C-Glycoside Syntheses. 3. Diastereodiversified C-Glycosides from D-Glucose†

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β-C-Glycosides with the D-*manno*, D-*allo*, and D-*altro* configurations can be easily obtained by anchimerically assisted inversions, starting from a common β-C-glycoside precursor, nitro(4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (**2**), which is easily accessible from D-glucose. The observed neighboring group reactions show some similarities to reactions previously observed for analogous O-glycosides, but also some significant differences due to the acetamidomethyl β-C-glycoside group, which is present in most of the compounds. The configurations and conformations of all compounds have been comprehensively studied by NMR methods. The result is a viable and extendable synthetic paradigm for the rational synthesis of a wide variety of unusual C-glycoside derivatives, potentially useful for biochemical studies.

Introduction

C-Glycopyranosyl compounds[1] have been found to exhibit biological activity, providing many applications in biochemistry and medicine.[2] For example, pseudomonic acid is an antimicrobial antibiotic; ambruticin is an antifungal antibiotic,[3] and hedamycin functions as an antitumor antibiotic.[4] These findings gave impetus to synthetic efforts leading to analogs, for studies of carbohydrate metabolism, enzyme inhibition,[5,6] and chiral synthons for the synthesis of complex molecules. Thus, during the past two decades, carbohydrate chemistry has been marked by advances in the development of specific methods for the synthesis of C-glycopyranosyl compounds.[7] Amino(glycopyranosyl)alkanes especially are expected to have application in the area of AIDs, HIV, and cancer therapy,[8] where they could be important intervenors in cell surface glycosylation.[9] The targeting of such a compound to a carbohydrate receptor on a bacterial surface[10] foreshadows the development of therapeutic agents addressing the carbohydrate regimen of pathogens.

Synthesis of a configurational variety of amino(glycopyranosyl)alkanes is thus an important goal. Neighboring group methodology, presented in a series of syntheses of diamino sugars and deoxy amino sugars,[11] from the common precursor D-glucosamine, has enabled us in the past to provide biomaterials for tests and comparisons to aid in the exploration of biomechanisms. In this paper we have used such methodology for the synthesis of unusual acetamido(glycopyranosyl)methanes from acetamido(4,6-*O*-benzylidene-β-D-glucopyranosyl)methane, that has become recently readily accessible.[12]

Results and Discussion

The condensation of nitromethane with 4,6-*O*-benzylidene-D-glucose (**1**), in the presence of the 1,3-proton transfer catalyst 2-hydroxypyridine and DBU gave a 77% optimized yield of the 4,6-*O*-benzylidenated nitro(β-D-glucopyranosyl)methane (**2**).[12,13] Compound **1** is the only easily accessible 4,6-*O*-benzylidene hexose, and consequently, compound **2** is the only member of its class. However, compound **2** offers unique possibilities to permutate the configurations in the 2- and 3-positions of the pyranose ring to obtain the three other possible configurations. When its di-*O*-acetyl derivative **3** was reduced with the Fe^0/aqueousTHF/CO_2 reagent developed in our group,[12] the results were only marginal. The use of a similar reagent was imperative, however, since other reducing reagents would compromise the 4,6-*O*-benzylidene group.[12] We reasoned that a Ni/Fe mixture, produced by reduction of the metal sulfates with $NaBH_4$, would be more reactive. Indeed, this reagent reacted exothermically with the di-*O*-acetyl derivative **3** to give acetamido(3-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (**4**) with concurrent O → N acyl migration[11c] and retention of the 3-*O*-acetyl group (Scheme 1). Crystalline **4** contained water of crystallization, which must be removed before mesylation to give **5**, which is an excellent starting material for the specific production of

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‡ From the Ph.D. thesis of Xiaojing Wang, *University of the Pacific*, **1993**.

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(13) In ref 12, the yield was 54%.

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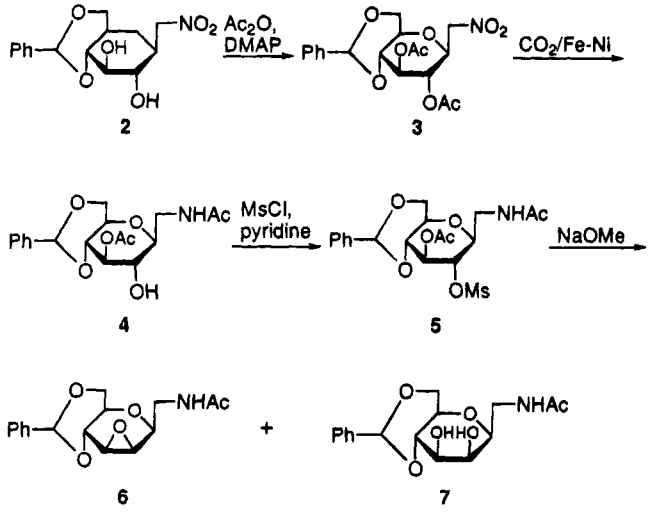
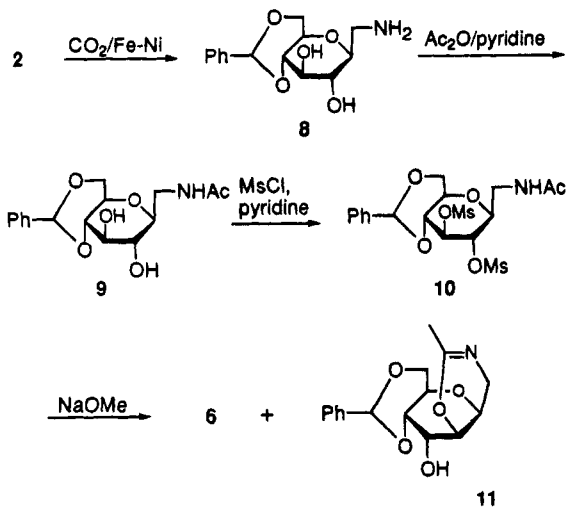
Scheme 1



Scheme 2



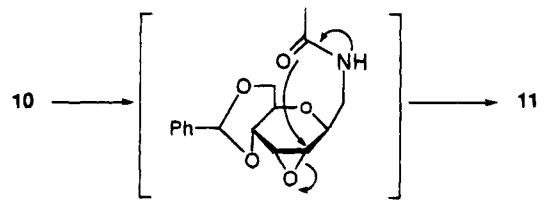
the D-*manno* epoxide **6**, formed through anchimeric displacement of the 2-mesyloxy group by a 3-alkoxide, an intermediate in the transesterification of the 3-*O*-acetyl group. Similar reactions are known in carbohydrate chemistry.[11g]

A side product (**7**), acetamido(4,6-*O*-benzylidene-β-D-mannopyranosyl)methane, was isolated from the mother liquor. This probably resulted from participation of the acetamido group, giving an oxazine intermediate, which was hydrolyzed by water during the workup. Similarly, the treatment of *trans* 2-acetamido-3-mesyloxy carbohydrate derivatives with NaOAc/$MeOCH_2CH_2OH/H_2O$ under reflux gives mostly simple inversion of the mesyloxy function *via* hydrolysis of an intermediate oxazoline derivative.[11a] The reaction of **5** with this reagent could similarly yield **7** or its *O*-acetyl derivative as the main product.

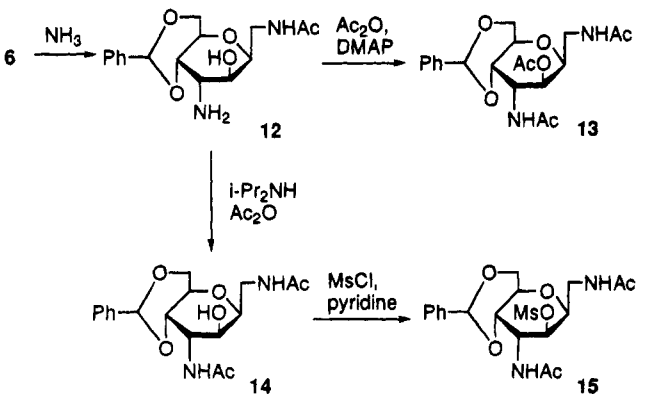
The free aminomethyl derivative **8** (Scheme 2), also obtained with a low level of byproducts, can be selectively N-acetylated, to give **9**. The yield in the mesylation of **9** was not optimized and may be improved by azeotropic drying of **9**, prior to reaction.

While the reaction of the monomesylated compound **5** with sodium methoxide in dichloromethane gave mostly the D-*manno* epoxide **6**, the 2,3-di-*O*-mesylated derivative **10** gave only a small amount of **6**, but mostly oxazine **11** (Scheme 2). Compounds **6** and **11** were separated by crystallization.

Scheme 3



Scheme 4



The oxazine **11** could not have been formed from *direct* anchimeric displacement of the 2-mesyloxy group by the acetamido group, since then the 3-mesyloxy group would have been retained or displaced by methoxide. Similarly to the corresponding O-glycosides,[16,18] reaction of **10** must have given mostly D-*allo* 2,3-epoxide which was unstable under the reaction conditions and was subsequently converted to **11** *via* neighboring group participation (Scheme 3).

Apparently, the axial proton on C-2 hinders a backside displacement of the 2-*O*-mesyl group, by the acetamido group, which may, however, easily open an epoxide, that exists as a half-chair.[11d] This relative ease of the anchimeric epoxide opening as compared to the direct anchimeric displacement may be surprising, but there is very old evidence for this effect: 1,6-anhydroglucose can be obtained from the β-glucosyl fluoride *via* a 1,2-epoxide intermediate, but not by direct backside displacement from α-glucosyl fluoride.[14,15] Noteworthy is the greater stability of the *altro*-oxazine **11**, as compared to the proposed intermediary *manno*-oxazine precursor of **7**. Apparently, the *cis*-3-OH group in the *manno*-oxazine stabilizes hydrate water that can "internally" hydrolyze the oxazine ring. In *altro*-oxazine **11**, the *trans*-3-OH group cannot be involved in the hydrolysis of the oxazine ring.

The 2,3-diaxial 3-amino-β-D-altropyranose derivative **12** was prepared in good yield by heating epoxide **6** with methanolic ammonia and ammonium hydroxide in a steel autoclave at 180 °C (Scheme 4).[16]

In agreement with the Fuerst–Plattner rule,[17] the 2,3-diequatorial 2-amino *gluco*-isomer was not detected.

Compound **12** was characterized by peracetylation to **13** and was also selectively N-acetylated (**14**) and O-mesylated to give compound **15**, which is analogous to benzoyl derivative **18**. Unlike **18**, compound **15** may be

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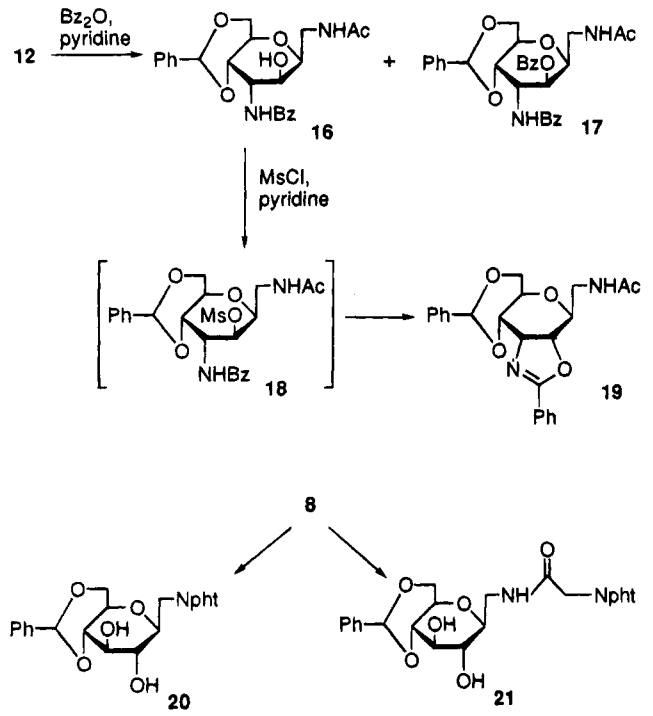
Scheme 5



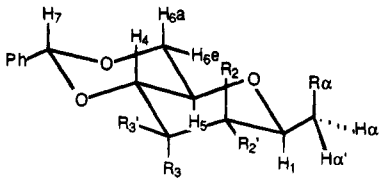
obtained pure and free of oxazoline, by a special, mild crystallization method.

The attempt to prepare compound **18** (Scheme 5) gave directly oxazoline derivative **19** by trans-diaxial neighboring group participation. There is precedence for this situation: methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(methylsulfonyl)-α-D-altropyranoside is difficult to purify, because of oxazoline formation during the crystallization. If the solvent was preheated and the compound was quickly dissolved, immediate cooling gave the pure compound.[18] The corresponding benzoyl compound was never obtained.

The lower half of Scheme 5 shows how the amino group may be protected with a nonparticipating phthaloyl group (compound **20**) or acylated with N-protected amino acids (compound **21**). All compounds shown in this paper could be partially or fully deprotected by standard methods,[11] to give the free C-glycopyranosyl compounds.

The configurations of all compounds were established with the aid of ^{1}H, ^{13}C and 2D NMR. The coupling constants between proton H2 and the "anomeric" proton H1 ($J_{H1,H2}$) of **2**–**5**, **8**–**10**, **20**, **21** ranged from 8.0 to 9.8 Hz and indicated that the C-glycosidic linkages between the pyranose rings and nitromethyl or acetamidomethyl groups had the β-D configuration. The coupling constants $J_{H1,H2}$ of **6**, **7**, **11**–**14**, **16** ranged from 3.5 to 5.4 Hz, which indicated that the proton H2 of these compounds took equatorial orientation. For **19**, a $J_{H1,H2}$ value was not observed; H2 had moved remarkably downfield (δ 5.91), which is likely due to the fact that H2 lies inside the deshielded area of the oxazoline ring (Scheme 5, Figure 1).

Proton NOE difference spectroscopy was used to study the solution conformation and configuration of substituents. The 4,6-benzylidene blocking group was transdiequatorially fused to the pyranose ring with an equatorial phenyl group. Molecular modeling[19] showed that



D-*gluco* derivatives (R_2 = R_3 = H)
[2] Rα = NO_2; R_2' = R_3' = OH
[3] Rα = NO_2; R_2' = R_3' = OAc
[4] Rα = NHAc; R_2' = OH; R_3' = OAc
[5] Rα = NHAc; R_2' = OMs; R_3' = OAc
[8] Rα = NH_2; R_2' = R_3' = OH
[9] Rα = NHAc; R_2' = R_3' = OH
[10] Rα = NHAc; R_2' = R_3' = OMs
[20] Rα = NPht; R_2' = R_3' = OH
[21] Rα = NHCOCH$_2$NPht; R_2' = R_3' = OH

D-*manno* derivatives (R_2' = R_3 = H)
[6] Rα = NHAc; R_2-R_3' = -O-
[7] Rα = NHAc; R_2 = R_3' = OH

D-*altro* derivatives (R_2' = R_3' = H)
[11] Rα-R_2 = -N=C(Me)O-; R_3 = OH
[12] Rα = NHAc; R_2 = OH; R_3 = NH_2
[13] Rα = NHAc; R_2 = OAc; R_3 = NH_2
[14] Rα = R_3 = NHAc; R_2 = OH
[15] Rα = R_3 = NHAc; R_2 = OMs
[16] Rα = NHAc; R_2 = OH; R_3 = NHBz
[17] Rα = NHAc; R_2 = OBz; R_3 = NHBz
[18] Rα = NHAc; R_2 = OMs; R_3 = NHBz

D-*allo* derivative (R_2 = R_3' = H)
[19] Rα = NHAc; R_2'-R_3 = -O(Ph)C=N-

Figure 1.

the distances between axial (benzylidene) H7 and axial H4, H6a were 2.29 Å. The distances between H4 and H2 (only in glucopyranosyl compounds **2**–**5**, **8**–**10**, **20**, **21**) were 2.53 Å. Irradiation of proton H7 produced a positive NOE for both H4 and H6a signals (12%). When H2 and H3 were equatorial, as in altro-derivatives **11**–**16**, a strong positive enhancement for the H4 (9%) signal was seen following the irradiation of proton H3.

In epoxide **6**, observation of a strong NOE from H2 to H1 (11%) unambiguously established the two protons on the same side of the mannopyranosyl ring. A large enhancement was observed for H4 (18%) when H3 was irradiated, indicating close proximity of H3 and H4 in a half chair. In oxazoline derivative **19**, a *cis* fusion of the phenyl oxazoline on C2 and C3 of allopyranose ring was apparent because of (1) strong positive enhancement for H2 (12%) and for H4 (9%) upon the irradiation of H3, and (2) a positive NOE for H4 (11%) and a negative NOE for H2 (−3%) following the irradiation of proton H7.

The solution conformations of the acetamidomethyl groups around the C-glycosidic bond were studied by both vicinal coupling constants[20] and NOE difference spectroscopy.

The observed coupling constants of H1 with the two methylene protons on Cα are the following: **6** (3.8, 3.3 Hz), **10** (4.5, 4.5 Hz), **12** (4.8, 5.1 Hz), **19** (6.5, 6.5 Hz), indicating anticoplanarity of H1 and acetamido group, but with a considerable distortion for **12** and **19**. Molecular modeling[19] of compounds **4**, **5**, **6**, **10**, and **12** confirmed this as the low energy conformation. In compounds **2**–**5**, **8**–**10**, **19**, and **21**, as expected, a positive enhancement at H2 (3%) was seen upon the irradiation of the NH proton. To completely understand the stereochemistry at the C-glycosidic bond, it was necessary to differentiate Hα and Hα′ (Figure 2).

Hα′ was in close proximity to H2 in space and Hα was far away from H2. It was expected that positive NOE enhancement should be observed between H2 and Hα′, but no NOE was expected between H2 and Hα. Increases

(18) Choudhary, M. S. M. S. thesis, University of the Pacific, **1967**.
(19) Cache Chemistry Design on Macintosh Quadra 950.

(20) The two Ha protons are magnetically nonequivalent and the vicinal coupling constants between H1 and Ha depend on the angular orientation, with the coupling constant 10–13 Hz for an antiperiplanar orientation, and 3–4 Hz for a *gauche* orientation. Goekjian, P. G.; Wu, T.-C.; Kishi, Y. *J. Org. Chem.* **1991**, *56*, 6412.

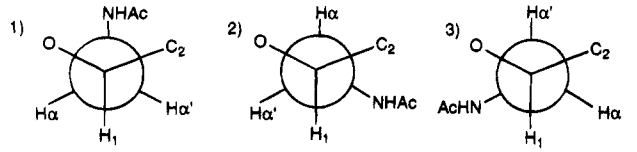


Figure 2. Three staggered comformations around C-glycosidic bond.

in signal strengths at H2 (4%), H1 (3%), and Hα (17%) were observed following the irradiation of Hα'; however, irradiation of Hα produced positive enhancement at H1 (3%) and Hα' (17%), but no enhancement was seen for H2 in compounds **4–6**, **10**, **12–16**, **19**. Thus the downfield resonance corresponded to Hα, and the one at highfield correlated to Hα'.

Conclusion

Starting from acetamido(4,6-*O*-benzylidene-β-D-glucopyranosyl)methane, 4,6-*O*-benzylidene-β-D-*manno*, D-*altro*, and D-*allo* configurations were shown to be easily accessible by anchimerically assisted configurational inversions. They are summarized in Figure 1.

Experimental Section

General Method. Melting points are uncorrected. Infrared spectra were recorded using KBr pellets. Optical rotations were measured at the sodium D line at $c = 1$, to $c = 2$. Analytical thin layer chromatography (TLC) was performed on precoated TLC plates with 0.25 mm of silica gel GF from Analtech, Inc. Plates were developed with system A: $CHCl_3$/MeOH (24:1); system B: $CHCl_3/Et_2O$ (3:1); system C: $CHCl_3$/THF (3:2); system D: CH_2Cl_2/Et_2O (1:1); system E: C_7H_{16}/$CHCl_3$/MeOH (9:6:1); system F: $CHCl_3$/dioxane (15:1); system G: $CHCl_3$/MeOH (3:2); system H: toluene/dioxane (9:1). Compounds were detected on the plates by extinction of UV light, and all by spraying with a H_2SO_4/MeOH (9:1) mixture followed by heating at 120 °C for up to 20 min. Flash chromatography separations were performed on J. T. Baker (40 mm) silica gel. The column size was 1.9 cm i.d. × 45 cm (30 g SiO_2). The reported elemental analyses were done by the analytical laboratory of the department of chemistry at UC Berkeley. The original pyranose positions are designated C1 (H1) through C6 (H6), and the C-glycosidic methylene Cα (Hα), in the listing of the NMR spectra (see Figure 1).

Nitro(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (3). Ac_2O (7.0 mL, 70 mmol) was slowly (in 20 min) added to a cold (4 °C), stirred suspension of **2** (10 g, 32 mmol), 4-(dimethylamino)pyridine (DMAP, 1.3 g, 11 mmol), and Et_3N (8.0 mL, 57 mmol) in THF (70 mL). The suspension cleared after 10 min and precipitated white crystals after 30 min. After stirring of the suspension at 0 °C (6 h) and at room temperature (2 h), crystals were filtered off and were washed with cold THF to give **3** (8.4 g; mp 193–194 °C). The mother liquor, after being concentrated *in vacuo*, afforded more **3** (3.2 g; mp 190–193 °C), which was recrystallized from absolute EtOH (2.6 g; mp 193–194 °C). Total yield of **3**: 11 g (90%); TLC system B: R_f 0.73; $[\alpha]^{25}_D$ ($CHCl_3$) −81.3°, lit.[12] mp 191–192 °C; $[\alpha]^{25}_D$ −80.9°. Spectral data were identical.

Acetamido(3-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (4). Saturated aqueous $KHCO_3$ (5.6 g, 56 mmol) was stirred with a solution of $FeSO_4 \cdot 7H_2O$ (37 g, 133 mmol) and $NiSO_4 \cdot 6H_2O$ (8.3 g, 32 mmol) in H_2O (200 mL) for 20 min. $NaBH_4$ (8.0 g, 210 mmol) was slowly added to give elemental Fe^0–Ni^0 which was filtered and was washed with deionized H_2O (800 mL). The wet precipitate was stirred with a solution of **3** (6.0 g, 15 mmol) in 200 mL THF/H_2O (1:1) under CO_2 (36 h). Reduction immediately commenced with evolution of heat, and the reaction process was monitored by TLC. After filtration, the filter cake was washed with THF (150 mL). The filtrate was evaporated *in vacuo* until THF was completely removed. The residual suspension was shaken overnight. The crystals were filtered and were washed with H_2O to give crude product (5.4 g). Chromatography (flash silica, 30% CH_2Cl_2/Et_2O) yielded two components: **4** (77%), TLC system A: R_f 0.50; mp 222–223 °C; $[\alpha]^{25}_D$ (MeOH) −48.0; IR [cm^{-1}] 3420 (OH), 3340 (NH), 1735 (OAc), 1690 (N–Ac), 1560 (NH), 700, 765 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.54 (m, 1H, $J = 9.0$ Hz), 4.36 (dd, 1H), 4.82 (t, 1H), 3.71 (t, 1H), 3.90 (dt, 1H, $J = 8.7$, 2.5 Hz), 3.47 (dd, 1H, $J = 2.5$ Hz), 3.57 (dd, 1H, $J = 8.7$ Hz), 5.54 (s, 1H), 3.50, 3.23 (dd, dd, 2H), 2.27 (d, 1H), 5.81 (t, 1H), 2.00 (s, 3H), 1.63 (s, 3H), 7.39 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 76.75, 71.41, 72.76, 80.57, 69.93, 67.73, 39.91, 100.70, 137.66, 128.89, 128.04, 126.35, 169.75, 169.43, 22.29, 20.68. Anal. Calcd for $C_{18}H_{25}O_8N$ (M + H_2O): C, 56.39; H, 6.57; N, 3.65. Found: C, 56.30; H, 6.46; N, 3.45. The second component (7%) was identical to compound **9**, by IR, ^1H NMR, and ^{13}C NMR spectra.

Acetamido(3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-methanesulfonyl-β-D-glucopyranosyl)methane (5). A cold (0 °C) solution of azeotropically dried (toluene/pyridine/vacuum) **4** (0.36 g, 1.0 mmol) in anhyd pyridine (1.8 mL) was treated with $MeSO_2Cl$ (0.30 mL, 4.0 mmol, 12 h), was left at room temperature (10 h), and was stirred into ice. Filtration gave crude **5** (0.28 g; mp 162–166 °C), recrystallized from THF/diisopropyl ether (DIPE) to give pure **5**: 0.23 g (52%); mp 169–170 °C. TLC system A: R_f 0.56; $[\alpha]^{25}_D$ ($CHCl_3$) −58.1; IR [cm^{-1}] 3340, 1540 (NH), 1740 (O–C=O), 1640 (N–C=O), 1345 (SO_3), 768, 700 (C_6C_5); ^1H NMR($CDCl_3$) δ 2.85 (m, 1H, $J = 8.0$ Hz), 3.74 (t, 1H, $J = 8.0$ Hz), 3.86 (t, 1H, $J = 8.0$ Hz), 3.77 (t, 1H, $J = 8.0$ Hz), 3.62 (dt, 1H, $J = 8.6$ Hz), 4.11 (dd, 1H, $J = 8.6$, 4.3 Hz), 4.36 (dd, 1H, $J = 4.3$ Hz), 5.64 (s, 1H), 4.29, 3.70 (dd, dd, 2H), 6.15 (t, 1H), 2.01, 1.96 (s, s, 6H), 2.19 (s, 3H), 7.46 (m, 5H); ^{13}C NMR($CDCl_3$) δ 76.59, 75.14, 71.78, 78.63, 70.80, 68.36, 39.48, 101.56, 136.69, 129.28, 128.35, 126.19, 170.40, 38.69, 23.19, 20.87. Anal. Calcd for $C_{19}H_{25}N_1O_9S_1$: C, 51.45; H, 5.68; N, 3.15. Found: C, 51.20; H, 5.34; N, 3.07.

Acetamido(2,3-anhydro-4,6-*O*-benzylidene-β-D-mannopyranosyl)methane (6). To a cooled (0 °C), stirred solution of **5** (10 g, 23 mmol) in CH_2Cl_2 (20 mL), was added $NaOCH_3$ (11 mL, 44 mmol). The reaction process was monitored by TLC. After 5 days, H_2O (30 mL) was added to the solution. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and were evaporated *in vacuo*. The white crystalline residue, washed with cold EtOH and air-dried, was pure **6** (5.3 g). From the mother liquor, additional pure **6** (0.9 g) was obtained after recrystallization from 95% EtOH, for a total yield of **6**: 91%; mp 228–229 °C; TLC system A: R_f 0.57; $[\alpha]^{25}_D$ ($CHCl_3$) −47.42; IR [cm^{-1}] 3300, 1560 (NH), 1640 (N–C=O), 698, 758 (C_6H_5); ^1H NMR ($CDCl_3$) δ 4.10 (dd, 1H, $J = 4.6$, 3.5 Hz), 3.23 (dd, 1H, $J = 4.6$, 3.5 Hz), 4.29 (dd, 1H, $J = 10.3$, 4.6 Hz), 3.70 (t, 1H, $J = 10.3$ Hz), 3.22 (m, 1H, $J = 4.0$ Hz), 3.49 (d, 1H, $J = 4.0$ Hz), 3.64 (d, 1H), 3.85 (ddd, 1H, $J = 3.8$ Hz), 3.35 (m, 1H, $J = 3.3$ Hz), 5.57 (s, 1H), 5.93 (br, 1H), 7.39 (m, 5H), 2.01 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 72.71, 53.18, 50.67, 74.41, 69.03, 68.46, 39.67, 101.26, 137.32, 128.96, 128.11, 126.22, 169.65, 22.34. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.58. Found: C, 62.69; H, 6.21; N, 4.49.

Acetamido(4,6-*O*-benzylidene-β-D-mannopyranosyl)methane (7). The mother liquor from **6** was subjected to flash chromatography with CH_2Cl_2/THF (1:2) as the eluent. The first fraction gave **9** (100 mg); the second gave crystals which were recrystallized from MeOH/DIPE to give **7** (80 mg): mp 239–240 °C; TLC system A: R_f 0.24; IR [cm^{-1}] 3470, 3430 (OH), 3310 (NH), 1650 (C=O), 670, 760 (C_6H_5); ^1H NMR (DMSO-d_6) δ 3.75 (m, 1H, $J = 3.7$ Hz), 3.51 (t, 1H, $J = 3.7$ Hz), 3.84 (m, 1H), 3.63 (t, 1H, $J = 9.8$ Hz), 3.77 (m, 1H, $J = 9.8$ Hz), 4.18 (dd, 1H, $J = 9.8$ Hz), 3.87 (m, 1H), 3.20, 3.07 (m, 2H, $J = 5.8$, 13.6 Hz), 5.63 (s, 1H), 7.97 (t, 1H, $J = 5.7$ Hz), 7.37 (m, 5H), 5.21 (d, 1H, $J = 3.8$ Hz), 5.13 (d, 1H, $J = 4.6$ Hz); ^{13}C NMR (DMSO-d_6) δ 65.23, 70.19, 67.92, 73.32, 76.91, 68.44, 39.94, 100.96, 138.06, 128.72, 127.94, 126.36, 169.91, 22.35. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.42; H, 6.55; N, 4.33. Found: C, 59.11; H, 6.55; N, 4.21.

Amino(4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (8) and *N*-Acetyl Derivative 9. The reduction of

compound **2** (3.0 g, 9.6 mmol) followed the conditions given for compound **3**, to give, after workup, crude compound **8** (2.5 g; mp 212–215 °C). Recrystallization from MeOH/H_2O gave pure **8**: 0.21 g (78%); mp 233–234 °C; TLC system G: R_f 0.26; $[\alpha]^{25}_D$ (MeOH) −37.0, lit.[12] mp 234–235°C, $[\alpha]^{25}_D$ −41.7°. Spectral data were identical. The acetamido derivative **9** was obtained as described,[12] by acetylation of **8** with 2 equiv of Ac_2O and pyridine (three portions) in THF/H_2O (2:1), in 95% yield.

Acetamido(4,6-*O*-benzylidene-2,3-di-*O*-methanesulfonyl-β-D-glucopyranosyl)methane (10). To a solution of **9** (0.33 g, 1.0 mmol) in anhyd pyridine (5 mL) was added dropwise $MeSO_2Cl$ (0.24 mL, 3.0 mmol) with stirring at 0 °C. After 24 h at 0 °C, the mixture was poured into crushed ice (20 g). The aqueous solution was extracted with $CHCl_3$ (6 × 20 mL), was dried ($MgSO_4$), and was evaporated *in vacuo*. Crude product (0.34 g, 73%) was recrystallized from absolute EtOH, to give **10**: 0.27 g (58%), mp 192–193 °C. TLC system A: R_f 0.36; $[\alpha]^{25}_D$ ($CHCl_3$) −64.25; IR [cm^{-1}] 3300, 1530 (NH), 1635 (N−C=O), 1350, 1335 (SO_3), 760, 690 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.65 (m, 1H, J = 9.5, 4.5 Hz), 4.61 (t, 1H, J = 9.5 Hz), 4.91 (t, 1H, J = 9.5 Hz), 3.70 (t, 1H, J = 9.8 Hz), 3.55 (td, 1H, J = 9.8, 4.5 Hz), 3.72 (m, 1H), 4.41 (dd, 1H, J = 9.8, 4.5 Hz), 5.54 (s, 1H), 6.07 (t, 1H), 3.90 (ddd, 1H, J = 16.0, 4.5, 7.3 Hz), 3.41 (dt, 1H, J = 16.0, 4.5 Hz), 3.27, 2.99 (s, 6H), 2.00 (s, 3H), 7.37 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 77.87, 76.64, 76.37, 80.05, 69.04, 67.49, 39.94, 100.43, 136.91, 129.10, 128.22, 126.08, 169.50, 39.11, 22.33. Anal. Calcd for $C_{18}H_{25}NO_{10}S_2$: C, 45.08; H, 5.25; N, 2.92. Found: C, 44.80; H, 5.17; N, 2.76.

4,6-*O*-Benzylidene-2′-methyl-β-D-glucopyrano[1,2:5′,6′]-2′-oxazine (11). A cold (0 °C) solution of **10** (0.14 g, 0.35 mmol) in CH_2Cl_2 (10 mL) was treated with $NaOCH_3$ (0.17 mL, 0.70 mmol). After 4 days at room temperature, H_2O (15 mL) was added. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and were evaporated *in vacuo*. The residual solid was recrystallized from 95% EtOH to give **11**: 50 mg (56%); mp 268–269 °C; TLC system A: R_f 0.35; $[\alpha]^{25}_D$ ($CHCl_3$) −140.9; IR [cm^{-1}] 3120 (OH), 1690 (C=N), 751, 692 (C_6H_5); ^1H NMR ($CDCl_3$) δ 4.15 (m, 1H), 4.33 (dd, 1H, J = 10.4, 5.0 Hz), 4.28 (m, 1H), 3.78 (t, 1H, J = 10.2 Hz), 4.02 (dt, 1H, J = 10.2, 5.0 Hz), 3.87 (dd, 1H, J = 9.5, 3.1 Hz), 4.25 (dd, 1H, J = 5.0, 3.1 Hz), 5.66 (s, 1H), 3.52 (br, 2H), 2.17 (s, 1H), 2.04 (s, N=C−C**H**$_3$), 7.40 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 73.33, 65.19, 65.10, 76.45, 64.51, 68.13, 46.08, 101.05, 136.80, 128.78, 127.95, 126.37, 154.64, 20.85. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.58. Found: C, 62.64; H, 6.29; N, 4.49. The mother liquor from the recrystallization was concentrated to give **6** (27%) identified by mp, IR, ^1H NMR, and ^{13}C NMR spectra.

Acetamido(3-amino-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranosyl)methane (12). A solution of **6** (3.0 g, 11 mmol) in saturated NH_3/MeOH (50 mL) and NH_4OH (30 mL) was heated in a stainless steel autoclave at 400 psi (180 °C, 12 h and 130 °C, 24 h). The solution was cooled to room temperature, was filtered, and was concentrated *in vacuo*. The solution of the residual oil in EtOH was decolorized with carbon and was evaporated *in vacuo*. The solution of the residual oil in a minimal amount of EtOH was shaken overnight to produce white crystals, which were recrystallized from MeOH to give pure **12**: 2.5 g (81%); mp 183–184 °C; TLC system A: R_f 0.33; $[\alpha]^{25}_D$ (MeOH) −29.2; IR [cm^{-1}] 3380 (NH), 3300 (NH_2), 3200 (OH), 1640 (N−C=O), 750, 690 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.09 (ddd, 1H, J = 5.4, 4.8 Hz), 3.91 (dd, 1H, J = 5.4 Hz), 4.03 (m, 1H, J = 4.0 Hz), 3.75 (dd, 1H, J = 8.8, 4.0 Hz), 3.93 (m, 1H, J = 8.8 Hz), 4.27 (dd, 1H, J = 2.3 Hz), 4.04 (dd, 1H, J = 8.8, 2.3 Hz), 3.51, 3.63 (m, 2H, J = 4.8, 5.1 Hz), 5.60 (s, 1H), 4.30 (d, 1H, J = 4.3 Hz), 3.85 (d, 2H), 6.05 (t, 1H, J = 4.4 Hz), 2.03 (s, 3H), 7.39 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 73.00, 70.50, 52.19, 76.97, 64.83, 68.49, 39.70, 100.90, 138.04, 128.73, 127.99, 126.26, 169.99, 22.34. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.87; N, 8.69. Found: C, 59.32; H, 6.88; N, 8.50.

Acetamido(3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranosyl)methane (13). A cooled (4 °C), stirred mixture of **12** (0.37 g, 1.2 mmol), DMAP (50 mg, 0.38 mmol), Et_3N (0.28 mL, 2.0 mmol), THF (5 mL), and Ac_2O (0.25 mL, 2.5 mmol) was kept for 3 h, and for 12 h at 25 °C, and was evaporated. The solution of the residual oil in CH_2Cl_2 (10 mL) was washed with cold 10% citric acid (2 × 5 mL), cold saturated $NaHCO_3$ (2 × 5 mL), and cold H_2O (2 × 5 ml), was dried ($MgSO_4$), and was concentrated *in vacuo* to give crude product (0.35 g). Recrystallization from THF/DIPE gave **13**: 0.30 g (65%); mp 159–160 °C; TLC system F: R_f 0.26; $[\alpha]^{25}_D$ (MeOH) −19.3; IR [cm^{-1}] 3340 (OH), 1740 (O−C=O), 1660 (N−C=O), 760, 705 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.66 (m, 1H, J = 4.9 Hz), 4.32 (m, 1H), 4.51 (dd, 1H, J = 2.8, 7.1 Hz), 4.33 (m, 1H), 3.86 (t, 1H, J = 9.8 Hz), 3.78 (m, 1H, J = 9.8 Hz), 4.34 (m, 1H), 3.65, 3.25 (m, 2H), 5.64 (s, 1H), 6.10 (t, 1H, J = 6.9 Hz), 5.95 (d, 1H, J = 2.8 Hz), 7.38 (m, 5H), 2.19 (s, 3H), 2.02, 1.98 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 72.4, 70.13, 47.2, 74.36, 65.95, 68.24, 39.63, 100.68, 137.68, 128.8, 128.05, 126.11, 169.65, 169.61, 169.45, 22.46, 22.30, 20.59. Anal. Calcd for $C_{20}H_{28}N_2O_8$ (M + H_2O): C, 56.58; H, 6.65; N, 6.60. Found: C, 56.34; H, 6.58; N, 6.50.

Acetamido(3-acetamido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranosyl)methane (14). A stirred mixture of **12** (1.3 g, 4.4 mmol) in MeOH (10 mL) was treated, in 4 h intervals, with Ac_2O (0.20 mL, 2.2 mmol), *N,N*-diisopropylethylamine (DIPEA, 0.05 mL, 2.6 mmol), Ac_2O (0.20 mL, 2.2 mmol), DIPEA (0.05 mL, 2.6 mmol), Ac_2O (0.40 mL, 4.4 mmol), and DIPEA (0.18 mL, 10 mmol). The solvent was evaporated *in vacuo*. The solution of the residual oil in ethyl acetate (30 mL) was washed with cold 10% citric acid (1 × 15 mL), cold saturated $NaHCO_3$ (2 × 15 mL), and cold H_2O (2 × 15 mL) and was dried ($MgSO_4$). Evaporation *in vacuo* gave a residue, recrystallized from MeOH/DIPE to give **14**: 0.9 g (62%); mp 211–211.5 °C; TLC system A: R_f 0.43; $[\alpha]^{25}_D$ (MeOH) −20.1; IR [cm^{-1}] 3420, 3380, (two NH), 3310 (OH), 1660, 1640 (two N−C=O), 750, 690 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.20 (m, 1H, J = 5.4, 9.4 Hz), 3.24 (m, 1H, J = 5.4 Hz), 3.73 (m, 1H, J = 5.4 Hz), 3.81 (t, 1H, J = 9.8 Hz), 3.65 (m, 1H, J = 9.8 Hz), 4.21 (m, 1H, J = 9.8, 4.6 Hz), 4.35 (m, 1H, J = 4.6 Hz), 5.63 (s, 1H), 3.69 (m, 2H), 5.97 (t, 1H, J = 7.8 Hz), 5.83 (d, 1H), 2.01, 1.61 (s, 6H), 7.37 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 73.74, 68.56, 50.34, 74.23, 65.83, 68.56, 39.71, 100.82, 137.86, 128.74, 128.00, 126.17, 22.50, 22.35, 169.83, 169.64. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 59.33; H, 6.63; N, 7.68. Found: C, 58.98; H, 6.65; N, 7.54.

Acetamido(3-acetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-(methanesulfonyl)-β-D-altropyranosyl)methane (15). $MeSO_2Cl$ (0.22 mL, 3.0 mmol) was slowly added to a cooled (0 °C), stirred solution of **14** (0.35 g, 1.0 mmol) in anhyd pyridine (4.0 mL). After 24 h, crushed ice (10 g) was added. The mixture, after being stirred for 3 h, was extracted with CH_2Cl_2 (5 × 15 mL). The organic phase was washed with cold 10% citric acid (20 mL), cold saturated $NaHCO_3$ (20 mL), cold H_2O (20 ml) and was dried ($MgSO_4$). Crude product obtained after evaporation of the solvent was recrystallized from preheated MeOH by immediate addition of ice to give **15**: 0.21 g (50%); mp 113–114 °C; TLC system A: R_f 0.62; $[\alpha]^{25}_D$ ($CHCl_3$) +15.8; IR [cm^{-1}] 3420, 3350 (two NH), 1645, 1635 (two N−C=O), 1340 (SO_3), 760, 690 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.16 (m, 1H), 4.32 (q, 1H, J = 3.5 Hz), 3.93 (dd, 1H, J = 3.5, 5.8 Hz), 4.14 (dd, 1H, J = 5.8, 8.0 Hz), 3.72 (m, 1H, J = 8.0 Hz), 3.75 (dd, 1H), 3.78 (dd, 1H), 5.63 (s, 1H), 6.26 (t, 1H), 6.45 (d, 1H, J = 3.5 Hz), 4.96, 4.37 (ddd, 2H), 7.43 (m, 5H), 3.38 (s, 3H), 2.04, 1.98 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 73.59, 71.95, 50.61, 75.41, 67.41, 68.92, 38.53, 102.19, 136.67, 129.50, 128.47, 126.11, 37.79, 23.21, 23.12, 172.58, 171.08. Anal. Calcd for $C_{19}H_{28}N_2O_9S$ (M + H_2O): C, 49.56; H, 6.13; N, 6.08. Found: C, 49.30; H, 6.10; N, 5.81.

Acetamido(3-benzamido-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranosyl)methane (16). A stirred mixture of **12** (0.50 g, 1.7 mmol) in THF (20 mL) and H_2O (10 mL) was treated in 4 h intervals with Bz_2O (0.20 g, 0.85 mmol), pyridine (0.07 mL, 0.85 mmol), Bz_2O (0.20 g, 0.85 mmol), pyridine (0.07 mL, 0.85 mmol), Bz_2O (0.40 g, 1.7 mmol), and pyridine (0.28 mL, 3.4 mmol). The solvent was evaporated *in vacuo*. The solution of the residual oil in CH_2Cl_2 (20 mL) was washed with H_2O (3 × 15 mL) and was dried ($MgSO_4$). After evaporation *in vacuo*, the residue was recrystallized from THF/DIPE to give crude **16** (0.65 g), purified by recrystallization from MeOH: 0.58 g (88%); mp 229–230 °C; TLC system A: R_f 0.45;

$[\alpha]^{25}_D$ ($CHCl_3$) +24.1; IR [cm^{-1}] 3380, 3360 (NH), 3300 (OH), 1645, 1635 (two N—C=O), 750, 695, 685 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.68 (m, 1H, J = 4.8, 8.2 Hz), 3.75 (m, 1H, J = 4.8 Hz), 3.27 (m, 1H, J = 5.8 Hz), 3.85 (t, 1H, J = 10.6 Hz), 4.36 (m, 1H), 4.31 (dd, 1H, J = 3.5 Hz), 4.51 (dd, 1H, J = 3.5 Hz), 5.66 (s, 1H), 3.69, 3.77 (m, 2H), 6.30 (t, 1H, J = 6.6 Hz), 6.49 (d, 1H, J = 3.5 Hz), 1.97 (s, 3H), 4.68 (br, 1H), 7.45 (m, 10 H); ^{13}C NMR (DMSO-d_6) δ 73.7, 68.8, 50.91, 74.39, 65.69, 68.60, 39.66, 100.89, 137.91, 128.77, 128.09, 126.14, 134.70, 131.21, 128.00, 127.76, 169.9, 167.55, 22.33. Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.77; H, 6.14; N, 6.56. Found: C, 64.70; H, 6.09; N, 6.34.

Acetamido(3-benzamido-2-*O*-benzoyl-4,6-*O*-benzylidene-3-deoxy-β-D-altropyranosyl)methane (17). The mother liquor from **16** was subjected to flash chromatography (5 cm i.d. × 45 cm) with CH_2Cl_2/THF (9:1) as the eluent. Fractions 20–26 gave **16** (40 mg). Fractions 8–15 gave crystals which were recrystallized from MeOH to give **17**: 100 mg; mp 191–192 °C; $[\alpha]^{25}_D$ ($CHCl_3$) +31.4; TLC system A: R_f 0.65; IR [cm^{-1}] 3360, 3340 (NH), 1650, 1640 (N—C=O, O—C=O), 750, 685 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.83 (m, 1H, J = 6.6 Hz), 3.88 (m, 1H, J = 6.6 Hz), 3.61 (m, 1H, J = 6.6 Hz), 3.94 (dd, 1H, J = 8.5, 6.6 Hz), 4.56 (m, 1H, J = 8.5 Hz), 4.43, 4.36 (m, 2H), 5.64 (s, 1H), 3.85 (m, 2H), 7.24 (br, 1H), 6.69 (br, 1H), 1.90 (s, 3H), 7.89–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 74.15, 69.28, 52.53, 74.37, 67.00, 67.82, 40.03, 102.00, 137.04, 133.88, 133.7, 132.17, 131.79, 129.25, 128.81, 128.58, 128.40, 127.11, 127.05, 126.02, 169.40, 168.66, 22.19. Anal. Calcd for $C_{30}H_{30}N_2O_7$: C, 67.89; H, 5.70; N, 5.28. Found: C, 67.81; H, 5.83; N, 5.51.

1-(Acetamidomethyl)-4,6-*O*-benzylidene-1-deoxy-2'-phenyl-β-D-allopyrano[2,3:4',5']-2'-oxazoline (19). To a cooled (−10 °C), stirred solution of **16** (1.7 g, 4.0 mmol) in anhyd pyridine (6.0 mL), was slowly added $MeSO_2Cl$ (0.45 mL, 6.0 mmol). After 24 h, at −10 °C, the mixture was treated with crushed ice (10 g) and was extracted with CH_2Cl_2 (5 × 15 mL). The organic phase was washed with cold 10% citric acid (2 × 30 mL), cold saturated $NaHCO_3$ (2 × 30 mL), and cold H_2O (2 × 20 ml) and was dried ($MgSO_4$). After evaporation *in vacuo*, the residual oil was crystallized from MeOH to give **19**: 0.80 g (50%); mp 235 °C dec; TLC system A: R_f 0.56; $[\alpha]^{25}_D$ ($CHCl_3$) +26.0; IR [cm^{-1}] 3350 (NH), 1720 (C=N), 1640 (N—C=O), 760, 695 (C_6H_5); ^1H NMR ($CDCl_3$) δ 4.05 (t, 1H, J = 6.5 Hz), 5.91 (d, 1H, J = 3.5 Hz), 4.58 (dd, 1H, J = 3.5, 7.3 Hz), 4.34 (dd, 1H, J = 9.3, 4.4 Hz), 3.92 (m, 1H, J = 9.3 Hz), 3.92 (m, 1H), 4.45 (d, 1H, J = 6.1 Hz), 5.75 (s, 1H), 6.23 (br, 1H), 6.57 (br, 1H), 2.98 (ddd, 1H, J = 14.0, 6.5, 7.4 Hz), 3.72 (ddd, 1H, J = 14.0, 6.5 Hz), 1.95 (s, 3H), 7.52, 7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 73.19, 67.91, 69.18, 75.08, 50.31, 69.24, 38.81, 102.12, 137.1, 128.77, 128.42, 126.04, 166.00, 133.84, 132.10, 130.08, 128.73, 127.23, 170.14, 169.06, 23.21. Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.85. Found: C, 67.58; H, 5.85; N, 6.48.

Phthalimido(4,6-*O*-benzylidene-β-D-glucopyranosyl)-methane (20). A solution of **8** (1.5 g, 4.8 mmol) in THF (40 mL) and H_2O (20 mL) was vigorously stirred with freshly recrystallized N-(ethyloxycarbonyl)phthalimide (1.1 g, 4.8 mmol) for 12 h and was concentrated *in vacuo*, to give, at 0 °C, crude **20**: 1.7 g; mp 200–205 °C. Recrystallization from THF afforded pure **20**: 1.4 g (70%); mp 203–204 °C; TLC system A, R_f 0.27; $[\alpha]^{25}_D$ (MeOH) −23.5; IR [cm^{-1}] 3480, 3360 (OH), 1710 (N—C=O), 740, 720 (C_6H_5); ^1H NMR ($CDCl_3$) δ 3.43 (m, 1H, J = 9.0 Hz), 3.82 (t, 1H, J = 9.0 Hz), 3.37 (t, 1H, J = 9.0 Hz), 3.65 (t, 1H, J = 10.5 Hz), 3.75 (dt, 1H, J = 6.5 Hz), 3.48 (m, 1H), 4.30 (dd, 1H, J = 10.5, 3.9 Hz), 5.47 (s, H), 3.96, 4.10 (dd, 2H, J = 14.7, 3.48 Hz), 1.85 (br, 2H), 7.35 (m, 5H), 7.88 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 77.07, 73.87, 73.60, 80.70, 69.80, 67.76, 39.68, 100.56, 137.81, 128.76,127.95, 126.32, 131.59, 134.41,123.05, 167.80. Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15; N, 3.40. Found: C, 63.96; H, 5.35; N, 3.12.

N-Phthaloylglycinamido-(4,6-*O*-benzylidene-β-D-glucopyranosyl)methane (21). A mixture of **8** (1.5 g, 4.8 mmol), MgO (0.24 g, 6.0 mmol), THF (40 mL), and H_2O (20 mL) was treated at 5 °C with phthaloylglycyl chloride (1.0 g, 4.5 mmol) in THF (5 mL), which was slowly added. The mixture was stirred for 10 h at room temperature. The precipitate was filtered off. The filtrate was concentrated *in vacuo*. When most THF had evaporated, crude **21** (mp 215–220 °C) crystallized, which was washed with cold H_2O, cold MeOH, and cold Et_2O. Recrystallization from THF gave pure **21**: 1.6 g (70%); TLC system D, R_f 0.34; mp 226–227 °C; $[\alpha]^{25}_D$ (pyridine) −27.8; IR [cm^{-1}] 3440 (OH), 3320, 1550 (NH), 1720, 1650 (N—C=O), 750, 690 (C_6H_5); ^1H NMR (DMSO-d_6) δ 3.09 (m, 1H, J = 7.7 Hz), 3.67 (dd, 1H, J = 7.7 Hz), 3.33 (t, 1H, J = 7.7 Hz), 3.38 (t, 1H, J = 7.7 Hz), 3.43 (m, 1H), 3.64 (m, 1H), 4.20 (dd, 1H, J = 7.2, 2.5 Hz), 4.24 (m, 2H), 5.58 (s, 1H), 5.33, 5.28 (d, d, 2H, J = 6.0 Hz), 7.38 (m, 5H), 7.89 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 79.16, 73.79, 72.27, 80.89, 70.08, 67.96, 39.95, 100.66, 137.86, 128.81, 128.00, 126.35, 40.68, 131.74, 134.60, 123.19, 167.63, 166.43. Anal. Calcd for $C_{24}H_{24}N_2O_8$: C, 61.53; H, 5.16; N, 5.96. Found: C, 61.37; H, 5.42; N, 5.87.

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