A New Procedure for the Synthesis of D-Glucosamine α-*C*-Glycosides

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Reaction of (2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)benzylamine with vinylmagnesium bromide and subsequent mercuriocyclisation of the obtained open-chain product, provides a stereoselective entry to α-*C*-glycosides of D-glucosamine.

The synthesis of *C*-glycosides has recently gained attention owing to their biological interest[1] and their synthetic utility.[2] One of the sugars playing a central role in the biology of carbohydrates is D-glucosamine. This sugar is a fundamental constituent of biological systems such as the bacterial cell walls and chitin. Despite the importance of D-glucosamine, to our knowledge only two examples of the synthesis of *C*-glycosides of this sugar have been reported,[3,4] only the latter showing reasonable yields and stereoselectivity.

As part of a project directed towards the synthesis of potential inhibitors of metabolic processes, we were interested in efficient methods of obtaining α-*C*-glucosides of D-glucosamine.

The main procedures which allow us to obtain α-*C*-glucopyranosides, such as the reaction of a suitably protected glucopyranose with a Wittig reagent and the subsequent electrophilic-cyclisation of the product,[5] or the Lewis acid-catalysed reaction of the appropriate glucopyranosyl derivative with allyltrimethylsilane,[6] were unsuccessful when applied to many D-glucosamine derivatives.[7] We now present a different approach which is directed towards obtaining a 2-amino-2-deoxy-*C*-glycopyranoside system by vinylation of a glycofuranosylamine, followed by cyclisation of the obtained unsaturated open-chain product (as in Scheme 1).

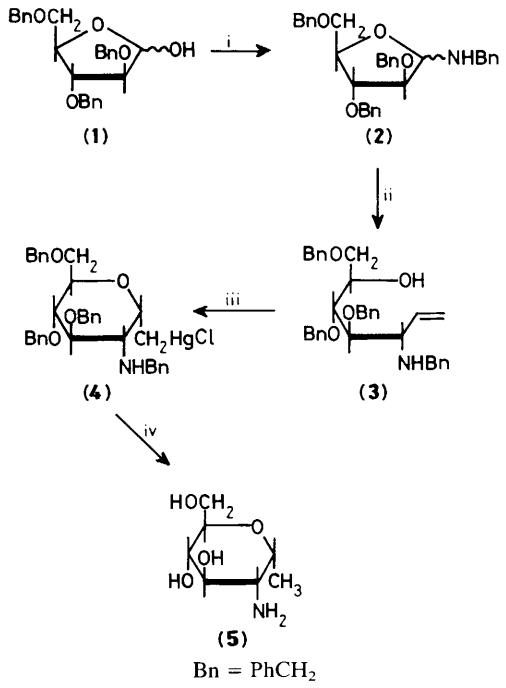
A key point of this procedure is the efficiency and stereoselectivity of the vinylation of the suitably protected furanosylamine. In the absence of literature examples of reactions or organometallic reagents with glycosylamines, we hoped that, by analogy with our results[8] on the vinylation of 2,3,5-tri-*O*-benzyl-D-arabinose (**1**), (2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-benzylamine (**2**) could react with a vinyl-metallic reagent, and that the reaction would afford preferentially a product with a *gluco* configuration.

(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)benzylamine (**2**),† prepared in 95% yield from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose (**1**), reacted with vinylmagnesium bromide to afford the 3-benzylamino-1,2,3-trideoxy-4,5,7-tri-*O*-benzyl-D-glucohept-1-enitol (**3**)† in 71% yield and 88% diastereoisomeric excess.‡

The cyclisation of (**3**), to afford the *C*-glycoside, was effected with $Hg(CF_3CO_2)_2$. It gave stereoselectively the

† All new compounds gave satisfactory elemental analyses. N.m.r. spectra were recorded in $CDCl_3$ on a Varian XL 200 spectrometer; the ^{13}C values of the aromatic carbons are omitted. (**2**) M.p. 72—74 °C (from Et_2O); ^1H n.m.r.: δ 2.27 (NH), 3.51—3.68 (m, H-5 and H-5′), 3.80—4.30 (m, 5H), 4.46—4.67 (m, 3 OCH_2Ph), 4.82 (d, *J* 4.5 Hz, 0.4H, H-1 of the α anomer), 4.84 (d, *J* 2.5 Hz, 0.6H, H-1 of the β anomer), 7.4 (m, 20 H). (**3**) Oil, $[\alpha]_D^{25}$ +12.3° (*c* 1, $CHCl_3$); ^1H n.m.r.: δ 2.83 (NH and OH), 3.34—3.98 (m, 8H), 4.40—4.91 (m, 3 OCH_2Ph), 5.15 (dd, *J* 17.5 and 1.5 Hz, H-1a), 5.24 (dd, *J* 10 and 1.5 Hz, H-1b), 5.79 (ddd, *J* 17.5, 10 and 9 Hz, H-2), 7.4 (m, 20 H); ^{13}C n.m.r.: δ 50.71, 59.52, 70.65, 71.77, 72.80, 73.26, 73.71, 82.98, 117.75, 127.25. (**4**) M.p. 79—80 °C (from Et_2O), $[\alpha]_D^{25}$ +11.6° (*c* 1, $CHCl_3$); ^1H n.m.r.: δ 1.37 (dd, *J* 12 and 4.5 Hz, H-1a), 1.56 (NH), 1.72 (dd, *J* 12 and 8.5 Hz, H-1b), 2.62 (br. dd, *J* 4.5 and 6 Hz, H-3), 3.52 (dd, *J* 6 and 5 Hz, H-4), 3.57 (t, *J* 5 Hz, H-5), 3.62 (dd, *J* 10.5 and 5 Hz, H-7a), 3.62 (d, *J* 13 Hz, NCHPh), 3.76 (dd, *J* 10.5 and 5 Hz, H-7b), 3.77 (d, *J* 13 Hz, NCHPh), 3.90 (br. q, *J* 5 Hz, H-6), 4.33 (dt, *J* 8.5, 4.5, and 4.5 Hz, H-2), 4.39–4.69 (m, 3 OCH_2Ph), 7.4 (m, 20 H); ^{13}C n.m.r.: δ 24.42, 52,46, 56.89, 68.67, 71.00, 72.94, 73.25, 73.38, 73.38, 75.70, 76.10. (**5**) M.p. 135—140 °C decomp. (from MeOH–Et_2O, highly hygroscopic), $[\alpha]_D^{25}$ +44.5° (*c* 1, MeOH): ^1H n.m.r.: δ 1.23 (d, *J* 7 Hz, Me), 3.16 (dd, *J* 10 and 6 Hz, H-5), 3.31 (1H, br. t, *J* 9Hz), 3.54—3.83 (4H, m), 4.28 (dq, *J* 6 and 7 Hz, H-6).

‡ Deduced by ^{13}C n.m.r. The *manno*-isomer was separated by chromatography.



Scheme 1. *Reagents and conditions:* i, H_2NBn, CH_2Cl_2, 4 Å molecular sieves; ii, CH_2=$CHMgBr$, THF, room temp.; iii, $Hg(OCOCF_3)_2$, THF, O °C, then aq. KCl; iv, $NaBH_4$, EtOH, then H_2–Pd/C, MeOH, 40 atm, 50 °C, 32 h.

α-*C*-glucoside (**4**)† (77% yield), which was easily separated from the β-anomer (20% yield) by chromatography.

Once more the mercuriocyclisation of such a type of structure afforded mainly the product with a 1,2-*cis* relationship. This empirical rule is now well documented[5,9] and recently described in terms of the 'inside alkoxy' effect;[9] we can now observe that an amino-group also produces the same effect. Compound (**4**) was converted into the 5-amino-2,6-anhydro-5,7-dideoxy-D-glycero-L-guloheptitol (**5**)† by reduction with $NaBH_4$ and subsequent catalytic hydrogenation with Pd/C.

The conversion of the chloromercuriomethyl moiety to a variety of functional groups is well documented also in the carbohydrate field[1b,1d,1e,5a] and our work to synthesize through this procedure non-metabolizable analogues of D-glucosamine metabolites is in progress.

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