Why Are the Hydroxy Groups of Partially Protected *N*-Acetylglucosamine Derivatives Such Poor Glycosyl Acceptors, and What Can Be Done about It? A Comparative Study of the Reactivity of *N*-Acetyl-, *N*-Phthalimido-, and 2-Azido-2-deoxy-glucosamine Derivatives in Glycosylation. 2-Picolinyl Ethers as Reactivity-Enhancing Replacements for Benzyl Ethers

David Crich* and Vadim Dudkin

Contribution from the Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

Received January 9, 2001

Abstract: Competition experiments were used to determine that the 4-OH of a 2-deoxy-2-azidoglucose derivative is more reactive than that of the corresponding *N*-phthalimido glucose derivative which, in turn, is more easily glycosylated than the *N*-acetyl derivative. Glycosylation of the 4-OH groups of the *N*,*N*-diacetyl and *N*-acetyl-*N*-benzyl glucosamine was also found to be superior to that of the simple *N*-acetyl substance. The 3-*O*-picolinyl ether of a 4,6-*O*-benzylidene-protected *N*-acetylglucosamine was shown to have a strong intramolecular hydrogen bond to the adjacent acetamide group. This interaction does not persist in the 3-*O*-picolinyl-6-*O*-benzyl *N*-acetylglucosamine derivative, owing to a probable competing hydrogen bond between the 4-OH and the picolinyl ether. However, in the 3-*O*-picolinyl-4-*O*-benzyl *N*-acetylglucosamine regioisomer the picolinyl-acetamide hydrogen bond persists and leads to an enhancement of reactivity of the 6-OH, over and above that in the corresponding 3-*O*-benzyl ether, due to disruption of the typical intermolecular amide hydrogen bonding scheme. It is demonstrated that the picolinyl ether is readily removed by hydrogenolysis at atmospheric pressure and room temperature.

Introduction

Part of the perceived wisdom in preparative carbohydrate chemistry is that the 4-hydroxy group of *N*-acetyl glucosamine derivatives (e.g., **1**) is a very poor nucleophile (glycosyl acceptor) in glycosylation reactions.[1] We have no reason to doubt this principle. Indeed in our own work on β-mannosylation, methyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (the anomer of **1**) was by far the least reactive of a spectrum of primary, secondary, and tertiary alcohols assayed.[2] This lack of reactivity is unfortunate and severely hampers the synthesis of a very broad spectrum of biologically important oligosaccharides and glycoconjugates in which glycosidic bonds to the *N*-acetyl glucosamine 4-OH are an essential component.[3−6] Not the least of these is the common core pentasaccharide of the *N*-linked glycoproteins, the very heart of which is an exceptionally difficult β-mannoside of *N*-acetylglucosamine 4-OH.[3−6] In view of the importance of such linkages numerous strategies have evolved with the aim of circumventing the lack of reactivity of the said hydroxy group. Chief among these has been the use of 2-azido-2-deoxy-glucopyranosides (e.g., **2**) and of *N*-phthalimido glucosaminopyranosides (e.g., **3**), both of which necessitate adjustment of the amino functionality after glycosylation. Interestingly, given the very widespread application of these two derivatives,[7] there appears to have been no systematic comparison of their reactivity.[8] The aims of the investigations set out here were multiple and included: (i) determination of the relative reactivities of **1**, **2**, and **3**, (ii) understanding why **1** is such a poor nucleophile, and (iii) using that understanding to design and develop simpler, better surrogates for **1**.

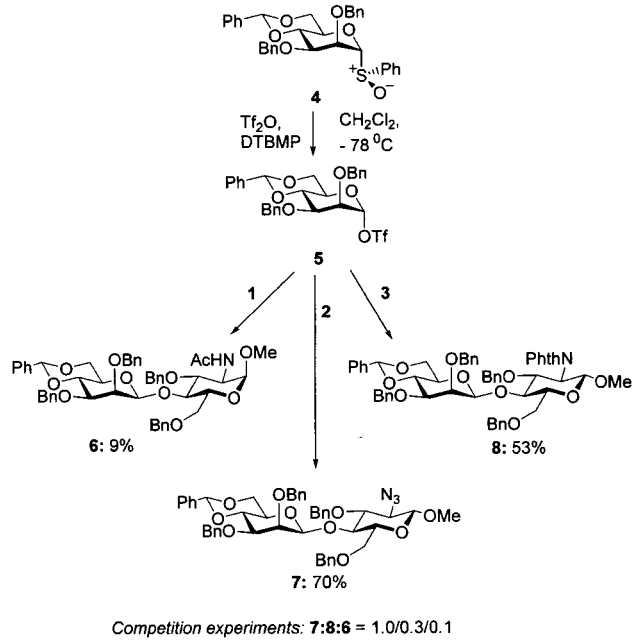
Results and Discussion

We began our study with the preparation of the two known acceptors **1**,[9] and **3**.[10,11] and a third very readily prepared one **2**, which was accessible by standard methods.[12] Each was coupled under a set of standard conditions with the mannosyl sulfoxide **4**,[2] which was activated to triflate **5**[13] prior to addition

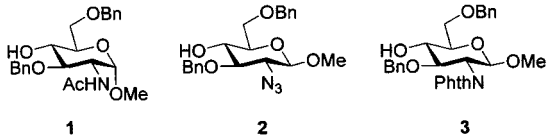
(1) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−224.
(2) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(3) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.
(4) Varki, A. *Glycobiology* **1993**, *3*, 97−130.
(5) Lehmann, J. *Carbohydratres. Structure and Biology*; Thieme: Stuttgart, 1998.
(6) *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; OUP: New York, 1999; p 624.
(7) For some of the many examples see the chapters by Schmidt, R. R.; Jung, K.-H., by Nicolaou, K. C.; Ueno, H., and by Fraser-Reid, B.; Madsen, R. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.
(8) Debendham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann./Recl.* **1997**, 791−802.
(9) Rana, S. S.; Barlow, J. J.; Matta, K. L. *Carbohydr. Res.* **1983**, *113*, 257−271.
(10) Alais, J.; David, S. *Carbohydr. Res.* **1990**, *201*, 69−77.
(11) van der Ven, J. G. M.; Kerekgyarto, J.; Kamerling, J. P.; Liptak, A.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1994**, *264*, 45−62.
(12) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073−2077.
(13) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

10.1021/ja010086b CCC: $20.00
Published on Web 06/21/2001

Scheme 1



of the acceptors (Scheme 1). In each case the saccharides were isolated and shown to be the β-anomers, as anticipated, on the basis of the mannose H-5 chemical shift and the mannose $^1J_{CH}$ anomeric coupling constant.[2] The byproducts from these reactions were not quantified but did consist in the main of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-mannopyranose as is typical in couplings to less reactive alcohols by this method.

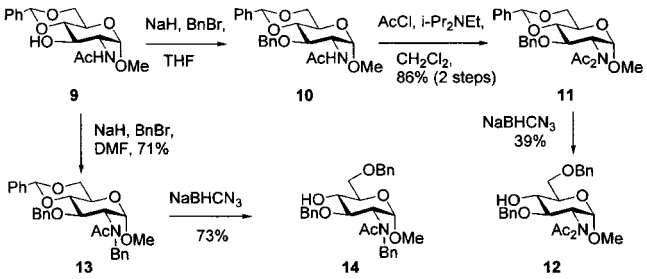


With authentic samples of **6**, **7**, and **8** in hand a competition experiment was conducted in which **4** was allowed to react, via **5**, with an equimolar mixture of **1**, **2**, and **3**. Analysis of the crude reaction mixture by HPLC determined the ratio of **6**:**7**:**8** to be 0.1:1.0:0.3 with good agreement from two separate experiments. These simple experiments demonstrate that with a reactive glycosyl donor, such as **5**, the azido acceptor **2** is some 10 times more reactive than the *N*-acetyl acceptor **1**, with the phthalimido-protected glucosamine acceptor **3** falling between the two. The azide **2** is therefore clearly the acceptor of choice for such couplings.

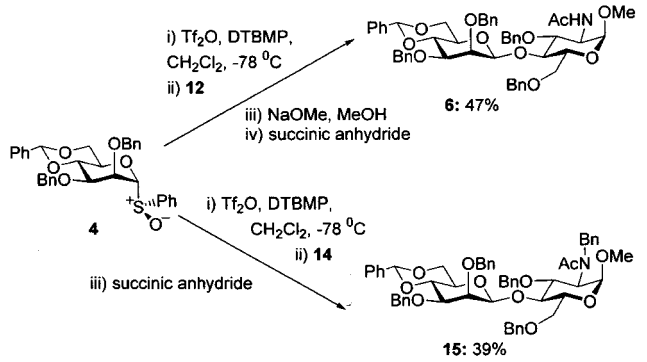
N,*N*-Diacetylglucosamine derivatives and *N*-benzyl-*N*-acetylglucosamines have been previously employed as glycosyl donors but not as acceptors. Accordingly, we prepared the imide **12** and tertiary amide **14** as set out in Scheme 2.

Coupling of **12** with sulfoxide **4** under the standard conditions gave a crude reaction mixture that was complicated by partial imide hydrolysis, both at the level of unreacted **12** (giving **1**) and in terms of the coupled product. The crude reaction mixture was therefore treated with sodium methoxide in methanol to complete hydrolysis of the imides to the acetamides. Subsequent treatment of the reaction mixture with succinic anhydride, to render any alcohols present more polar, and chromatography on silica gel enabled isolation of disaccharide **6** in 47% yield (Scheme 3). Coupling of **14** and sulfoxide **4** was more straightforward, although it was again necessary to derivatize the residual alcohols as hemisuccinates to facilitate separation,

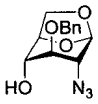
Scheme 2



Scheme 3



and resulted in the isolation of disaccharide **15** in 39% yield (Scheme 3). An experiment in which equimolar quantities of **1** and **14** were allowed to compete for triflate **5** produced disaccharides **6** and **15**, respectively, in the ratio 1/2.2. No such competition experiment could be conducted between **1** and **12**, owing to the partial deacetylation of the disaccharide derived from **12** (vide supra). It is nevertheless evident that both **12** and **14** are superior to **1** and somewhat comparable to phthalimide **3** in terms of reactivity as glycosyl acceptors, but inferior to azide **2**. Unfortunately, both harbor undesirable characteristics: the instability of the imide function in **12** and the complication of NMR spectra due to the presence of two amide rotamers in **14**, which render them less attractive in general than **3** and, especially, **2**.



A final option, the 1,6-anhydro-2-deoxy-2-azido glucose derivative **16** was excluded from our study as, although it is a moderately reactive mannosyl acceptor, the β/α-selectivity was a less than optimal 5/1.[2] Moreover, the preparation of **16** is somewhat lengthy and detracts from its overall usefulness.[14,15] All in all, it is clear that among the spectrum of *N*-acetylglucosamine derivatives currently available as acceptors the 2-azido-2-deoxy-system is the most reactive one, at least in β-mannosylations as practiced in this laboratory.

It is patently obvious that **1** differs from its more reactive surrogates **2**, **3**, **12**, **14**, and **16** by the possession of an amide N−H capable of hydrogen bonding. Similarly, it requires no great leap of imagination to surmise that it is hydrogen bonding that is in some way responsible for the lack of reactivity of **1**. Following this line of thought we reasoned that disrupting any

(14) Tailler, D.; Jacquinet, J.-C.; Noirot, A.-M.; Beau, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3163−3164.

(15) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346−1353.

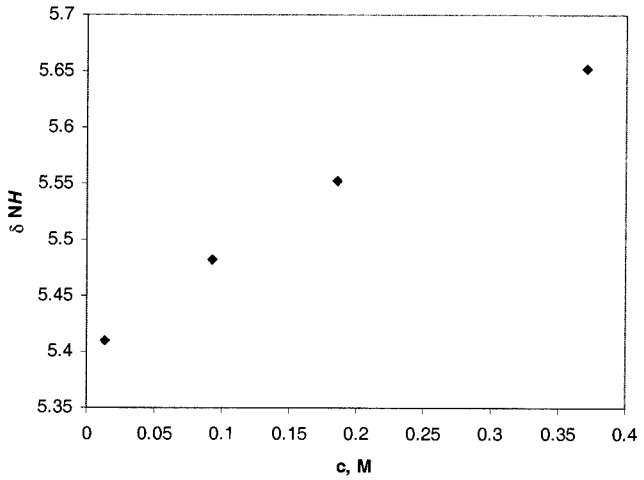


Figure 1. Concentration dependence of the N*H* chemical shift of **1** in $CDCl_3$ at room temperature.

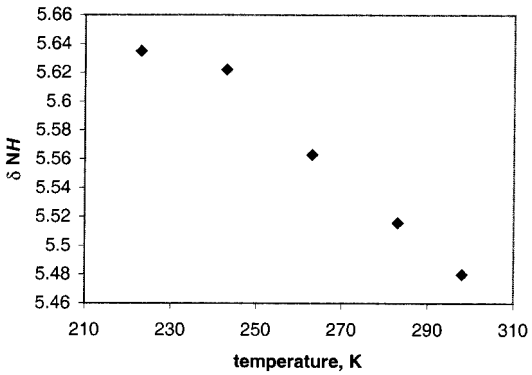


Figure 2. Chemical shift temperature dependence of the N*H* in a 0.05 M $CDCl_3$ solution of **1**.

hydrogen bonding would increase the reactivity of **1** and thus, perhaps, enable us to design a simple reactive *N*-acetylglucosamine derivative. Ideally, such a derivative would not require deprotection of any latent amide after coupling, such as is required with each of the surrogates studied above. An essential prerequisite to design is understanding, and therefore, we first investigated the nature of any hydrogen bonding, intra- or intermolecular, in **1**. Vasella has conducted an extensive study of hydrogen bonding in a wide range of *N*-acetylglycosamine derivatives and has found examples of both intra- and intermolecular hydrogen bonding, in nonpolar solvents, depending on the configuration at the two flanking ring carbons.[16,17] We therefore investigated the concentration and temperature dependence of the N*H* in $CDCl_3$ solution for **1**. At room temperature δ_{NH} of **1** fell off almost linearly with concentration (Figure 1) which strongly suggests an intermolecular phenomenon. Linear regression of the $\Delta\delta/\Delta T$ plot (Figure 2) taken for a 0.05 M solution of **1** gave a "reduced temperature coefficient" of −2.1. In nonpolar solvents such as $CDCl_3$ a coefficient of this magnitude is usually interpreted as being characteristic of an intramolecular hydrogen bond or of a non-hydrogen-bonded state.[16−19] We note that the interpretation of $\Delta\delta/\Delta T$ values is not as straightforward in relatively nonpolar solvents as it is in

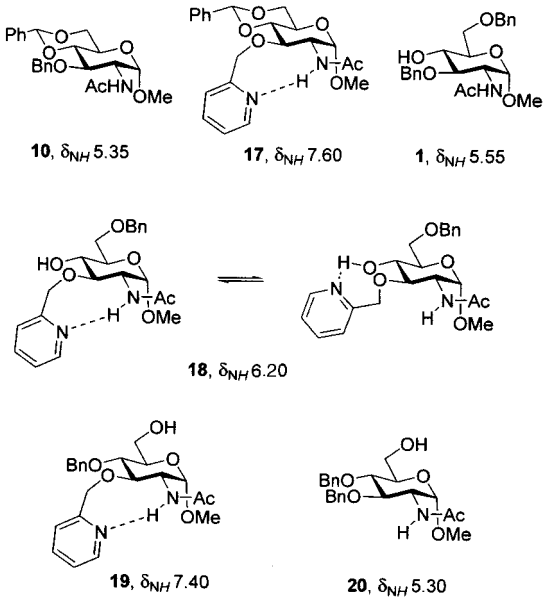


Figure 3.

both DMSO and water.[20] It seems apparent that there is neither a pure intermolecular nor a pure intramolecular hydrogen-bonding scheme in $CDCl_3$ solutions of **1**. Rather it is likely that a dynamic situation, incorporating both, exists and that this will increasingly favor the intermolecular system at the lower temperatures and higher concentrations of the glycosylation reaction.

We therefore focused on a method of disrupting an intermolecular hydrogen-bonding network. The addition of simple heterocycles, capable of binding amides, to the reaction medium was briefly considered and dismissed on the grounds that any group sufficiently exposed to bind the amide would almost certainly also be a competing nucleophile in glycosylation reactions. We therefore turned to the design of novel protecting groups incorporating hydrogen-bond acceptors. Specifically we hypothesized that a 3-*O*-(2-picolinyl) ether, replacing a benzyl ether, would be ideally poised to form a hydrogen bond with the adjacent acetamide N*H*, thereby disrupting the intermolecular hydrogen-bonding system. Toward this end a solution of alcohol **9** in THF was treated with an excess of sodium hydride followed by *o*-picolinyl chloride hydrochloride. The resulting 3-*O*-Pic ether **17** was isolated in 96% yield as a crystalline solid. In $CDCl_3$ solution at room temperature a 0.04 M solution of **17** had δ_{NH} of 7.60, which, when contrasted with that of δ_{NH} of 5.35 for **10** under the same conditions of temperature and concentration, was suggestive of the formation of a strong intramolecular hydrogen bond (Figure 3). Reduction of **17** with sodium cyanoborohydride and HCl in ether, according to the standard Garegg conditions,[21] afforded 6-*O*-benzyl derivative **18** in 75% yield. Unfortunately, the intramolecular hydrogen bond was not nearly as strong in **18** as demonstrated by the δ_{NH} of 6.20. We attribute this to both the 4-O*H* and the 2-N*H* competing to form a hydrogen bond with the picolinyl group which has the effect of restoring the intermolecular hydrogen-bonding capabilities of the amide (Figure 3). This, in retrospect, obvious problem was confirmed by reduction of **17** with

(16) Fowler, P.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 269−287.

(17) Vasella, A.; Witzig, C. *Helv. Chim. Acta* **1995**, *78*, 1971−1982.

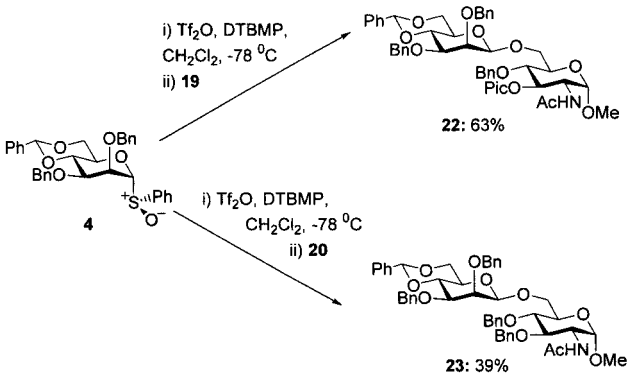
(18) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164−1173.

(19) Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048−7050.

(20) For application of $\Delta\delta/\Delta$T relationships to carbohydrates in polar solvents see: Buffington, L. A.; Blackburn, D. W.; Hamilton, C. L.; Jarvis, T. C.; Knowles, J. J.; Lodwick, P. A.; McAllister, L. M.; Neidhart, D. J.; Serumgard, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 2451−2454.

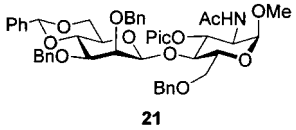
(21) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97−101.

Scheme 4



dibutylboron triflate·THF.[22] This reaction provided the regioisomer **19** in 87% yield, whose δ_{NH} of 7.40 at the same temperature and concentration again suggested a strong intramolecular hydrogen bond (Figure 3). This chemical shift is to be contrasted with that of 5.30 determined for the 3-*O*-benzyl analogue **20** under the standard conditions.

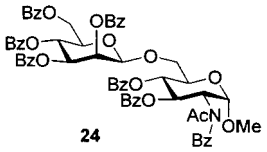
The lack of effectiveness of the 3-*O*-Pic ether in **18** was confirmed on attempted coupling to **4** under the standard conditions when the disaccharide **21** was isolated in only 8% yield. Evidently, **18** is neither better nor worse than **1** as a glycosyl acceptor in the sulfoxide-mediated β-mannosylation sequence.



21

Although the 6-OH group is somewhat further removed than the 4-OH from the 2-NHAc, it might reasonably be expected that the hydrogen-bonding acetamide NH might still have a detrimental, albeit reduced, effect on the reactivity of *N*-acetylglucosamine 6-OH in glycosylation. Indeed, in our initial work on β-mannosylations we noted that methyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside was significantly less reactive than methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside.[2] This being the case the 3-*O*-Pic derivative **19** should be a better glycosyl acceptor than the 3-*O*-benzyl analogue **20**. In the event, in separate couplings under the standard conditions, the isolated yields of disaccharides **22** and **23** were 63 and 39%, respectively (Scheme 4). The approximately 50% increase in yield with the 3-*O*-Pic acceptor does not reveal the full extent of the advantages that **19** presents over **20**. These reside, in addition to the increased yield, in the cleaner reaction mixture, resulting from higher conversion, and thus greatly facilitated isolation. As with acceptors **1**−**3** a set of reactions were conducted in which the glycosyl triflate **5** derived from **4** was invited to compete for coupling with an equimolar mixture of **19** and **20**. In each of three separate competition experiments **19** was found to be approximately twice as reactive as **20**. We consider these experiments with **19** and **20**, together with the NH chemical shifts set out in Figure 3, to be a proof of the principle that successful disruption of intermolecular hydrogen bonding in *N*-acetylglucosamine derivatives renders them better glycosyl acceptors.

There is little to be gained from the introduction of a novel protecting group if it cannot be removed readily. Disaccharide **22** was therefore subjected to hydrogenolysis over Pearlman's catalyst in methanol/dioxane at room temperature and pressure. As befits a replacement for a benzyl ether, the 3-*O*-Pic group was cleanly removed under these conditions along with the benzyl and benzylidene groups. To facilitate isolation on the small scale employed the disaccharide hexol obtained from the hydrogenolysis was immediately converted to the heptabenzoate **24**, which was isolated in 66% overall yield for the two steps.



24

All of the couplings employed in the proof of concept experiments described above were made using our β-mannoside adaptation[2] of Kahne's sulfoxide method.[23,24] This was not only because β-mannosylation continues to be a focus of our research[25,26] but also because the Kahne method enables glycosylation of some of the most delicate and unreactive acceptors,[23,27] yet does not fare well with the *N*-acetylglucosamines, as we have demonstrated. Nevertheless, it was felt that a brief investigation of another popular glycosylation method, namely Schmidt's trichloroacetimidate method,[28] was justified. To this end, in parallel reactions, the trichloroacetimidate **25** was activated in dichloromethane with catalytic TMSOTf in the presence of **19** and **20**. Coupling with **20** was smooth, and disaccharide **26** was isolated in 26% yield as a 1/1 α/β mixture. With acceptor **19**, however, no reaction was observed, and the trichloroacetimidate was found to be essentially unchanged in the recovered reaction mixture. We rationalize this observation in terms of the picolinyl group in **19** binding the TMSOTf and so preventing activation of the donor. We conclude that the picolinyl ethers will not be compatible with glycosylation methods requiring donor activation by Lewis acids. On the other hand any method conducted in the presence of excess base should be compatible with the picolinyl ether. One such method is the new dehydrative glycosylation, introduced by Gin and co-workers, in which a glycopyranose is activated with a combination of diphenyl sulfoxide, triflic anhydride, and a hindered base.[29,30] To test this hypothesis **27** was coupled in separate flasks with 1 equiv of **19** or **20** with activation by the diphenyl sulfoxide/Tf_2O combination in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP). With **19** an 87% isolated yield of disaccharide **28** was obtained, whereas with **20** the yield of disaccharide **26** was only 18% after the same reaction time. It is therefore clear that the reactivity-enhancing advantages of the picolinyl ether are not confined to the sulfoxide method. We also stress here the application of the crystalline, hindered base TTBP that we have very recently introduced as cost-effective replacement for the very widely used, but expensive, low-melting and hygroscopic DTBMP.[31]

(22) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355−358.

(23) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.

(24) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239−9248.

(25) Crich, D.; Dudkin, V. *Org. Lett.* **2000**, *2*, 3941−3943.

(26) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067−4069.

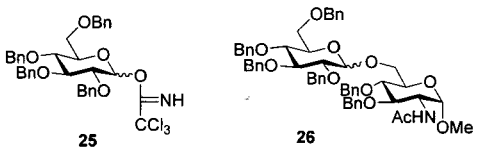
(27) Thompson, C.; Ge, M.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 1237−1244.

(28) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.

(29) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

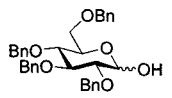
(30) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

(31) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.

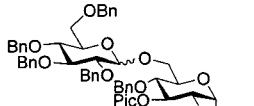


25

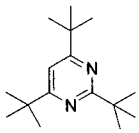
26



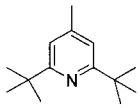
27



28



TTBP



DTBMP

The experiments presented here establish the principle of using 2-picolinyl ethers to disrupt intermolecular hydrogen bonding of adjacent amides and so of enhancing the reactivity of *N*-acetylglucosamine hydroxyl groups. The method falls down when the picolinyl ether is sandwiched immediately between the amide and the reactive hydroxyl group, as in **18** owing to a competition for the hydrogen bond accepting pyridine nitrogen. This renders the method ineffective in terms of enhancing the reactivity of the *N*-acetylglucosamine 4-OH, the most important of the cases considered, by means of a 3-*O*-picolinyl ether. In principle this situation can be overcome by locating a suitable hydrogen bond acceptor at the anomeric position of *N*-acetylglucosamine from where hydrogen bonding with the 4-OH group is unlikely to compete. It is unlikely, however, that a simple 2-picolinyl glycoside will suffice since, to form a hydrogen bond with the 2-acetamido group, the exo-anomeric effect must be overcome. Indeed, picolinyl 2-acetamido-3,4,6-tri-*O*-acetyl-*β*-D-glucoside showed no evidence for the formation of hydrogen bond between the pyridine and the acetamide. Studies directed toward the design and implementation of a suitable anomeric group are currently underway and will be reported in due course.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were run at 500 and 125 MHz, respectively, unless otherwise stated. All solvents were dried and distilled by standard procedures. All reactions were run under a dry argon atmosphere. Triflic anhydride was distilled from phosphorus pentoxide.

Methyl 2-Azido-2-deoxy-3,6-di-*O*-benzyl-*β*-D-glucopyranoside (2). Methyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**3**)[10,11] (471 mg, 0.94 mmol) and ethylenediamine (2.76 mL, 46 mmol) were dissolved in ethanol (10 mL), and the reaction mixture was refluxed for 15 h and concentrated. The residue was dissolved in acetonitrile (10 mL) together with DMAP (116 mg, 0.94 mmol), cooled to 0 °C, and TfN_3 (5.88 mL of 0.4 M solution, 2.35 mmol) was added dropwise. The reaction mixture was stirred for 20 h at room temperature and concentrated. The residue was purified by flash chromatography to give azide (**2**) as colorless oil (364 mg, 97%). $[\alpha]_D = -4.0°$ (c = 2.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 2.73 (br s, 1H), 3.28 (dd, J = 10.0, 11.5 Hz, 1H), 3.35−3.43 (m, 2H), 3.57 (s, 3H) 3.66 (t, J = 11.0 Hz, 1H), 3.74−3.79 (m, 2H), 4.19 (d, J = 8.3 Hz, 1H), 4.57 (d, J = 12.8 Hz, 1H), 4.65 (d, J = 12.8 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.93 (d, J = 11.0 Hz, 1H), 7.30−7.52 (m, 10H); FAB-HRMS: Calcd for $C_{21}H_{25}N_3O_5$ $[M + Na]^+$ 422.1692, Found: 422.1693.

General Mannosylation Protocol. To a stirred solution of sulfoxide **4**[2] (0.2 mmol) and DTBMP (82.1 mg, 0.4 mmol) in CH_2Cl_2 (8.0 mL) at −78 °C was added Tf_2O (37.0 mL, 0.22 mmol) and, 5 min later, the solution of the glycosyl acceptor (0.4 mmol) in CH_2Cl_2 (2 mL) dropwise. The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to 0 °C over 2 h and maintained there for a further 0.5 h before quenching with saturated aqueous $NaHCO_3$, washing with brine, drying, concentrating, and purifying by chromatography on silica gel.

Methyl 2-Acetamido-2-deoxy-3,6-di-*O*-benzyl-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl]-(1→4)-α-D-glucopyranoside (6). Alcohol **1**[9] was coupled to donor **4**, according to the general protocol to give **6** as a white foam in 9% yield. $[\alpha]_D = +22.8°$ (c = 0.50, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.84 (s, 3H), 3.10 (dt, J = 4.8, 9.7 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.36−3.42 (m, 1H), 3.50−3.63 (m, 5H), 3.71 (d, J = 3.0, 10.7 Hz, 1H), 3.99 (t, J = 9.7 Hz, 1H), 4.08 (t, J = 9.5 Hz, 1H), 4.11−4.22 (m, 2H), 4.36 (d, J = 12.0 Hz, 1H), 4.46 (s, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.1 Hz, 1H), 4.73 (d, J = 3.7 Hz, 1H), 4.76 (d, J = 11.6 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 4.89 (d, J = 11.7 Hz, 1H), 4.95 (d, J = 12.1 Hz, 1H), 5.23 (br d, J = 8.4 Hz, 1H), 5.52 (s, 1H), 7.21−7.50 (m, 25H); ^{13}C NMR (75 MHz) δ 52.4, 55.3, 67.4, 68.6, 68.7, 70.5, 72.8, 73.7, 74.4, 75.1, 77.3, 78.0, 78.3, 78.5, 78.9, 98.6, 101.5, 101.9, 128.3, 128.4, 128.5, 128.7, 128.9, 137.8, 138.8, 138.9, 139.4, 169.9; FAB-HRMS: Calcd for $C_{50}H_{55}NO_{11}$ $[M + H]^+$ 846.3853, Found: 846.3696.

Methyl 2-Azido-2-deoxy-3,6-di-*O*-benzyl-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl]-(1→4)-*β*-D-glucopyranoside (7). Alcohol **2** was coupled to donor **4** according to the general protocol to give **7** as a colorless oil in 70% yield. $[\alpha]_D = -38.8°$ (c = 2.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 3.08 (dt, J = 4.7, 9.7 Hz, 1H), 3.31 (m, 1H), 3.36 (s, 3H), 3.37−3.45 (m, 3H), 3.50 (t, J = 10.4 Hz, 1H), 3.58 (s, 3H), 3.65 (dd, J = 1.8, 11.1 Hz, 1H), 3.78 (m, 1H), 3.97 (t, J = 9.0 Hz, 1H), 4.01−4.17 (m, 3H), 4.39 (d, J = 12.3 Hz, 1H), 4.49 (s, 1H), 4.56−4.68 (m, 4H), 4.76 (d, J = 12.5 Hz, 1H), 4.80 (d, J = 12.8 Hz, 1H), 4.89 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 10.7 Hz, 1H), 5.53 (s, 1H), 7.23−7.54 (m, 25H); ^{13}C NMR (75 MHz) δ 57.3, 65.8, 67.5, 68.6, 72.8, 73.8, 74.9, 75.3, 77.2, 78.5, 78.9, 81.7, 101.50, 101.53, 103.0, 126.2, 127.5, 127.7, 128.0, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 129.0, 129.2, 137.8, 138.6, 138.7; FAB-HRMS: Calcd for $C_{48}H_{51}N_3O_{10}$ $[M + H]^+$ 830.3653, Found: 830.3727.

Methyl 3,6-Di-*O*-benzyl-2-phthalimido-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl]-(1→4)-*β*-D-glucopyranoside (8). Alcohol **3**[10,11] was coupled to donor **4** according to the general protocol to give **8** as a colorless oil in 53% yield. $[\alpha]_D = +7.4°$ (c = 0.78, $CHCl_3$); ^{1}H NMR (300 MHz) δ 3.14 (dt, J = 4.2, 9.8 Hz, 1H), 3.40 (s, 3H), 3.42 (m, 1H), 3.50 (m, 1H), 3.58 (m, 2H), 3.69 (dd, J = 2.8, 10.7 Hz, 1H), 3.75 (d, J = 3.0 Hz, 1H), 4.05 (m, 2H), 4.15 (m, 2H), 4.25 (m, 2H), 4.42 (d, J = 12.1 Hz, 1H), 4.44 (d, J = 12.1 Hz, 1H), 4.54 (br s, 1H), 4.59 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 12.8 Hz, 1H), 4.75 (d, J = 12.4 Hz, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.88 (d, J = 12.6 Hz, 1H), 4.91 (d, J = 11.8 Hz, 1H), 5.05 (d, J = 8.4 Hz, 1H), 5.52 (s, 1H), 6.82−6.87 (m, 3H), 6.91−6.96 (m, 2H), 7.21−7.52 (m, 20H), 7.60−7.80 (m, 4H); ^{13}C NMR (75 MHz) δ 55.7, 56.8, 67.4, 68.6, 68.7, 72.7, 73.7, 74.8, 74.9, 75.1, 77.3, 78.5, 78.9, 79.6, 99.4, 101.5, 102.0, 107.0, 123.4, 126.2, 127.1, 127.5, 127.7, 127.9, 128.0, 128.2, 128.3, 129.5, 128.7, 129.5, 131.9, 131.8, 137.8, 137.9, 138.7, 138.9; FAB-HRMS: Calcd for $C_{56}H_{55}NO_{12}$ $[M + 2H]^+$ 935.3881, Found: 935.3922.

Competition Experiment. The mixture of acceptors **1**, **2**, and **3**, (0.2 mmol each) was mannosylated as described in general protocol using 0.2 mmol of sulfoxide **4**. The resulting mixture of products was analyzed using HPLC. The ratio of mannosides **6**:**7**:**8** was determined as 0.1:1.0:0.3

Methyl *N*,*N*-Diacetyl-2-amino-2-deoxy-3,6-di-*O*-benzyl-α-D-glucopyranoside (12). Benzylation of **9**[9] gave the known amide **10**,[9] of which 230 mg, (0.56 mmol) and Hunig's base (0.5 mL) were placed in 50 mL flask, and acetyl chloride (1.0 mL) was added, followed by 30 mL of dichloromethane. The resulting solution was stirred for 12 h and then poured into saturated aqueous $NaHCO_3$, extracted with dichloromethane, washed with brine, and concentrated. Short column chromatography afforded methyl *N*,*N*-diacetyl-2-amino-2-deoxy-4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (**11**) (220 mg, 86%), which was immediately used in the next step. ^{1}H NMR (300 MHz) δ 2.27 (s, 6H), 3.36 (s, 3H), 3.72−3.85 (m, 2H), 3.88 (dd, J = 4.6, 9.8

Hz, 1H), 4.30 (dd, $J = 4.6$, 10.0 Hz, 1H), 4.50−4.65 (m, 2H), 4.71 (d, $J = 11.4$ Hz, 1H), 4.73 (d, $J = 3.5$ Hz, 1H), 4.91 (d, $J = 11.4$ Hz, 1H), 5.59 (s, 1H), 7.23−7.51 (m, 10H). The above diacetate (**11**) and $NaBH_3CN$ (250 mg, 4 mmol) were dissolved in 15 mL of THF and cooled to 0 °C, and a 1 M solution of HCl in diethyl ether was added dropwise until gas evolution ceased. The reaction mixture was stirred at this temperature for 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with dichloromethane, washed with brine, and concentrated. Column chromatography gave monoacetate **1** (110 mg, 50%) and title diacetate **12** (87 mg, 39%) as colorless oil, which decomposed on standing and was therefore used immediately in the next step. ^{1}H NMR (300 MHz) δ 2.30 (s, 6H), 2.49 (br s, 1H), 3.35 (s, 3H), 3.66−3.78 (m, 4H), 4.26 (dd, $J = 3.6$, 10.9 Hz, 1H), 4.47 (dd, $J = 7.6$, 10.9 Hz, 1H), 4.55 (d, $J = 12.1$ Hz, 1H), 4.62 (d, $J = 12.1$ Hz, 1H), 4.73 (d, $J = 3.6$ Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.80 (d, $J = 11.6$ Hz, 1H), 7.25−7.38 (m, 10H); ^{13}C NMR (75 MHz) δ 26.6, 55.5, 59.9, 69.8, 70.3, 73.2, 73.6, 73.9, 78.8, 99.8, 127.9, 128.1, 128.7, 138.5, 139.4, 175.9.

Methyl *N*-Acetyl-*N*-benzyl-2-amino-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (13). Alcohol **9**[9] (3.89 g, 12.0 mmol) was dissolved in DMF (100 mL) and treated with NaH (1.0 g, 25 mmol) followed by benzyl bromide (3.0 mL, 25 mmol). The reaction mixture was stirred for 15 h at room temperature and poured into saturated aqueous $NaHCO_3$, extracted with chloroform, washed with brine, and concentrated. The residue was separated by column chromatography to give acetate **10** (860 mg, 16%) and title compound **13** (4.230 g, 71%). $[\alpha]_D = +184.8°$ ($c = 1.25$, $CHCl_3$); ^{1}H NMR δ 1.94 and 2.35 (s, 3H), 2.84 and 2.94 (s, 3H), 3.76−3.95 and 4.01−4.21 (m, 5H), 4.23−4.42 (m, 3H), 4.61−4.88 and 5.16−5.22 (m, 3H), 5.62 (s, 3H), 7.00−7.55 (m, 15H); ^{13}C NMR (75 MHz) δ 22.0, 45.6, 48.2, 52.1, 54.7, 55.8, 62.0, 62.5, 69.1, 72.7, 73.1, 74.5, 84.0, 100.0, 100.7, 101.2, 125.2−128.9, 137.5, 138.0, 139.0, 138.5, 172.8, 173.0; FAB-HRMS: Calcd for $C_{30}H_{33}NO_6$ [M + H$^+$] 504.2386, Found: 504.2372.

Methyl *N*-Acetyl-*N*-benzyl-2-amino-2-deoxy-3,6-di-*O*-benzyl-α-D-glucopyranoside (14). 4,6-*O*-Benzylidene-protected compound **13** (1.11 g, 2.21 mmol) and $NaBH_3CN$ (1.39 g, 22.1 mmol) were dissolved in THF (70 mL) and cooled to 0 °C, and a 1 M solution of HCl in diethyl ether was added dropwise until gas evolution ceased. The reaction mixture was stirred at this temperature for 2 h, quenched with saturated aqueous $NaHCO_3$, extracted with dichloromethane, washed with brine, and concentrated. Column chromatography gave title alcohol **14** (810 mg, 73%). $[\alpha]_D = +200.3°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR δ 1.90 and 2.31 (s, 3H), 2.71 and 2.82 (s, 3H), 2.95 (br s, 1H), 3.62−3.83 (m, 2H), 4.12 and 4.25 (d, $J = 17.1$, 15.5 Hz, 1H), 4.45−4.61 (m, 3H), 4.62−4.68 and 5.16 (m, 2H), 4.82 and 4.96 (d, $J = 11.9$, 15.5 Hz, 7.01−7.40 (m, 15H); ^{13}C NMR (75 MHz) δ 22.5, 22.8, 46.1, 48.3, 54.7, 54.79, 54.83, 61.3, 65.3, 69.9, 70.8, 72.2, 72.7, 73.85, 73.90, 74.06, 74.9, 76.5, 76.9, 99.5, 99.7, 125.3−128.8, 137.8−139.6, 172.8, 173.9; FAB-HRMS: Calcd for $C_{30}H_{35}NO_6$ [M + Na$^+$] 528.2362, Found: 528.2369.

Methyl *N*-Acetyl-*N*-benzyl-2-amino-2-deoxy-3,6-di-*O*-benzyl-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl]-(1→4)-α-D-glucopyranoside (15). Alcohol **14** was coupled to donor **4** according to the general protocol, and the crude residue was dissolved in dichloromethane (5 mL) together with succinic anhydride (2.0 mmol), $MgBr{\cdot}OEt_2$ (258 mg, 1.0 mmol), and triethylamine (0.2 mL, 1.5 mmol). The resulting mixture was stirred for 3 days, filtered, and subjected to column chromatography to afford title disaccharide **15** (73 mg, 39%). $[\alpha]_D = +39.4°$ ($c = 1.47$, $CHCl_3$); ^{1}H NMR δ 1.86 and 2.29 (s, 3H), 2.77 and 2.86 (s, 3H), 3.08 (m, 1H), 3.30−3.71 (m, 6H), 3.84−4.14 (m, 5H), 4.16−4.48 (m, 4H), 4.55−5.20 (m, 8H), 5.48 and 5.51 (s, 1H), 6.98−7.53 (m, 30H); ^{13}C NMR δ 22.3, 22.8, 29.1, 29.7, 54.7, 54.8, 67.2, 67.3, 68.2, 68.4, 69.8, 70.3, 72.5, 73.3, 73.6, 73.8, 74.3, 74.86, 74.91, 75.0, 75.2, 78.16, 78.22, 78.6, 79.0, 79.3, 99.4, 99.7, 101.25, 101.31, 101.7, 125.2−128.9, 137.6−139.8, 172.7, 173.7; FAB-HRMS: Calcd for $C_{57}H_{61}NO_{11}$ [M + H]$^+$ 936.4323, Found: 936.4384.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2-picolinyl)-α-D-glucopyranoside (17). To the suspension of NaH (400 mg, 10.0 mmol) in THF (5 mL) was added dropwise the solution of alcohol **9** (647 mg, 2 mmol) in the mixture of THF (15 mL) and DMF (15 mL), and the whole was stirred to homogeneity. A solution of 2-picolinyl chloride hydrochloride in DMF (15 mL) was then added slowly with vigorous stirring during 1 h. Stirring was continued for 3 h at which point the reaction was quenched with methanol, concentrated to about half of the volume, and diluted with water. Extraction with ethyl acetate, drying, and concentration afforded a solid residue which, after flash chromatography, gave the title compound **17** as a white solid (796 mg, 96%): mp 232−233 °C; $[\alpha]_D = +84.1°$ ($c = 2.0$, $CHCl_3$); ^{1}H NMR δ 2.05 (s, 3H), 3.39 (s, 3H), 3.76−3.85 (m, 3H), 3.97 (dd, $J = 8.6$, 10.0 Hz, 1H), 4.15−4.19 (m, 1H), 4.28−4.31 (m, 1H), 4.93 (d, $J = 15.0$ Hz, 1H), 5.05 (d, $J = 3.6$ Hz, 1H), 5.06 (d, $J = 15.0$ Hz, 1H), 5.61 (s, 1H), 7.22 (dd, $J = 5.5$, 6.8 Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.37−7.42 (m, 3H), 7.48−7.52 (m, 2H), 7.61 (d, $J = 6.2$ Hz, 1H), 7.68 (dt, $J = 1.7$, 7.5 Hz, 1H), 8.57 (d, $J = 5.0$ Hz, 1H); ^{13}C NMR δ 23.7, 52.4, 55.1, 70.0, 70.4, 71.4, 72.8, 73.6, 84.0, 99.0, 121.9, 123.0, 127.7, 128.6, 137.5, 138.5, 148.8, 158.5, 170.2; FAB-HRMS: Calcd for $C_{28}H_{30}N_2O_6$ [M + H]$^+$ 491.2182, Found: 491.2226.

Methyl 2-Acetamido-2-deoxy-6-*O*-benzyl-3-*O*-(2-picolinyl)-α-D-glucopyranoside (18). 4,6-*O*-Benzylidene-protected compound **17** was treated with $NaBH_3CN$ as described for **14** to produce alcohol **18** in 75% yield as a white solid: mp 122−124 °C; $[\alpha]_D = +50.1°$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR δ 2.06 (s, 3H), 3.39 (s, 3H), 3.66−3.89 (m, 6H), 4.23−4.30 (m, 1H), 4.63 (s, 2H), 4.75 (d, $J = 15.0$ Hz, 1H), 4.78 (d, $J = 3.8$ Hz, 1H), 4.95 (d, $J = 15.0$ Hz, 1H), 6.21 (d, $J = 8.9$ Hz, 1H), 7.17 (d, $J = 7.7$ Hz, 1H), 7.20−7.39 (m, 6H), 7.68 (dt, $J = 1.7$, 8.0 Hz, 1H), 8.54 (d, $J = 5.1$ Hz, 1H); ^{13}C NMR δ 23.7, 52.4, 55.1, 70.0, 70.4, 71.4, 72.8, 73.6, 84.0, 98.8, 122.0, 123.0, 127.7, 128.5, 137.5, 138.5, 148.8, 158.5, 170.2; FAB-HRMS: Calcd for $C_{22}H_{28}N_2O_6$ [M + H]$^+$ 417.2026, Found: 417.2047.

Methyl 2-Acetamido-2-deoxy-4-*O*-benzyl-3-*O*-(2-picolinyl)-α-D-glucopyranoside (19). 4,6-*O*-Benzylidene-protected compound **17** (750 mg, 1.8 mmol) was placed in 100 mL flask and treated with solution of BH_3 in THF (1.0 M, 18 mL, 18 mmol). After 5 min stirring the reaction mixture was cooled to 0 °C, and a solution of Bu_2BOTf in dichloromethane (1.0 M, 1.8 mL, 1.8 mmol) was added dropwise. Stirring was continued for 1 h at 0 °C, and then a solution of HCl in diethyl ether (1.0 M, 30 mL) was carefully added; the reaction mixture was left stirring overnight at room temperature, concentrated, redissolved in dichloromethane, and washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Column chromatography of the residue afforded alcohol **19** as a white solid (653 mg, 87%): mp 158−160 °C; $[\alpha]_D = +84.0°$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR δ 1.99 (s, 3H), 2.34 (br s, 1H), 3.35 (s, 3H), 3.66 (dt, $J = 9.5$, 3.3 Hz, 1H), 3.73 (t, $J = 9.5$ Hz, 1H), 3.79 (m, 1H), 3.85 (dd, $J = 1.7$, 11.7 Hz, 1H), 3.91 (dd, $J = 8.8$, 10.7 Hz, 1H), 4.09 (m, 1H), 4.74 (d, $J = 10.8$ Hz, 1H), 4.89 (d, $J = 11.8$ Hz, 1H), 4.99 (dt, $J = 14.3$ Hz, 1H), 4.97 (d, $J = 3.8$ Hz, 1H), 5.01 (d, $J = 14.3$ Hz, 1H), 7.23 (dd, $J = 5.0$, 7.1 Hz, 1H), 7.28−7.38 (m, 6H), 7.43 (d, $J = 6.9$ Hz, 1H), 7.69 (dt, $J = 1.3$, 7.7 Hz, 1H), 8.58 (br d, $J = 5.1$ Hz, 1H); ^{13}C NMR δ 23.8, 54.4, 55.5, 62.0, 71.7, 75.1, 75.4, 79.2, 80.8, 98.6, 122.0, 122.9, 128.3, 128.4, 128.9, 137.4, 138.4, 149.1, 159.1, 170.9, FAB-HRMS: Calcd for $C_{22}H_{28}N_2O_6$ [M + H]$^+$ 417.2026, Found: 417.2029.

Methyl 2-Acetamido-2-deoxy-6-*O*-benzyl-3-*O*-(2-picolinyl)-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl]-(1→4)-α-D-glucopyranoside (21). Alcohol **18** was coupled to donor **4** according to the general protocol to give **21** as a colorless oil in 8% yield. $[\alpha]_D = +7.4°$ ($c = 0.74$); ^{1}H NMR δ 2.05 (s, 3H), 3.17 (dt, $J = 4.8$, 9.5 Hz, 1H), 3.39 (s, 3H), 3.43 (dd, $J = 3.0$, 10.0 Hz, 1H), 3.57−3.62 (m, 2H), 3.69 (d, $J = 3.0$ Hz, 1H), 3.73−3.85 (m, 3H), 3.91−3.97 (m, 1H), 4.01 (t, $J = 9.1$ Hz, 1H), 4.11−4.17 (m, 1H), 4.28 (dd, $J = 4.7$, 10.2 Hz, 1H), 4.39 (d, $J = 12.2$ Hz, 1H), 4.46 (br s, 1H), 4.62 (d, $J = 12.4$ Hz, 1H), 4.68 (d, $J = 14.6$ Hz, 1H), 4.75 (d, $J = 11.3$ Hz, 1H), 4.79 (d, $J = 12.6$ Hz, 1H), 4.83 (d, $J = 11.7$ Hz, 1H), 4.94 (d, $J = 15.7$ Hz, 1H), 5.07 (d, $J = 15.5$ Hz, 1H), 5.20 (d, $J = 3.4$ Hz, 1H), 5.62 (s, 1H), 6.99 (d, $J = 7.8$ Hz, 1H), 7.20−7.45 (m, 20H), 7.52 (dd, $J = 2.1$, 8.1 Hz, 1H), 7.61 (dt, $J = 1.4$, 7.7 Hz, 1H), 8.43 (d, $J = 4.6$ Hz, 1H), 8.57 (d, $J = 4.6$ Hz, 1H); ^{13}C NMR δ 23.6, 54.6, 55.6, 67.4, 68.5, 68.9, 70.4, 72.8, 73.9, 75.4, 77.4, 78.1, 78.5, 78.6, 79.0, 98.1, 101.6, 101.7, 122.0, 122.6, 126.3, 127.5, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 128.8, 129.1, 137.8, 137.9, 138.8, 170.9; FAB-HRMS: Calcd for $C_{49}H_{54}N_2O_{11}$ [M+Na$^+$] 869.3625, Found: 869.3700.

Methyl 2-Acetamido-2-deoxy-4-*O*-benzyl-3-*O*-(2-picolinyl)-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (22). Alcohol **19** was coupled to donor **4** according to the general protocol to give **22** as a white solid in 63% yield: mp 215−217 °C; ^{1}H NMR δ 1.97 (s, 3H), 3.27−3.33 (m, 1H), 3.31 (s, 3H), 3.50−3.57 (m, 3H), 3.82 (ddd, J = 1.5, 5.5, 10.0 Hz, 1H), 3.84 (d, J = 3.5 Hz, 1H), 3.91 (dd, J = 9.0, 11.0 Hz, 1H), 3.97 (t, J = 10.0 Hz, 1H), 4.16−4.23 (m, 3H), 4.25 (br s, 1H), 4.31 (dd, J = 4.5, 10.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 12.5 Hz, 1H), 4.74 (d, J = 12.5 Hz, 1H), 4.86 (d, J = 11.5 Hz, 1H), 4.88 (d, J = 12.0 Hz, 1H), 4.93 (d, J = 3.0 Hz, 1H), 4.94 (d, J = 14.0 Hz, 1H), 4.99 (d, J = 12.0 Hz, 1H), 5.03 (d, J = 14.0 Hz, 1H), 5.64 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.22−7.52 (m, 21H), 7.53 (dd, J = 1.5, 8.0 Hz, 1H), 7.72 (dt, J = 1.5, 8.0 Hz, 1H), 8.59 (m, 1H); ^{13}C NMR δ 23.9, 54.1, 55.4, 68.0, 68.9, 69.0, 70.7, 72.9, 75.1, 75.4, 76.1, 78.2, 79.1, 79.5, 81.5, 98.4, 101.8, 102.7, 122.1, 123.0, 126.5, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 137.4, 138.0, 138.4, 138.8 149.2, 159.0, 170.7; FAB-HRMS: Calcd for $C_{49}H_{54}N_2O_{11}$ [M + H]$^+$ 847.3806, Found: 847.3887.

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-benzyl-[2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (23). Alcohol **20**[32] was coupled to donor **4** according to the general protocol to give **8** as a colorless oil in 39% yield: mp = 230 °C; $[\alpha]_D$ = +30.1° (c = 1.0, $CHCl_3$); ^{1}H NMR δ 1.87 (s, 3H), 3.28 (dt, J = 4.6, 9.5 Hz, 1H), 3.31 (s, 3H), 3.49−3.57 (m, 3H), 3.72 (dd, J = 8.9, 10.6 Hz, 1H), 3.79−3.83 (m, 2H), 3.96 (t, J = 10.2 Hz, 1H), 4.17 (dd, J = 1.8, 10.3 Hz, 1H), 4.20−4.29 (m, 3H), 4.32 (dd, J = 5.3, 11.1 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 12.6 Hz, 1H), 4.65−4.70 (m, 2H), 4.73 (d, J = 12.4 Hz, 1H), 4.83−4.89 (m, 3H), 4.99 (d, J = 11.9 Hz, 1H), 5.47 (d, J = 9.5 Hz, 1H), 5.64 (s, 1H), 7.42−7.50 (m, 25H); ^{13}C NMR δ: 23.9, 53.0, 55.3, 68.0, 68.9, 69.0, 70.7, 72.8, 75.2, 75.3, 75.4, 76.1, 78.1, 78.4, 79.0, 81.1, 98.8, 101.8, 102.6, 126.5, 128.0, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 128.96, 129.0, 129.3, 138.0, 138.4, 138.7, 170.1; FAB-HRMS: Calcd for $C_{50}H_{55}NO_{11}$ [M + H]$^+$ 846.3853, Found: 846.3696.

Methyl *N*-Acetyl-*N*-benzoyl-3,4-di-*O*-benzoyl-[2,3,4,6-tetra-*O*-benzoyl-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (24). Disaccharide **22** (4.5 mg, 0.0053 mmol) was dissolved in the mixture of 1,4-dioxane (2 mL), and methanol (10 mL) and 10% $Pd(OH)_2$/C (5.0 mg) was added. The reaction mixture was stirred for 20 h under atmospheric pressure of hydrogen and then concentrated. The residue was dried carefully and then dissolved in pyridine (0.5 mL) and treated with benzoyl chloride (0.2 mL). After overnight stirring the reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with chloroform, washed with brine, and concentrated. Preparative TLC of the residue provided perbenzoylated compound **24** (4.0 mg, 66%). $[\alpha]_D$ = −10.5° (c = 0.2, $CHCl_3$); ^{1}H NMR δ 1.75 (s, 3H), 2.84 (s, 3H), 3.79 (dd, J = 11.0, 14.0 Hz, 1H), 4.04 (dd, J = 2.0, 14.0 Hz, 1H), 4.08 (m, 1H), 4.15 (m, 1H), 4.44 (dd, J = 5.5, 15.0 Hz, 1H), 4.64 (dd, J = 3.0, 15.0 Hz, 1H), 4.92 (d, J = 4.5 Hz, 1H), 5.04 (s, 1H), 5.23 (t, J = 12.0 Hz, 1H), 5.39 (dd, J = 4.5, 14.0 Hz, 1H), 5.59 (dd, J = 4.0, 13.0 Hz, 1H), 5.97−6.03 (m, 2H), 6.39 (dd, J = 12.0, 14.0 Hz, 1H), 7.22−7.58 (m, 21H), 7.74−8.08 (m, 14H); ^{13}C NMR (75 MHz) δ 29.8, 54.8, 57.3, 63.0, 67.0, 69.7, 69.8, 71.0, 71.8, 72.1, 72.6, 77.3, 98.7, 100.0, 128.4, 128.6, 129.0, 129.2, 129.6, 129.8, 129.9, 130.0, 130.2, 133.0, 133.1, 133.3, 133.4, 133.6, 135.7, 142.8, 165.0, 165.4, 165.5, 165.7, 165.9, 166.2, 169.9, 173.6; FAB-HRMS: Calcd for $C_{64}H_{55}NO_{18}$ [M + H]$^+$ 1126.3498, Found: 1126.3670.

Methyl 2-Acetamido-2-deoxy-4-*O*-benzyl-3-*O*-(2-picolinyl)-[2,3,4,6-tetra-*O*-benzyl-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (28). Triflic anhydride (24 μL, 0.14 mmol) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[33] (54 mg, 0.1 mmol) and diphenyl sulfoxide (57 mg, 0.28 mmol) in a mixture of toluene and dichloromethane (3:1, 1.0 mL) at −78 °C. After stirring at this temperature for 10 min and then at −40 °C for 1 h, TTBP (124 mg, 0.5 mmol) in dichloromethane (0.5 mL) and a solution of acceptor **19** (42 mg, 0.1 mmol) in dichloromethane (1.0 mL) were added sequentially at −40 °C. The solution was then stirred at this temperature for 30 min and then at 0 °C for 25 min and finally at room temperature for 4 h before the addition of excess triethylamine (0.1 mL). The reaction was diluted with dichloromethane and washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by column chromatography to give the title disaccharide as a 1/1.2 α/β mixture of anomers (81.5 mg, 87%). ^{1}H NMR δ 1.88 (s, 3H), 3.28 and 3.31 (s, 3H), 3.46−3.89 (m, 10H), 3.96−4.13 (m, 2H), 4.40−5.06 (m, 14H), 5.33 (d, J = 8.5 Hz, 1H), 7.11−7.42 (m, 30H); ^{13}C NMR δ 23.9, 30.1, 52.9, 53.1, 53.4, 69.1, 69.4, 70.7, 70.8, 71.1, 73.2, 73.8, 73.9, 75.1, 75.2, 75.28, 75.33, 75.4, 75.9, 76.9, 78.0, 78.2, 78.3, 79.1, 79.12, 80.3, 80.7, 80.8, 82.2, 82.5, 85.2, 97.6, 98.8, 98.9, 104.2, 127.9−128.9, 138.3−138.9, 170.3; FAB-HRMS: Calcd for $C_{56}H_{62}N_2O_{11}$ [M + Na^+] 961.4251, Found: 961.4291.

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-benzyl-[2,3,4,6-tetra-*O*-benzyl-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (26). Acceptor **20** was reacted with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[33] exactly as in previous experiment to give the 1/2.4 α/β anomeric mixture of **26** (17.0 mg, 18%). ^{1}H NMR δ 2.0 (s, 3H), 3.32 and 3.35 (s, 3H), 3.42−3.87 (m, 10H), 3.95−4.23 (m, 2H), 4.40−4.62 (m, 5H), 4.67−4.83 (m, 4H), 4.85−5.20 (m, 5H), 7.10−7.44 (m, 33H), 7.70−7.77 (m, 1H), 8.56−8.59 (m, 1H); ^{13}C NMR δ 23.9, 30.1, 54.0, 54.2, 55.5, 66.1, 68.9, 68.94, 69.5, 70.7, 70.72, 71.2, 73.1, 73.9, 74.1, 75.1, 75.3, 75.33, 75.4, 75.5, 75.9, 76.2, 78.0, 78.3, 79.4, 79.6, 80.3, 80.31, 81.3, 81.3, 82.2, 82.5, 85.2, 97.6, 98.5, 98.6, 104.2, 122.8, 122.9, 123.3, 127.8−128.8, 138.4−139.2, 147.5, 147.6, 158.3, 170.8; FAB-HRMS: Calcd for $C_{57}H_{63}NO_{11}$ [M + Na^+] 960.4300, Found: 960.4330.

Acknowledgment. We thank the NIHGMS for support of this work (GM 57335).

JA010086B

(32) Falcone-Hindley, M. L.; Davis, J. T. *J. Org. Chem.* **1998**, *63*, 5555−5561.

(33) Perrine, T. D.; Glaudemans, C. P. J.; Ness, R. K.; Kyle, J.; Fletcher, H. *J. Org. Chem.* **1967**, *32*, 664−669.