Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 305–317

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of *C*-glycosylphosphonates from their ketols. Reconsideration of an abandoned route

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Received 8 October 1999; accepted 26 October 1999

Abstract

Isosteric phosphonate analogues of glycosyl 1-phosphates have been obtained by addition of $LiCH_2P(O)(OMe)_2$ to glyconolactones followed by Et_3SiH–TMSOTf reductive dehydroxylation of the resultant ketols. The compounds prepared include four β-linked pyranose derivatives (D-*galacto*, 2-azido-2-deoxy-D-*galacto*, D-*gluco*, D-*manno*) and one β-linked furanose derivative (D-*manno*). In the latter case the ketol was activated as its 2-acetate. In agreement with an observation in another laboratory, the dehydroxylation of a model ketol phosphonate failed with the use of Et_3SiH–$BF_3 \cdot Et_2O$.

1. Introduction

Carbohydrate processing in living organisms is mainly performed with nucleoside diphosphate sugars as glycosyl donors and glycosyltransferases as active catalysts.[1] The search for competitive inhibitors of glycosyltransferases constitutes the basis for the development of potential drugs against carbohydrate-based metabolic disorders.[2] Consequently, considerable attention is currently focused on the synthesis of enzymatically resistant analogues of glycosyl phosphates. Among them, isosteric phosphonates[3] in which the oxygen atom of the phosphoesteric linkage has been replaced by a CH_2 or a CF_2 group are of primary importance.[4] Various synthetic approaches to glycosylmethylphosphonates **A** have been described over the years in which the phosphorylmethyl group was introduced by multi-step processes[3] to ensure the control of the stereochemistry of the *C*-glycosidic bond. In particular, the synthesis of 2-amino-2-deoxy derivatives, a class of compounds of special interest because of the widespread biological activity of various glycosylamine phosphates, required an appropriate multi-step sequence for the introduction of the amino and phosphorylmethyl groups with the correct relative stereochemistry.[5] However, the direct installation of the phosphorylmethyl group at the anomeric carbon of aldoses by a tandem Horner–Emmons–Michael-type reaction with different stabilized phosphorus ylides invariably

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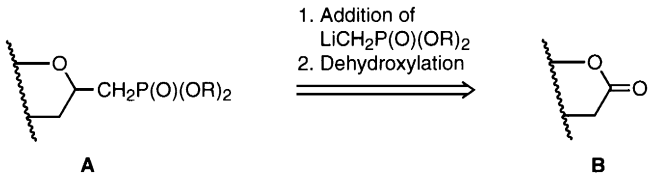
0957-4166/00/$ - see front matter
PII: S0957-4166(99)00477-2

led to mixtures of anomeric *C*-glycosides in both the *pyrano*[6] and *furano*[7] series. An alternative, quite straightforward entry to compounds **A** was envisaged by reaction of lithium dialkyl methylphosphonate with glyconolactones **B** followed by reductive dehydroxylation of the resulting ketol.[8] Unfortunately, this route was reported not to be viable because the reduction step under the standard Kishi conditions[9] employing triethylsilane–boron trifluoride proved unsuccessful. However, this method appeared quite attractive to us because various sugar lactones were readily available in our laboratory in the context of other *C*-glycoside syntheses.[10] Hence, the challenge lay in finding new conditions that allow for the reduction of ketol phosphonates and demonstrating to some extent the general applicability of the method for the synthesis of compound **A**. The successful results of our efforts are reported below.

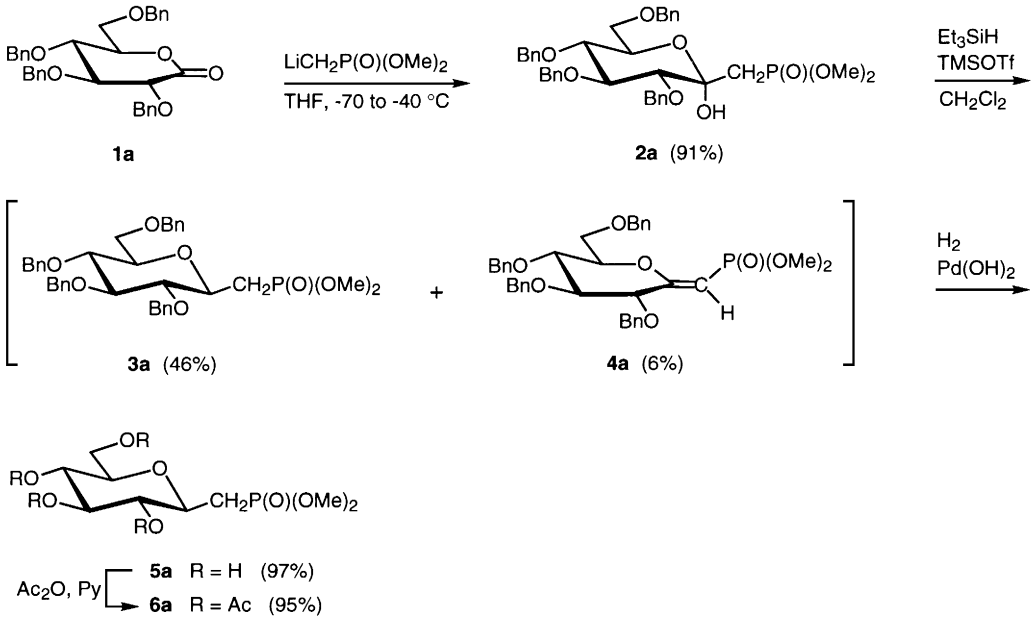


A **B**

2. Results and discussion

We initially examined the reduction of the known[11] ketol phosphonate[12] **2a** that in turn was prepared in very good yield (91%) by addition of lithium dimethyl methylphosphonate to 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone **1a** (Scheme 1). It was first confirmed that treatment of **2a** with excess triethylsilane and boron trifluoride etherate (Et_3SiH–$BF_3 \cdot Et_2O$) in dichloromethane at room temperature did not afford any dehydroxylated product while a substantial amount of unaltered starting material was recovered. This observation is in agreement with the unsuccessful reduction of the same compound **2a** reported by Nicotra under the above conditions.[8] However, when $BF_3 \cdot Et_2O$ was replaced with trimethylsilyl triflate (TMSOTf), the reductive dehydroxylation of **2a** occurred readily in a rather short time (45 min) to give a mixture of two different *C*-glycosides, i.e. the β-*C*-glucosylphosphonate **3a** and the phosphono exocyclic enol ether[13] **4a** in an 8:1 ratio and 52% overall yield. Interestingly, when the initial concentration of **2a** was reduced from 1 M to 0.1 M, the enol ether **4a** was the main product (**3a**:**4a** 1:1.5, 47% total yield). The catalytic hydrogenation of the mixture of **3a** and **4a** over $Pd(OH)_2$ resulted in the formation of the single β-*C*-glycoside **5a** (97% yield) as a consequence of the removal of the *O*-benzyl groups and reduction of the exocyclic carbon–carbon double bond. The glucosylmethylphosphonate **5a** was fully characterized through its tetra-*O*-acetyl derivative **6a**.

Thus, it is noteworthy that the simple replacement of the boron by the silicon Lewis acid promoter allows an entry to a sugar phosphonate by a method that was earlier not considered feasible.[8] The use of the Et_3SiH–TMSOTf system was suggested by our earlier work on the synthesis of furyl[14] and thiazolyl[15] *C*-glycosides from the corresponding ketols. An explanation of the above successful deoxygenation is tentatively advanced. The ^1H NMR spectrum of compound **2a** showed a long range (W) coupling of HO-2 with H-3. This spectroscopic feature is consistent[16] with the α-D configuration in which HO-2, C-2, C-3, and H-3 are coplanar (Fig. 1), as favoured by the *exo*-anomeric effect. Moreover, this particular orientation of the HO-2 group allows for a strong intramolecular hydrogen bonding with the phosphono oxygen as shown by the downfield chemical shift of HO-2 (5.77 ppm) in its ^1H NMR spectrum. It is very likely that $BF_3 \cdot Et_2O$ is unable to disrupt such a stable arrangement and promote the formation of the sugar oxycarbenium ion **7a**, the polar reaction intermediate that would lead to the product **5a** via stereoselective hydride addition from Et_3SiH. On the other hand the efficiency of TMSOTf leading to **7a**



Scheme 1.

may be due to some stabilization of the latter by the presence of resulting trifluoromethanesulfonate acting as a counterion.[17] The hydride addition to the *gluco* oxycarbenium ion **7a** occurs with high facial selectivity as shown in Fig. 1, thus leading exclusively to the β-D-linked sugar phosphonate **5a** as shown by ^{1}H NMR analysis ($J_{2,3}$=10.0 Hz). This result merits special note, since a low α/β selectivity was registered for the TMSOTf-promoted coupling at room temperature of another ketol of the *gluco* series with various oxygen[18] and phosphorus nucleophiles[4] as well as the reduction[15] in the presence of triethylsilane. Finally, the formation of the exocyclic enol ether **4a** may be explained by the loss of a proton of the methylene group of **7a**. Fortunately, the reduction of the exocyclic carbon–carbon double bond of **4a** was also highly stereoselective and converged on the formation of the same phosphonate **5a**.

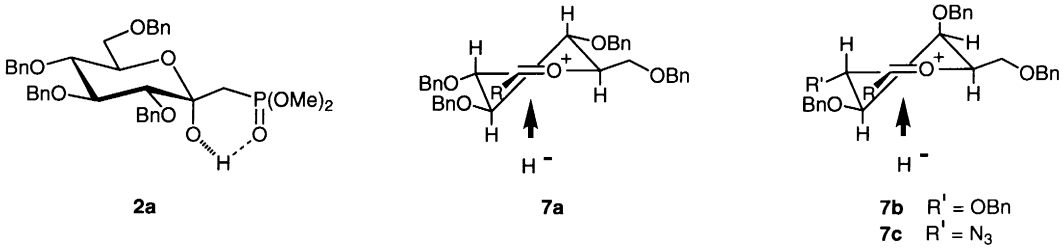
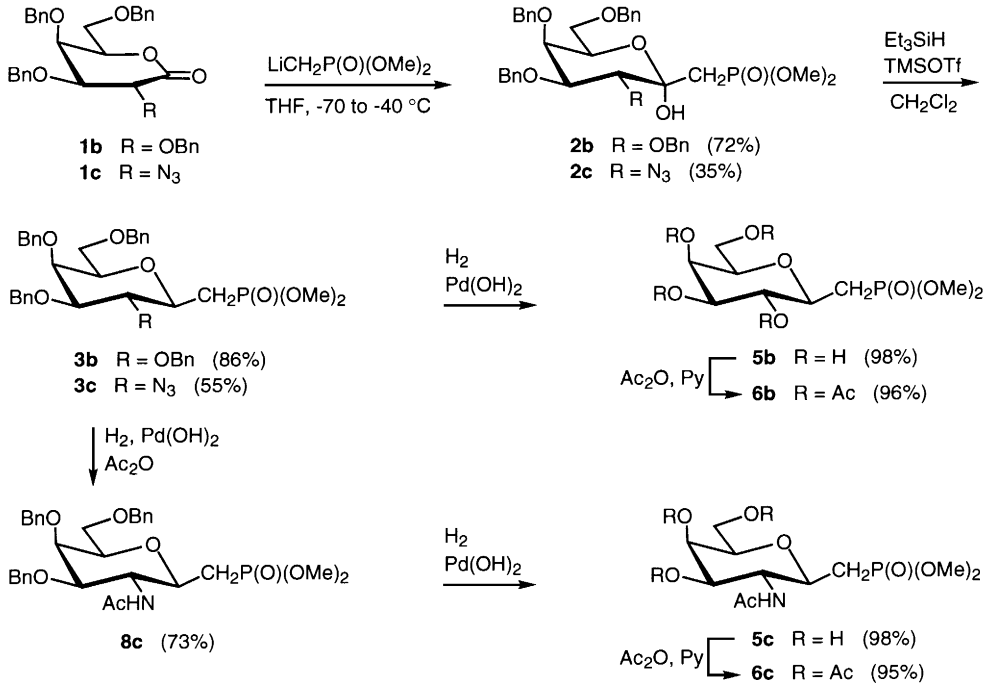


Fig. 1. Structure of ketol **2a** showing the intramolecular hydrogen bonding and stereochemical models for the hydride addition to the oxycarbenium ions **7a** (*gluco*), **7b** and **7c** (*galacto*) (R=$CH_2P(O)(OMe)_2$)

The above Et_3SiH–TMSOTf promoted reduction was successfully applied to the *galactopyrano* and *mannopyrano* series. Quite rewardingly the ketol phosphonate[12] **2b**, obtained from 2,3,4,6-tetra-*O*-benzyl-D-galactonolactone[15b] **1b**, afforded exclusively the β-linked galactosylmethylphosphonate **3b** in remarkably good yield (86%) (Scheme 2). Also the 3-azido derivative[12] **2c**, prepared in the same way from the 2-azido-2-deoxy-galactonolactone[15b] **1c**, was readily reduced to the corresponding β-D-linked methylphosphonate **3c** although in lower yield (55%).

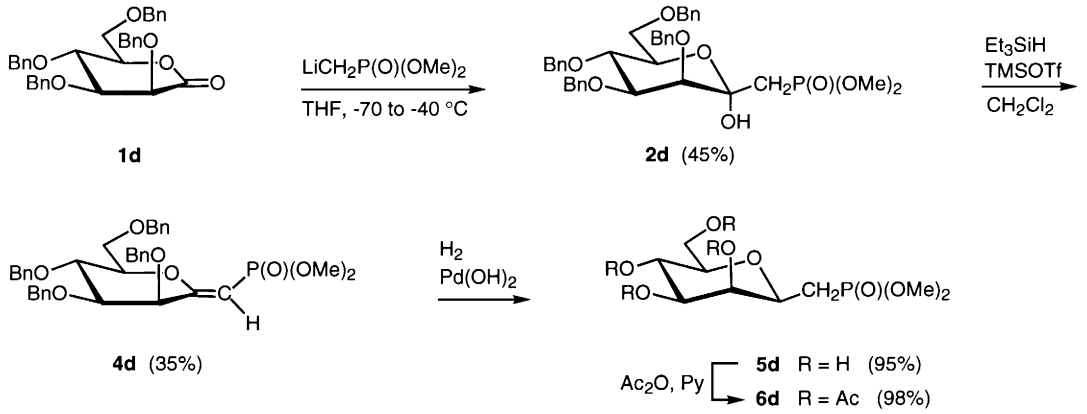


Scheme 2.

The high stereoselectivity of these reductions is in line with the stereochemical models **7b** and **7c** (Fig. 1). This result was expected based on earlier observations regarding the reduction[15b] and other reactions of a related *galactopyrano* compound.[10] The *O*-benzyl ether groups of **3b** were cleaved by catalytic hydrogenation and the resultant *C*-galactosylmethylphosphonate **5b** was characterized as the acetyl derivative **6b**. The transformation of **3c** to the target acetamido-galactosylmethylphosphonate **5c** was conveniently carried out in two sequential steps, the first involving the reduction of the azido group and its acetylation to give compound **8c**, the second involving the removal of the *O*-benzyl groups. The stepwise execution of these reactions gave better results than the one-pot reaction sequence. Finally, **5c** was characterized as the tri-*O*-acetyl derivative **6c**. It is worth pointing out that the β-D-linkage in **5b** and **5c** was easily assigned through their ^{1}H NMR spectra, showing coupling constant values $J_{2,3}$ of 9.6 and 10.0 Hz, respectively, typical of a *trans*-diaxial relationship in *C*-pyranosides adopting a $^4C_1$ conformation.

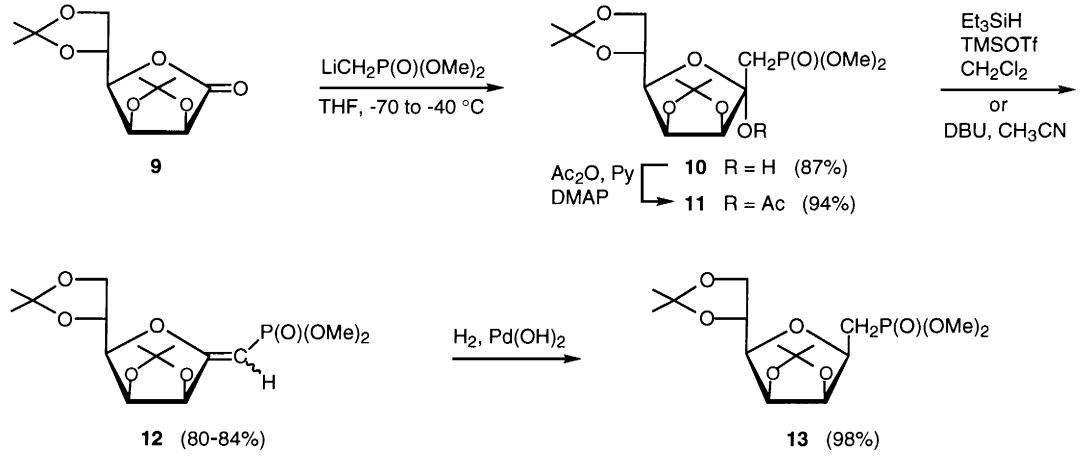
The reduction of the ketol phosphonate[12] **2d** derived from the 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone **1d** afforded only the phosphono exocyclic enol ether[13] **4d** as a reaction product in modest yield (35%). Part of the unreacted ketose **2d** (34%) was recovered from the reaction mixture (Scheme 3). Following the same reaction scheme carried out for the *gluco* series, compound **4d** was subjected to the catalytic hydrogenation to give the β-D-linked mannosylmethylphosphonate **5d** in very high yield (95%) that in turn was characterized as the tetra-*O*-acetyl derivative **6d**. Thus, also in this case, the method proved to be successful for the synthesis of the target *C*-glycosylphosphonate. In this series the assignment of the stereochemistry of the final product **5d** was less straightforward than in the above series. However, the well resolved ^{1}H NMR spectrum of the acetate **6d** showed a substantial NOE between H-2 and both H-4 and H-6, thus indicating two *trans*-diaxial relationships for the anomeric proton.

In contrast to the ketopyranoses **2a**–**d**, the α-D-ketofuranose **10** derived from the mannonolactone **9**



Scheme 3.

turned out to be resistant to reduction by the Et_3SiH–TMSOTf system as most of the compound **10** was recovered unaltered under the above reaction conditions (Scheme 4). Guided by earlier research in our laboratory regarding the successful reduction of thiazolylketoses through their acetates,[15] we considered the activation of the hydroxy group of **10** by conversion into the ketose acetate **11**. This simple transformation was efficiently carried out (94% yield) by acetylation of **10** with Ac_2O/pyridine in the presence of 4-*N*,*N*-(dimethylamino)pyridine (DMAP). Deoxygenation of **11** occurred readily on treatment with Et_3SiH–TMSOTf in dichloromethane at 0°C to give the exocyclic enol ether[13] **12** in excellent isolated yield (84%) as a 2:1 *Z:E* mixture. The stereoselective reduction of the carbon–carbon double bond of **12** by catalytic hydrogenation afforded the β-D-linked mannofuranosylmethylphosphonate **13** as a single product. The anomeric carbon–carbon β-linkage in this compound was readily established by the strong NOE between H-2 and H-5 proving their *cis*-relationship. On the other hand, the α-D-configuration of the precursor, the acetate **11**, was tentatively assigned by the close similarity of its ^1H NMR spectrum and that of the ketol[12] **10**. In closing this section it is worth mentioning that the conversion of **11** to **12** can also be carried out under basic conditions via a 1,2-elimination process. Accordingly, we found that treatment of **11** with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in refluxing acetonitrile afforded **12** in 80% isolated yield and 3:1 *Z:E* ratio. Unfortunately, the same procedure could not be extended to the acetates derived from ketopyranoses **2a**–**d** due to the unexpected difficult acetylation of these compounds under various conditions.



Scheme 4.

In conclusion, the above results suggest that the dehydroxylation of ketol phosphonates as an entry to *C*-glycosylmethylphosphonates should be recommended. The use of Et_3SiH–TMSOTf as a reducing system has been proven to operate efficiently in five model compounds, i.e. four pyranoses and one furanose. Each compound appeared to have its own behaviour with respect to the formation of two products, the target carbon-linked glycosylphosphonate and the exocyclic enol ether. Therefore, the extension of this approach to other systems should be carefully considered in light of the above results.

3. Experimental

3.1. General methods

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[19] and freshly distilled prior to use. Commercially available, activated 4-Å powdered molecular sieves (50 μm average particle size) were used without further activation. Flash column chromatography[20] was performed on silica gel 60 (230–400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20±2°C in $CHCl_3$. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. ^{1}H (300 MHz) and ^{31}P (121 MHz) NMR were recorded at rt for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by decoupling and/or two-dimensional experiments. Lactones **1a**–**e** were prepared in multigram scale as previously reported.[15b]

3.2. 3,4,5,7-Tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl-α*-D-gluco-*2-heptulopyranose **2a***

To a cooled (−70°C), stirred solution of freshly distilled dimethyl methylphosphonate (406 μL, 3.75 mmol) in anhydrous THF (7.5 mL) was added butyllithium (2.3 mL, 3.75 mmol, of a 1.6 M solution in hexanes) and, after 20 min, a solution of lactone **1a** (1.35 g, 2.50 mmol) in anhydrous THF (2.5 mL) during 10 min. The mixture was allowed to reach −40°C over a 1 h period, then was diluted with 1 M phosphate buffer at pH=7 (50 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was crystallized from cyclohexane to give pure **2a** (1.31 g, 79%). The mother liquor was concentrated and eluted from a column of silica gel with AcOEt to afford **2a** (0.20 g, 12%) as a solid. Mp 84–85°C (cyclohexane), lit.[11] 112–113°C (Et_2O–petroleum ether); $[\alpha]_D$=−18.6 (*c* 1.0, $CHCl_3$), lit.[11] $[\alpha]_D$=−15.6 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.39–7.20 (m, 20H, 4 Ph), 5.77 (dd, 1H, $J_{3,OH}$=1.7, $J_{P,OH}$=1.1 Hz, OH), 5.00 and 4.67 (2 d, 2H, *J*=11.7 Hz, PhCH_2), 4.94 (s, 2H, PhCH_2), 4.88 and 4.60 (2 d, 2H, *J*=11.0 Hz, PhCH_2), 4.50 (s, 2H, PhCH_2), 4.14 (dd, 1H, $J_{3,4}$=9.5, $J_{4,5}$=9.0 Hz, H-4), 4.10 (ddd, 1H, $J_{5,6}$=10.1, $J_{6,7a}$=2.0, $J_{6,7b}$=3.6 Hz, H-6), 3.75 (dd, 1H, $J_{7a,7b}$=10.7 Hz, H-7a), 3.73 (dd, 1H, H-5), 3.69 and 3.64 (2 d, 6H, $J_{H,P}$=11.1 Hz, 2 OMe), 3.61 (dd, 1H, H-7b), 3.28 (dd, 1H, H-3), 2.31 (dd, 1H, $J_{1a,1b}$=15.2, $J_{1a,P}$=17.6 Hz, H-1a), 1.68 (dd, 1H, $J_{1b,P}$=18.6 Hz, H-1b). ^{31}P NMR: δ 32.2. Anal. calcd for $C_{37}H_{43}O_9P$: C, 67.06; H, 6.54. Found: C, 67.28; H, 6.49.

3.3. 3,4,5,7-Tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl-α*-D-galacto-*2-heptulopyranose **2b***

The lactone **1b** (1.35 g, 2.50 mmol) was treated with $LiCH_2P(O)(OMe)_2$ (1.5 equiv.) as described for the preparation of **2a**. Column chromatography of the residue (AcOEt) gave **2b** (1.19 g, 72%) as a syrup; $[\alpha]_D$=−18.4 (*c* 1.0). ^{1}H NMR: δ 7.40–7.25 (m, 20H, 4 Ph), 5.84 (dd, 1H, $J_{3,OH}$=1.6, $J_{OH,P}$=1.1 Hz, OH),

5.00 and 4.68 (2 d, 2H, J=11.6 Hz, PhCH_2), 4.95 and 4.62 (2 d, 2H, J=11.5 Hz, PhCH_2), 4.77 (s, 2H, PhCH_2), 4.44 and 4.40 (2 d, 2H, J=11.5 Hz, PhCH_2), 4.25 (ddd, 1H, $J_{5,6}$=1.2, $J_{6,7a}$=6.8, $J_{6,7b}$=6.2 Hz, H-6), 4.10 (dd, 1H, $J_{3,4}$=9.8, $J_{4,5}$=2.8 Hz, H-4), 4.02 (dd, 1H, H-5), 3.74 (d, 1H, H-3), 3.67 and 3.62 (2 d, 6H, $J_{H,P}$=11.2 Hz, 2 OMe), 3.56 (dd, 1H, $J_{7a,7b}$=9.4 Hz, H-7a), 3.52 (dd, 1H, H-7b), 2.38 (dd, 1 H, $J_{1a,1b}$=15.3, $J_{1a,P}$=17.7 Hz, H-1a), 1.74 (dd, 1H, $J_{1b,P}$=18.6 Hz, H-1b). ^{31}P NMR: δ 32.1. Anal. calcd for $C_{37}H_{43}O_9P$: C, 67.06; H, 6.54. Found: C, 67.19; H, 6.51.

3.4. 3-Azido-4,5,7-tri-O-*benzyl-1,3-dideoxy-1-dimethoxyphosphoryl*-α-D-galacto-*2-heptulopyranose* ***2c***

The lactone **1c** (1.18 g, 2.50 mmol) was treated with $LiCH_2P(O)(OMe)_2$ (1.5 equiv.) as described for the preparation of **2a**. Column chromatography of the residue (1:1 cyclohexane:AcOEt, then AcOEt) gave **2c** (0.52 g, 35%) as a solid; mp 99–100°C (cyclohexane); $[\alpha]_D$=+42.9 (*c* 1.0). ^{1}H NMR: δ 7.45–7.26 (m, 15H, 3 Ph), 6.07 (dd, 1H, $J_{3,OH}$=1.9, $J_{P,OH}$=1.2 Hz, OH), 4.89 and 4.57 (2 d, 2H, J=11.2 Hz, PhCH_2), 4.78 and 4.72 (2 d, 2H, J=11.0 Hz, PhCH_2), 4.48 and 4.44 (2 d, 2H, J=11.5 Hz, PhCH_2), 4.26 (ddd, 1H, $J_{5,6}$=1.0, $J_{6,7a}$=7.2, $J_{6,7b}$=6.2 Hz, H-6), 4.10–4.06 (m, 2H, H-4, H-5), 3.74 (d, 6H, $J_{H,P}$=11.2 Hz, 2 OMe), 3.62 (dd, 1H, $J_{7a,7b}$=9.1 Hz, H-7a), 3.59 (dd, 1H, $J_{3,4}$=9.7 Hz, H-3), 3.56 (dd, 1H, H-7b), 2.64 (dd, 1H, $J_{1a,1b}$=15.2, $J_{1a,P}$=18.0 Hz, H-1a), 2.15 (dd, 1H, $J_{1b,P}$=18.7 Hz, H-1b). ^{31}P NMR: δ 31.9. Anal. calcd for $C_{30}H_{36}N_3O_8P$: C, 60.29; H, 6.07; N, 7.03. Found: C, 60.21; H, 6.03; N, 7.10.

3.5. 3,4,5,7-Tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl*-α-D-manno-*2-heptulopyranose* ***2d***

The lactone **1d** (1.35 g, 2.50 mmol) was treated with $LiCH_2P(O)(OMe)_2$ (1.5 equiv.) as described for the preparation of **2a**. Column chromatography of the residue (AcOEt) gave first unreacted **1d** (0.47 g, 35%). Eluted second was **2d** (0.75 g, 45%) as a syrup; $[\alpha]_D$=+24.2 (*c* 1.0). ^{1}H NMR: δ 7.41–7.18 (m, 20H, 4 Ph), 5.81 (bs, 1H, OH), 5.01 and 4.63 (2 d, 2H, J=11.6 Hz, PhCH_2), 4.88 and 4.57 (2 d, 2H, J=11.0 Hz, PhCH_2), 4.78 (s, 2H, PhCH_2), 4.58 and 4.46 (2 d, 2H, J=11.9 Hz, PhCH_2), 4.18 (dd, 1H, $J_{3,4}$=2.6, $J_{4,5}$=9.4 Hz, H-4), 4.06 (ddd, 1H, $J_{5,6}$=9.7, $J_{6,7a}$=4.8, $J_{6,7b}$=1.7 Hz, H-6), 3.96 (dd, 1H, H-5), 3.75 (dd, 1H, $J_{7a,7b}$=11.0 Hz, H-7a), 3.73 (d, 1H, H-3), 3.72 and 3.64 (2 d, 6H, $J_{H,P}$=11.1 Hz, 2 OMe), 2.61 (dd, 1H, $J_{1a,1b}$=15.1, $J_{1a,P}$=18.0 Hz, H-1a), 1.69 (dd, 1H, $J_{1b,P}$=17.8 Hz, H-1b). ^{31}P NMR: δ 32.3. Anal. calcd for $C_{37}H_{43}O_9P$: C, 67.06; H, 6.54. Found: C, 66.90; H, 6.57. The use of 3 equiv. of $LiCH_2P(O)(OMe)_2$ did not improve the yield of **2d**.

3.6. 2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl*-D-glycero-D-gulo-*heptitol* ***3a*** *and 2,6-anhydro-3,4,5,7-tetra*-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl*-D-gluco-*hept-1-enitol* ***4a***

Method a: To a cooled (0°C), stirred mixture of **2a** (199 mg, 0.30 mmol), activated 4-Å powdered molecular sieves (0.30 g), triethylsilane (476 μL, 3.00 mmol), and anhydrous CH_2Cl_2 (3.0 mL) was added trimethylsilyl triflate (54 μL, 0.30 mmol). The mixture was stirred at 0°C for 10 min, then warmed to room temperature, stirred for an additional 50 min, and treated with trimethylsilyl triflate (54 μL, 0.30 mmol). After 30 min the mixture was diluted with Et_3N (ca. 0.2 mL) and CH_2Cl_2 (50 mL), filtered through Celite, and concentrated. Column chromatography of the residue (2:1 AcOEt:cyclohexane, then AcOEt) gave first a 10:1 mixture of an uncharacterized product and **2a** (62 mg, ca. 30%). Eluted second was a 1.5:1 mixture of **4a** and **3a** (91 mg, 47%). **4a**: ^{1}H NMR selected data: δ 5.07 (dd, 1H, $J_{1,3}$=0.6, $J_{1,P}$=12.0 Hz, H-1), 4.12 (ddd, 1H, $J_{5,6}$=9.8, $J_{6,7a}$=2.0, $J_{6,7b}$=3.1 Hz, H-6), 3.96 (ddd, 1H, $J_{3,4}$=6.0, $J_{3,P}$=1.1 Hz, H-3), 3.88 (dd, 1H, $J_{4,5}$=6.8 Hz, H-5), 3.84 (dd, 1H, $J_{7a,7b}$=11.5 Hz, H-7a), 3.79 (dd, 1H, H-

4), 3.78 (dd, 1H, H-7b). ^{31}P NMR: δ 20.6. **3a**: ^{1}H NMR selected data: δ 4.93 and 4.88 (2 d, 2H, *J*=11.8 Hz, PhC*H*$_2$), 4.93 and 4.67 (2 d, 2H, *J*=11.3 Hz, PhC*H*$_2$), 4.84 and 4.60 (2 d, 2H, *J*=11.4 Hz, PhC*H*$_2$), 4.57 and 4.53 (2 d, 2H, *J*=12.0 Hz, PhC*H*$_2$), 2.29 (ddd, 1H, $J_{1a,1b}$=15.5, $J_{1a,2}$=2.3, $J_{1a,P}$=19.5 Hz, H-1a), 1.90 (ddd, 1H, $J_{1b,2}$=9.4, $J_{1b,P}$=16.4 Hz, H-1b). ^{31}P NMR: δ 32.4.

Method b: To a stirred solution of **2a** (331 mg, 0.50 mmol), triethylsilane (794 μL, 5.00 mmol), and anhydrous CH_2Cl_2 (0.5 mL) was added dropwise trimethylsilyl triflate (90 μL, 0.50 mmol). The mixture was stirred at room temperature for 45 min, then diluted with Et_3N (ca. 0.2 mL), and concentrated. Column chromatography of the residue (2:1 AcOEt:cyclohexane, then AcOEt) gave first a 15:1 mixture of an uncharacterized product and **2a** (86 mg, ca. 26%). Eluted second was a 8:1 mixture of **3a** and **4a** (168 mg, 52%).

3.7. 2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl*-D-glycero-L-manno-*heptitol* ***3b***

To a stirred solution of **2b** (331 mg, 0.50 mmol), triethylsilane (794 μL, 5.00 mmol), and anhydrous CH_2Cl_2 (0.5 mL) was added dropwise trimethylsilyl triflate (90 μL, 0.50 mmol). The mixture was stirred at room temperature for 45 min, then diluted with Et_3N (ca. 0.2 mL), and concentrated. Column chromatography of the residue (AcOEt) gave **3b** (278 mg, 86%) as a syrup; $[\alpha]_D$=−6.5 (*c* 1.2). ^{1}H NMR: δ 7.40–7.25 (m, 20H, 4 Ph), 5.00 and 4.67 (2 d, 2H, *J*=11.5 Hz, PhC*H*$_2$), 4.96 and 4.63 (2 d, 2H, *J*=11.0 Hz, PhC*H*$_2$), 4.77 and 4.68 (2 d, 2H, *J*=11.6 Hz, PhC*H*$_2$), 4.47 and 4.42 (2 d, 2H, *J*=11.5 Hz, PhC*H*$_2$), 4.02 (dd, 1H, $J_{4,5}$=2.3, $J_{5,6}$=0.6 Hz, H-5), 3.74–3.54 (m, 6H), 3.67 and 3.66 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 2.35 (ddd, 1H, $J_{1a,1b}$=15.5, $J_{1a,2}$=1.8, $J_{1a,P}$=20.0 Hz, H-1a), 1.95 (ddd, 1H, $J_{1b,2}$=9.8, $J_{1b,P}$=16.0 Hz, H-1b). ^{31}P NMR: δ 32.3. Anal. calcd for $C_{37}H_{43}O_8P$: C, 68.72; H, 6.70. Found: C, 68.92; H, 6.72.

3.8. 2,6-Anhydro-3-azido-4,5,7-tri-O-*benzyl-1,3-dideoxy-1-dimethoxyphosphoryl*-D-glycero-L-manno-*heptitol* ***3c***

To a stirred solution of **2c** (299 mg, 0.50 mmol), triethylsilane (794 μL, 5.00 mmol), and anhydrous CH_2Cl_2 (0.5 mL) was added dropwise trimethylsilyl triflate (90 μL, 0.50 mmol). The mixture was stirred at room temperature for 45 min, then diluted with Et_3N (ca. 0.2 mL), and concentrated. Column chromatography of the residue (3:1 AcOEt:cyclohexane, then AcOEt) gave **3c** (157 mg, 55%) as a syrup; $[\alpha]_D$=−14.2 (*c* 1.0). ^{1}H NMR: δ 7.42–7.24 (m, 15H, 3 Ph), 4.90 and 4.57 (2 d, 2H, *J*=11.4 Hz, PhC*H*$_2$), 4.77 and 4.67 (2 d, 2H, *J*=11.5 Hz, PhC*H*$_2$), 4.47 and 4.43 (2 d, 2H, *J*=11.6 Hz, PhC*H*$_2$), 4.01 (dd, 1H, $J_{4,5}$=2.8, $J_{5,6}$=0.6 Hz, H-5), 3.73 (dd, 1H, $J_{2,3}$=$J_{3,4}$=9.8 Hz, H-3), 3.72–3.56 (m, 3H, H-6, 2 H-7), 3.72 and 3.70 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 3.52 (dd, 1H, H-4), 3.48 (dddd, 1H, $J_{1a,2}$=2.3, $J_{1b,2}$=9.5, $J_{2,P}$=13.2 Hz, H-2), 2.36 (ddd, 1H, $J_{1a,1b}$=15.5, $J_{1a,P}$=20.0 Hz, H-1a), 2.06 (ddd, 1H, $J_{1b,P}$=16.8 Hz, H-1b). ^{31}P NMR: δ 31.8. Anal. calcd for $C_{30}H_{36}N_3O_7P$: C, 61.95; H, 6.24; N, 7.22. Found: C, 60.11; H, 6.28; N, 7.13.

3.9. 2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1-deoxy-1-dimethoxyphosphoryl*-D-manno-*hept-1-enitol* ***4d***

To a cooled (0°C), stirred mixture of **2d** (199 mg, 0.30 mmol), activated 4-Å powdered molecular sieves (0.30 g), triethylsilane (476 μL, 3.00 mmol), and anhydrous CH_2Cl_2 (3.0 mL) was added trimethylsilyl triflate (108 μL, 0.60 mmol). The mixture was stirred at 0°C for 10 min, then warmed to room temperature, stirred for an additional 30 min, diluted with Et_3N (ca. 0.2 mL) and CH_2Cl_2 (50 mL), filtered through Celite, and concentrated. Column chromatography of the residue (2:1 AcOEt:cyclohexane,

then AcOEt) gave first benzyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-dimethoxyphosphoryl-α-D-*manno*-2-heptulopyranoside as a syrup (13 mg, 6%); $[\alpha]_D=-6.1$ (*c* 1.0). ^{1}H NMR selected data: δ 4.54 (d, 1H, $J_{3,4}$=2.5 Hz, H-3), 4.19 (dd, 1H, $J_{4,5}$=9.5 Hz, H-4), 4.02 (dd, 1H, $J_{5,6}$=9.0 Hz, H-5), 3.74–3.67 (m, 3H, H-6, 2 H-7), 3.66 and 3.63 (2 d, 6H, $J_{H,P}$=10.8 Hz, 2 OMe), 2.85 (dd, 1H, $J_{1a,1b}$=15.9, $J_{1a,P}$=19.0 Hz, H-1a), 2.50 (dd, 1H, $J_{1b,P}$=18.4 Hz, H-1b). ^{31}P NMR: δ 28.8. MALDI-TOF MS: 776.8 (M^++Na), 792.2 (M^++K). Anal. calcd for $C_{44}H_{49}O_9P$: C, 70.20; H, 6.56. Found: C, 70.41; H, 6.48. Eluted second was unreacted **2d** slightly contaminated by the benzyl glycoside (68 mg, 34%). Eluted third was **4d** (68 mg, 35%); $[\alpha]_D=+2.8$ (*c* 1.0). ^{1}H NMR: δ 7.39–7.17 (m, 20H, 4 Ph), 5.04 (dd, 1H, $J_{1,3}$=0.7, $J_{1,P}$=12.0 Hz, H-1), 4.73 and 4.51 (2 d, 2H, *J*=12.3 Hz, PhCH_2), 4.68 and 4.58 (2 d, 2H, *J*=12.0 Hz, PhCH_2), 4.63 and 4.47 (2 d, 2H, *J*=11.5 Hz, PhCH_2), 4.62 and 4.55 (2 d, 2H, *J*=12.0 Hz, PhCH_2), 4.20 (ddd, 1 H, $J_{3,4}$=2.6, $J_{3,P}$=1.2 Hz, H-3), 4.06 (dd, 1H, $J_{4,5}$=4.8, $J_{5,6}$=8.0 Hz, H-5), 3.99 (ddd, 1H, $J_{6,7a}$=3.0, $J_{6,7b}$=4.3 Hz, H-6), 3.82 (ddd, 1H, $J_{4,P}$=1.2 Hz, H-4), 3.78–3.75 (m, 2H, 2 H-7), 3.68 and 3.67 (2 d, 6H, $J_{H,P}$=11.5 Hz, 2 OMe). ^{31}P NMR: δ 20.5. Anal. calcd for $C_{37}H_{41}O_8P$: C, 68.93; H, 6.41. Found: C, 69.08; H, 6.51.

When the reaction was carried out as described for the preparation of the *C*-galactoside **3b** (1 M solution of **2d** in CH_2Cl_2, 1 equiv. of TMSOTf, rt, 1 h), a complex mixture of products was formed from which the benzyl glycoside and the ketose **2d** were isolated in ca. 25 and 10% yields, respectively.

3.10. 2,6-Anhydro-1-deoxy-1-dimethoxyphosphoryl-D-glycero-D-gulo-*heptitol* ***5a***

A vigorously stirred 1.5:1 mixture of **4a** and **3a** (194 mg, 0.3 mmol), 20% palladium hydroxide on carbon (194 mg), AcOEt (3 mL), and MeOH (3 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated to give **5a** (83 mg, 97%) at least 95% pure by NMR analysis. ^{1}H NMR (D_2O): δ 3.82–3.62 (m, 2H), 3.71 and 3.70 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 3.54 (dddd, 1H, $J_{1a,2}$=2.5, $J_{1b,2}$=$J_{2,3}$=10.0, $J_{2,P}$=12.0 Hz, H-2), 3.44–3.31 (m, 3H), 3.18–3.14 (m, 1H), 2.44 (ddd, 1H, $J_{1a,1b}$=15.9, $J_{1a,P}$=19.8 Hz, H-1a), 2.07 (ddd, 1H, $J_{1b,P}$=16.2 Hz, H-1b).

3.11. 2,6-Anhydro-1-deoxy-1-dimethoxyphosphoryl-D-glycero-L-manno-*heptitol* ***5b***

The *C*-galactoside **3b** (194 mg, 0.3 mmol) was hydrogenated as described for the preparation of **5a** to give **5b** (84 mg, 98%) at least 95% pure by NMR analysis. ^{1}H NMR (D_2O): δ 3.85 (dd, 1H, $J_{4,5}$=3.3, $J_{5,6}$=0.5 Hz, H-5), 3.66 (d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 3.63–3.51 (m, 3H, H-6, 2 H-7), 3.49 (dd, 1H, $J_{3,4}$=9.3 Hz, H-4), 3.43 (dddd, 1H, $J_{1a,2}$=2.1, $J_{1b,2}$=9.8, $J_{2,3}$=9.6, $J_{2,P}$=11.0 Hz, H-2), 3.32 (dd, 1H, H-3), 2.41 (ddd, 1H, $J_{1a,1b}$=15.8, $J_{1a,P}$=20.0 Hz, H-1a), 2.02 (ddd, 1H, $J_{1b,P}$=16.3 Hz, H-1b).

3.12. 3-Acetamido-2,6-anhydro-4,5,7-tri-O-*benzyl-1,3-dideoxy-1-dimethoxyphosphoryl*-D-glycero-L-manno-*heptitol* ***8c***

A vigorously stirred mixture of **3c** (174 mg, 0.3 mmol), 20% palladium hydroxide on carbon (174 mg), and AcOEt (6 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 2 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated. A solution of the crude amine in acetic anhydride (2.0 mL) was kept at room temperature for 1 h, then concentrated. Column chromatography of the residue (4:1 acetone:AcOEt, then acetone) gave **8c** (131 mg, 73%) as a solid; mp 115–116°C (Et_2O–cyclohexane); $[\alpha]_D=+28.8$ (*c* 1.0). ^{1}H NMR: δ 7.42–7.25 (m, 15H, 3 Ph), 5.17 (d,

1H, $J_{3,NH}$=8.9 Hz, NH), 4.95 and 4.62 (2 d, 2H, J=11.6 Hz, PhCH_2), 4.72 and 4.40 (2 d, 2H, J=12.0 Hz, PhCH_2), 4.48 and 4.46 (2 d, 2H, J=11.5 Hz, PhCH_2), 4.18 (ddd, 1H, $J_{2,3}$=10.0, $J_{3,4}$=10.6 Hz, H-3), 4.02 (dd, 1H, $J_{4,5}$=2.7, $J_{5,6}$=0.6 Hz, H-5), 3.73–3.58 (m, 4H, H-2, H-6, 2 H-7), 3.67 and 3.66 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 3.51 (dd, 1H, H-4), 2.16–2.07 (m, 2H, 2 H-1), 1.92 (s, 3H, Ac). ^{31}P NMR: δ 33.0. Anal. calcd for $C_{32}H_{40}NO_8P$: C, 64.31; H, 6.75; N, 2.34. Found: C, 64.24; H, 6.79; N, 2.30.

3.13. 3-Acetamido-2,6-anhydro-1,3-dideoxy-1-dimethoxyphosphoryl-D-glycero-L-manno-*heptitol* ***5c***

The *C*-galactoside **8c** (119 mg, 0.2 mmol) was hydrogenated as described for the preparation of **5a** to give **5c** (64 mg, 98%) at least 95% pure by NMR analysis. ^{1}H NMR selected data (D_2O): δ 3.86 (dd, 1H, $J_{4,5}$=3.0, $J_{5,6}$=0.7 Hz, H-5), 3.74 (dd, 1H, $J_{2,3}$=$J_{3,4}$=10.0 Hz, H-3), 3.65 and 3.64 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 2.13 (ddd, 1H, $J_{1a,1b}$=15.8, $J_{1a,2}$=3.1, $J_{1a,P}$=19.5 Hz, H-1a), 2.04 (ddd, 1H, $J_{1b,2}$=9.6, $J_{1b,P}$=16.6 Hz, H-1b), 1.92 (s, 3H, Ac).

3.14. 2,6-Anhydro-1-deoxy-1-dimethoxyphosphoryl-D-glycero-D-galacto-*heptitol* ***5d***

The exocyclic enol ether **4d** (129 mg, 0.2 mmol) was hydrogenated as described for the preparation of **5a** to give **5d** (54 mg, 95%) at least 95% pure by NMR analysis. ^{1}H NMR (D_2O): δ 3.76 (ddd, 1H, $J_{1a,2}$=$J_{2,P}$=9.0, $J_{2,3}$=0.8, $J_{1b,2}$=4.6 Hz, H-2), 3.70 (dd, 1H, $J_{6,7a}$=2.2, $J_{7a,7b}$=12.5 Hz, H-7a), 3.68 (dd, 1H, $J_{3,4}$=3.3 Hz, H-3), 3.62 and 3.61 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 3.54 (dd, 1H, $J_{6,7b}$=5.8 Hz, H-7b), 3.49 (dd, 1H, $J_{4,5}$=9.8 Hz, H-4), 3.40 (dd, 1H, $J_{5,6}$=9.5 Hz, H-5), 3.19 (ddd, 1H, H-6), 2.20 (ddd, 1H, $J_{1a,1b}$=15.9, $J_{1a,P}$=17.0 Hz, H-1a), 2.06 (ddd, 1H, $J_{1b,P}$=19.3 Hz, H-1b).

3.15. 3,4,5,7-Tetra-O-*acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl*-D-glycero-D-gulo-*heptitol* ***6a***

A solution of crude **5a** (83 mg, ca. 0.29 mmol) in pyridine (1.5 mL) and acetic anhydride (1.5 mL) was kept at room temperature overnight, then concentrated. The residue was eluted from a column of silica gel with 1:1 acetone:AcOEt to give **6a** (125 mg, 92% overall yield from the **3a**/**4a** mixture) as a white solid; mp 121–122°C (Et_2O); $[\alpha]_D$=+3.5 (*c* 1.0). ^{1}H NMR (C_6D_6): δ 5.29 (dd, 1H, $J_{3,4}$=8.9, $J_{4,5}$=9.4 Hz, H-4), 5.21 (dd, 1H, $J_{5,6}$=9.6 Hz, H-5), 4.96 (dd, 1H, $J_{2,3}$=9.5 Hz, H-3), 4.15 (dd, 1H, $J_{6,7a}$=4.6, $J_{7a,7b}$=12.3 Hz, H-7a), 4.04 (dd, 1H, $J_{6,7b}$=2.2 Hz, H-7b), 3.84 (dddd, 1H, $J_{1a,2}$=2.8, $J_{1b,2}$=9.2, $J_{2,P}$=11.5 Hz, H-2), 3.48 and 3.34 (2 d, 6H, $J_{H,P}$=10.8 Hz, 2 OMe), 3.23 (ddd, 1 H, H-6), 2.00 (ddd, 1H, $J_{1a,1b}$=15.6, $J_{1a,P}$=19.8 Hz, H-1a), 1.85 (ddd, 1H, $J_{1b,P}$=15.5 Hz, H-1b), 1.71, 1.68, 1.64, and 1.60 (4 s, 12H, 4 Ac). ^{31}P NMR: δ 30.3. Anal. calcd for $C_{17}H_{27}O_{12}P$: C, 44.94; H, 5.99. Found: C, 45.17; H, 5.92.

3.16. 3,4,5,7-Tetra-O-*acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl*-D-glycero-L-manno-*heptitol* ***6b***

Crude **5b** (84 mg, ca. 0.29 mmol) was acetylated and purified as described for the preparation of **6a** to give **6b** (128 mg, 94% overall yield from **3b**) as a syrup; $[\alpha]_D$=+16.3 (*c* 1.1). ^{1}H NMR (C_6D_6): δ 5.46 (dd, 1H, $J_{4,5}$=3.5, $J_{5,6}$=1.3 Hz, H-5), 5.37 (dd, 1H, $J_{2,3}$=9.6, $J_{3,4}$=10.2 Hz, H-3), 5.11 (dd, 1H, H-4), 4.06 (d, 2H, $J_{6,7}$=6.5 Hz, 2 H-7), 3.90 (dddd, 1H, $J_{1a,2}$=3.3, $J_{1b,2}$=8.9, $J_{2,P}$=10.8 Hz, H-2), 3.44 and 3.32 (2 d, 6H, $J_{H,P}$=10.9 Hz, 2 OMe), 3.37 (dt, 1H, H-6), 2.11 (ddd, 1H, $J_{1a,1b}$=15.5, $J_{1a,P}$=19.5 Hz, H-1a), 2.02 (ddd, 1H, $J_{1b,P}$=17.1 Hz, H-1b), 1.71, 1.64, 1.62, and 1.60 (4 s, 12H, 4 Ac). ^{31}P NMR: δ 30.8. Anal. calcd for $C_{17}H_{27}O_{12}P$: C, 44.94; H, 5.99. Found: C, 45.19; H, 6.07.

3.17. 3-Acetamido-4,5,7-tri-O-acetyl-2,6-anhydro-1,3-dideoxy-1-dimethoxyphosphoryl-D-glycero-L-manno-heptitol **6c**

Crude **5c** (64 mg, ca. 0.20 mmol) was acetylated as described for the preparation of **6a**. Column chromatography of the residue (acetone) gave **6c** (84 mg, 93% overall yield from **8c**) as a solid; mp 179–181°C (Et_2O); $[\alpha]_D$=+3.4 (*c* 1.0). ^{1}H NMR (C_6D_6): δ 7.07 (d, 1H, $J_{3,NH}$=9.5 Hz, NH), 5.64 (dd, 1H, $J_{4,5}$=3.3, $J_{5,6}$=0.8 Hz, H-5), 5.33 (dd, 1H, $J_{3,4}$=10.9 Hz, H-4), 4.70 (ddd, 1H, $J_{2,3}$=10.0 Hz, H-3), 4.28 (dd, 1H, $J_{6,7a}$=7.4, $J_{7a,7b}$=11.3 Hz, H-7a), 4.20 (dd, 1H, $J_{6,7b}$=5.4 Hz, H-7b), 4.12 (dddd, 1H, $J_{1a,2}$=2.2, $J_{1b,2}$=9.8, $J_{2,P}$=11.8 Hz, H-2), 3.98 (ddd, 1H, H-6), 3.54 and 3.14 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 2.36 (ddd, 1H, $J_{1a,1b}$=15.9, $J_{1a,P}$=19.3 Hz, H-1a), 2.18 (ddd, 1H, $J_{1b,P}$=16.0 Hz, H-1b), 1.82, 1.74, 1.72, and 1.66 (4 s, 12H, 4 Ac). ^{31}P NMR: δ 32.0. Anal. calcd for $C_{17}H_{28}NO_{11}P$: C, 45.04; H, 6.23; N, 3.09. Found: C, 45.16; H, 6.31; N, 3.00.

3.18. 3,4,5,7-Tetra-O-acetyl-2,6-anhydro-1-deoxy-1-dimethoxyphosphoryl-D-glycero-D-galacto-heptitol **6d**

Crude **5d** (54 mg, ca. 0.19 mmol) was acetylated and purified as described for the preparation of **6a** to give **6d** (81 mg, 89% overall yield from **4d**) as a syrup. The trituration with pentane of this syrup afforded a low melting solid which could not be recrystallized; $[\alpha]_D$=−14.6 (*c* 0.5). ^{1}H NMR (C_6D_6): δ 5.53 (dd, 1H, $J_{4,5}$=$J_{5,6}$=10.0 Hz, H-5), 5.44 (dd, 1H, $J_{2,3}$=0.9, $J_{3,4}$=3.4 Hz, H-3), 5.17 (dd, 1H, H-4), 4.27 (dd, 1H, $J_{6,7a}$=5.0, $J_{7a,7b}$=12.3 Hz, H-7a), 4.15 (dd, 1H, $J_{6,7b}$=2.1 Hz, H-7b), 3.94 (dddd, 1H, $J_{1a,2}$=$J_{2,P}$=8.3, $J_{1b,2}$=5.3 Hz, H-2), 3.47 and 3.37 (2 d, 6H, $J_{H,P}$=10.9 Hz, 2 OMe), 3.32 (ddd, 1H, H-6), 2.11 (ddd, 1H, $J_{1a,1b}$=15.4, $J_{1a,P}$=17.8 Hz, H-1a), 1.80 (ddd, 1H, $J_{1b,P}$=19.5 Hz, H-1b), 1.76, 1.72, 1.65, and 1.57 (4 s, 12H, 4 Ac). ^{31}P NMR: δ 30.1. Anal. calcd for $C_{17}H_{27}O_{12}P$: C, 44.94; H, 5.99. Found: C, 44.85; H, 6.05.

3.19. 1-Deoxy-1-dimethoxyphosphoryl-3,4:6,7-di-O-isopropylidene-α-D-manno-2-heptulofuranose **10**

The lactone **9** (775 mg, 3.00 mmol) was treated with $LiCH_2P(O)(OMe)_2$ (1.5 equiv.) as described for the preparation of **2a**. Column chromatography of the residue (AcOEt) gave **10** (998 mg, 87%) as a syrup; $[\alpha]_D$=+7.1 (*c* 1.0). ^{1}H NMR: δ 5.48 (s, 1H, OH), 4.84 (ddd, 1H, $J_{3,4}$=5.4, $J_{4,5}$=3.7, $J_{4,P}$=1.2 Hz, H-4), 4.47 (dd, 1H, $J_{3,P}$=0.8 Hz, H-3), 4.38 (ddd, 1H, $J_{5,6}$=7.3, $J_{6,7a}$=6.2, $J_{6,7b}$=5.0 Hz, H-6), 4.17 (dd, 1H, H-5), 4.05 (dd, 1H, $J_{7a,7b}$=8.4 Hz, H-7a), 3.99 (dd, 1H, H-7b), 3.80 and 3.74 (2 d, 6H, $J_{H,P}$=11.1 Hz, 2 OMe), 2.40 (dd, 1H, $J_{1a,1b}$=15.5, $J_{1a,P}$=17.6 Hz, H-1a), 2.22 (dd, 1H, $J_{1b,P}$=18.3 Hz, H-1b), 1.46, 1.42, 1.36, and 1.32 (4 s, 12H, 4 Me). ^{31}P NMR: δ 32.3. Anal. calcd for $C_{17}H_{29}O_{10}P$: C, 47.12; H, 7.12. Found: C, 47.28; H, 7.07.

3.20. 2-O-Acetyl-1-deoxy-1-dimethoxyphosphoryl-3,4:6,7-di-O-isopropylidene-α-D-manno-2-heptulofuranose **11**

A solution of **10** (764 mg, 2.00 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (24 mg, 0.20 mmol) in pyridine (10 mL) and acetic anhydride (10 mL) was kept overnight at room temperature, then concentrated. The residue was eluted from a short column (3×10 cm, d×h) of silica gel with 3:1 AcOEt:acetone to give **11** (798 mg, 94%) as a syrup; $[\alpha]_D$=+5.3 (*c* 1.0). ^{1}H NMR: δ 4.89 (d, 1H, $J_{3,4}$=5.4 Hz, H-3), 4.84 (ddd, 1H, $J_{4,5}$=3.6, $J_{4,P}$=0.7 Hz, H-4), 4.41 (ddd, 1H, $J_{5,6}$=7.8, $J_{6,7a}$=6.2, $J_{6,7b}$=4.3 Hz, H-6), 4.12 (dd, 1H, $J_{7a,7b}$=8.8 Hz, H-7a), 4.06 (dd, 1H, H-5), 4.05 (dd, 1H, H-7b), 3.78 and 3.74 (2 d, 6H, $J_{H,P}$=11.0 Hz, 2 OMe), 2.98 (dd, 1H, $J_{1a,1b}$=15.7, $J_{1a,P}$=19.3 Hz, H-1a), 2.76 (dd, 1H, $J_{1b,P}$=18.8 Hz,

H-1b), 2.10 (s, 3H, Ac), 1.50, 1.48, 1.40, and 1.36 (4 s, 12 H, 4 Me). ^{31}P NMR: δ 27.8. Anal. calcd for $C_{17}H_{29}O_{10}P$: C, 48.11; H, 6.89. Found: C, 48.30; H, 6.83.

3.21. (Z,E)-2,5-Anhydro-1-deoxy-1-dimethoxyphosphoryl-3,4:6,7-di-O-*isopropylidene*-D-manno-*hept-1-enitol* ***12***

Method a: To a cooled (0°C), stirred solution of **11** (212 mg, 0.50 mmol) and triethylsilane (794 μL, 5.00 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise trimethylsilyl triflate (90 μL, 0.50 mmol). The mixture was stirred at 0°C for 20 min, then diluted with Et_3N (ca. 0.2 mL) and concentrated. Column chromatography of the residue (1:1 AcOEt:acetone) gave a 2:1 mixture of *Z*-**12** and *E*-**12** (153 mg, 84%). A pure sample of the major isomer *Z*-**12** (having lower R_f value) was obtained by crystallization of this mixture with Et_2O. *E*-**12**: ^{1}H NMR: δ 5.63 (ddd, 1H, $J_{1,3}$=1.3, $J_{3,4}$=5.9, $J_{3,P}$=2.2 Hz, H-3), 4.91 (ddd, 1H, $J_{1,4}$=0.5, $J_{1,P}$=7.8 Hz, H-1), 4.83 (ddd, 1H, $J_{4,5}$=3.8 Hz, H-4), 4.45 (ddd, 1H, $J_{5,6}$=7.3, $J_{6,7a}$=6.3, $J_{6,7b}$=4.6 Hz, H-6), 4.18 (dd, 1H, H-5), 4.13 (dd, 1H, $J_{7a,7b}$=9.0 Hz, H-7a), 4.05 (dd, 1H, H-7b), 3.74 and 3.70 (2 d, 6H, $J_{H,P}$=11.5 Hz, 2 OMe), 1.46, 1.41, 1.37 (3 s, 12H, 4 Me). ^{31}P NMR: δ 22.3. *Z*-**12**: mp 103–104°C (Et_2O); $[\alpha]_D$=+118.0 (*c* 0.8). ^{1}H NMR: δ 5.11 (ddd, 1H, $J_{1,3}$=1.0, $J_{3,4}$=5.5, $J_{3,P}$=3.8 Hz, H-3), 4.76 (ddd, 1H, $J_{4,5}$=3.5, $J_{4,P}$=2.0 Hz, H-4), 4.74 (dd, 1H, $J_{1,P}$=9.7 Hz, H-1), 4.46 (ddd, 1H, $J_{5,6}$=7.5, $J_{6,7a}$=5.7, $J_{6,7b}$=4.8 Hz, H-6), 4.38 (dd, 1H, H-5), 4.14 (dd, 1H, $J_{7a,7b}$=9.0 Hz, H-7a), 4.11 (dd, 1H, H-7b), 3.71 and 3.70 (2 d, 6H, $J_{H,P}$=11.5 Hz, 2 OMe), 1.47, 1.46, 1.39, and 1.38 (4 s, 12H, 4 Me). ^{31}P NMR: δ 20.3. Anal. calcd for $C_{15}H_{25}O_8P$: C, 49.45; H, 6.92. Found: C, 49.39; H, 6.98. The deoxygenation did not take place when the ketose **10** was used as the starting material (0.1 M CH_2Cl_2 solution, 2 equiv. of TMSOTf, rt, 1 h).

Method b: A solution of **11** (212 mg, 0.50 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (150 μL, 1.00 mmol) in anhydrous CH_3CN (2.5 mL) was refluxed for 1.5 h, then cooled to room temperature and concentrated. The residue was eluted from a column of silica gel with 1:1 AcOEt:acetone to give a 3:1 mixture of *Z*-**12** and *E*-**12** (146 mg, 80%). The use of refluxing toluene or THF led to lower yields of **12**.

3.22. 2,5-Anhydro-1-deoxy-1-dimethoxyphosphoryl-3,4:6,7-di-O-*isopropylidene*-D-glycero-D-galacto-*heptitol* ***13***

A vigorously stirred mixture of **12** (109 mg, 0.3 mmol of a 2:1 *Z*:*E* mixture), 20% palladium hydroxide on carbon (109 mg), and AcOEt (6 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated to give **13** (107 mg, 98%) at least 95% pure by NMR analysis. An analytical sample was obtained by column chromatography (1:1 acetone:AcOEt); mp 51–53°C (pentane); $[\alpha]_D$=−6.3 (*c* 1.0). ^{1}H NMR: δ 4.78 (dd, 1H, $J_{3,4}$=6.0, $J_{4,5}$=3.6 Hz, H-4), 4.68 (ddd, 1H, $J_{2,3}$=3.5, $J_{3,P}$=0.7 Hz, H-3), 4.40 (ddd, 1H, $J_{5,6}$=7.4, $J_{6,7a}$=6.0, $J_{6,7b}$=4.9 Hz, H-6), 4.10 (dd, 1H, $J_{7a,7b}$=8.7 Hz, H-7a), 4.04 (dd, 1H, H-7b), 3.88 (dddd, 1H, $J_{1a,2}$=6.8, $J_{1b,2}$=6.6, $J_{2,P}$=8.2 Hz, H-2), 3.78 and 3.77 (2 d, 6H, $J_{H,P}$=10.9 Hz, 2 OMe), 3.54 (dd, 1H, H-5), 2.32 (ddd, 1H, $J_{1a,1b}$=15.3, $J_{1a,P}$=18.4 Hz, H-1a), 2.21 (ddd, 1H, $J_{1b,P}$=18.1 Hz, H-1b), 1.48, 1.46, 1.39, and 1.35 (4 s, 12H, 4 Me). ^{31}P NMR: δ 31.2. Anal. calcd for $C_{15}H_{27}O_8P$: C, 49.18; H, 7.43. Found: C, 49.40; H, 7.37.

Acknowledgements

We thank Mr. Paolo Formaglio (University of Ferrara) for NMR measurements. Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Italy) is gratefully acknowledged.

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