80. Deoxy-nitrosugars

12th Communication[1])

Synthesis of Isosteric Mono-Phosphonate Analogues of β- and α-D-Fructose 2,6-Bisphosphate

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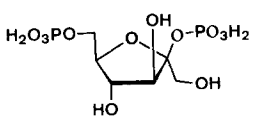
A synthesis of the isosteric mono-phosphonate analogues **2a** and **19** of the β- and α-D-fructose 2,6-bisphosphate, respectively, is described. Chain elongation of the 1-deoxy-1-nitro-D-arabinose **3** *(Scheme 1)* by a *Henry* reaction with paraformaldehyde followed by protection of the resulting alcohol (methoxymethyl ether) and a radical-chain substitution by nitromethane anion gave the key intermediates, the *gluco*-anhydroalditol **6** and the *manno*-anhydroalditol **7**. These products equilibrated under basic conditions. Conversion of **7** to the aldehyde **9**, *Abramov* reaction of **9** with diphenyl phosphite followed by deoxygenation according to *Barton* gave the phosphonate **11** *(Scheme 2)*. Selective hydrogenolysis of **11**, phosphorylation and deprotection gave **2** which was converted to the tetrasodium salt **2a**. Similarly, **6** was transformed into the isosteric phosphonate analogue **19** of the α-D-fructose 2,6-bisphosphate *(Scheme 3)*.

Introduction. – The recent discovery of β-D-fructose 2,6-bisphosphate[2]) (**1**) in animals [3–5] and then in plants [6–8] has been of crucial importance for our understanding of glycolysis (glucose utilisation) and gluconeogenesis (*de novo* biosynthesis). β-D-Fructose 2,6-bisphosphate is the regulating agent of these metabolic pathways. It activates glycolysis by stimulating 6-phosphofructo-1-kinase *(EC 2.7.1.11)*, which converts fructose 6-phosphate into fructose 1,6-bisphosphate, and it deactivates gluconeogenesis by inhibiting fructose-1,6-bisphosphatase *(EC 3.1.3.11)*, the enzyme which catalyses the reverse reaction [9–11].



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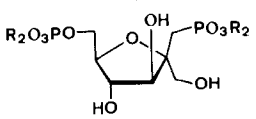


2 R=H
2a R=Na

Since **1** is very prone to hydrolytic and enzymatic degradation to D-fructose 6-phosphate, analogues such as **2** in which the P–O bond of the phosphate monoester at the anomeric center is replaced by a non-hydrolysable P–C bond could prove useful for biochemical and pharmacological studies.

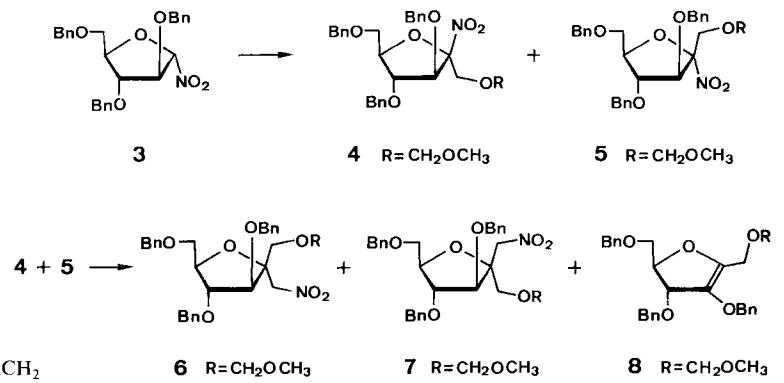
[1]) 11th Communication: [1].

[2]) The β-D-configuration of **1** was deduced from its ^{13}C-NMR spectrum [2].

Our approach to the synthesis of the isosteric phosphonate analogue **2** of β-D-fructose 2,6-bisphosphate is based on the expectation that the substitution of a tertiary NO_2 group by a nitromethane moiety as reported by *Kornblum* and *Erickson* [12] is applicable to protected 2-deoxy-2-nitrouloses such as **4** or **5**, *i.e.* to tertiary nitro ethers[3]) *(Scheme 1)*. Substitution of the NO_2 group of **4** by nitromethane anion to introduce the second C-substituent should give **7**, which can be converted to the desired compound **2**. The key step of the synthesis is the stereochemically controlled substitution of the anomeric NO_2 group by the nitromethane anion.

Results. – Base-catalysed reaction of 1-deoxy-1-nitro-D-arabinose **3** [14] with excess paraformaldehyde followed by protection of the resulting OH group as the methoxymethyl ether (formaldehyde dimethyl acetal in presence of P_2O_5 [15]) gave the nitro compounds **4** (53%) and **5** (13%) *(Scheme 1)*. Their configurations were inferred from their ^{1}H-NMR spectra. The known shielding effect of the NO_2 group on a vicinal H_{cis} [16] indicates the depicted configurations (H–C(3) at 4.37 ppm for **5** and at > 4.52 ppm for **4**).

Scheme 1



3 **4** R = CH_2OCH_3 **5** R = CH_2OCH_3

6 R = CH_2OCH_3 **7** R = CH_2OCH_3 **8** R = CH_2OCH_3

Treatment of the mixture **4**/**5** (4:1) with 4 equiv. of CH_3NO_2 and 8 equiv. of NaH in DMSO [12] gave the *gluco*-anhydroalditol **6** (49%), the *manno*-anhydroalditol **7** (17%), and the *erythro*-hex-2-enitol **8** (6%). The configuration at C(2) of **6** and **7** was deduced from the nuclear *Overhauser* effects between H–C(3) and CH_2NO_2 in **6** and between H–C(3) and $CH_2OCH_2OCH_3$ in **7**. The *gluco*- and *manno*-configurations of **6** and **7**, respectively, are not in contradiction with their ^{13}C-NMR spectra (75.52 ppm for CH_2NO_2 in **6** and, 75.10 ppm for CH_2NO_2 in **7**), considering the known shielding effect of an alkoxy group on a vicinal C_{cis} [17] [18]. Fortuitously, the epimers **6** and **7** equilibrated upon treatment with $Bu_4NF \cdot 3H_2O$[4]). Starting with a solution of either **6** or **7** in THF[5]), **6**/**7** was obtained in a final ratio of 45/55. The equilibration allowed to accumulate the desired isomer **7**.

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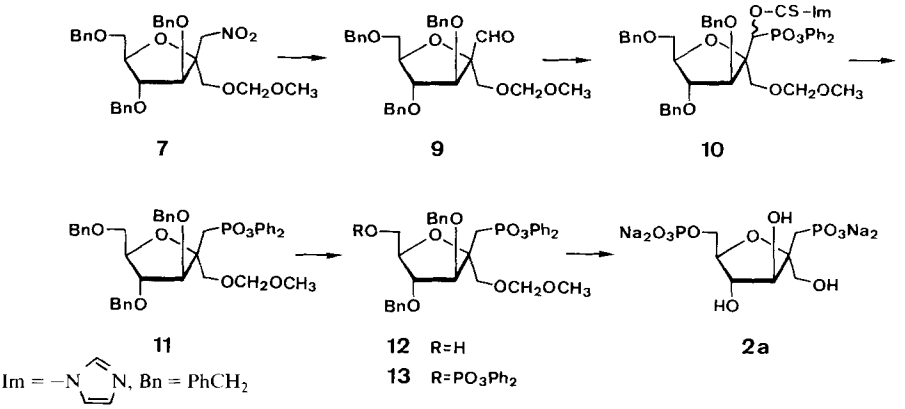
[3]) The reaction follows a radical-chain mechanism ('$S_{RN}1$ reaction'). For radical-chain reactions of halonitro ethers compare [1] [13].

[4]) The equilibration most certainly occurs by β-elimination/β-addition. Similar equilibrations of aldose derivatives are known [17] [19] [20].

[5]) Equilibration in MeOH gave **6**/**7** 65:35.

Scheme 2



The nitro compound **7** was converted into the aldehyde **9** (74%) by ozonolysis of the nitronate anion [21] *(Scheme 2)*. *Abramov* reaction of **9** with an excess of diphenyl phosphite in the presence of Et_3N followed by treatment of the resulting α-hydroxyphosphonates with *N,N'*-thiocarbonyldiimidazole [22] [23] gave **10** (70%) as a *ca.* 9:1 mixture of diastereoisomers[6]). Deoxygenation of the imidazolylthiocarbonyloxy derivatives **10** with Bu_3SnH in refluxing toluene [22] [23] gave the phosphonate **11** (79%). Signals of the $CH_2PO_3Ph_2$ group appeared in the ^{1}H-NMR spectrum of **11** at 2.87 and 2.65 ppm (*ABX*, $J(P,H) = 19.5$ Hz, $J_{gem}(H,H) = 15.4$ Hz; *cf.* [24]) and in the ^{13}C-NMR spectrum at 29.05 ppm (*dt*, $J(P,C) = 142.8$ Hz; *cf.* [18] [25]).

Selective hydrogenolysis of **11** with 10% Pd/C in MeOH gave **12** (62%) and starting material **11** (15%). The reaction was stopped when more polar products were formed (TLC monitoring; see *Exper. Part*). In the ^{13}C-NMR spectra, OH–C(6) of **12** gave rise to a typical signal at 61.33 ppm, whilst the signal of $PhCH_2O$–*C*(6) of **11** appeared at > 68.7 ppm. The alcohol **12** was phosphorylated with diphenyl phosphorochloridate in pyridine [26] to give **13** (91%). The ^{31}P-NMR spectra of **13** showed two signals, one at +21.52 ppm for $C-PO_3Ph_2$ and the other at −11.47 ppm for $O-PO_3Ph_2$.

The intermediate **13** was deprotected first by treatment with H_2 and 10% Pd/C (hydrogenolysis of the two benzyloxy groups), then with H_2 and PtO_2 (hydrogenolysis of the four phenyl ester groups), and finally by heating in H_2O to 40° (hydrolysis of the formaldehyde-acetal group). The free phosphonic acid **2** was converted to the tetrasodium salt **2a** by passage through a short column of *Dowex CCR-2* (Na^+ form). The salt **2a** was purified by flash chromatography on silylated silica gel. The structure of **2a** was in agreement with the MS (FAB: $M + 1$ at 427), the ^{1}H-NMR (3.67 and 3.61 ppm, *AB*, $J = 12.3$, CH_2OH; 1.95 ppm, *d*, $J(P,H) = 18.5$, $CH_2PO_3Na_2$), the ^{13}C-NMR (32.42 ppm, *dt*, $J(P,C) = 128.5$, $CH_2PO_3Na_2$), and the ^{31}P-NMR spectra (+20.19 ppm for $C-PO_3Na_2$ and +2.10 ppm for $O-PO_3Na_2$; *cf.* [13] [18] [27] [28]). It was confirmed by elemental analysis.

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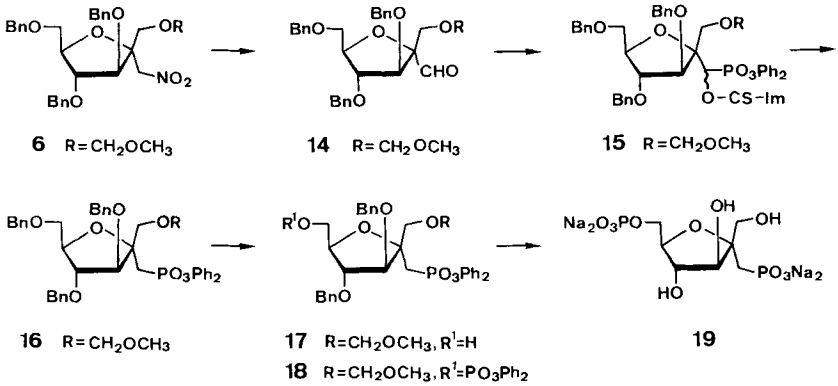
[6]) The ^{1}H-NMR spectrum of the diastereoisomers showed two sets of two signals corresponding to imidazolyl protons (major isomer: 8.16 and 7.39 ppm; minor isomer: 8.48 and 7.73 ppm). In the ^{31}P-NMR spectrum, two signals appeared at 8.81 and at 8.80 ppm. Ratios are based on the integrals in the ^{1}H-NMR and ^{31}P-NMR spectra.

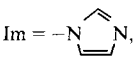
Scheme 3



6 R=CH_2OCH_3 **14** R=CH_2OCH_3 **15** R=CH_2OCH_3

16 R=CH_2OCH_3 **17** R=CH_2OCH_3, R'=H **19**

18 R=CH_2OCH_3, R'=PO_3Ph_2

Im =  , Bn = $PhCH_2$

In an analogous way, the isosteric phosphonate analogue **19** *(Scheme 3)* of the α-D-fructose 2,6-bisphosphate was prepared from the primary nitro compound **6** (→**14** (63%) →**15** (63%) →**16** (77%) →**17** (81%) →**18** (88%) →**19** (84%); see *Exper. Part*). Ozonolysis of the nitronate anion derived from **6** gave **14**. Again, *Abramov* reaction of this aldehyde gave a mixture of α-hydroxyphosphonates, from which the imidazolylthiocarbonyloxy derivatives **15** were obtained as a *ca.* 4:1 mixture of diastereoisomers[7]). Deoxygenation of **15** with Bu_3SnH gave the phosphonate **16**. In its ^{1}H-NMR spectrum, the $CH_2PO_3Ph_2$ group gave rise to signals at 2.87 and 2.70 ppm (*ABX*, J(P,H) = 19.0, J_{gem}(H,H) = 15.5); in the ^{13}C-NMR spectrum signals appeared at 30.43 ppm (*dt*, J(P,C) = 138.6 Hz).

Selective hydrogenolysis of **16** gave **17** and starting material **16** (5%). Again, the signal of OH–C(6) in the ^{13}C-NMR spectrum of **17** appeared at a typical position (62.59 ppm; for **16**, C(6) at > 70.51 ppm). Phosphorylation of **17** gave **18**. Phosphorylation at C(6) was confirmed by the presence in the ^{13}C-NMR spectrum of **18** of two triplets with a P,C coupling (68.65 ppm, J(P,C) = 4.0 and 68.13 ppm J(P,C) = 6.4), the other triplet belonging to $CH_2OCH_2OCH_3$. Deprotection of **18** as described for **13** led to the isosteric phosphonate analogue **19** of α-D-fructose 2,6-bisphosphate. The MS (FAB of the free acid: M + 1 at 339), the ^{1}H-NMR (3.63 and 3.51 ppm, *AB*, J = 12.0, CH_2OH; 2.00 and 1.80 ppm, *ABX*, J(P,H) = 18.6, J_{gem}(H,H) = 14.7, $CH_2PO_3Na_2$), the ^{13}C-NMR (64.41 ppm, *dt*, J(P,C) = 4.9, and 64.28 ppm, *dt*, J(P,C) = 2.0 for C(6) and CH_2OH; 36.11 ppm, *dt*, J(P,C) = 126.1, $CH_2PO_3Na_2$), and the ^{31}P-NMR spectra (+19.19 ppm for C–PO_3Na_2 and +3.35 ppm for O–PO_3Na_2). The elemental analysis were in agreement with the structure of compound **19**.

We thank the *Swiss National Science Foundation* and *Sandoz*, Basle, for generous support.

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

Experimental Part

General. See [29]. The silylated silica gel was obtained from *Merck*, Darmstadt (Germany) (Art. *7719*). ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR: *Varian-HA-100* (^{13}C(25.2 MHz)), *Varian-XL-200* (^{1}H(200 MHz), ^{13}C(50 MHz), ^{31}P(80 MHz)), or *Bruker-AM-400* spectrometer (^{1}H(400 MHz), ^{13}C(100 MHz), ^{31}P(160 MHz)); $CDCl_3$ soln. unless otherwise specified; δ's in ppm relative to TMS (^{1}H-NMR and ^{13}C-NMR) as internal standard or relative to H_3PO_4 (^{31}P-NMR) as external reference (uncorrected). MS: *Varian-112S* (EI: 70 eV; Cl: isobutan) and *Varian-711* spectrometer (FAB, bombardement with 8-keV Xe-atoms, glycerol matrix). FC = flash chromatography.

*3,4,6-Tri-*O*-benzyl-2-deoxy-1-*O*-methoxymethyl-2-nitro-β- and -α-*D*-fructofuranose* (**4** and **5**, resp.). A mixture of 3 g (6.67 mmol) of *2,3,5-tri-*O*-benzyl-1-deoxy-1-nitro-α-*D*-arabinofuranose* (**3**) [13], 3 g (100 mmol) of paraformaldehyde, and 200 mg (0.6 mmol) of $Bu_4NF \cdot 3H_2O$ in 75 ml of CH_2Cl_2 was stirred at r.t. for 24 h. The heterogeneous mixture was filtered and the filtrate diluted with 200 ml of CH_2Cl_2. Usual workup gave an oil which was purified by FC (150 g of SiO_2, AcOEt/CH_2Cl_2/hexane 1:1:3). The two products obtained (2.5 g, R_f (AcOEt/CH_2Cl_2/hexane 1:1:3) 0.31 and 0.35) were taken up in 50 ml of THF and treated with 6.3 ml (5.4 g, 71 mmol) of formaldehyde dimethyl acetal and 2 g of P_2O_5 (200 mg every 30 min). After stirring at r.t. for 6 h, the mixture was filtered, concentrated to half of the volume, and partitioned between AcOEt and brine. Usual workup afforded an oil which was purified by FC (250 g of SiO_2, toluene/AcOEt 70:1) to give 1.85 g (53%) of **4** and 0.45 g (13%) of **5**.

Data of **4**. R_f (AcOEt/CH_2Cl_2/hexane 1:1:3) 0.52, $[\alpha]_D^{25} = +70.1°$ (c = 1.2). IR: 3090*w*, 3060*w*, 3005*m*, 2950*m*, 2935*m*, 2895*m*, 2870*m*, 1565*s*, 1495*m*, 1453*m*, 1363*m*, 1150*s*, 1110*s*, 1048*s*, 1027*s*, 950*m*, 915*m*. ^{1}H-NMR (200 MHz): 7.36–7.15 (*m*, 15 arom. H); 4.65–4.52 (*m*, 8 H); 4.40 (*s*, 2 H); 4.28, 3.96 (*AB*, J = 11.2, 2 H); 4.03 (*dd*, J = 4.0, 2.0, H–C(4)); 3.67 (*dd*, J = 10.5, 4.9, H–C(6)); 3.60 (*dd*, J = 10.5, 6.5, H–C(6)); 3.29 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 137.79 (*s*); 136.99 (*s*); 136.41 (*s*); 128.61 (*d*); 128.41 (*d*); 128.35 (*d*); 128.31 (*d*); 127.92 (*d*); 127.71 (*d*); 127.66 (*d*); 118.15 (*s*); 96.57 (*t*); 87.50 (*d*); 85.29 (*d*); 81.26 (*d*); 73.36 (*t*); 73.02 (*t*); 71.76 (*t*); 68.74 (*t*); 67.19 (*t*); 55.55 (*q*). CI-MS: 492 ($M^+ - OCH_3$), 477 ($M^+ - NO_2$). Anal. calc. for $C_{29}H_{33}NO_8$ (523.58): C 66.53, H 6.35, N 2.68; found: C 66.52, H 6.38, N 2.52.

Data of **5**. R_f (AcOEt/CH_2Cl_2/hexane 1:1:3) 0.47, $[\alpha]_D^{25} = -15.0°$ (c = 1.0). IR: 3090*w*, 3065*w*, 3030*m*, 3005*m*, 2930*m*, 2890*m*, 1560*s*, 1495*m*, 1453*m*, 1362*m*, 1310*w*, 1150*s*, 1110*s*, 1045*s*, 1028*s*, 915*m*. ^{1}H-NMR (200 MHz): 7.37–7.16 (*m*, 15 arom. H); 4.73–4.41 (*m*, 8 H); 4.41 (*ddd*, J = 6.5, 6.1, 5.5, H–C(5)); 4.37 (*d*, J = 6.1, H–C(3)); 4.16, 4.05 (*AB*, J = 11.0, 2 H); 4.15 (*t*, J = 6.1, H–C(4)); 3.96 (*dd*, J = 10.5, 6.5, H–C(6)); 3.75 (*dd*, J = 10.5, 5.5, H–C(6)); 3.34 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 137.89 (*s*); 137.30 (*s*); 136.50 (*s*); 128.48 (*d*); 128.41 (*d*); 128.33 (*d*); 128.19 (*d*); 128.07 (*d*); 127.93 (*d*); 127.70 (*d*); 115.79 (*s*); 96.83 (*t*); 83.75 (*d*); 83.54 (*d*); 82.55 (*d*); 73.72 (*t*); 73.43 (*t*); 72.70 (*t*); 70.30 (*t*); 67.44 (*t*); 55.64 (*q*). CI-MS: 492 ($M^+ - OCH_3$), 477 ($M^+ - NO_2$). Anal. calc. for $C_{29}H_{33}NO_8$ (523.58): C 66.53, H 6.35, N 2.68; found: C 66.79, H 6.50, N 2.64.

Reaction of **4**/**5** *with* CH_3NO_2. To a suspension of 3.10 g (129 mmol) of NaH in 28 ml of DMSO under N_2, 3.48 ml (3.94 g, 64.6 mmol) of CH_3NO_2 was added dropwise over 15 min. After the foaming had subsided (30 min), a soln. of 8.47 g (16.17 mmol) of **4**/**5** (4:1) in 28 ml of DMSO was added. The dark mixture was irradiated with a 60-W lamp and stirred for 5.5 h. The soln. was acidified with 3.8 ml of AcOH, stirred for 15 min, and then partitioned between AcOEt and brine. Usual workup afforded an oil which was purified by medium-pressure LC (500 g of SiO_2, AcOEt/CH_2Cl_2/hexane 1:15:15) to give 3.51 g (40%) of **6**, 1.05 g (12%) of 7, 1.25 g (14%) of **6**/**7**, and 0.431 g (6%) of **8**. A second chromatography on SiO_2 of the 1.25 g of **6**/**7** gave 0.76 g (9%) of **6** and 0.43 g (5%) of **7** (overall yield: 4.27 g (49%) of **6** and 1.48 g (17%) of **7**).

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-methoxymethyl-2-*C*-nitromethyl-*D*-glucitol* (**6**). R_f (AcOEt/CH_2Cl_2/hexane 1:15:15) 0.25, $[\alpha]_D^{25} = +16.3°$ (c = 1.72). IR: 3090*w*, 3060*w*, 3000*m*, 2930*m*, 2890*m*, 2870*m*, 1550*s*, 1495*m*, 1453*m*, 1375*m*, 1150*s*, 1100*s* (br.), 1070 (sh), 1045*s*, 1028*s*, 955*m*, 910*m*. ^{1}H-NMR (200 MHz): 7.37–7.19 (*m*, 15 arom. H); 4.85, 4.76 (*AB*, J = 11.7, CH_2NO_2); 4.65, 4.61 (*AB*, J = 6.5, 2 H); 4.60–4.50 (*m*, 6 H); 4.30 (*ddd*, J = 7.2, 5.3, 3.0, H–C(5)); 4.18 (*d*, J = 1.7, H–C(3)); 4.10 (*dd*, J = 3.0, 1.7, H–C(4)); 3.85, 3.74 (*AB*, J = 10.5, 2 H–C(1)); 3.59 (*dd*, J = 10.0, 5.3, H–C(6)); 3.47 (*dd*, J = 10.0, 7.2, H–C(6)); 3.32 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 138.00 (*s*); 137.34 (*s*); 137.23 (*s*); 128.47 (*d*); 128.44 (*d*); 128.33 (*d*); 127.94 (*d*); 127.77 (*d*); 127.68 (*d*); 96.93 (*t*); 84.99 (*s*); 84.58 (*d*); 84.00 (*d*); 82.87 (*d*); 75.52 (*t*); 73.31 (*t*); 72.62 (*t*); 71.90 (*t*); 70.05 (*t*); 66.55 (*t*); 55.45 (*q*). CI-MS: 537, 414. Anal. calc. for $C_{30}H_{35}NO_8$ (537.60): C 67.02, H 6.56, N 2.61; found: C 66.98, H 6.74, N 2.53.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-methoxymethyl-2-*C*-nitromethyl-*D*-mannitol* (**7**). R_f (AcOEt/CH_2Cl_2/hexane 1:15:15) 0.18, $[\alpha]_D^{25} = -9.5°$ (c = 1.0). IR: 3090*w*, 3060*w*, 3010*m*, 2930*m*, 2890*m*, 2865*m*, 1550*s*, 1495*m*, 1453*m*, 1400*m*, 1375*m*, 1365*m*, 1320*m*, 1150*s*, 1110*s* (br.), 1075 (sh), 1042*s*, 1025*s*, 960*m*, 913*m*. ^{1}H-NMR (200 MHz): 7.37–7.16 (*m*, 15 arom. H); 4.77, 4.66 (*AB*, J = 12.5, 2 H); 4.65, 4.62 (*AB*, J = 7.0, 2 H); 4.53 (*s*, 4 H); 4.45 (*s*, 2 H); 4.22 (*ddd*, J = 6.5, 5.0, 3.8, H–C(5)); 4.15 (*d*, J = 2.5, H–C(3)); 4.11 (*dd*, J = 3.8, 2.5, H–C(4)); 3.8 (*s*, 2

H–C(1)); 3.56 (*dd*, J = 10.5, 5.0, H–C(6)); 3.50 (*dd*, J = 10.5, 6.5, H–C(6)); 3.33 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 138.02 (*s*); 137.50 (*s*); 137.00 (*s*); 128.44 (*d*); 128.33 (*d*); 128.01 (*d*); 127.84 (*d*); 127.68 (*d*); 96.77 (*t*); 86.05 (*d*); 84.05 (*s*); 83.71 (*d*); 82.44 (*d*); 75.10 (*t*); 73.41 (*t*); 72.65 (*t*); 71.99 (*t*); 70.11 (*t*); 67.22 (*t*); 55.46 (*q*). CI-MS: 537, 414. Anal. calc. for $C_{30}H_{35}NO_8$ (537.60): C 67.02, H 6.56, N 2.61; found: C 66.91, H 6.45, N 2.50.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-methoxymethyl-*D-erythro-*hex-2-enitol* (**8**). R_f (AcOEt/CH_2Cl_2/hexane 1:15:15) 0.1, $[\alpha]_D^{25}$ = +26.0° (c = 1.36). IR: 3090*w*, 3060*w*, 3030*w*, 3000*m*, 2930*m*, 2885*m*, 2865*m*, 1550*w*, 1495*w*, 1450*m*, 1360*m*, 1310*m*, 1290*m*, 1180*m*, 1150*m*, 1097*s*, 1037*s*, 1028 (sh), 910*m*. ^{1}H-NMR (200 MHz): 7.35–7.23 (*m*, 15 arom. H); 4.85–4.45 (*m*, 10 H); 4.13, 4.08 (*AB*, J = 13.0, 2 H); 3.52 (*dd*, J = 9.9, 5.4, H–C(6)); 3.34 (*s*, CH_3O); 3.27 (*dd*, J = 9.9, 7.2, H–C(6)). ^{13}C-NMR (50 MHz): 142.94 (*s*); 138.07 (*s*); 137.85 (*s*); 137.18 (*s*); 135.22 (*s*); 128.36 (*d*); 128.31 (*d*); 128.09 (*d*); 127.98 (*d*); 127.93 (*d*); 127.70 (*d*); 127.65 (*d*); 95.69 (*t*); 82.50 (*d*); 80.27 (*d*); 73.63 (*t*); 73.41 (*t*); 69.72 (*t*); 69.40 (*t*); 58.52 (*t*); 55.26 (*q*). EI-MS: 477 (1), 446 (1), 385 (1), 355 (1), 323 (1), 294 (1), 263 (4), 249 (2), 233 (3), 217 (3), 187 (3), 181 (23), 163 (8), 91 (100). Anal. calc. for $C_{29}H_{32}O_6$ (476.58): C 73.08, H 6.77; found: C 73.14, H 6.74.

Anomerization of Pure **6** *and* **7** *by* $Bu_4NF \cdot 3H_2O$. A) *From* **6** *in THF*. A soln. of 100 mg (0.186 mmol) of **6**, 12 mg (0.038 mmol) of $Bu_4NF \cdot 3H_2O$ in 1 ml of THF was stirred for 14 h at r.t. Usual workup with AcOEt and brine afforded an oil which was purified by FC (10 g of SiO_2, AcOEt/hexane 1:3) to give 94 mg (94%) of a 45:55 mixture of **6**/**7**, ratio determined by the integrals of the signals of H–C(1) at 3.85 and 3.74 ppm (*AB* syst.) for **6** and at 3.8 ppm (*s*) for **7**.

B) *From* **7** *in THF*. Similarly, treatment of 100 mg (0.186 mmol) of **7** gave, after chromatography, 95 mg (95%) of a 44:56 mixture of **6**/**7**.

C) *From* **7** *in MeOH*. Similarly, treatment of 100 mg (0.186 mmol) of **7** in 1 ml of MeOH gave, after chromatography, 94 mg (94%) of **6**/**7** (65:35).

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-*C*-methoxymethoxymethyl-*D-glucose (**9**). To 18.6 ml of a 0.4M soln. of NaOMe in MeOH, 4 g (7.44 mmol) of **7** was added. The mixture was stirred for 15 min at r.t., then cooled to −78°, and treated with O_3 until **7** had disappeared (TLC monitoring). The soln. was purged with N_2 and warmed to r.t. After concentration to half of the volume, the residue was partitioned between AcOEt and brine. Usual workup followed by chromatography (400 g of SiO_2, AcOEt/hexane 1:3) gave 2.78 g (74%) of **9**. R_f (AcOEt/hexane 1:2) 0.33, $[\alpha]_D^{25}$ = +24.6° (c = 1.32). IR: 3080*w*, 3060*w*, 3025*w*, 3000*m*, 2930*m*, 2885*m*, 2865*m*, 1735*s*, 1493*m*, 1452*m*, 1363*m*, 1308*w*, 1148*s*, 1090*s* (br.), 1043*s*, 1028*s*, 970*m*, 913*m*, 690*m*. ^{1}H-NMR (200 MHz): 9.64 (*d*, J = 0.6, CHO); 7.35–7.15 (*m*, 15 arom. H); 4.61–4.35 (*m*, 9 H); 4.17–4.13 (*m*, 2 H); 3.90 (*d*, J = 10.6, 1 H); 3.76 (*dd*, J = 10.6, 0.6, 1 H); 3.72 (*dd*, J = 10.1, 5.0, H–C(6)); 3.64 (*dd*, J = 10.1, 6.2, H–C(6)); 3.31 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 200.55 (*d*); 138.03 (*s*); 137.52 (*s*); 136.87 (*s*); 128.41 (*d*); 128.31 (*d*); 127.95 (*d*); 127.80 (*d*); 127.67 (*d*); 96.67 (*t*); 90.00 (*s*); 86.81 (*d*); 83.59 (*d*); 82.93 (*d*); 73.41 (*t*); 72.39 (*t*); 71.98 (*t*); 69.86 (*t*); 67.27 (*t*); 55.33 (*q*). EI-MS: 476 (1), 461 (1), 415 (1), 370 (1), 325 (1), 308 (1), 295 (1), 279 (1), 247 (1), 237 (1), 219 (1), 217 (1), 181 (5), 145 (3), 126 (1), 111 (1), 108 (2), 107 (3), 106 (4), 105 (5), 98 (1), 97 (2), 92 (9), 91 (100), 77 (5), 45 (16). Anal. calc. for $C_{30}H_{34}O_7$ (506.62): C 71.12, H 6.76; found: C 70.92, H 6.95.

*Diphenyl [2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-(imidazol-1-yl)thiocarbonyl-2-*C*-methoxymethoxymethyl-*D/L*-glycero-*D*-glucitol-1-yl]phosphonate* (**10**). Under N_2, a mixture of 3 g (5.92 mmol) of **9**, 4.61 ml (5.61 g, 24 mmol) of diphenyl phosphite and 247 µl (179 mg, 1.77 mmol) of Et_3N was stirred at r.t. for 1 h. Chromatography of the mixture (500 g of SiO_2, AcOEt/hexane 1:2) gave 3.55 g (81%) of the α-hydroxyphosphonates. These products were taken up in 25 ml of THF, and 1.7 g (9.58 mmol) of *N,N'*-thiocarbonyldiimidazole was added. The mixture was stirred under N_2 at r.t. for 4 h, then concentrated *i.v.*, and the product isolated by FC (300 g of SiO_2, AcOEt/hexane 1:2): 3.54 g (70% from **9**) of **10** as a *ca.* 9:1 mixture of diastereoisomers. R_f (AcOEt/hexane 1:1) 0.38, $[\alpha]_D^{25}$ = −20.4° (c = 0.99). IR: 3160*w*, 3135*w*, 3080*w*, 3060*w*, 3000*m*, 2930*m*, 2895*m*, 2865*m*, 2825*w*, 1590*m*, 1488*s*, 1466*s*, 1452*m*, 1390*s*, 1360*m*, 1330*s*, 1285*s*, 1180*s*, 1160*s*, 1105*s*, 1095*s*, 1070*s*, 1040*s*, 1026*s*, 1008*s*, 950*s*, 937*s*, 914 (sh), 835*w*. ^{1}H-NMR (200 MHz): 8.48 (*s*, 0.15 H); 8.16 (*s*, 0.85 H); 7.73 (*s*, 0.15 H); 7.39 (*s*, 0.85 H); 7.38–6.86 (*m*, 26 H); 4.66–3.91 (*m*, 14 H); 3.57 (*d*, J = 4.2, 0.3 H); 3.43 (*d*, J = 4.6, 1.7 H); 3.29 (*s*, 0.45 H); 3.26 (*s*, 2.55 H). ^{13}C-NMR (50 MHz): 182.93 (*s*); 182.82 (*s*); 150.28 (*sd*, J(P,C) = 9.4); 149.96 (*sd*, J(P,C) = 9.4); 137.90 (*s*); 137.58 (*s*); 137.21 (*s*); 137.03 (*s*); 130.0–118.13 (*d*); 96.95 (*t*); 86.48 (*dd*, J(P,C) = 6.1); 86.30 (*sd*, J(P,C) = 2.4); 83.95 (*d*); 81.62 (*d*); 76.79 (*dd*, J(P,C) = 166.9); 73.12 (*t*); 72.98 (*t*); 72.20 (*t*); 70.08 (*t*); 68.11 (*dt*, J(P,C) = 1.8); 55.52 (*q*); minor isomer: 83.13 (*d*); 81.15 (*d*); 73.37 (*t*); 69.25 (*t*); 68.23 (*t*). ^{31}P-NMR (80 MHz): +8.81 (0.9 P); +8.80 (0.1 P). Anal. calc. for $C_{46}H_{47}N_2O_{10}PS$ (850.93): C 64.92, H 5.57, N 3.29, P 3.63, S 3.76; found: C 65.18, H 5.51, N 3.27, P 3.40, S 3.53.

*Diphenyl (2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-*D-glucitol-1-yl)phosphonate* (**11**). A mixture of 3.5 g (4.11 mmol) of **10** and 80 ml of dry toluene was added dropwise over 75 min to a stirred refluxing soln. of 200 ml of toluene and 4.35 ml of Bu_3SnH (4.78 g, 16.4 mmol) under N_2. After 4 h, (TLC:

reduction complete), the soln. was cooled and concentrated *i.v.* The residue was purified by FC (300 g of SiO_2, AcOEt/hexane 1:2): 2.35 g (79%) of **11** as an oil. R_f (AcOEt/hexane 1:2) 0.22, $[\alpha]_D^{25} = -2.4°$ (*c* = 1.45). IR: 3085*w*, 3065*w*, 3000*m*, 2930*m*, 2890*m*, 2870*m*, 2825*w*, 1593*m*, 1490*s*, 1453*m*, 1390*w*, 1268*s*, 1186*s*, 1160*s*, 1150*s*, 1107*s*, 1072*s*, 1040*s*, 1038*s*, 1009*m*, 930*s* (br.), 903*m*, 690*m*. ^{1}H-NMR (400 MHz): 7.35–7.09 (*m*, 25 arom. H); 4.67–4.45 (*m*, 8 H); 4.20 (*ddd*, *J* = 6.2, 5.2, 4.3, H–C(5)); 4.16 (*d*, *J* = 2.6, H–C(3)); 4.12 (*dd*, *J* = 4.3, 2.6, H–C(4)); 4.03, 3.86 (*AB*, *J* = 10.1, 2 H); 3.60 (*dd*, *J* = 10.0, 5.2, H–C(6)); 3.52 (*dd*, *J* = 10.0, 6.2, H–C(6)); 3.32 (*s*, CH_3O); 2.87 (*dd*, *J*(P,H) = 19.5, *J* = 15.4, H–C(1)); 2.65 (*dd*, *J*(P,H) = 19.5, *J* = 15.4, H–C(1)). ^{13}C-NMR (50 MHz): 150.63 (*s*); 150.44 (*s*); 150.36 (*s*); 138.16 (*s*); 137.80 (*s*); 137.75 (*s*); 129.66 (*d*); 129.49 (*d*); 128.32 (*d*); 128.28 (*d*); 128.23 (*d*); 127.82 (*d*); 127.71 (*d*); 127.58 (*d*); 127.48 (*d*); 124.75 (*d*); 120.81 (*d*); 120.72 (*d*); 120.63 (*d*); 120.54 (*d*); 96.82 (*t*); 85.70 (*dd*, *J*(P,C) = 6.7); 84.58 (*s*); 84.41 (*d*); 81.56 (*d*); 73.24 (*t*); 72.13 (*t*); 71.89 (*t*); 70.63 (*t*); 68.71 (*t*); 55.36 (*q*); 29.05 (*dt*, *J*(P,C) = 142.8). ^{31}P-NMR (80 MHz): +22.00. Anal. calc. for $C_{42}H_{45}O_9P$ (724.82): C 69.60, H 6.26, P 4.27; found: C 69.36, H 6.22, P 4.15.

*Diphenyl (2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-*D*-glucitol-1-yl)phosphonate* (**12**). A soln. of 2 g (2.76 mmol) of **11** in 100 ml of MeOH was treated with 200 mg of 10% Pd/C and hydrogenolysed under normal pressure until TLC showed the appearance of small amount of didebenzylated products with R_f (AcOEt/hexane 1:1) 0.28 and 0.05. Filtration, concentration *i.v.*, and chromatography (200 g of SiO_2, AcOEt/hexane 1:2): 306 mg (15%) of **11** and 1.09 g (62%) of **12** as an oil. R_f (AcOEt/hexane 1:1) 0.50, $[\alpha]_D^{25} = -13.8°$ (*c* = 1.47). IR: 3380*m* (br.), 3065*w*, 3000*m*, 2935*m*, 2890*m*, 2825*w*, 1592*s*, 1490*s*, 1453*m*, 1400*m*, 1362*m*, 1310*m*, 1255*s*, 1184*s*, 1160*s*, 1110*s*, 1072*s*, 1043*s*, 1028*s*, 1010*s*, 945*s* (br.), 903*s*, 848*w*, 830*w*, 685*m*. ^{1}H-NMR (200 MHz): 7.38–7.09 (*m*, 20 arom. H); 4.63 (*s*, 6 H); 4.44 (*dd*, *J* = 6.8, 5.6, H–C(4)); 4.26 (*d*, *J* = 5.6, H–C(3)); 4.50–4.20 (*m*, 1 H, exchange with D_2O); 3.98 (*ddd*, *J* = 6.8, 3.0, 2.3, H–C(5)); 3.74 (*dd*, *J* = 12.6, 2.3, H–C(6)); 3.74 (*s*, 2 H); 3.60–3.53 (*m*, H–C(6)); 3.32 (*s*, CH_3O); 2.95 (*dd*, *J*(P,H) = 19.6, *J* = 15.8, H–C(1)); 2.48 (*dd*, *J*(P,H) = 19.6, *J* = 15.8, H–C(1)). ^{13}C-NMR (50 MHz): 150.31 (*s*); 150.26 (*s*); 137.91 (*s*); 137.72 (*s*); 129.62 (*d*); 129.49 (*d*); 128.33 (*d*); 127.69 (*d*); 127.54 (*d*); 124.98 (*d*); 120.73 (*d*); 120.64 (*d*); 120.60 (*d*); 120.56 (*d*); 96.71 (*t*); 86.37 (*dd*, *J*(P,C) = 6.7); 82.15 (*d*); 81.92 (*s*); 81.82 (*d*); 72.73 (*t*); 72.50 (*t*); 70.84 (*dt*, *J*(P,C) = 3.2); 61.33 (*t*); 55.39 (*q*); 29.92 (*dt*, *J*(P,C) = 145.6). ^{31}P-NMR (80 MHz): +23.30. Anal. calc. for $C_{35}H_{39}O_9P$ (634.68): C 66.23, H 6.19, P 4.87; found: C 66.09, H 6.21, P 4.71.

*2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-1-(diphenoxyphosphoryl)-*D*-glucitol 6-(Diphenyl Phosphate)* (**13**). To a soln. of 400 mg (0.63 mmol) of **12** in 4 ml of abs. pyridine under N_2 at 0°, 195 µl (254 mg, 0.945 mmol) of diphenyl phosphorochloridate was added. This mixture was stirred at r.t. for 30 min and then partitioned between AcOEt and brine. Usual workup afforded a residue which was purified by chromatography (50 g of SiO_2, AcOEt/hexane 1:2): 496 mg (91%) of **13** as an oil. R_f (AcOEt/hexane 1:1) 0.56, $[\alpha]_D^{25} = +1.5°$ (*c* = 1.13). IR: 3065*m*, 3000*m*, 2940*m*, 2890*m*, 1590*s*, 1488*s*, 1453*m*, 1393*w*, 1365*w*, 1280*s* (br.), 1184*s*, 1160*s*, 1100*s* (br.), 1070*s*, 1040*s*, 1025*s*, 1010*s*, 950*s* (br.), 903*s*, 825*w*, 685*m*. ^{1}H-NMR (400 MHz): 7.33–7.07 (*m*, 30 arom. H); 4.62–4.44 (*m*, 6 H); 4.26–4.23 (*m*, 3 H); 4.12 (*d*, *J* = 1.9, H–C(3)); 4.11–4.07 (*m*, 1 H); 4.00, 3.81 (*AB*, *J* = 10.2, 2 H); 3.26 (*s*, CH_3O); 2.83 (*dd*, *J*(P,H) = 19.6, *J* = 15.3, H–C(1)); 2.61 (*dd*, *J*(P,H) = 19.6, *J* = 15.3, H–C(1)). ^{13}C-NMR (50 MHz): 150.46 (*s*); 150.39 (*s*); 150.32 (*s*); 150.28 (*s*); 137.37 (*s*); 129.68 (*d*); 129.53 (*d*); 128.38 (*d*); 128.32 (*d*); 127.82 (*d*); 127.72 (*d*); 127.52 (*d*); 125.28 (*d*); 124.79 (*d*); 120.67 (*d*); 120.57 (*d*); 120.46 (*d*); 120.01 (*d*); 119.92 (*d*); 96.78 (*t*); 85.52 (*s*); 85.09 (*dd*, *J*(P,C) = 6.2); 83.99 (*d*); 81.04 (*dd*, *J*(P,C) = 8.5); 72.32 (*t*); 72.02 (*t*); 68.57 (*t*); 68.17 (*dt*, *J*(P,C) = 6.0); 55.32 (*q*); 28.92 (*dt*, *J*(P,C) = 142.1). ^{31}P-NMR (80 MHz): +21.52; −11.47. Anal. calc. for $C_{47}H_{48}O_{12}P_2$ (866.86): C 65.12, H 5.58, P 7.14; found: C 65.14, H 5.75, P 7.32.

*Tetrasodium 2,5-Anhydro-1-deoxy-2-*C*-hydroxymethyl-1-phosphonato-*D*-glucitol 6-Phosphate* (**2a**). A soln. of 2.5 g (2.88 mmol) of **13** in 100 ml of MeOH was treated with 500 mg of 10% Pd/C and hydrogenolysed under normal pressure until the disappearance of the product with R_f (AcOEt/hexane 1:1) 0.25 (44 h). After filtration, 1.6 g of PtO_2 was added and the hydrogenolysis was continued until TLC showed the disappearance of UV-active products and the presence of a product with R_f (PrOH/NH_3/H_2O 4:3:1) 0.53 (24 h). After filtration and concentration *i.v.*, the residue was taken up in 20 ml of H_2O and heated to 50° for 6 h. The soln. was diluted with 50 ml of H_2O and washed with AcOEt (2 × 2 ml). The aq. phase was treated with *Dowex CCR-2* (Na^+ form) and lyophilised. The product was purified by FC (100 g of SiO_2 silylated, 150 ml of EtOH/H_2O 3:1 then 300 ml of EtOH/H_2O 2:1), concentrated *i.v.*, lyophilised, and dried *i.v.* over P_2O_5: 770 mg (63%) of **2a**. R_f (PrOH/NH_3/H_2O 4:3:1) 0.25, $[\alpha]_D^{25} = +9.3°$ (*c* = 0.97 H_2O). ^{1}H-NMR (400 MHz, D_2O): 4.09 (*t*, *J* = 6.5, 1 H); 4.01 (*d*, *J* = 5.9, H–C(3)); 4.00–3.80 (*m*, 3 H); 3.67, 3.61 (*AB*, *J* = 12.3, CH_2OH); 1.95 (*d*, *J*(P,H) = 18.5, 2 H–C(1)). ^{13}C-NMR (100 MHZ, D_2O): 85.07 (*s*); 79.91 (*dd*, *J*(P,C) = 7.0); 79.70 (*d*); 77.14 (*d*); 65.20 (*dt*, *J*(P,C) = 5.1); 64.97 (*t*); 32.42 (*dt*, *J*(P,C) = 128.5). ^{31}P-NMR (80 MHz, D_2O): +20.19; +2.10. FAB-MS: 427 (*M* + 1), 405 (*M* + 2 − Na), 387 (*M* + 2 − Na − H_2O), 383 (*M* + 3 − 2 Na), 365 (*M* + 3 − 2 Na − H_2O), 361 (*M* + 4 − 3 Na). Anal. calc. for $C_7H_{12}Na_4O_{11}P_2$ (426.08): C 19.73, H 2.84, P 14.53; found: C 19.60, H 3.12, P 14.30.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-*C*-methoxymethoxymethyl-*D*-mannose* (**14**) was prepared, as described for **9** (see above), from 4.65 ml of a 0.4M soln. of NaOMe in MeOH and 1 g (1.86 mmol) of **6**. Chromatography (100 g of SiO_2, AcOEt/hexane 1:3) gave 595 mg (63%) of **14**. R_f (AcOEt/hexane 1:2) 0.35, $[\alpha]_D^{25} = +34.7°$ ($c = 1.24$). IR: 3090*w*, 3060*w*, 3030*w*, 3000*m*, 2930*m*, 2870*m*, 2825*w*, 1730*s*, 1496*w*, 1453*m*, 1400*w*, 1363*m*, 1310*w*, 1150*m*, 1100*s* (br.), 1073*s*, 1042*s*, 1028 (sh), 948*m*, 913*m*. ^{1}H-NMR (200 MHz): 9.71 (*d*, $J = 1.1$, CHO); 7.34–7.17 (*m*, 15 arom. H); 4.60–4.32 (*m*, 9 H); 4.15 (*d*, $J = 1.8$, H–C(3)); 4.03 (*t*, $J = 1.8$, H–C(4)); 4.00 (*d*, $J = 10.7$, H–C(1)); 3.78 (*dd*, $J = 10.7, 1.1$, H–C(1)); 3.67 (*dd*, $J = 9.8, 5.7$, H–C(6)); 3.58 (*dd*, $J = 9.8, 7.5$, H–C(6)); 3.27 (*s*, CH_3O). ^{13}C-NMR (50 MHz): 203.77 (*d*); 138.07 (*s*); 137.18 (*s*); 137.08 (*s*); 128.46 (*d*); 128.38 (*d*); 128.30 (*d*); 127.98 (*d*); 127.81 (*d*); 127.73 (*d*); 127.69 (*d*); 127.60 (*d*); 96.63 (*t*); 91.64 (*s*); 84.30 (*d*); 81.87 (*d*); 73.24 (*t*); 72.71 (*t*); 71.21 (*t*); 69.97 (*t*); 68.91 (*t*); 55.25 (*q*). EI-MS: 506 (1), 476 (1), 461 (1), 415 (1), 383 (1), 325 (1), 263 (1), 235 (1), 219 (1), 187 (1), 182 (1), 181 (8), 175 (1), 168 (1), 157 (1), 146 (1), 145 (7), 129 (1), 127 (1), 126 (2), 107 (1), 92 (9), 91 (100), 84 (5), 45 (11). Anal. calc. for $C_{30}H_{34}O_7$ (506.62): C 71.12, H 6.76; found: C 70.95, H 6.64.

*Diphenyl [2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-(imidazol-1-yl)thiocarbonyl-2-*C*-methoxymethoxymethyl-*D*/*L*-glycero-*D*-mannitol-1-yl]phosphonate* (**15**). Under N_2, a mixture of 150 mg (0.296 mmol) of **14**, 230 µl (280 mg, 1.2 mmol) of diphenylphosphite and 4.2 µl (3 mg, 0.03 mmol) of Et_3N was stirred at r.t. for 12 h. Chromatography of the mixture (50 g of SiO_2, AcOEt/hexane 1:2) gave 162 mg (74%) of the α-hydroxyphosphonates. These products were taken up in 1 ml of THF, and 78 mg (0.437 mmol) of *N,N'*-thiocarbonyldiimidazole was added. The reaction mixture was stirred under N_2 for 2 h, then concentrated *i.v.*, and the residue was purified by FC (20 g of SiO_2, AcOEt/hexane 1:2): 158 mg (63% from **14**) of **15** as a *ca.* 4:1 mixture of diastereoisomers. R_f (AcOEt/hexane 1:1) 0.30, $[\alpha]_D^{25} = -8.7°$ ($c = 0.97$). IR: 3160*w*, 3135*w*, 3065*w*, 3000*m*, 2930*m*, 2880*m*, 2870*m*, 2830*w*, 1590*m*, 1532*w*, 1488*s*, 1468*s*, 1453*s*, 1390*s*, 1360*m*, 1330*s*, 1288*s*, 1180*s*, 1160*s*, 1105*s*, 1093*s*, 1072*s*, 1043*s*, 1027*s*, 1010*s*, 955*s*, 940*s*, 915 (sh), 905 (sh), 830*w*. ^{1}H-NMR (200 MHz): 8.35 (*t*, $J = 1.0, 0.2$ H); 8.30 (*t*, $J = 1.0, 0.8$ H); 7.65 (*dd*, $J = 1.7, 1.2, 0.2$ H); 7.55 (*t*, $J = 1.6, 0.8$ H); 7.34–6.92 (*m*, 26 H); 4.88–4.84 (*m*, 1 H); 4.66–4.00 (*m*, 11 H); 3.93 (*s*, 2 H); 3.51–3.34 (*m*, 2 H); 3.24 (*s*, 2.4 H); 3.20 (*s*, 0.6 H). ^{13}C-NMR (50 MHz): 183.20 (*d*); 183.06 (*d*); 150.18 (*sd*, $J(P,C) = 9.4$); 149.96 (*sd*, $J(P,C) = 8.9$); 138.05–118.26 (*d* + *s*); 97.24 (*t*); 85.90 (*sd*, $J(P,C) = 4.2$); 84.90 (*dd*, $J(P,C) = 2.8$); 84.51 (*d*); 81.60 (*d*); 77.55 (*dd*, $J(P,C) = 165$); 73.25 (*t*); 73.06 (*t*); 72.07 (*t*); 69.97 (*t*); 67.52 (*td*, $J(P,C) = 3.6$); 55.45 (*q*); minor isomer: 97.15 (*t*); 85.77 (*s*); 84.22 (*d*); 81.39 (*d*); 72.35 (*t*); 70.13 (*t*); 55.33 (*q*). ^{31}P-NMR (80 MHz): +8.69 (0.83 P); +7.87 (0.17 P). Anal. calc. for $C_{46}H_{47}N_2O_{10}PS$ (850.93): C 64.92, H 5.57, N 3.29, P 3.63, S 3.76; found: C 65.12, H 5.56, N 3.14, P 3.49, S 3.65.

*Diphenyl (2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-*D*-mannitol-1-yl)phosphonate* (**16**). A mixture of 500 mg (0.58 mmol) of **15** in 10 ml of dry toluene was added dropwise, over 75 min, to a stirred refluxing soln. of 25 ml of toluene and 560 µl of Bu_3SnH (613 mg, 2.11 mmol) under N_2. When TLC indicated the reaction was complete (2 h), the soln. was cooled and then concentrated *i.v.* The residue was purified by FC (50 g of SiO_2, AcOEt/hexane 1:2): 323 mg (77%) of **16**. R_f (AcOEt/hexane 1:2) 0.24, $[\alpha]_D^{25} = +18.1°$ ($c = 1.06$). IR: 3080*w*, 3060*w*, 3000*w*, 2930*m*, 2885*m*, 2865*m*, 1592*m*, 1490*s*, 1452*m*, 1394*m*, 1362*m*, 1308*m*, 1268*s*, 1183*s*, 1160*s*, 1143*s*, 1100*s*, 1070*s*, 1044*s*, 1027*s*, 1007*s*, 935*s* (br.), 902*m*. ^{1}H-NMR (200 MHz): 7.30–7.11 (*m*, 25 arom. H); 4.64 (*s*, 2 H); 4.56 (*s*, 2 H); 4.53 (*s*, 2 H); 4.51 (*s*, 2 H); 4.45 (*d*, $J = 2.4$, H–C(3)); 4.31 (*ddd*, $J = 6.4, 5.1, 3.6$, H–C(5)); 4.10 (*dd*, $J = 3.6, 2.4$, H–C(4)); 3.98, 3.94 (*AB*, $J = 10.0$, 2 H); 3.60 (*dd*, $J = 10.0, 5.1$, H–C(6)); 3.50 (*dd*, $J = 10.0, 6.4$, H–C(6)); 3.30 (*s*, CH_3O); 2.87 (*dd*, $J(P,H) = 19.0$, $J = 15.5$, H–C(1)); 2.70 (*dd*, $J(P,H) = 19.0$, $J = 15.5$, H–C(1)). ^{13}C-NMR (50 MHz): 150.38 (*sd*, $J(P,C) = 8.8$); 138.18 (*s*); 137.80 (2*s*); 129.55 (*d*); 128.32 (*d*); 128.25 (*d*); 127.84 (*d*); 127.61 (*d*); 127.50 (*d*); 124.87 (*d*); 120.67 (*d*); 120.58 (*d*); 97.02 (*t*); 86.20 (*dd*, $J(P,C) = 8.5$); 84.58 (*d*); 84.30 (*sd*, $J(P,C) = 1.6$); 81.75 (*d*); 73.19 (*t*); 72.35 (*t*); 71.72 (*t*); 70.51 (*t*); 68.73 (*td*, $J(P,C) = 3.5$); 55.32 (*q*); 30.43 (*dt*, $J(P,C) = 138.6$). ^{31}P-NMR (80 MHz): +20.97. Anal. calc. for $C_{42}H_{45}O_9P$ (724.82): C 69.60, H 6.26, P 4.27; found: C 69.31, H 6.23, P 4.19.

*Diphenyl (2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-*D*-mannitol-1-yl)phosphonate* (**17**). A soln. of 1 g (1.37 mmol) of **16** in 50 ml of MeOH was treated with 100 mg of 10% Pd/C and hydrogenolysed under normal pressure until TLC showed the appearance of small amounts of didebenzylated products with R_f (AcOEt/hexane 1:1) 0.05 and 0.08. Filtration, concentration *i.v.*, and chromatography (100 g of SiO_2, AcOEt/hexane 1:1): 50 mg (5%) of starting material **16** and 709 mg (81%) of **17** as an oil. R_f (AcOEt/hexane 1:1) 0.28, $[\alpha]_D^{25} = +31.0°$ ($c = 1.28$). IR: 3570*w*, 3460*w* (br.), 3065*w*, 3000*m*, 2930*m*, 2895*m*, 2825*w*, 1590*s*, 1490*s*, 1452*m*, 1395*m*, 1360*m*, 1308*m*, 1268*s*, 1184*s*, 1160*s*, 1145*s*, 1110*s*, 1085*s*, 1063*s*, 1045*s*, 1028*s*, 1008*m*, 935*s*, 903*s*. ^{1}H-NMR (200 MHz): 7.36–7.08 (*m*, 20 arom. H); 4.70–4.46 (*m*, 7 H); 4.24 (*dd*, $J = 5.4, 3.8$, H–C(4)); 4.15 (*ddd*, $J = 5.4, 3.8, 2.8$, H–C(5)); 3.93, 3.84 (*AB*, $J = 10.7$, 2 H); 3.66 (*dd*, $J = 12.0, 2.8$, H–C(6)); 3.59–3.52 (*m*, H–C(6)); 3.31 (*s*, CH_3O); 2.72 (*dd*, $J(P,H) = 19.5$, $J = 15.5$, H–C(1)); 2.62 (*dd*, $J(P,H) = 19.5$, $J = 15.5$, H–C(1)); 2.65–2.55 (*m*, 1 H, exchange with D_2O). ^{13}C-NMR (50 MHz): 150.44 (*s*); 150.36 (*s*); 150.27 (*s*); 150.18 (*s*); 137.72 (*s*); 137.64 (*s*); 129.64 (*d*); 129.55 (*d*); 128.40 (*d*); 127.83 (*d*); 127.76 (*d*); 127.57 (*d*); 125.00 (*d*); 124.94 (*d*); 120.62 (*d*); 120.53 (*d*);

96.87 (*t*); 86.09 (*dd*, J(P,C) = 7.4); 83.21 (*sd*, J(P,C) = 2.6); 82.81 (*d*); 82.63 (*d*); 72.71 (*t*); 72.29 (*t*); 69.38 (*dt*, J(P,C) = 6.9); 62.59 (*t*); 55.51 (*q*); 30.88 (*dt*, J(P,C) = 140.2). ^{31}P-NMR (80 MHz): +20.50. Anal. calc. for $C_{35}H_{39}O_9P$ (634.68): C 66.23, H 6.19, P 4.87; found: C 66.24, H 6.19, P 4.71.

*2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-2-*C*-methoxymethoxymethyl-1-(diphenoxyphosphoryl)-*D*-mannitol 6-(Diphenyl Phosphate)* (**18**). To a soln. of 300 mg (0.47 mmol) of **17** in 3 ml of abs. pyridine under N_2 at 0°, 117 µl (152 mg, 0.567 mmol) of diphenyl phosphorochloridate was added. The mixture was stirred at r.t. for 30 min and then partitioned between AcOEt and brine. Usual workup afforded a residue which was purified by chromatography (30 g of SiO_2, AcOEt/hexane 1:2): 360 mg (88%) of **18** as an oil. R_f (AcOEt/hexane 1:1) 0.47, $[\alpha]_D^{25}$ = +16.9° (*c* = 1.86). IR: 3065*m*, 3025*m*, 3000*m*, 2925*m*, 2885*m*, 1590*s*, 1488*s*, 1452*m*, 1395*m*, 1363*m*, 1280*s* (br.), 1180*s*, 1160*s*, 1110*s*, 1090*s*, 1070*s*, 1040*s*, 1024*s*, 1008*s*, 950*s* (br.), 903*s*, 685*m*, 665*m*. ^{1}H-NMR (400 MHz): 7.30–7.08 (*m*, 30 arom. H); 4.62, 4.58 (*AB*, J = 6.0, 2 H); 4.56, 4.51 (*AB*, J = 12.0, 2 H); 4.44 (*d*, J = 2.4, H–C(3)); 4.42, 4.38 (*AB*, J = 11.7, 2 H); 4.35–4.15 (*m*, 3 H); 4.07 (*dd*, J = 2.6, 2.4, H–C(4)); 3.93, 3.85 (*AB*, J = 10.2, 2 H); 3.27 (*s*, CH_3O); 2.80 (*dd*, J(P,H) = 19.5, J = 15.0, H–C(1)); 2.73 (*dd*, J(P,H) = 19.5, J = 15.0, H–C(1)). ^{13}C-NMR (50 MHz): 150.46 (*s*); 150.38 (*s*); 150.32 (*s*); 150.20 (*s*); 137.47 (*s*); 137.35 (*s*); 129.71 (*d*); 129.57 (*d*); 128.38 (*d*); 127.74 (*d*); 127.57 (*d*); 125.32 (*d*); 124.93 (*d*); 120.61 (*d*); 120.52 (*d*); 120.03 (*d*); 119.93 (*d*); 96.99 (*t*); 85.72 (*dd*, J(P,C) = 8.5); 84.93 (*sd*, J(P,C) = 1.9); 84.05 (*d*); 80.96 (*dd*, J(P,C) = 8.7); 72.65 (*t*); 71.94 (*t*); 68.65 (*dt*, J(P,C) = 4.0); 68.13 (*dt*, J(P,C) = 6.4); 55.35 (*q*); 30.60 (*dt*, J(P,C) = 139.0). ^{31}P-NMR (80 MHz): +20.61; −11.48. Anal. calc. for $C_{47}H_{48}O_{12}P_2$ (866.86): C 65.12, H 5.58, P 7.14; found: C 64.86, H 5.48, P 7.36.

*Tetrasodium 2,5-Anhydro-1-deoxy-2-*C*-hydroxymethyl-1-phosphonato-*D*-mannitol 6-Phosphate* (**19**). A soln. of 250 mg (0.28 mmol) of **18** in 10 ml of MeOH was treated with 50 mg of 10% Pd/C and hydrogenolysed under normal pressure until TLC indicated the disappearance of the products with R_f (AcOEt/hexane 1:1) 0.28 and 0.32 (4 h). After filtration, 50 mg of PtO_2 was added, and the hydrogenolysis was continued until TLC showed the disappearance of the UV-active products and the presence of a product with R_f ($PrOH/NH_3/H_2O$ 4:3:1) 0.71 (12 h). After filtration and concentration *i.v.*, the residue was taken up in 2 ml of H_2O and heated to 40° for 2 h. The soln. was diluted with 5 ml of H_2O and washed with AcOEt (2 × 1 ml). The aq. phase was treated with *Dowex CCR-2* (Na^+ form) and lyophilised. The product was purified by FC (10 g SiO_2 silylated, $EtOH/H_2O$ 2:1), concentrated *i.v.*, lyophilised, and dried over P_2O_5: 102 mg (84%) of **19**. R_f ($PrOH/NH_3/H_2O$ 4:3:1) 0.22, $[\alpha]_D^{25}$ = +2.9° (*c* = 0.91 H_2O). ^{1}H-NMR (200 MHz, D_2O): 4.30–3.70 (*m*, 5 H); 3.63, 3.51 (*AB*, J = 12.0, 2 H); 2.00 (*dd*, J(P,H) = 18.6, J = 14.7, H–C(1)); 1.80 (*dd*, J(P,H) = 18.6, J = 14.7, H–C(1)). ^{13}C-NMR (50 MHz, D_2O): 83.33 (*s*); 81.32 (*d*); 79.02 (*dd*, J(P,C) = 8.1); 74.54 (*d*); 64.41 (*dt*, J(P,C) = 4.9); 64.28 (*dt*, J(P,C) = 2.0); 36.11 (*dt*, J(P,C) = 126.1). ^{31}P-NMR (80 MHz, D_2O): +19.11; +3.35. FAB-MS (free acid): 339 (*M* + 19), 361 (*M* + Na). Anal. calc. for $C_7H_{12}Na_4O_{11}P_2$ (426.08): C 19.73, H 2.84, P 14.53; found: C 19.71, H 3.09, P 14.24.

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