

Experimental Section

The synthesis of **G1**–**G3** has been recently reported.^[8]

Langmuir and LB films: Spreading solutions were prepared by dissolving **G1**–**G3** in CHCl_3 (1.0–3.0 mg mL^{-1}). Stock solutions proved stable for several months at room temperature. Stock solution (50 μL) was spread on the water surface with a microsyringe, and the film was left for 15–20 min to equilibrate before the compression was started. Data were collected with a KSV LB5000 system (KSV Instruments, Helsinki, Finland) using a symmetrical compression Teflon trough and hydrophilic barriers in a dust-free environment. The whole setup was in a Plexiglas enclosure resting on a vibration-free table, and the trough temperature was controlled to $\pm 0.1^\circ\text{C}$. All isotherms were taken at 20°C unless otherwise specified. Ultra pure water ($\rho = 18.2 \text{ M}\Omega\text{cm}^{-1}$) obtained from a Milli-RO3 Plus system combined with a Milli-Q185 Ultra Purification system from Millipore was used for the subphase. Surface pressure was measured by the Wilhelmy plate method. The monolayers were compressed with speeds ranging from 1.2 to $10 \text{ Å}^2\text{molecule}^{-1} \text{ min}^{-1}$, with almost no incidence of the barrier velocity on the observed behavior.

LB films were obtained by transfer on glass slides or silicon wafers (100) rendered hydrophobic through silanization of the surface with octadecyltrichlorosilane. The vertical dipping method was used for **G1** and **G3**, while **G2** could only be transferred with the horizontal (LS) method. Dipping parameters were not very stringent and usually kept around the following values: trough 30 – 40°C , dipping speed ≈ 0.5 – 4 mm min^{-1} . Transfers were performed at surface pressures 12, 15, and 22 mN m^{-1} for **G1**, **G2**, and **G3**, respectively. It has been possible to build Y-type multilayer films of **G1** and **G3**.

Grazing incidence X-ray analysis (GIXA): The studies of LB films were performed on a X'PERT-MPD device (Philips), equipped with a program-mable divergence slit ($1/32^\circ$), a Soller slit collimator, a flat Ge monochromator, and proportional Xe detector. A nickel-filtered $\text{Cu}_{\text{K}\alpha}$ line ($\lambda = 0.1542 \text{ nm}$) was used.

All measurements were recorded immediately after the film transfer, but the diffraction patterns remained stable for as long as several weeks without special care being taken for the storage of the film.

BAM: BAM was performed using a BAM2plus (Nanofilm Technologies GmbH) illuminated by an Ar laser. Images were recorded on a CCD camera of field $620 \mu\text{m} \times 500 \mu\text{m}$.

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Acetamidoglycosylation with Glycal Donors: A One-Pot Glycosidic Coupling with Direct Installation of the Natural C(2)-N-Acetylamino Functionality**

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The 2-*N*-acetylamino-2-deoxy class of carbohydrates is ubiquitous among biologically important complex oligosaccharides and glycoconjugates, including, inter alia, glycosaminoglycans, peptidoglycans, and blood group antigens.^[1] As a result, the efficient preparation of this group of glycosides

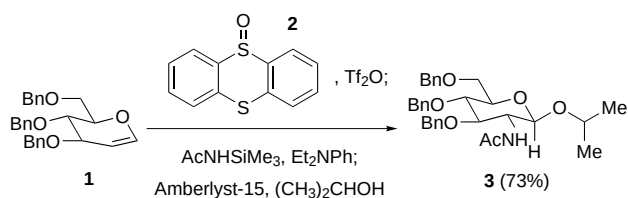
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has been a major focus in carbohydrate synthesis.^[2] At present, however, only a handful of methods exist for the introduction of a nitrogen substituent onto the C2-position of a carbohydrate substrate. The most direct synthetic routes usually involve methods of glycal activation in which various *N*-acetylamino precursor functionalities are introduced at the C2-position. Among these are the methods developed by Lemieux et al. for the introduction of oxime^[3] and azide^[4] groups at C2, the sulfonamidoglycosylation procedure of Danishefsky et al.,^[5] the phosphoramidoglycosylation strategy of Descotes and Lafont,^[6] the Fitzsimmons–Leblanc protocol for the formation of pyrano-oxadiazine [4 + 2] cycloadducts,^[7] and most recently the use of activated manganese nitrido complexes by Carrier and co-workers for the introduction of a C2-trifluoroacetamido substituent.^[8] These methods,^[9] although effective in the transfer of nitrogen to the glycal donor, must also entail further functional group manipulations in order to install the naturally occurring acetamido group at C2 as well as to form the glycosidic bond with the desired glycosyl acceptor. We now report a novel method for nitrogen transfer that efficiently effects the direct installation of the native C2-*N*-acetylamino functionality onto glycal donors and, additionally, allows glycosidic coupling with various glycosyl acceptors in an overall one-pot acetamidoglycosylation procedure. In this protocol, a new sulfonium reagent derived from thianthrene-5-oxide (**2**) is employed for glycal activation.

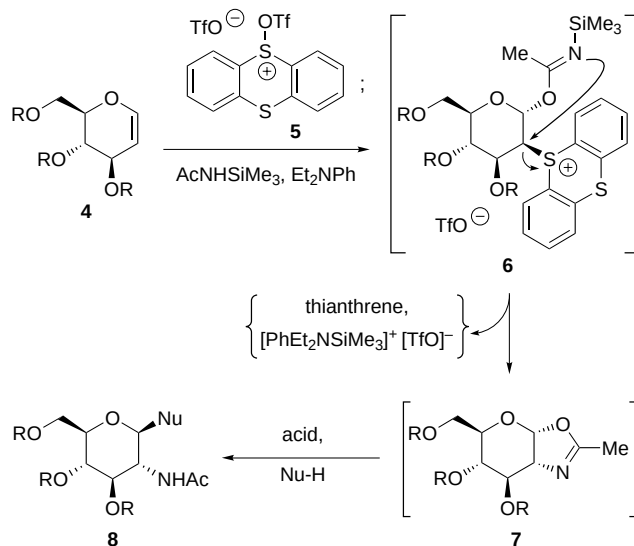
Our acetamidoglycosylation reaction using glycal donors involves an exceedingly simple procedure, exemplified by the glycosylation of 2-propanol with tri-*O*-benzyl-D-glucal (**1**) to generate isopropyl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**3**, Scheme 1). In this protocol,



Scheme 1. Acetamidoglycosylation of 2-propanol.

triflic anhydride (2 equiv) is added to a solution of glucal **1** (1 equiv) and thianthrene-5-oxide^[10] (**2**, 2 equiv) in a mixture of chloroform and dichloromethane (4:1) at -78°C . Following an initial activation period of 10 min, the acid scavenger *N,N*-diethylaniline (4 equiv) and solid *N*-trimethylsilyl-acetamide (*N*-TMS-acetamide, 3 equiv) were added sequentially, and the reaction mixture was stirred at 23°C for 2 h. Amberlyst-15 acidic resin and the glycosyl acceptor (2-propanol, 3 equiv) were then added, leading to the formation of the isopropyl glycoside **3** in 73% yield.

Such a transformation could proceed by way of the reaction pathway proposed in Scheme 2, in which the initial step involves low-temperature activation of thianthrene-5-oxide with triflic anhydride to generate thianthrene bis(triflate) (**5**) in situ.^[11] Electrophilic activation of the enol ether functionality in **4** by **5** would lead to the formation of a pyranoside intermediate incorporating an oxocarbenium triflate func-



Scheme 2. Proposed reaction pathway for acetamidoglycosylation.

tionality at C1 and a thianthrene sulfonium moiety at C2.^[12] The introduction of the acetamido group proceeds upon addition of the acid scavenger *N,N*-diethylaniline^[13] and *N*-TMS-acetamide. A key function of the *N*-trimethylsilyl protecting group in this amide reagent is to provide steric shielding at the nitrogen atom to favor initial addition of the amide oxygen atom onto C1 of the activated glycal, thereby generating the putative acetimidate intermediate **6**.^[14] Subsequent intramolecular displacement of the C2-thianthrene-sulfonium moiety by the imide nitrogen accompanied by loss of the *N*-TMS protective group (either as TMSOTf or more likely as its *N,N*-diethylaniline adduct) would generate the bicyclic dihydrooxazole (oxazoline) intermediate **7**. Acid-mediated oxazoline ring-opening in the presence of a glycosyl acceptor would then afford the desired glycoside **8** in the final stage of the acetamidoglycosylation.

Using this procedure several glycosylations were performed with a series of selectively protected glycal donors (Table 1). It is worth highlighting that the yield in each of these one-pot operations is the result of glycal activation, nitrogen transfer by oxazoline formation, oxazoline ring-opening, and glycosidic bond formation. Thus, the acetamidoglycosylation of simple alkyl alcohols (e.g., 2-propanol, benzyl alcohol, dihydrocholesterol; entries 1,^[15] 2, 4, 5, 6, 8, 9, and 11) as well as of the carbohydrate acceptor methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside^[16] (entries 3, 7, and 10) led to the formation of the corresponding C2-acetamidoglycosides and C2-acetamidodisaccharides directly from protected glycal donors. In addition, glycal protective groups such as benzyl, triisopropylsilyl,^[17] and allyl^[18] ethers (entries 1–4, 8–11), as well as the acid-labile isopropylidene ketal (entries 5–7), can be used in this glycosylation process. The examples with 6-*O*-allyl-3,4-di-*O*-benzyl-D-glucal (entries 8–10) illustrate the propensity of the thianthrene sulfoxide/triflic anhydride reagent combination to selectively react with the glycal enol ether functionality in the presence of simple alkenes. Moreover, relatively mild Lewis acids such as MgI_2 or LiClO_4 can be employed in the place of Amberlyst-15 in certain cases (entries 5 and 6) for

Table 1. Acetamidoglycosylation with glycal donors.

Entry	Donor	Product (Yield)
1		 69%
2		 70%
3		 60%
4		 54%
5 ^[a]		 66%
6 ^[b]		 69%
7		 45%
8		 57%
9		 63%
10		 55%
11 ^[c]		 45%

[a] MgI_2 (1.1 equiv) was used for oxazoline ring-opening instead of Amberlyst-15. [b] LiClO_4 (2.2 equiv) was used for oxazoline ring-opening instead of Amberlyst-15. [c] Glycosylation was performed with 5 equiv of glycosyl acceptor.

the final stage of the reaction (oxazoline ring-opening) in order to minimize unwanted removal of acid-labile protective groups. Finally, direct acetamidoglycosylation with galactal donors can be accomplished (e.g., 3,4,6-tri-*O*-benzyl-D-galactal, entry 11) albeit in moderate overall yield, presumably a

result of the lability of the galactal-derived oxazoline intermediate which is generated in situ (vide infra).

In these reactions, an excess of both the sulfoxide and the triflic anhydride reagent (2 equiv) is required to maximize yields, as this presumably ensures rapid and complete activation of the glycal at low temperature. As a result, the subsequent reagents (TMS-NHAc and glycosyl acceptor) are also employed in a mild excess; however, virtually all of the excess acceptor can be recovered at the end of the reaction. Overall, the yields of these acetamidoglycosylation reactions are comparable to existing methods for nitrogen transfer to glycals, which would still require additional steps for N-protective group exchange and glycosidic bond formation.

Several points are worth noting with respect to the proposed reaction pathway outlined in Scheme 2. First, it is presumed that the addition of thianthrene bis(triflate) (**5**) occurs onto the β -face of **4**. Although this mode of activation may appear sterically unfavorable, the stereoselective addition of electrophilic reagents onto the β -face of glycals leading to 1,2-transdial-*substituted* pyranosides (as in **6**) is certainly preceded as illustrated by numerous examples in the halosulfonamidation of glycals.^[5] Second, the reagent thianthrene-5-oxide (**2**) is believed to undergo reduction to form thianthrene during the course of the C2-*N*-acetamido transfer process. Indeed, in these acetamidoglycosylation reactions, 0.7–0.9 equivalents of thianthrene was isolated as a principal by-product, which is consistent with the proposed reaction cascade. Finally, the bicyclic oxazoline intermediate **7** is invoked as an intermediate in the acetamidoglycosylation process. When activation of 3,4,6-tri-*O*-benzyl-D-glucal (**1**) (thianthrene-5-oxide, Ti_2O ; TMSNHAc, PhNEt_2) is performed in CDCl_3 , ^1H NMR analysis of the reaction mixture clearly shows the oxazoline **9**^[19] (Figure 1) as the principal

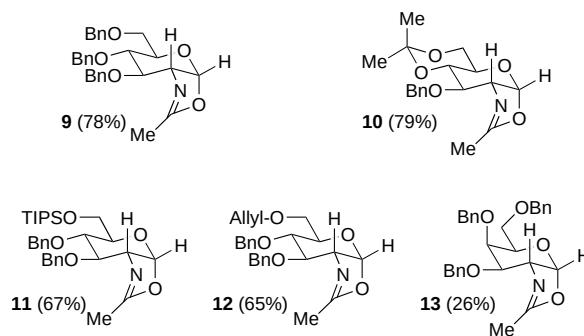


Figure 1. Isolated oxazoline intermediates.

carbohydrate species in solution. Moreover, oxazoline intermediates **9**, **10**, **11**,^[20] **12**,^[20] and **13** can be isolated prior to the introduction of the acid and glycosyl acceptor (Figure 1), lending support to the proposed reaction pathway in Scheme 2. (The poor yield of the galactal-derived oxazoline **13** is a result of its increased hydrolytic lability compared with **9**–**12** in the purification process).^[21] Although these observations do not preclude the possibility of formation of a reactive 1,2-*N*-acetyl aziridine intermediate in situ, such a species has not been detected in our acetamidoglycosylation reaction. Efforts are currently underway to investigate the mechanistic

details of the glycal activation process, as well as extending the method to the introduction of other C2-nitrogen functionalities.

In summary, a new method for C2-aza-glycosylation with glycal donors has been developed. The method involves a novel process for nitrogen transfer to glycals that: 1) employs thianthrene-5-oxide and triflic anhydride as a new reagent combination for glycal activation; and 2) effects, for the first time, the direct installation of the naturally occurring C2-*N*-acetylamino functionality onto glycal donors in conjunction with glycosidic coupling to various glycosyl acceptors in an overall one-pot procedure.

Experimental Section

Representative acetamidoglycosylation procedure:

Dihydrocholesteryl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy- β -D-glucopyranoside: Triflic anhydride (81 μ L, 0.480 mmol, 2.0 equiv) was added to a solution of tri-*O*-benzyl-D-glucal (100 mg, 0.240 mmol, 1 equiv) and thianthrene-5-oxide (112 mg, 0.480 mmol, 2.0 equiv) in a mixture of chloroform and dichloromethane (5 mL; 4:1) at -78°C . The reaction mixture was stirred at this temperature for 10 min, followed by the sequential addition of *N,N*-diethylaniline (152 μ L, 0.960 mmol, 4.0 equiv) and solid *N*-TMS-acetamide (72 mg, 0.552 mmol, 2.3 equiv). The reaction mixture was immediately warmed to 23°C and was stirred at this temperature for 2 h. The solution was cooled to -78°C , Amberlyst-15 (145 mg) and dihydrocholesterol (280 mg, 0.720 mmol, 3.0 equiv) were added, and the mixture was then stirred at 23°C for 17 h. The reaction was filtered, and the filtrate was partitioned between dichloromethane (80 mL) and saturated aqueous sodium chloride solution (100 mL). The aqueous phase was further extracted with dichloromethane (70 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by silica gel flash column chromatography to afford dihydrocholesteryl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy- β -D-glucopyranoside (144 mg, 70% yield) as a white solid. M.p. $176\text{--}177^{\circ}\text{C}$; TLC (silica gel) $R_f = 0.39$ (20% ethyl acetate in benzene); $[\alpha]_D^{20} = +27.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.33\text{--}7.27$ (m, 13H), 7.21–7.19 (m, 2H), 5.55 (d, $^3J(\text{H,H}) = 7.3$ Hz, 1H; NH), 5.01 (d, $^3J(\text{H,H}) = 8.0$ Hz, 1H; H1), 4.83 (d, $^3J(\text{H,H}) = 11.5$ Hz, 1H), 4.79 (d, $^3J(\text{H,H}) = 11.0$ Hz, 1H), 4.66 (d, $^3J(\text{H,H}) = 11.5$ Hz, 1H), 4.61 (d, $^3J(\text{H,H}) = 12.3$ Hz, 1H), 4.58 (d, $^3J(\text{H,H}) = 10.9$ Hz, 1H), 4.55 (d, $^3J(\text{H,H}) = 12.1$ Hz, 1H), 4.26 (dd, $^3J(\text{H,H}) = 9.9$, 8.2 Hz, 1H), 3.75 (dd, $^3J(\text{H,H}) = 9.9$, 1.7 Hz, 1H), 3.68 (m, 1H), 3.56 (m, 3H), 3.18 (dt, $^3J(\text{H,H}) = 9.9$, 7.8 Hz, 1H), 1.96 (m, 1H), 1.91–1.76 (m, 2H), 1.84 (s, 3H), 1.70–1.43 (m, 7H), 1.36–0.92 (m, 21H), 0.89 (d, $^3J(\text{H,H}) = 6.6$ Hz, 3H), 0.87 (d, $^3J(\text{H,H}) = 2.3$ Hz, 3H), 0.85 (d, $^3J(\text{H,H}) = 2.5$ Hz, 3H), 0.77 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3): $\delta = 170.35$, 138.61, 138.31, 138.12, 128.46, 128.41, 128.33, 127.94, 127.86, 127.74, 127.72, 127.71, 127.55, 98.07, 80.31, 79.03, 78.75, 74.75, 74.67, 74.59, 73.35, 69.13, 58.22, 56.45, 56.25, 54.35, 44.65, 42.57, 40.02, 39.50, 37.03, 36.15, 35.77, 35.53, 35.45, 34.57, 32.06, 29.43, 28.76, 28.24, 28.00, 24.19, 23.80, 23.63, 22.81, 22.55, 21.20, 18.65, 12.26, 12.04; FTIR (neat film): $\bar{\nu}$ 3286, 3064, 3031, 2932, 2866, 1655, 1557, 1496, 1453, 1373, 1311, 1118, 1072, 1027 cm^{-1} ; HRMS (FAB $^+$): m/z : calcd for $\text{C}_{56}\text{H}_{80}\text{NO}_6$ ($M + \text{H}^+$) 862.5986; found 862.5988.

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- [20] The gluco-oxazolines **11** and **12** were each isolated as diastereomeric mixtures containing minor amounts of their corresponding manno-oxazoline stereoisomers in diastereomeric ratios of 9:1 and 10:1, respectively.
- [21] The intermediates **9–13** were isolated by chromatography on Et₃N-neutralized silica gel to minimize oxazoline hydrolysis.

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