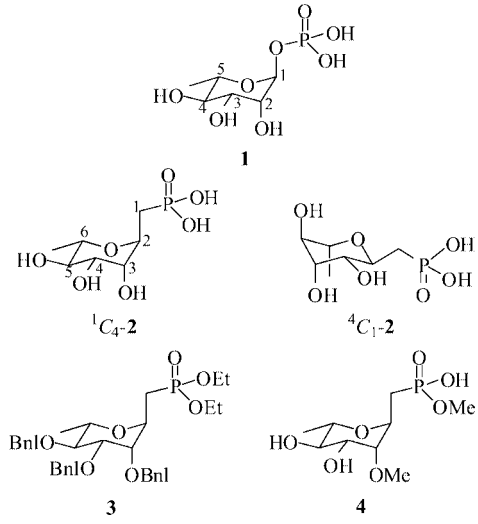

Figure 1. Structures of the natural α-L-rhamnosyl-1-phosphate (**1**) and its phosphono analogues **2**, **3**, and **4**.

This hypothesis is confirmed by the spectroscopic data observed for the perbenzylated phosphono analogue of the α-L-rhamnosyl phosphate **3**.[5] This protected derivative of

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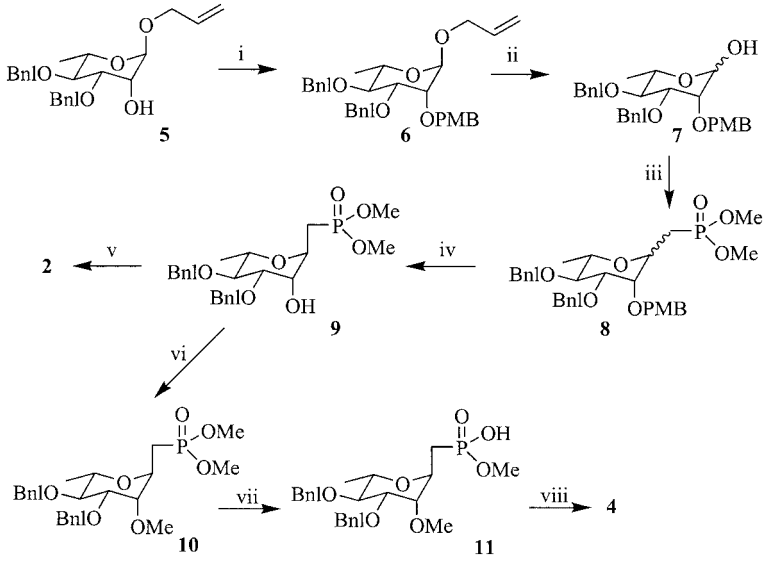
**2** shows that the $^1$H NMR vicinal coupling constants of the pyranose ring are incompatible with a ring geometry of the $^1C_4$ type as the sole populated conformation and are in good agreement with an equilibrium between the $^1C_4$ and $^4C_1$ chair conformations. As a consequence, the similarity between the analogue and the natural reference compound ceases to exist and this becomes a problem for the phosphono analogues of α-L-rhamnose, if the preservation of the conformational features is a requisite for their biological activity. On the other hand, the $J_{4,5}$ and $J_{5,6}$ coupling constants observed for the ammonium salt of (α-L-rhamnopyranosyl)methylphosphonic acid (**2**)[5] are higher than those of the protected derivative, thus indicating that the equilibrium is shifted towards the $^1C_4$ conformation. However, the $J_{2,3}$ coupling constant, which is diagnostic of the relative orientation of the substituents at positions 2 and 3, was not determined[5] such that an ultimate assessment on the conformational preference of this compound cannot be determined.

A different scenario may emerge when the rhamnosidic residue is inserted in a polysaccharide chain, as in the *Streptococcus pneumoniae* $^{19}$F polysaccharide. In this case, its phosphono analogue can be mimicked by compound **4**, which presents two methyl groups at the points of chain elongation; this simple compound **4** can be considered the minimum substructure representing a rhamnosylphosphonate inserted in the polysaccharide chain. Theoretical calculations on compound **4** predicted a conformational equilibrium between the $^1C_4$ and $^4C_1$ conformations with a 14% contribution of the latter conformation to the overall population.[6] However, due to a degree of uncertainty in the theoretical calculations of the modeling of highly polar molecules, such as carbohydrates bearing ionizable groups, an experimental validation of the behavior of the dimethyl derivative **4** appears necessary. With this aim, we describe here the synthesis of compound **2** and its dimethyl derivative **4**. Their spectroscopic characterization has been used to shed light on the conformational behavior of these α-L-rhamnosyl-1-phosphate mimics.

## Results and Discussion

The syntheses of the target compounds **2** and **4** required the preparation of phosphonate **9** as a key intermediate and this is outlined in Scheme 1. The 2-hydroxy group of the known allyl rhamnopyranoside **5**[7] was protected as a *p*-methoxybenzyl ether, and the allyl group was then removed under standard conditions to afford rhamnopyranose **7** in 96% yield. Reaction of **7** with the tetramethyl methylenediphosphonate anion[5] gave an α,β-unsaturated phosphonate, which spontaneously underwent an intramolecular Michael reaction to yield compound **8** in 77% yield. Two isomers were formed and the preference of the desired α-isomer was detected by $^1$H NMR spectroscopy; the 2-H signal of the major product appeared at $\delta$ = 4.42 ppm, analogous to the 2-H resonance of the corresponding perbenzylated compound **3**.[5]

Since the diastereoisomers of **8** could not be separated by flash chromatography, the mixture was treated with DDQ in order to selectively remove the *p*-methoxybenzyl group. The product was obtained in 81% yield, and the anomeric mixture was separated by flash chromatography. The desired dibenzyl α-phosphonate **9** was isolated and fully characterized. The $^1$H NMR spectrum shows vicinal coupling constants ($J_{2,3}$ = 5.0 Hz; $J_{4,5}$ = $J_{5,6}$ = 6.3 Hz) that are very similar to those observed for the corresponding perbenzylated compound **3**,[5] revealing the presence of a conformational equilibrium between the $^1C_4$ and $^4C_1$ geometries and also confirming the expected trend for the pro-




Scheme 1. Reagents and conditions: i) PMBCl, NaH, THF; ii) *t*BuOK, DMSO, then $I_2$, py, THF/$H_2O$; iii) $[(MeO)_2PO]_2CH_2$, NaH, DME, 0 °C → room temp.; iv) DDQ, DCM/$H_2O$; v) $Me_3SiI$, $CCl_4$, 0 °C; vi) MeI, $Ag_2O$, DMF; vii) PhSH, TEA, THF; viii) $H_2$, $Pd(OH)_2$/C, MeOH.

tected phosphono analogues of the natural phosphate **1**. The (α-L-rhamnopyranosyl)methylphosphonic acid (**2**) was obtained from **9** by removal of the protecting groups with $Me_3SiI$.[5]

On the other hand, the dimethyl derivative **4** was obtained in three steps from **9**. The 3-hydroxy group of **9** was first methylated by treatment with MeI in the presence of $Ag_2O$[8] to give **10**. Next, one of the ester methyl groups was selectively removed,[9] which led to compound **11**, which was debenzylated by catalytic hydrogenation to yield compound **4** in quantitative yield.

Compounds **2** and **4** were fully characterized. In particular, all the resonances in their $^1H$ NMR spectra were assigned, and the vicinal coupling constants of the ring hydrogen atoms, diagnostic of the conformational preference of the compounds, were determined (Table 1). Our previous theoretical conformational study of compound **4**[6] indicated a greater preference for the $^1C_4$ conformation, though a 14% contribution of the $^4C_1$ conformation to the overall population was predicted. The same computational approach was applied to compound **2**, which gave similar results. For the most stable $^1C_4$ and $^4C_1$ conformations of both compounds, the vicinal coupling constants have been calculated by using the Haasnoot et al. equation[10] and are reported in Table 1 and are compared with the experimental data. The experimental values are close to those for the $^1C_4$ conformation but very different from those for the $^4C_1$ conformation, indicating a greater preference for the former geometry or even its exclusive presence.

Table 1. Comparison of the experimental $^1H$ NMR vicinal coupling constants (Hz) of compounds **2** and **4** with those calculated for their $^1C_4$ and $^4C_1$ conformations.

| | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6}$ |
|---|---|---|---|---|
| **2** (exp.) | 2.0 | 3.2 | 9.5 | 9.5 |
| $^1C_4$ (calcd.) | 1.3 | 3.1 | 9.0 | 9.2 |
| $^4C_1$ (calcd.) | 9.1 | 3.0 | 2.8 | 1.3 |
| **4** (exp.) | 1.7 | 3.5 | 9.1 | 9.1 |
| $^1C_4$ (calcd.) | 1.1 | 3.7 | 9.5 | 9.2 |
| $^4C_1$ (calcd.) | 7.9 | 4.8 | 2.8 | 1.5 |

The data for phosphonate **4**, closely related to those of compound **2**, suggests that this compound still maintains the same conformational preference as α-L-rhamnopyranosyl phosphate **1**.

## Conclusions

α-L-Rhamnopyranosyl)methylphosphonic acid **2** and its dimethyl derivative **4** have been synthesized from allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside **5**, through the selectively protected common phosphono intermediate **9**. The complete NMR spectroscopic characterization of the compounds and the comparison of the experimental vicinal coupling constants with the computed values indicated a marked preference, or even the exclusive presence, of the $^1C_4$ conformation, in analogy with the natural phosphate. Our study provides experimental proof that the methylene group is isosteric to the anomeric oxygen atom in stabilized analogues of α-rhamnopyranosyl phosphates. This can be seen as a new stimulus towards the syntheses of phosphono analogues of natural phosphates with high guarantees of good mimic properties.

## Experimental Section

**General:** $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AVANCE-500 spectrometer at a sample temperature of 298 K. $^1H$ and $^{13}C$ NMR spectra for compound **2** were recorded with a sample concentration of 25 mM in $D_2O$ (99.9%D) at pD of 1.55. The pD value corresponded to the reading on a pH meter equipped with a glass electrode calibrated with pH 4.01 and 7.01 standard buffers in $H_2O$ and is not corrected for the deuterium isotope effect. Acetonitrile was used as internal standard for $^1H$ NMR ($\delta$ = 2.0 ppm) and $^{13}C$ NMR ($\delta$ = 0.2 ppm) in $D_2O$ solutions, whereas NMR spectra recorded in $CDCl_3$ or $CD_3OD$ were calibrated by using the signal of TMS as an internal reference. Spectra for compound **4** were recorded with a sample concentration of 25 mM in $CD_3OD$ (99.8%D). One bond $^1H$ NMR–$^{13}C$ NMR correlation maps were obtained from HMQC experiments. Optical rotations were measured with a 241 Perkin–Elmer polarimeter at 20 °C. Mass spectra were recorded in the negative or positive mode on a Thermo Quest Finningan LCQ™DECA spectrometer using electrospray ionization as indicated. All reactions were monitored by TLC on Silica Gel 60 F-254 plates (Merck), spots being developed with 5% sulfuric acid in methanol/water (1:1), or with a phosphomolybdenate-based reagent. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Organic solutions were dried with sodium sulfate. All evaporations were carried out under reduced pressure at 40 °C. Dry solvents were distilled prior to use: THF and 1,2-dimethoxyethane (DME) were distilled from sodium; dichloromethane (DCM) was distilled from calcium hydride. DMF, DMSO, and methanol were dried using 4 Å molecular sieves; triethylamine (TEA) was distilled from calcium hydride. NaH was washed three times with hexane prior to use. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

**Allyl 3,4-Di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-L-rhamnopyranoside (6):** Allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**5**)[7] (1.50 g, 3.90 mmol) was dissolved in dry THF (15 mL), and *p*-methoxybenzyl chloride (0.64 mL, 4.68 mmol) and NaH (60% dispersion in mineral oil, 0.31 g, 7.80 mmol) were added, and the mixture was stirred at room temperature for 4 d. It was then quenched with MeOH, concentrated, and the residue dissolved in EtOAc (40 mL), and washed with water (50 mL). The aqueous layer was further extracted with EtOAc (2×40 mL). The combined organic layers were dried and concentrated, and the product was isolated by flash chromatography (hexane/EtOAc, 8:2) to afford **6** as a white solid (1.87 g, 95%). $[\alpha]_D^{20}$ = –34.2 (*c* = 1.0, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 1.33 (d, $J_{5,6}$ = 6.0 Hz, 3 H, 6-H), 3.61 (t, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 3.70 (dq, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.0 Hz, 1 H, 5-H), 3.77–3.81 (m, 4 H, $OCH_3$, 2-H), 3.87 (dd, $J_{2,3}$ = 2.7, $J_{3,4}$ = 9.5 Hz, 1 H, 3-H), 3.90 (br. dd, $J_{a,a'}$ = 13.0, $J_{a,b}$ = 6.9 Hz, 1 H, $OCH_aH_{a'}$-$CH_b$=$CH_2$), 4.11 (br. dd, $J_{a,a'}$ = 13.0, $J_{a',b}$ = 5.2 Hz, 1 H, $OCH_aH_{a'}$-$CH_b$=$CH_2$), 4.56–4.70 (m, 5 H, $CH_2$Ph), 4.76 (br. s, 1 H, 1-H), 4.95 (d, $J_{gem}$ = 10.7 Hz, 1 H, $CH_2$Ph), 5.14 (br. d, $J_{b,c}$ = 10.5 Hz, 1 H, $CH_b$=$CH_cH_d$), 5.20 (br. d, $J_{b,d}$ = 17.0 Hz, 1 H, $CH_b$=$CH_cH_d$), 5.79–5.89 (m, 1 H, $CH_b$=$CH_cH_d$), 6.81–6.85 (m, 2 H, arom.), 7.25–7.36 (m, 12 H, arom.) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 18.0, 55.3, 67.7, 68.1, 72.1, 72.4, 74.3, 75.4, 80.2, 80.6, 97.2, 113.8, 114.0, 117.1, 127.5–130.4 (13C), 133.9, 138.6, 138.7, 159.3 ppm. ESI-MS

(positive-ion mode): $m/z$ = 522.2 $[M + NH_4]^+$. $C_{31}H_{36}O_6$ (504.61): calcd. C 73.79, H 7.19; found C 74.01, H 7.35.

**3,4-Di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-L-rhamnopyranose (7):** *t*BuOK (4.0 g, 36.0 mmol) was slowly added to a solution of compound **6** (1.80 g, 3.60 mmol) in dry DMSO (75 mL). After 3 h, the solvent was evaporated under reduced pressure (high vacuum pump), and the residue dissolved in $CHCl_3$ (100 mL), washed with $H_2O$ (1 × 80 mL), dried, and concentrated. The crude was dissolved in THF/$H_2O$ (4:1, 90 mL), and pyridine (1.16 mL, 14.40 mmol) and iodine (1.83 g, 7.20 mmol) were added, and the mixture was stirred at room temperature for 3 h. The mixture was then diluted with EtOAc (150 mL), washed with saturated $Na_2S_2O_3$ (1 × 80 mL), 5% HCl (1 × 80 mL), water (1 × 80 mL), dried, and the solvents evaporated. The crude was purified by flash chromatography (hexane/EtOAc, 75:25) to give compound **7** as a colorless oil (1.60 g, 96%). $[\alpha]_D^{20}$ = –18.6 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.32 (d, $J_{5,6}$ = 6.2 Hz, 2.4 H, 6-H major), 1.34 (d, $J_{5,6}$ = 6.2 Hz, 0.6 H, 6-H minor), 2.79 (br. s, 1 H, OH), 3.32–3.39 (m, 0.2 H, 5-H min.), 3.54–3.58 (m, 0.4 H, 3-H and 4-H min.), 3.62 (t, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 0.8 H, 4-H maj.), 3.76–3.85 (m, 4 H, $OCH_3$, 2-H), 3.88–3.96 (m, 1.6 H, 3-H and 5-H maj.), 4.57–4.77 (m, 5 H, 1-H min. and C$H_2$Ph), 4.92–5.05 (m, 1.2 H, C$H_2$Ph), 5.12 (br. s, 0.8 H, 1-H maj.), 6.81–6.91 (m, 2 H, arom.), 7.24–7.42 (m, 12 H, arom.) ppm. $^{13}$C NMR ($CDCl_3$, selected signals): $\delta$ = 17.9 (6-C min.), 18.1 (6-C maj.), 55.3 ($OCH_3$), 93.0 (1-C maj.), 93.3 (1-C min.) ppm. ESI-MS (positive-ion mode): $m/z$ = 482.1 $[M + NH_4]^+$. $C_{28}H_{32}O_6$ (464.55): calcd. C 72.39, H 6.94; found C 72.45, H 7.00.

**Dimethyl 2,6-Anhydro-1,7-dideoxy-4,5-di-*O*-benzyl-3-*O*-*p*-methoxybenzyl-L-*glycero*-L-*talo*-heptit-1-yl Phosphonate and Dimethyl 2,6-Anhydro-1,7-dideoxy-4,5-di-*O*-benzyl-3-*O*-*p*-methoxybenzyl-L-*glycero*-L-*galacto*-heptit-1-yl Phosphonate (8):** A solution of tetramethyl methylenediphosphonate (4.50 g, 19.38 mmol) in dry 1,2-dimethoxyethane (6 mL) was slowly added to a suspension of NaH (0.46 g, 19.38 mmol) in dry DME (15 mL) at 0 °C. After 30 min, a solution of compound 7 (1.50 g, 3.23 mmol) in dry DME (5 mL) was added, and the resulting mixture was allowed to warm to room temperature. After 2 days, it was quenched with MeOH (8 mL) and concentrated. The residue was dissolved in EtOAc (200 mL), and washed with saturated $NH_4Cl$ (1 × 100 mL) and brine (1 × 100 mL). The aqueous layers were further extracted with $Et_2O$, and the combined organic layers were then dried, and the solvents evaporated. The crude was purified by flash chromatography (toluene/acetone, 7:3) to give compound **8** as a colorless oil (1.60 g, 87%). $^1$H NMR ($CDCl_3$): $\delta$ = 1.30 (d, $J_{6,7}$ = 6.0 Hz, 0.9 H, 7-H min.), 1.35 (d, $J_{6,7}$ = 6.0 Hz, 2.1 H, 7-H maj.), 1.74–1.85 (m, 0.3 H, 1a-H min), 2.06 (dd, $J_{1,2}$ = 7.3, $J_{1,P}$ = 19.3 Hz, 1.4 H, 1-H maj.), 2.09–2.19 (m, 0.3 H, 1b-H min.), 3.34–3.41 (m, 0.3 H, 6-H min.), 3.54–3.84 (m, 13 H, $ArOCH_3$, $2POCH_3$, 2-H min, 3-H, 4-H, 5-H, 6-H maj), 4.35–4.44 (m, 0.7 H, 2-H maj.), 4.48–4.99 (m, 6 H, 3 $CH_2$Ph), 6.82–6.89 (m, 2 H, arom.), 7.22–7.42 (m, 12 H, arom.) ppm. $^{13}$C NMR ($CDCl_3$, selected signals): $\delta$ = 17.8 (7-C maj.), 18.1 (7-C min.), 26.4 [d, $J$(C,P) = 140.7 Hz, 1-C maj.], 27.7 (d, $J_{C,P}$ = 141.5 Hz, 1-C min.), 51.9 (d, $J_{C,P}$ = 6.7 Hz, $POCH_3$ min.), 52.3 (d, $J_{C,P}$ = 6.7 Hz, $POCH_3$ maj.), 52.6 (d, $J_{C,P}$ = 6.7 Hz, $POCH_3$ maj.), 52.8 (d, $J_{C,P}$ = 6.7 Hz, $POCH_3$ min.), 55.3 ($OCH_3$) ppm. ESI-MS (positive-ion mode): $m/z$ (%) = 1162.9 (100) [2 M + Na]$^+$, 588.1 (40) $[M + NH_4]^+$. $C_{31}H_{39}O_8P$ (570.61): calcd. C 65.25, H 6.89; found C 65.52, H 7.04.

**Dimethyl 2,6-Anhydro-1,7-dideoxy-4,5-di-*O*-benzyl-L-*glycero*-L-*talo*-heptit-1-yl Phosphonate (9):** DDQ (0.76 g, 3.36 mmol) was added to a mixture of compound **8** (1.60 g, 2.80 mmol) in $CH_2Cl_2$/$H_2O$ (18:1, 60 mL). The reaction mixture was stirred at room temperature for 2 h, it was then diluted with $CH_2Cl_2$ (50 mL), washed with saturated $NaHCO_3$ (2 × 80 mL) and brine (1 × 80 mL), and dried and concentrated. The crude was purified by flash chromatography (toluene/acetone, 6:4 to 2:8), which first gave 0.30 g of the minor isomer and then 0.74 g of the major isomer **9** as a colorless oil (overall yield 82%). $[\alpha]_D^{20}$ = –7.5 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.32 (d, $J_{6,7}$ = 6.3 Hz, 3 H, 7-H), 2.06 (ddd, $J_{1a,2}$ = 8.5, $J_{1a,1b}$ = 15.5, $J_{1a,P}$ = 18.4 Hz, 1 H, 1a-H), 2.15 (ddd, $J_{1b,2}$ = 5.7, $J_{1a,1b}$ = 15.5, $J_{1b,P}$ = 19.5 Hz, 1 H, 1b-H), 2.62 (d, $J_{OH,3}$ = 5.7 Hz, 1 H, OH), 3.46 (t, $J_{5,6}$ = $J_{5,4}$ = 6.3 Hz, 1 H, 5-H), 3.69–3.82 (m, 8 H, 2 $OCH_3$, 4-H, 6-H), 3.86 (ddd, $J_{2,3}$ = 4.7, $J_{3,4}$ = 3.5, $J_{OH,3}$ = 5.7 Hz, 1 H, 3-H), 4.23 (dddd, $J_{1a,2}$ = 8.5, $J_{1b,2}$ = 5.7, $J_{2,3}$ = 4.7, $J_{2,P}$ = 10.5 Hz, 1 H, 2-H), 4.56–4.72 (m, 4 H, 2C$H_2$Ph), 7.24–7.36 (m, 10 H, arom.) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.3 (7-C), 26.7 (d, $J_{C,P}$ = 142.7 Hz, 1-C), 52.4 (d, $J_{C,P}$ = 6.2 Hz, $POCH_3$), 52.6 (d, $J_{C,P}$ = 6.2 Hz, $POCH_3$), 69.1 (d, $J_{C,P}$ = 10.8 Hz, 3-C), 69.2 (2-C), 70.1 (6-C), 72.3 (O*C*$H_2$Ph), 73.9 (O*C*$H_2$Ph), 78.3 (4-C and 5-C), 127.8–128.6 (10 C arom.), 138.0 (2 C arom.) ppm. ESI-MS (positive-ion mode): $m/z$ (%) = 917.9 (100) [2 M + $NH_4$]$^+$, 467.9 (35) $[M + NH_4]^+$, 451.1 (65) $[M + H]^+$. $C_{23}H_{31}O_7P$ (450.56): calcd. C 61.33, H 6.94; found C 61.21, H 6.69.

**Dimethyl 2,6-Anhydro-1,7-dideoxy-4,5-di-*O*-benzyl-3-*O*-methyl-L-*glycero*-L-*talo*-heptit-1-yl Phosphonate (10):** Compound **9** (0.17 g, 0.38 mmol) was dissolved under argon in dry DMF (10.5 mL). $CH_3I$ (0.28 mL, 4.53 mmol) and $Ag_2O$ (0.70 mg, 3.02 mmol) were added, and the mixture was stirred in the dark at room temperature for 72 h, during which time a further aliquot of $CH_3I$ (0.52 mL, 8.31 mmol) and $Ag_2O$ (0.35 g, 1.51 mmol) were added. The mixture was then diluted with $Et_2O$, filtered through Celite, and washed with $H_2O$ (1 × 80 mL). The aqueous layer was extracted with $Et_2O$ (2 × 50 mL), and the combined organic layers were dried and concentrated. Product **10** was recovered after flash chromatography (toluene/acetone, 1:1) as a colorless oil (0.12 g, 70%). $[\alpha]_D^{20}$ = –5.3 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.30 (d, $J_{6,7}$ = 6.5 Hz, 3 H, 7-H), 1.98 (ddd, $J_{1a,2}$ = 6.5, $J_{1a,1b}$ = 15.5, $J_{1a,P}$ = 19.7 Hz, 1 H, 1a-H), 2.09 (ddd, $J_{1b,2}$ = 7.7, $J_{1a,1b}$ = 15.5, $J_{1b,P}$ = 19.0 Hz, 1 H, 1b-H), 3.43 (s, 3 H, $OCH_3$), 3.49 (t, $J_{2,3}$ = $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 3.50 (t, $J_{4,5}$ = $J_{5,6}$ = 7.5 Hz, 1 H, 5-H), 3.57–3.64 (m, 1 H, 6-H), 3.68–3.74 [m, 7 H, $PO(OCH_3)_2$, 4-H], 4.33–4.40 (m, 1 H, 2-H), 4.56–4.84 (m, 4 H, 2C$H_2$Ph), 7.23–7.37 (m, 10 H, arom.) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.9 (7-C), 26.1 (d, $J_{C,P}$ = 142 Hz, 1-C), 52.4 (d, $J_{C,P}$ = 6.4 Hz, $POCH_3$), 52.7 (d, $J_{C,P}$ = 6.5 Hz, $POCH_3$), 58.1 ($OCH_3$), 68.3 (2-C), 69.8 (6-C), 72.8 (O*C*$H_2$Ph), 74.8(O*C*$H_2$Ph), 77.5 (4-C), 79.0 (d, $J_{C,P}$ = 9.8 Hz, 3-C), 79.9 (5-C), 127.7–128.4 (10 C arom.), 138.1 (arom.), 138.4 (arom.) ppm. ESI-MS (positive-ion mode): $m/z$ (%) = 951.0 (100) [2 M + Na]$^+$), 946.1 (55) [2 M + $NH_4$]$^+$, 482.0 (30) $[M + NH_4]^+$, 465.2 (25) $[M + H]^+$. $C_{24}H_{33}O_7P$ (464.49): calcd. C 62.06, H 7.16; found C 61.86, H 6.81.

**Methyl 2,6-Anhydro-1,7-dideoxy-4,5-di-*O*-benzyl-3-*O*-methyl-L-*glycero*-L-*talo*-heptit-1-yl Phosphonate (11):** Compound **10** (0.11 g, 0.24 mmol) was dissolved in dry THF (2.5 mL). Freshly distilled thiophenol (0.098 mL, 0.96 mmol) and TEA (0.16 mL, 1.20 mmol) were added, and the solution was stirred at room temperature. After 48 h, the mixture was diluted with TEA, and the solvents evaporated to dryness. Flash chromatography ($CH_2Cl_2$/MeOH, from 9:1 to 7:3) gave compound **11** as a white solid (0.050 g, 46%). $[\alpha]_D^{20}$ = +11.1 ($c$ = 1.0, $CH_3OH$). $^1$H NMR ($CD_3OD$): $\delta$ = 1.25 (d, $J_{6,7}$ = 6.4 Hz, 3 H, 7-H), 1.90–2.00 (m, 2 H, 2 × 1-H), 3.45–3.51 (m, 4 H, 5-H and $OCH_3$), 3.56–3.65 (m, 4 H, 6-H and $POCH_3$), 3.82–3.87 (m, 2 H, 3-H and 4-H), 4.35–4.42 (m, 1 H, 2-H), 4.61–4.87 (m, 4 H, 2 × C$H_2$Ph), 7.23–7.36 (m, 10 H, arom.) ppm. $^{13}$C NMR ($CD_3OD$): $\delta$ = 18.6 (7-C), 28.1 (d, $J_{C,P}$ = 135.5 Hz, 1-C), 51.8 (d, $J_{C,P}$ = 5.8 Hz, $POCH_3$), 58.4 ($OCH_3$), 70.5 (6-C), 72.1 (2-C), 72.7

(O*C*$H_2$Ph), 76.0 (O*C*$H_2$Ph), 80.1 (m, 2 C, 3-C and 4-C), 81.5 (5-C), 128.7–129.4 (10 C arom.), 139.8 (arom.), 139.9 (arom.) ppm. ESI-MS (negative-ion mode): *m*/*z* = 449.5 [M – 1]$^-$. $C_{23}H_{31}O_7P$ (450.46): calcd. C 61.33, H 6.94; found C 61.40, H 7.13.

**Methyl 2,6-Anhydro-1,7-dideoxy-3-*O*-methyl-L-*glycero*-L-*talo*-hept-it-1-yl Phosphonate (4):** Compound **11** (0.04 g, 0.089 mmol) was dissolved in MeOH (2 mL), and a catalytic amount of palladium hydroxide on charcoal was added under argon. The mixture was hydrogenated at atmospheric pressure for 40 h, then diluted with MeOH, filtered through a MILLIPORE filter, and the solvents evaporated to dryness giving compound **4** as a white solid (0.024 g, quant.). $[\alpha]_D^{20}$ = +0.5 (*c* = 1.0, $CH_3OH$). $^1$H NMR ($CD_3OD$): $\delta$ = 1.26 (d, $J_{6,7}$ = 6.3 Hz, 3 H, 7-H), 1.92–2.05 (m, 2 H, 2×1-H), 3.34 (t, $J_{4,5}$ = $J_{5,6}$ = 9.1 Hz, 1 H, 5-H), 3.47 (s, 3 H, $OCH_3$), 3.50 (dq, $J_{5,6}$ = 9.1, $J_{6,7}$ = 6.3 Hz, 1 H, 6-H), 3.62 (d, $J_{C,P}$ = 10.7 Hz, 3 H, $POCH_3$), 3.67 (dd, $J_{2,3}$ = 1.75, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 3.71 (dd, $J_{3,4}$ = 3.5, $J_{4,5}$ = 9.1 Hz, 1 H, 4-H), 4.35–4.42 (m, 1 H, 2-H) ppm. $^{13}$C NMR ($CD_3OD$): $\delta$ = 18.2 (7-C), 27.2 (d, $J_{C,P}$ = 139.7 Hz, 1-C), 52.4 (d, $J_{C,P}$ = 6.3 Hz, $POCH_3$), 58.2 ($OCH_3$), 70.2 (6-C), 71.5 (2 C, 2-C and 4-C), 74.5 (5-C), 83.1 (d, $J_{C,P}$ = 11.2 Hz, 3-C) ppm. ESI-MS (negative-ion mode): *m*/*z* = 269.4 [M – 1]$^-$. $C_9H_{19}O_7P$ (270.22): calcd. C 40.00, H 7.09; found C 39.83, H 6.88.

**2,6-Anhydro-1,7-dideoxy-L-*glycero*-L-*talo*-heptit-1-yl Phosphonic Acid (2):** Compound **2** was synthesized from **9** (0.08 g, 0.18 mmol) by reaction with $Me_3SiI$ according to the procedure of Nicotra et al.,[5b] but recovered in its acid form after loading on a cation exchange resin column (Dowex 50×8, $H^+$ form), elution with methanol, and evaporation of the solvent under reduced pressure (0.036 g, 85%). $^1$H NMR ($D_2O$): $\delta$ = 1.20 (d, $J_{6,7}$ = 6.2 Hz, 3 H, 7-H), 2.02 (ddd, $J_{1a,2}$ = 6.5, $J_{1a,1b}$ = 15.5, $J_{1a,P}$ = 20.0 Hz, 1 H, 1a-H), 2.17 (ddd, $J_{1b,2}$ = 8.5, $J_{1a,1b}$ = 15.5, $J_{1b,P}$ = 18.8 Hz, 1 H, 1b-H), 3.38 (t, $J_{4,5}$ = $J_{5,6}$ = 9.5 Hz, 1 H, 5-H), 3.55 (dq, $J_{5,6}$ = 9.5, $J_{6,7}$ = 6.2 Hz, 1 H, 6-H), 3.74 (dd, $J_{3,4}$ = 3.2, $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 3.94 (dd, $J_{2,3}$ = 2.0, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 3.96–4.03 (m, 1 H, 2-H) ppm. $^{13}$C NMR ($D_2O$): $\delta$ = 16.4 (7-C), 26.7 (d, $J_{C,P}$ = 133.5 Hz, 1-C), 69.0 (6-C), 69.4 (4-C), 71.1 (d, $J_{C,P}$ = 11.3 Hz, 3-C), 71.8 (5-C), 73.7 (2-C) ppm. ESI-MS (negative-ion mode): *m*/*z* = 241.3 [M – 1]$^-$. $C_7H_{15}O_7P$ (242.16): calcd. C 34.72, H 6.24; found C 34.85, H 6.47.

**Computational Methods:** The conformational behavior of compound **2** was investigated through a DFT approach at the B3LYP/6-31G(d) level using the Gaussian03 package according to the same procedure already described for compound **4**.[6]

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