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One-step synthesis of N-protected glycosylamines from sugar hemiacetals

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Abstract—Protected pentofuranose, hexofuranose and hexopyranose hemiacetals were found to react efficiently with amines carrying a deactivating group (alkoxycarbonyl, tosyl or phosphoryl group) in the presence of a Lewis acid to give the corresponding, stable glycosylamines. Such glycosylamine derivatives are useful substrates for further elaboration into nitrogen-containing natural products and carbohydrate mimetics.

Keywords: Sugar hemiacetal; *N*-Glycosylamines; Lewis acid; Amination

1. Introduction

In addition to their fundamental importance as precursors of N-linked glycoconjugates,[1] glycosylamines have useful properties as synthetic equivalents of the Schiff bases of *aldehydo*-sugars; for example, in chain-extension reactions the addition of organometallic reagents to *N*-benzyl[2] and *N*,*N*-dibenzyl[3] glycosylamines and to related compounds[4] provides indeed the corresponding open-chain products, often with a good degree of stereoselectivity. This reaction has been used as the key step in the synthesis of diverse iminosugars and of carbohydrate-like natural products.[2–4] However, just like free glycosylamines,[5] these *N*-alkyl glycosylamines are not stable and are very sensitive to hydrolysis, thus regenerating the starting aldoses. By contrast, glycosylamines carrying a deactivating group at nitrogen (acyl, alkoxycarbonyl, etc.) are stable and can be easily isolated. Kobayashi and co-workers have recently demonstrated that N-alkoxycarbonylated glycosylamines[6] as well as model cyclic hemiaminals[7] could be prepared in one step from glycosyl acetates and benzyl carbamate, and that these compounds were substrates for the Lewis acid-catalysed additions of various silylated nucleophiles. In the course of our work on pyrrolidine galactofuranose mimics,[8,9] we have investigated the scope of the formation of N-protected glycosylamines from 'deactivated' amines and found that, under Lewis acidic conditions, these glycosylamines could be reached directly from the free hemiacetal form of the starting carbohydrate derivative. We report in this article the results of our studies on the synthesis of N-protected glycosylamines from diverse furanoid and pyranoid hemiacetals.

2. Results and discussion

The synthesis of *N*-alkoxycarbonyl D-glucofuranosylamines such as **2a**, which we use as the starting material for the synthesis of 1,4-dideoxy-1,4-imino-D-galactitol derivatives,[8] was initially performed from the acetate of 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose, under the

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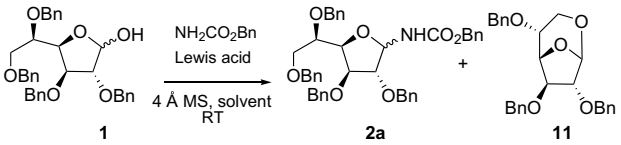
Table 1. Reactions of **1** with benzyl carbamate under different conditions[a]



Entry	Lewis acid (2 equiv)	Reaction time	Conversion[b] (%)	Yield[c] (**2a**) (%)	Fraction of **11** (%)
1	TMSOTf	6 h 30 min	100	56	~20
2	TMSOTf	30 min	93	58	n.d.[d]
3	TMSOTf (0.1 equiv)	30 min	20	13	n.d.
4	TMSOTf (MeCN)	30 min	81	45	n.d
5	$BF_3{\cdot}Et_2O$	6 h 30 min	100	50	14
6	$HNTf_2$	6 h 30 min	100	48	18
7	$Sc(OTf)_3$	24 h	Near 0	—	—
8	$Bi(OTf)_3$	6 h 30 min	100	53	24
9	$Zn(OTf)_2$	24 h	n.d.[e]	7	—
10	$MgBr_2$	24 h	0	—	—

[a] All reactions were performed using 1 equiv of Lewis acid except entry 3 (0.1 equiv), with 2 equiv of benzyl carbamate, and in dichloromethane except entry 5 (acetonitrile).
[b] % Conversion from NMR analysis of crude mixtures.
[c] Isolated yields.
[d] n.d.: not determined.
[e] Sluggish reaction and degradation products formed.

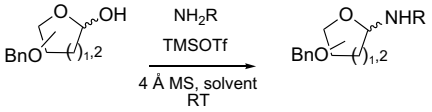
conditions described by Kobayashi and co-workers.[6] We rapidly found out, however, that the conversion of **1** into its acetate was not necessary, and that the amination could be performed directly onto the free sugar hemiacetal **1**.[8,10] Investigations to determine the best reaction conditions are reported in Table 1. While no reaction between **1** and benzyl carbamate takes place even after several days (RT, CH_2Cl_2), the addition of trimethylsilyl triflate promotes a rapid reaction and leads to the expected *N*-*Z* glycosylamine **2a** (entries 1 and 2). With 1 equiv of Lewis acid and 2 equiv of *Z*-NH_2, the conversion is complete and the glycosylamine isolated in a yield of 56%, together with a fraction containing **2a** and the internal anhydride **11**[8] (amount estimated: ~20%). This by-product, resulting from the participation of the 6-*O*-benzyloxy group with concomitant debenzylation,[11] could not be completely eliminated.

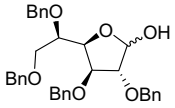
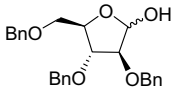
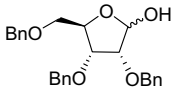
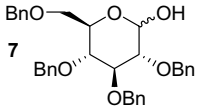
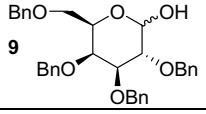
Notably, the two anomers of **2a**, **2aα** and **2aβ**, could be separated by flash chromatography and fully characterised. With a catalytic amount of Lewis acid (0.1 equiv), the reaction was incomplete (entry 3), and with acetonitrile as the solvent, a substantial amount of the (1→1)-linked disaccharide formed by condensation of **1** with itself was formed (about 20%) (entry 4). Satisfactory yields of **2a** were also obtained using boron trifluoride etherate, triflimide or bismuth triflate (entries 5, 6 and 8) as activators, whereas no reaction or complex mixtures were observed with scandium or zinc triflate, and with magnesium bromide.

This study was then extended to other 'deactivated' amines, including *p*-toluenesulfonamide and diethyl phosphoramidate, and to a series of protected aldose hemiacetals in the D-*arabino*- and D-*ribo*-pentofuranose series (**3** and **5**), and in the D-*gluco*- and D-*galacto*-hexopyranose series (**7** and **9**). All the reactions were performed using either TMSOTf or $BF_3{\cdot}Et_2O$ as activators in dichloromethane, with 2 equiv of amine reagent. The results are reported in Table 2. Using benzyl carbamate, all of these hemiacetals were converted nearly quantitatively into the corresponding *N*-glycosyl benzyl carbamates. The products (**2a**, **4a**,[6] **6a**,[6] **8a**[6] and **10a**) were isolated in yields ranging from 39% to 91%, the lower yields being due to difficulties of separation during their purification by chromatography (silica gel or deactivated silica gel). No by-product arising from benzyloxy group participation was observed in these cases. The *N*-tosyl glycofuranosylamines (**2b**, **4b**, **6b**) were obtained in excellent yields from **1**, **3** and **5**, respectively (70–96%), and the corresponding pyranosylamines (**8b** and **10b**) in 49% and 69% yields from **7** and **9**. The pyranoid derivatives **8b** and **10b** were more difficult to purify than the furanoid glycosylamines. In addition, we were pleased to find that the same process could be applied to the N-glycosylation of a dialkyl phosphoramidate, although the yields were not as good as with the other amine reagents (products **2c**, **8c**, **10c**). The reaction led to *N*-glycosyl phosphoramidates, a little known class of compounds which are of interest as mimics of glycosyl phosphates.[12]

As the formation of these glycosylamines involves a reaction of free hemiacetals, the question arises as to its mechanism: is the C–N bond formed by the way of the N-acylated Schiff base of the starting aldose or by the way of an S_N1-type mechanism resembling a glycosylation process? The reactions with the benzyl carbamate

Table 2. Reactions of aldose hemiacetals with protected amines[a]



Entry	Substrate	Protected amine	Reaction time (h)	Product #	Yield (%)
1		NH_2CO_2Bn	0.5	**2a**	58
2[b]		NH_2SO_2Tol	12	**2b**	70
3		$NH_2PO(OEt)_2$	5	**2c**	32[c]
4		NH_2CO_2Bn	0.75	**4a**[d]	91
5[b]		NH_2SO_2Tol	2	**4b**	96
6		$NH_2PO(OEt)_2$	24	**4c**	—
7		NH_2CO_2Bn	5	**6a**[d]	39
8[b]		NH_2SO_2Tol	15	**6b**	88
9		$NH_2PO(OEt)_2$	20	**6c**	—
10		NH_2CO_2Bn	22	**8a**[d]	80
11[b]		NH_2SO_2Tol	8	**8b**	49
12		$NH_2PO(OEt)_2$	8	**8c**	26
13		NH_2CO_2Bn	22	**10a**	48
14		NH_2SO_2Tol	8	**10b**	69
15		$NH_2PO(OEt)_2$	8	**10c**	42

[a] Conditions: TMSOTf, 1 equiv; NH_2R, 2 equiv in CH_2Cl_2.
[b] In this case, the reaction was performed using $BF_3{\cdot}Et_2O$.
[c] The formation of several by-products was observed.
[d] Identical to the compounds reported by Kobayashi and co-workers.[6]

of benzylamine (BnNHCOOBn) as amine reagent may provide a hint: all of the hemiacetals described did react with this reagent to provide the expected *N*-benzyl *N*-carbamoylated glycosylamines. The products issued from **7** and **9** were isolated in 56% and 46%, respectively, whereas the furanosylamines could not be obtained in a pure form. Since the formation of an N-alkylated, N-acylated Schiff base (iminium salt) from the open-chain form of the aldoses would be very unlikely with this reagent, these results suggest that the N-glycosylation reported herein occur by the way of an S_N1-type reaction involving an oxocarbenium ion intermediate and thus are related to O-glycosylation processes.

Finally, we also investigated the reaction using amides as nucleophiles: the direct N-glycosylation of amides is a notoriously difficult reaction and few solutions have been reported so far.[13,14] The desired N-glycosylated amides, however, were not formed under the conditions reported in this article.

In conclusion, we have shown that the reaction of protected aldose hemiacetals with deactivated amines (*N*-alkoxycarbonyl-, *N*-sulfonyl- or *N*-phosphoryl-amines) in the presence of a Lewis acid provides the corresponding glycosylamines readily. As shown by us and others, these protected glycosylamines constitute useful substrates for further elaboration into nitrogen-containing natural products and carbohydrate mimetics of biological interest such as iminosugars. In addition, N-glycosylated sulfamides were recently found to have significant activities as carbonic anhydrase inhibitors.[15]

3. Experimental

3.1. General methods[‡]

Unless otherwise stated, all reactions requiring anhydrous conditions were carried out using oven-dried glassware under an atmosphere of dry Ar. THF and diethyl ether were freshly distilled from sodium/benzophenone under Ar prior to use. Dichloromethane

[‡] *Editor's note:* According to authors, a number of new compounds are unstable and the required combustion analyses could not be performed. Pertinent NMR spectra run at high sensitivity have then been provided in the Supplementary data section.

and MeCN was distilled from calcium hydride. All reagent-grade chemicals were obtained from commercial suppliers and were used as received, unless otherwise stated.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer either as neat films on NaCl windows or as KBr pellets. Low-resolution mass spectra were recorded with a Perkin–Elmer Sciex API 3000 in the ESI mode, or with a Finnigan MAT 95 XL in the CI mode. High resolution mass spectra (HRESIMS) were recorded with a Micromass ZABSpec TOF spectrometer at the *Centre Régional de Mesures Physiques de l'Ouest* (Université de Rennes).

^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Bruker DPX 250 Avance (250 MHz) or on Bruker Avance 400 or 500 MHz spectrometers. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal or to TMS as internal standard. *J* values are quoted in Hz. Carbon multiplicities were assigned by distortionless enhancement by polarisation transfer (DEPT) experiments ^{31}P NMR spectra were recorded with ^{1}H decoupling.

Specific rotations were measured at room temperature (20 °C) in a 1 dm cell with a Perkin–Elmer 341 polarimeter. Analytical thin layer chromatography was performed using Silica Gel $60F_{254}$ precoated plates (E. Merck) with visualisation by ultraviolet light, phosphomolybdate solution (2% in H_2SO_4–EtOH 1:7) and/or exposure to I_2 vapors. Flash chromatography was performed on Silica Gel 60 (230–400 mesh) with EtOAc and petroleum ether (PE) as eluants, unless otherwise indicated.

3.2. General procedure for glycosylamines 2a, 2b, 2c, 8a, 8b, 8c, 10a, 10b, 10c

In a dry flask (10 mL), under Ar, the Lewis acid (TMSOTf; $BF_3{\cdot}Et_2O$ for **2b**, **8b** and **10b**) (1 equiv) was added by portion to a mixture of substrate **1**, **7** or **9** (1 equiv), amine reagent (2 equiv) and 4 Å molecular sieves, in anhyd CH_2Cl_2 (substrate concentration 1 M). The orange mixture was stirred at room temperature during the time indicated in Table 2. After quenching by the addition of triethylamine, filtration over Celite and rinsing with EtOAc, the solvent was evaporated to provide a yellow oily product. The crude product was then purified by flash chromatography on silica gel.

3.3. General procedure for pentofuranosylamines 4a, 4b, 6a, 6b

In a dry flask (10 mL), under Ar, the Lewis acid (TMSOTf; $BF_3{\cdot}Et_2O$ for **4b** and **6b**) (1 equiv) was added dropwise to a mixture of substrate **3** or **5** (1 equiv), amine reagent (2 equiv) and 4 Å molecular sieves, in anhyd CH_2Cl_2 (substrate concentration 1 M). The mixture was stirred at room temperature during the time indicated in Table 2. Solids were removed by filtration over Celite and saturated aq phase $NaHCO_3$ (2 mL) was added to the filtrate. The organic phase was separated and the aq phase extracted with ethyl acetate. The organic phases were dried then concentrated under diminished pressure. The crude product was purified by flash chromatography on silica gel.

3.4. *N*-Benzyloxycarbonyl 2,3,5,6-tetra-*O*-benzyl-α,β-D-glucofuranosylamine (2a)

Compound **2a** (58% yield) was obtained from **1**[10] (38 mg, 0.07 mmol). Purification by flash chromatography (99.5:0.5 toluene–acetone + εEt_3N) afforded compound **2a** (27.2 mg, 58%). The anomers of **2a** (~1:1) could be separated by careful flash chromatography and fully characterised.

Compound **2aα**: colourless oil; $[\alpha]_D^{25}$ +8 (*c* 0.79, $CHCl_3$); IR (NaCl); *v* 3432, 3066, 3017, 1727, 1498, 1454, 1359, 1215, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.68 (dd, 1H, $J \sim 5.25$ Hz, $J \sim 10.5$ Hz, $H6_a$), 3.82 (d, 1H, $J \sim 3.75$ Hz, H2), 3.88 (dd, 1H, $J \sim 10.75$ Hz, $J \sim 1.25$ Hz, $H6_b$), 3.94–3.99 (m, 1H, H5), 4.07 (d, 1H, $J \sim 3$ Hz, H3), 4.25 (dd, 1H, $J \sim 9.25$ Hz, $J \sim 3$ Hz, H4), 4.36–4.55 (m, 7H, OCH_2Ph), 4.78 (d, 1H, $J \sim 11.5$ Hz, OCH_2Ph), 5.12 (br s, 2H, OCH_2Ph), 5.78–5.93 (m, 2H, NH and H1), 7.23–7.33 (m, 25H, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 67.03 (O*C*H_2Ph), 71.02 (*C*6), 72.49, 72.77 and 73.42 (O*C*H_2Ph), 76.08 (*C*5), 78.33 (*C*4), 80.05 (*C*2), 80.66 (*C*3), 82.60 (*C*1), 127.5–128.7 ($CH_{Ar's}$), 136.28, 136.90, 137.66, 138.68 and 138.91 (Cq_{Ar}), 155.69 (*C*=O); (+) ESIMS: *m*/*z* 691.5 $[M+NH_4]^+$, 696.0 $[M+Na]^+$.

Compound **2aβ**: colourless oil; $[\alpha]_D^{25}$ −32 (*c* 0.96, $CHCl_3$); IR (NaCl); *v* 3415, 3062, 3030, 2925, 2863, 1731, 1504, 1495, 1453, 1207, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.68 (dd, 1H, $J \sim 5.5$ Hz, $J \sim 10.5$ Hz, $H6_a$), 3.86 (br s, 1H, H2), 3.90 (d, 1H, $J \sim 10.5$ Hz, $H6_b$), 4.00 (ddd, 1H, $J \sim 9$ Hz, $J \sim 5.5$ Hz, $J \sim 1.5$ Hz, H5), 4.07 (d, 1H, $J \sim 3.5$ Hz, H3), 4.25 (dd, 1H, $J \sim 9.5$ Hz, $J \sim 3$ Hz, H4), 4.66–4.72 (m, 7H, OCH_2Ph), 4.82 (d, 1H, $J \sim 11.5$ Hz, OCH_2Ph), 5.10 (AB, 2H, $J \sim 12$ Hz, OCH_2Ph), 5.66–5.72 (m, 2H, H1 and NH), 7.16–7.34 (m, 25H, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 66.90 (O*C*H_2Ph), 71.46 (*C*6), 71.69, 72.52, 72.70 and 73.58 (O*C*H_2Ph), 76.69 (*C*5), 80.57 (*C*4), 80.84 (*C*3), 84.37 (*C*2), 86.08 (*C*1), 127.52–128.58 ($CH_{Ar's}$), 136.37, 137.27, 137.35, 138.62 and 138.95 (Cq_{Ar}), 155.02 (*C*=O); (+) MALDI-TOFMS: *m*/*z* 696.3 $[M+Na]^+$, 712.2 $[M+K]^+$; HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{42}H_{43}NO_7Na$, 696.2937; found, 696.2940. Anal. (mixture of **2aα** and **2aβ**) Calcd for $C_{42}H_{43}NO_7$: C, 74.87; H, 6.43; N, 2.08. Found: C, 75.10; H, 6.46; N, 2.02.

3.5. *N*-*p*-Tolylsulfonyl 2,3,5,6-tetra-*O*-benzyl-α,β-D-glucofuranosylamine (2b)

Compound **2b** was obtained from **1** (132 mg, 0.245 mmol). After purification by flash chromatography (9:1 petroleum ether–EtOAc) compound **2b** (119 mg, 70%) was obtained as a colourless oil and as an equimolar mixture of α/β anomers.

IR (NaCl); *ν* 3253, 3063, 3031, 2249, 1725, 1599, 1496, 1454, 1343, 1209, 1165 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz); *δ* 2.33 (s, 1.5H, CH_3), 2.36 (s, 1.5H, CH_3), 3.04 (dd, 0.5H, $J \sim 15$ Hz, $J \sim 5.2$ Hz, $H6_a$), 3.27–3.34 (m, 1H, $H6_b$, $H6'_a$), 3.53–3.58 (m, 1H, $H6'_b$, H5), 3,82–3,85 (m, 0.5H, H5′), 3.89 (d, 0.5H, $J \sim 5$ Hz, H2′), 3.95 (s, 0.5H, H2), 3.98 (d, 0.5H, $J \sim 5$ Hz, H3), 4.00–4.05 (m, 1H, H3′, H4), 4.18 (dd, 0.5H, $J \sim 9.5$ Hz, $J \sim 5$ Hz, H4′), 4.34–4.58 (m, 7H, OCH_2Ph), 4.69 (d, 0.5H, $J \sim 10$ Hz, OCH_2Ph) and 4.71 (d, 0.5H, $J \sim 10$ Hz, OCH_2Ph), 5.39 (d, 0.5H, $J \sim 11$ Hz, H1), 5.56–5.67 (m, 1.5H, H1′ and NH), 7.14–7.38 (m, 22H, $CH_{Ar's}$), 7.69 (d, 1H, $J \sim 10$ Hz, $CH_{Ar's}$), 7.76 (d, 1H, $J \sim 10$ Hz, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 21.59 (CH_3), 21.64 (CH_3), 70.12 (C6), 71.22 (C6), 71.87, 72.15, 72.52, 72.58, 73.08, 73.26, 73.43 and 73.47 (OCH_2Ph), 75.68 (C5), 76.26 (C5), 78.54 (C4), 80.30 (C3), 80.34 (C3), 80.79 (C2 and C4), 84.41 (C1 or C2), 84.44 (C1 or C2), 88.02 (C1), 127.35–129.48 ($CH_{Ar's}$), 136.66, 136.82, 137.09, 137.48, 138.56, 138.66, 138.70, 138.84, 138.97, 139.01, 143.08 and 143.18 (Cq_{Ar}); (+) ESIMS: *m*/*z* 702 $[M+NH_4]^+$; HR-ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{41}H_{43}NO_7SNa$, 716.26579; found, 716.2660.

3.6. *N*-Diethylphosphoryl 2,3,5,6-tetra-*O*-benzyl-α,β-D-glucofuranosylamine (2c)

Compound **2c** was obtained from **1** (137 mg, 0.253 mmol) after purification by flash chromatography (9:1 petroleum ether–EtOAc). The colourless oil (54 mg, 32%) was obtained as a 3:2 mixture of α/β anomers.

IR (NaCl); 3385, 2981, 2927, 1724, 1454, 1269, 1097, 1027, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 1.26 (t, 6H, $J \sim 7.2$ Hz, CH_3), 3.62–3.68 (m, 1H, $H6_a$), 3.75–4.11 (m, 9H, $H6_b$, H2, H3, H5, CH_3CH_2, NH), 4.22 (dd, 1H, $J \sim 3.6$ and 9.6 Hz, H4), 4.39–4.62 (m, 7H, OCH_2Ph), 4.79 and 4.83 (2d, 1H, $J \sim 11.6$, $2OCH_2Ph$), 5.06 (dd, 0.4H, $J \sim 7.2$ and 12 Hz, H1β), 5.27–5.32 (m, 0.6H, H1α), 7.11–7.43 (m, 20H, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 16.18–16.37 (m, CH_3), 62.50–62.59 (m, CH_2CH_3), 71.37 (OCH_2Ph), 71.62 (*C*6), 72.52, 72.61, 72.90, 72.93, 73.57 and 73.60 (OCH_2Ph), 76.11 (*C*5), 77.36 (*C*5), 78.07 (*C*4), 80.34 (d, *C*4), 80.41 (*C*2), 80.69 (*C*3), 80.75 (*C*3), 84.18 (d, *C*1α), 85.30 (d, *C*2), 87.78 (*C*1β), 127.56–128.76 ($CH_{Ar's}$), 137.02, 137.25, 137.42, 137.78, 138.56, 138.63, 138.95 and 138.98 (Cq_{Ar}); ^{31}P NMR ($CDCl_3$, 162 MHz): *δ* 5.51 (s), 6.65 (s); (+) ESIMS: *m*/*z* 676.5 $[M+H]^+$, 698.5 $[M+Na]^+$; HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{38}H_{46}NO_8NaP$, 698.2858; found, 698.2843.

3.7. *N*-Benzyloxycarbonyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranylamine (4a)

Compound **4a** was obtained from **3**[16] (50 mg, 0.12 mmol) after purification by flash chromatography (9:1→4:1 petroleum ether–EtOAc) as a colourless oil (60 mg, 91%) (1:1 mixture of α/β anomers).

NMR spectral data identical to those reported by Kobayashi and co-workers.[6] (+) HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{34}H_{35}NO_6Na$, 576.23621; found, 576.2361.

3.8. *N*-*p*-Tolylsulfonyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosylamine (4b)

Compound **4b** was obtained from **3**[15] (50 mg, 0.12 mmol) after purification by flash chromatography (petroleum ether–EtOAc 4:1 then 7:3). The colourless oil (65 mg, 96%) was obtained as a 1:1 mixture of α/β anomers.

IR (NaCl); 3282, 3029, 2924, 2867, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): *δ* 2.37 (s, 1.5H, CH_3), 2.38 (s, 1.5H, CH_3), 3.31–3.43 (m, 2H, H5), 3.87–4.01 (m, 3H, H2, H3, H4), 4.36–4.56 (m, 6H, OCH_2Ph), 5.43–5.54 and 5.75–5.82 (2AB, 2H, $J \sim 10.8$ Hz, H1, NH), 7.19–7.34 (m, 17H, $CH_{Ar's}$), 7.74 and 7.77 (2d, 2H, $J \sim 8.5$ Hz, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): *δ* 21.7 (CH_3), 69.9 (C5), 70.0 (C5), 71.7, 71.9, 72.0, 72.3, 73.3 and 73.5 (OCH_2Ph), 80.9, 81.3, 82.3, 82.6, 82.7, 83.9 (C1), 85.2, 87.8 (C1), 127.2–129.6 ($CH_{Ar's}$), 136.9 (2 C), 137.1, 137.6, 137.7, 138.1, 138.6, 138.8, 143.3 and 143.4 (Cq_{Ar}); (+) ESIMS: *m*/*z* 591 $[M+NH_4]^+$, 596 $[M+Na]^+$; (+) HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{33}H_{35}NO_6SNa$, 596.20773; found, 596.20712.

3.9. *N*-Benzyloxycarbonyl 2,3,5-tri-*O*-benzyl-α-D-ribofuranosylamine (6a)

Compound **6a**[6] was obtained from **5**[17] (200 mg, 0.48 mmol) as a ∼1:1 mixture of α/β anomers (^1H NMR of crude product). Purification of the mixture by flash chromatography (9:1→17:3→4:1 petroleum ether–EtOAc) yielded only the **6a**β anomer (100 mg, 39%) as a colourless oil.

Compound **6aβ**: $[\alpha]_D^{25}$ +53 (*c* 1.7, $CHCl_3$); IR (NaCl); 3418, 3014, 2925, 2865, 1734, 1508, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): *δ* 3.42–3.45 (m, 2H, H5), 3.96 (m, 1H, H2), 4.04 (br t, 1H, H3), 4.23–4.68 (s and 2 AB, 7H, H4, OCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 5.71 (dd, 1H, $J \sim 5.4$ Hz $J \sim 9.5$ Hz, H1), 6.35 (d, 1H, $J \sim 9.5$ Hz, NH), 7.20–7.33 (m, 20H, $CH_{Ar's}$); ^{13}C

NMR ($CDCl_3$, 62.5 MHz): δ 66.8 (O*C*H_2Ph), 70.1 (C5), 72.6 and 73.6 (O*C*H_2Ph), 76.6 and 77.9 (C2 and C3), 81.2 (C1), 81.3 (C4), 127.6–128.5 ($CH_{Ar's}$), 136.4, 137.4, 137.7 and 137.9 (Cq_{Ar}), 156.0 (C=O); (+) ESIMS: *m*/*z* 554 $[M+H]^+$, 571 $[M+NH_4]^+$, 576 $[M+Na]^+$; (+) HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{34}H_{35}NO_6Na$, 576.23566; found, 576.23490.

3.10. *N*-(*p*-Toluenesulfonyl) 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranosylamine (6b)

Compound **6b** was obtained from **5**[16] (60 mg, 0.14 mmol) as a colourless oil (70 mg, 88%) (2:1 mixture of anomers) after flash chromatography (petroleum ether–EtOAc 4:1 then 7:3).

IR (NaCl); 3271, 3028, 2924, 2867, 1724, 1599, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.36 (s, 2H, 3 × 0.67H, CH_3 M), 2.38 (s, 1H, 3 × 0.33H, CH_3 m), 3.27–3.43 (m, 2H, H5), 3.90–4.08 (several m, 3H, H2, H3, H4), 4.30–4.72 (m, 6H, O*C*H_2Ph), 5.28 (dd, 0.33H, $J \sim 2.2$ Hz, $J \sim 9.1$ Hz, H1 m), 5.46–5.56 (m, 1H, H1 M, NH m), 6.25 (d, 0.67H, $J \sim 9.1$ Hz, NH M), 7.18–7.33 (m, 17H, $CH_{Ar's}$), 7.62 (d, 0.66H, *J* 8.2 ~ Hz, $CH_{Ar's}$), 7.78 (d, 1.34H, $J \sim 8.2$ Hz, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.6 (CH_3), 68.7 (C5), 69.9 (C5), 72.2, 72.4, 72.9, 73.5 and 73.7 (O*C*H_2Ph), 76.1, 76.9, 77.7, 81.1, 81.2, 81.6, 83.3 (C1 M), 87.6 (C1 m), 127.0–129.5 ($CH_{Ar's,}$), 137.1, 137.3, 137.5, 137.6, 137.9, 138.1, 139.3, 143.0 and 143.4 (Cq_{Ar}); (+) ESIMS: *m*/*z* 574 $[M+H]^+$, 596 $[M+Na]^+$.

3.11. *N*-Benzyloxycarbonyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosylamine (8a)

Compound **8a** was prepared from commercial tetra-*O*-benzyl-D-glucopyranose **7** (100 mg, 0.185 mmol). After purification by flash chromatography (17:3 petroleum ether–EtOAc) compound **8a** (100 mg, 80%) was obtained as a colourless oil (1:1 mixture of anomers).

NMR spectral data identical to those reported by Kobayashi and co-workers.[6] (+) ESIMS: *m*/*z* 691.5 $[M+NH_4]^+$, 696.5 $[M+Na]^+$. HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{42}H_{43}NO_7Na$, 696.29372; found, 696.2941.

3.12. *N*-*p*-Toluenesulfonyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosylamine (8b)

Compound **8b** was prepared from **7** (100 mg, 0.185 mmol). After purification by flash chromatography (4:1 petroleum ether–EtOAc) compound **8b** (63 mg, 49%) was obtained as a colourless oily product (1:1 mixture of anomers).

IR (NaCl); 3055, 2987, 2306, 1422, 1265, 1069, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.31 (s, 1.5H, CH_3), 2.32 (s, 1.5H, CH_3), 2.90–3.02 (m, 0.5H, $H6_a$), 3.26–3.75 (m, 5.5H), 4.27–4.53 (m, 4H, O*C*H_2Ph), 4.62–4.90 (m, 4.5H, O*C*H_2Ph and H1), 5.20 (d, 0.5H, $J \sim 10$ Hz, NH), 5.32–5.36 (m, 0.5H, H1), 5.51 (d, 0.5H, $J \sim 3$ Hz, NH), 7.07–7.36 (m, 22H, $CH_{Ar's}$), 7.72–7.81 (m, 2H, $CH_{Ar's}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.60 (*C*H_3), 67.37 (*C*6), 68.32 (*C*6′), 70.48 (*C*H), 72.67, 73.51, 73.66, 75.01, 75.17, 75.77 and 75.87 (O*C*H_2Ph), 76.47 (*C*2), 76.97 (*C*H), 77.33 (*C*2), 79.68 (*C*1), 80.59 (*C*H), 82.01 (*C*H), 84.33 (*C*1), 85.67 (*C*H), 127.37–129.56 (*C*$H_{Ar's}$), 136.94, 137.39, 137.68, 137.94, 137.97, 138.11, 138.16, 138.41, 138.46, 138.63, 143.38 and 143.71 (*C*q_{Ar}); HRESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{41}H_{43}NO_7SNa$, 716.26579; found, 716.2670.

3.13. *N*-Diethylphosphoryl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosylamine (8c)

Compound **8c** was obtained from **7** (100 mg, 0.185 mmol). After purification by flash chromatography (1:1 petroleum ether–EtOAc) compound **8c** (32 mg, 26%) was obtained as a colourless oily product and as the β-anomer predominantly.

IR (NaCl); 3422, 3185, 2924, 2857, 1725, 1453, 1234, 1161, 1093, 1028, 973 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (m, 6H, CH_3), 3.28 (t, 1H, $J \sim 10$ Hz, H2), 3.41–3.48 (m, 2H, NH, H3 or H4), 3.61–3.70 (m, 4H, H3 or H4, H5, 2H6), 4.03–4.10 (m, 4H, C*H*$_2$CH$_3$), 4.33 (dt, 1H, $J \sim 8.5$, $J \sim 8.5$, $J \sim 11.5$ Hz, H1), 4.44–4.63 (m, 3H, O*C*H_2Ph), 4.70–4.92 (m, 5H, O*C*H_2Ph), 7.15–7.35 (m, 20H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 16.14 (*C*H_3), 16.26 (*C*H_3), 62.72–62.85 (several d, PO*C*H_2CH$_3$), 68.73 (*C*6), 72.91, 75.08, 75.22 and 75.84 (O*C*H_2Ph), 76.16 (*C*H), 77.92 (*C*H), 82.46 (d, *C*2), 83.76 (*C*1), 86.05 (d, *C*H), 127.81–128.55 (*C*$H_{Ar's}$), 137.99, 138.04, 138.19 and 138.53 (*C*q_{Ar}); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 6.12 (s); (+) ESIMS: *m*/*z* 676.5 $[M+H]^+$, 698.5 $[M+Na]^+$.

3.14. *N*-Benzyloxycarbonyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranosylamine (10a)

Compound **10a** was prepared from commercial tetra-*O*-benzyl-D-galactopyranose **9** (100 mg, 0.185 mmol). After purification by flash chromatography (4:1 petroleum ether–EtOAc) compound **10a** (60.4 mg, 48%) was obtained as a colourless oily product (1:1 mixture of anomers).

IR (NaCl); 3415, 3063, 3030, 2869, 1731, 1522, 1454, 1265, 1100, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 3.47–3.72 (m, 4H), 3.82–4.16 (m, 2H), 4.33–4.49 (m, 2H), 4.49–4.74 (m, 4H), 4.76–4.95 (m, 2H), 4.99–5.19 (m, 2.5H), 5.53–5.61 (m, 0.5H), 7.11–7.46 (m, 25H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 67.08 (*C*H_2), 67.21 (*C*H_2), 68.08 (*C*H_2), 68.15 (*C*H_2), 72.75 (*C*H_2), 73.03 (*C*H_2), 73.06 (*C*H_2), 73.54 (*C*H), 73.59 (*C*H_2), 74.06

(CH_2), 74.49 (CH_2), 74.66 (*C*H), 74.87 (*C*H), 75.12 (*C*H), 75.17 (*C*H), 77.36 (*C*H), 78.19 (*C*H), 82.12 (*C*H), 83.59 (*C*H), 127.59–128.64 ($CH_{Ar's}$), 136.18, 136.31, 137.72, 137.86, 138.12, 138.26, 138.37, 138.55 and 138.59 (Cq_{Ar}), 155.75 (*C*=O), 156.23 (*C*=O); (+) ESIMS: *m*/*z* 691.5 $[M+NH_4]^+$, 696.5 $[M+Na]^+$; HR-ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{42}H_{43}NO_7Na$, 696.29372; found, 696.2944.

3.15. *N*-*p*-Toluenesulfonyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranosylamine (10b)

Compound **10b** was prepared from **9** (100 mg, 0.185 mmol). After purification by flash chromatography (4:1 petroleum ether–EtOAc) compound **9** (88 mg, 69%) was obtained as a colourless oily product (1:1 mixture of anomers).

IR (NaCl); 3423, 3063, 3030, 2915, 2970, 1496, 1454, 1330, 1164, 1096, 1076, 896 cm^{-1}; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.55 (*C*H_3), 68.11 (*C*H_2), 73.07 (*C*H_2), 73.46 (*C*H_2), 73.52 (*C*H_2), 74.76 (*C*H_2), 74.84 (*C*H), 74.88 (*C*H), 75.27 (*C*H), 77.73 (*C*H), 83.29 (*C*H), 84.64 (*C*H), 127.36–129.59 ($CH_{Ar's}$), 137.9–138.7 (Cq_{Ar}), 143.25 (Cq_{Ar}); (+) ESIMS: *m*/*z* 711.5 $[M+H]^+$, *m*/*z* 716.5 $[M+Na]^+$.

3.16. *N*-Diethylphosphoryl 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranosylamine (10c)

Compound **10c** was obtained from **9** (100 mg, 0.185 mmol). After purification by flash chromatography (1:1 petroleum ether–EtOAc) compound **10c** (52 mg, 42%) was obtained as a colourless oily product and as the β-anomer predominantly.

IR (NaCl); 3385, 2869, 2924, 1724, 1454, 1237, 1272, 1097, 1027, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (t, 6H, $J \sim 7.5$ Hz, CH_3), 3.40 (t, 1H, $J \sim 11$ Hz, H2), 3.50–3.65 (m, 5H, H4, H3, 2H6 and NH), 3.92–4.09 (m, 5H, CH_2CH$_3$ and H5), 4.30 (dt, 1H, $J \sim 8$, $J \sim 8.5$, $J \sim 11.5$ Hz, H1), 4.41 (AB, 2H, $J \sim 11.7$ Hz, OCH_2Ph), 4.60 (d, 1H, OCH_2Ph), 4.71 (AB, 2H, $J \sim 11.5$, OCH_2Ph), 4.80 (d, 1H, $J \sim 11$ Hz, OCH_2Ph), 4.89 (d, 1H, $J \sim 11$ Hz, OCH_2Ph), 4.94 (d, 1H, $J \sim 11$ Hz, OCH_2Ph), 7.25–7.34 (m, 20H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 16.09 (*C*H_3), 16.22 (*C*H_3), 62.53–62.67 (m, PO*C*H_2CH$_3$), 68.76 (*C*H_2), 72.91 (*C*H_2), 73.58 (2C, *C*H), 74.63 (*C*H), 74.84 (*C*H_2), 75.44 (*C*H_2), 79.5 (d, *C*H), 83.76 (d, *C*H), 84.09 (*C*H), 127.66–128.54 ($CH_{Ar's}$), 137.90, 137.26, 137.32 and 137.56 (Cq_{Ar}); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 6.26 (s), 7.54 (s); (+) ESIMS: *m*/*z* 676.5 $[M+H]^+$, 698.5 $[M+Na]^+$.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.11.022.

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