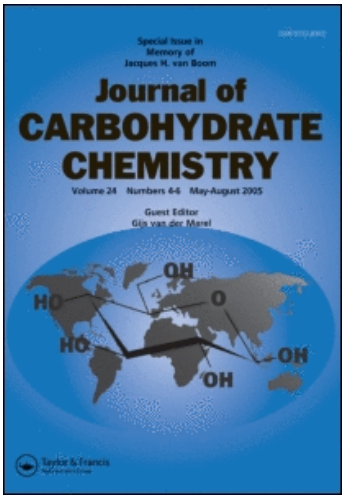

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Carrel, Frédéric R. and Seeberger, Peter H.(2007) 'Protecting Group Manipulations on Glycosyl Phosphate Triesters', Journal of Carbohydrate Chemistry, 26: 2, 125 — 139
To link to this Article: DOI: 10.1080/07328300701298204
URL: http://dx.doi.org/10.1080/07328300701298204

Journal of Carbohydrate Chemistry, 26:125–139, 2007

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300701298204

Protecting Group Manipulations on Glycosyl Phosphate Triesters

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Glucosyl and mannosyl phosphate triester building blocks were differentially protected by protecting group manipulations on competent glycosyl donors. Dibutyl 3,4-di-*O*-benzyl-6-*O*-(fluorenylmethoxycarbonyl)-2-*O*-pivaloyl-β-D-glucopyranoside phosphate, not accessible by other methods, was prepared this way.

Keywords Glycosyl phosphate triester, Protecting group manipulation

INTRODUCTION

Glycosyl phosphate triesters have become an important class of glycosylating agents for the synthesis of oligosaccharides. Compared to glycosyl trichloroacetimidates and glycosyl halides, glycosyl phosphates are relatively stable. Most glycosyl phosphates can be stored for months at 4°C and are less prone to hydrolysis during purification on silica gel. Upon activation with stoichiometric amounts of TMSOTf, glycosyl phosphates are highly reactive as most glycosylations proceed at low temperatures (β-phosphate: -60°C, α-phosphate: -30°C). Therefore, glycosyl phosphates are attractive glycosylating agents for solution[1] and solid-phase oligosaccharide synthesis.[2]

Glycosyl phosphate triesters can be synthesized from different precursor types. Starting from lactols, glycosyl phosphates can be obtained by reaction with dialkylchlorophosphate,[3] by dehydrative glycosylation,[4] or by triester phosphite formation followed by oxidation.[5] Regioselective opening of 1,2-orthoesters using dialkylphosphate is an efficient method to afford glycosyl phosphates.[6] 1,2-Glucals can be converted to glycosyl phosphates

Received December 13, 2006; accepted February 21, 2007.
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via a three-step one-pot procedure: epoxidation of the double bond, followed by regioselective opening of the epoxide at C(1) using dialkylphosphate, and finally protection at C(2).[7] Finally, other glycosylating agents such as glycosyl trichloroacetimidates,[8] glycosyl halides,[5b] pentenyl glycosides,[9] or MOP-glycosides[10] can be converted to glycosyl phosphates by activation and trapping of the oxycarbenium intermediate with dialkylphosphate.

Glycosyl phosphate triesters mostly are used directly as glycosylating agents. To date, few chemical transformations on glycosyl phosphate triesters have been reported with the phosphate moiety remaining intact. A radical dehalogenation on sialic acid phosphate,[5b] debenzylation,[8b] and deacetylation[8a] have been reported. Deacetylation at C(6), followed by formation of the corresponding triflate and subsequent S_N2 displacement, has been disclosed.[8c] The C(2) hydroxyl group of glycosyl phosphates has been benzoylated,[1b,7a] acetylated,[1b,7d] and pivaloylated.[7b] In addition, triethylsilyl,[7b] 2-(azidomethyl)benzoate,[1a] and *p*-chlorophenyl carbonate[11] groups have been placed on glycosyl phosphates. However, most of these C(2)-protecting group manipulations were part of the three-step one-pot procedure from 1,2-glucals.

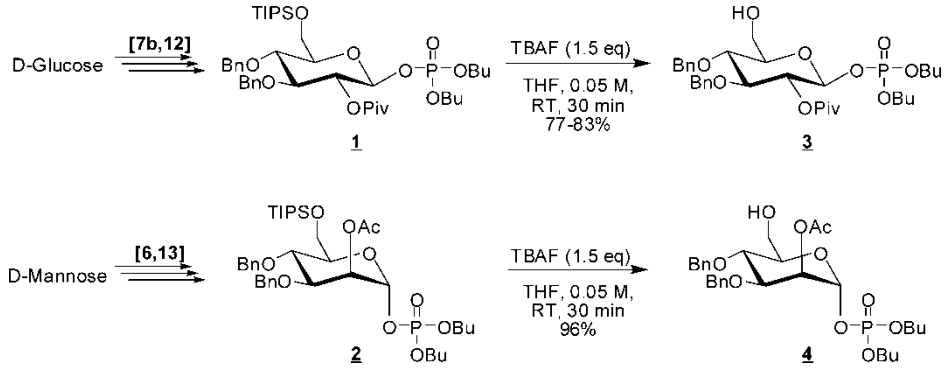
Here, we report protecting group manipulations on glycosyl phosphate triesters. Each phosphate was isolated by silica gel flash column chromatography and for most, no degradation was observed for months upon storage at $-18^{\circ}C$.

RESULTS AND DISCUSSION

Dibutyl 3,4-di-*O*-benzyl-2-*O*-pivaloyl-6-*O*-triisopropylsilyl-β-D-glucopyranoside phosphate **(1)**[7b,12] and dibutyl 2-*O*-acetyl-3,4-di-*O*-benzyl-6-*O*-triisopropylsilyl-α-D-mannopyranoside phosphate **(2)**[6,13] were synthesized as substrates for the subsequent studies. Since glycosyl phosphates are generally not stable under acidic conditions, both glycosyl phosphates **1** and **2** were desilylated by treatment with TBAF in THF to afford the corresponding C(6) hydroxyl containing glucosyl phosphate **3** and mannosyl phosphate **4** in good to excellent yield (Sch. 1).

Placement of esters and carbonates was investigated for the C(6)-protection of glucosyl phosphate **3**. Using 2-azido-2-methylpropanoyl anhydride ("A-cap anhydride"),[14] **3** was successfully esterified to produce **5** in 67% yield. A C(6) Fmoc group was introduced by treatment with FmocCl and pyridine in CH_2Cl_2 to afford the desired carbonate **6** in 95% yield (Sch. 2).

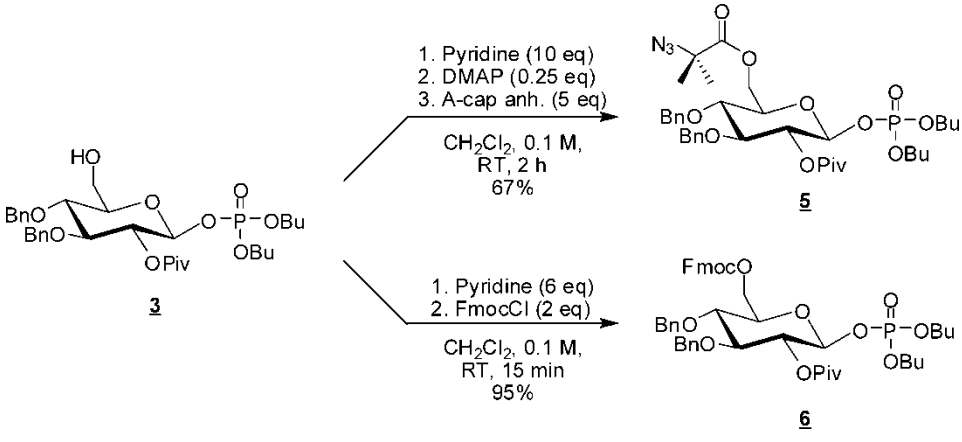
Mannosyl phosphate **4** can be protected in analogous fashion. Treatment of **4** with the A-cap anhydride afforded the corresponding ester 7 in 93% yield. Under FmocCl/pyridine conditions, **4** gave the expected carbonate **8** in 94% yield. Standard silylation conditions using TIPSCl and imidazole in DMF transformed **4** into the corresponding silylether **2** in 68% yield (Sch. 3).



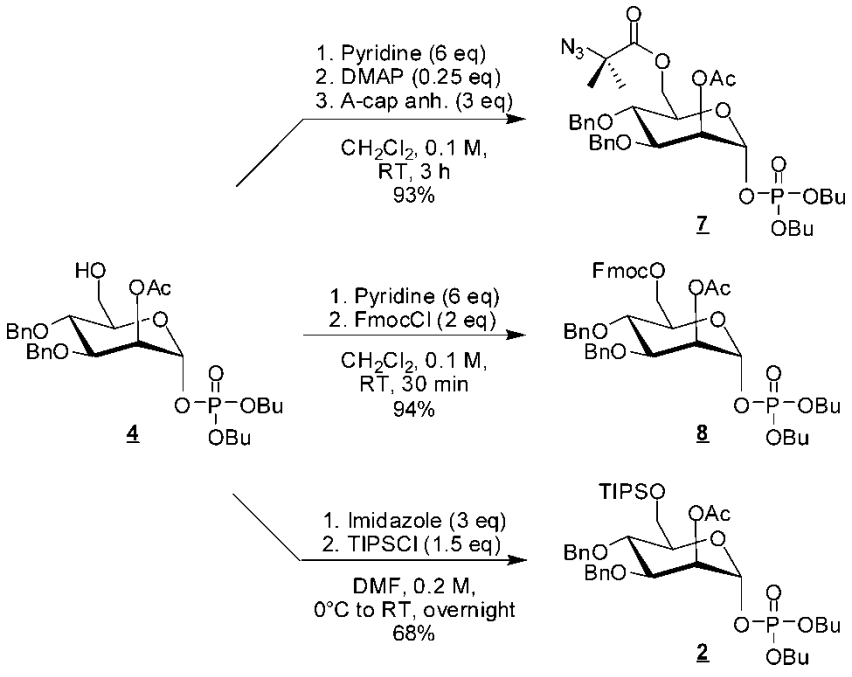
Scheme 1

The encouraging results for the protection of the C6 hydroxyl group prompted investigations concerning the protection of the C(2)-hydroxyl group of glycosyl phosphates. Attempts to cleave the acetyl group of **2** using K_2CO_3 in MeOH yielded, however, the corresponding C(2)-OH methyl-α-glycoside **9** (α-selectivity determined by measurement of the $^1J_{C(1)\text{-}H(1)} = 169$ Hz).[15] This finding suggests that the intermediate C(2)-alkoxide displaced the phosphate moiety to afford the epoxide that was opened by excess methanol. Similar results were obtained with sodium methoxide in methanol. As expected, an equimolar amount of sodium methoxide was required to drive the reaction to completion. The lower basicity of the diester phosphate anion compared to sodium methoxide may explain this observation (Sch. 4).

We had planned to synthesize 3,4-di-*O*-benzyl-6-*O*-(fluorenylmethoxycarbonyl)-2-*O*-pivaloyl-β-D-glucopyranoside phosphate (**6**) from 1,2-glucals using the three-step one-pot procedure.[7b] Treatment of 3,4-di-*O*-benzyl-D-glucal[2b] with



Scheme 2

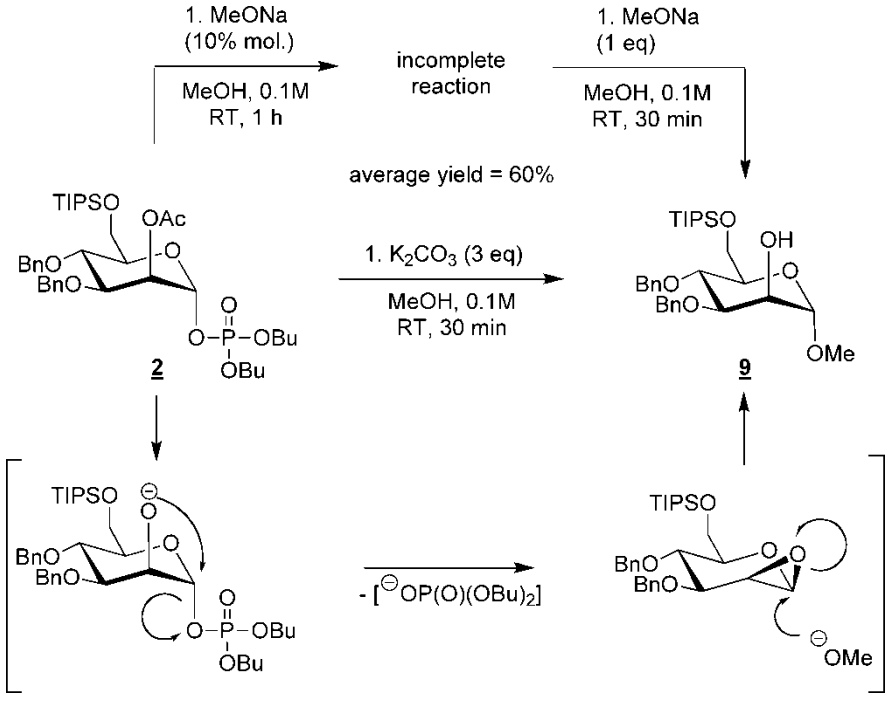


Scheme 3

FmocCl in pyridine afforded **10** in quantitative yield. On a 0.2-mmol scale, glucal **10** was epoxidized using dimethyldioxirane, followed by epoxide opening with dibutylphosphate and pivaloylation at C(2) using PivCl and DMAP to afford the desired phosphate **6** in 80% yield (β/α selectivity $\sim$10/1) (Sch. 5).

Problems with this reaction were encountered during scale-up. On a 5-mmol scale, phosphate **6** was contaminated with considerable amounts of the corresponding 2,6-bis-pivaloylated phosphate **11** that was inseparable by silica gel flash column chromatography. Formation of **11** is caused by DMAP, which cleaves the Fmoc group at C(6) and allows for further pivaloylation at this position. The structure of **11**, as well as the ratio between **6** and **11** (70%/23%), was determined by addition of 1% triethylamine in the chromatography eluent. Under these basic conditions, the Fmoc group of **6** was cleaved to afford a mixture of glycosyl phosphates **3** and **11** (Sch. 6), which were separable by silica gel flash column chromatography.

Several ways to avoid or reduce the formation of **11** were investigated. Replacement of DMAP by pyridine[7a] did not result in pivaloylated product. Lowering of the reaction temperature did not yield any success as C(2) protection started at around -30°C, a temperature at which **11** was concomitantly formed. The reaction was improved by using equimolar amounts of premixed DMAP and PivCl. However, more equivalents were required (5 eq. each) and the protection reaction proceeded quickly only at rt, but the ratio of **6** and **11**

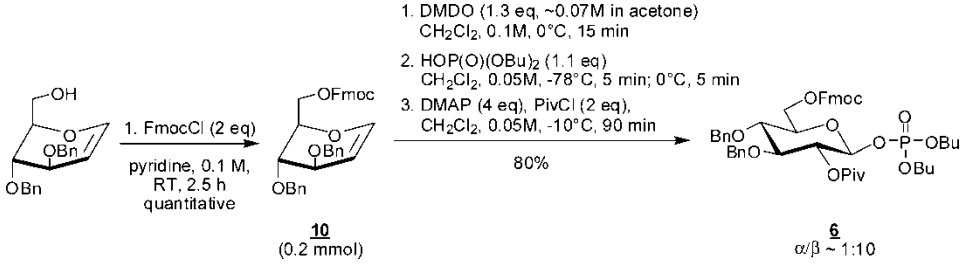


Scheme 4

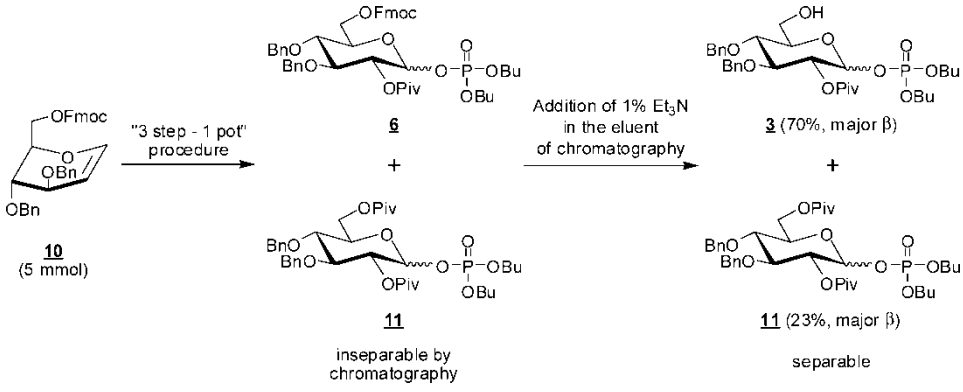
clearly improved. After chromatography, phosphate **6** was recovered pure in 64%, separated from fractions contaminated by **11** (~24%).

The problems we encountered with this synthesis prompted us to establish suitable protecting group manipulations on glycosyl phosphate **1** for the synthesis of **6.** The silyl ether of **1** was removed under basic treatment with TBAF to afford **3** in 83% yield before the hydroxyl group at C(6) was protected using FmocCl and pyridine to afford **6** in 95% yield.

All glycosyl phosphates triesters that were synthesized here were purified by silica gel flash column chromatography. Due to the slightly acidic character



Scheme 5



Scheme 6

of the silica gel, precautions were taken during purification. Chromatography often resulted in small amounts of lactols that were difficult to separate from the glycosyl phosphates. Neutralization of the silica gel, either by addition of 1% triethylamine or pyridine in the eluent, was required to avoid hydrolysis of the glycosyl phosphate. Most of the glycosyl phosphates triesters synthesized here were stable for months at $-18^{\circ}C$.

CONCLUSIONS

We demonstrated that protecting group manipulations can be executed on glycosyl phosphate triesters without affecting the phosphate moiety. Due to the acid labile character of the phosphate, all deprotection, protection, and purification maneuvers had to be carried out in basic media.

EXPERIMENTAL

General Methods

All chemicals were reagent grade and were used as supplied unless otherwise noted. Dichloromethane (CH_2Cl_2) and tetrahydrofurane (THF) were purified by a J. C. Meyer Solvent Dispensing System (two packed columns of neutral alumina). Solvents for chromatography and workup procedures were distilled from commercially available technical grade solvents. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by UV and/or by dipping the plates in a cerium sulphate-ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Fluka silica gel 60 (40–63 μm). $^{1}H/^{13}C/^{31}P$ NMR

spectra were recorded on a Varian Mercury XL 300 spectrometer. The ^{1}H NMR spectra (300 MHz) are expressed in ppm relative to $CHCl_3$ (7.26 ppm) as internal reference; the coupling constants are reported in Hz. The same is valid for ^{13}C NMR spectra (75 MHz, internal reference $CDCl_3$: 77.0 ppm). For ^{31}P NMR spectra (121 MHz), the H_3PO_4 ($\delta = 0$ ppm) was used as internal reference. Optical rotation $[\alpha]_D$ was recorded on a Jasco DIP-370 spectrometer using a sodium lamp (589 nm) at rt, with a 10 cm/1 mL cell. The solvent is specified as well as the concentration (i.e., C = 1 = 10 mg/mL). IR spectra were recorded as $CHCl_3$ solutions on a Perkin-Elmer 1600 FT-IR spectrometer and are expressed in cm^{-1}. High-resolution mass spectroscopy (HRMS) was performed by the MS service at the Laboratory of Organic Chemistry at ETH Zürich; 2,5-dihydroxybenzoic acid (DHB) was used as matrix.

Dibutyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-6-*O*-triisopropylsilyl-α-D-mannopyranoside Phosphate (2)

To a stirred solution of **4** (238 mg, 0.40 mmol) in DMF (2 mL) was added imidazole (82 mg, 1.2 mmol) at rt. The solution was cooled to 0°C and TIPSCl (128 μL, 0.6 mmol) was added. The solution was allowed to warm to rt overnight. After 21 h, the solution was treated with Et_2O (10 mL) and water (3 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel flash column chromatography (gradient AcOEt/cyclohexane from (1:9) to (1:4), eluent with 1% NEt_3, R_f [AcOEt/hexane(1:4)] = 0.23) to afford **2** (203 mg, 68%) as colorless oil. Spectral data are consistent with those reported previously.[6b]

Dibutyl 3,4-Di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside Phosphate (3)

To a stirred solution of **1** (2.063 g, 2.6 mmol) in THF (52 mL) was added TBAF (1 M in THF, 3.9 mL, 3.9 mmol) at rt. After 30 min, the reaction mixture was dried over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel flash column chromatography (gradient EtOAc:cyclohexane from (1:2) to (2:1) v/v, eluent with 1% NEt_3, R_f [EtOAc:ratio;cyclohexane(1:1)] = 0.30) to afford **3** (1.276 g, 77%) as white solid. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H, $J = 7.3$, $2^{*}CH_3$(Bu)), 1.20 (s, 9H, $3^{*}CH_3$(Piv)), 1.32–1.46 (m, 4H, $2^{*}CH_2$(Bu)), 1.58–1.70 (m, 4H, $2^{*}CH_2$(Bu)), 2.30 (bs, 1H, H(OH)), 3.58 (ddd, 1H, $J_{4,5} = 9.9$ Hz, $J_{5,6} = 3.6$ Hz, $J_{5,6} = 2.5$ Hz, H-5), 3.72 (dd, 1H, $J = 8.8$ Hz, $J = 8.0$ Hz, H-3 or 4), 3.76 (dd, 1H, $J_{6a,6b} = 12.4$ Hz, $J_{5,6a} = 3.8$ Hz, H-6a), 3.83–3.91 (m, 2H, H-6b, H-3 or 4), 3.99–4.10 (m, 4H, $2^{*}OCH_2$(Bu)), 4.73, 4.77 (2d, 2H, $J = 11.3$ Hz,

CH_2(Bn)), 4.68, 4.80 (2d, 2H, $J = 11.0$ Hz, CH_2(Bn)), 5.115 (dd, 1H, $J_{2,3} = 7.4$ Hz, $J_{1,2} = 6.9$ Hz, H-2), 5.31 (dd, 1H, $J_{1,2} = 6.9$ Hz, $J_{1,P} = 6.1$ Hz, H-1), 7.23–7.36 (m, 10*H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.4 (2*CH_3(Bu)), 18.5, 18.5 (2*CH_2(Bu)), 27.0 (3*CH_3(Piv)), 32.1, 32.0 (2*CH_2(Bu)), 38.7 (C_q(Piv)), 61.2 (C6), 67.9–68.0 (m, 2*OCH_2(Bu)), 72.6 (d, $J = 10.3$ Hz, C2), 74.4, 74.9, 76.0, 76.2, 82.4 (C3, C4, C5, 2*CH_2(Bn)), 96.3 (d, $J = 5.4$ Hz, C1), 127.3, 127.9 (2*CH_{Ar}), 127.6, 128.0, 128.3, 128.4 (4*2CH_{Ar}), 137.6, 137.7 (2*C_{qAr}), 176.7 (COO(Piv)); ^{31}P NMR ($CDCl_3$) δ –2.120; $[\alpha]_D$ – 9.1° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3386, 3065, 3007, 2965, 2934, 2875, 1738, 1497, 1479, 1455, 1398, 1362, 1275, ~1200, 1136, 1095, 1037, 914, 822; HRMS Calcd for $C_{33}H_{49}O_{10}PNa$: 659.2956. Found: 659.2945.

Dibutyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-α-D-mannopyranoside Phosphate (4)

To a stirred solution of **2** (2.64 g, 3.51 mmol) in THF (70 mL) was added TBAF (1 M in THF, 5.3 mL, 5.3 mmol) at rt. After 30 min, the solution was treated with a saturated aqueous solution of $NaHCO_3$ (25 mL) and the THF was mostly evaporated. The resulting solution was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvents evaporated. The residue was purified by silica gel flash column chromatography (gradient EtOAc:cyclohexane from (2:1) to (2.5:1) v/v, eluent with 1% NEt_3, R_f [EtOAc:hexane(3:1)] = 0.53) to afford **4** (2.00 g, 96%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93, 0.94 (2t, 6H, $J = 7.1$ Hz, 2*CH_3(Bu)), 1.32–1.47 (m, 4H, 2*CH_2(Bu)), 1.60–1.74 (m, 4H, 2*CH_2(Bu)), 2.15 (s, 3H, CH_3(OAc)), 3.76–3.91 (m, 4H), 3.97–4.10 (m, 5H), 4.55, 4.72 (2d, 2H, $J = 11.3$ Hz, CH_2(Bn)), 4.64, 4.91 (2d, 2H, $J = 10.8$ Hz, CH_2(Bn)), 5.42 (dd, 1H, $J_{2,3} = 3.0$ Hz, $J_{1,2} = 2.2$ Hz, H-2), 5.62 (dd, 1H, $J_{1,P} = 6.0$ Hz, $J_{1,2} = 2.2$ Hz, H-1), 7.27–7.39 (m, 10*H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.5 (2*CH_3(Bu)), 18.5 (2*CH_2(Bu)), 20.8 (CH_3(OAc)), 32.0, 32.1 (2*CH_2(Bu)), 61.5 (C6), 67.8–68.2 (m, C2, 2*OCH_2(Bu)), 71.9, 73.3, 73.7, 75.2, 77.0 (C3, C4, C5, 2*CH_2(Bn)), 95.5 (d, $J = 5.4$ Hz, C1), 127.8, 128.3 (2*CH_{Ar}), 127.9, 128.0, 128.3 (4*2CH_{Ar}), 137.5, 137.9 (2*C_{qAr}), 169.8 (COO(OAc)); ^{31}P NMR ($CDCl_3$) δ –2.233; $[\alpha]_D$ 26.2° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3436, 3008, 2964, 2935, 2876, 1746, 1603, 1497, 1455, 1373, 1261, ~1200, 1168, 1078, 1029, 962; HRMS Calcd for $C_{30}H_{43}O_{10}PNa$: 617.2486. Found: 617.2475.

Dibutyl 6-*O*-(2-Azido-2-methylpropanoyl)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside Phosphate (5)

To a stirred solution of **3** (127 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) were added successively pyridine (161 μL, 2 mmol), DMAP (6.1 mg, 0.05 mmol), and

2-azido-2-methylpropanoyl anhydride (240 mg, 1 mmol) at rt. After 2 h at rt, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The residue was coevaporated with toluene (10 mL) and then purified by silica gel flash column chromatography (gradient EtOAc:hexane from (1:3) to (1:2) v/v, eluent with 1% NEt_3, R_f [EtOAc/hexane(1:2.5)] = 0.32) to give **5** (100 mg, 67%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 7.5 Hz, CH_3(Bu)), 0.92 (t, 3H, J = 7.5 Hz, CH_3(Bu)), 1.20 (s, 9H, 3*CH_3(Piv)), 1.30–1.42 (m, 4H, 2*CH_2(Bu)), 1.47 (s, 6H, 2*CH_3(A-tag)), 1.56–1.68 (m, 4H, 2*CH_2(Bu)), 3.64–4.10 (2 m, 7H, H-3, H-4, H-5, 2*OCH_2(Bu)), 4.27 (dd, 1H, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6a}$ = 3.5 Hz, H-6a), 4.58 (bd, 1H, $J_{6a,6b}$ = 11.8 Hz, H-6b), 4.72, 4.78 (2d, 2H, J = 10.9 Hz, CH_2(Bn)), 4.57, 4.83 (2d, 2H, J = 10.8 Hz, CH_2(Bn)), 5.12 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{1,2}$ = 8.1 Hz, H-2), 5.25 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $J_{1,P}$ = 6.5 Hz, H-1), 7.21–7.36 (m, 10*H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7 (2*CH_3(Bu)), 18.7, 18.7 (2*CH_2(Bu)), 24.5 (2*CH_3(A-Tag)), 27.2 (3*CH_3(Piv)), 32.1–32.2 (m, 2*CH_2(Bu)), 38.9 (C_q(Piv)), 63.1, 63.2 (C6, C_q-N_3(A-Tag)), 67.8–68.0 (m, 2*OCH_2(Bu)), 72.7 (d, J = 9.4 Hz, C2), 73.5, 75.2, 76.9, 82.7 (C3, C4, C5, 2*CH_2(Bn)), 96.4 (d, J = 5.4 Hz, C1), 127.7, 128.9 (2*CH_{Ar}), 127.3, 127.9, 128.3, 128.5 (4*2CH_{Ar}), 137.1, 137.4 (2*C_{qAr}), 172.1, 176.5 (COO(Piv) + COO(A-tag)); ^{31}P NMR ($CDCl_3$) δ −2.190; IR (chloroform, cm^{-1}) 3008, 2966, 2936, 2875, 2112, 1740, 1498, 1479, 1455, 1390, 1367, 1275, ~1200, 1137, 1095, 1029, 909, 878; HRMS Calcd for $C_{37}H_{54}N_3O_{11}PNa$: 770.3388. Found: 770.3375.

Dibutyl 3,4-Di-*O*-benzyl-6-*O*-(fluorenylmethoxycarbonyl)-2-*O*-pivaloyl-β-D-glucopyranoside Phosphate (6)

*Synthesis using Dibutyl 3,4-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside phosphate **3***

To a stirred solution of **3** (636 mg, 1 mmol) in CH_2Cl_2 (10 mL) were added pyridine (480 μL, 6 mmol) and FmocCl (516 mg, 2 mmol) at rt. After 15 min, the solvents were evaporated. Residual pyridine was coevaporated with toluene (2 × 5 mL). The residue was purified by silica gel flash column chromatography (gradient acetone/toluene from (1:99) to (5:95) v/v, eluent with 1% pyridine, R_f [EtOAc:hexane(1:2)] = 0.29) to give **6** (812 mg, 95%) as colorless oil.

*Synthesis using 3,4-di-O-benzyl-6-O-(fluorenylmethoxycarbonyl)-D-glucal **10***

To a stirred solution of **10** (110 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added DMDO (~0.07 M in acetone, 3.7 mL, 0.26 mmol) at 0°C. After 15 min, the solvents were removed under vacuum at 0°C. The residue was diluted with

CH_2Cl_2 (4 mL) and cooled to -78°C. Dibutylphosphate (44 μL, 0.22 mmol) was added dropwise over 3 min and the solution was allowed to warm to 0°C and stirred for 7 min. The solution was cooled to -10°C; DMAP (98 mg, 0.8 mmol) and PivCl (49 μL, 0.4 mmol) were added and the solution was stirred for 90 min at -10°C. The reaction mixture was treated with a mixture of EtOAc (20 mL) and hexane (60 mL). The white precipitate was filtered through a pad of silica gel and further eluted (first with EtOAc:hexane (1:3) + 1% NEt_3 v/v (80 mL); then with EtOAc:hexane (1:2) + 1% NEt_3 v/v (90 mL)). The solvents were evaporated and the residue was purified by silica gel flash column chromatography (EtOAc:hexane (1:2) + 1% NEt_3 v/v) to give **6** (137 mg, $\alpha/\beta \sim 1{:}10$, 80%) as colorless oil.

When reaction was run on a 1-mmol scale, we observed formation of the corresponding 2,6-bis-pivaloylated analog **11**, inseparable from **6** by chromatography on silica gel. On larger scale, we also observed Fmoc cleavage due to the presence of NEt_3 in the chromatography eluent.

^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, $J = 7.5$ Hz, CH_3(Bu)), 0.93 (t, 3H, $J = 7.5$ Hz, CH_3(Bu)), 1.23 (s, 9H, 3*CH_3(Piv)), 1.31–1.47 (m, 4H, 2*CH_2(Bu)), 1.51–1.71 (m, 4H, 2*CH_2(Bu)), 3.70–4.54 (m, 12H, H-3, H-4, H-5, 2*H-6, OCH_2(Fmoc), CH(Fmoc), 2*OCH_2(Bu)), 4.75, 4.81 (2d, 2H, $J = 11.0$ Hz, CH_2(Bn)), 4.60, 4.83 (2d, 2H, $J = 10.9$ Hz, CH_2(Bn)), 5.10 (m, 1H, $J_{2,3} = 8.4$ Hz, $J_{1,2} = 8.0$ Hz, H-2), 5.235 (dd, 1H, $J_{1,2} = 8.0$ Hz, $J_{1,P} = 6.9$ Hz, H-1), 7.22–7.43 (m, 14H, 10*H_{Ar}(Bn) + 4*H_{Ar}(Fmoc)), 7.62 (dm, 2H, $J = 7.5$ Hz, 2*H_{Ar}(Fmoc)), 7.77 (d, 2H, $J = 7.5$ Hz, 2*H_{Ar}(Fmoc)); ^{13}C NMR ($CDCl_3$) δ 13.7 (2*CH_3(Bu)), 18.8, 18.8 (2*CH_2(Bu)), 27.3 (3*CH_3(Piv)), 32.2–32.3 (m, 2*CH_2(Bu)), 39.1 (C_q(Piv)), 46.9 (CH(Fmoc)), 66.1 (C6), 68.0–68.3 (m, 2*OCH_2(Bu)), 72.9 (d, $J = 9.5$ Hz, C2), 70.2, 73.8, 75.3, 75.4, 76.9, 82.9 (C3, C4, C5, OCH_2(Fmoc), 2*CH_2(Bn)), 96.6 (d, $J = 5.1$ Hz, C1), 120.3–128.7 (8*CH_{Ar}(Fmoc) + 10*CH_{Ar}(Bn)); 137.5, 137.9 (2*C_q(Bn)), 141.4, 141.5, 143.4, 143.5 (4*C_q(Fmoc)), 155.1 (OC(O)O(Fmoc)), 177.0 (COO(Piv)); ^{31}P NMR ($CDCl_3$) δ −2.488; $[\alpha]_D$ 10.6° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3008, 2964, 2906, 2876, 1742, 1497, 1478, 1452, 1398, 1363, 1262, 1132, 1096, 916, 820; HRMS Calcd for $C_{48}H_{59}O_{12}PNa$: 881.3636. Found: 881.3619.

Dibutyl 2-*O*-Acetyl-6-*O*-(2-azido-2-methylpropanoyl)-3,4-di-*O*-benzyl-α-D-mannopyranoside Phosphate (7)

To a stirred solution of **4** (83 mg, 0.140 mmol) in CH_2Cl_2 (1.4 mL) were added successively at rt pyridine (68 μL, 0.837 mmol), DMAP (4.3 mg, 0.035 mmol), and 2-azido-2-methylpropionic anhydride (100 mg, 0.487 mmol). After 3 h, the solution was diluted with CH_2Cl_2 (5 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried

over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel flash column chromatography (eluent EtOAc/hexane (1:2) v/v, eluent with 1% NEt_3, R_f [EtOAc:hexane(1:2)] = 0.34) to afford **7** (91 mg, 93%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.94, 0.94 (2t, 6H, $J = 7.2$ Hz, 2*CH_3(Bu)), 1.34–1.47 (m, 4H, 2* CH_2(Bu)); 1.495, 1.515 (2s, 6H, 2*CH_3(A-Tag)), 1.66 (broad quintuplet, 4H, $J = 6.6$ Hz, 2*CH_2(Bu)), 2.13 (s, 3H, CH_3(OAc)), 3.90 (dd, 1H, $J = 9.9$ Hz, $J = 9.3$ Hz, H-4 or 5), 3.99–4.11 (m, 6H, H-3, 2*OCH_2(Bu), H-4 or 5), 4.41 (dd, 1H, $J_{6a,6b} = 11.8$ Hz, $J_{5,6a} = 3.0$ Hz, H-6a), 4.51 (dd, 1H, $J_{6a,6b} = 11.8$ Hz, $J_{5,6b} = 1.9$ Hz, H-6b), 4.55, 4.73 (2d, 2H, $J = 11.3$ Hz, CH_2(Bn)), 4.58, 4.95 (2d, 2H, $J = 11.0$ Hz, CH_2(Bn)), 5.43 (dd, 1H, $J_{2,3} = 2.5$ Hz, $J_{1,2} = 1.9$ Hz, H-2), 5.60 (dd, 1H, $J_{1,P} = 6.3$ Hz, $J_{1,2} = 1.9$ Hz, H-1), 7.26–7.38 (m, 10*H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.5 (2*CH_3(Bu)), 18.5 (2*CH_2(Bu)), 20.6 (CH_3(Ac)), 24.3, 24.3 (2*CH_3(A-Tag)), 32.0–32.2 (m, 2*CH_2(Bu)), 63.0, 63.2 + 63.0 (C6, C_q-N_3(A-Tag)), 67.6–68.0 (m, C2, 2*OCH_2(Bu)), 71.3, 71.8, 73.2, 75.4, 77.0 (C3, C4, C5,2*CH_2(Bn)), 95.3 (d, $J = 4.9$ Hz, C1), 127.9–128.4 (10*CH_{Ar}), 137.2, 137.7 (2*C_{qAr})), 169.7 (COO(OAc)), 172.3 (COO(A-Tag)); ^{31}P NMR ($CDCl_3$) δ −2.729; $[\alpha]_D$ 27.0° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3008, 2965, 2936, 2875, 2113, 1744, 1497, 1454, 1373, 1261, ~1200, 1168, 1145, 1073, 1029, 963, 912, 878; HRMS Calcd for $C_{34}H_{48}N_3O_{11}P$: 728.2919. Found: 728.2906.

Dibutyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-6-*O*-(fluorenylmethoxycarbonyl)-α-D-mannopyranoside Phosphate (8)

To a stirred solution of **4** (810 mg, 1.36 mmol) in CH_2Cl_2 (13.6 mL) were added pyridine (657 μL, 8.17 mmol) and FmocCl (702 mg, 2.72 mmo1) at rt. After 30 min, the solution was diluted with CH_2Cl_2 (40 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel flash column chromatography (EtOAc/cyclohexane (1:3) v/v, R_f [EtOAc:cyclohexane(1:3)] = 0.19) to afford **8** (1048 mg, 94%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93, 0.94 (2t, 6H, $J = 7.4$ Hz, 2*CH_3(Bu)), 1.34–1.48 (m, 4H, 2*CH_2(Bu)), 1.61–1.73 (m, 4H, 2*CH_2(Bu)), 2.17 (s, 3H, CH_3(OAc)), 3.86 (dd, 1H, $J = 9.9$ Hz, $J = 9.6$ Hz, H-4), 4.01–4.17 (m, 6H, 2*OCH_2(Bu), H-5, H-3), 4.25 (dd, 1H, $J = 7.4$ Hz, $J = 7.1$ Hz, CH(Fmoc)), 4.36–4.50 (m, 4H, 2*H-6, OCH_2(Fmoc)), 4.57, 4.75 (2d, 2H, $J = 11.3$ Hz, CH_2(Bn)), 4.59, 4.94 (2d, 2H, $J = 10.7$ Hz, CH_2(Bn)), 5.46 (dd, 1H, $J_{2,3} = 2.8$ Hz, $J_{1,2} = 1.9$ Hz, H-2), 5.66 (dd, 1H, $J_{1,P} = 6.6$ Hz, $J_{1,2} = 1.9$ Hz, H-1), 7.27–7.44 (m, 10*H_{Ar}(Bn) + 4*H_{Ar} (Fmoc)), 7.60 (m, 2H, 2*H_{Ar} (Fmoc)), 7.77 (bd, 2H, $J = 7.4$ Hz, 2*H_{Ar}(Fmoc)); ^{13}C NMR ($CDCl_3$) δ 13.5 (2*CH_3(Bu)), 18.5 (2*CH_2(Bu)), 20.8 (CH_3(OAc)), 32.0–32.2 (m, 2*CH_2(Bu)), 46.6 (CH(Fmoc)),

66.3 (C6), 67.8–68.1 (m, C2, $2^{*}OCH_2Bu$)), 69.9, 71.3, 71.9, 73.2, 75.3, 77.0 (CH_2(Fmoc), $2^{*}CH_2$(Bn), C3, C4, C5), 95.2 (d, $J = 5.4$ Hz, C1), 120.0–128.4 ($8^{*}CH_{Ar}$(Fmoc) + $10^{*}CH_{Ar}$ (Bn)), 137.4, 137.7 ($2^{*}C_{qAr}$(Bn)), 141.4, 143.1, 143.3 ($4^{*}C_{qAr}$(Fmoc)), 154.9 (OC(O)O (Fmoc)), 169.8 (COO(OAc)); ^{31}P NMR (121 MHz, $CDCl_3$) δ −2.648; $[\alpha]_D$ 19.1° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3007, 2963, 2934, 2875, 1746, 1602, 1496, 1452, 1374, 1261, ~1200, 1168, 1102, 1028, 963; HRMS Calcd for $C_{45}H_{53}O_{12}PNa$: 839.3167. Found. 839.3173.

Methyl 3,4-Di-*O*-benzyl-6-*O*-(triisopropylsilyl)-α-D-mannopyranoside (9)

Method using K_2CO_3

To a stirred solution of **2** (150 mg, 0.2 mmol) in MeOH (2 mL) was added K_2CO_3 (83 mg, 0.6 mmo1) at rt. After 30 min, the solution was diluted with CH_2Cl_2 (10 mL) and treated with H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated.

Method using MeONa

To a stirred solution of **2** (150 mg, 0.2 mmol) in MeOH (2 mL) was added MeONa (1 mg, 0.02 mmo1) at rt. After 1 h, more MeONa (10 mg, 0.2 mmol) was added to drive the reaction to completion. The solvents were evaporated 30 min later.

Purification

Both crude products were gathered and purified by silica gel flash column chromatography (acetone/cyclohexane (1:5) v/v, eluent with 1% NEt_3, R_f [acetone/cyclohexane(1:5)] = 0.20) to afford **9** (171 mg, average yield = 60%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.18–1.06 (m, $21^{*}H$(TIPS)), 2.43 (d, 1H, $J = 3.3$ Hz, H(OH)), 3.37 (s, 3H, MeO), 3.66 (ddd, 1H, $J_{4,5} = 9.6$ Hz, $J_{5,6a} = 5.0$ Hz, $J_{5,6b} = 1.8$ Hz, H-5), 3.80 (dd, 1H, $J_{4,5} = 9.6$ Hz, $J_{3,4} = 9.1$ Hz, H-4), 3.87–3.94 (m, 2H, H-6a, H-3), 3.98 (dd, 1H, $J_{6a,6b} = 11.0$ Hz, $J_{5,6b} = 2.0$ Hz, H-6), 4.04 (ddd, $J_{2,3} = 3.6$ Hz, $J_{2,OH} = 3.3$ Hz, $J_{1,2} = 1.7$ Hz, H-2), 4.69, 4.74 (2d, 2H, $J = 11.7$ Hz, CH_2(Bn)), 4.76 (d, 1H, $J_{1,2} = 1.7$ Hz, H-1), 4.67, 4.91 (2d, 2H, $J = 11.1$ Hz, CH_2(Bn)), 7.27–7.42 (m, $10^{*}H_{Ar}$); ^{13}C NMR ($CDCl_3$) δ11.9 ($3^{*}CH$(TIPS)), 17.9, 17.9 ($6^{*}CH_3$(TIPS)), 54.4 (MeO), 62.9 (C6), 68.3, 71.9, 72.5, 74.2, 75.0, 80.2 ($2^{*}CH_2$(Bn), C2, C3, C4, C5), 100.0 (C1), 127.6–128.4 ($10^{*}CH_{Ar}$), 137.9, 138.4 ($2^{*}C_{qAr}$); $[\alpha]_D$ 46.5° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3574, 3067, 3008, 2943, 2867, 1602, 1496, 1454, 1384, 1363, 1260, 1110, 1058, 1028, 883; HRMS Calcd for $C_{30}H_{46}O_6SiNa$: 553.2956. Found: 553.2948.

3,4-Di-*O*-benzyl-6-*O*-(fluorenylmethoxycarbonyl)-D-glucal (10)

To a stirred solution of 3,4-di-*O*-benzyl-D-glucal (3.26 g, 10 mmol) in pyridine (100 mL) was added FmocCl (5.16 g, 20 mmol) at rt. After 90 min, the solution was diluted with CH_2Cl_2 (300 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel flash column chromatography (adsorbed silica gel, gradient from acetone/hexane (1:9) to (1:4) v/v, R_f [acetone/hexane(1:4)] = 0.40) to afford **10** (5.431 g, 99%) as yellowish oil. ^{1}H NMR ($CDCl_3$) δ 3.91 (dd, 1H, $J_{4,5} = 8.1$ Hz, $J_{3,4} = 5.6$ Hz, H(C4)), 4.21–4.34 (m, 3H, H-3, H-5, CH(Fmoc)), 4.46–4.48 (m, 2H, 2*H-6), 4.57 (d, 2H, $J = 4.0$ Hz, OCH_2(Fmoc)), 4.62, 4.72 (2d, 2H, $J = 9.7$ Hz, CH_2(Bn)), 4.76, 4.94 (2d, 2H, $J = 11.5$ Hz, CH_2(Bn)), 5.01 (dd, 1H, $J_{1,2} = 6.2$ Hz, $J_{2,3} = 2.8$ Hz, H-2), 6.49 (dd, 1H, $J_{1,2} = 6.2$ Hz, $J_{1,3} = 0.9$ Hz, H-1), 7.32–7.49 (m, 10*H_{Ar}(Bn) + 4*H_{Ar} (Fmoc)), 7.69 (bd, 2H, $J = 7.5$ Hz, 2*H_{Ar}(Fmoc)), 7.82 (d, 2H, $J = 7.5$ Hz, 2*H_{Ar}(Fmoc)); ^{13}C NMR ($CDCl_3$) δ 46.8 (CH(Fmoc)), 66.3 (C6), 70.1, 70.5, 73.7, 73.9, 74.9, 75.1 (OCH_2(Fmoc), 2*CH_2(Bn), C3, C4, C5), 100.1 (C2), 120.0–128.5 (8*CH_{Ar}(Fmoc), 10*CH_{Ar}(Bn)), 137.8, 138.1 (2*C_q(Bn)), 141.2, 143.3, 143.3 (4*C_q(Fmoc)), 144.3 (C1), 154.9 (OC(O)O (Fmoc)); $[\alpha]_D$ 5.4° (*c* 1.0, chloroform); IR (chloroform, cm^{-1}) 3068, 3008, 2956, 2866, 1747, 1648, 1497, 1478, 1452, 1397, 1331, 1262, ~1200, 1101, 1028, 970; HRMS Calcd for $C_{35}H_{32}O_6Na$: 571.2091. Found: 571.2082.

Dibutyl 3,4-Di-*O*-benzyl-2,6-di-*O*-pivaloyl-β-D-glucopyranoside Phosphate (11)

Byproduct of the large-scale DMDO reaction: R_f [EtOAc: cyclohexane(1:3)] = 0.30. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6H, 2*CH_3(Bu)), 1.20, 1.21 (2s, 18H, 2*[3*CH_3(Piv)]), 1.31–1.45 (m, 4H, 2*CH_2(Bu)), 1.56–1.67 (m, 4H, 2*CH_2(Bu)), 3.64–3.77 (m, 3H), 3.94–4.08 (m, 4H), 4.19 (dd, 1H, $J_{6a,6b} = 11.5$ Hz, $J_{5,6a} = 3.1$ Hz, H-6a), 4.495 (bd, 1H, $J_{6a,6b} = 11.5$ Hz, H-6b), 4.71, 4.78 (2d, 2H, $J = 11.0$ Hz, CH_2(Bn)), 4.56, 4.80 (2d, 2H, $J = 10.7$ Hz, CH_2(Bn)), 5.12 (dd, 1H, $J_{2,3} = 8.2$ Hz, $J_{1,2} = 8.2$ Hz, H-2), 5.25 (dd, 1H, $J_{1,2} = 8.0$ Hz, $J_{1,P} = 6.9$ Hz, H(C1)), 7.20–7.36 (m, 10*H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.4, 13.5 (2*CH_3(Bu)), 18.4, 18.5 (2*CH_2(Bu)), 27.0, 27.1 (2*[3*CH_3(Piv)]), 31.9–32.0 (m, 2*CH_2(Bu)), 38.7 (2*C_q(Piv)), 61.9 (C6), 67.6–67.9 (m, 2*OCH_2(Bu)), 72.8 (d, $J = 9.2$ Hz, C2), 73.8, 75.1, 75.2, 77.0, 82.6 (C3, C4, C5, 2*CH_2(Bn)), 96.4 (d, $J = 4.9$ Hz, C1), 127.7, 128.0 (2*CH_{Ar}), 127.3, 127.9, 128.3, 128.5 (4*2CH_{Ar}), 137.7, 137.6 (2*C_q(Bn)), 176.7, 177.8 (2*COO(Piv)); ^{31}P NMR ($CDCl_3$) δ –2.440; $[\alpha]_D$ 2.7° (*c* 1.0, chloroform); IR (chloroform,

cm^{-1}) 3007, 2965, 2935, 2875, 1736, 1603, 1497, 1479, 1456, 1398, 1364, 1277, 1138, 1095, 1036, 906, 821; HRMS Calcd for $C_{38}H_{57}O_{11}PNa$: 743.3531. Found: 743.3518.

ACKNOWLEDGEMENTS

This research was supported by ETH Zürich and the Swiss National Science Foundation (SNF Grant 200121-101593).

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