Conversion of Glucosamine to Galactosamine and Allosamine Derivatives: Control of Inversions of Stereochemistry at C-3 and C-4

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The reactions of sodium benzoate with a series of trimesylates derived from glucosamine have been examined in an attempt to gain facile access to galactosamine analogues. Trimesylate **17**, in which the amino group was protected as a phthalimide, underwent double displacement at positions 4 and 6 to give the dibenzoate **18** with the desired galactosamine configuration. In contrast, trimesylates **21** and **27**, in which the amino groups were protected as acetamides, unexpectedly underwent double displacement at positions 3 and 6, giving products **22** and **28**, respectively, with allosamine configurations.

Introduction

Galactosamine is a commonly occurring constituent of natural oligosaccharides and glycoproteins, found α-linked to serine or threonine on *O*-glycans and *β*-linked in glycosphingolipids. We required access to a range of suitably protected derivatives of galactosamine, as part of a program directed at solid-phase carbohydrate chemistry.[1] However, due to the expense of galactosamine, we decided to develop a synthetic route to this amino sugar from the readily available and inexpensive glucosamine. There are reports of the conversion of protected glucosamines to their epimeric galactosamines, but all published routes suffer from either excessive length, poor yields, or the need for harsh reaction conditions. Gross et al. converted a 4,6-dimesylate derivative of glucosamine to the corresponding galactosamine by a double displacement with potassium acetate.[2] More recently, an enzymic deacetylation of the primary 6-acetate of an *N*-acetylglucosamine derivative was employed as the key step in a synthetic sequence culminating in the displacement of a 4-triflate by cesium acetate,[3] and Takeda and Horito have shown that a 4-triflate of a glucosamine derivative can undergo intramolecular displacement by neighboring acyl groups to give a product with the galactosamine configuration.[4] Our aim was to develop a high-yielding, relatively short route to galactosamine derivatives for application to carbohydrate-based libraries.

Allosamine (2-amino-2-deoxyallose) is a relatively rare amino sugar. It is not commercially available, and only in 1986 was it found to exist naturally, constituting the disaccharide moiety of the powerful and selective chitinase inhibitor, allosamidin.[5]

Results and Discussion

Our first synthetic strategy to the galactosamine donor **7** is shown in Scheme 1. The thioacetate **1**[6] was deacetylated with sodium methoxide in methanol, and then the resulting thiolate was methylated in situ with iodomethane to give the thioether **2** in excellent yield. Protection of the 4- and 6-hydroxyl groups of compound **2** as the benzylidene derivative proved to be difficult, and after much experimentation the best conditions found employed camphorsulfonic acid as a catalyst in neat benzaldehyde, which gave the acetal **3** in moderate yield. Conversion of the remaining hydroxyl group of compound **3** to the benzoate ester was accomplished with benzoic anhydride in pyridine to give compound **4**, and then the benzylidene acetal was removed with warm aqueous acetic acid to give the diol **5**. Conversion of compound **5** to the dimesylate **6** was achieved with methanesulfonyl chloride in pyridine.

Displacement of the mesylate groups in compound **6** was attempted with several nucleophiles, including nitrite ion and acetate ion, without success. However, conversion of the dimesylate **6** to the tribenzoate was accomplished with sodium benzoate in hot DMF, giving compound **7** with the desired galactosamine configuration, in very good yield.

In an attempt to shorten the synthetic route, we envisioned a procedure whereby we would take advan-

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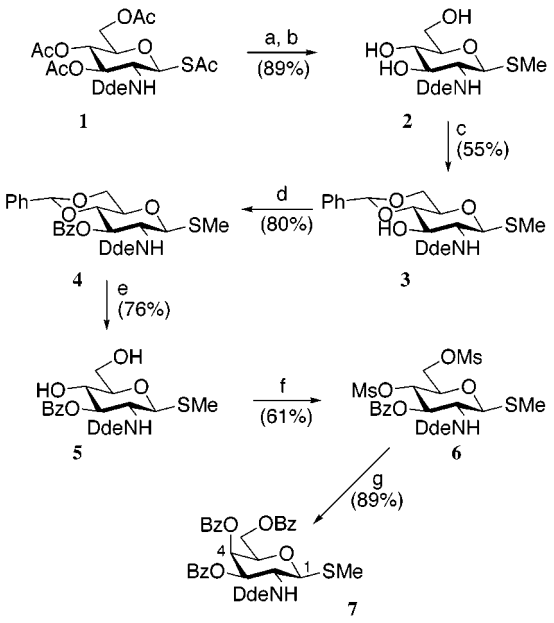
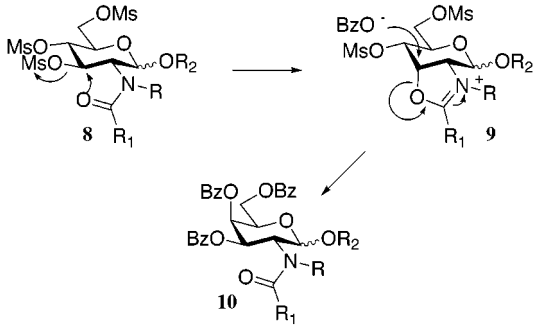
Scheme 1[a]

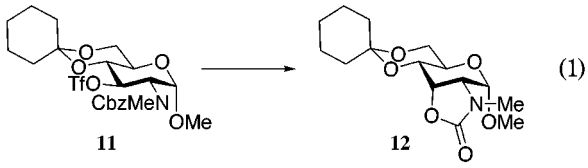


[a] Reagents and conditions: (a) NaOMe, MeOH, rt; (b) MeI, rt; (c) PhCHO, CSA, rt; (d) $(PhCO)_2O$, pyridine, DMAP, 0 °C to rt; (e) HOAc, H_2O, 65 °C; (f) MsCl, CH_2Cl_2, pyridine, −15 °C to rt; (g) NaOBz, DMF, 140 °C. Bz = benzoyl; Dde = 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl; CSA = camphorsulfonic acid.

Scheme 2



tage of the protecting group on the amine to control the stereochemistry at position 3, via neighboring group participation. Our plan was to use the *N*-acyl group of compound **8** to displace the mesylate at the position 3, forming an intermediate oxazolinium ion **9**. This would be opened by subsequent intermolecular attack by the benzoate nucleophile, giving compound **10** with overall retention of configuration at position 3. In conjunction with inversion of configuration at position 4, this procedure would result in the product **10** having the required galactosamine configuration (Scheme 2). There is some literature precedence to support this hypothesis. For example, the triflate **11** has been shown to undergo facile ring closure to the oxazolidinone **12** by warming in pyridine solution[7] (eq 1), and similar reactions, also in the glucosamine series, have been reported.[8,9] We are not aware, however, of any examples of carbohydrate-derived oxazolinium ions such as **9** reacting intermolecularly with nucleophiles.



(1)

To investigate the possible differing reactivities of glucosamine substrates possessing N-protection with differing electron-withdrawing strengths, we examined the reactions of the *N*-acetyl **21**, the *N*-benzyloxycarbonyl **23**, and the *N*-phthaloyl derivatives **17** of glucosamine.

The route to the trimesylate **17** is outlined in Scheme 3. Reaction of glucosamine hydrochloride **13** with phthalic anhydride in aqueous sodium bicarbonate gave the phthaloyl derivative **14** in moderate yield.[10] Acetylation of compound **14** under standard conditions afforded the crystalline tetraacetate **15**, which was obtained as a 5:1 mixture of α/β anomers. Tetraacetate **15** was converted to the triol **16** via the intermediate anomeric bromide,[10] and mesylation of compound **16** gave the crystalline trimesylate **17**. When the trimesylate **17** was stirred in hot DMF with an excess of sodium benzoate, the dibenzoate **18**, possessing the required galactosamine configuration, was obtained in almost quantitative yield. This result demonstrated that the phthaloyl protecting group on the amine of compound **17** did not participate in the displacement of the mesylate at position 3, as had been anticipated (Scheme 2). Indeed, substitution at position 3 of compound **17** was prevented.

We have also examined the analogous displacement reaction of the *N*-acetylglucosamine derivative **21**. This compound (**21**) was prepared by the route outlined in Scheme 4. Refluxing *N*-acetylglucosamine **19** with acidic ion-exchange resin in methanol led to the methyl glycoside **20**,[11] obtained as the pure α-anomer after two recrystallizations from 2-propanol. The triol **20** was converted to the crystalline trimesylate **21** with methanesulfonyl chloride in pyridine.[12] Treatment of compound **21** under the same conditions used to convert trimesylate **17** to compound **18** (sodium benzoate in hot DMF) gave an unexpected result. Unlike the case of compound **17**, where the mesylate at position 4 was displaced and the mesylate at position 3 was unreactive, compound **21** displayed the opposite reactivity. Thus, the 4-mesylate group of compound **21** proved to be unreactive, and the 3-mesylate underwent displacement to give the dibenzoate **22**, with the allosamine configuration. Again it seems that the *N*-acetyl group did not participate in the 3-mesylate displacement as had been anticipated. The lack of reactivity of the 3-mesylate of compound **17**, when compared with trimesylate **21**, was most likely due to a combination of steric and dipolar effects.

The reaction of the trimesylate **23** derived from *N*-benzyloxycarbonylglucosamine was also examined. Reaction of the trimesylate **23** [13] with sodium benzoate in DMF at 140 °C led only to decomposition, and no identifiable products could be isolated. When the reaction was repeated, but at a lower temperature, the monoben-

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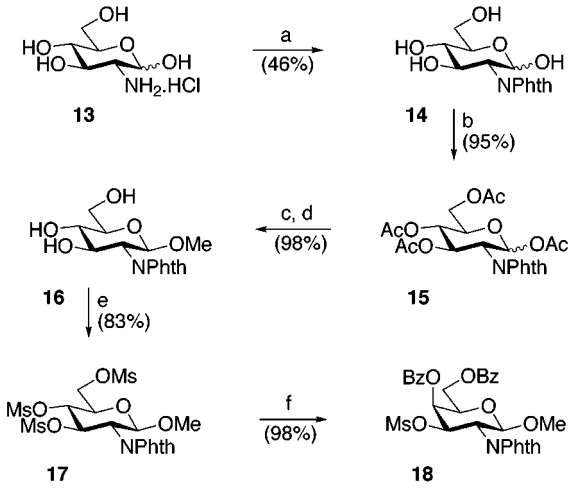
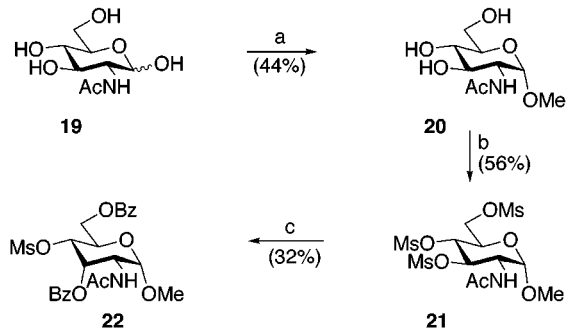
Scheme 3[a]



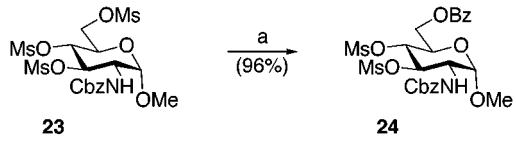
[a] Reagents and conditions: (a) phthalic anhydride, $NaHCO_3$, H_2O, rt; (b) Ac_2O, pyridine, rt; (c) 33% HBr/AcOH, rt; (d) MeOH, rt; (e) MsCl, 0 °C to rt; (f) NaOBz, DMF, 140 °C.

Scheme 4[a]



[a] Reagents and conditions: (a) Dowex (H^+), MeOH, reflux; (b) MsCl, pyridine, 4 °C; (c) NaOBz, DMF, 140 °C.

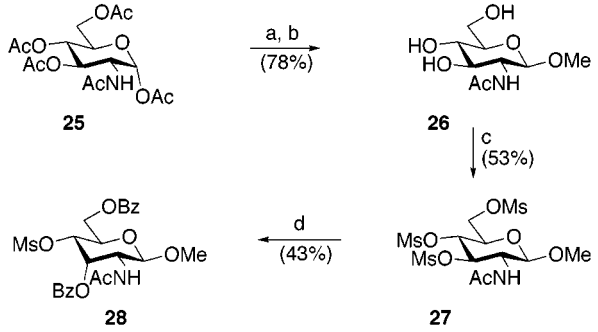
zoate **24**, arising from single displacement of the primary mesylate of compound **23** by benzoate ion, was obtained in excellent yield (eq 2; (a) NaOBz, DMF, 100 °C).



(2)

We initially attributed the remarkable difference in reactivities of the trimesylates **17** and **21** to their different amine protection. However, since compound **17** is a β-glucoside and compound **21** is an α-glucoside, it was conceivable that the configuration of the anomeric group at position 1 was influencing the reactivities of the mesylate groups in these molecules. To clarify this ambiguity, we prepared the trimesylate **27** (the C-1 epimer of **21**) and examined its reactivity under the same reaction conditions, which led to the dibenzoates **18** and **22**. The synthetic route to the trimesylate **27** is shown in Scheme 5. The tetraacetate **25** [3] was converted to the anomeric bromide, and then this was reacted with methanol, leading to the β-methyl glycoside **26**. Compound **26** was converted to the trimesylate **27** with methanesulfonyl chloride in pyridine, and this, when heated with sodium benzoate in hot DMF, gave the dibenzoate **28**, possessing the allosamine configuration,

Scheme 5[a]



[a] Reagents and conditions: (a) 33% HBr/AcOH, rt; (b) MeOH, rt; (c) MsCl, pyridine, 4 °C; (d) NaOBz, DMF, 140 °C.

in a reaction analogous to that shown in Scheme 4 for the α-anomer **21**.

Conclusions

We have shown that the nature of the protecting group on the amino group of glucosamine derivatives can profoundly affect the reactivities of mesylate groups present elsewhere in the molecule. These differing reactivities have allowed us to prepare either galactosamine or allosamine derivatives, in short, high-yielding routes, from inexpensive glucosamine.

Experimental Section

General Methods. Reactions were carried out under argon atmosphere. Solvents were dried according to established procedures by distillation under argon from an appropriate drying agent. Commercially available starting materials and reagents were purchased from Aldrich Chemical Co., Inc. ^{1}H NMR spectra were obtained using either a Bruker AM 500 instrument or a Varian Gemini 300 instrument. ^{13}C NMR were obtained on a Varian Gemini 300 instrument. Chemical shifts are expressed in ppm (δ). Coupling constants are reported in Hz. FAB-MS were obtained on a VG Analytical ZAB-SE instrument, using either 3-nitrobenzyl alcohol or thioglycerol with NaI solution added when no protonated species were observed. Electrospray MS were obtained on a Perkin-Elmer API 3000 instrument using acetonitrile−water as the mobile phase.

Methyl 3,4,6-Tris-*O*-benzoyl-2-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethylamino)-2-deoxy-1-thio-β-D-glucopyranoside (7). The dimesylate **6** (640 mg, 0.98 mmol) and sodium benzoate (1.0 g, 6.9 mmol) were suspended in DMF (20 mL), and the mixture was stirred at 140 °C for 24 h. The mixture was cooled and filtered, and then the filtrate was concentrated and the residue was taken up in EtOAc and refiltered. The filtrate was concentrated to give the tribenzoate **7** as a colorless oil (600 mg, 89%). R_f (1:1 EtOAc/hexane): 0.60. Anal. Calcd for $C_{38}H_{39}NO_9S$: C, 66.56; H, 5.73; N, 2.04. Found: C, 66.49; H, 5.75; N, 2.01. FABMS: 708 $(M + Na)^+$, 686 $(MH)^+$. ^{1}H NMR (500 MHz, ($CDCl_3$) 0.95, 6H, s, 2 × Me; 2.30, 3H, s, SMe; 2.36, 4H, s, 2 × CH_2; 2.57, 3H, s, NCMe; 4.35−4.41, 3H, m, H5,6,6; 4.66−4.69, 1H, m, H2; 4.86, 1H, d (J 9.8), H1; 5.52, 1H, dd (J 10.3, 3.2), H3; 5.99, 1H, d (J 3.3), H4; 7.29−8.12, 15H, m, 15 × Ar-H; 14.01, 1H, br s, NH.

Methyl 2-Phthalimido-2-deoxy-4,6-bis-(*O*-benzoyl)-3-(*O*-methanesulfonyl)-β-D-galactopyranoside (18). Procedure as for compound **7**. Scale: 1.26 mmol. Product **18**: a tan foam, 790 mg (98%). ES-MS: 610 $(MH)^+$, 627 $(M + NH_4)^+$, 632 $(M + Na)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) 2.85, 3H, s, SMe; 3.50, 3H, s, OMe; 4.34, 1H, t (J 6.5), H5; 4.42, 1H, dd (J 11.3, 6.6), $H6_A$; 4.68, 1H, dd (J 11.5, 6.2), $H6_B$; 4.69, 1H, dd (J 11.1, 8.4), H2; 5.38, 1H, d (J 8.4), H1; 5.80, 1H, dd (J 11.1, 3.6), H3; 5.97, 1H, d (J 3.2), H4; 7.35−8.16, 14H, m, 14 × Ar-H. ^{13}C

NMR (75 MHz, $CDCl_3$) 38.3, 52.0, 56.9, 61.9, 68.1, 70.9, 73.1, 99.2, 123.3, 123.4, 128.3, 128.6, 129.3, 129.6, 129.9, 131.5, 133.1, 133.7, 134.1, 165.6, 165.8. HRMS (TOF) calcd for $C_{30}H_{31}N_2O_{11}S$ $(M + NH_4)^+$ 627.1649, found 627.1629.

Methyl 2-Acetamido-2-deoxy-3,6-bis-(*O*-benzoyl)-4-(*O*-methanesulfonyl)-α-D-allopyranoside (22). Procedure as for compound **7**. Scale: 1.26 mmol. Product **22**: purified by flash chromatography and elution with 0−1% MeOH in EtOAc to give a brown gum, 210 mg (32%). ES-MS: 522 $(MH)^+$. ^1H NMR (500 MHz, $CDCl_3$): 2.03, 3H, s, Ac; 3.06, 3H, s, SMe; 3.41, 3H, s, OMe; 4.30, 1H, ddd (*J* 10.5, 4.1, 2.0), H5; 4.33, 1H, br dt (*J* 9.0, 3.6), H2; 4.40, 1H, t (*J* 2.9), H3; 4.53, 1H, dd (*J* 12.3, 4.3), $H6_A$; 4.68, 1H, dd (*J* 12.3, 2.0), $H6_B$; 4.80, 1H, d (*J* 4.1), H1; 4.82, 1H, dd (*J* 10.3, 3.0), H4; 6.49, 1H, d (*J* 9.0), NH; 7.40−7.58 and 8.03−8.06, 10H, m, 10 × Ar-H. ^{13}C NMR (75 MHz, $CDCl_3$): 22.9, 38.7, 49.0, 56.1, 62.5, 62.6, 68.9, 74.3, 98.7, 128.4, 128.5, 128.6, 132.9, 133.0, 133.2, 166.1, 170.0. HRMS (TOF): calcd for $C_{24}H_{28}NO_{10}S$ $(M + H)^+$ 522.1434, found 522.1414.

Methyl 6-*O*-Benzoyl-2-benzyloxycarbonylamino-2-deoxy-3,4-bis-(*O*-methanesulfonyl)-α-D-glucopyranoside (24). Procedure as for compound **7**, except that compound **23**[13] was heated at 100 °C. Scale: 1.26 mmol. Product **24**: purified by dissolving in a small amount of EtOAc/hexane (1:1) and filtering through a plug of silica. Evaporation of the filtrate gave a colorless foam, 730 mg (96%). R_f (1:1 EtOAc/hexane): 0.50. ES-MS: 588 $(MH)^+$, 605 $(M + NH_4)^+$, 610 $(M + Na)^+$. ^1H NMR (300 MHz, $CDCl_3$): 2.85, 3H, s, SMe; 3.15, 3H, s, SMe; 3.36, 3H, s, OMe; 4.06−4.20, 2H, m, H2 and H5; 4.52, 1H, dd (*J* 4.2, 12.4), $H6_A$; 4.75, 1H, d (*J* 3.4), H1; 4.78, 1H, br d (*J* 12.1), $H6_B$; 4.90, 1H, t (*J* 9.5), H3; 4.93, 1H, t (*J* 9.6), H4; 5.04, 1H, d (*J* 12.1), $PhCH_A$; 5.17, 1H, d (*J* 12.1), $PhCH_B$; 5.43, 1H, d (*J* 9.9), NH; 7−28−7.56 and 8.06−8.09, 10H, m, 10 × Ar-H. ^{13}C NMR (75 MHz, $CDCl_3$): 38.4, 38.9, 53.9, 55.5, 62.2, 67.2, 67.8, 73.5, 77.7, 98.3, 128.3, 128.4, 128.6, 129.5, 129.6, 133.0, 135.9, 155.6, 165.9. HRMS (TOF): calcd for $C_{25}H_{32}NO_{12}S_2$ $(M + H)^+$ 588.1209, found 588.1198.

Methyl 2-Acetamido-2-deoxy-3,5-bis-(*O*-benzoyl)-4-(*O*-methanesulfonyl)-β-D-allopyranoside (28). Procedure as for compound **7**. Scale: 0.628 mmol. Product **28**: purified by flash chromatography and elution with 50−100% EtOAc in hexane to give a pale yellow oil, 140 mg (43%). R_f (3:1 EtOAc/hexane): 0.47. ES-MS: 522 $(MH)^+$, 539 $(M + NH_4)^+$, 548 $(M + Na)^+$. ^1H NMR (500 MHz, $CDCl_3$): 1.93, 3H, s, Ac; 3.03, 3H, s, SMe; 3.51, 3H, s, OMe; 4.30−4.36, 1H, m, H5; 4.41, 1H, dt (*J* 3.0, 8.0), H2; 4.49, 1H, dd (*J* 4.4, 12.3), $H6_A$; 4.76, 1H, dd (*J* 3.0, 12.3), $H6_B$; 4.81, 1H, d (*J* 7.9), H1; 5.12, 1H, dd (*J* 3.0, 8.9), H4; 5.96, 1H, d (*J* 8.1), NH; 6.04, 1H, t (*J* 3.0), H3; 7.43−7.66 and 8.05−8.10, 10H, m, 10 × Ar-H. ^{13}C NMR (75 MHz, $CDCl_3$): 23.0, 29.6, 38.9, 51.2, 56.3, 62.6, 69.4, 71.3, 73.1, 100.3, 128.4, 128.5, 128.9, 129.5, 129.7, 129.8, 133.2, 133.9, 165.3, 166.0, 170.0. HRMS (TOF): calcd for $C_{24}H_{28}NO_{10}S$ $(M + H)^+$ 522.1434, found 522.1436.

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Supporting Information Available: The detailed experimental procedures and characterization data for compounds **2**−**6**, **14**−**17**, **20**, **21**, **26**, and **27** and the ^1H NMR spectra of compounds **22**, **24**, and **28**. This information is available free of charge via the Internet at http://pubs.acs.org.

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