179. Deoxy-nitrosugars

7th Communication[1])

Synthesis of Methyl Shikimate and of Diethyl Phosphashikimate from D-Ribose

by **Sohail Mirza** and **Andrea Vasella***

Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

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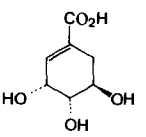
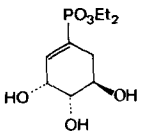
Summary

The chain elongation of the deoxy-nitroribose **6** by a *Michael* addition to the vinylphosphonate **7** followed by a solvolysis gave the heptulosephosphonate **11** (87%). From **11**, the key intermediates **15** and **16** (77%) were obtained by a highly diastereoselective reduction, followed by detritylation, periodate cleavage, and silylation. Methoxycarbonylation of **15** and **16** gave **17** and **18** which were converted into methyl shikimate (**21**; 79%) by intramolecular olefination and partial deprotection. Similarly, phosphonoylation of **16** gave **22** (99%) which was transformed into the diethyl phosphashikimate **2** (53% from **6**).

The importance of shikimic acid (**1**) as a biosynthetic intermediate is well recognized [2], and several syntheses of **1** including three enantiospecific ones [3–5] have been reported. In all these enantiospecific syntheses carbohydrates have been used as starting material and, the problem of chain extension and of the formation of cyclohexenes from carbohydrates had to be solved. We have proposed a solution to the problem of chain elongation using 1-deoxy-1-nitroaldoses [6]. The synthesis of **1** and of the corresponding phosphashikimic acid derivative **2** allows to extend the scope of this method and to look further at the synthesis of carbocycles from carbohydrates (*cf.* [5]).



1

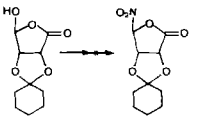


2

We had planned to first extend the chain of a 1-deoxy-1-nitro sugar[2]) by a *Michael* addition to the vinylphosphonate **5** [10] *(Scheme)*, then generate an aldehydophosphonate, and finally cyclize this intermediate by an intramolecular olefination.

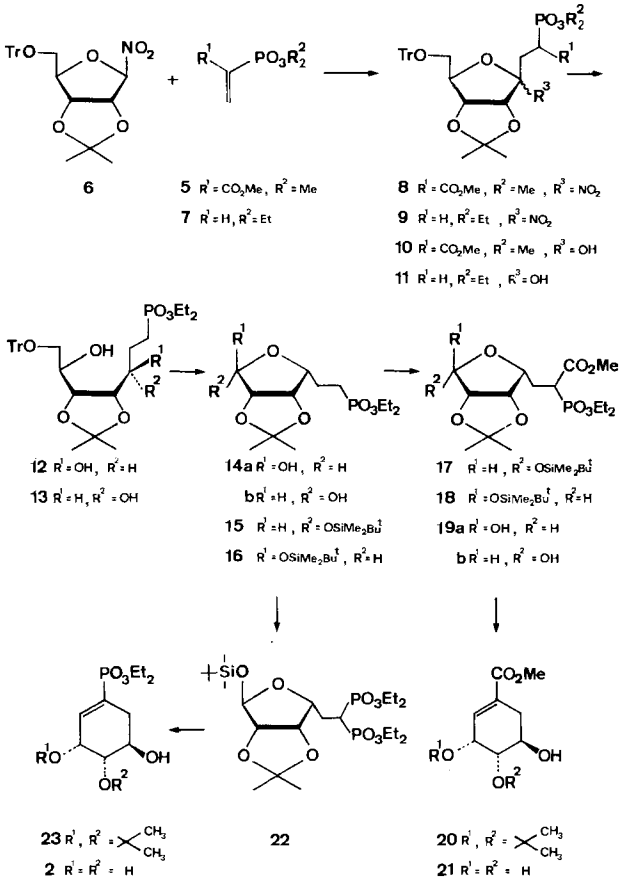
[1]) 6th Communication: [1].

[2]) We had intended to use the nitro sugar **4**, but the attempts (*cf.* [7]) to prepare it from the oxime of the erythruronolactone **3** [8] failed. Concerning the stability of such nitrolactones *cf.* [9].



3 **4**

Scheme



The base-catalyzed addition of the easily available 1-deoxy-1-nitroribose derivative **6** [6] *(Scheme)* to the vinylphosphonate **5** proceeded rapidly, but the products (presumed to be **8**) proved to be unstable and decomposed to a mixture containing at best small amounts of the desired hemiacetal **10**. A similar addition of **6** to the vinylphosphonate **7**[3]) followed by heating the crude addition products **9** in wet formamide gave a 5.5.:1 mixture[4]) of the anomeric phosphonates **11** (87%). The reduction of **11** with $NaBH_4$ in MeOH gave a 22:1 mixture[5]) (97%) of the diastereoisomeric diols **12** and **13**, whilst a similar reduction in EtOH gave these diols in 73.5% and 18.5% yield, respectively. Detritylation [13] of the major diol followed by treatment with periodate gave the *lyxo*-phosphonates **14** (85%) as a 4.9:1 mixture of anomers[4]). The *lyxo*-configuration was deduced from the ^{1}H-NMR spectra ($J_{1,2} = J_{3,4} = 3.5$ Hz for the β-D-anomer and $J_{1,2} = 0$; $J_{3,4} = 3.5$ Hz for the α-D-anomer) and proved by transformation of **14**

[3]) For the use of **7** as *Michael* acceptor see [11] [12].

[4]) Ratio based on signal integrals in the ^{1}H-NMR and ^{31}P-NMR spectra (see *Exper. Part*).

[5]) As determined by HPLC (*Zorbax-Sil*, AcOEt/hexane/MeOH 9:15:1, τ_R (**13**)/τ_R (**12**) = 0.86).

into methyl shikimate (**21**). Silylation of **14** by (*t*-butyl)dimethylsilyl chloride gave the silyl glycosides **15** (12%) and **16** (81%), which were separated and treated separately first with BuLi [14] and then with methyl chloroformate to give the esters **17** (95%) and **18** (94%), respectively, each one as an approximately 1:1 mixture of diastereoisomers. Both these mixtures were converted (Bu_4NF) into the hemiacetals **19** which, upon treatment with NaOMe cyclized to the shikimic acid derivative **20** (86%). A very similar cyclization has recently been described by *Fleet et al.* [5] in their excellent synthesis of shikimic acid (**1**). Treatment of **20** according to [5] gave **21** (97%) which was also prepared form authentic **1** [15]. Compound **21** was obtained in an overall yield of 50% from **6** (38% from D-ribose)[6]). The conversion of **21** into free **1** (80%) [16] is a known procedure.

The key intermediate **16** was used for a synthesis of the phosphashikimate **2**. Treatment of **16** with lithium diisopropylamide and then with diethyl phosphorochloridate gave the bisphosphonate **22** in over 95% yield. In a similar way as described for **18**, desilylation and cyclization led to the protected phosphashikimate **23** (91%). This compound was hydrolyzed to the phosphashikimate **2**, which was thus obtained in an overall yield of 53% from **6** (40% from D-ribose)[6]), illustrating the potentiality of **16** as an intermediate for the synthesis of shikimic-acid analogues.

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Experimental Part

General. See [18]. ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra were measured with a *Varian-XL-200* spectrometer (^{1}H(200 MHz), ^{13}C(50 MHz), ^{31}P (80 MHz)) or with a *Bruker-AM-400* spectrometer (^{1}H(400 MHz), ^{13}C(100.6 MHz), ^{31}P(160 MHz)) in $CDCl_3$ (unless otherwise specified). The chemical shifts are reported in ppm relative to TMS (for ^{1}H- and ^{13}C-NMR) as internal standard or relative to H_3PO_4 (for ^{31}P-NMR) as external reference. IR spectra were measured with a *Perkin-Elmer-298* spectrophotometer ($CHCl_3$ solutions). For the chromatography the following solvent mixtures were used: A = AcOEt; B = AcOEt/hexane 7:3; C = AcOEt/hexane 3:2; D = AcOEt/MeOH 9:1; E = AcOEt/MeOH 4:1; F = AcOEt/EtOH 19:1. TLC: substances were detected by spraying the plates with a 10% solution of phosphomolybdic acid in EtOH, followed by heating at about 200°. Anal. HPLC was performed on a *Kontron* apparatus (LC pump *410*) with a UV detector set at 254 nm.

*Diethyl (1,2-Dideoxy-4,5-*O*-isopropylidene-7-*O*-trityl-*D*-ribo-3-heptulofuranos-1-yl)phosphonate* (**11**). $Bu_4NF \cdot 3H_2O$ (6.0 g, 19.02 mmol) was added in one portion to a stirred mixture of the nitroribose **6** [6] (30.0 g, 65.08 mmol), diethyl vinylphosphonate (**7**, *Aldrich*, 12.0 g, 73.18 mmol), and THF (300 ml), at 0°. The mixture was stirred for 1 h at 0°, diluted with formamide (100 ml), and heated at *ca.* 60° (bath temp.) for 24 h after addition of $NaHCO_3$ (8.0 g, 95.23 mmol). The mixture was cooled to r.t. and poured into sat. aq. NH_4Cl (100 ml). Workup with AcOEt and chromatography (A) afforded 33.9 g (87%) of **11** as an oil which solidified on standing, m.p. 42–50°. R_f (A) 0.36, $[\alpha]_D^{25} = -17.9$ (c = 1.1, $CHCl_3$; $[\alpha]_D$ did not change with time). IR: 3400 br., 2986*s*, 2938*w*, 2872w, 1727*w*, 1598*w*, 1489*w*, 1448*m*, 1382*m*, 1372*m*, 1236*s*, 1159*s*, 1058*s*, 1030*s*, 967*s*, 900*w*, 870*w*. ^{1}H-NMR: 1.28 (*t*, J = 7, 3H); 1.29 (*t*, J = 7, 3H); 1.30 (*s*, 2.55 H); 1.37 (*s*, 0.45 H); 1.47 (*s*, 2.55 H); 1.59 (*s*, 0.45 H); 1.80–2.24 (*m*, 4 H); 3.31 (*dd*, J = 10.2 and 4.8, 1 H); 3.39 (*dd*, J = 10.2 and 4.2, 1 H); 3.95–4.18 (*m*, 4 H); 4.23 (*m*, 1 H, H–C(6)); 4.44 (*d*, J = 6, 1 H, H–C (4)); 4.76 (*dd*, J = 6 and 1.8, 1 H, H–C (5)); 4.78 (br., 1 H, OH); 7.16–7.57 (*m*, 15 H, $C(C_6H_5)_3$). ^{13}C-NMR: 16.37 (*qd*, J(P,C) = 6.3); 19.77 (*td*, J(P,C) = 141.9); 25.25 (*q*); 26.63 (*q*); 28.19 (*td*, J(P,C) = 4.2); 61.61 (*td*, J(P,C) = 6.5); 65.12 (*t*); 82.60 (*d*); 84.93 (*d*); 86.35 (*d*); 87.69 (*s*); 106.81 (*s*); 107.11 (*s*); 112.53 (*s*); 127.25 (*d*); 127.91 (*d*); 128.67 (*d*); 143.13(*s*); 143.71 (*s*). ^{31}P-NMR: 17.79 (*s*, 0.05 P); 32.82 (*s*, 0.15 P); 34.38 (*s*, 0.80 P). Anal. calc. for $C_{33}H_{41}O_8P$ (596.7): C 66.42, H 6.94, P 5.19; found: C 66.12, H 7.13, P 5.05.

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[6]) The compound **6** is available from D-ribose in 75% yield [6] [17].

*Diethyl 1,2-Dideoxy-4,5-O-isopropylidene-7-O-trityl-*D*-altro-hepitol-1-phosphonate* (**13**) *and Diethyl 1,2-Dideoxy-4,5-O-isopropylidene-7-O-trityl-*D*-allo-heptitol-1-phosphonate* (**12**). A) $NaBH_4$ (671 mg, 17.75 mmol) was added in small portions over 1 h to a vigorously stirred mixture of **11** (3.5 g, 5.87 mmol) and abs. EtOH (35 ml), maintained at 0°. The resulting mixture was allowed to warm to r.t. and taken to dryness *in vacuo*. The residue was partitioned between AcOEt and brine. Normal workup followed by chromatography (B) gave first 654 mg (18.6%) of **13** and then 2.58 g (73.5%) of **12**.

Data of **13**. M.p. 128–130°, R_f (A) 0.27, $[\alpha]_D^{25} = +13.5$ ($c = 1.0$, $CHCl_3$). IR: 3585*w*, 3460 br., 2995*s*, 2938*m*, 2910*w*, 1600*w*, 1490*w*, 1450*m*, 1392*m*, 1383*m*, 1370*m*, 1342*w*, 1278*w*, 1240*s*, 1163*m*, 1060*s*, 1029*s*, 986*s*, 900*w*, 870*w*. ^{1}H-NMR: 1.22 (*s*, 3 H); 1.26 (*s*, 3 H); 1.33 (*t*, $J = 7$, 6 H); 1.58–2.24 (*m*, 4 H); 3.27 (*dd*, $J = 10$ and 7, 1 H); 3.46 (br. 1 H, OH); 3.50 (*dd*, $J = 10$ and 2.8, 1 H); 3.73–4.24 (*m*, 8 H); 4.45 (br. 1 H, OH); 7.19–7.62 (*m*, 15 H, $C(C_6H_5)_3$). ^{13}C-NMR: 16.42 (*qd*, J(P,C) = 6.1); 21.47 (*td*, J(P,C) = 141.6), 25.48 *(q)*; 26.99 (*td*, J(P,C) = 4.3); 27.95 *(q)*; 61.56 (*td*, J(P,C) = 6.7); 65.08 *(t)*; 68.62 *(d)*; 68.97 *(d)*; 77.42 *(d)*; 80.51 *(d)*; 87.01 *(s)*; 108.57 *(s)*; 127.10 *(d)*; 127.85 *(d)*; 128.60 *(d)*; 143.71 *(s)*. ^{31}P-NMR: 34.06 *(s)*. Anal. calc. for $C_{33}H_{43}O_8P$ (598.7): C 66.20, H 7.25, P 5.17; found: C 66.20, H 7.33, P 5.05.

Data of **12**. M.p. 99–100°, R_f (A) 0.21, $[\alpha]_D^{25} + 5$ ($c = 1.1$, $CHCl_3$). IR: 3575 br., 3430 br., 2995*s*, 2938*m*, 1600*w*, 1490*w*, 1450*m*, 1392*w*, 1384*m*, 1373*m*, 1240*s*, 1161*m*, 1060*s*, 1032*s*, 965*m*, 900*w*, 888*w*, 869*w*. ^{1}H-NMR: 1.32 (*t*, $J = 7$, 6 H); 1.32 (*s*, 3 H); 1.36 (*s*, 3 H); 1.72–2.16 (*m*, 4 H); 2.87 (*d*, $J = 7.2$, 1 H, OH); 2.97 (br., 1 H, OH); 3.29 (*dd*, $J = 10$ and 4, 1 H); 3.45 (*d*, $J = 10$, 1 H); 3.94–4.26 (*m*, 8 H); 7.19–7.56 (*m*, 15 H, $C(C_6H_5)_3$). ^{13}C-NMR: 16.56 (*qd*, J(P,C) = 5.9); 22.37 (*td*, J(P,C) = 141.4); 25.18 *(q)*; 27.38 *(q)*; 28.01 (*td*, J(P,C) = 4.4); 61.64 (*td*, J(P,C) = 6.5); 65.23 *(t)*; 68.52 *(d)*; 69.00 (*dd*, J(P,C) = 7); 77.10 *(d)*; *79.61 (d)*; 88.89 *(s)*; 108.15 *(s)*; 127.04 *(d)*; 127.78 *(d)*; 128.62 *(d)*; 143.74 *(s)*. ^{31}P-NMR: 33.63 *(s)*. Anal. calc. for $C_{33}H_{43}O_8P$ (598.7): C 66.20, H 7.25, P 5.17; found: C 65.95, H 7.42, P 5.02.

B) Treatment of **11** (200 mg, 0.34 mmol) with $NaBH_4$ (38 mg, 1 mmol) in dry MeOH (2 ml) in the manner described under *A* furnished 195 mg (97%) of **13**/**12** in the ratio 1:22 (HPLC, *Zorbax-Sil*, AcOEt/hexane/MeOH 9:15:1, τ_R (**13**) 4.9 min, τ_R (**12**) 5.7 min).

*Diethyl 5,6-Dideoxy-2,3-O-isopropylidene-*D*-lyxo-hexofuranos-6-yl-phosphonate* (**14**). A) Anh. $ZnBr_2$ (*Fluka*; 1.6 g, 7.1 mmol) was added in one portion to a vigorously stirred solution of **12** (420 mg, 0.70 mmol) in dry CH_2Cl_2 (2 ml), and the mixture was stirred for 30 min. It was then cooled to 0°, diluted with MeOH (5 ml, dropwise addition) and treated with a solution of $NaIO_4$ (62 mg, 0.74 mmol) in H_2O (3 ml). The mixture was stirred for 10 min and filtered through *Celite*. The solvent was evoparated, and the residue was partitioned between AcOEt and brine. Usual workup afforded an oil, which was chromatographed (D) to give 193 mg (85%) of **14** as a mixture of anomers. M.p. 77–78°, R_f (A) 0.10, $[\alpha]_D^{25} = +9.2$ ($c = 1$, $CHCl_3$). IR: 3670*w*, 3605*w*, 3280 br., 2995*s*, 2940*m*, 2912*w*, 1480*w*, 1444*w*, 1410*w*, 1393*w*, 1384*s*, 1374*s*, 1240*s*, 1162*s*, 1097*s*, 1060*s*, 1030*s*, 967*s*, 866*m*. ^{1}H-NMR: 1.31 (*s*, 3 H); 1.33 (*t*, $J = 7$, 6 H); 1.45 (*s*, 2.5 H); 1.52 (*s*, 0.5 H); 1.73–2.14 (*m*, 4 H plus 0.83 H, OH); 3.89 (*d*, $J = 12$, 0.17 H, OH); 3.97–4.24 (*m*, 5 H); 4.48 (*dd*, $J = 6$ and 3.5, 0.17 H, H–C(2)); 4.58 (*d*, $J = 6$, 0.83 H, H–C (2)); 4.65 (*dd*, $J = 6$ and 3.5, 1 H, H–C(3)); 4.95 (*dd*, $J = 12$ and 3.5, 0.17 H, H–C(1)); 5.34 (*s*, 0.83 H, H–C (1)). ^{13}C-NMR: 16.39 (*qd*, J(P,C) = 3.7); 22.34 (*td*, J(P,C) = 142.4); 25.00 *(q)*; 26.11 *(q)*; 61.58 (*td*, J(P,C) = 5.5); 61.63 (*td*, J(P,C) = 6.2); 79.69 (*dd*, J(P,C) = 17.1); 80.24 (*dd*, J(P,C) = 15.8); 86.11 *(d)*; 96.66 *(d)*; 100.90 *(d)*; 112.4 *(s)*; 113.21 *(s)*. ^{31}P-NMR: 32.05 (*s*, 0.17P); 32.43 (*s*, 0.83P). Anal. calc. for $C_{13}H_{25}O_7P$ (324.35): C 48.14, H 7.78, P 9.55; found: C 48.38, H 7.80, P 9.30.

B) Ice-cooled 70% aq. AcOH (75 ml) was added to **12** (9.0 g, 15.03 mmol), and the mixture was stirred at r.t. for 6 h. The solvent was removed (high vacuum), the residue was dissolved in MeOH (90 ml), cooled to 0°, and treated with $NaHCO_3$ (2.0 g, 23.81 mmol). A solution of $NaIO_4$ (3.32 g, 15.52 mmol) in H_2O (15 ml) was added, and the mixture was stirred for 10 min. Manipulation as before afforded 3.72 g (76%) of **14**, identical with the sample prepared above.

*Diethyl[1-O-((*t*-Butyl)dimethylsilyl)-5,6-dideoxy-2,3-O-isopropylidene-α-*D*-lyxo-hexofuranos-6-yl]phosphonate* (**16**) *and Diethyl [1-O-((*t*-butyl)dimethylsilyl)-5,6-dideoxy-2,3-O-isopropylidene-β-*D*-lyxo-hexofuranos-6-yl]phosphonate* [**15**]. A mixture containing **14** (175 mg, 0.54 mmol), (*t*-butyl)dimethylsilyl chloride (122 mg, 0.81 mmol) and imidazol (110 mg, 1.62 mmol) in dry CH_2Cl_2 (2 ml) was stirred overnight at r.t. and filtered. The residue was washed with CH_2CL_2 (2x), and the combined filtrate was concentrated *in vacuo* to furnish an oil, which was chromatographed (C) to give 189 mg (81%) of **16**, followed by 27 mg (12%) of **15**.

Data of **16**. R_f (A) 0.32, $[\alpha]_D^{25} = +24.8$ ($c = 1.1$, $CHCl_3$). IR: 2980*s*, 2948*s*, 2930*s*, 2855*m*, 1461*w*, 1441*w*, 1381*m*, 1371*m*, 1243*s*, 1158*m*, 1106*s*, 1076*s*, 1022*s*, 962*s*, 899*w*, 852*s*, 837*s*. ^{1}H-HMR: 0.08 (*s*, 3 H); 0.10 (*s*, 3 H); 0.87 (*s*, 9 H); 1.30 (*s*, 3 H); 1.32 (*t*, $J = 7.1$, 6 H); 1.44 (*s*, 3 H); 1.74–2.13 (*m*, 4 H); 3.98–4.22 (*m*, 5H); 4.54 (*d*, $J = 5.8$, 1 H, H–C(2)); 4.67 (*dd*, $J = 5.8$ and 3.5, 1 H, H–C(3)); 5.27 (*s*, 1 H, H–C(1)). Anal. calc. for $C_{19}H_{39}O_7PSi$ (438.64): C 52.02, H 8.98, P 7.06; found: C 52.22, H 9.21, P 7.20.

Data of **15**. R_f (A) 0.17, $[\alpha]_D^{25} = -9.9$ ($c = 1.1$, $CHCl_3$). IR: 2980*s*, 2955*s*, 2915*s*, 2855*s*, 1459*m*, 1441*m*, 1380*m*, 1370*m*, 1242*s*, 1159*m*, 1105*s*, 1054*s*, 1028*s*, 965*s*, 860*s*, 834*s*. ^{1}H-NMR: 0.13 (*s*, 6 H); 0.92 (*s*, 9 H); 1.32 (*t*, $J = 7$, 6 H); 1.34 (*s*, 3 H); 1.50 (*s*, 3 H); 1.75–2.23 (*m*, 4 H); 3.65 (*m*, 1 H, H–C(4)); 4.17 (*m*, 4 H); 4.52 (*dd*, $J = 6$ and 3.5, 1 H, H–C(2)); 4.61 (*dd*, $J = 6$ and 3.8, 1 H, H–C(3)); 4.97 (*d*, $J = 3.5$, 1 H H–C(1)). Anal. calc. for $C_{19}H_{39}O_7PSi$ (438.64): C 52.02, H 8.98, P 7.06; found: C 52.06, H 9.02, P 7.00.

*Methyl (6*R*)- and (6*S*)-1-*O-((t-butyl)dimethylsilyl)-5,6-dideoxy-6-diethoxyphosphoryl-2,3-*O*-isopropylidene-α-*D*-lyxo-heptofuranuronate* (**18**). BuLi (1.6M in hexane, 0.47 ml, 0.75 mmol) was added dropwise to a stirred solution of **16** (110 mg, 0.25 mmol) in dry THF (3 ml), at −78° under Ar. After 15 min, methyl chloroformate (118 mg, 97 µl, 1.25 mmol) was added, and the mixture was stirred for 3 h at −78°. MeOH (0.1 ml) was added, followed by sat. aq. NH_4Cl (5 ml), and the mixture was allowed to warm to r.t. Normal workup and chromatography (C) furnished 117 mg (94%) of **18** as a mixture of diastereoisomers. R_f (A) 0.39, $[\alpha]_D^{25} = +22.2$ ($c = 1.25$, $CHCl_3$). IR: 2982*s*, 2952*s*, 2926*s*, 2854*m*, 1733*s*, 1460*m*, 1436*m*, 1381*m*, 1371*m*, 1330*m*, 1290*m*, 1248*s*, 1159*s*, 1107*s*, 1075*s*, 1024*s*, 1001*s*, 972*s*, 901*w*, 853*s*, 838*s*. ^{1}H-NMR: 0.08 (*s*, 3 H); 0.09 (*s*, 3 H); 0.85 (*s*, 4.5 H); 0.86 (*s*, 4.5 H); 1.29 (*s*, 3 H); 1.33 (*t*, $J = 7$, 6 H); 1.44 (*s*, 3 H); 2.11–2.58 (*m*, 2 H); 3.24 (*m*, 1 H); 3.74 (*s*, 1.5 H); 3.75 (*s*, 1.5 H); 3.96–4.31 (*m*, 5 H); 4.51 (*d*, $J = 5.8$, 1 H, H–C(2)); 4.65 (*dd*, $J = 5.8$ and 3.7, 1 H, H–C(3)); 5.24 (*s*, 1 H, H–C(1)). Anal. calc. for $C_{21}H_{41}O_9PSi$ (496.68): C 50.78, H 8.34, P 6.24; found: C 51.02, H 8.39, P 6.31.

*Methyl (6*R*)- and (6*S*)-1-*O-((t-butyl)dimethylsilyl)-5,6-dideoxy-6-diethoxyphosphoryl-2,3-*O*-isopropylidene-β-*D*-lyxo-heptofuranuronate* (**17**). Treatment of **15** (210 mg, 0.48 mmol) as described for **16** afforded 226 mg (95%) of **17**, isolated as a mixture of diastereoisomers. R_f (A) 0.33 and 0.28, $[\alpha]_D^{25} = -5$ ($c = 1.2$, $CHCl_3$). IR: 2982*m*, 2946*m*, 2928*m*, 2854*m*, 1732*s*, 1459*w*, 1435*w*, 1389*w*, 1380*m*, 1370*m*, 1329*w*, 1245*s*, 1159*m*, 1102*s*, 1045*s*, 1024*s*, 971*m*, 858*m*, 835*s*. ^{1}H-NMR: 0.13 (*s*, 6 H); 0.92 (*s*, 9 H); 1.33 (*s*, 3H); 1.33 (*t*, $J = 7$, 6 H); 1.34 (*s*, 1.5 H); 1.49 (*s*, 1.5 H); 2.13–2.60 (*m*, 2H); 3.12–3.71 (*m*, 2H); 3.75 (*s*, 3 H); 4.02–4.27 (*m*, 4 H); 4.46 (*dd*, $J = 6.5$ and 3.5, 1 H, H–C(2)); 4.53 (*dd*, $J = 6.5$ and 3.8, 0.5 H, H–C(3)); 4.57 (*dd*, $J = 6.5$ and 3.8, 0.5 H, H–C(3)); 4.93 (*d*, $J = 3.5$, 0.5 H, H–C(1)); 4.97 (*d*, $J = 3.5$, 0.5 H, H–C(1)). Anal. calc. for $C_{21}H_{41}O_9PSi$ (496.68): C 50.78, H 8.34, P 6.24; found: C 51.06, H 8.60, P 6.20.

*Methyl (3*R*, 4*S*, 5*R*)-5-Hydroxy-3,4-isopropylidenedioxy-1-cyclohexenecarboxylate* (**20**) *and Methyl (3*R*, 4*S*, 5*R*)-3,4,5-Trihydroxy-1-cyclohexenecarboxylate* (**21**). A solution of **17**/**18** (1:1 mixture, 58 mg, 0.12 mmol) in dry THF (2 ml) was treated with $Bu_4NF \cdot 3\,H_2O$ (95 mg, 0.30 mmol), stirred for 1 h at r.t. and poured into sat. aq. NH_4Cl (5 ml). Usual workup with AcOEt gave an oil, which was thoroughly dried and taken up in a solution of NaOMe in MeOH (0.2M, 2 ml). The mixture was stirred for 1 h at r.t., neutralized with AcOH/MeOH 1:1 and taken to dryness *in vacuo*. The residue was partitioned between sat. aq. NH_4Cl and AcOEt. Workup followed by chromatography (C) gave 23 mg (86%) of **20**. R_f (A) 0.51. ^{1}H–NMR: 1.41 (*s*, 3 H); 1.45 (*s*, 3 H); 2.26 (*dd*, $J = 17.2$ and 8.4, 1 H, H–C(6)); 2.38 (br., 1 H, OH); 2.82 (*dd*, $J = 17.2$ and 4.6, 1 H, H–C(6)); 3.78 (*s*, 3H); 3.93 (*m*, 1 H, H–C(5)); 4.12 (*dd*, $J = 6.5$, 1 H, H–C(4)); 4.77 (*m*, 1 H, H–C(3)); 6.95 (*m*, 1 H, H–C(2)).

The compound **20** was deacetonated [5]: a mixture containing **20** (15 mg, 0.07 mmol) and *Dowex* (50 W, H^+ form; 100 mg) in MeOH (0.5 ml) was stirred for 1 h and filtered through *Celite*. Evaporation of the solvent and chromatography (E) furnished 12 mg (97%) of **21**. M.p. 112–113° ([19]: 113–114°), R_f (A) 0.14, $[\alpha]_D^{25} = -129.5$ ($c = 0.7$, EtOH) ([19]: −130 ($c = 1.88$, EtOH)). ^{1}H-NMR (400 MHz, CD_3OD): 2.22 (*m*, 1 H, H–C(6)); 2.72 (*m*, 1 H, H–C(6)); 3.71 (*dd*, $J = 7.2$ and 4.2, 1 H, H–C(4)); 3.74 (*s*, 3 H, CO_2CH_3); 4.03 (*dt*, $J = 7.2$ and 5.1, 1 H, H–C(5)); 4.40 (*m*, 1 H, H–C(3)); 6.81 (*m*, 1 H, H–C(2)). Identical with an authentic sample [15].

*Tetraethyl [1-*O*-((t-butyl)dimethylsilyl)-5,6-dideoxy-2,3-*O*-isopropylidene-α-*D*-lyxo-hexofuranose-6,6-diyl]bisphosphonate* (**22**). BuLi (1.6M in hexane, 0.31 ml, 0.50 mmol) was added dropwise under Ar to a stirred solution of $(i\text{-}Pr)_2$ NH (49 mg, 68 µl, 0.48 mmol) in dry THF (2 ml) at 0°, and the mixture was stirred for 10 min. A solution of **16** (72 mg, 0.16 mmol) in dry THF (1 ml) was added dropwise, followed by diethyl phosphorochloridate (85 mg, 70 µl, 0.49 mmol) and the mixture was stirred for 20 min at 0° before being poured into sat. aq. NH_4Cl (5 ml). Normal workup with AcOEt and chromatography (A) gave 93 mg (99%) of **22**. R_f (A) 0.10, $[\alpha]_D^{25} = +20.6$ ($c = 1.1$, $CHCl_3$). IR: 2986*s*, 2954*m*, 2928*m*, 2855*w*, 1470*w*, 1462*w*, 1442*w*, 1390*m*, 1382*m*, 1371*m*, 1246*s*, 1160*m*, 1127*m*, 1105*m*, 1072*s*, 1042*s*, 1027*s*, 972*s*, 902*w*, 858*s*, 837*m*. ^{1}H-NMR: 0.09 (*s*, 6H); 0.87 (*s*, 9 H); 1.30 (*s*, 3 H); 1.33 (*t*, $J = 7.1$, 12 H); 1.43 (*s*, 3 H); 2.15–2.83 (*m*, 3 H); 4.04–4.35 (*m*, 8 H); 4.51 (*td*, $J = 7$ and 3.6, 1 H, H–C(4)); 4.57 (*d*, $J = 5.8$, 1 H, H–C(2)); 4.76 (*dd*, $J = 5.8$ and 3.6, 1 H, H–C(3)); 5.30 (*s*, 1 H, H–C(1)). Anal. calc. for $C_{23}H_{48}O_{10}P_2Si$ (574.74): C 48.06, H 8.94, P 10.78; found: C 48.13, H 8.66, P 10.50.

Diethyl (3R, 4S, 5R)-5-Hydroxy-3,4-isopropylidenedioxy-1-cyclohexenephosphonate (**23**) *and Diethyl (3R, 4S, 5R)-3,4,5-Trihydroxy-1-cyclohexenephosphonate* (**2**). A solution of **22** (1.35 g, 2.35 mmol) in dry THF (45 ml) was treated with $Bu_4NF \cdot 3\ H_2O$ (925 mg, 2.93 mmol) and stirred for 1 h at r.t. Workup as before gave an oil, which was taken up in a solution of NaOEt in EtOH (0.7M, 10 ml) and stirred for 1 h. Normal workup followed by chromatography (F) afforded 653 mg (91%) of **23**. R_f (E) 0.52. IR: 3600*w*, 3300 br., 2980*s*, 2935*m*, 2870*w*, 1440*w*, 1380*m*, 1371*m*, 1339*w*, 1310*w*, 1235*s*, 1158*m*, 1093*s*, 1054*s*, 1025*s*, 964*s*, 891*w*, 868*m*. ^{1}H-NMR: 1.33 (*t*, J = 7.1, 6 H); 1.40 (*s*, 3 H); 1.45 (*s*, 3 H); 2.12–2.73 (*m*, 3 H, 2 H–C(6), OH); 3.91 (*td*, J = 8 and 5, 1 H, H–C(5)); 4.00–4.29 (*m*, 5 H, 2 CH_3CH_2O, H–C(4)); 4.72 (*m*, 1 H, H–C(3)); 6.74 (*md*, J(P,H) = 21, 1 H, H–C(2)).

The compound **23** (590 mg, 1.93 mmol) was deacetonated as described for **20** to give, after chromatography (D), 479 mg (93%) of **2** as a viscous oil. R_f (E) 0.21, $[\alpha]_D^{25} = -73$ (c = 1.2, EtOH). ^{1}H-NMR (400 MHz, CD_3OD): 1.32 (*t*, J = 7.1, 6 H); 2.11 (*m*, 1 H, H–C(6)); 2.59 (*m*, 1 H, H–C(6)); 3.66 (*dd*, J = 7 and 4.2, 1 H, H–C(4)); 3.93 (*m*, 1 H, H–C(5)); 4.02 (*qd* appearing as a *quint.*, J = 7.1, 4 H, 2 CH_3CH_2O); 4.37 (*m*, 1 H, H–C(3)); 6.60 (*md*, J(P,H) = 22, 1 H, H–C(2)). ^{13}C-NMR (100.6 MHZ, CD_3OD): 16.56 (*qd*, J(P,C) = 6.5); 31.70 (*td*, J(P,C) = 9.5); 63.52 (*td*, J(P,C) = 6.3); 63.54 (*td*, J(P,C) = 6.3); 67.30 (*dd*, J(P,C) = 20.9); 68.33 (*dd*, J(P,C) = 13.1); 72.50 (*dd*, J(P,C) = 3); 128.00 (*d*, J(P,C) = 180.7); 143.42 (*dd*, J(P,C) = 7.5). ^{31}P-NMR (160 MHz, CD_3OD): 19.99 (*s*). Anal. calc. for $C_{10}H_{19}O_6P$ (266.26): C 45.11, H 7.21, P 11.63; found: C 45.05, H 7.43, P 11.43.

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