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A FACILE REGIOSELECTIVE 1,6-*O*-DIACETYLATION METHOD OF METHYL-GLYCOPYRANOSIDES AND THEIR DIMETHYL PHOSPHONATES

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Abstract: A general method of 1,6-di-O-acetylation of methyl-α/β-glycopyranosides and a strategy to synthesize protected dimethyl (2,3,4-tri-*O*-benzyl-α-D-glycosyl) phosphonate having a free OH at C-6 are reported.

Saccharides play an important role in the development, growth, function and survival of the organism. [1] Many oligosaccharides have biological activities contain 1-6 units, such as gentiobiose, dextran and etc.. [2] A kind of sulfated mannose polysaccharide with anti-HIV activity from the Pacific tunicate *Didemnum malle* discovered recently also consists of 1-6 units. [3] So protected

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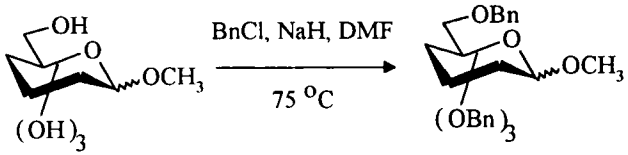
sugars having acetyl or free hydroxyl groups at 1-C and 6-C are important starting materials for the preparation of oligo- and polysaccharides and glycoconjugates.

Our current interest in glycosyl phosphonate as glycosyltransferase inhibitors directed our attention to the search for a facile method for the synthesis of the required starting materials, namely benzyl protected α or β-hexopyranoses having 1-OH or/and 6-OH or 1-OAc or/and 6-OAc. These compounds can be easily converted into glycosyl donors [4] containing -C(=NH)CCl_3, -SEt, -SPh, -SMe, halides and phosphate[5] and phosphonate[6] as inhibitors at the anomeric carbon. The most widely used and traditional method of preparation of 1,6-diacetylhexoses is a multistep procedure to synthesize the 1,6-anhydropyranoses first, and then to open the ring to afford the desired materials. [7] Longer synthetic routes lead, in general, to anomeric mixtures, difficult to separate and with the consequent loss of yield.

We now report a direct and general regio- and stereoselective diacetylation procedure at 1-C and 6-C for methyl tetra-*O*-benzyl-α/β-D-glycopyranoses **2a-2c** (as shown in Scheme I) by treatment with Ac_2O/H_2SO_4 without solvent, to give in good to excellent yield the corresponding diacetylated derivatives at 1-C and 6-C **3a-3c** (as shown in Scheme II). Selective hydrolysis easily affords the corresponding 1-OH or/and 6-OH groups benzyl protected glycopyranoses. Diacetyl derivatives reacted directly with $P(OMe)_3$ under Ar in the presence of trimethylsilyl triflate (TMSOTf) to give glycosyl phosphonates (shown in Scheme III), which are potential inhibitors of glycosidases and glycosyltransferases. [6]

The method has been successfully applied to methyl tetra-*O*-benzyl-α-D-mannopyranose and corresponding glucopyranose, galactopyranose and other hexopyranoses. Generally, α-pyranoses only give α-isomers, but for β-pyranoses, the products are mixtures of α- and β-isomers. Longer reaction times and higher temperatures give three or four acetyl α- and β-isomers. The relative reactivity of differently located groups was different. For α-D-glucopyranose, the order is: 1-OMe > 6-OBn > 3-OBn > 4-OBn > 2-OBn, while for α-D-mannopyranose it is: 1-OMe > 6-OBn > 4-OBn > 3-OBn >2-OBn, as observed previously. [8]

Scheme I



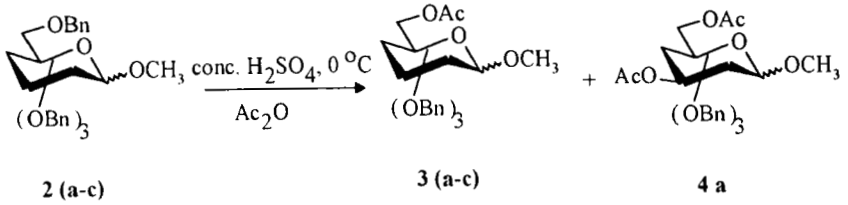
1 (a-c) **2 (a-c)**

Table I. The Preparation of Benzylated Compounds

Substrates (1a-c)	Products (2a-c)	Temp. (°C)	R. T. (h)	Yield* (%)
Methyl α-D-glucopyranoside	**2a**	75	24	94
Methyl α-D-galactopyranoside	**2b**	75	24	89.5
Methyl α-D-mannopyranoside	**2c**	75	24	97

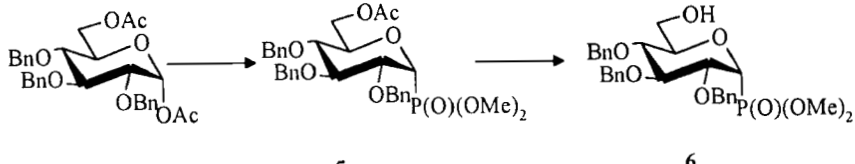
*note: Isolated yield

Scheme II



2 (a-c) **3 (a-c)** **4 a**

Scheme III



3a **5** **6**

Experimental

General methods. Optical rotations were measured with a Perkin-Elmer Model 241 MC Polarimeter at 25 °C. TLCs were performed on precoated plates of Silica Gel HF_{254} (0.5 mm, Qingdao, China) and detected by 10% sulfuric acid in methanol. Flash column chromatography was performed on Silica Gel H (400 mesh). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM-300 spectrometer with tetramethylsilane as the internal standard (unless otherwise specified). Mass spectra were recorded on a VG QUATTRO MS instrument.

General procedure for preparation of methyl 2,3,4,6-tetra-*O*-benzyl-D-glycopyranosides:

A mixture of methyl D-glycopyranosides (5.0 g), sodium hydride (8.5 g

Table II: The Preparation of 1,6-*O*-Di-acetyl-2,3,4-tri-*O*-benzyl-α/β-D-glycopyranosides

Substrates (2a-c)	Products	$Ac_2O:H_2SO_4$	R. T. (min)	Yield* (%)
Methyl 2,3,4,6-tetra-*O*-benzyl α-D-glucopyranoside	**3a**	100:1	7	95 (α)
Methyl 2,3,4,6-tetra-*O*-benzyl β-D-galactopyranoside	**3b**	100:1	10	72 (α/β 4.3/1)
Methyl 2,3,4,6-tetra-*O*-benzyl α-D-mannopyranoside	**3c**	100:1	10	90.5 (α)
Methyl 2,3,4,6-tetra-*O*-benzyl α-D-glucopyranoside	**3a + 4a**	100:1	90	82 (α and β)

*note: Isolated yield

60%, Fluka) and benzyl chloride (125 mL) was heated at 70-75 °C with stirring for about 3 h, and was monitored by TLC (petroleum ether/ethyl acetate, 3/1). After the reaction was complete, the insoluble material was removed and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography eluting with petroleum ether/ethyl acetate (5/1), affording **2 (a-c)**.

General procedure for the preparation of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glycopyranoses:

To a solution of methyl 2,3,4,6-tetra-*O*-benzyl-D-glycopyranosides (3

mmol) and acetic anhydride (7.2 mL) concentrated sulfuric acid (0.072 mL) was added dropwise at 0 °C. After 7 to 10 min at the same temperature the mixture was quenched by addition of saturated sodium hydrogen carbonate solution and worked up as routine. The crude product was purified by column chromatography eluting with petroleum ether/ethyl acetate (10/1→6/1), affording **3 (a-c)** and **4a**.

General procedure for the preparation of dimethyl (2,3,4-tri-*O*-benzyl-α-D-glycosyl) phosphonate (6):

To a solution of 1.00 g (1.873 mmol) of **3a** and 0.5 mL (4.25 mmol) of $P(OMe)_3$ in 5 mL of CH_2Cl_2 under Ar at 0 °C, 0.6 mL (3.3 mmol) of TMSOTf were added. After 12 h, 0.3 mL (2.5 mmol) of $P(OMe)_3$ and 0.3 mL (1.7 mmol) of TMSOTf were added. After addition 12 h (0-5 °C), the mixture was worked up as usual , and the residue was separated by flash chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane 1/1/1) to afford 0.561 g (87.3%) of 5 and 0.487 g of reactant. 0.305 g of 5 was hydrolyzed in 10 mL of MeONa/MeOH (0.2 M) overnight. After completion, the mixture was neutralized with Dowex-50w (H^+), the crude was separated by chromatography (petroleum ether/ethyl acetate/dichloromethane 1/1/1) to give 1.381 g (100%) of **6**.

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (2a):

$[\alpha]_D$ = +20.9 ° (*c* 0.7, $CHCl_3$), R_f = 0.8 (petroleum ether/ethyl acetate, 3/1); EIMS (m/z): 553 (M-1), 253, 181, 91; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, OCH_3), 3.58 (dd, 1H, $J_{1,2}$ = 2.7 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 4.01 (t, 1H, $J_{2,4}$ = 8.9 Hz, H-3), 3.65 (m, 1H, H-5), 3.75 (m, 2H, H-6a, H-6b), 4.66 (d, 1H, H-1), 5.00 and 4.84 (AB, each 1H, J = 10.8 Hz, $PhCH_2$), 4.85 and 4.48 (AB, each 1H, J = 10. 9 Hz,

$PhCH_2$), 4.82 and 4.48 (AB, each 1H, J = 11.6 Hz, $PhCH_2$), 4.68 and 4.62 (AB, each 1H, J = 12.2 Hz, $PhCH_2$), 7.23-7.38 (m, 20H, 4 C_6H_5); ^{13}C NMR ($CDCl_3$) δ 55.17, 57.72, 68.67, 70.18, 73.38, 73.53, 75.00, 77.82, 80.01, 82.18, 98.26 (C-1), 128.4-127.5, 138.9-138.0.

Methyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (2b):

$[\alpha]_D$ = -3.94 ° (*c* 2.03, $CHCl_3$), R_f = 0.64 (petroleum ether/ethyl acetate, 3/1); EIMS (m/z): 553 (M-1), 253, 181, 91; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.30 (m, 20H, $4C_6H_5$), 4.95 and 4.62 (AB, each 1H, J = 11.7 Hz, $PhCH_2$), 4.90 and 4.76 (AB, each 1H, J = 11.0 Hz, $PhCH_2$), 4.73 (d, 2H, $PHCH_2$), 4.46 and 4.40 (AB, each 1H, J = 11.8 Hz, $PhCH_2$), 4.28 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.90 (bd, 1H, $J_{3,4}$ = 2.8 Hz, H-4), 3.81 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 3.62-3.57 (m, 3H, H-5, H-6a, H-6b), 3.55 (s, 3H, CH_3O), 3.52 (dd, 1H, H-3); Anal. Calcd. for $C_{35}H_{38}O_6$ (554.68): C, 75.78; H, 6.90. Found: C, 75.20; H, 6.71.

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (2c):

$[\alpha]_D$ = +31.57 ° (*c* 1.38, $CHCl_3$), R_f = 0.71 (petroleum ether/ethyl acetate, 3/1); EIMS (m/z): 553 (M-1), 91; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.15 (m, 20H, $4C_6H_5$), 4.92 and 4.54 (AB, each 1H, J = 10.8 Hz, $PhCH_2$), 4.81 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 4.77 (s, 2H, $PhCH_2$), 4.70 and 4.58 (AB, each 1H, J = 12.1 Hz, $PhCH_2$), 4.63 (s, 2H, $PhCH_2$), 4.02 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.92 (dd, 1H, $J_{2,3}$ = 3.0 Hz, H-3), 3.83-3.74 (m, 4H, H-2, H-5, H-6a, H-6b), 3.35 (s, 3H, CH_3O); Anal. Calcd. for $C_{35}H_{38}O_6$ (554.68): C, 75.78; H, 6.90. Found: C, 75.35; H, 6.88.

1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (3a):

$[\alpha]_D$ = +51.3 ° (*c* 0.15, $CHCl_3$), R_f = 0.57 (petroleum ether/ethyl acetate, 3/1);

EIMS (m/z): 534 (M), 91(base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.24 (m, 15H, $3C_6H_5$), 6.36 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.04 and 4.88 (AB, each 1H, J = 10.8 Hz, $PhCH_2$), 4.76 and 4.68 (AB, each 1H, J = 11.5 Hz, $PhCH_2$), 4.74 and 4.62 (AB, each 1H, J = 10.7 Hz, $PhCH_2$), 4.40-4.20 (m, 2H, H-6a, H-6b), 4.03 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.2 Hz,H-3), 3.97 (ddd, 1H, $J_{4,5}$ = 9.9 Hz, $J_{5,6a}$ = 4.0 Hz, $J_{5,6b}$ = 2.2 Hz, H-5), 3.72 (dd, 1H, H-2), 3.62 (dd, 1H, H-4), 2.19 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.3, 138.5, 137.7, 137.6, 130.6-126.7, 89.7 (C-1), 81.7, 80.1, 79.4, 79.0, 78.5, 62.7, 57.1, 21.06, 20.8; Anal. Calcd. for $C_{31}H_{34}O_8$ (534.61): C, 69.60; H, 6.41. Found: C, 69.33; H, 6.39.

1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α/β-D-galactopyranose (α/β: 4.3/1) (3b):

$[\alpha]_D$ = +41.15 ° (*c* 0.3, $CHCl_3$); EIMS (m/z): 533 (M-1), 473, 329, 91(base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.30 (m, 15H, $3C_6H_5$), 6.44 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.05 and 4.66 (AB, each 1H, J = 11.4 Hz, $PhCH_2$), 4.92 and 4.81 (AB, each 1H, J = 11.6 Hz, $PhCH_2$), 4.76 and 4.72 (AB, each 1H, J = 11.5 Hz, $PhCH_2$), 4.23 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.16 (dd, 1H, $J_{5,6a}$ = 5.6 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 4.10 (dd, 1H, $J_{5,6b}$ = 5.6 Hz, H-6b), 4.05 (dd, 1H, H-5), 3.96 (d, 1H, $J_{3,4}$ = 2.7 Hz, H-4), 3.93 (dd, 1H, H-3), 2.15 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO).

1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranose (3c):

$[\alpha]_D$ = +29.15 ° (*c* 6.21, $CHCl_3$), R_f = 0.42 (petroleum ether/ethyl acetate, 3/1); EIMS (m/z): 533 (M-1), 443, 191, 91(base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 15H, $3C_6H_5$), 6.19 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.96 and 4.60 (AB, each

1H, J = 10.5 Hz, $PhCH_2$), 4.78 and 4.72 (AB, each 1H, J = 12.4 Hz, $PhCH_2$), 4.58 (s, 2H, $PhCH_2$), 4.33 (m, 2H, H-6a, H-6b), 4.00 (dd, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 3.90-3.80 (m, 2H, H-3, H-5), 3.74 (dd, 1H, H-2), 2.06 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO); Anal. Calcd. for $C_{31}H_{34}O_8$ (534.61): C, 69.60; H, 6.41. Found: C, 70.13; H, 6.40.

1,3,6-Tri-*O*-acetyl-2,4-di-*O*-benzyl-α/β-D-glucopyranose (α/β: 1.2/1) (4a):

R_f = 0.51 (petroleum ether/ethyl acetate, 3/1); EIMS (m/z): 485 (M-1), 91(base); ^1H NMR (300 MHz, $CDCl_3$) δ α anomer: 7.37-7.16 (m, 10H, $2C_6H_5$), 6.33 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 5.52 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 4.75-4.45 (m, 4H, 2 $PhCH_2$), 4.26 (bd, 2H, H-6a, H-6b), 4.00 (m, 1H, H-5), 3.58 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 3.57 (dd, 1H, $J_{1,2} = 3.4$ Hz, $J_{2,3} = 9.6$ Hz, H-2), 2.13 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO); β anomer: 7.37-7.16 (m, 10H, $2C_6H_5$), 6.65 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 5.32 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 4.71-4.41 (m, 4H, 2 $PhCH_2$), 3.88 (t, 1H, H-4), 3.71 (m, 1H, H-5), 3.51 (dd, 1H, $_{2,3} = 11.3$ Hz, H-2), 2.08 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 1.90 (s, 3H, CH_3CO).

Dimethyl (6-*O*-acetyl-2,3,4-*O*-tri-benzyl-α-D-glucopyranosyl) phosphonate (5):

R_f = 0.28 (petroleum ether/ethyl acetate/dichloromethane, 1/1/1); EIMS (m/z): 589 (M); HREIMS: 584.2168 (Calcd. for $C_{31}H_{37}O_9P$, 584.2175); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 24.45; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.24 (m, 15H, $3C_6H_5$), 4.98 and 4.82 (AB, each 1H, J = 10.9 Hz, $PhCH_2$),), 4.87 and 4.57 (AB, each 1H,

J = 8.5 Hz, $PhCH_2$), 4.80 and 4.68 (AB, each 1H, J = 9.4 Hz, $PhCH_2$), 4.49 (dd, 1H, $J_{1,2}$ = 7.0 Hz, $J_{P,H1}$ = 11.3 Hz, H-1), 4.34 (t, 1H, $J_{2,3} = J_{3,4}$ = 8.6 Hz, H-3), 4.29 (bs, 1H, H-6a), 4.19 (dd, 1H, $J_{5,6b}$ = 4.7 Hz, $J_{6a,6b}$ = 15.9 Hz, H-6b), 4.14 (m, 1H, H-5), 3.94(dt, 1H, $J_{P,H2}$ = 31.2 Hz, H-2), 3.82 (d, 3H, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.6 Hz, CH_3O), 3.74 (d, 3H, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.8 Hz, CH_3O), 3.45 (t, 1H, $J_{3,4} = J_{4,5}$ = 8.7 Hz, H-4), 2.01 (s, 3H, CH_3CO).

Dimethyl (2,3,4-*O*-tri-benzyl-α-D-glucopyranosyl) phosphonate (6):

R_f = 0.33 (petroleum ether/ethyl acetate: 1/1); EIMS (m/z): 543 (M+1), 451, 329, 181, 91 (base); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 25.14; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 15H, $3C_6H_5$), 4.93 and 4.81 (AB, each 1H, J = 11.1 Hz, $PhCH_2$),), 4.83 and 4.63 (AB, each 1H, J = 11.2 Hz, $PhCH_2$), 4.76 and 4.65 (AB, each 1H, J = 11.3 Hz, $PhCH_2$), 4.46 (dd, 1H, $J_{1,2}$ = 7.0 Hz, $J_{P,H1}$ = 11.1 Hz, H-1), 4.28 (t, 1H, $J_{2,3} = J_{3,4}$ = 8.5 Hz, H-3), 3.97-3.63 (m, 4H, H-2, H-5, H-6a, H-6b), 3.76 (d, 3H, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.8 Hz, CH_3O), 3.70 (d, 3H, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.8 Hz, CH_3O), 3.45 (t, 1H, $J_{3,4} = J_{4,5}$ = 8.7 Hz, H-4).

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