Generation of α-D-Glucopyranosylacetonitrilium Ions. Concerning the Reverse Anomeric Effect

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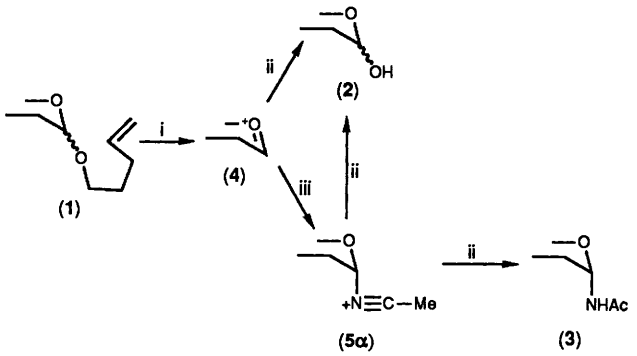
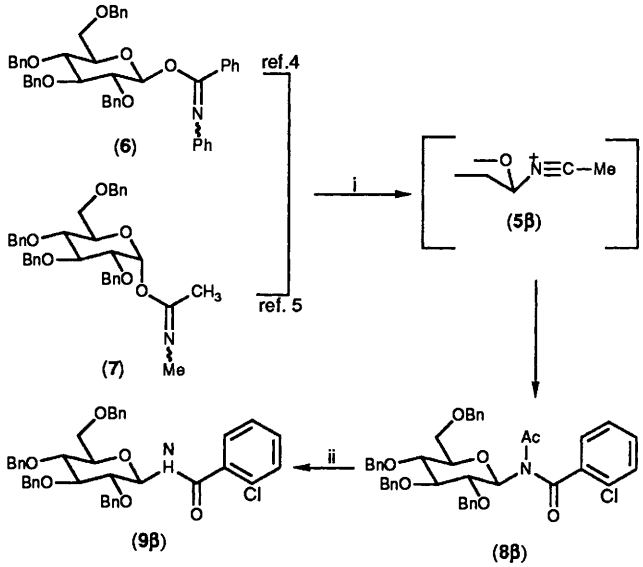
Reaction of the α- and β-anomers of the pent-4-enyl D-glucopyranoside (**10**) with *N*-bromosuccinimide in dry acetonitrile generated stereospecifically the α-D-glucopyranosylacetonitrilium ion (**5α**), which reacts *in situ* with 2-chlorobenzoic acid to afford the α-imide (**8α**). The result is in contrast to that predicted by the reverse anomeric effect and previous work on trapping carbohydrate acetonitrilium ions with 2-chlorobenzoic acid. The unusually large J_{12} 7.3 Hz for 1-H of (**8α**) is rationalised by a substantial flattening of the pyranose ring at C-1 and C-2. Molecular dynamic studies on the model α-imide (**12**) support a flattened $^4C_1$ conformation. Treatment of imide (**8α**) with sodium methoxide leads to the α-2-chlorobenzamide (**9α**), which was substantiated by independent synthesis of the β-2-chlorobenzamide (9β).

We have recently shown that use of *N*-bromosuccinimide (NBS) in 1% aqueous acetonitrile causes cleavage of the glycosidic acetal in pent-4-enyl glycopyranosides (**1**), leading to the formation of the corresponding pyranose (**2**) or *N*-acetylglycopyranosylamines (**3**), the latter product dominating in cases where strain is introduced into the glycopyranosyl ring.[1] The cyclic oxocarbenium ion (**4**) is considered to be the intermediate, trapping water to form the pyranose (**2**), or acetonitrile to generate the α-acetonitrilium ion (**5α**), which subsequently reacts with water to give the α-acetamide (**3**). Alternatively, (**2**) may result from S_N2 displacement of the acetonitrilium ion in (**5α**), followed by anomerisation (Scheme 1). The precise sequence of events notwithstanding, it is unclear why introducing strain into the substrate should alter the reaction pathway so as to favour α-acetamide formation (**3**).



Scheme 1. *Reagents:* i, NBS; ii, water; iii, MeCN.

Interestingly, the intermediacy of glycosylacetonitrilium ions has been advocated previously be several workers.[2-5] However, whereas Pavia *et al.*,[2] and Lemieux and Ratcliffe,[3] favoured α-ions (**5α**), Sinay and Pougny,[4] and Schmidt and Michel,[5] have advocated the β-counterpart (**5β**), because of the so-called reverse anomeric effect.[6] The reverse anomeric effect as originally defined[7] is the tendency of positively charged substituents at C-1 of a pyranose ring to adopt the equatorial orientation. Accordingly, the product from reaction of the imidates (**6**)[4] and (**7**)[5] with 2-chlorobenzoic acid in acetonitrile was said to be the β-imide (**8β**), $[\alpha]_D^{20}$ −3.8° (*c* 1, $CHCl_3$)[5] (Scheme 2). The value J_{12} 7.0 Hz for 1-H (δ 6.09)[5] observed in (**8β**) was considered to



Scheme 2.[4,5] *Reagents and conditions:* i, 2-ClH_4CO_2H, MeCN; ii, NaOMe, CH_2Cl_2.

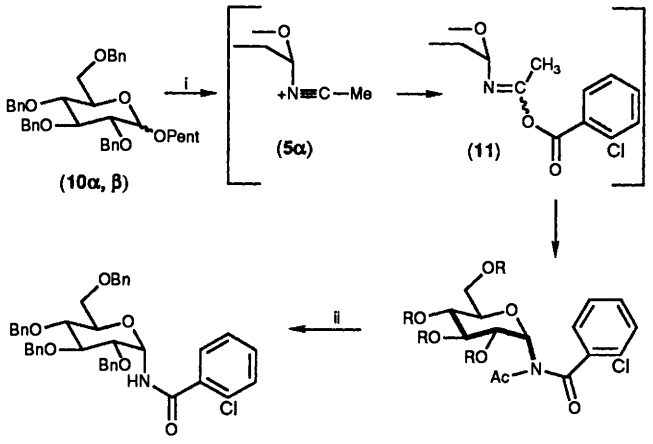
be compatible with a $^4C_1$ conformation of the molecule containing the imide moiety in an equatorial anomeric orientation.*

In this paper we disclose our results concerning treatment of the α- and β-anomers of pent-4-enyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (10) with NBS and 2-chlorobenzoic acid in acetonitrile that lead us to reinterpret the assignment of β-orientation to the glucopyranosylacetonitrilium ions (5β) obtained from compounds (**6**) and (**7**).

The α- and β-anomers of glycoside (**10**) were synthesized and separated as previously described.[1] Reaction of each anomer with NBS and 2-chlorobenzoic acid in acetonitrile led to formation of the α-imide (**8α**) [68% from (**10β**); 64% from (**10α**)], the specific rotation $\{[\alpha]_D^{21}$ −4.0° (*c* 0.49, $CHCl_3)\}$ and ^1H NMR resonance (δ 5.97, $J_{1,2}$ 7.3 Hz) being similar to those reported for the presumed β-imide (**8β**)[5] (Scheme 3). Accompanying formation of imide (**8α**) in our reactions were

* Range of vicinal coupling constants (Hz) for axial (a) and equatorial (e) protons of pyranoid chair forms of carbohydrate derivatives;[8] J_{aa} 8.6–11.5, J_{ea} 1.5–5.8, and J_{ee} 0.6–3.5.

minor amounts of several debenzylated analogues of (**8α**) and the pyranose (**13**), whose identities were substantiated by acetylation and ^{1}H NMR analysis. It is likely that the pyranose (**13**) is formed from traces of water in the acetonitrile, while debenzylation results from bromine generated under the reaction conditions. Indeed, brominolysis of per-*O*-benzylated glycosides is a known protocol for effective deprotection.[9]

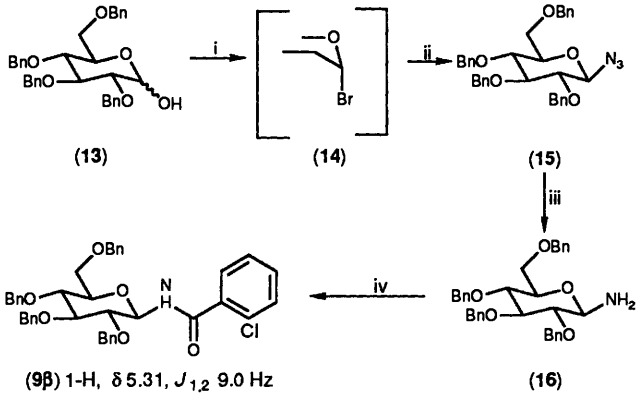


Scheme 3. *Reagents and conditions:* i, 2-ClC$_6$H$_4$CO$_2$H, NBS, MeCN; ii, NaOMe, CH_2Cl_2. Pent = $CH_2CH_2CH_2CH{=}CH_2$.

Although the magnitude of the 1-H coupling constant ($J_{1,2}$ 7.3 Hz) seemed inappropriate for imide (**8α**) in a $^4C_1$ conformation,* several other aspects of the ^{1}H NMR spectrum were in accord with such an assignment. First, the significant downfield chemical shifts of 3-H (δ 4.26) and 5-H (δ 4.25–4.20) were best reconciled with the deshielding effect of the *syn* axial C-1 amido residues. Secondly, difference NOE studies showed a 15% enhancement for 2-H on irradiation of 1-H, with no observed effect on either 3-H or 5-H. Furthermore, treatment of compound (**8α**) with sodium methoxide gave a 2-chlorobenzamide whose structure was assigned as (**9α**) $\{[\alpha]_D^{20}$ +61.7° (*c* 0.45, $CHCl_3$)$\}$ in view of the similarities of the ^{1}H NMR parameters (1-H at δ 5.99, $J_{1,2}$ 5.1 Hz after deuterium exchange of the N*H*COAr proton) to those found in the previously prepared α-acetamides (**3**)[1] (Scheme 3). Interestingly, both Sinay and Pougny,[4] and Schmidt and Michel,[5] reported that treatment of the presumed imide (**8β**) with sodium methoxide led to formation of the presumed β-2-chlorobenzamide (**9β**), exhibiting a similar specific rotation $\{[\alpha]_D^{20}$ +65° (*c* 1, $CHCl_3$)$\}$[5] and resonance for 1-H (δ 6.04, *J* 4.5 Hz)[5] to that assigned to the α-2-chlorobenzamide (**9α**) in this work.

Although formation of amide (**9α**) from (**8α**) seemed most plausible, it was conceivable that (**9α**) could indeed have arisen from the β-imide (**8β**) by loss of the *N*-acetyl group occurring with concomitant anomerisation at C-1. Base-catalysed anomerisation reactions are known, but none have been reported with *N*-amido-*N*-glycosides.[10]

In order to examine the possibility of anomerisation, as well as to confirm the α-anomeric configuration of the 2-chlorobenzamide (**9α**), the β-2-chlorobenzamide (**9β**) was synthesized unambiguously by adaptation of a route previously developed to β-acetamides.[1] Thus, the α-D-glucopyranosyl bromide (**14**) was prepared from pyranose (**13**)[1] by the procedure of Bihovsky *et al.*,[11] and immediately treated with sodium azide in *N*,*N*-dimethylformamide (DMF) to give, stereospecifically, the β-D-glucopyranosyl azide (**15**) (49% overall yield). A similar strategy for synthesis of azide (**15**) from the chloro-analogue of (**14**) had been employed by De Las Heras and co-workers.[12] Although Ogawa *et al.*[13] have chemospecifically reduced the azide function in compound (**15**) using atmospheric hydrogenation over Lindlar catalyst (18 h), in our hands use of 5% Pd/C as catalyst led to a substantially shorter reaction time (3 h). The resulting amine (**16**) (95%)[14] was acylated with 2-chlorobenzoyl chloride to afford the β-2-chlorobenzamide (**9β**) $\{[\alpha]_D^{22}$ −4.6° (*c* 0.3, $CHCl_3$)$\}$ (68%) (Scheme 4).



Scheme 4. *Reagents and conditions:* i, HBr, CH_2Cl_2; ii, NaN_3, DMF; iii, H_2, 5% Pd/C, MeOH; iv, 2-ClC$_6$H$_4$CO$_2$H, pyridine–Et_2O.

The anomeric configuration of the 2-chlorobenzamide prepared (in Scheme 4) was clearly established as (**9β**) by virtue of the parameter $J_{1,2}$ 9.0 Hz (after deuterium exchange of the N*H*COAr proton) for 1-H (δ 5.31).* By corollary, the configuration of amide (**9α**) is also established (*vide infra*).

Treatment of amide (**9β**) with excess of sodium methoxide did not affect the material, which suggests that base-catalysed anomerisation of *N*-amido-*N*-glycosides is unlikely. This conclusion provides evidence that the α-2-chlorobenzamide (**9α**) results from the α-imide (**8α**). Formation of the latter seems best rationalised by the addition of 2-chlorobenzoic acid to the intermediate α-D-glucopyranosylacetonitrilium ion (**5α**) to give intermediate (**11**), which then rearranges to the α-imide (**8α**) (Scheme 3). Given the absence of any β-imide (**8β**), reaction of the prior formed α-acetonitrilium ion (**5α**) with 2-chlorobenzoic acid must be considerably faster than any anomerisation process leading to the β-acetonitrilium ion (**5β**) and operation of the so-called reverse anomeric effect. Furthermore, since general evidence has indicated that the amido moiety possesses little anomeric effect and would therefore prefer an equatorial orientation on steric grounds,[15] formation of imide (**8α**) must represent the kinetic product of the reaction.

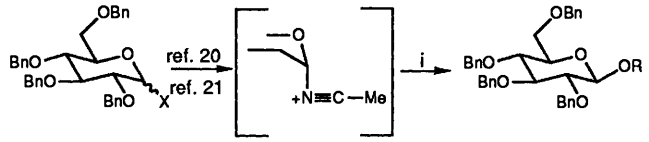
We propose that the unusually large $J_{1,2}$ 7.3 Hz coupling constant in imide (**8α**) can be explained by a substantial flattening of the pyranose ring at C-1 and C-2. Unfortunately compound (**8α**) proved to be an oil which ruled out *X*-ray studies. Consequently, in seeking evidence for this flattened $^4C_1$ conformation we turned to molecular dynamics, choosing as a model compound *N*-acetyl-2-chloro-*N*-(2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl)benzamide (**12**). After initially constructing the molecule as a $^4C_1$ structure, the conformational space of the imide group was sampled using the MM2 force field in the modelling program Macromodel version 2.0[16] to determine the global minimum-energy conformation, which was then subjected to an *in vacuo* simulation using molecular dynamics at 27 °C for 3 ps. The time-averaged conformation of model (**12**) adhered to a flattened $^4C_1$. The dihedral angle between 1-H and 2-H amounted to ~35°, which leads to a value, $J_{1,2} \approx 6.5$

* Footnote as on p. 747.

Hz, based on the electronegativity-related coupling-constant equation devised by Altona and co-workers.[17,*] This value is in good agreement with that observed ($J_{1,2}$ 7.3 Hz) in the α-imide (**8α**).

It appears that the observed flattening is due largely to the steric bulk of the imide moiety, since upon removal of the *N*-acetyl group the resulting α-2-chlorobenzamide (**9α**) shows a value $J_{1,2}$ 5.1 Hz, more akin with a standard $^4C_1$ conformation.† A consequence of this steric congestion, predicted by the molecular dynamics model, is that the *N*-acetyl carbonyl group bisects 3-H and 5-H. As a result, these protons should be deshielded, as was indeed observed in the ^{1}H NMR spectrum of compound (**8α**).

Our results show that the acetonitrilium ion resulting from addition of the acetonitrile to the cyclic oxocarbenium ion (**4**) is α-orientated, in keeping with well established trends in comparable glycosyl systems.[19] In this respect it has been demonstrated that use of acetonitrile as a solvent in low-temperature glycosidation reactions of some 2,3,4,6-tetra-*O*-benzyl substrates of glucopyranosyl fluorides (**17**)[20] and phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**18**)[21] leads to enhanced β-selectivity (Scheme 5). These results are in accord with kinetic



(**17**) X = α,β - F
(**18**) X = β - SPh

(**5α**)

Scheme 5.[20,21] *Reagent:* i, ROH.

formation of intermediate α-D-glucopyranosylacetonitrilium ions, that then undergo S_N2 displacement at the anomeric centre. Although Schmidt and Rucker[22] have proposed that intermediate β-D-glucopyranosylacetonitrilium ions control the α-stereoselective glycosidation of 2,3,4-tri-*O*-benzyl-D-glucopyranuronic acid derivatives, it is more than likely that neighbouring participation of the C-5 carboxy group is responsible for this stereochemical control, given the β-stereoselectivity of the 2,3,4,6-tetra-*O*-benzyl derivatives described above.

Studies aimed at the synthetic utility of α-D-glucopyranosylacetonitrilium ions are in progress.

Experimental

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluant specified in parentheses. All reactions requiring anhydrous conditions were conducted in oven-dried apparatus under a static atmosphere of argon. Organic extracts were dried over $MgSO_4$ and evaporated at aspirator pressure using a rotary evaporator unless otherwise stated. Light petroleum refers to the fraction boiling between 35 to 60 °C. Diethyl ether (referred to as ether), dichloromethane, pyridine, methanol, acetonitrile, and DMF were dried and distilled before use using standard methods.[23] NBS was recrystallised from hot water and dried *in vacuo* over phosphorus pentoxide. Chemical shifts are reported in δ values relative to tetramethylsilane. ^{1}H NMR spectra were recorded in deuteriochloroform on a Varian XL-300 spectrometer. Unless otherwise stated IR spectra were recorded in chloroform on a Perkin-Elmer 297 instrument. Optical rotations were measured for chloroform solutions using a Perkin-Elmer 241 instrument. Mass spectra were recorded on a Hewlett-Packard 59-88A GCMS by chemical ionisation (with methane–ammonia as the reagent gas). Accurate mass determinations were recorded on a VG-705 by chemical ionisation (with ammonia as the reagent gas, an accelerating voltage of 8 kV, and ~10 000 resolution). TLC was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) and spots visualised using a mixture of ammonium molybdate(VI) tetrahydrate and cerium(IV) sulphate tetrahydrate in 10% aqueous sulphuric acid. M.p.s were recorded with a Buchi 510 apparatus and are uncorrected. Elemental combustion analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

Reaction of Pent-4-enyl 2,3,4,6-Tetra-O-benzyl-D-glucopyranoside (**10**) *with NBS and 2-Chlorobenzoic Acid.*—NBS (45.5 mg, 0.26 mmol) and 2-chlorobenzoic acid (17.8 mg, 0.11 mmol) were added to a solution of the α-anomer (**10α**) (61.9 mg, 0.10 mmol) in dry acetonitrile (2 ml). The reaction flask was wrapped in silver foil and the mixture was stirred under argon at room temperature for 4 h. The resulting green solution was then quenched with 10% sodium thiosulphate (1 ml) and the acetonitrile removed under reduced pressure. The resulting residue was partitioned between water (20 ml) and dichloromethane (25 ml), the layers thoroughly stirred and separated, and the aqueous layer was further extracted with dichloromethane (4 × 25 ml). The combined organic layers were washed with water (2 × 25 ml), dried, and the solvent removed under reduced pressure. Flash chromatography of the residue (light petroleum–ethyl acetate, 17:3) gave N-*acetyl*-2-*chloro*-N-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*benzamide* (**8α**) as an oil (47.2 mg, 64%), $[\alpha]_D^{21}$ −4.0° (*c* 0.49); ν_{max} 1 725 ($COCH_3$) and 1 680 cm^{-1} (NCOAr); δ_H‡ 7.34–7.04 (24 H, 4 × CH_2Ph and ArH), 5.97 (1 H, d, *J* 7.3 Hz, 1-H), 4.77–4.39 (8 H, m, 4 × CH_2Ph), 4.26 (1 H, t, *J* 7.9 Hz, 3-H), 4.25–4.20 (1 H, m, 5-H), 3.93 (1 H, t, *J* 7.6 Hz, 2-H), 3.65–3.58 (2 H, m, 4-H and 6-H_A), 3.51 (1 H, dd, J_1 10.8, J_2 2.1 Hz, 6-H_B), and 2.09 (3 H, s, COMe) (Found: C, 72.0; H, 6.1; N, 1.8. $C_{43}H_{42}ClNO_7$ requires C, 71.7; H, 5.9; N, 1.9%).

In an identical manner the β-anomer (**10β**) (31.7 mg) gave (**8α**) (25.6 mg, 68%) after 7 h.

2-*Chloro*-N-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*benzamide* (**9α**).—To a solution of compound (**8α**) (11.2 mg, 0.02 mmol) in dry dichloromethane (1 ml) was added dropwise 0.62M-sodium methoxide in methanol (40 μl, 0.03 mmol). The resulting solution was stirred at room temperature under argon for 1.5 h, then saturated aqueous ammonium chloride (1 ml), water (20 ml), and dichloromethane (25 ml) were added. The layers were thoroughly stirred and separated, and the aqueous layer was further extracted with dichloromethane (3 × 25 ml). The combined dried extracts were evaporated under reduced pressure and the residue was purified by flash chromatography (light petroleum–ethyl acetate, 1:1) to give the *title compound* (8.7 mg, 83%) as an oil, $[\alpha]_D^{20}$ +61.7° (*c* 0.45); ν_{max} 3 420 (NH), 1 675 (NCOAr), and 1 500 cm^{-1} (NCOAr); δ_H‡ 7.71 (1 H, dd, J_1 6.7, J_2 1.6 Hz, 6-H′), 7.41–7.11 (23 H, m, 4 × CH_2Ph and ArH), 7.02 (1 H, d, *J* 6.5 Hz, exchanged with D_2O, NH), 5.99 (1 H, br t, addition of D_2O caused br t to collapse to d, *J* 5.1 Hz, 1-H), 4.95–4.48 (8 H, m, 4 × CH_2Ph), 3.92 (1 H, dd, J_1 9.3, J_2 5.4 Hz, 2-H),

* Equation used:
$J_{HH} = 13.86\cos^2\varphi - 0.81\cos\varphi + \Sigma\Delta\chi_i\{0.56 - 2.32\cos^2(\tau_i\varphi + 17.9|\Delta\chi_i|)\}$
where φ is the proton–proton torsion angle; and χ_i is the sum of the electronegativity differences between the substituents attached to the ethane fragment and hydrogen. Electronegativity[18] for –O– 3.31 and H 2.0. For the imide moiety ~3.21, calculated from proton chemical shifts of *N*-ethylacetamide and use of a modified Dailey and Shoolery equation,[18] where τ_i is +1 or −1 according to the orientation of the substituent.[17]

† Footnote as on p. 747.

‡ The 2-chlorobenzamide nucleus locants are primed.

and 3.83–3.63 (5 H, m, 3-, 4-, and 5-H and 6-H_2) (Found: M^+ + 1, 678.2637. $C_{41}H_{40}{}^{35}ClNO_6$ requires M + 1, 678.2622).

2,3,4,6-*Tetra*-O-*benzyl*-β-D-*glucopyranosyl Azide* (**15**).—Dichloromethane (2 ml) at 0 °C was saturated with dry hydrogen bromide and then mixed with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**13**)[1] (101.8 mg, 0.19 mmol). After 5 min the solvent was evaporated off under reduced pressure at room temperature and the residue was extracted with ether (5 ml). The cooled extract was quickly washed with cold saturated aqueous sodium hydrogen carbonate (6 ml), which was further extracted with cold ether (5 ml). The combined extracts were dried over calcium chloride and potassium carbonate, and the solvent was removed under reduced pressure to give 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**14**)[11] (108 mg), which was immediately taken up in dry DMF (2 ml) and treated with sodium azide (13.5 mg, 0.21 mmol). After 21 h at room temperature under argon the solvent was removed under reduced pressure (0.1 mmHg) with no heating and the residue was partitioned between water (30 ml) and dichloromethane (50 ml). The layers were thoroughly stirred and separated, and the aqueous layer was further extracted with dichloromethane (2 × 50 ml). The combined dried extracts were evaporated under reduced pressure and the crude product was purified by flash chromatography (light petroleum–ethyl acetate, 9:1) to give the azide as an oil (52.6 mg, 49%), $[\alpha]_D^{22}$ −1.9° (*c* 0.43) {lit.,[13] $[\alpha]_D^{25}$ +4.5° (*c* 1.55, $CHCl_3$)}; ν_{max}(film) 2 120 cm^{-1} (N_3); δ_H 7.35–7.13 (20 H, m, 4 × CH_2Ph), 4.92–4.53 (9 H, 4 × CH_2Ph and 1-H), 3.75–3.52 (5 H, m, 3-, 4-, and 5-H and 6-H_2), and 3.38 (1 H, apparent ddd, J_1 ~7.7, J_2 ~7.7, J_3 2.4 Hz, 2-H); *m/z* 583 (100%, M^+ + 18).

1-*Amino*-2,3,4,6-*tetra*-O-*benzyl*-1-*deoxy*-β-D-*glucopyranose* (**16**).—A solution of azide (**15**) (22.4 mg) in methanol (4 ml) containing 5% Pd/C (3.2 mg) was hydrogenated at atmospheric pressure and room temperature. After 3 h the mixture was filtered through Celite, which was then thoroughly washed with methanol (2 × 10 ml). The combined filtrates were evaporated under reduced pressure to give the amine as a solid (20.4 mg, 95%), m.p. 105–106 °C (from ether–hexane) (lit.,[14b] 106.5–107.5 °C); $[\alpha]_D^{22}$ +17.2° (*c* 0.22) {lit.,[14b] $[\alpha]_D^{25}$ +22.6° (*c* 1.24, $CHCl_3$)}; δ_H 7.40–7.08 (20 H, m, 4 × CH_2Ph), 5.01–4.47 (8 H, m, 4 × CH_2Ph), 4.12 (1 H, d, *J* 8.8 Hz, 1-H), 3.72–3.44 (5 H, m, 3-, 4-, and 5-H and 6-H_2), 3.21 (1 H, t, *J* 8.7 Hz, 2-H), and 1.64 (2 H, s, NH_2, masked by water resonance); *m/z* 540 (100%, M^+ + 1).

2-*Chloro*-N-(2,3,4,6-*tetra*-O-*benzyl*-β-D-*glucopyranosyl*)-*benzamide* (**9β**).—To a cooled solution (0 °C) of compound (**16**) (16.9 mg) in dry ether (4 ml) was added 2-chlorobenzoyl chloride (~10 μl) and dry pyridine (~20 μl). The resulting mixture was stirred under argon at 0 °C for a further 1.25 h, after which it was filtered and the white precipitate was collected and washed with ether (40 ml). The combined filtrates were evaporated under reduced pressure and the crude product was purified by flash chromatography (gradient of 20–30% ethyl acetate in light petroleum) to give the *title compound* as a solid (14.4 mg, 68%), m.p. 156–158 °C (from ether); $[\alpha]_D^{22}$ −4.6° (*c* 0.31); ν_{max} 3 430 (NH), 1 700 (NCOAr), and 1 510 cm^{-1} (NCOAr); δ_H* 7.52 (1 H, dd, J_1 7.3, J_2 1.3 Hz, 6′-H), 7.41–7.11 (23 H, m, 4 × CH_2Ph and ArH), 6.25 (1 H, d, *J* 9.1 Hz, exchanged with D_2O, NH), 5.31 (1 H, t, *J* 9.1 Hz, addition of D_2O caused t to collapse to d, *J* 9.0 Hz, 1-H), 4.91–4.47 (8 H, m, 4 × CH_2Ph), 3.82–3.57 (5 H, m, 3-, 4-, and 5-H and 6-H_2), and 3.46 (1 H, t, *J* 8.8 Hz, 2-H) (Found: C,72.7; H, 6.1; N, 2.1. $C_{41}H_{40}ClNO_6$ requires C, 72.6; H, 5.9; N, 2.1%).

Acknowledgements

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