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# Synthetic approaches to 2-deoxyglycosyl phosphates

Jutta Niggemann, Thisbe K. Lindhorst [1], Martina Walfort [2], Lothar Laupichler, Henry Sajus and Joachim Thiem *

*Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13 (Germany)*

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## ABSTRACT

By the use of the *N*-iodosuccinimide (NIS)-procedure, various glycals could be converted into 2-deoxy-2-iodoglycosyl phosphates. Treatment of glycals **1** and **7** with NIS and dibenzyl phosphate gave the corresponding $\alpha$-1,2-*trans*-diaxial 2-deoxy-2-iodoglycosyl phosphates **2** and **8** as the main products. The $\beta$-1,2-*trans*-diequatorial compounds **3** and **9** were isolated as by-products. Analogous reaction of glycals **4** and **10** gave the corresponding 2-deoxy-2-iodoglycosyl phosphates **5**, **6**, **11**, and **12** as crude products, which were characterized by $^1$H NMR spectroscopy. Classical phosphorylation of 2-deoxyglycosyl chlorides **14** and **16** with silver dibenzyl phosphate gave the corresponding dibenzyl 2-deoxy-$\alpha$-glycosyl phosphates **15** and **17**. Alternatively, glycosylation of tri-*O*-acetyl-D-glucal (**1**) using dibenzyl phosphate and triphenylphosphine hydrobromide afforded **15** in lower yield. The application of *S*-(2-deoxyglycosyl) phosphorodithioates as glycosyl donors provided the most convenient way to dibenzyl 2-deoxyglycosyl phosphates. The $\alpha$-glycosyl phosphates **15**, **20**, and **22** could be synthesized by reaction of the 2-deoxyglycosyl dithiophosphates **18**, **19**, and **21** with dibenzyl phosphate and activation by iodonium di-*sym*-collidine perchlorate. Similary, the 2,6-dideoxyglycosyl dithiophosphates **23** and **25** gave the 2,6-dideoxy phosphates **24** and **26**; however, the isolation of these labile compounds could not be effected.

## INTRODUCTION

Glycosyl phosphates are important intermediates in a variety of biosynthetic processes such as in sugar nucleotide metabolism[1]. Selective deoxygenation in the sugar moieties gives rise to compounds of close structural analogy to natural derivatives, which may serve as enzyme inhibitors or substrate analogs. The synthesis of several 3-, 4-, or 6-deoxyglycosyl phosphates as precursors to the corresponding sugar nucleotides has previously been developed[2]. However, due to their hydrolytic instabilitiy, the synthesis of 2-deoxyglycosyl phosphates remained difficult and was not satisfactorily achieved[3]. The only alternative approach to the synthesis of 2-deoxy-$\alpha$-D-glycopyranosyl phosphates appeared to be enzymatic

[1] Present address: The University of British Columbia, Department of Chemistry, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1.
[2] New address: GERTEC GmbH, Viehoferstr. 11, 4300 Essen, Germany.
* Corresponding author.

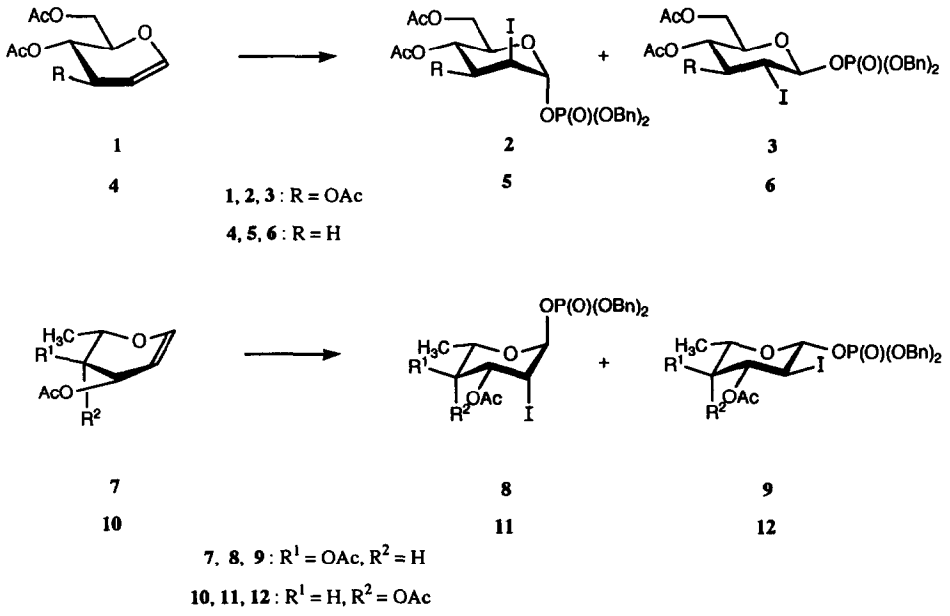
synthesis. Withers et al.[4] reported in 1988 the enzymatic conversion of 2-deoxy-α-D-*arabino*-hexopyranose 6-phosphate into 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate. Previously, Klein et al.[5], by $^1$H NMR spectroscopy, observed the enzymatic formation of the same compound from glucal, and recently Thiem and Evers[6] elaborated this into a preparative enzymatic synthesis.

In this paper, we demonstrate several synthetic approaches to 2-deoxyglycosyl phosphates, of which the use of 2-deoxyglycosyl dithiophosphates[7] has proved to be the most convenient way.

## RESULTS AND DISCUSSION

Glycals are attractive starting materials for the stereospecific synthesis of 2-deoxyglycosides by use of the NIS-procedure[8]. Starting from various glycals, the corresponding 2-deoxy-2-iodoglycosyl phosphates could be obtained. By reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with NIS[9] as iodonium donor and dibenzyl phosphate as nucleophile for 24 h at room temperature, with the exclusion of light and moisture, two products were obtained which were separated by HPLC and characterized by $^1$H NMR spectroscopy. The main product was the expected α-1,2-*trans*-diaxial 2-deoxy-2-iodomannopyranosyl phosphate **2** (43% yield) and as by-product the β-1,2-diequatorial compound **3** was isolated in 11% yield. The $^1$H NMR spectrum of **2** showed typical coupling constants for a *manno*-glycosyl phosphate with $J_{1,2}$ 1.3 and $J_{1,P}$ 5.7 Hz, whereas the by-product showed a large coupling ($J_{1,2}$ 9.1 Hz) besides $J_{1,P}$ 7.4 Hz. Due to the +M effect of the iodo-substituent at C-2, for both compounds the resonance of H-2 was shifted to higher field (δ 4.31 and 4.02). The NIS-mediated phosphorylation reaction could also be applied to the corresponding 3-deoxyglycal **4** (di-*O*-acetylamicetal), which was synthesized in three steps from tri-*O*-acetyl-D-glucal (**1**) according to Fraser-Reid et al.[10] by reductive allylic rearrangement of a hex-2-enopyranoside[11]. The NIS-reaction provided two products in a ratio of **5**:**6** = 2.5:1, which could be characterized by $^1$H NMR spectroscopy. The isolation of these labile compounds could not be accomplished. The analogous reaction of 3,4-di-*O*-acetyl-L-rhamnal (**7**) gave the α-phosphate **8** ($J_{1,2}$ 1.4, $J_{1,P}$ 5.6 Hz) in 52% yield besides 15% of the β by-product **9** ($J_{1,2}$ 9.2, $J_{1,P}$ 7.2 Hz). Surprisingly, the corresponding conversion of 3,4-di-*O*-acetyl-L-fucal (**10**) gave the 2-deoxy-2-iodoglycosyl phosphates **11** and **12** only as crude products together with further by-products which could not be completely removed. Unfortunately, reduction of the 2-iodo functionality of the α-glycosyl phosphates **2** and **8** to give 2-deoxy compounds failed, employing all reported standard conditions; instead, a complete elimination to the corresponding glycals **1** and **7** was observed. Based on these results, we turned our attention to direct stereoselective methods of phosphorylation, which circumvented the introduction of a temporary anchimeric assistance.

Glycosylation of 2-deoxyglycosyl halides using silver dibenzyl phosphate[12] as nucleophile was tried as an alternative. Instead of the highly unstable 2-deoxy-

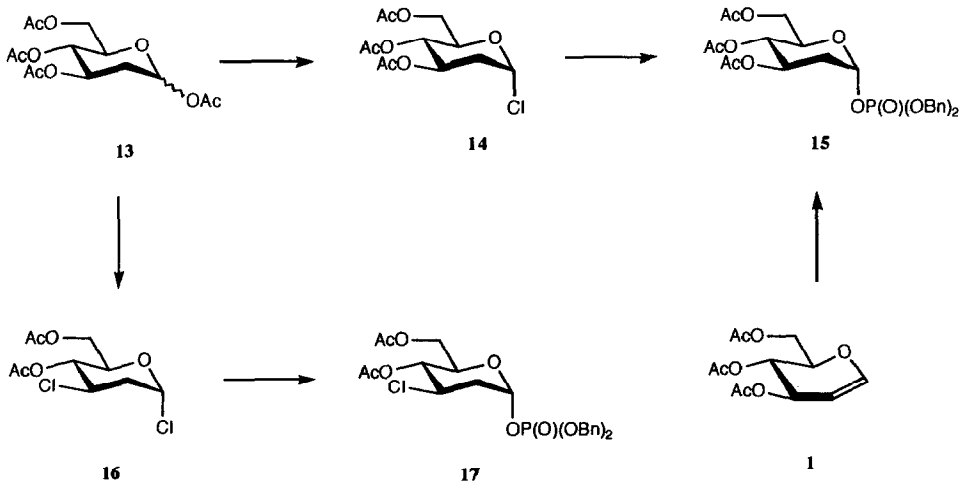



Scheme 1.

glycosyl bromides, we chose the corresponding chlorides. By the use of boron trichloride[13], the glycosyl chloride **14** was prepared from the corresponding peracetylated 2-deoxy sugar **13**[14] in 58% yield. Subsequent phosphorylation could be accomplished by reaction with silver dibenzyl phosphate at 80°C in toluene to obtain **15** in 45% yield as the anomerically pure $\alpha$ compound. The proton-decoupled $^{13}C$ NMR spectrum showed a doublet for C-1 at $\delta$ 95.86 with a coupling constant of $J_{C\text{-}1,P}$ 5.7 Hz, and the signal for C-2 at $\delta$ 35.10 with a coupling constant of $J_{C\text{-}2,P}$ 8.3 Hz. The anomeric configuration was supported by the $^1H$ NMR spectrum. The $\alpha$ anomer showed coupling constants of $J_{1,2a}$ 3.5 Hz and, due to the W-configuration, $^4J_{2a,P}$ of 3.5 Hz.

In an attempt to increase the yield of compound **14**, the use of dichloromethyl methyl ether[15] and $ZnCl_2$ as reagents for the preparation of the glycosyl chloride **14** was also investigated. Surprisingly, the 3-chloro-3-deoxyglycosyl chloride **16** was isolated as the only product in 61% yield. The chloro substituent at C-3 can clearly be assigned from the downfield shift for H-3 from 5.48 in compound **14** to 4.45 in compound **16**. The equatorial position of the chloro substituent was readily detected by the typical coupling patterns of H-3 and H-4.

Previously, the formation of the corresponding 3-bromo-2,3-dideoxyglycosyl bromide has been reported by application of trimethylsilyl bromide[16]. By use of an excess of reagent and longer reaction times, the glycosyl bromide initially formed was further converted into the 3-bromo-3-deoxyglycosyl bromide. This may be rationalized by a regioselective and electrophilic attack of trimethylsilyl bromide on the 3-acetoxy function and subsequent formation of a 3,4-acetoxonium ion. Its




Scheme 2.

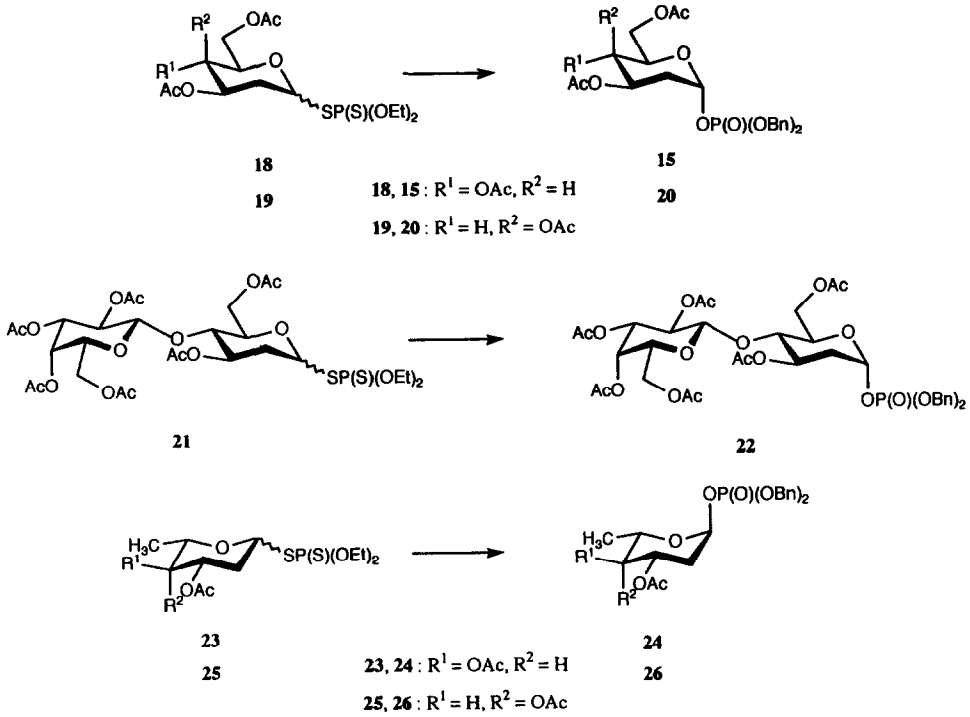
regioselective and nucleophilic ring opening by bromide gave the double inverted compound. By analogy with this reaction, formation of the 3-chloro-substituted glycosyl chloride **16** can be explained, which was in fact isolated as the only product by use of dichloromethyl methyl ether as solvent and an increased reaction temperature. Subsequent treatment of **16** with silver dibenzyl phosphate afforded compound **17** in 55% yield.

Due to the low overall yields of compounds **15** and **17**, which where especially decreased by the synthesis of the corresponding chloride donors, we turned our attention towards other synthetic approaches employing glycosyl donors of higher stability.

Recently, the use of the reagent system triphenylphosphine hydrobromide ($PPh_3 \cdot HBr$) has been suggested by Falck and co-workers[17] for direct stereoselective syntheses of 2-deoxy-α-glycosides starting from easily accessible glycals as precursors. Reaction of tri-*O*-acetyl-D-glucal (**1**) and dibenzyl phosphate with the commercially available $PPh_3 \cdot HBr$ complex yielded 35% of the corresponding dibenzyl 2-deoxy-α-D-glycosyl phosphate **15** besides large amounts of starting material in a sluggish reaction.

The successful use of *S*-(2-deoxyglycosyl) phosphorodithioates[7] as efficient glycosyl donors for the synthesis of a wide variety of 2-deoxy-α-glycosides[18] made the application of these glycosyl donors also attractive for a phosphorylation reaction under appropriate conditions.

*S*-(2-Deoxyglycosyl) phosphorodithioates can be prepared in quantitative yields from the corresponding glycals by reaction with *O,O*-diethyl hydrogen phosphorodithioate. These thioester derivatives showed high stability, but could easily be activated by iodonium di-*sym*-collidine perchlorate [I(*sym*-coll)$_2$ClO$_4$][19]. By reaction of the 2-deoxy-*arabino* and -*lyxo* precursors **18** and **19** and the 2-deoxylactose




Scheme 3.

donor **21** with I(*sym*-coll)$_2$ClO$_4$ and dibenzyl phosphate as nucleophile, the corresponding $\alpha$-glycosyl phosphates **15**, **20**, and **22** were obtained in 75, 61, and 68% yield, respectively, after workup and chromatography. NMR observations during the reaction showed that anomeric mixtures of the glycosyl phosphates were formed within 15 min, but, in the course of extended reaction times, anomerization took place to form the $\alpha$ anomers predominantly. Following column chromatography on silica gel, only the $\alpha$ anomers could be isolated. Due to their instability, correct elemental analyses of the 2-deoxyglycosyl phosphates could not be obtained.

In order to extend the reaction towards 2,6-dideoxyglycosyl phosphates, the corresponding 2,6-dideoxyglycosyl donors **23** and **25** were prepared under similar conditions. After only 15 min and the usual workup, NMR investigations of the crude mixtures clearly proved the nearly quantitative formation of the 2,6-dideoxyglycosyl phosphates as anomeric mixtures. Surprisingly, we were only able to isolate the corresponding 2,6-dideoxyglycosyl phosphate **24** in very low yield and **26** not at all. Whereas in the cases of **15**, **20**, and **22**, no problems of purification appeared, compounds **24** and **26** readily hydrolyzed during purification by column chromatography on silica gel and the corresponding 1-hydroxy compounds were isolated.

In summary, the use of *S*-(2-deoxyglycosyl) phosphorodithioates as stereoselective glycosyl donors opens a convenient synthetic method towards 2-deoxyglycosyl

phosphates. Due to their enhanced lability, the isolation of the 2,6-dideoxyglycosyl phosphates remains a problem.

## EXPERIMENTAL

*General methods.*—All reactions were monitored by TLC on Silica Gel 60 $F_{254}$ (Merck) with detection by UV absorption and/or charring after spraying with 10% $H_2SO_4$ in EtOH. Flash chromatography was performed on Silica Gel 60 (230–400 mesh, Merck) and HPLC on a Knauer–Nucleosil 100 column (diam. 32 mm). Melting points were determined with a Reichert melting-point microscope and are uncorrected. Optical rotations were determined with a Perkin–Elmer 243 polarimeter. The $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker AC-250, WM 300, and AMX-400 spectrometers. Microanalyses were performed by the Microanalytical Laboratory für Organische Chemie Institut, Universität Hamburg. Owing to the low stability of all deoxygenated $\alpha$-dibenzyl phosphates, only limited satisfactory elemental analytical data could be obtained.

*General procedures.*—**A** (*N-Iodosuccinimide-mediated glycosylation*). A solution of the glycal (0.5 mmol) and dibenzyl phosphate (1.0 mmol) in dry $CH_2Cl_2$ (4 mL) and dry MeCN (3 mL) was stirred with 3A molecular sieves with exclusion of light and moisture for 30 min. Then NIS (0.6 mmol) was added and the mixture stirred overnight at room temperature. The mixture was diluted with $CH_2Cl_2$, filtered, washed with aq 10% sodium thiosulfate and water, dried, and concentrated in vacuo.

**B** (*Dithiophosphate-mediated glycosylation*). A solution of *S*-(2-deoxyglycosyl) *O,O*-diethyl dithiophosphate (1.0 mmol) and dibenzyl phosphate (2.0 mmol) in dry $CH_2Cl_2$ (2 mL) was stirred with 4A molecular sieves. With exclusion of moisture, I(*sym*-coll)$_2ClO_4$ (1.5 mmol) was added and the mixture was stirred for 1 h at room temperature. Then the mixture was diluted with $CH_2Cl_2$, washed with aq 10% sodium thiosulfate and water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The remaining syrup was purified by flash chromatography.

*Dibenzyl (3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-*D*-mannopyranosyl) phosphate* (**2**) *and dibenzyl (3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-*D*-glucopyranosyl) phosphate* (**3**).—Compound **1** (101 mg, 0.37 mmol) was treated as described in the general procedure **A**. The products were separated by HPLC (4:1 toluene–EtOAc) to yield **2** (107 mg, 43%) as colourless crystals and **3** (27 mg, 11%) as a colourless syrup.

Compound **2** had: mp 86°C; $[\alpha]_D^{20}$ +18.2° (*c* 9.6, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.70–7.50 (m, 10 H, aryl-H), 5.92 (dd, H-1), 5.40 (dd, H-4), 5.16–5.02 (m, 4 H, 2 C$H_2$Ph), 4.52 (dd, H-3), 4.31 (dd, H-2), 4.11 (dd, H-6a), 4.07 (ddd, H-5), 3.98 (dd, H-6b), 2.09, 2.04, 2.02 (3 s, 9 H, 3 OCOC$H_3$); $J_{1,2}$ 1.3, $J_{1,P}$ 5.7, $J_{2,3}$ 4.4, $J_{3,4}$ 9.5, $J_{4,5}$ 9.9, $J_{5,6a}$ 4.2, $J_{5,6b}$ 2.1, $J_{6a,6b}$ 12.1 Hz. Anal. Calcd for $C_{26}H_{30}IO_{11}P$ (676.4): C, 46.17; H, 4.47. Found: C, 46.26; H, 4.39.

Compound **3** had: $[\alpha]_D^{20}$ +39.8° (*c* 10.2, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.40–7.30 (m, 10 H, aryl-H), 5.51 (dd, H-1), 5.31 (dd, H-3), 5.22–5.15 (m, 4 H, 2

C$H_2$Ph), 5.00 (dd, H-4), 4.25 (dd, H-6b), 4.10 (dd, H-6a), 4.02 (dd, H-2), 3.80 (ddd, H-5), 2.10, 2.02, 1.97 (3 s, 9 H, 3 OCOC$H_3$); $J_{1,2}$ 9.1, $J_{1,P}$ 7.4, $J_{2,3}$ 11.1, $J_{3,4}$ 9.2, $J_{4,5}$ 10.3, $J_{5,6a}$ 4.8, $J_{5,6b}$ 2.1, $J_{6a,6b}$ 12.1 Hz. Anal. Calcd for $C_{26}H_{30}IO_{11}P$ (676.4): C, 46.17; H, 4.47. Found: C, 46.37; H, 4.48.

*Dibenzyl (4,6-di-*O*-acetyl-2,3-dideoxy-2-iodo-α-*D*-*arabino*-hexopyranosyl) phosphate* (**5**) *and dibenzyl (4,6-di-*O*-acetyl-2,3-dideoxy-2-iodo-β-*D*-*ribo*-hexopyranosyl) phosphate* (**6**).—Compound **4** (418 mg, 1.73 mmol) was treated as described in the general procedure **A** to yield **5** and **6** in a ratio of 2.5:1 (on the basis of $^1$H NMR analysis) as a crude mixture (1.04 g, 97%).

For **5**, $^1$H NMR (250 MHz, $CDCl_3$): δ 7.40–7.30 (m, 10 H, aryl-H), 5.77 (dd ~ d, H-1), 5.19 (ddd ~ dt, H-4), 5.13–5.05 (m, 4 H, 2 C$H_2$Ph), 4.16 (dd, H-6b), 4.15 (dd, H-6a), 4.06 (ddd, H-5), 3.98 (ddd ~ dq, H-2), 2.25 (ddd, H-3*e*), 2.07 (ddd ~ dq, H-3*a*), 2.04–2.00 (2 s, 6 H, 2 OCOC$H_3$); $J_{1,2}$ 1.2, $J_{1,P}$ 6.0, $J_{2,3a}$ 4.4, $J_{2,3e}$ 3.6, $J_{3a,3e}$ 14.0, $J_{3a,4}$ 10.4, $J_{3e,4}$ 4.4, $J_{4,5}$ 10.4, $J_{5,6a}$ 5.2, $J_{5,6b}$ 2.8, $J_{6a,6b}$ 9.0 Hz.

For **6**: $^1$H NMR (250 MHz, $CDCl_3$): δ 5.47 (dd, H-1), 4.71 (ddd ~ dt, H-4), 4.20 (ddd ~ dt, H-2), 3.90 (ddd, H-5); $J_{1,2}$ 7.2, $J_{1,P}$ 9.0, $J_{2,3a}$ 4.4, $J_{3a,4}$ 10.4, $J_{3e,4}$ 4.4, $J_{4,5}$ 10.4, $J_{5,6a}$ 5.2, $J_{5,6b}$ 2.8 Hz.

*Dibenzyl (3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-*L*-mannopyranosyl) phosphate* (**8**) *and dibenzyl (3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-β-*L*-glucopyranosyl) phosphate* (**9**). —Compound **7** (400 mg, 1.86 mmol) was treated as described in the general procedure **A**. The products were separated by HPLC (4:1 toluene–EtOAc) to yield **8** (600 mg, 52%) and **9** (170 mg, 15%) as colourless crystals.

Compound **8** had: mp 79°C; $[\alpha]_D^{20}$ −14.6° (*c* 0.59, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.37–7.31 (m, 10 H, aryl-H), 5.87 (dd ~ d, H-1), 5.15–5.00 (m, 5 H, H-4, 2 C$H_2$Ph), 4.45 (dd, H-3), 4.35 (dd, H-2), 3.99 (dq, H-5), 2.07, 2.03 (2 s, 6 H, 2 OCOC$H_3$), 1.10 (d, 3 H, H-6); $J_{1,2}$ 1.4, $J_{1,P}$ 5.6, $J_{2,3}$ 4.4, $J_{3,4}$ 9.5, $J_{4,5}$ 9.8, $J_{5,6}$ 6.2 Hz. Anal. Calcd for $C_{24}H_{28}IO_9P$ (618.0): C, 46.60; H, 4.57. Found C, 47.23; H, 4.89.

Compound **9** had: mp 76°C, $[\alpha]_D^{20}$ −49.2° (*c* 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40–7.31 (m, 10 H, aryl-H), 5.46 (dd, H-1), 5.25 (dd, H-3), 5.17–5.09 (m, 4 H, 2 C$H_2$Ph), 4.74 (dd ~ t, H-4), 3.98 (dd, H-2), 3.71 (dq, H-5), 2.07, 2.01 (2 s, 6 H, 2 OCOC$H_3$), 1.20 (d, 3 H, H-6); $J_{1,2}$ 9.2, $J_{1,P}$ 7.2, $J_{2,3}$ 11.2, $J_{3,4}$ 9.0, $J_{4,5}$ 9.8, $J_{5,6}$ 6.2 Hz. Anal. Calcd for $C_{24}H_{28}IO_9P$ (618.0): C 46.60; H 4.57. Found C 46.73; H 4.72.

*Dibenzyl (3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-*L*-talopyranosyl) phosphate* (**11**) *and dibenzyl (3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-β-*L*-galactopyranosyl) phosphate* (**12**).—Compound **10** (500 mg, 2.33 mmol) was treated as described in the general procedure **A**. The products were separated by HPLC (1:2 n-hexane–diethyl ether) to yield **11** (330 mg, 23%) and **12** (202 mg, 14%) as crude products.

For **11**, $^1$H NMR (300 MHz, $CDCl_3$): δ 7.48–7.32 (m, 10 H, aryl-H), 5.68 (dd, H-1), 5.28 (dd, H-3), 5.16–5.09 (m, 4 H, 2 C$H_2$Ph), 5.06 (dd, H-4), 4.30 (dd, H-5), 4.16 (dd, H-2), 2.16, 2.00 (2 s, 6 H, 2 OCOC$H_3$), 1.19, (d, 3 H, H-6); $J_{1,2}$ 8.9, $J_{1,P}$ 7.5, $J_{2,3}$ 11.7, $J_{3,4}$ 3.4, $J_{4,5}$ 1.2, $J_{5,6}$ 6.4 Hz.

For **12**, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.38–7.28 (m, 10 H, aryl-H), 5.93 (dd, H-1), 5.28 (dd, H-3), 5.22–5.16 (m, 4 H, 2 C*H*$_2$Ph), 5.11 (dd, H-4), 4.32 (ddd, H-2), 4.23 (dq, H-5), 2.12, 2.03 (2 s, 6 H, 2 OCOC*H*$_3$), 0.97 (d, 3 H, H-6); $J_{1,2}$ 3.0, $J_{1,P}$ 5.6, $J_{2,3}$ 11.8, $J_{3,4}$ 3.0, $J_{4,5}$ 0.8, $J_{5,6}$ 6.6 Hz.

*3,4,6-Tri*-O-*acetyl-2-deoxy-α*-D-arabino-*hexopyranosyl chloride* (**14**).—To a solution of **13** (0.93 g, 2.80 mmol) in dry $CH_2Cl_2$ (15 mL) was added a 1.0 M solution of $BCl_3$ in hexane (3.2 mL) at 0°C. After stirring for 30 min, the mixture was concentrated to dryness in vacuo and the resulting residue was purified by flash chromatography (4:1 toluene–EtOAc + 3% triethylamine) to yield **14** (505 mg, 58%) as a yellow syrup; $[\alpha]_D^{20}$ +124.0° (*c* 1.1, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 6.23 (dd, H-1), 5.48 (ddd, H-3), 5.07 (dd ~ t, H-4), 4.35 (dd, H-6a), 4.29 (ddd, H-5), 4.09 (dd, H-6b), 2.54 (ddd, H-2*e*), 2.19 (ddd, H-2*a*), 2.09, 2.06, 2.03 (3 s, 9 H, 3 OCOC*H*$_3$); $J_{1,2a}$ 3.8, $J_{1,2e}$ 1.4, $J_{2a,2e}$ 13.6, $J_{2a,3}$ 11.2, $J_{2e,3}$ 5.2, $J_{3,4}$ 9.6, $J_{4,5}$ 10.0, $J_{5,6a}$ 4.4, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 12.4 Hz.

*Dibenzyl (3,4,6-tri*-O-*acetyl-2-deoxy-α*-D-arabino-*hexopyranosyl) phosphate* (**15**). —*Approach A*. To a solution of **14** (505 mg, 1.64 mmol) in dry toluene (20 mL) was added silver dibenzyl phosphate (631 mg, 1.64 mmol) and the mixture was stirred at 80°C for 2 h with exclusion of light and moisture. The solution was then filtered and concentrated in vacuo, and the residue purified by flash chromatography (10:1 toluene–EtOAc + 3% triethylamine) to yield **15** (406 mg, 45%) as a colourless syrup.

*Approach B*. A solution of tri-*O*-acetyl-D-glucal (**1**; 272 mg, 1.0 mmol) and dibenzyl phosphate (417 mg, 1.5 mmol) in dry $CH_2Cl_2$ (2 mL) was treated with $PPh_3 \cdot HBr$ (686 mg, 2.0 mmol) and stirred for 24 h at room temperature. Then the mixture was diluted with $CHCl_3$ and washed with satd aq $NaHCO_3$ and water. After drying the organic phase over $MgSO_4$, filtration, and evaporation of the solvent, the remaining syrup was purified by column chromatography (3:1 toluene–acetone + 1% triethylamine) to yield **15** (193 mg, 35%) as a colourless syrup.

*Approach C*. Glycosyl dithiophosphate **18** (458 mg, 1.0 mmol) was treated as described in the general procedure **B**. The crude reaction product was purified by column chromatography (3:1 toluene–acetone + 1% triethylamine) to yield **15** (413 mg, 75%) as a colourless syrup.

Compound **15** had: $[\alpha]_D^{20}$ +70.5° (*c* 1.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.50–7.30 (m, 10 H, aryl-H), 5.85 (m, H-1), 5.29 (ddd, H-3), 5.15–5.08 (m, 4 H, 2 C*H*$_2$Ph), 5.04 (dd ~ t, H-4), 4.22 (dd, H-6a), 4.07 (ddd, H-5), 3.89 (dd, H-6b), 2.26 (ddd, H-2*e*), 2.06, 2.04, 2.03 (3 s, 9 H, 3 OCOC*H*$_3$), 1.87 (dddd ~ ddt, H-2*a*); $J_{1,2a}$ 3.6, $J_{1,2e}$ 1.0, $J_{2a,2e}$ 13.2, $J_{2a,3}$ 11.7, $J_{2a,P}$ 3.6, $J_{2e,3}$ 5.2 Hz, $J_{3,4}$ 10.0, $J_{4,5}$ 10.0, $J_{5,6a}$ 4.0, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 12.7 Hz; $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 170.59, 170.01, 169.71 (3 s, 3 O*C*OCH$_3$), 128.7–128.0 (m, C-aryl), 95.86 (d, $^2J_{1,P}$ 5.7 Hz, C-1), 69.83, 68.43, 67.99 (3 s, C-3,4,5), 69.7–69.5 (m, *C*H$_2$Ph), 61.63 (C-6), 35.10 (d, $^3J_{2,P}$ 8.3 Hz, C-2), 20.9–20.0 (m, OCO*C*H$_3$).

*4,6-Di*-O-*acetyl-3-chloro-2,3-dideoxy-α*-D-arabino-*hexopyranosyl chloride* (**16**).—

To a solution of **13** (1.28 g, 3.85 mmol) in dichloromethyl methyl ether (5 mL) was added a catalytic amount of $ZnCl_2$, and with exclusion of moisture the mixture was kept at 65–70°C until TLC (2:1 toluene–EtOAc + 3% triethylamine) indicated the formation of the glycosyl chloride. The mixture was concentrated, the residue taken up in $CH_2Cl_2$, and the solution filtered, washed with cold satd aq $NaHCO_3$, and dried with $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography (5:1 toluene–EtOAc +3% triethylamine) to yield **16** (0.67 g, 61%) as a yellow syrup; $[\alpha]_D^{20}$ +73.2° (*c* 1.2, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): δ 6.21 (dd ~ d, H-1), 5.12 (dd ~ t, H-4), 4.45 (ddd, H-3), 4.31 (dd, H-6a), 4.20 (ddd, H-5), 4.08 (dd, H-6b), 2.67 (ddd, H-2*e*), 2.47 (ddd, H-2*a*), 2.14, 2.10 (2 s, 6 H, 2 $OCOCH_3$); $J_{1,2a}$ 3.2, $J_{1,2e}$ 1.2, $J_{2a,2e}$ 14.0, $J_{2a,3}$ 12.0, $J_{2e,3}$ 5.0, $J_{3,4}$ 10.0, $J_{4,5}$ 10.0, $J_{5,6a}$ 4.4, $J_{5,6b}$ 2.2, $J_{6a,6b}$ 12.0 Hz.

*Dibenzyl (4,6-di-*O*-acetyl-3-chloro-2,3-dideoxy-α-*D*-*arabino*-hexopyranosyl) phosphate* (**17**).—Compound **16** (752 mg, 1.95 mmol) was phosphorylated as described for the preparation of **15**. The product was purified by flash chromatography (10:1 toluene–EtOAc +3% triethylamine) to yield **17** (565 mg, 55%) as a syrup; $[\alpha]_D^{20}$ +47.1° (*c* 1.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40–7.00 (m, 10 H, aryl-H), 5.72 (m, H-1), 5.06 (dd ~ t, H-4), 5.12–4.97 (m, 4 H, 2 $CH_2$Ph), 4.16 (dd, H-6a), 4.07 (ddd, H-3), 3.94 (ddd, H-5), 3.86 (dd, H-6b), 2.27 (ddd, H-2*e*), 2.20–2.10 (m, 7 H, 2 $OCOCH_3$, H-2*a*); $J_{1,2e}$ 1.0, $J_{2a,2e}$ 13.5, $J_{2a,3}$ 12.5, $J_{2e,3}$ 3.5, $J_{3,4}$ 10.0, $J_{4,5}$ 10.0, $J_{5,6a}$ 4.0, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 12.5 Hz; $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.57 (m, $OCOCH_3$), 128.8–128.0 (m, C-aryl), 95.43 (d, $^2J_{1,P}$ 5.8 Hz, C-1), 70.76, 70.49 (2 s, C-4,5), 69.8–69.6 (m, $CH_2$Ph), 61.77 (C-6), 53.77 (C-3), 39.69 (d, $^3J_{2,P}$ 7.9 Hz, C-2), 20.65, 20.60 (2 s, 2 $OCOCH_3$).

*Dibenzyl (3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-lyxo-hexopyranosyl) phosphate* (**20**).—Glycosyl dithiophosphate **19** (200 mg, 0.43 mmol) was treated as described in the general procedure **B**. The crude product was purified by column chromatography (1:1 toluene–acetone 1% triethylamine) to yield **20** (145 mg, 61%) as a colourless syrup; $[\alpha]_D^{20}$ +53.6° (*c* 1.0, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.50–7.30 (m, 10 H, aryl-H), 5.90 (ddd, H-1), 5.33 ($m_c$, H-4), 5.21 (ddd, H-3), 5.15–5.05 (m, 4 H, 2 $CH_2$Ph), 4.25 (ddd ~ dt, H-5), 4.05 (dd, H-6a), 3.93 (dd, H-6b), 2.12, 1.99, and 1.93 (3 s, 9 H, 3 $OCOCH_3$), 2.10 (dddd, H-2*a*), 1.83 (ddd, H-2*e*); $J_{1,2a}$ 2.8, $J_{1,2e}$ 1.6, $J_{1,P}$ 3.6, $J_{2a,2e}$ 12.8, $J_{2a,3}$ 12.4, $J_{2a,P}$ 1.6, $J_{2e,3}$ 4.8, $J_{2e,4}$ 1.6, $J_{3,4}$ 2.8, $J_{4,5}$ 1.2, $J_{5,6a}$ 6.4, $J_{5,6b}$ 6.4, $J_{6a,6b}$ 11.2 Hz; $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.30, 170.02, 169.81 (3 s, 3 $OCOCH_3$), 135.0–128.0 (m, C-aryl), 96.63 (d, $^2J_{1,P}$ 5.6 Hz, C-1), 69.7–69.5 (m, $CH_2$Ph), 68.65 (C-5), 65.91, 65.10 (2 s, C-3,4), 61.73 (C-6), 30.32 (d, $^3J_{2,P}$ 8.0 Hz, C-2), 20.7–20.5 (m, $OCOCH_3$).

*Dibenzyl [3,6-di-*O*-acetyl-2-deoxy-3-O-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-α-*D*-arabino-hexopyranosyl] phosphate* (**22**).—Glycosyl dithiophosphate **21** (776 mg, 1.0 mmol) was treated as described in the general procedure **B**. The crude product was purified by column chromatography (1:1 toluene–acetone +1% triethylamine) to yield **22** (562 mg, 68%) as a colourless syrup; $[\alpha]_D^{20}$ +40.0° (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.50–7.30 (m, 10 H, aryl-H), 5.79 (ddd,

H-1), 5.37 (dd, H-4′), 5.29 (ddd, H-3), 5.13 (dd, H-2′), 5.18–5.01 (m, 4 H, 2 C$H_2$Ph), 4.96 (dd, H-3′), 4.54 (d, H-1′), 4.23 (dd, H-6′b), 4.17 (dd, H-6b), 4.05 ($m_c$, H-6′a), 4.05 ($m_c$, H-6a), 3.97 (ddd, H-5), 3.87 (ddd, H-5′), 3.70 (dd, H-4), 2.27 (ddd, H-2*e*), 2.24–1.96 (6 s, 18 H, 6 OCOC$H_3$), 1.76 (dddd ~ ddt, H-2*a*); $J_{1,2a}$ 3.2, $J_{1,2e}$ 0.5, $J_{1,P}$ 3.1, $J_{2a,2e}$ 13.5, $J_{2a,3}$ 10.6, $J_{2a,P}$ 3.5, $J_{2e,3}$ 5.5, $J_{3,4}$ 9.0, $J_{4,5}$ 9.1, $J_{5,6a}$ 6.7, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 11.0, $J_{1',2'}$ 8.2, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.1, $J_{4',5'}$ 0.5, $J_{5',6'a}$ 7.3, $J_{5',6'b}$ 2.0, $J_{6'a,6'b}$ 11.7 Hz; $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 100.53 (C-1′), 94.97 (d, $^2J_{C\text{-}1,P}$ 5.7 Hz, C-1), 34.20 (d, $^3J_{2,P}$ 7.6 Hz C-2).

*Dibenzyl (3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-*arabino*-hexopyranosyl) phosphate* (**24**). —Glycosyl dithiophosphate **23** (200 mg, 0.5 mmol) was treated as described in the general procedure **B**. The crude product was purified by column chromatography (3:1 toluene–EtOAc +3% triethylamine) to yield **24** (18 mg, 7%) as a colourless syrup; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10 H, aryl-H), 5.71 (m, H-1), 5.16 (ddd, H-3), 5.02–4.98 (m, 4 H, 2 C$H_2$Ph), 4.68 (dd ~ t, H-4), 3.90 (dq, H-5), 2.17 (ddd, H-2*e*), 1.98, 1.94 (2 s, 6 H, 2 OCOC$H_3$), 1.74 (dddd ~ ddt, H-2*a*), 1.01 (d, H-6); $J_{1,2a}$ 3.5, $J_{1,2e}$ 1.5, $J_{2a,2e}$ 13.5, $J_{2a,3}$ 11.5, $J_{2a,P}$ 3.5, $J_{2e,3}$ 5.0, $J_{3,4}$ 9.5, $J_{4,5}$ 10.0, $J_{5,6}$ 6.0 Hz; $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.09, 170.05 (2 s, 2 O*C*OCH$_3$), 128.7–127.9 (m, C-aryl), 95.90 (d, $^2J_{1,P}$ 5.7 Hz, C-1), 69.6–69.4 (m, *C*H$_2$Ph), 73.94, 68.00, 67.91 (3 s, C-3,4,5), 35.50 (d, $^3J_{2,P}$ 8.4 Hz, C-2), 30.94 (s, C-6), 20.95, 20.79 (2 s, 2 OCO*C*H$_3$).

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REFERENCES

1 H. Nikaido and W.Z. Hassid, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 351–483; N.K. Kochetkov and V.N. Shibaev, *ibid.*, 28 (1973) 307–399.
2 G. Srivastava, G. Alton, and O. Hindsgaul, *Carbohydr. Res.*, 207 (1990) 259–276; U.B. Gokhale, O. Hindsgaul, and M.M. Palcic, *Can. J. Chem.*, 68 (1990) 1063–1071; S.G. Withers, M.D. Percival, and I.P. Street, *Carbohydr. Res.*, 187 (1989) 43–66; J. Niggemann and J. Thiem, *Liebigs Ann. Chem.*, (1992) 535–538.
3 V.N. Shibaev, Y. Y. Kusov, S. Kuchar, and N.K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 4 (1973) 922–926.
4 M.D. Percival and S.G. Withers, *Can. J. Chem.*, 66 (1988) 1970–1972.
5 H.W. Klein, D. Palm, and E.J.M. Helmreich, *Biochemistry*, 21 (1982) 6675–6684.
6 B. Evers, Diploma Thesis, University of Hamburg, 1992; J. Thiem and B. Evers, unpublished results.
7 M. Michalska and J. Borowiecka, *J. Carbohydr. Chem.*, 2 (1983) 99–103.
8 J. Thiem, H. Karl, and J. Schwentner, *Synthesis*, (1978) 696–698.
9 Y.D. Vanka and G. Kumaravel, *Tetrahedron Lett.*, 25 (1984) 233–236.
10 B. Fraser-Reid, S.J.K. Tam, and B. Radatus, *Can. J. Chem.*, 53 (1975) 2005–2016.
11 R.J. Ferrier and N. Prasad, *J. Chem. Soc., C*, (1969) 570–575.
12 F. Lynen, *Ber. Dtsch. Chem. Ges.*, 73 (1940) 367–375.
13 G.R. Perdomo and J.J. Krepinsky, *Tetrahedron Lett.*, 28 (1987) 5595–5598.

14 W.G. Overend, M. Stacey, and J. Stanêk, *J. Chem. Soc.*, (1949) 2841–2845.
15 H. Gross, I. Farkas, and R. Bognar, *Z. Chem.*, 18 (1978) 201–210.
16 J. Thiem and S. Köpper, *J. Carbohydr. Chem.*, 2 (1983) 75–97.
17 V. Bolitt, C. Mioskowski, S.-G. Lee, and J.R. Falck, *J. Org. Chem.*, 55 (1990) 5812–5813.
18 L. Laupichler, H. Sajus, and J. Thiem, *Synthesis*, (1992) 1133–1136.
19 R.U. Lemieux and A.R. Morgan, *Can J. Chem.*, 43 (1965) 2190–2198.